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(54) **COMPILATIONS OF NUCLEIC ACIDS AND ARRAYS AND METHODS OF USING THEM**

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(57) **ABSTRACT**

In one aspect the invention provides compilations of nucleic acids, articles of manufacture, e.g., arrays, and methods for the detection of chromosomal abnormalities, such as a chromosomal aneuploidies, deletions, amplifications, and the like, and the diagnosis or prognosis of syndromes associated with a contiguous gene abnormality. Kits are also provided.

COMPILATIONS OF NUCLEIC ACIDS AND ARRAYS AND METHODS OF USING THEM

TECHNICAL FIELD

[0001] This invention relates to molecular biology, genetic diagnostics and array, or "biochip," technology. In one aspect the invention provides compilations of nucleic acids, articles of manufacture, e.g., arrays, and methods for the detection of chromosomal abnormalities, such as a chromosomal aneuploidies, amplifications, deletions, and the like, and the diagnosis or prognosis of syndromes associated with a contiguous gene abnormality.

BACKGROUND

[0002] Genomic DNA microarray based comparative genomic hybridization (CGH) has the potential to perform faster, more efficiently and cheaper than traditional CGH methods, which rely on comparative hybridization on individual metaphase chromosomes. Array-based CGH uses immobilized nucleic acids arranged as an array on a biochip or a microarray platform. The so-called array or chip CGH approach can provide DNA sequence copy number information across the entire genome in a single, timely, cost-effective and sensitive procedure. The resolution of chip CGH is primarily dependent upon the number, size and map positions of the DNA elements within the array. Typically, bacterial artificial chromosomes, or BACs, which can each accommodate on average about 150 kilobases (kb) of cloned genomic DNA, are used in the production of the array.

[0003] The principle of the array CGH approach is simple. Equitable amounts of total genomic DNA from cells of a test sample and a reference sample (e.g., a sample from cells known to be free of chromosomal aberrations) are differentially labeled with fluorescent dyes and co-hybridized to the array of BACs, which contain the cloned genomic DNA fragments that collectively cover the cell's genome. The resulting co-hybridization produces a fluorescently labeled array, the coloration of which reflects the competitive hybridization of sequences in the test and reference genomic DNAs to the homologous sequences within the arrayed BACs. Theoretically, the copy number ratio of homologous sequences in the test and reference genomic DNA samples should be directly proportional to the ratio of their respective fluorescent signal intensities at discrete BACs within the array. The versatility of the approach allows the detection of constitutional variations in DNA copy number in clinical cytogenetic samples such as amniotic samples, chorionic villus samples (CVS), blood samples and tissue biopsies. It also allows detection of somatically acquired genomic changes in tumorigenically altered cells, for example, from bone marrow, blood or solid tumor samples.

SUMMARY

[0004] The invention provides novel compilations, or sets, libraries or collections, of nucleic acids and articles of manufacture, e.g., articles of manufacture, e.g., arrays, and methods of making and using them. These compilations, or sets, libraries or collections, of nucleic acids and arrays can be used in the detection of a chromosomal abnormality, such as a chromosomal aneuploidy, or in the diagnosis or prognosis of a syndrome associated with a contiguous gene abnormality.

[0005] The invention provides an articles of manufacture, e.g., an array, for the detection of a chromosomal abnormality or a diagnosis of a syndrome associated with a contiguous gene abnormality, comprising: a plurality of nucleic acids segments, wherein each nucleic acid segment is immobilized to a discrete and known spot on a substrate surface to form an array of nucleic acids, and each spot comprises a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome. In alternative aspects, the segment of genomic nucleic acid comprises: chromosome 1, locus 1p;36, and the syndrome detected is 1p Deletion Syndrome; chromosome 1, locus 7p11.2, and the syndrome detected is Smith-Magenis syndrome (SMS); chromosome 3, locus 3p25-pter, and the syndrome detected is 3p Deletion Syndrome; chromosome 3, locus 3p21-pter, and the syndrome detected is 3p Duplication Syndrome; chromosome 4, locus 4p16.3, and the syndrome detected is Wolf-Hirschhorn Syndrome; chromosome 4, locus 4p15.2-16.1, and the syndrome detected is 4p Duplication Syndrome; chromosome 5, locus 5p15.2-pter, and the syndrome detected is Cri du Chat Syndrome; chromosome 7, locus 7p13.3, and the syndrome detected is Miller-Dieker Syndrome; chromosome 7, locus 7q11.23, and the syndrome detected is Williams Syndrome; chromosome 8, locus 8q24.1, and the syndrome detected is Langer-Giedion Syndrome (LGS); chromosome 8, locus 8q24.1, and the syndrome detected is Trichorhinophalangeal Syndrome (TRPS); chromosome 8, locus 8q13.3, and the syndrome detected is branchio-oto-renal (BOR) syndrome; chromosome 9, locus 9p, e.g., locus 9p22-pter, and the syndrome detected is 9p Deletion Syndrome; chromosome 10, locus 10p13-p14, and the syndrome detected is DiGeorge Syndrome II; chromosome 11, locus 11p13, and the syndrome detected is WAGR Syndrome; chromosome 11, locus 11p15.5, and the syndrome detected is Beckwith-Wiedemann Syndrome; chromosome 11, locus 11p11.2, and the syndrome detected is Potocki-Shaffer Syndrome (Multiple Exostoses II Locus); chromosome 13, locus 13q22, and the syndrome detected is Hirschsprung disease and Waardenburg syndrome; chromosome 15, locus 15q12, and the syndrome detected is Angelman Syndrome; chromosome 15, locus 15q12, and the syndrome detected is Prader-Willi Syndrome; chromosome 16, locus distal 16p13.3, and the syndrome detected is Rubinstein-Taybi Syndrome; chromosome 16, pericentromeric region, and the syndrome detected is idiopathic epilepsy and paroxysmal dyskinesia; chromosome 17, locus 17p12, and the syndrome detected is Charcot-Marie-Tooth Disease Type 1A(CMT-1A); chromosome 17, locus 17p12, and the syndrome detected is Hereditary Neuropathy with Liability to Pressure Palsies; chromosome 17, locus 17p13.3, and the syndrome detected is Miller-Dieker Syndrome/Isolated Lissencephaly; chromosome 17, locus 17p11.2, and the syndrome detected is Smith-Magenis Syndrome; chromosome 20, locus 20p11.2-p 12, and the syndrome detected is Alagille Syndrome; chromosome 22, locus 22q11.2, and the syndrome detected is DiGeorge/Velocardiofacial Syndrome; chromosome X, locus Xp21, and the syndrome detected is Adrenal Hypoplasia Congenita (AHC); chromosome X, locus Xp21, and the syndrome detected is Duchenne/Becker Muscular Dystrophy; chromosome X, locus Xp21, and the syndrome detected is Glycerol Kinase Deficiency; chromosome X, locus Xp22, and the syndrome detected is Pelizaeus-Merzbacher Disease; chro-

mosome X, locus Xp22.3, and the syndrome detected comprises steroid sulfatase deficiency; chromosome X, locus Xp22.3, and the syndrome detected is Leri-Weill syndrome; chromosome Y, locus SRY locus/Yp, and the syndrome detected comprises abnormalities of the SRY locus; chromosome X, locus Xp22.3, and the syndrome detected is Kallman Disease; chromosome X, locus Xp21, and the syndrome detected is Sex Reversal (DSS); chromosome 17, locus 17p11.2, and the syndrome detected is 17p11.2 Duplication Syndrome; and, chromosome 17, locus 17p1.2, and the syndrome detected is Smith-Magenis syndrome (SMS).

[0006] In alternative aspects, the array further comprises at least one spot comprising a nucleic acid segment acting as a positive control, at least one spot comprising a nucleic acid segment acting as a negative control, or a combination thereof.

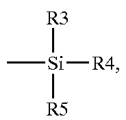
[0007] In alternative aspects of the array, about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99%, or more, or 100% of the spots comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

[0008] In one aspect, the array-immobilized genomic nucleic acid segments in a first spot are substantially or completely non-overlapping in sequence compared to the array-immobilized genomic nucleic acid segments in a second spot. The array-immobilized genomic nucleic acid segments in a spot can be non-overlapping in sequence compared to the array-immobilized genomic nucleic acid segments in about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99%, or more or all of other genomic nucleic acid-comprising spots on the array.

[0009] In one aspect, at least one cloned genomic nucleic acid segment is spotted in duplicate or triplicate on the array. All the duplicate spot(s) or triplicate spot(s) can have a different amount of nucleic acids segments immobilized. In alternative aspects, about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99%, or more or all the cloned genomic nucleic acid segments are spotted in duplicate or triplicate on the array.

[0010] In alternative aspects, about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99%, or more or all of the array-immobilized genomic nucleic acid comprise a detectable label.

[0011] In one aspect, the array-immobilized genomic nucleic acids are covalently bound to the substrate surface. The array-immobilized genomic nucleic acid can be covalently bound to a compound having the general formula: R1-X-R2, wherein R1 is a cyclic ether, an aldehyde, or a chloromethylphenyl moiety; X is a moiety chemically suitable for linking the R1 moiety to the R2 moiety, and the R2 moiety has the general formula



[0012] wherein R3, R4 and R5 comprise identical or different alkoxy group or chloro groups.

[0013] The array-immobilized genomic nucleic acid can be covalently bound to a compound having the general formula: R1-X-R2, wherein R1 is an amino group, R2 is an alkoxysilane group or a chlorohalide group; and X is a moiety chemically suitable for linking the R1 group and the R2 group. The array-immobilized genomic nucleic acid can be covalently bound to a compound having the general formula

R1-X—Si(OR2)m(Cl)n(R)k,

[0014] wherein m+k is the integer 3, and n can be 0 if m is greater than 0, or n+k is the integer 3 and m can be 0 if n is greater than 0; X is an inert linker; R1 comprises a group reactive toward the biological molecule; R is an alkyl group; and, R2 is an alkyl group.

[0015] In one aspect, the cloned nucleic acid segment is cloned in a construct comprising an artificial chromosome, wherein the artificial chromosome can comprise a bacterial artificial chromosome (BAC), a human artificial chromosome (HAC) a yeast artificial chromosome (YAC), a transformation-competent artificial chromosome (TAC) or a bacteriophage P1-derived artificial chromosome (PAC). In one aspect, the cloned nucleic acid segment is cloned in a construct comprising a vector selected from the group consisting of a cosmid vector, a plasmid vector and a viral vector.

[0016] In alternative aspects, the cloned nucleic acid segment is between about 50 kilobases (0.5 megabase) to about 500 kilobases (5 megabases) in length, between about 100 kilobases (1 megabase) to about 400 kilobases (4 megabases) in length, and is about 0.5, about 1, about 2, about 5, about 10, about 15, about 25, about 50, about 100, about 200, about 300, about 400, about 500 or about 600 kilobases in length.

[0017] The invention provides an articles of manufacture (e.g., arrays) for the detection of a chromosomal abnormality or the diagnosis of a syndrome associated with a contiguous gene abnormality, comprising: a plurality of nucleic acids segments, wherein each nucleic acid is immobilized to a discrete and known spot on a substrate surface to form an array of nucleic acids, and each spot comprises a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome, and the plurality of nucleic acids segments comprise: chromosome 1, locus 1p36, wherein the syndrome detected is 1p Deletion Syndrome; chromosome 3, locus 3p25-pter, wherein the syndrome detected is 3p Deletion Syndrome; chromosome 3, locus 3p21-pter, wherein the syndrome detected is 3p Duplication Syndrome; chromosome 4, locus 4p16.3, wherein the syndrome detected is Wolf-Hirschhorn Syndrome; chromosome 4, locus 4p15.2-16.1, wherein the syndrome detected is 4p Duplication Syndrome; chromosome 5, locus 5p15.2-pter, wherein the syndrome detected is Cri du Chat Syndrome; chromosome 7, locus 7p13.3, wherein the syndrome detected is Miller-Dieker Syndrome; chromosome 7, locus 7q11.23, wherein the syndrome detected is William's Syndrome; chromosome 8, locus 8q24.1, wherein the syndrome detected is Langer-Giedion Syndrome (LGS); chromosome

8, locus 8q24.1, wherein the syndrome detected is Trichorhinophalangeal Syndrome (TRPS); chromosome 9, locus 9p, wherein the syndrome detected is 9p Deletion Syndrome; chromosome 10, locus 10p13-p14, wherein the syndrome detected is DiGeorge Syndrome II; chromosome 11, locus 11p13, wherein the syndrome detected is WAGR Syndrome; chromosome 11, locus 11p15.5, wherein the syndrome detected is Beckwith-Wiedemann Syndrome; chromosome 11, locus 11p11.2, wherein the syndrome detected is Potocki-Shaffer Syndrome (Multiple Exostoses II Locus); chromosome 15, locus 15q12, wherein the syndrome detected is Angelman Syndrome; chromosome 15, locus 15q12, wherein the syndrome detected is Prader-Willi Syndrome; chromosome 16, locus distal 16p13.3, wherein the syndrome detected is Rubinstein-Taybi Syndrome; chromosome 17, locus 17p12, wherein the syndrome detected is Charcot-Marie-Tooth Disease Type 1A(CMT-1A); chromosome 17, locus 17p12, wherein the syndrome detected is Hereditary Neuropathy with Liability to Pressure Palsies; chromosome 17, locus 17p13.3, wherein the syndrome detected is Miller-Dieker Syndrome/Isolated Lissencephaly; chromosome 17, locus 17p11.2, wherein the syndrome detected is Smith-Magenis Syndrome; chromosome 20, locus 20p11.2-p12, wherein the syndrome detected is Alagille Syndrome; chromosome 22, locus 22q11.2, wherein the syndrome detected is Digeorge/Velocardiofacial Syndrome; chromosome X, locus Xp21, wherein the syndrome detected is Adrenal Hypoplasia Congenita (AHC); chromosome X, locus Xp21, wherein the syndrome detected is Duchenne/Becker Muscular Dystrophy; chromosome X, locus Xp21, wherein the syndrome detected is Glycerol Kinase Deficiency; chromosome X, locus Xp22, wherein the syndrome detected is Pelizaeus-Merzbacher Disease; chromosome X, locus Xp22.3, wherein the syndrome detected comprises steroid sulfatase deficiency; chromosome Y, locus SRY locus/Yp, wherein the syndrome detected comprises abnormalities of the SRY locus; chromosome X, locus Xp22.3, and the syndrome detected is Kallman Disease; chromosome X, locus Xp21, and the syndrome detected is Sex Reversal (DSS); and, chromosome 17, locus 17p11.2, and the syndrome detected is 17p11.2 Duplication Syndrome.

[0018] The invention provides an articles of manufacture (e.g., arrays) for the detection of a chromosomal abnormality or the diagnosis of a syndrome associated with a contiguous gene abnormality comprising a plurality of nucleic acids segments, wherein each nucleic acid segment is immobilized to a discrete and known spot on a substrate surface to form an array of nucleic acids, and the nucleic acid segments are selected from the group consisting of chromosome 1, locus 1p36; chromosome 3, locus 3p25-pter; chromosome 3, locus 3p21-pter; chromosome 4, locus 4p16.3; chromosome 4, locus 4p15.2-16.1; chromosome 5, locus 5p15.2-pter; chromosome 7, locus 7p13.3; chromosome 7, locus 7q11.23; chromosome 8, locus 8q24.1; chromosome 8, locus 8q24.1; chromosome 9, locus 9p; chromosome 10, locus 10p13-p14; chromosome 11, locus 11p13; chromosome 11, locus 11p15.5; chromosome 11, locus 11p11.2; chromosome 15, locus 15q12; chromosome 16, locus distal 16p13.3; chromosome 17, locus 17p12; chromosome 17, locus 17p13.3; chromosome 17, locus 17p11.2; chromosome 20, locus 20p11.2-p12; chromosome 22, locus 22q11.2; chromosome X, locus Xp21; chromosome X, locus Xp22; chromosome X, locus Xp22.3; and, chromosome Y, locus SRY locus/Yp. In alternative aspects, an array of the invention comprises at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39 and 40 members of this group of nucleic acid segments.

[0019] In alternative aspects, the articles of manufacture (arrays) of the invention further comprising at least one spot comprising a nucleic acid segment acting as a positive control, at least one spot comprising a nucleic acid segment acting as a negative control, or, the array includes positive control and negative control spots.

[0020] The invention provides a method of detecting a chromosomal abnormality or for diagnosis of a syndrome associated with a contiguous gene abnormality in an individual comprising the following steps: (a) providing an article of manufacture (array) of the invention; (b) providing a sample comprising a substantially full complement of genomic DNA from the individual; (c) contacting the genomic DNA of step (b) or a nucleic acid comprising a sequence equivalent to the genomic DNA of step (b) with the article of manufacture under conditions wherein the nucleic acid in the sample can specifically hybridize to the genomic nucleic acid segments immobilized on the article of manufacture; (g) measuring the location and amount of genomic DNA specifically hybridized to the genomic nucleic acid segments immobilized on the article of manufacture, thereby detecting a chromosomal abnormality or making a diagnosis of a syndrome associated with a contiguous gene abnormality in an individual. In one aspect, detecting the chromosomal abnormality in the individual can detect a disease or a condition or a syndrome in the individual. In alternative aspects, individual can be a human, an embryo, a fetus.

[0021] In one aspect, the individual is suspected of having a chromosomal abnormality. The individual can be suspected of having a disease or condition associated with a karyotype abnormality. The disease can comprise a cancer. The sample can comprise a body fluid sample, a cell sample or a tissue sample. The sample can comprise a cancer cell or a tumor cell sample. The sample can be a biopsy sample, a blood sample, a urine sample, a cerebral spinal fluid (CSF) sample, an amniotic fluid sample, a chorionic villus sample, or an embryonic cell or embryo tissue sample.

[0022] The method can further comprise associating the sample nucleic acid or the nucleic acid immobilized to the article of manufacture with a detectable label. The detectable label can be covalently associated with the nucleic acid. The detectable label can comprise a fluorescent label, e.g., a Cy5™ or equivalent, a Cy3™ or equivalent, a rhodamine, a fluorescein or an aryl-substituted 4,4-difluoro-4-bora-3a, 4a-diaza-s-indacene dye or equivalents.

[0023] In alternative aspects of the method, the labeling of the nucleic acid segments comprises random prime labeling and nick translation labeling.

[0024] In alternative aspects of the method, about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, 99%, or all of the array-immobilized genomic nucleic acid comprises a detectable label.

[0025] The methods can comprise use of a device that can detect a detectable label. The device can measure which spots on the substrate surface are associated with a detect-

able label. The device can measure how much detectable label is on which spot on the substrate surface. The device can comprise a charge-coupled device (CCD). The device can be capable of multicolor fluorescence imaging.

[0026] The methods of the invention, or, the articles of manufacture (arrays) of the invention, can further comprise a computer processor to analyze multicolor fluorescence imaging data. The method, or, the arrays of the invention, also can further comprise use of a computer and a computer program algorithm to interpret data imaged from the array and display results.

[0027] The methods of the invention can further comprising a washing step, wherein nucleic acid in the sample not specifically hybridized to the genomic nucleic acid segments immobilized on the array are removed. In alternative aspects, the washing step comprises use of a solution comprising a salt concentration of about 0.02 molar at pH 7 at a temperature of at least about 50° C.; the washing step comprises use of a solution comprising a salt concentration of about 0.15 M at a temperature of at least about 72° C. for about 15 minutes; and, the washing step comprises use of a solution comprising a salt concentration of about 0.2×SSC at a temperature of at least about 50° C. for at least about 15 minutes. Further exemplary methods are set forth below.

[0028] The method of the invention can further comprise steps for a comparative genomic hybridization (CGH), the method further comprising: associating the nucleic acid in the first sample of step (b) with a detectable label; providing a second sample comprising nucleic acid complementary to a substantially complete genome, wherein the nucleic acid comprises a detectable label distinguishable from the detectable label associated with the first sample genomic nucleic acid, and the karyotype of the genome of the second sample is known; contacting the array with the nucleic acid of the first sample and the nucleic acid of the second sample under conditions wherein the nucleic acid of the samples can specifically hybridize to the array-immobilized nucleic acid; measuring the location and amount of nucleic acid from the first and second sample specifically hybridized to the genomic nucleic acid segments immobilized on the array, thereby performing a comparative genomic hybridization. The nucleic acid from the first and the second sample can be from the same individual (e.g., wherein the samples are taken at different times, or from different tissues or fluids), from related individuals, from the same species, related species or different or unrelated species. The nucleic acid from the first and the second sample can be from a human sample. The substantially complete genome of the second sample can comprise a wild type genome, e.g., a genome substantially or completely lacking a known contiguous gene abnormality.

[0029] The invention provides a kit comprising the following components: (a) an article of manufacture (e.g., an array) for the detection of a chromosomal abnormality or a diagnosis of a syndrome associated with a contiguous gene abnormality, comprising a plurality of nucleic acids segments, wherein each nucleic acid is immobilized to a discrete and known spot on a substrate surface to form an array of nucleic acids, and each spot comprises a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome; and, (b) instructions for using the array to detect a chromosomal abnormality.

[0030] In alternative aspects, the kit further comprises materials to prepare a sample comprising a genomic nucleic acid for application to the array; materials to label the sample genomic nucleic acid; a sample of wild type genomic nucleic acid, or any genomic nucleic acid of known karyotype, or any combination or all of these.

[0031] In one aspect of the kit, the wild type genomic nucleic acid is labeled. The wild type genomic nucleic acid can comprise a label different (e.g., distinguishable) from that used to label the sample genomic nucleic acid. The wild type genomic nucleic acid can comprise a human wild type genomic nucleic acid.

[0032] The invention provides compilations (i.e., a libraries, sets (such as a clone set) or collections) of nucleic acids for the detection of a chromosomal abnormality or for the diagnosis or prognosis of a syndrome associated with a contiguous gene abnormality, comprising a plurality of nucleic acids segments, wherein each nucleic acid segment comprises a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome. The segment of genomic nucleic acid can be derived from a cloned copy of a genome, an amplified copy of a genome, an isolated copy of a genome, a completely artificial copy of a sequence of a genome and the like.

[0033] In alternative aspects of the compilations (sets, libraries, collections) of nucleic acids of the invention, a segment of genomic nucleic acid comprises chromosome 1, locus 1p;36, and the syndrome detected can be 1p Deletion Syndrome, chromosome 1, locus 1p;36, and the syndrome detected can be 1p Deletion Syndrome; chromosome 1, locus 7p11.2, and the syndrome detected can be Smith-Magenis syndrome (SMS); chromosome 3, locus 3p25-pter, and the syndrome detected can be 3p Deletion Syndrome; chromosome 3, locus 3p21-pter, and the syndrome detected can be 3p Duplication Syndrome; chromosome 4, locus 4p16.3, and the syndrome detected can be Wolf-Hirschhorn Syndrome; chromosome 4, locus 4p15.2-16.1, and the syndrome detected can be 4p Duplication Syndrome; chromosome 5, locus 5p15.2-pter, and the syndrome detected can be Cri du Chat Syndrome; chromosome 7, locus 7p13.3, and the syndrome detected can be Miller-Dieker Syndrome; chromosome 7, locus 7q11.23, and the syndrome detected can be Williams Syndrome; chromosome 8, locus 8q24.1, and the syndrome detected can be Langer-Giedion Syndrome (LGS); chromosome 8, locus 8q24.1, and the syndrome detected can be Trichorhinophalangeal Syndrome (TRPS); chromosome 8, locus 8q13.3, and the syndrome detected can be branchio-oto-renal (BOR) syndrome; chromosome 9, locus 9p, e.g., locus 9p22-pter, and the syndrome detected can be 9p Deletion Syndrome; chromosome 10, locus 10p13-p14, and the syndrome detected can be DiGeorge Syndrome II; chromosome 11, locus 1p13, and the syndrome detected can be WAGR Syndrome; chromosome 11, locus 11p15.5, and the syndrome detected is Beckwith-Wiedemann Syndrome; chromosome 11, locus 11p11.2, and the syndrome detected can be Potocki-Shaffer Syndrome (Multiple Exostoses II Locus); chromosome 13, locus 13q22, and the syndrome detected can be Hirschsprung disease and Waardenburg syndrome; chromosome 15, locus 15q12, and the syndrome detected can be Angelman Syndrome; chromosome 15, locus 15q12, and the syndrome detected can be Prader-Willi Syndrome; chromosome 16,

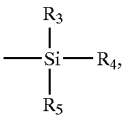
locus distal 16p13.3, and the syndrome detected can be Rubinstein-Taybi Syndrome; chromosome 16, pericentromeric region, and the syndrome detected can be idiopathic epilepsy and paroxysmal dyskinesia; chromosome 17, locus 17p12, and the syndrome detected can be Charcot-Marie-Tooth Disease Type 1A(CMT-1A); chromosome 17, locus 17p12, and the syndrome detected can be Hereditary Neuropathy with Liability to Pressure Palsies; chromosome 17, locus 17p13.3, and the syndrome detected can be Miller-Dieker Syndrome/Isolated Lissencephaly; chromosome 17, locus 17p11.2, and the syndrome detected can be Smith-Magenis Syndrome; chromosome 20, locus 20p11.2-p12, and the syndrome detected can be Alagille Syndrome; chromosome 22, locus 22q11.2, and the syndrome detected can be Digeorge/Velocardiofacial Syndrome; chromosome X, locus Xp21, and the syndrome detected can be Adrenal Hypoplasia Congenita (AHC); chromosome X, locus Xp21, and the syndrome detected can be Duchenne/Becker Muscular Dystrophy; chromosome X, locus Xp21, and the syndrome detected can be Glycerol Kinase Deficiency; chromosome X, locus Xp22, and the syndrome detected can be Pelizaeus-Merzbacher Disease; chromosome X, locus Xp22.3, and the syndrome detected can comprise steroid sulfatase deficiency; chromosome X, locus Xp22.3, and the syndrome detected can be Leri-Weill syndrome; chromosome Y, locus SRY locus/Yp, and the syndrome detected can comprise abnormalities of the SRY locus; chromosome X, locus Xp22.3, and the syndrome detected can be Kallman Disease; chromosome X, locus Xp21, and the syndrome detected can be Sex Reversal (DSS); chromosome 17, locus 17p11.2, and the syndrome detected is 17p11.2 Duplication Syndrome; and, chromosome 17, locus 17p11.2, and the syndrome detected can be Smith-Magenis syndrome (SMS) or any combination or all of these syndromes or conditions. The compilations (libraries, sets, collections) of nucleic acids of the invention can comprise members comprising all or any subset of nucleic acids from these chromosomal segments. In one aspect, each chromosomal segment is on a different member (nucleic acid segment) of the compilation of the invention. In another aspect, at least one member (nucleic acid segment) of the compilation has two or more of the above-listed chromosomal segments.

[0034] In alternative aspects, about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or more of the nucleic acid segments associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome. In one aspect, the nucleic acid segments are derived from genomic nucleic acid. In one aspect, 100% of the nucleic acid segments are associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome or comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

[0035] In one aspect, the nucleic acids segments are immobilized onto a substrate surface (a substrate means). Any substrate surface can be used, e.g., a solid surface such as nitrocellulose, glass, quartz, fused silica, plastics and the like, or a semi-solid surface. The substrate surfaces can be flat or planar, be shaped as wells, capillary tubes, raised regions, etched trenches, pores, beads, filaments, or the like. The nucleic acid segments can be immobilized on a surface as an array.

[0036] In alternative aspects, about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or more or all of the nucleic acid segments comprise a detectable label.

[0037] In one aspect, the nucleic acid segments further comprise a compound having the general formula: R_1—X—R_2, wherein R_1 is a cyclic ether, an aldehyde, or a chloromethylphenyl moiety; X is a moiety chemically suitable for linking the R_1 moiety to the R_2 moiety, and the R_2 moiety has the general formula



[0038] wherein R_3, R_4 and R_5 comprise identical or different alkoxy group or chloro groups.

[0039] In one aspect, the nucleic acid segments further comprise a compound having the general formula: R_1—X—R_2, wherein R_1 is an amino group, R_2 is an alkoxysilane group or a chlorohalide group; and X is a moiety chemically suitable for linking the R_1 group and the R_2 group.

[0040] In one aspect, the nucleic acid segments further comprise a compound having the general formula

$$R_1\text{—X—Si}(OR_2)_m(Cl)_n(R)_k,$$

[0041] wherein m+k is the integer 3, and n can be 0 if m is greater than 0, or n+k is the integer 3 and m can be 0 if n is greater than 0; X is an inert linker; R1 comprises a group reactive toward the biological molecule; R is an alkyl group; and, R_2 is an alkyl group.

[0042] In one aspect, at least one nucleic acid segment is cloned in a cloning vehicle, e.g., a construct comprising an artificial chromosome. The artificial chromosome comprises a bacterial artificial chromosome (BAC), a human artificial chromosome (HAC) a yeast artificial chromosome (YAC), a transformation-competent artificial chromosome (TAC) and a bacteriophage P1-derived artificial chromosome (PAC) and the like. In one aspect, at least one nucleic acid segment is cloned in a construct comprising a vector selected from the group consisting of a cosmid vector, a plasmid vector and a viral vector.

[0043] In alternative aspects, the nucleic acid segments are between about 15 kilobases (0.15 megabase) to about 1000 kilobases (10 megabases) in length, 25 kilobases (0.25 megabase) to about 750 kilobases (7.5 megabases) in length, 50 kilobases (0.5 megabase) to about 500 kilobases (5 megabases) in length, between about 100 kilobases (1 megabase) to about 400 kilobases (4 megabases) in length, between about 150 kilobases (1.5 megabase) or about 300 kilobases (3 megabases) in length.

[0044] In one aspect, the compilation (or libraries, or sets, or collections) of nucleic acids can be used for the detection of a chromosomal abnormality or the diagnosis or prognosis of a syndrome associated with a contiguous gene abnormality. The compilation (or libraries, or sets, or collections can comprise a plurality of nucleic acid segments associated

with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome. In one aspect, the plurality of nucleic acids segments comprise chromosome 1, locus 1p36, wherein the syndrome detected can be 1p Deletion Syndrome; chromosome 3, locus 3p25-pter, wherein the syndrome detected can be 3p Deletion Syndrome; chromosome 3, locus 3p21-pter, wherein the syndrome detected can be 3p Duplication Syndrome; chromosome 4, locus 4p16.3, wherein the syndrome detected can be Wolf-Hirschhorn Syndrome; chromosome 4, locus 4p15.2-16.1, wherein the syndrome detected can be 4p Duplication Syndrome; chromosome 5, locus 5p15.2-pter, wherein the syndrome detected can be Cri du Chat Syndrome; chromosome 7, locus 7p13.3, wherein the syndrome detected can be Miller-Dieker Syndrome; chromosome 7, locus 7q11.23, wherein the syndrome detected can be William's Syndrome; chromosome 8, locus 8q24.1, wherein the syndrome detected can be Langer-Giedion Syndrome (LGS); chromosome 8, locus 8q24.1, wherein the syndrome detected can be Trichorhinophalangeal Syndrome (TRPS); chromosome 9, locus 9p, wherein the syndrome detected can be 9p Deletion Syndrome; chromosome 10, locus 10p13-p14, wherein the syndrome detected can be DiGeorge Syndrome II; chromosome 11, locus 11p13, wherein the syndrome detected can be WAGR Syndrome; chromosome 11, locus 11p15.5, wherein the syndrome detected can be Beckwith-Wiedemann Syndrome; chromosome 11, locus 11p11.2, wherein the syndrome detected can be Potocki-Shaffer Syndrome (Multiple Exostoses II Locus); chromosome 15, locus 15q12, wherein the syndrome detected can be Angelman Syndrome; chromosome 15, locus 15q12, wherein the syndrome detected can be Prader-Willi Syndrome; chromosome 16, locus distal 16p13.3, wherein the syndrome detected can be Rubinstein-Taybi Syndrome; chromosome 17, locus 17p12, wherein the syndrome detected can be Charcot-Marie-Tooth Disease Type 1A(CMT-1A); chromosome 17, locus 17p12, wherein the syndrome detected can be Hereditary Neuropathy with Liability to Pressure Palsies; chromosome 17, locus 17p13.3, wherein the syndrome detected can be Miller-Dieker Syndrome/Isolated Lissencephaly; chromosome 17, locus 17p11.2, wherein the syndrome detected can be Smith-Magenis Syndrome; chromosome 20, locus 20p11.2-p12, wherein the syndrome detected can be Alagille Syndrome; chromosome 22, locus 22q11.2, wherein the syndrome detected can be Digeorge/Velocardiofacial Syndrome; chromosome X, locus Xp21, wherein the syndrome detected can be Adrenal Hypoplasia Congenita (AHC); chromosome X, locus Xp21, wherein the syndrome detected can be Duchenne/Becker Muscular Dystrophy; chromosome X, locus Xp21, wherein the syndrome detected can be Glycerol Kinase Deficiency; chromosome X, locus Xp22, wherein the syndrome detected can be Pelizaeus-Merzbacher Disease; chromosome X, locus Xp22.3, wherein the syndrome detected comprises steroid sulfatase deficiency; chromosome Y, locus SRY locus/Yp, wherein the syndrome detected comprises abnormalities of the SRY locus; chromosome X, locus Xp22.3, and the syndrome detected can be Kallman Disease; chromosome X, locus Xp21, and the syndrome detected can be Sex Reversal (DSS); and, chromosome 17, locus 17p11.2, and the syndrome detected can be 17p11.2 Duplication Syndrome.

[**0045**] A compilation of nucleic acids, wherein each nucleic acid segment is associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome, and the nucleic acid segments are selected from the group consisting of chromosome 1, locus 1p36; chromosome 3, locus 3p25-pter; chromosome 3, locus 3p21-pter; chromosome 4, locus 4p16.3; chromosome 4, locus 4p15.2-16.1; chromosome 5, locus 5p15.2-pter; chromosome 7, locus 7p13.3; chromosome 7, locus 7q11.23; chromosome 8, locus 8q24.1; chromosome 8, locus 8q24.1; chromosome 9, locus 9p; chromosome 10, locus 10p13-p14; chromosome 11, locus 11p13; chromosome 11, locus 11p15.5; chromosome 11, locus 11p11.2; chromosome 15, locus 15q12; chromosome 16, locus distal 16p13.3; chromosome 17, locus 17p12; chromosome 17, locus 17p13.3; chromosome 17, locus 17p11.2; chromosome 20, locus 20p11.2-p12; chromosome 22, locus 22q11.2; chromosome X, locus Xp21; chromosome X, locus Xp22; chromosome X, locus Xp22.3; and, chromosome Y, locus SRY locus/Yp.

[**0046**] In one aspect, the nucleic acids segments are immobilized onto a substrate surface (a substrate means). Any substrate surface can be used, e.g., a solid surface such as nitrocellulose, glass, quartz, fused silica, plastics and the like, or a semi-solid surface. The substrate surfaces can be flat or planar, be shaped as wells, capillary tubes, raised regions, etched trenches, pores, beads, filaments, or the like. The nucleic acid segments can be immobilized on a surface as an array.

[**0047**] The invention provides methods of detecting a chromosomal abnormality or for the diagnosis or prognosis of a syndrome associated with a contiguous gene abnormality in an individual comprising the following steps: (a) providing a compilation of nucleic acids of the invention; (b) providing a sample comprising a substantially full complement of genomic DNA from the individual; (c) contacting the genomic DNA of step (b) or a nucleic acid comprising a sequence equivalent to the genomic DNA of step (b) with the compilation of nucleic acids of step (a) under conditions wherein the nucleic acid in the sample can specifically hybridize to the compilation of nucleic acids; (g) measuring the location and amount of genomic DNA specifically hybridized to the compilation of nucleic acids of step (a), thereby detecting a chromosomal abnormality or making a diagnosis of a syndrome associated with a contiguous gene abnormality in an individual. In one aspect, detecting the chromosomal abnormality in the individual detects a disease or a condition or a syndrome in the individual. The individual can be a human. The individual can be an embryo.

[**0048**] In one aspect, the individual is suspected of having a chromosomal abnormality. In one aspect, the individual is suspected of having a disease or condition associated with a karyotype abnormality. The disease can comprise a cancer.

[**0049**] In one aspect, the sample comprises a body fluid sample, a cell sample or a tissue sample. The sample can comprise a cancer cell or a tumor cell sample. In one aspect, the sample is a biopsy sample, a blood sample, a urine sample, a cerebral spinal fluid (CSF) sample, an amniotic fluid sample a chorionic villus sample or an embryonic cell or embryo tissue sample.

[**0050**] The method can further comprise associating the sample nucleic acid or the compilation of nucleic acids with a detectable label. The detectable label can be covalently or non-covalently associated with the nucleic acid. The detectable label can comprise a fluorescent label, such as Cy5™ or

equivalent or Cy3™ or equivalent. The fluorescent label can comprise a rhodamine, a fluorescein or an aryl-substituted 4,4-difluoro-4-bora-3a, 4a-diaza-s-indacene dye or equivalents.

[0051] In one aspect, the labeling of the nucleic acid segments involves random prime labeling or nick translation labeling. In alternative aspects, about 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99% or more or all of the nucleic acid segments comprise a detectable label.

[0052] The methods can further comprise use of a device that can detect a detectable label. The device can comprise a charge-coupled device (CCD). The device can be capable of multicolor fluorescence imaging.

[0053] The methods can further comprise use of a computer processor to analyze multicolor fluorescence imaging data. The methods can further comprise use of a computer and a computer program algorithm to interpret imaged data and display results.

[0054] The methods can further comprise a washing step, wherein nucleic acid in the sample not specifically hybridized to the compilation of nucleic acids are removed. The washing step can comprise use of a solution comprising a salt concentration of about 0.02 molar at pH 7 at a temperature of at least about 50° C. The washing step can comprise use of a solution comprising a salt concentration of about 0.15 M at a temperature of at least about 72° C. for about 15 minutes. The washing step can comprise use of a solution comprising a salt concentration of about 0.2×SSC at a temperature of at least about 50° C. for at least about 15 minutes.

[0055] The methods can further comprise associating the nucleic acid in the first sample with a detectable label. The methods can further comprise providing a second sample comprising nucleic acid complementary to a substantially complete genome, wherein the nucleic acid comprises a detectable label distinguishable from the detectable label associated with the first sample genomic nucleic acid, and the karyotype of the genome of the second sample is known. The methods can further comprise contacting the compilation of nucleic acids with the nucleic acid of the first sample and the nucleic acid of the second sample under conditions wherein the nucleic acid of the samples can specifically hybridize to the compilation of nucleic acids. The methods can further comprise measuring the location and amount of nucleic acid from the first and second sample specifically hybridized to the compilation of nucleic acids.

[0056] In one aspect, the nucleic acid from the first and the second sample are from the same species. The nucleic acid from the first and the second sample can be from a human sample. In one aspect, the substantially complete genome of the second sample comprises a wild type genome.

[0057] The invention provides kits comprising the following components: (a) a compilation of nucleic acids of the invention, e.g., a compilation of nucleic acids comprising a plurality of nucleic acids segments, wherein each nucleic acid is associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome. In one aspect, the kit comprises instructions for using the compilation of nucleic acids of step (a) to detect a chromosomal abnormality. In the kit, the compilation of nucleic acids can be in one or a plurality of containers, e.g., vials, test tubes and the like. The kits can further comprise materials to prepare a sample comprising a genomic nucleic acid for application to the compilation of nucleic acids, materials to label the sample genomic nucleic acid and/or a sample of wild type genomic nucleic acid. The wild type genomic nucleic acid can be labeled. The wild type genomic nucleic acid can comprise a label different from that used to label the sample genomic nucleic acid. The wild type genomic nucleic acid can comprise a human wild type genomic nucleic acid.

[0058] The invention provides a method for selecting a genomic nucleic acid segment for use as a hybridization target in a hybridization reaction, e.g., a comparative genomic hybridization (CGH) reaction, for the detection of a chromosomal aneuploidy comprising (a) selecting a chromosomal segment that hybridizes to a single locus under stringent conditions, wherein the locus comprises a segment of the chromosome comprising the aneuploidy to be detected; (b) selecting a chromosomal segment having at least about 15% to 25% unique sequence not present in the other regions of the genome such that at least 75% to 85% of the sequence within the chromosomal segment is repetitive, except for chromosomal segments from the X chromosome or Y chromosome, which can have up to 90% to 95% repetitive sequences; and (c) selecting a clone selected in both step (a) and step (b), thereby selecting a genomic nucleic acid segment for use as a hybridization target in a comparative genomic hybridization (CGH) reaction for the detection of a chromosomal aneuploidy. In alternative aspects, the method comprises selecting a chromosomal segment having at least about 10%, 15%, 20%, 25% and 30% unique sequence not present in the other regions of the genome.

[0059] The invention provides an article of manufacture, e.g., an array, comprising a plurality of nucleic acid segments, wherein each nucleic acid segment comprises the following characteristics: (a) each nucleic acid segment comprises a genomic nucleic acid sequence that hybridizes to a single locus of the genome under stringent conditions; and (b) each nucleic acid segment has at least about 15% to 25% unique sequence not present in the other regions of the genome such that at least 75% to 85% of the sequence within the chromosomal segment is repetitive, except for chromosomal segments from the X chromosome or Y chromosome, which can have up to 90% to 95% repetitive sequences. In alternative aspects, the chromosomal segments have at least about 10%, 15%, 20%, 25% and 30% unique sequence not present in the other regions of the genome.

[0060] The invention provides a library, collection, set or compilation of nucleic acid segments, wherein each member of the library, collection, set or compilation comprises the following characteristics: (a) each member of the library comprises a genomic nucleic acid sequence that hybridizes to a single locus of the genome under stringent conditions; and (b) each member of the library has at least about 15% to 25% unique sequence not present in the other regions of the genome such that at least 75% to 85% of the sequence within the chromosomal segment is repetitive in nature, except for chromosomal segments from the X chromosome or Y chromosome, which can have up to 90% to 95% repetitive sequences. In alternative aspects, the nucleic acid segments have at least about 10%, 15%, 20%, 25% and 30%

unique sequence not present in the other regions of the genome. The library, collection, set or compilation of nucleic acid segments can be used as hybridization target in comparative genomic hybridization (CGH) reactions for the detection of chromosomal aneuploidies.

[0061] The invention provides methods for selecting a genomic nucleic acid segment (e.g., a genomic fragment) for use as a hybridization target in a hybridization reaction, e.g., a comparative genomic hybridization (CGH) reaction, for the detection of a chromosomal abnormality, such as an aneuploidy, an amplification, a deletion and the like, comprising (a) selecting a chromosomal segment that hybridizes to a single locus under stringent conditions (see below, including Examples, for exemplary hybridization conditions), wherein the locus comprises a segment of the chromosome comprising the aneuploidy to be detected; (b) selecting a chromosomal segment having at least about 15% to 25% unique sequence not present in the other regions of the genome such that up to 75% to 85% of the sequence within the chromosomal segment is repetitive, except for chromosomal segments from the X chromosome or Y chromosome, which can have up to 90% to 95% repetitive sequences; and (c) selecting a clone selected in both step (a) and step (b), thereby selecting a genomic nucleic acid segment for use as a hybridization target in a comparative genomic hybridization (CGH) reaction for the detection of a chromosomal aneuploidy. In alternative aspects, the method comprises selecting a chromosomal segment having at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 35%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more unique sequence not present in the other regions of the genome. In alternative aspects, the X chromosome or Y chromosome can have up to 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more repetitive sequences.

[0062] The invention provides an article of manufacture, e.g., an array, comprising a plurality of nucleic acid segments, wherein each nucleic acid segment comprises the following characteristics: (a) each nucleic acid segment comprises a genomic nucleic acid sequence that hybridizes to a single locus of the genome under stringent conditions; and (b) each nucleic acid segment has at least about 15% to 25% unique sequence not present in the other regions of the genome such that at least 75% to 85% of the sequence within the chromosomal segment is repetitive, except for chromosomal segments from the X chromosome or Y chromosome, which can have up to 90% to 95% repetitive sequences. In alternative aspects, the chromosomal segments can have at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 35%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more unique sequence not present in the other regions of the genome. In alternative aspects, the X chromosome or Y chromosome can have up to 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more repetitive sequences.

[0063] The invention provides a library, collection, set (e.g., clone set) or compilation of nucleic acid segments, wherein each member of the library, collection, set or compilation comprises the following characteristics: (a) each member of the library comprises a genomic nucleic acid sequence that hybridizes to a single locus of the genome under stringent conditions; and (b) each member of the library has at least about 15% to 25% unique sequence not present in the other regions of the genome such that up to 75% to 85% of the sequence within the chromosomal segment is repetitive in nature, except for chromosomal segments from the X chromosome or Y chromosome, which can have up to 90% to 95% repetitive sequences. In alternative aspects, the nucleic acid segments have at least about 10%, 15%, 20%, 25% and 30% unique sequence not present in the other regions of the genome. The library, collection, set or compilation of nucleic acid segments can be used for multiple purposes, one of which is hybridization target in comparative genomic hybridization (CGH) reactions for the detection of chromosomal aneuploidies. In alternative aspects, the chromosomal segments can have at least about 10%, 15%, 20%, 25%, 30%, 35%, 40%, 35%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more unique sequence not present in the other regions of the genome. In alternative aspects, the X chromosome or Y chromosome can have up to 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more repetitive sequences.

[0064] In one aspect, the stringent hybridization conditions comprise post-hybridization washing conditions comprising: pre-warming the following hybridization solutions at 50° C. in individual Petri dishes: 2×SSC, 50% deionized formamide, 2×SSC, 0.1% NP-40, 0.2×SSC; soaking the array (e.g., a slide) in 2×SSC, 0.5% SDS briefly at room temperature (RT), or alternatively, just 2×SSC can be used; transfering the array (slide) to the pre-warmed 2×SSC, 50% formamide; washing the slides by incubating in the shaking incubator at 50° C. for 20 minutes. In one aspect, the post-hybridization washing conditions comprise repeating the wash using a pre-warmed 2×SSC, 0.1% NP-40. In one aspect, the post-hybridization washing conditions comprise repeating the wash using a pre-warmed 0.2×SSC for 10 minutes. In one aspect, the post-hybridization washing conditions comprise rinsing the slides with distilled deionized water. In one aspect, this last wash does not exceed 10 seconds. In one aspect, the arrays (slides) are immediately dried under forced air.

[0065] The details of one or more embodiments of the invention are set forth in the accompanying drawings and the description below. Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

[0066] All publications, patents, patent applications, GenBank sequences and ATCC deposits cited herein are hereby expressly incorporated by reference for all purposes.

DETAILED DESCRIPTION

[0067] The invention provides novel compilations, or sets (e.g., clone sets), libraries or collections, of nucleic acids and articles of manufacture, e.g., arrays. Also provided are methods of making and using them. In one aspect, these compilations, or sets, libraries or collections, of nucleic acids and arrays are used in the detection of a chromosomal abnormality, such as a chromosomal aneuploidy (an abnormality involving a chromosome number that is not an exact multiple of the haploid number). They can also be used in the diagnosis or prognosis of a syndrome associated with a contiguous gene abnormality.

[0068] The invention provides novel compilations, or sets, libraries or collections, of nucleic acids and arrays and methods for the detection of a chromosomal abnormality or a diagnosis or prognosis of a syndrome associated with a contiguous gene abnormality. These compilations, or sets,

libraries or collections, of nucleic acids and/or arrays can be used for routine or directed genetic screening of embryos, fetuses, children or adults. These compilations, or sets, libraries or collections, of nucleic acids and/or arrays can be used to aid in the diagnosis or prognosis of a syndrome, particularly when it is suspected that a patient may have symptoms associated with one or more chromosomal abnormalities, but those symptoms are not definitively diagnostic. Screening of individuals before symptoms appear will allow preventative or prophylactic treatment regimes.

[0069] The invention provides methods for selecting genomic fragments, or clone sets (including, e.g., libraries, collections or compilations of fragments or clones), that are effective as hybridization targets in the detection of chromosomal abnormalities, such as aneuploidies (i.e., abnormalities involving a chromosome number that is not an exact multiple of the haploid number), amplification, deletions and the like. In one aspect, these libraries, collections or compilations of genomic fragments or clones are immobilized on articles of manufacture, e.g., arrays. In one aspect, articles of manufacture, e.g., arrays, comprising these libraries, collections or compilations of genomic fragments or clones (e.g., clone sets) are used to perform comparative genomic hybridization (CGH) to detect chromosomal aneuploidies.

[0070] The selection process comprises selection of any clone containing a specific region of the chromosome that only hybridizes to a single locus (e.g., in silico and/or in situ). This insures specificity. The selection process can also comprise selection of chromosome fragments (e.g., clones) containing a fragment of the genome containing at least 15% unique sequences, i.e., sequences that are not present in the other regions of the genome. In other words, in one aspect, it allows up to 85% of the sequence within the fragment to be repetitive in nature, except for X chromosome and Y chromosome fragments (e.g., clones) (alternative aspects allow up to between about 30% to 95% or 99% of the sequence within the fragment to be repetitive). The X chromosome and Y chromosome segments can be up to 90% to 95% repetitive (alternative aspects allow up to between about 50% to 95% or 99% of the sequence within the X chromosome and Y chromosome fragments to be repetitive). In one aspect, selection process comprises both of these steps, i.e., selection of chromosome fragments (e.g., clones) containing a specific region of a chromosome that only hybridize to a single locus and chromosome fragments (e.g., clones) containing a fragment of the genome containing at least 15% unique sequences.

[0071] In aspect, the article of manufacture, e.g., array, comprises up to about 2500 (in one aspect, 2474) chromosome fragments (e.g., clones) selected by this method, for example, as described below. The genomic clones can be BAC, PAC, MAC, plasmids, recombinant viruses or phagemids and/or cosmids and the like. In one aspect, the selected chromosome fragments (e.g., clones) are cross-linked (immobilized) to a solid surface, e.g., an article of manufacture such as an array. In one aspect, the selected chromosome fragments (e.g., clones) are immobilized as described in U.S. Pat. No. 6,048,695. The article of manufacture can be an array comprising the selected chromosome fragments (e.g., clones) immobilized on a glass slide. In one aspect, the slide is hybridized with fluorescently labeled test and control target DNA. In aspect, the libraries, collections or compilations of fragments or clones of the invention comprise up to about 2500 (in one aspect, 2474) chromosome fragments (e.g., clones) selected by this method, for example, as described below.

[0072] In one aspect, the articles of manufacture, e.g., arrays, comprise a plurality of nucleic acids segments immobilized on a surface, for example, as an array, or "biochip," as they are sometimes called. As is typical of an array or array-like format, each segment can be immobilized onto a discrete and known area, or "spot," on the array. Each "spot" comprises a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome. In one aspect, while there may be many nucleic acids molecules immobilized on a particular spot, there is only one specie or representation of a genomic nucleic acid segment associated with a chromosomal abnormality per spot. All of the spots of the array of the invention can include genomic nucleic acid segment associated with a chromosomal abnormalities. In alternative embodiments, as noted above, varying subpopulations of array spots can comprise such genomic nucleic acid segments. Some spots can include nucleic acid segments that serve as positive and negative controls; in one aspect, the test samples are "spiked" with known types and amounts of nucleic acids to serve as positive and negative controls.

[0073] Also provided are kits comprising the compilations, or sets, libraries or collections, of nucleic acids and/or arrays of the invention. The kits can include instructions for use of the compilations, or sets, libraries or collections, of nucleic acids and/or arrays and practicing the methods of the invention, and, for the convenience of the practitioner, materials for extracting genomic DNA from a sample and preparing that DNA, including labeling of the genomic nucleic acid. In one aspect, the kits can also include labeled "wild type" genomic nucleic acid, e.g., human genomic nucleic acid that is "wild type," or genomic nucleic acid not known to have any or substantially having no chromosomal abnormalities and/or any contiguous gene abnormalities. The "wild type" genomic nucleic acid can comprise a substantially complete genome; which is useful if the practitioner will be performing a comparative genomic hybridization (CGH).

[0074] Definitions

[0075] Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs. As used herein, the following terms have the meanings ascribed to them unless specified otherwise.

[0076] The terms "array" or "microarray" or "DNA array" or "nucleic acid array" or "chip" or "biochip" as used herein is a plurality of target elements, each target element comprising a defined amount of one or more biological molecules, e.g., genomic nucleic acid segments, immobilized on a defined location on a substrate surface; as described in further detail, below.

[0077] The term "aryl-substituted 4,4-difluoro-4-bora-3a, 4a-diaza-s-indacene dye" as used herein includes all "boron dipyrromethene difluoride fluorophore" or "BODIPY" dyes and "dipyrromethene boron difluoride dyes" (see, e.g., U.S. Pat. No. 4,774,339), or equivalents, are a class of fluorescent dyes commonly used to label nucleic acids for their detec-

tion when used in hybridization reactions; see, e.g., Chen (2000) J. Org Chem. 65:2900-2906: Chen (2000) J. Biochem. Biophys. Methods 42:137-151. See also U.S. Pat. Nos. 6,060,324; 5,994,063; 5,614,386; 5,248,782; 5,227,487; 5,187,288.

[0078] The terms "cyanine 5" or "Cy5™" and "cyanine 3" or "Cy3™" refer to fluorescent cyanine dyes produced by Amersham Pharmacia Biotech (Piscataway, N.J.) (Amersham Life Sciences, Arlington Heights, Ill.), as described in detail, below, or equivalents. See U.S. Pat. Nos. 6,027,709; 5,714,386; 5,268,486; 5,151,507; 5,047,519. These dyes are typically incorporated into nucleic acids in the form of 5-amino-propargyl-2'-deoxycytidine 5'-triphosphate coupled to Cy5™ or Cy3™.

[0079] The terms "fluorescent dye" and "fluorescent label" as used herein includes all known fluors, including rhodamine dyes (e.g., tetramethylrhodamine, dibenzorhodamine, see, e.g., U.S. Pat. No. 6,051,719); fluorescein dyes; "BODIPY" dyes and equivalents (e.g., dipyrromethene boron difluoride dyes, see, e.g., U.S. Pat. No. 5,274,113); derivatives of 1-[isoindolyl]methylene-isoindole (see, e.g., U.S. Pat. No. 5,433,896); and all equivalents. See also U.S. Pat. Nos. 6,028,190; 5,188,934.

[0080] The terms "hybridizing specifically to" and "specific hybridization" and "selectively hybridize to," as used herein refer to the binding, duplexing, or hybridizing of a nucleic acid molecule preferentially to a particular nucleotide sequence under stringent conditions. The term "stringent conditions" refers to conditions under which one nucleic acid will hybridize preferentially to second sequence (e.g., a sample genomic nucleic acid hybridizing to an immobilized nucleic acid probe in an array), and to a lesser extent to, or not at all to, other sequences. A "stringent hybridization" and "stringent hybridization wash conditions" in the context of nucleic acid hybridization (e.g., as in array, Southern or Northern hybridizations) are sequence dependent, and are different under different environmental parameters. Stringent hybridization conditions as used herein can include, e.g., hybridization in a buffer comprising 50% formamide, 5×SSC, and 1% SDS at 42° C., or hybridization in a buffer comprising 5×SSC and 1% SDS at 65° C., both with a wash of 0.2×SSC and 0.1% SDS at 65° C. Exemplary stringent hybridization conditions can also include a hybridization in a buffer of 40% formamide, 1 M NaCl, and 1% SDS at 37° C., and a wash in 1×SSC at 45° C. Those of ordinary skill will readily recognize that alternative but comparable hybridization and wash conditions can be utilized to provide conditions of similar stringency.

[0081] However, the selection of a hybridization format is not critical, as is known in the art, it is the stringency of the wash conditions that set forth the conditions which determine whether a soluble, sample nucleic acid will specifically hybridize to an immobilized nucleic acid. Wash conditions can include, e.g.: a salt concentration of about 0.02 molar at pH 7 and a temperature of at least about 50° C. or about 55° C. to about 60° C.; or, a salt concentration of about 0.15 M NaCl and a temperature of at least about 72° C. for at least about 15 minutes; or, a salt concentration of about 0.2×SSC at a temperature of at least about 50° C. or about 55° C. to about 60° C. for at least about 15 to about 20 minutes; or, the hybridization complex is washed twice with a solution with a salt concentration of about 2×SSC containing 0.1% SDS at room temperature for 15 minutes and then washed twice by 0.1×SSC containing 0.1% SDS at 68° C. for 15 minutes; or, equivalent conditions. Stringent conditions for washing can also be, e.g., 0.2×SSC/0.1% SDS at 42° C. See Sambrook, Ausubel, or Tijssen (cited herein) for detailed descriptions of equivalent hybridization and wash conditions and for reagents and buffers, e.g., SSC buffers and equivalent reagents and conditions.

[0082] The phrase "labeled with a detectable composition" or "labeled with a detectable moiety" as used herein refers to a nucleic acid comprising a detectable composition, i.e., a label, as described in detail, below. The label can also be another biological molecule, as a nucleic acid, e.g., a nucleic acid in the form of a stem-loop structure as a "molecular beacon," as described below. This includes incorporation of labeled bases (or, bases which can bind to a detectable label) into the nucleic acid by, e.g., nick translation, random primer extension, amplification with degenerate primers, and the like. The label can be detectable by any means, e.g., visual, spectroscopic, photochemical, biochemical, immunochemical, physical or chemical means. Examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin.

[0083] The term "nucleic acid" as used herein refers to a deoxyribonucleotide or ribonucleotide in either single- or double-stranded form. The term encompasses nucleic acids containing known analogues of natural nucleotides. The term also encompasses nucleic-acid-like structures with synthetic backbones. DNA backbone analogues provided by the invention include phosphodiester, phosphorothioate, phosphorodithioate, methylphosphonate, phosphoramidate, alkyl phosphotriester, sulfamate, 3'-thioacetal, methylene(methylimino), 3'-N-carbamate, morpholino carbamate, and peptide nucleic acids (PNAs); see Oligonucleotides and Analogues, a Practical Approach, edited by F. Eckstein, IRL Press at Oxford University Press (1991); Antisense Strategies, Annals of the New York Academy of Sciences, Volume 600, Eds. Baserga and Denhardt (NYAS 1992); Milligan (1993) J. Med. Chem. 36:1923-1937; Antisense Research and Applications (1993, CRC Press). PNAs contain non-ionic backbones, such as N-(2-aminoethyl) glycine units. Phosphorothioate linkages are described, e.g., by U.S. Pat. Nos. 6,031,092; 6,001,982; 5,684,148; see also, WO 97/03211; WO 96/39154; Mata (1997) Toxicol. Appl. Pharmacol. 144:189-197. Other synthetic backbones encompassed by the term include methyl-phosphonate linkages or alternating methylphosphonate and phosphodiester linkages (see, e.g., U.S. Pat. No. 5,962,674; Strauss-Soukup (1997) Biochemistry 36:8692-8698), and benzylphosphonate linkages (see, e.g., U.S. Pat. No. 5,532,226; Samstag (1996) Antisense Nucleic Acid Drug Dev 6:153-156). The term nucleic acid is used interchangeably with gene, DNA, RNA, cDNA, mRNA, oligonucleotide primer, probe and amplification product.

[0084] The term "genomic DNA" or "genomic nucleic acid" includes nucleic acid isolated from a nucleus of one or more cells, and, includes nucleic acid derived from (e.g., isolated from, amplified from, cloned from, synthetic versions of) genomic DNA. The genomic DNA can be from any

source, as discussed in detail, below. The term "wild type genomic nucleic acid" means a sample of genomic nucleic acid having no known or substantially no known contiguous gene abnormalities.

[0085] The term "a sample comprising a nucleic acid" or "sample of nucleic acid" as used herein refers to a sample comprising a DNA or an RNA, or nucleic acid representative of DNA or RNA isolated from a natural source, in a form suitable for hybridization (e.g., as a soluble aqueous solution) to another nucleic acid or polypeptide or combination thereof (e.g., immobilized probes). The nucleic acid may be isolated, cloned or amplified; it may be, e.g., genomic DNA, episomal DNA, mitochondrial DNA, mRNA, or cDNA; it may be a genomic segment that includes, e.g., particular promoters, enhancers, coding sequences, and the like; it may also include restriction fragments, cDNA libraries or fragments thereof, etc. The nucleic acid sample may be extracted from particular cells, tissues or body fluids, or, can be from cell cultures, including cell lines, or from preserved tissue sample, as described in detail, below.

[0086] As used herein, the terms "computer" and "processor" are used in their broadest general contexts and incorporate all such devices. The methods of the invention can be practiced using any computer/processor and in conjunction with any known software or methodology. For example, a computer/processor can be a conventional general-purpose digital computer, e.g., a personal "workstation" computer, including conventional elements such as microprocessor and data transfer bus. The computer/processor can further include any form of memory elements, such as dynamic random access memory, flash memory or the like, or mass storage such as magnetic disc optional storage.

[0087] Generating and Manipulating Nucleic Acids

[0088] Making and using the compilations, or sets, libraries or collections, of nucleic acids and/or arrays of the invention, and practicing the methods of the invention may involve the isolation, synthesis, cloning, amplification, labeling and hybridization (e.g., CGH) of nucleic acids. As described herein, the compilations, or sets, libraries or collections, of nucleic acids, the nucleic acid for analysis and the immobilized nucleic acid on the array can be representative of genomic DNA, including defined parts of, or entire, chromosomes, or entire genomes. Comparative genomic hybridization (CGH) reactions, see, e.g., U.S. Pat. Nos. 5,830,645; 5,976,790, are discussed in further detail, below. Nucleic acid samples, the compilations, or sets, libraries or collections, of nucleic acids and, in some aspects, immobilized nucleic acids, can be labeled with a detectable moiety, e.g., a fluorescent dye(s) or equivalent. For example, a first sample can be labeled with a fluor and a second sample labeled with a second dye (e.g., Cy3™ and Cy5™). In one aspect, each sample nucleic acid is labeled with at least one different detectable moiety, e.g., different fluorescent dyes, than those used to label the other samples of nucleic acids.

[0089] In some cases, the nucleic acids may be amplified using standard techniques such as PCR. Amplification can also be used to subclone or label the nucleic acid prior to the hybridization. The sample and/or the immobilized nucleic acid can be labeled, as described herein. The sample or the probe on the array an be produced from and collectively can be representative of a source of nucleic acids from one or more particular (pre-selected) portions of, e.g., a collection of polymerase chain reaction (PCR) amplification products, substantially an entire chromosome or a chromosome fragment, or substantially an entire genome, e.g., as a collection of clones, e.g., BACs, PACs, YACs, and the like (see below). The array-immobilized nucleic acid or genomic nucleic acid sample may be processed in some manner, e.g., by blocking or removal of repetitive nucleic acids or by enrichment with selected nucleic acids.

[0090] In one aspect, samples are applied to the immobilized probes (e.g., on the array) and, after hybridization and washing, the location (e.g., spots on the array) and amount of each dye are read. The compilations, or sets, libraries or collections, of nucleic acids or plurality of immobilized nucleic acid segments can be representative of any segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome; including, e.g., part of or all of a chromosome or genome. The compilations, or sets, libraries or collections, of nucleic acids or array-immobilized nucleic acid can be in the form of cloned DNA, e.g., YACs, BACs, PACs, and the like, as described herein. As is typical of array technology, in one aspect, each "spot" on the array has a known sequence, e.g., a known segment of genome or other sequence. The invention can be practiced in conjunction with any method or protocol or device known in the art, which are well described in the scientific and patent literature.

[0091] General Techniques

[0092] The nucleic acids used to practice this invention, whether RNA, cDNA, genomic DNA, vectors, viruses or hybrids thereof, may be isolated from a variety of sources, genetically engineered, amplified, and/or expressed/generated recombinantly. Any recombinant expression system can be used, including, in addition to bacterial cells, e.g., mammalian, yeast, insect or plant cell expression systems.

[0093] Alternatively, these nucleic acids can be synthesized in vitro by well-known chemical synthesis techniques, as described in, e.g., Carruthers (1982) Cold Spring Harbor Symp. Quant. Biol. 47:411-418; Adams (1983) J. Am. Chem. Soc. 105:661; Belousov (1997) Nucleic Acids Res. 25:3440-3444; Frenkel (1995) Free Radic. Biol. Med. 19:373-380; Blommers (1994) Biochemistry 33:7886-7896; Narang (1979) Meth. Enzymol. 68:90; Brown (1979) Meth. Enzymol. 68:109; Beaucage (1981) Tetra. Lett. 22:1859; U.S. Pat. No. 4,458,066. Double stranded DNA fragments may then be obtained either by synthesizing the complementary strand and annealing the strands together under appropriate conditions, or by adding the complementary strand using DNA polymerase with a primer sequence.

[0094] Techniques for the manipulation of nucleic acids, such as, e.g., subcloning, labeling probes (e.g., random-primer labeling using Klenow polymerase, nick translation, amplification), sequencing, hybridization, G-banding, CGH, SKY, FISH and the like are well described in the scientific and patent literature, see, e.g., Sambrook, ed., MOLECULAR CLONING: A LABORATORY MANUAL (2ND ED.), Vols. 1-3, Cold Spring Harbor Laboratory, (1989); CURRENT PROTOCOLS IN MOLECULAR BIOLOGY, Ausubel, ed. John Wiley & Sons, Inc., New York (1997); LABORATORY TECHNIQUES IN BIOCHEMISTRY AND MOLECULAR BIOLOGY: HYBRIDIZATION

WITH NUCLEIC ACID PROBES, Part I. Theory and Nucleic Acid Preparation, Tijssen, ed. Elsevier, N.Y. (1993).

[0095] Cloning of Genomic Nucleic Acids

[0096] The compilations, or sets, libraries or collections, of nucleic acids or genomic nucleic acids used in the arrays and methods of the invention, e.g., those immobilized onto arrays or used as samples, can be obtained and manipulated by cloning into various vehicles. If necessary, genomic nucleic acid samples can be screened and re-cloned or amplified from any source of genomic DNA. Thus, in various aspects, forms of genomic nucleic acid used in the methods of the invention (including arrays and samples) include genomic DNA, e.g., genomic libraries, contained in mammalian and human artificial chromosomes, satellite artificial chromosomes, yeast artificial chromosomes, bacterial artificial chromosomes, PI artificial chromosomes, recombinant vectors and viruses, plasmids, and the like.

[0097] Mammalian artificial chromosomes (MACs) and human artificial chromosomes (HAC) are, e.g., described in Ascenzioni (1997) Cancer Lett. 118:135-142; Kuroiwa (2000) Nat. Biotechnol. 18:1086-1090; U.S. Pat. Nos. 5,288,625; 5,721,118; 6,025,155; 6,077,697). MACs can contain inserts larger than 400 kilobase (Kb), see, e.g., Mejia (2001) Am. J. Hum. Genet. 69:315-326. Auriche (2001) EMBO Rep. 2:102-107, has built a human minichromosomes having a size of 5.5 kilobase.

[0098] Satellite artificial chromosomes, or, satellite DNA-based artificial chromosomes (SATACs), are, e.g., described in Warburton (1997) Nature 386:553-555; Roush (1997) Science 276:38-39; Rosenfeld (1997) Nat. Genet. 15:333-335). SATACs can be made by induced de novo chromosome formation in cells of different mammalian species; see, e.g., Hadlaczky (2001) Curr. Opin. Mol. Ther. 3:125-132; Csonka (2000) J. Cell Sci. 113 (Pt 18):3207-3216.

[0099] Yeast artificial chromosomes (YACs) can also be used and typically contain inserts ranging in size from 80 to 700 kb. YACs have been used for many years for the stable propagation of genomic fragments of up to one million base pairs in size; see, e.g., U.S. Pat. Nos. 5,776,745; 5,981,175; Feingold (1990) Proc. Natl. Acad. Sci. USA 87:8637-8641; Tucker (1997) Gene 199:25-30; Adam (1997) Plant J.11:1349-1358; Zeschnigk (1999) Nucleic Acids Res. 27:21.

[0100] Bacterial artificial chromosomes (BACs) are vectors that can contain 120 Kb or greater inserts, see, e.g., U.S. Pat. Nos. 5,874,259; 6,277,621; 6,183,957. BACs are based on the *E. coli* F factor plasmid system and simple to manipulate and purify in microgram quantities. Because BAC plasmids are kept at one to two copies per cell, the problems of rearrangement observed with YACs, which can also be employed in the present methods, are eliminated; see, e.g., Asakawa (1997) Gene 69-79; Cao (1999) Genome Res. 9:763-774.

[0101] P1 artificial chromosomes (PACs), bacteriophage P1-derived vectors are, e.g., described in Woon (1998) Genomics 50:306-316; Boren (1996) Genome Res. 6:1123-1130; Ioannou (1994) Nature Genet. 6:84-89; Reid (1997) Genomics 43:366-375; Nothwang (1997) Genomics 41:370-378; Kern (1997) Biotechniques 23:120-124). P1 is a bacteriophage that infects *E. coli* that can contain 75 to 100 Kb DNA inserts (see, e.g., Mejia (1997) Genome Res 7:179-186; Ioannou (1994) Nat Genet 6:84-89). PACs are screened in much the same way as lambda libraries. See also Ashworth (1995) Analytical Biochem. 224:564-571; Gingrich (1996) Genomics 32:65-74.

[0102] Other cloning vehicles can also be used, for example, recombinant viruses; cosmids, plasmids or cDNAs; see, e.g., U.S. Pat. No. 5,501,979; 5,288,641; 5,266,489.

[0103] These vectors can include marker genes, such as, e.g., luciferase and green fluorescent protein genes (see, e.g., Baker (1997) Nucleic Acids Res 25:1950-1956). Sequences, inserts, clones, vectors and the like can be isolated from natural sources, obtained from such sources as ATCC or GenBank libraries or commercial sources, or prepared by synthetic or recombinant methods.

[0104] Amplification of Nucleic Acids

[0105] Amplification using oligonucleotide primers can be used to generate or manipulate, e.g., subclone, nucleic acids of the compilations, or sets, libraries or collections, of nucleic acids or the nucleic acids used in the arrays and methods of the invention, to incorporate label into immobilized or sample nucleic acids, to detect or measure levels of nucleic acids hybridized to an array, and the like. Amplification, typically with degenerate primers, is also useful for incorporating detectable probes (e.g., Cy5™- or Cy3™-cytosine conjugates) into nucleic acids representative of test or control genomic DNA to be used to hybridize to immobilized genomic DNA. Amplification can be used to quantify the amount of nucleic acid is in a sample, see, e.g., U.S. Pat. No. 6,294,338. The skilled artisan can select and design suitable oligonucleotide amplification primers. Amplification methods are also well known in the art, and include, e.g., polymerase chain reaction, PCR(PCR PROTOCOLS, A GUIDE TO METHODS AND APPLICATIONS, ed. Innis, Academic Press, N.Y. (1990) and PCR STRATEGIES (1995), ed. Innis, Academic Press, Inc., N.Y., ligase chain reaction (LCR) (see, e.g., Wu (1989) Genomics 4:560; Landegren (1988) Science 241:1077; Barringer (1990) Gene 89:117); transcription amplification (see, e.g., Kwoh (1989) Proc. Natl. Acad. Sci. USA 86:1173); and, self-sustained sequence replication (see, e.g., Guatelli (1990) Proc. Natl. Acad. Sci. USA 87:1874); Q Beta replicase amplification (see, e.g., Smith (1997) J. Clin. Microbiol. 35:1477-1491), automated Q-beta replicase amplification assay (see, e.g., Burg (1996) Mol. Cell. Probes 10:257-271) and other RNA polymerase mediated techniques, e.g., nucleic acid sequence based amplification, or, "NASBA," see, e.g., Birch (2001) Lett. Appl. Microbiol. 33:296-301; Greijer (2001) J. Virol. Methods 96:133-147. See also Berger (1987) Methods Enzymol. 152:307-316; Sambrook; Ausubel; U.S. Pat. Nos. 4,683,195 and 4,683,202.

[0106] Hybridizing Nucleic Acids

[0107] In practicing the methods of the invention, samples of nucleic acid, e.g., isolated, cloned or amplified genomic nucleic acid, are hybridized to the compilations, or sets, libraries or collections, of nucleic acids or the immobilized nucleic acids. In alternative aspects, the hybridization and/or wash conditions are carried out under moderate to stringent conditions. The invention provides methods for selecting a genomic nucleic acid segment for use as a hybridization target in a hybridization reaction, e.g., a comparative

genomic hybridization (CGH) reaction, for the detection of a chromosomal abnormality comprising, inter alia, selecting a chromosomal segment that hybridizes to a single locus under stringent conditions. Exemplary hybridization conditions, including stringent hybridization conditions, are set forth below.

[0108] An extensive guide to the hybridization of nucleic acids is found in, e.g., Sambrook Ausubel, Tijssen. Stringent hybridization and wash conditions can be selected to be about 5° C. lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. Very stringent conditions are selected to be equal to the T_m for a particular probe.

[0109] Exemplary stringent hybridization conditions for hybridization of complementary nucleic acids which have more than 100 complementary residues on an array can comprise 42° C. using standard hybridization solutions (see, e.g., Sambrook), with the hybridization being carried out overnight. Exemplary highly stringent wash conditions can also comprise 0.15 M NaCl at 72° C. for about 15 minutes. Exemplary stringent wash conditions can also comprise a 0.2×SSC wash at 65° C. for 15 minutes (see, e.g., Sambrook). In one aspect, a high stringency wash is preceded by a medium or low stringency wash to remove background probe signal. An exemplary medium stringency wash for a duplex of, e.g., more than 100 nucleotides, comprises 1×SSC at 45° C. for 15 minutes. An exemplary low stringency wash for a duplex of, e.g., more than 100 nucleotides, can comprise 4×to 6×SSC at 40° C. for 15 minutes.

[0110] In alternative aspects, in making the compilations, or sets, libraries or collections, of nucleic acids or arrays, and practicing the methods of the invention, the fluorescent dyes Cy3™ and Cy5™ can be used to differentially label nucleic acid fragments from two samples, e.g., nucleic acid generated from a control (e.g., "wild type"), versus a test cell or tissue sample, or, to label the compilations, or sets, libraries or collections, of nucleic acids or array-immobilized nucleic acid and/or sample nucleic acid. Many commercial instruments are designed to accommodate the detection of these two dyes. To increase the stability of Cy5™, or fluors or other oxidation-sensitive compounds, antioxidants and free radical scavengers can be used in hybridization mixes, the hybridization and/or the wash solutions. Thus, Cy5™ signals are dramatically increased and longer hybridization times are possible.

[0111] In alternative aspects, the methods of the invention are carried out in a controlled, unsaturated humidity environment, and, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention can further comprise apparatus or devices capable of controlling humidity. Controlling humidity is one parameter that can be manipulated to increase hybridization sensitivity. Thus, in one aspect, in practicing the methods of the invention, hybridization can be carried out in a controlled, unsaturated humidity environment; hybridization efficiency is significantly improved if the humidity is not saturated. The hybridization efficiency can be improved if the humidity is dynamically controlled, i.e., if the humidity changes during hybridization. Array devices comprising housings and controls that allow the operator to control the humidity during pre-hybridization, hybridization, wash and/or detection stages can be used. The device can have detection, control and memory components to allow pre-programming of the humidity (and temperature and other parameters) during the entire procedural cycle, including pre-hybridization, hybridization, wash and detection steps.

[0112] In alternative aspects, the methods of the invention can incorporate hybridization conditions comprising temperature fluctuations and, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention can further comprise apparatus or devices capable of controlling temperature, e.g., an oven. Hybridization has much better efficiency in a changing temperature environment as compared to conditions where the temperature is set precisely or at relatively constant level (e.g., plus or minus a couple of degrees, as with most commercial ovens). Reaction chamber temperatures can be fluctuatingly modified by, e.g., an oven, or other device capable of creating changing temperatures.

[0113] In alternative aspects, the methods of the invention can comprise hybridization conditions comprising osmotic fluctuations, and, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention can further comprise apparatus or devices capable of controlling osmotic conditions, e.g., generate a e.g., a solute gradient. Hybridization efficiency (i.e., time to equilibrium) can also be enhanced by a hybridization environment that comprises changing hyper-/hypo-tonicity, e.g., a solute gradient. A solute gradient is created in a device. For example, a low salt hybridization solution is placed on one side of the array hybridization chamber and a higher salt buffer is placed on the other side to generate a solute gradient in the chamber.

[0114] Fragmentation and Digestion of Nucleic Acid

[0115] In practicing the methods of the invention, the compilations, or sets, libraries or collections, of nucleic acids, the immobilized and/or sample nucleic acids can be cloned, labeled or immobilized in a variety of lengths. For example, in one aspect, the genomic nucleic acid segments can have a length smaller than about 200 bases. Use of labeled genomic DNA limited to this small size significantly improves the resolution of the molecular profile analysis, e.g., in array-based CGH. For example, use of such small fragments allows for significant suppression of repetitive sequences and other unwanted, "background" cross-hybridization on the immobilized nucleic acid. Suppression of repetitive sequence hybridization greatly increases the reliability of the detection of copy number differences (e.g., amplifications or deletions) or detection of unique sequences.

[0116] The resultant fragment lengths can be modified by, e.g., treatment with DNase. Adjusting the ratio of DNase to DNA polymerase in a nick translation reaction changes the length of the digestion product. Standard nick translation kits typically generate 300 to 600 base pair fragments. If desired, the labeled nucleic acid can be further fragmented to segments below 200 bases, down to as low as about 25 to 30 bases, random enzymatic digestion of the DNA is carried out, using, e.g., a DNA endonucleases, e.g., DNase (see, e.g., Herrera (1994) J. Mol. Biol. 236:405-411; Suck (1994) J. Mol. Recognit. 7:65-70), or, the two-base restriction endonuclease CviJI (see, e.g., Fitzgerald (1992) Nucleic Acids Res. 20:3753-3762) and standard protocols, see, e.g., Sambrook, Ausubel, with or without other fragmentation procedures.

[0117] Other procedures can also be used to fragment genomic DNA, e.g. mechanical shearing, sonication (see, e.g., Deininger (1983) Anal. Biochem. 129:216-223), and the like (see, e.g., Sambrook, Ausubel, Tijssen). For example, one mechanical technique is based on point-sink hydrodynamics that result when a DNA sample is forced through a small hole by a syringe pump, see, e.g., Thorstenson (1998) Genome Res. 8:848-855. See also, Oefner (1996) Nucleic Acids Res. 24:3879-3886; Ordahl (1976) Nucleic Acids Res. 3:2985-2999. Fragment size can be evaluated by a variety of techniques, including, e.g., sizing electrophoresis, as by Siles (1997) J. Chromatogr. A. 771:319-329, that analyzed DNA fragmentation using a dynamic size-sieving polymer solution in a capillary electrophoresis. Fragment sizes can also be determined by, e.g., matrix-assisted laser desorption/ionization time-of-flight mass spectrometry, see, e.g., Chiu (2000) Nucleic Acids Res. 28:E31.

[0118] Syndromes Associated with a Contiguous Gene Abnormality

[0119] In one aspect, the invention provides compilations, or sets, libraries or collections, of nucleic acids and arrays and methods for the detection of a chromosomal abnormality or for the diagnosis or prognosis of a syndrome associated with a contiguous gene abnormality. Any set or combination of genomic nucleic acid segments associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome, without limitation, can be used in making and using the compilations, or sets, libraries or collections, of nucleic acids or arrays and practicing the methods of the invention, including genomic nucleic acid segments not specifically exemplified herein. For example, the compilations, or sets, libraries or collections, of nucleic acids or arrays and methods of the invention can comprise genomic nucleic acid segments set forth in the literature, see, e.g., Charles R. Scriver, et al., (2000) "The Metabolic and Molecular Bases of Inherited Disease," 8th edition, New York, McGraw-Hill; Pat Gilbert (2000) "The A-Z Reference Book of Syndromes and Inherited Disorders: A Manual for Health, Social and Education Workers" 3 Ed edition, Stanley Thomes Pub Ltd.; Suzanne B. Cassidy, et al. (Ed), (2001) "Management of Genetic Syndromes," Wiley-Liss.

[0120] The compilations, or sets, libraries or collections, of nucleic acids or arrays and methods of the invention can be used for the differential diagnosis of genetically linked diseases or syndromes, formulating appropriate treatment plans and estimating a prognosis. The methods of the invention can be used in situations where the causality, diagnosis, or prognosis (e.g., severity, metastatic potential) of a pathology or condition is associated with one or more genetic defects, e.g., a syndrome caused by a contiguous chromosomal defect.

[0121] For example, determining the presence of a contiguous gene defect can be helpful in predicting diagnosing and the prognosis of cancer, classifying a cancer or formulating a treatment plan or prognosis. For example, metastasis suppressor genes on human chromosomes for cutaneous melanoma, as well as a variety of other forms of human cancer, have been located on, e.g., 7q21-22, 7q31.2-32, 8p21-12, 10q11-22, 11p13-11.2, 12p11-q13, 12q24-ter, and 17pter-q23 (see, e.g., Goldberg (2000) Am. J. Hum. Genet. 67(2):417-431; Ichikawa (2000) Asian J. Androl. 2(3):167-171). Accordingly, the methods and arrays of the invention can be used for predicting, diagnosing and the prognosis of cancers.

[0122] 1p Deletion Syndrome

[0123] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 1, locus 1p;36, and the syndrome detected is 1p Deletion Syndrome. Patients with deletion of band 1p36.33, have had clinical findings of obesity and hyperphagia; and the overlap of manifestations with Prader-Willi syndrome. See, e.g., Eugster (1997) Am. J. Med. Genet. 70(4):409-412. Patients with karyotypic abnormalities resulting in monosomy for a portion of 1p36.3 can have microcephaly, mental retardation, prominent forehead, deep-set eyes, depressed nasal bridge, flat midface, relative prognathism, and abnormal ears. See, e.g., Reish (1995) Am. J. Med. Genet. 59(4):467-475.

[0124] 3p Deletion Syndrome

[0125] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 3, locus 3p25-pter, and the syndrome detected is

[0126] 3p Deletion Syndrome.

[0127] Chromosome 3p deletions are thought to be involved in the pathogenesis of sporadic endocrine pancreatic tumors (EPTs); also, von Hippel-Lindau's disease (VHL gene at 3p25.5) has been associated with EPTs. Chromosome 3p deletion is frequently involved in solid human tumors. See, e.g., Barghom (2001) J. Pathol. 194(4):451-458. Allele loss in some regions of chromosome 3p has been detected in primary breast tumors. See, e.g., Maitra (2001) Am. J. Pathol. 159(1): 119-130.

[0128] 3p Duplication Syndrome and "C Syndrome"

[0129] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 3, locus 3p21-pter, and the syndrome detected is 3p Duplication Syndrome. A partial trisomy of chromosome 3P, an inverted duplication 3p22-->3pter (dup(3)(pter—>p26::p22(p26::p26-->ter)), was found to be associated with psychomotor retardation and slight dysmorphism. A partial 3p trisomy, a 3p/17p translocation: t(3;7)(p253;p133), was found to be associated with mental retardation and poor speech development. See, e.g., Smeets (2001) Genet. Couns. 12(1):85-89. "C syndrome," a multiple congenital anomaly/mental retardation (MCA/MR) syndrome, was found to be associated with a duplication of 3p. See, e.g., McGaughran (2000) Am. J. Med. Genet. 94(4):311-315.

[0130] Wolf-Hirschhorn Syndrome and Pitt-Rogers-Danks Syndrome

[0131] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 4, locus 4p16.3, and the syndrome detected is Wolf-Hirschhorn Syndrome. Wolf-Hirschhorn syndrome (WHS) is a well-known congenital malformation syndrome

caused by deletion of the short arm of chromosome 4 (4p-). Most cases occur de novo and are of paternal origin. WHS children have severe developmental disabilities. The phenotype of adult WHS is in general similar to that of childhood WHS. Growth retardation, microcephaly and mental retardation are the rule in both adults and children. Facial dysmorphism also remains similar. The main difference lies in the absence of serious internal (cardiac) abnormalities in adult WHS. See, e.g., Battaglia (2001) Adv. Pediatr. 48:75-113; Marcelis (2001) Genet. Couns. 12:35-48. See, e.g., Kant (1997) J. Med. Genet. 34(7):569-572. Pitt-Rogers-Danks syndrome has also been associated with deletions on chromosome 4p16.

[0132] 4p Duplication Syndrome

[0133] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 4, locus 4p15.2-16.1, and the syndrome detected is 4p Duplication Syndrome. Duplications of the distal half of 4p give rise to the partial trisomy 4 syndrome, characterized by a "boxer" nose configuration and deep-set eyes. These signs are usually observed even in cases of small terminal duplications. A "tandem" duplication of 4p16.1p16.3 has been detected in association with a subtle deletion of 4p16.3pter on the same chromosome in a patient with the WHS phenotype. See, e.g., Zollino (1999) Am. J. Med. Genet. 82(5):371-375.

[0134] Cri du Chat Syndrome

[0135] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 5, locus 5p15.2-pter, and the syndrome detected is Cri du Chat Syndrome. Most patients with cri-du-chat syndrome have a de novo deletion of the short arm of chromosome 5 (5p). Patients show phenotypic and cytogenetic variability. Examples of deletions include: terminal –46,XX,del(5) (pter - - - p15.2:); interstitial –46,XX, del(5) (pter - - - p15.2::p13.3 - - - qter); 46,XX,der(5)t(5;11) (p15;q25)mat. Clinically, younger patients can have a typical high-pitched cry, psychomotor retardation, microcephaly, growth rate failure, and craniofacial abnormalities including round face, hypertelorism, broad nasal bridge, downward slanting palpebral fissures, and micrognathia. See, e.g., Mainardi (2001) J. Med. Genet. 38(3):151-158; Van Buggenhout (2000) Am. J. Med. Genet. 90(3):203-215.

[0136] Miller-Dieker Syndrome

[0137] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 7, locus 7p13.3, and the syndrome detected is Miller-Dieker Syndrome. Trisomy 5p and Miller-Dieker syndromes frequently are the result of unbalanced segregations of reciprocal translocations of chromosomes 5 and 17 with other autosomes. Miller-Dieker Syndrome has been associated with a breakpoint in chromosome 17p13. Miller-Dieker syndrome patients can present with mental retardation, postnatal growth deficiency, generalized muscular hypotonia, seizures, microcephaly, cortical atrophy, partial agenesis of corpus callosum, cerebral ventriculomegaly, facial anomalies. See, e.g., Mutchinick (1999) Am. J. Med. Genet. 85(2):99-104; Pollin (1999) Am. J. Med. Genet. 85(4):369-375.

[0138] Williams Syndrome

[0139] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 7, locus 7q11.23, and the syndrome detected is William's Syndrome. Williams syndrome is typically due to a contiguous gene deletion at 7q11.23, and has been associated with a distinctive facial appearance, cardiac abnormalities, infantile hypercalcemia, and growth and developmental retardation, including mild to severe mental retardation. For example, Williams syndrome was seen in a karyotype having microdeletions at 7q11.23 and 7q36 and additional chromosomal material at 7q36. See, e.g., Donnai (2000) Am. J. Med. Genet. 97(2):164-171; Wouters (2001) Am. J. Med. Genet. 102(3):261-265.

[0140] Langer-Giedion Syndrome (LGS) or TRPS II

[0141] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 8, locus 8q24.1, and the syndrome detected is Langer-Giedion Syndrome (LGS) or tricho-rhino-phalangeal syndrome type II (TRPS II). It comprises the clinical features of two autosomal dominant diseases, TRPS I, and a form of multiple cartilaginous exostoses caused by mutations in the EXT1 gene. In contrast to TRPS I patients, most TRPS II patients have cytogenetically visible deletions and are often mentally retarded. See, e.g., Hilton (2001) Genomics 71(2):192-199; Nardmann (1997) Hum. Genet. 99(5):638-643. Other syndromes with contiguous deletions of chromosome 8q include Cohen syndrome (8q22-q23), Klip-Feil syndrome (8q22.2), hereditary spastic paraplegia (8q24), and benign adult familial myoclonic epilepsy (8q23.3-q24.1).

[0142] Trichorhinophalangeal Syndrome (TRPS) or TRPS I

[0143] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 8, locus 8q24.1, and the syndrome detected is Trichorhinophalangeal Syndrome (TRPS) or TRPS I. TRPS I individuals typically have dysmorphic features and severe short stature. TRPS comprises a distinctive combination of hair, facial and bony abnormalities with variable expression. The absence of generalized shortness of all phalanges, metacarpals and metatarsals distinguish it from TRPS III, and absence of exostosis and mental retardation rule out TRPS II. See, e.g., George (1998) J. Eur. Acad. Dermatol. Venereol. 11(1):66-68; Naselli (1998) Pediatr. Radiol. 28(11):851-855.

[0144] 9p Deletion Syndrome

[0145] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 9, locus 9p, e.g., locus 9p22-pter, and the syndrome detected is 9p Deletion Syndrome. This syndrome has been associated with de novo deletions in the short arm of chromosome 9. Patients can have developmental delay/mental retardation, seizures and learning disabilities. Mental retardation can be of variable degrees and there can be a marked deficit in visuo-praxic and visuo-spatial skills associated with memory disturbance. See, e g., Chilosi (2001)

Am. J. Med. Genet. 100(2):138-144. In contrast, cases of tetrasomy 9p are extremely rare; the principal clinical manifestations of this condition are characteristic craniofacial abnormalities, generalized hypotonia and severe mental retardation, see, e g., Kobayashi (2000) J. Craniomaxillofac. Surg. 28(3):165-170.

[0146] DiGeorge Syndrome II

[0147] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 10, locus 10p13-p14, and the syndrome detected is DiGeorge Syndrome II. This syndrome is characterized by neural-crest-related developmental defects. Partial monosomy 10p is a rare chromosomal condition and a significant proportion of patients show features of DiGeorge syndrome (DGS) and velocardiofacial syndrome (VCFS). One patient with DiGeorge syndrome (DGS) phenotype had an unbalanced translocation [45,XY,−10,−22,+der(10), t(10;22)(p13;q11)] resulting in monosomy of 10p3-pter and 22q11-pter. See, e.g., Dasouki (1997) Am. J. Med. Genet. 73(1):72-75; Lichtner (2000) J. Med. Genet. 37(1):33-37; Epstein (2001) Trends Genet. 17(10):S13-17.

[0148] WAGR Syndrome II

[0149] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 11, locus 11p13, and the syndrome detected is WAGR Syndrome. The Wilms' tumor-aniridia-genital anomalies-mental retardation (WAGR) syndrome is associated with an increased risk for developing Wilms' tumor. WAGR (Wilms' tumor, aniridia, genital anomalies, and mental retardation) syndrome anomalies have been associated with balanced reciprocal 7;11 translocation and an 11p13 breakpoint. See, e.g., Crolla (1997) J. Med. Genet. 34(3):207-212; Ariel (1996) Pediatr. Pathol. Lab. Med. 16(6):1013-1021.

[0150] Beckwith-Wiedemann Syndrome (BWS)

[0151] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 11, locus 11p15.5, and the syndrome detected is Beckwith-Wiedemann Syndrome. Beckwith-Wiedemann syndrome (BWS) is an imprinting disorder characterized by somatic overgrowth, congenital malformations, and predisposition to childhood tumors. Chromosome 11p15.5 have been reported to have an imprinted gene cluster of 1 Mb, which has been implicated in a wide variety of malignancies and BWS. See, e.g., Li (2001) Genomics 74(3):370-376; Horike (2000) Hum. Mol. Genet. 9(14):2075-2083.

[0152] Potocki-Shaffer Syndrome (Multiple Exostoses II Locus)

[0153] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 11, locus 11p11.2, and the syndrome detected is Potocki-Shaffer Syndrome (Multiple Exostoses II Locus). Potocki-Shaffer Syndrome is caused by a proximal deletion in the short arm of chromosome 11. Patients having the syndrome can have oval defects of the parietal bones (parietal foramina). See, e.g., Wu (2000) Am. J. Hum. Genet. 67(5):1327-1332.

[0154] Angelman Syndrome (AS)

[0155] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 15, locus 15q12 or 15q13, and the syndrome detected is Angelman Syndrome. It has been reported to be caused by the haploinsufficiency of the 15q11-q13 region, and, de novo deletions of chromosome 15q11-q13. It has also been reported that Angelman syndrome can be caused by genetic abnormalities affecting the maternal copy of chromosome region 15q12. It has been observed that extra copies of this same genomic region, in the form of inv-dup(15) or intra-chromosomal duplications, of maternal origin, are usually associated with a severe neurological phenotype characterized by developmental delay and untreatable seizures. See, e.g., Torrisi (2001) Am. J. Med. Genet. 106(2):125-128; Baumer (1999) Hum. Genet. 105(6):598-602; Greger (1997) Am. J. Hum. Genet. 60(3):574-580.

[0156] Prader-Willi Syndrome (PWS)

[0157] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 15, locus 15q12, and the syndrome detected is Prader-Willi Syndrome (PWS). PWS is a neuroendocrine disorder reported to be due to: a large paternally derived chromosome deletion of 15q11q13, to maternal uniparental disomy (UPD), or imprinting mutation (IC). Severe learning disabilities (e.g., attention-deficit hyperactivity disorder), dyslexia, and excessive daytime sleepiness are common symptoms in PWS. See, e.g., Manni (2001) Clin. Neurophysiol. 112(5):800-805; Fernandez-Novoa (2001) Rev. Neurol. 32(10):935-938.

[0158] Rubinstein-Taybi Syndrome (RTS)

[0159] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 16, locus distal 16p13.3, and the syndrome detected is Rubinstein-Taybi Syndrome (RTS). RTS is a malformation syndrome characterized by facial abnormalities, broad thumbs, broad big toes, and mental retardation. In a subset of RTS patients, microdeletions, translocations, and inversions involving chromosome band 16p13.3 can be detected. Immunodeficiency can be a prominent feature of this syndrome and may predispose these patients to recurrent infections. See, e.g., Petrij (2000) J. Med. Genet. 37(3):168-176; Villella (2000) Arch. Dis. Child. 83(4):360-361.

[0160] Charcot-Marie-Tooth Disease Type 1A(CMT-1A)

[0161] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 17, locus 17p12, and the syndrome detected is Charcot-Marie-Tooth Disease Type 1A(CMT-1A). Charcot-Marie-Tooth neuropathy type 1 (CMT1) is a genetically heterogeneous group of chronic demyelinating polyneuropathies with loci mapping to chromosome 17 (CMT1A), chromosome 1 (CMT1B) and to another unknown autosome (CMT1C). CMT1A accounts for 70-90% of cases of Charcot-Marie-Tooth Disease Type 1 and is most frequently caused by the tandem duplication of a 1.4-Mb genomic fragment on chromosome 17p12. Locus 17p12 is also asso-

ciated with the peripheral neuropathies, such as hereditary neuropathy with liability to pressure palsies (HNPP) (see below). Some analyses have suggested that the syndrome is associated with de novo 17p11.2 duplication, paternal in origin, arising from unequal crossing over due to homologous recombination between flanking repeat gene clusters. X-linked dominant Charcot-Marie-Tooth (CMTX) disease is a motor and sensory neuropathy caused by mutations in the connexin 32 (CX32) gene. See, e.g., Badano (2001) Clin. Chem. 47(5):838-843; Potocki (2000) Nat. Genet. 24(1):84-87.

[0162] Hereditary Neuropathy (HNPP)

[0163] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 17, locus 17p12, and the syndrome detected is Hereditary Neuropathy with Liability to Pressure Palsies (HNPP). HNPP is an autosomal dominant disorder that results in a recurrent, episodic demyclinating neuropathy. It also can be characterized by reversible episodes of sensorimotor deficits after neural compression injuries. Also known as tomaculous neuropathy, HNPP is further characterized ultrastructurally by multiple focal thickenings (tomacula) of peripheral myelin and has an autosomal dominant inheritance. HNPP is associated with a 1.5-Mb deletion in chromosome 17p11.2-12 and results from reduced expression of the PMP22 gene. See, e.g., Mersiyanova (2000) Hum. Mutat.15(4):340-347; Chance (2001) Phys. Med. Rehabil. Clin. N. Am. 12(2):277-291; Lane (2001) J. Hand Surg. [Am] 26(4):670-674.

[0164] Miller-Dieker Syndrome/Isolated Lissencephaly

[0165] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 17, locus 17p13.3, and the syndrome detected is Miller-Dicker Syndrome/Isolated Lissencephaly. The Miller-Dieker syndrome (type I lissencephaly) is a neuronal migration disorder that is associated with microdeletions in the short arm of chromosome 17, at locus 17p13.3. For example, one patient was found to have a de novo balanced translocation with breakpoint at 8p11.23 and 17p13.3. In contrast, neurofibromatosis type I (NF1) is an autosomal dominant condition associated with mutations in the long arm of chromosome 17, and characterized by neurofibromas, cafe-au-lait spots and axillary freckling. See, e.g., King (2000) Acta Neuropathol. (Berl) 99(4):425-427; Honda (1998) Brain Dev. 20(3):190-192.

[0166] Smith-Magenis Syndrome (SMS)

[0167] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 17, locus 17p11.2, and the syndrome detected is Smith-Magenis Syndrome (SMS). SMS is a clinically recognizable syndrome comprising multiple congenital anomalies and mental retardation. Its symptoms can include facial anomalies, brachydactyly, severe mental retardation, and self-injuring behavior. SMS is associated with a microdeletion (an interstitial deletion) of the short arm of chromosome 17, locus 17p11.2. Interestingly, a patient with a del(17)(p11.2p12) karyotype displayed symptoms of both SMS and Joubert syndrome (JS), the later characterized by cerebellar vermis hypoplasia, hypotonia, ataxic gait, developmental delay, and abnormal respiratory pattern. A prenatal case of SMS found dysmorphic facial features, tetralogy of Fallot, a thymic duct remnant, pancreatic islet cell hyperplasia, and abnormal lung fissuring. See, e.g., Juyal (1996) Am. J. Hum. Genet. 58(5):998-1007; Natacci (2000) Am. J. Med. Genet. 95(5):467-472; Thomas (2000) Fetal Diagn. Ther. 15(6):335-337.

[0168] Alagille Syndrome (AGS)

[0169] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 20, locus 20p11.2-p12, and the syndrome detected is Alagille Syndrome (AGS), also known as arteriohepatic dysplasia. Patients can have a deletion in chromosome 20p, with 20p11.23-p12.2 as the area of minimal overlap. One AGS case had aparacentric inversion (PAI) of chromosome 20p12.2p13. Locus 20p11.2-p12 encodes a ligand for the Notch1 transmembrane receptor, which plays a key role in cell-to-cell signaling during differentiation. See, e.g., Yuan (1997) Acta Paediatr. Jpn 39(6):647-652; Hol (1995) Hum. Genet. 95(6):687-690.

[0170] Digeorge/Velocardiofacial Syndrome (VCFS)

[0171] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 22, locus 22q11.2, and the syndrome detected is Digeorge/Velocardiofacial Syndrome (VCFS). VCFS can result from a microdeletion on chromosome 22, locus 22q11.2. VCFS is associated with a broad clinical spectrum characterized by multiple congenital malformations, including cleft palate and cardiac anomalies, that frequently overlaps the DiGeorge syndrome. Estimates suggest that the 22q11.2 deletion occurs in approximately 1 in 4000 live births. Clinical studies indicate that more than 30% of children with VCFS will develop schizophrenia. Velofacial hypoplasia (Sedlackova syndrome) and velocardiofacial (Shprintzen) syndrome are also both associated with del 22q11.2. See, e.g., Eliez (2001) Am. J. Psychiatry 158(3):447-453; Fokstuen (2001) Eur. J. Pediatr. 160(1):54-57; Duke (2000) Arch. Otolaryngol. Head Neck Surg. 126(9):1141-1145.

[0172] Adrenal Hypoplasia Congenita (AHC)

[0173] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome X, locus Xp21, and the syndrome detected is Adrenal Hypoplasia Congenita (AHC). AHC patients have a deletion on the short arm of the X chromosome, locus p21.1 to p22.1. AHC is a developmental disorder of the human adrenal cortex and has been proposed to be caused by deletion or mutation of the DAX-1 gene within locus p21.1 to p22.1; DAX-1 is a member of the nuclear hormone receptor superfamily. The Xp21 syndrome should be considered in any infant with adrenal insufficiency. Measurement of serum triglycerides and creatine kinase activity and karyotype screening tests will facilitate early diagnosis. See, e.g., Peter (1998) J. Clin. Endocrinol. Metab. 83(8):2666-2674; Cole (1994) Clin. Chem. 40(11 Pt 1):2099-2103, and the Glycerol kinase deficiency (GKD) discussion, below.

[0174] Duchenne/Becker Muscular Dystrophy

[0175] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome X, locus Xp21, and the syndrome detected is Duchenne/Becker Muscular Dystrophy. Cardiac abnormalities, cardiomyopathy and skeletal muscle weakness have been described in female carriers of the Xp21 (Duchenne and Becker) muscular dystrophies. Duchenne and Becker dystrophies have been associated with the absence or altered expression of dystrophin in cardiac and skeletal muscles. They are frequently complicated by cardiac hypertrophy and dilated cardiomyopathy. See, e.g., Grain (2001) Neuromuscul. Disord. 11(2):186-191; Crilley (2000) J. Am. Coll. Cardiol. 36(6):1953-1958, and the Glycerol kinase deficiency (GKD) discussion, below.

[0176] Glycerol Kinase Deficiency (GKD)

[0177] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome X, locus Xp21, and the syndrome detected is Glycerol Kinase Deficiency (GKD). Glycerol kinase deficiency (GKD) is an X-linked recessive disorder having a deletion on the short arm of the X chromosome, locus p21.1 to p22.1. There are two types. an isolated form and a complex form. The clinical and biochemical phenotype of isolated GKD may vary from a life-threatening childhood metabolic crisis to asymptomatic adult 'pseudohypertriglyceridaemia', resulting from hyperglycerolaemia. The complex GKD is an Xp2l contiguous gene syndrome involving the glycerol kinase locus together with the adrenal hypoplasia congenita (AHC) or Duchenne muscular dystrophy (DMD) loci or both. Complex GKD patients can have an "hourglass" appearance of the middle of the face; hypertelorism; rounded palpebral fissures; esotropia; wide, flattened earlobes; and a downturned mouth. See, e.g., Sjarif (2000) J. Inherit. Metab. Dis. 23(6):529-547; Scheuerle (1995) J. Pediatr. 126(5 Pt 1):764-767.

[0178] Pelizaeus-Merzbacher Disease (PMD)

[0179] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome X, locus Xp22, and the syndrome detected is Pelizaeus-Merzbacher Disease (PMD). PMD is an X-linked recessive dysmyelinating disorder of the central nervous system. Most patients have point mutations in exons of the proteolipid protein (PLP1) gene or duplication of a genomic region that includes the PLP1 gene, on locus Xp22, on the short arm of the X chromosome. See, e.g., Hobson (2001) Hum. Mutat. 17(2):152; Hodes (2000) Am. J. Hum. Genet. 67(1):14-22; Inoue (1999) Ann. Neurol. 45(5):624-632.

[0180] Steroid Sulfatase Deficiency

[0181] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome X, locus Xp22.3, and the syndrome detected comprises steroid sulfatase deficiency. X chromosome deletions in the Xp22.3 region can result in steroid sulfatase deficiency and X-linked ichthyosis. In one patient, an interstitial deletion in Xp22.3 involved the Kallmann (KAL) gene, the steroid sulfatase (STS) gene and a putative mental retardation locus (MRX). X-linked ichthyosis (XLI) is an inborn error of metabolism due to steroid sulfatase (STS) deficiency. X-linked ichthyosis is a disorder of keratinization characterized by a generalized desquamation of large, adherent, dark brown scales. Extracutaneous manifestations include corneal opacity and cryptorchidism. See, e.g., Weissortel (1998) Clin. Genet. 54(1):45-51; Santolaya-Forgas (1997) Fetal Diagn. Ther. 12(1):36-39; Valdes-Flores (2001) Am. J. Med. Genet. 102(2): 146-148.

[0182] Abnormalities of the SRY Locus

[0183] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome Y, locus SRY locus/Yp, and the syndrome detected comprises abnormalities of the SRY (sex-determining region on the Y chromosome) locus. SRY has been identified at band Yp11.31p11.32 in normal XY males and in woman with XY gonadal dysgenesis. SRY signals have also been identified on Xp22 in one XX male. Ullrich-Turner syndrome (UTS) has been associated with Y fragments and gonadoblastomas. Thus, some clinicians have suggested that UTS patients should be examined for Y chromosome material, and that positive cases should have their dysgenic gonads excised due to the high risk of malignancy. See, e.g., Kadandale (2000) Am. J. Med. Genet. 95(1):71-74; Damiani (1999) J. Pediatr. Endocrinol. Metab. 12(6):827-831; Kadandale (2000) Microb. Comp. Genomics 5(2):71-74.

[0184] Sex Reversal (DSS)

[0185] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome X, locus Xp21, and the syndrome detected is Sex Reversal (DSS). The Xp21 locus contains the gene Ahch, also known as Dax1. Ahch encodes a transcription factor that has been implicated in sex determination and gonadal differentiation. Mutations in human AHC cause X-linked, adrenal hypoplasia congenita (AHC) and hypogonadotropic hypogonadism (HH). Studies have found Xp duplications in patients with sex reversal, with female or ambiguous genitalia occurring in spite of an intact Yp or SRY gene. Five different exchanges have been described two or more times: t(X;Y)(p21;q11), t(X;Y)(p22;p11), t(X;Y)(p22;q11-12), t(X;Y) (q22;q12), and t(X;Y)(q28;q12). See, e.g., Yu (1998) Nat. Genet. 20(4):353-7; Vasquez (1999) Genet. Couns. 10(3):301-334.

[0186] Kallman's Disease or Kallmann's Syndrome (KS)

[0187] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome X, locus Xp22.3, and the syndrome detected is Kaliman's Disease or Kallmann's syndrome (KS). KS is characterized by hypogonadotrophic hypogonadism in association with anosmia or hyposmia. KS can be associated with X-linked ichthyosis (XLI) in a contiguous gene syndrome comprising a genetic defect in the Xp22.3 region. KS has also been associated with olfactory neuroblastoma. See, e.g., Maya-Nunez (1999) Clin. Endocrinol. (Oxf) 50(2):157-162; Zappia (1992) J. Otolaryngol. 21(1):16-19.

[0188] 17p11.2 Duplication Syndrome and Birt-Hogg-Dube Syndrome (BHD)

[0189] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention

comprise a segment of genomic nucleic acid comprising chromosome 17, locus 17p11.2, and the syndrome detected is 17p1.2 Duplication Syndrome. Duplication of locus 17p11.2 may be associated with Birt-Hogg-Dube syndrome (BHD), an autosomal dominant neoplasia syndrome characterized mainly by benign skin tumors (e.g., benign tumors of the hair follicle), and to a lesser extent, renal tumors, lung cysts, and spontaneous pneumothorax. The gene for BHD may associated with renal neoplasia and for lung and hair-follicle developmental defects. See, e.g., Schmidt (2001) Am. J. Hum. Genet. 69(4):876-82; Khoo (2001) Oncogene 20(37):5239-5242.

[0190] Smith-Magenis Syndrome (SMS)

[0191] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 17, locus 17p11.2, and the syndrome detected is Smith-Magenis syndrome (SMS). SMS is a clinically recognizable contiguous gene syndrome ascribed to interstitial deletions of chromosome 17p11.2. SMS patients have clinically recognizable multiple congenital anomalies and mental retardation, including self-injury, tantrums, and sleep disturbance. SMS patients have a phase shift of their circadian rhythm of melatonin with a paradoxical diurnal secretion of the hormone. See, e.g., De Leersnyder (2001) J. Med. Genet. 38(9):586-590; De Leersnyder (2001) J. Pediatr. 139(1): 111-116; Smith (1998) Am. J. Med. Genet. 81(2):186-191.

[0192] Idiopathic Epilepsy and Paroxysmal Dyskinesia

[0193] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 16, pericentromeric region, and the syndrome detected is idiopathic epilepsy and paroxysmal dyskinesia. This is a homogeneous syndrome of autosomal dominant infantile convulsions and paroxysmal (dystonic) choreoathetosis (ICCA). Use of the arrays and methods of the invention may be particularly useful because motor manifestations of epilepsy and of paroxysmal dyskinesia may be difficult to differentiate clinically. See, e.g., Guerrini (2001) Epilepsia 42 Suppl 3:36-41.

[0194] Hirschsprung Disease Type 2 and Waardenburg Syndrome

[0195] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 13, locus 13q22, and the syndrome detected is Hirschsprung disease, including Hirschsprung disease type 2, and Waardenburg syndrome. Hirschsprung disease is a developmental disorder resulting from the arrest of the craniocaudal migration of enteric neurons from the neural crest along gastrointestinal segments of variable length. Waardenburg-Shah syndrome is an auditory pigmentary disorder. Hirschsprung disease, malrotation, isochromia, a profound sensorineural hearing loss, and several other anomalies were found in an infant with an interstitial deletion of 13q, see, e.g., Shanske (2001) Am. J. Med. Genet. 102(3):231-236.

[0196] Branchio-oto-renal (BOR) Syndrome

[0197] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising 8, locus 8q13.3, and the syndrome detected is branchio-oto-renal (BOR) syndrome. Branchio-oto-renal (BOR) syndrome is an autosomal dominant disorder involving hearing loss, branchial defects, ear pits and renal abnormalities. The arrays and methods of the invention can be used to distinguish it from oto-facio-cervical (OFC) syndrome, which is clinically similar to BOR syndrome, with clinical features in addition to those of BOR syndrome. See, e.g., Rickard (2001) Hum. Genet. 108(5):398-403.

[0198] Smith-Magenis Syndrome (SMS)

[0199] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome 1, locus 7p11.2, and the syndrome detected is Smith-Magenis syndrome (SMS). Smith-Magenis syndrome (SMS) is a multiple congenital anomaly/mental retardation (MCA/MR) syndrome link to a contiguous-gene deletion syndrome, involving chromosome 17p11.2,whose incidence is estimated to be 1:25,000 live births. SMS is characterized by a specific physical, behavioral and developmental pattern. The main clinical features consist of a broad flat midface with brachycefaly, broad nasal bridge, brachydactily, speech delay, hoarse deep voice and peripheral neuropathy. See, e.g., Di Cicco (2001 Int. J. Pediatr. Otorhinolaryngol. 59(2):147-150.

[0200] Leri-Weill Syndrome

[0201] In one aspect, the compilations, or sets, libraries or collections, of nucleic acids or arrays of the invention comprise a segment of genomic nucleic acid comprising chromosome X, locus Xp22.3, and the syndrome detected is Leri-Weill syndrome. Leri-Weill syndrome is characterized by short stature (SHOX), chondrodysplasia punctata (ARSE), bilateral Madelung deformity and mental retardation. See, e.g., Spranger (1999) Am. J. Med. Genet. 83(5):367-371.

[0202] Chromosome abnormalities are common causes of congenital malformations and spontaneous abortions. They include structural abnormalities, polyploidy, trisomy, and mosaicism. Very few autosomal trisomies survive to birth, the three most common being those for chromosome 13, 18 and 21 giving rise to the syndromes named Patau, Edward's and Down's respectively (see, e.g., Moore (2000) Eur. J. Hum. Genet. 8:223-228). Thus, in alternative aspects, the arrays methods of the invention are used to diagnose Patau Syndrome, Edward's Syndrome and Down's Syndrome. See, e.g., Djalali (2000) Prenat. Diagn. 20:934-935. Table 1 sets forth in summary form exemplary contiguous gene syndromes that can be diagnosed by the compilations, or sets, libraries or collections, of nucleic acids, arrays and methods of the invention:

TABLE 1

Chromosome Loci Profiles of Contiguous Gene Syndromes

Chromosome number	Locus	Syndrome
1	1p36	1p Deletion Syndrome
3	3p25 - pter	3p Deletion Syndrome
3	3p21 - pter	3p Duplication Syndrome
4	4p16.3	Wolf-Hirschhorn Syndrome

TABLE 1-continued

Chromosome Loci Profiles of Contiguous Gene Syndromes

Chromosome number	Locus	Syndrome
4	4p15.2 - 16.1	4p Duplication Syndrome
5	5p15.2 - pter	Cri du Chat Syndrome
7	7p13.3	Miller-Dieker Syndrome
7	7p11.23	William's Syndrome
8	8q24.1	Langer-Giedion Syndrome (LGS)
8	8q24.1	Trichorhinophalangeal Syndrome (TRPS)
9	9p, usually 9p22 - pter	9p Deletion Syndrome
10	10p13p14	DiGeorge Syndrome II
11	11p13	WAGR Syndrome
11	11p15.5	Beckwith-Wiedemann Syndrome
11	11p11.2	Potocki-Shaffer Syndrome (Multiple Exostoses II Locus)
15	15q12	Angelman Syndrome
15	15q12	Prader-Willi Syndrome
16	Distal 16p13.3	Rubinstein-Taybi Syndrome
17	17p12	Charcot-Marie-Tooth Disease Type 1A(CMT-1A)
17	17p12	Hereditary Neuropathy with Liability to Pressure Palsies
17	17p13.3	Miller-Dieker Syndrome/Isolated Lissencephaly
17	17p11.2	Smith-Magenis Syndrome
20	20p11.2p12	Alagille Syndrome
22	22q11.2 (also see 1-p13p14)	Digeoege/Velocardiofacial Syndrome
X	Xp21	Adrenal Hypoplasia Congenita (AHC)
X	Xp21	Duchenne/Becker Muscular Dystrophy
X	Xp21	Glycerol Kinase Deficiency
X	Xp22	Pelizaeus-Merzbacher Disease
X	Xp22.3	Steroid Sulfatase Deficiency
Y	SRY locus/Yp	Abnormalities of the SRY locus

[0203] The compilations, or sets, libraries or collections, of nucleic acids, arrays and methods of the invention can also be used to detect aneuploidy of chromosomes 13, 18, 21, X, and Y from genomic DNA from newborn uncultured blood samples (see, e.g., Jalal (1997) Mayo Clin. Proc. 72:705-710). Chromosomal abnormalities have been reported to occur in approximately 1%-2% of viable pregnancies studied by chorionic villus sampling at 9-11 weeks of gestation. See, e.g., Harrison (1993) Hum. Genet. 92:353-358.

[0204] In in vitro fertilization (IVF) programs, preimplantation genetic diagnosis (PGD) of oocytes and embryos has become the technique of choice to select against abnormal embryos before embryo transfer. Thus, in alternative aspects, the compilations, or sets, libraries or collections, of nucleic acids, arrays and methods of the invention are used for preimplantation genetic diagnosis and the diagnosis of chromosomal abnormalities and structural abnormalities in oocytes and embryos. See, e.g., Fung (2001) J. Histochem. Cytochem. 49:797-798. Thus, in alternative aspects, the compilations, or sets, libraries or collections, of nucleic acids, arrays and methods of the invention are used with chorionic villus sampling (CVS) and fetal karyotyping. See, e.g., Sanz (2001) Fetal Diagn. Ther. 16:95-97.

[0205] Genetic defects are frequent among transgenic animals produced by pronuclear microinjection. A successful method for the screening of founder animals for a chromosomal abnormality prior to mating would greatly reduce the costs associated with the propagation of the transgenic lines, and improve the efficiency of transgenic livestock production. Thus, in alternative aspects, the compilations, or sets, libraries or collections, of nucleic acids, arrays and methods of the invention are used in the production of transgenic animals, particularly, the screening of founder animals for gene defects prior to mating. See, e.g., Ibanez (2001) Mol. Reprod. Dev. 58:166-172.

[0206] Comparative Genomic Hybridization (CGH)

[0207] In one aspect, compilations, or sets, libraries or collections, of nucleic acids, the arrays and methods of the invention incorporate array-based comparative genomic hybridization (CGH) reactions to detect chromosomal abnormalities, e.g., contiguous gene abnormalities, in cell populations, such as tissue, e.g., biopsy or body fluid samples. CGH is a molecular cytogenetics approach that can be used to detect regions in a genome undergoing quantitative changes, e.g., gains or losses of sequence or copy numbers. Analysis of genomes of tumor cells can detect a region or regions of anomaly under going gains and/or losses.

[0208] CGH reactions compare the genetic composition of test versus controls samples; e.g., whether a test sample of genomic DNA (e.g., from a cell population suspected of having one or more subpopulations comprising different, or cumulative, genetic defects) has amplified or deleted or mutated segments, as compared to a "negative" control, e.g., "normal" or "wild type" genotype, or "positive" control, e.g., a known cancer cell or a cell with a known defect, e.g., a translocation or deletion or amplification or the like.

[0209] Making and using the compilations, or sets, libraries or collections, of nucleic acids, arrays and practicing the methods of the invention can incorporate all known methods and means and variations thereof for carrying out comparative genomic hybridization, see, e.g., U.S. Pat. Nos. 6,197,501; 6,159,685; 5,976,790; 5,965,362; 5,856,097; 5,830,645; 5,721,098; 5,665,549; 5,635,351; and, Diago (2001) American J. of Pathol. May;158(5):1623-1631; Theillet (2001) Bull. Cancer 88:261-268; Werner (2001) Pharmacogenomics 2:25-36; Jain (2000) Pharmacogenomics 1:289-307.

[0210] Arrays, or "BioChips"

[0211] The invention provides articles of manufacture, such as arrays, comprising the compilations, or sets, libraries or collections, of nucleic acids of the invention. Making and using the compilations, or sets, libraries or collections, of nucleic acids, arrays and practicing the methods of the present invention can incorporate any known "array," also referred to as a "microarray" or "DNA array" or "nucleic acid array" or "biochip," or variation thereof. Arrays are generically a plurality of "target elements," or "spots," each target element comprising a defined amount of one or more biological molecules, e.g., polypeptides, nucleic acid molecules, or probes, immobilized on a defined location on a substrate surface. Typically, the immobilized biological molecules are contacted with a sample for specific binding, e.g., hybridization, between molecules in the sample and the array. Immobilized nucleic acids can contain sequences from specific messages (e.g., as cDNA libraries) or genes (e.g., genomic libraries), including, e.g., substantially all or a subsection of a chromosome or substantially all of a

genome, including a human genome. Other target elements can contain reference sequences, such as positive and negative controls, and the like. The target elements of the arrays may be arranged on the substrate surface at different sizes and different densities. Different target elements of the arrays can have the same molecular species, but, at different amounts, densities, sizes, labeled or unlabeled, and the like. The target element sizes and densities will depend upon a number of factors, such as the nature of the label (the immobilized molecule can also be labeled), the substrate support (it is solid, semi-solid, fibrous, capillary or porous), and the like. Each target element may comprise substantially the same nucleic acid sequences, or, a mixture of nucleic acids of different lengths and/or sequences. Thus, for example, a target element may contain more than one copy of a cloned piece of DNA, and each copy may be broken into fragments of different lengths, as described herein. The length and complexity of the nucleic acid fixed onto the array surface is not critical to the invention. The array can comprise nucleic acids immobilized on any substrate, e.g., a solid surface (e.g., nitrocellulose, glass, quartz, fused silica, plastics and the like). See, e.g., U.S. Pat. No. 6,063,338 describing multi-well platforms comprising cycloolefin polymers if fluorescence is to be measured. Arrays used in the methods of the invention can comprise housing comprising components for controlling humidity and temperature during the hybridization and wash reactions.

[0212] In making and using the compilations, or sets, libraries or collections, of nucleic acids, arrays and practicing the methods of the invention, known arrays and methods of making and using arrays can be incorporated in whole or in part, or variations thereof, as described, for example, in U.S. Pat. Nos. 6,277,628; 6,277,489; 6,261,776; 6,258,606; 6,054,270; 6,048,695; 6,045,996; 6,022,963; 6,013,440; 5,965,452; 5,959,098; 5,856,174; 5,830,645; 5,770,456; 5,632,957; 5,556,752; 5,143,854; 5,807,522; 5,800,992; 5,744,305; 5,700,637; 5,556,752; 5,434,049; see also, e.g., WO 99/51773; WO 99/09217; WO 97/46313; WO 96/17958; see also, e.g., Johnston (1998) Curr. Biol. 8:R171-R174; Schummer (1997) Biotechniques 23:1087-1092; Kern (1997) Biotechniques 23:120-124; Solinas-Toldo (1997) Genes, Chromosomes & Cancer 20:399-407; Bowtell (1999) Nature Genetics Supp. 21:25-32. See also published U.S. patent applications Nos. 20010018642; 20010019827; 20010016322; 20010014449; 20010014448; 20010012537; 20010008765. The present invention can use any known array, e.g., GeneChips™, Affymetrix, Santa Clara, Calif.; SPECTRALCHIP™ Mouse BAC Arrays, SPECTRALCHIP™ Human BAC Arrays and Custom Arrays of Spectral Genomics, Houston, Tex., and their accompanying manufacturer's instructions.

[0213] In alternative embodiments, the compilations, or sets, libraries or collections, of nucleic acids of the invention, and the articles of manufacture, such as arrays, of the invention, can comprise one, several or all of the human genomic nucleic acid segments set forth below in Table 2 (listing 2474 clones derived from all/representing all 24 human chromosomes). These clones have RPI or CTB clone names; these descriptors for the clones can be found in Nature 409:953-958 (2001), "Integration of cytogenetic landmarks into the draft sequence of the human genome." The BAC Resource Consortium. The numbers in the right-hand column of Table 2 indicate the linear length of the cloned nucleic acid segment are megabases (Mb). These clones represent all 24 human chromosomes in about 1 Mb resolution.

TABLE 2

clone_id	chromosome	linear
RP11-421C4	1	0.7
RP1-283E3	1	0.9
RP4-703E10	1	2.4
RP1-163G9	1	2.8
RP11-447M5	1	4.4
RP3-491M17	1	4.7
RP11-33M12	1	5.4
RP3-438L4	1	6.4
RP3-330O12	1	8.2
RP4-633I8	1	9.1
RP11-476D13	1	9.6
AL358492.9	1	10.9
RP5-888M10	1	12
RP11-219C24	1	12.4
RP4-726F20	1	13.8
RP5-864I18	1	14.6
RP11-169K16	1	15.7
RP1-163M9	1	16.4
RP1-37C10	1	17.2
RP11-79D15	1	18
RP1-8B22	1	18.8
RP11-91K11	1	20.1
RP3-340N1	1	20.5
RP5-886K2	1	24.4
RP3-462O23	1	25.2
RP3-465N24	1	26
RP1-125I3	1	26.6
RP11-261P19	1	27.8
RP1-50O24	1	29
RP1-212P9	1	29.7
RP3-437I16	1	30.1
RP5-893G23	1	31.2
RP4-655C4	1	33.3
AL033524.11	1	34.1
RP3-423B22	1	35.5
RP1-93K19	1	36.2
RP1-117O3	1	37.9
RP5-1007G16	1	38.6
RP1-34M23	1	39.5
RP4-811I8	1	40.6
AL512599	1	41.7
RP1-92O14	1	44.4
RP5-1029K14	1	45.3
RP11-319C21	1	46.1
RP5-820O16	1	47.2
RP4-639P2	1	48.2
RP11-112C15	1	48.9
RP5-965L7	1	50.3
RP11-116M11	1	51.5
RP5-1013G21	1	52.1
RP11-253A20	1	52.4
RP4-814E15	1	53.4
RP5-1024N4	1	55.5
RP11-13N22	1	56.5
RP11-79A13	1	57.1
RP11-89O16	1	57.7
RP4-737A23	1	58.6
RP11-63G10	1	59.5
RP11-89D5	1	61.3
RP3-333A15	1	62.4
RP4-685B19	1	63.3
RP11-79O23	1	64
RP11-205P11	1	65.3
RP5-879H24	1	66.8
RP4-542O18	1	67.3
RP11-221L2	1	67.9
RP6-65F20	1	68.9
RP4-662P1	1	69.7
RP11-5P4	1	71.4
RP4-534K7	1	71.9
RP4-537F10	1	72.3

TABLE 2-continued

clone_id	chromosome	linear
RP11-75N16	1	73.4
RP11-26A10	1	74.7
RP11-131O15	1	75.7
RP11-89K2	1	76.9
RP11-88B10	1	78
RP11-492C3	1	79.5
RP4-595K12	1	79.7
RP5-1153M13	1	80.8
RP11-80G24	1	81.7
RP5-831O21	1	82.8
RP4-572F19	1	83.6
RP5-989D17	1	84.8
RP11-79I13	1	85.7
RP4-612J11	1	86
RP4-601K24	1	86.9
RP5-896C23	1	88
RP11-78E18	1	88.2
RP4-552O12	1	89.1
RP11-193H16	1	90.7
AL122002.16	1	91.7
RP5-1027O11	1	92.9
RP5-905H16	1	93.8
RP5-1007M22	1	94.5
RP5-871E2	1	95
RP11-99A8	1	95.6
RP11-47K11	1	96.5
RP11-79M15	1	98.2
RP11-163M2	1	98.9
RP4-713B5	1	99.7
RP11-148B18	1	100.9
RP11-48A6	1	101.7
RP11-335D10	1	102
RP11-122C9	1	103.2
RP4-672J20	1	104.5
RP11-79C3	1	105
RP11-90N15	1	105.4
RP11-411H5	1	108.5
RP11-79H19	1	109
RP11-259N12	1	110.5
RP4-669H10	1	113
RP5-1077K16	1	113.8
RP11-96F24	1	114.6
RP11-180N18	1	117.6
RP5-1125M8	1	118.9
RP4-773A18	1	119.2
RP4-580L15	1	120.3
RP5-1156J9	1	122.1
RP11-90J3	1	124
RP11-88D6	1	124.2
RP11-315I20	1	126.1
RP4-599G15	1	128.4
RP4-787H6	1	130.5
RP11-433J22	1	149.1
RP11-458I7	1	149.9
RP4-790G17	1	150.3
RP11-71L20	1	151.6
RP11-81P11	1	153.1
RP1-148L21	1	153.8
RP11-137P24	1	154.6
RP11-77I10	1	161
RP11-80F2	1	162.4
RP11-260G23	1	163.2
RP11-90A11	1	164.6
RP11-80B20	1	165
RP11-80D6	1	166.4
RP1-9E21	1	167.9
RP11-354K16	1	169.4
Z99572.1	1	170.8
RP11-81H19	1	172
RP11-89P2	1	173.2
RP11-79E17	1	174.4
RP11-469I6	1	175.5
RP1-105D12	1	175.8
RP3-395P12	1	176.4

TABLE 2-continued

clone_id	chromosome	linear
RP11-415M14	1	178.2
RP11-91K17	1	179
RP11-90C19	1	179.5
RP4-593C16	1	180.7
AL022171	1	182.3
RP11-12M5	1	183.3
RP11-375F5	1	184.2
RP11-46A10	1	184.6
RP11-98G7	1	185
RP11-317P15	1	186
RP11-452O22	1	187.7
RP11-63O2	1	188.7
RP1-53A19	1	189.7
RP11-79I7	1	190.3
RP4-799N4	1	191.8
RP11-71C11	1	192.9
RP11-91N1	1	193
RP11-113I24	1	194.4
RP3-419C19	1	197.7
RP11-101E13	1	197.9
RP11-358A9	1	198.8
RP11-173E24	1	201.4
RP11-88D12	1	201.7
RP11-91G12	1	202.5
RP11-88N22	1	204.3
RP11-80N24	1	205.1
AF190464.1	1	207
RP11-150L7	1	208.1
RP11-335O13	1	209.2
RP11-80N9	1	210.4
RP11-243M13	1	211.2
RP11-246J15	1	212.1
RP11-35C1	1	214.1
RP11-45F21	1	214.5
RP11-79M12	1	216.3
RP11-89N3	1	217
RP11-90A5	1	219.9
RP11-91G6	1	220.1
RP11-79H5	1	223.4
RP11-260A10	1	224.6
RP11-66M7	1	224.7
RP11-135J2	1	226.9
RP11-553F10	1	227.6
RP11-124J24	1	228.5
RP11-239E10	1	231.6
RP5-1090A23	1	232.2
RP11-543G21	1	232.7
RP11-275O4	1	234.5
RP5-915N17	1	235.4
RP11-108F13	1	236.5
RP11-543E8	1	237.6
RP5-865N13	1	238.9
RP5-1016N21	1	240.2
RP5-885P2	1	240.9
RP4-781K5	1	241.8
RP4-670F13	1	243.8
RP11-80P14	1	245.4
RP11-136B18	1	245.6
RP11-90L13	1	247
RP11-81J5	1	247.8
AL365366.19	1	249.3
RP11-28E22	1	250.4
RP1-241M7	1	251.9
RP11-152M6	1	252.5
RP11-656O22	1	252.7
RP11-88H4	1	254.4
RP11-91C5	1	254.5
RP11-407H12	1	256.1
RP11-438F14	1	256.1
RP11-1N7	2	0.1
RP11-90H11	2	1.6
RP11-352J11	2	1.7
AC011995.8	2	2.2
RP11-457A20	2	2.6

TABLE 2-continued

clone_id	chromosome	linear
RP11-36C8	2	2.9
RP11-513H7	2	4
RP11-350H23	2	4.9
AC007464.4	2	7.2
RP11-327F6	2	8
RP11-484O9	2	10.9
RP11-91E9	2	12.8
RP11-282G6	2	15.6
RP11-79E20	2	16.6
RP11-80H16	2	19.9
RP11-414D15	2	22.9
RP11-443B20	2	24.2
RP11-91I23	2	24.9
RP11-88F6	2	25.9
RP11-45M3	2	26.8
AC024386.5	2	27.8
RP11-328L16	2	28.7
RP11-62F14	2	30
RP11-93O2	2	31.1
RP11-444D15	2	31.2
RP11-3J7	2	32.4
RP11-77G15	2	34
RP11-119B15	2	35.7
RP11-89F19	2	38.3
RP11-555N21	2	39
RP11-299C5	2	42.5
RP11-119J12	2	44.3
AC084265.2	2	45.9
RP11-130P22	2	46.5
RP11-436K12	2	47.9
RP11-89G16	2	49.7
AC016714.5	2	53.9
RP11-321E13	2	56.2
RP11-494H5	2	56.8
RP11-482H16	2	57.4
RP11-81L7	2	58
RP11-90D1	2	60.2
RP11-81L13	2	61.3
RP11-79K21	2	62.1
RP11-355B11	2	62.7
RP11-240J3	2	64.9
RP11-90B13	2	65.7
RP11-88F20	2	66.2
RP11-79H11	2	66.6
RP11-340F16	2	67.3
RP11-474G23	2	68.1
RP11-179G23	2	69.5
RP11-401N16	2	70.7
RP11-175A7	2	71.5
RP11-356H17	2	72.4
AC013408	2	73.9
AC007681.3	2	76
AC016758	2	78.1
RP11-91F23	2	78.3
RP11-79C11	2	79.2
RP11-79D19	2	80.1
RP11-79O3	2	81.4
RP11-89C12	2	82.7
RP11-345F13	2	84.3
RP11-451C8	2	84.6
RP11-4C8	2	87.1
RP11-90C7	2	87.6
RP11-21P18	2	88.4
RP11-554H10	2	88.7
RP11-81F3	2	91.9
AC013270.5	2	92.5
RP11-89J19	2	93
RP11-629A22	2	94
RP11-38C17	2	94.8
RP11-89L1	2	95.5
RP11-90J9	2	96.3
RP11-315O22	2	101
RP11-83A12	2	101.3
RP11-289J14	2	101.9

TABLE 2-continued

clone_id	chromosome	linear
RP11-89O22	2	102.6
RP11-90O9	2	103
RP11-88F14	2	103.8
RP11-89O10	2	104.1
AC010978.7	2	104.6
RP11-464P18	2	105.4
RP11-79K7	2	106.4
AC092645.1	2	109.2
RP11-368K23	2	110.3
RP11-91C22	2	111.3
RP11-89L12	2	112.3
RP11-98C1	2	113.8
RP11-434I13	2	114.4
RP11-17N4	2	116.6
RP11-438O12	2	117.6
RP11-90K23	2	118.5
RP11-498O20	2	119.5
RP11-91G8	2	121.7
RP11-270M20	2	122.2
RP11-67G15	2	123.8
RP11-140B20	2	124.4
RP11-88B6	2	125.5
RP11-81H7	2	125.9
RP11-32C20	2	126.9
RP11-91K13	2	127.1
RP11-89B17	2	128.2
RP11-294I11	2	128.8
AC097499.2	2	129.8
RP11-467A23	2	130.8
RP11-289K3	2	131.8
RP11-81H1	2	132.9
AC010873.12	2	133.8
RP11-119N3	2	133.9
RP11-472M4	2	134.6
RP11-231E19	2	134.9
RP11-91C20	2	136.2
RP11-434H14	2	137.9
AC009957.10	2	138.2
RP11-67J2	2	138.9
RP11-357J9	2	139
RP11-29N17	2	141.8
RP11-90K5	2	143.6
AC018465.7	2	144.9
RP11-375H16	2	145.3
RP11-91A11	2	147.6
RP11-79A11	2	149
RP11-364H22	2	149.6
RP11-185M22	2	150.6
RP11-17E6	2	151.4
RP11-11C17	2	152.4
RP11-44N6	2	153.4
RP11-79B5	2	154.1
RP11-546J1	2	157.1
RP11-91K6	2	158.4
RP11-50J20	2	159.1
RP11-615B17	2	159.3
RP11-79L13	2	161
AC010876	2	161.5
AC092632.1	2	162.1
AC016723.10	2	165.9
RP11-79E23	2	167.2
RP11-91O10	2	167.8
RP11-80D14	2	170
RP11-81F17	2	170.1
RP11-91L3	2	170.8
RP11-79D11	2	171.8
RP11-91L23	2	172.2
RP11-91A9	2	172.3
RP11-79C17	2	172.6
AC013467.8	2	173.4
RP11-12N7	2	174.5
RP11-279N12	2	176.2
RP11-428I14	2	177.1
RP11-88L24	2	178.1

TABLE 2-continued

clone_id	chromosome	linear
RP11-30N9	2	179.4
RP11-131G20	2	179.8
RP11-69G4	2	181.5
RP11-598C21	2	182.4
AC074182.6	2	183
RP11-270G18	2	188.5
RP11-88L20	2	188.6
AC046197	2	189.8
RP11-192M8	2	190.4
RP11-59L22	2	191.1
RP11-30M1	2	193.5
RP11-90C17	2	194.1
RP11-387H5	2	195.4
RP11-89B13	2	195.7
RP11-2C13	2	197
AC020718.6	2	198.3
RP11-91M5	2	200.4
RP11-329O10	2	202.6
RP11-47E6	2	203.5
AC009498.3	2	203.9
RP11-15J24	2	204.4
RP11-89K8	2	205.2
RP11-90D19	2	205.9
RP11-89J16	2	206.8
RP11-13N10	2	207.7
RP11-90O3	2	208.9
RP11-79C24	2	210.5
RP11-300D24	2	211.3
RP11-560C24	2	212.6
RP11-44J16	2	213.6
AC073284.3	2	215.2
RP11-4B6	2	217.2
RP11-146N10	2	218.2
RP11-316O14	2	219.2
AC009310.3	2	219.7
RP11-23G2	2	220.9
AC009231.4	2	221.6
RP11-247E23	2	222.6
RP11-551D18	2	223.4
RP11-79C2	2	223.8
RP11-89F8	2	226.8
RP11-91J17	2	226.8
AC009950	2	227.6
RP11-91C14	2	228
RP11-252C12	2	229.1
RP11-69J7	2	230.4
RP11-71H20	2	231.2
RP11-91N19	2	232.5
RP11-176L22	2	232.7
RP11-79G2	2	234.2
RP11-21K1	2	234.7
RP11-680O16	2	235.7
RP11-155J6	2	236.4
RP11-88P18	2	237.5
RP11-118M12	2	239.8
RP11-89N23	2	240.3
RP11-463B12	2	241
RP11-204C23	3	3
RP11-32F23	3	4.1
RP11-63O1	3	4.8
RP11-91K16	3	6.3
RP11-33E18	3	7.9
RP11-271E2	3	9.2
RP11-21J23	3	10.4
RP11-91K4	3	11.5
RP11-115G3	3	13.3
RP11-105H19	3	13.8
RP11-57D6	3	15.7
RP11-255O19	3	18.3
RP11-80D24	3	19.7
RP11-451A20	3	22
RP11-90I9	3	22.3
RP11-79E6	3	23.7
RP11-89F18	3	25.8

TABLE 2-continued

clone_id	chromosome	linear
RP11-41F5	3	26.1
RP11-245E5	3	26.7
RP11-421F9	3	27.8
RP11-451C4	3	28
AC013500.4	3	29.8
RP11-11L6	3	30.7
RP11-103N21	3	31.8
RP11-56P22	3	35.9
RP11-286G5	3	37.2
RP11-90M23	3	38.6
RP11-90B15	3	40.7
RP11-241P3	3	42.6
RP11-219I21	3	43.1
RP11-24L15	3	44.3
RP11-348P10	3	45.3
RP11-91E8	3	46.4
RP11-425J9	3	47.6
RP11-91M18	3	48
RP11-804H8	3	51
RP11-89F17	3	51.6
RP11-865O5	3	53.6
RP11-124O2	3	54.8
RP11-189K9	3	55
RP11-754F19	3	57.2
RP11-80H18	3	58.2
RP11-79K17	3	59.2
RP11-34D21	3	60.7
RP11-88P20	3	63.2
RP11-108A8	3	64
RP11-89O2	3	64.9
RP11-129B22	3	65
RP11-88H12	3	66.2
RP11-146E16	3	67.9
RP11-89A12	3	68.2
RP11-79C12	3	68.3
RP11-81N13	3	68.3
RP11-444P10	3	70
RP11-90H15	3	71.6
RP11-522N9	3	73.1
RP11-781E19	3	74.8
RP11-89H10	3	76.1
RP11-79O5	3	76.4
RP11-447J13	3	78.2
RP11-79F5	3	80.3
RP11-220O14	3	80.7
AC018918	3	81.5
RP11-208G16	3	86.5
RP11-81P15	3	89.2
RP11-424C9	3	90
RP11-91A15	3	96.4
AC019233.7	3	97.4
RP11-91M15	3	98.4
RP11-449F7	3	100.5
RP11-114I8	3	103.1
AC018352.13	3	103.7
RP11-490H13	3	106.5
RP11-90I19	3	108
RP11-91B3	3	108.7
RP11-71D1	3	113.1
RP11-12P11	3	114.8
RP11-745L2	3	115
RP11-79H17	3	115.2
RP11-5K13	3	116.9
RP11-24O5	3	117.1
RP11-342J15	3	118.3
RP11-373C21	3	119.8
AC027296.12	3	120.3
RP11-91F9	3	120.6
RP11-169N13	3	122
RP11-217N3	3	123.3
RP11-10G15	3	125.6
RP11-79M2	3	126.7
RP11-25L9	3	128.6
RP11-59J16	3	130.5

TABLE 2-continued

clone_id	chromosome	linear
RP11-205A6	3	131.8
RP11-525K18	3	133
RP11-452H12	3	134.1
RP11-446K3	3	137.3
RP11-79L21	3	138.3
RP11-91K8	3	138.9
RP11-91O5	3	140.4
RP11-220J13	3	141.1
RP11-566E10	3	141.8
RP11-197K1	3	142.2
RP11-630C21	3	143.6
RP11-79L9	3	144.6
RP11-548O1	3	144.8
RP11-166D18	3	145.8
RP11-89E16	3	146.2
RP11-372E1	3	148.8
RP11-80H8	3	149
RP11-260J24	3	149.9
RP11-88H10	3	151.7
RP11-229G6	3	155.2
RP11-145F16	3	156.4
RP11-385G14	3	157.2
RP11-362A9	3	158.4
RP11-372M20	3	159.8
RP11-451C20	3	160.7
RP11-286N6	3	162.1
RP11-392A22	3	163.2
RP11-90N21	3	164
RP11-79A14	3	164.1
RP11-91L9	3	164.7
RP11-79M21	3	164.9
RP11-209H21	3	166.5
RP11-203L15	3	167.7
RP11-79G24	3	168.6
RP11-90M7	3	170.1
RP11-79F11	3	171.1
RP11-80L14	3	171.1
RP11-91B7	3	173.3
AC018356.25	3	176.1
RP11-151A21	3	176.4
RP11-172G5	3	177.2
RP11-91A17	3	179.4
RP11-44A1	3	180.2
RP11-89J17	3	180.7
RP11-278A4	3	183
RP11-114M1	3	183.4
RP11-91K9	3	183.7
RP11-89B3	3	185.1
RP11-45I24	3	185.4
RP11-510K16	3	186.2
RP11-275H4	3	186.7
RP11-259I19	3	187.9
RP11-102G2	3	188.4
RP11-63G1	3	189.7
RP11-79K10	3	190.5
RP11-379C23	3	191.6
RP11-88P6	3	192.6
RP11-67E18	3	194.6
RP11-54L9	3	196.1
RP11-88H6	3	197.1
RP11-608P9	3	197.6
RP11-91M9	3	198.2
RP11-326J2	3	200.1
RP11-313F11	3	201.8
RP11-778E2	3	202.9
RP11-338O10	3	204.6
AC018707.5	3	204.9
AC092535.3	4	0.7
RP11-572O17	4	1.1
RP11-262P20	4	1.2
RP11-478C1	4	1.9
RP3-323A24	4	2.8
RP11-520M5	4	4
RP11-808B21	4	4.5

TABLE 2-continued

clone_id	chromosome	linear
RP11-357G3	4	5.3
AC004555.2	4	7.6
RP11-101J14	4	9.3
RP11-17I9	4	10.6
RP11-34C20	4	11.9
RP11-79G9	4	13.4
RP11-81N5	4	14
RP11-89K12	4	14.6
RP11-81L15	4	15.5
RP11-91N13	4	16.8
RP11-206O9	4	17.1
RP11-89H17	4	18.2
RP11-79N22	4	19.4
RP11-11M9	4	20.1
RP11-91B20	4	20.8
RP11-151G21	4	21.9
RP11-238L9	4	22.2
RP11-88B22	4	23.9
RP11-660M5	4	26.9
RP11-239C17	4	28.4
RP11-89I6	4	31.6
RP11-53F2	4	32.1
RP11-363G1	4	32.2
RP11-81H11	4	33.9
RP11-79E3	4	35.8
RP11-81N11	4	36.6
RP11-108H14	4	38.9
RP11-24G16	4	40
RP11-472B18	4	41.5
RP11-138F23	4	42.7
RP11-227F19	4	43.4
RP11-91F19	4	44.4
RP11-90L23	4	45.1
RP11-89N6	4	49.7
RP11-109P3	4	50
AC022904.3	4	52.9
RP11-80L11	4	55.4
AC069068.9	4	56.4
RP11-7J22	4	57.4
RP11-319E12	4	58.3
RP11-89B16	4	59.8
RP11-91C3	4	61
RP11-24I7	4	62.8
RP11-63E13	4	66.5
RP11-89M12	4	68.3
RP11-642E20	4	69
RP11-529K3	4	70.5
RP11-121P15	4	71.3
RP11-89G2	4	71.7
RP11-373J21	4	72.7
RP11-155P6	4	73.8
RP11-88J6	4	74.6
RP11-144I19	4	76.2
RP11-49H14	4	77.5
RP11-79M16	4	78
RP11-17P19	4	78.4
AC021127.8	4	80.5
RP11-110P12	4	81.3
RP11-449B1	4	83
RP11-91J11	4	83.7
RP11-36G19	4	84.5
RP11-91E6	4	86.4
RP11-397E7	4	87.3
RP11-203P12	4	87.5
RP11-17P8	4	88.9
RP11-79M20	4	89.8
RP11-49M7	4	90.7
RP11-451M10	4	91.3
RP11-16I17	4	94.3
RP11-21O14	4	96.8
RP11-369I16	4	98.2
RP11-144B4	4	99.3
RP11-414I7	4	100.8
RP11-91G13	4	103

TABLE 2-continued

clone_id	chromosome	linear
RP11-26E14	4	104.5
RP11-91C2	4	105.2
RP11-88D10	4	107.8
RP11-80H22	4	109.9
RP11-81J9	4	110
RP11-89G6	4	110.3
RP11-144H4	4	111.1
RP11-380D23	4	112.1
RP11-18D18	4	112.9
RP11-89D13	4	113.2
RP11-73K9	4	113.8
RP11-260E23	4	115.2
RP11-362M19	4	116
RP11-778G8	4	118.8
RP11-21I10	4	119.7
RP11-101N17	4	119.9
AC007512.2	4	121.1
RP11-647P12	4	122.4
RP11-100E15	4	123.9
RP11-27C19	4	124.7
RP11-728C8	4	125.2
RP11-79I18	4	126.1
RP11-89D9	4	126.9
RP11-77P11	4	128.4
RP11-11P20	4	129.2
RP11-184M15	4	130.2
RP11-14N24	4	131.4
RP11-80P12	4	132.2
RP11-94J9	4	134.8
RP11-89P23	4	135.7
RP11-81F5	4	136.8
RP11-60A1	4	137.8
AC016487.5	4	138.3
RP11-53C1	4	139.6
AC019343.3	4	141
RP11-5K16	4	141.9
RP11-79E2	4	143
RP11-739G21	4	143.4
RP11-122I3	4	144.7
RP11-89E4	4	145.5
AC032008.2	4	147
RP11-91O3	4	148.1
RP11-56F3	4	149
RP11-24I21	4	150.6
RP11-77F4	4	152.3
RP11-73G16	4	153.3
RP11-119B13	4	154.6
RP11-136D2	4	157.9
RP11-17C4	4	158.7
RP11-89C4	4	159.8
RP11-81P7	4	160.9
AC011101.4	4	162.2
RP11-177L7	4	163.4
RP11-808H17	4	163.6
RP11-79E19	4	166.4
RP11-6F19	4	167
RP11-36G9	4	170
RP11-90E13	4	171.1
RP11-90D5	4	173.2
RP11-110O14	4	174.5
RP11-89D7	4	174.9
RP11-134F18	4	175.6
RP11-122D8	4	177.5
RP11-79K2	4	178
RP11-62B4	4	179
RP11-79G20	4	180.5
RP11-80P4	4	181.8
RP11-244K2	4	182.6
RP11-125M9	4	182.8
RP11-18D7	4	183.9
RP11-90E7	4	184.8
RP11-267E24	4	185.6
RP11-279K24	4	186.8
RP11-597P9	4	187.5

TABLE 2-continued

clone_id	chromosome	linear
RP11-91J3	4	188.5
AC025775.4	5	1.9
RP11-20B3	5	2.7
RP11-89N22	5	3.2
AC010635.5	5	6.2
RP11-58A5	5	7.1
RP11-72C10	5	8.2
RP11-79G1	5	8.6
RP11-145B1	5	9.6
RP11-91M12	5	10.3
RP11-91E7	5	11.1
RP11-91M19	5	12
RP11-88L18	5	13.7
RP11-81P9	5	14.7
RP11-135M13	5	16.4
AC018409.3	5	17.5
RP11-260E18	5	19.4
RP11-91E20	5	21.8
RP11-91L13	5	21.9
RP11-90G17	5	22.9
RP11-5N11	5	26.2
RP11-422J14	5	26.5
RP11-89M18	5	27.5
RP11-81B23	5	28
RP11-79I8	5	30.4
RP11-80D4	5	31.2
AC025447.4	5	32.9
RP11-67N10	5	33.6
RP11-90P7	5	35.8
AC008830.4	5	39.6
RP11-91I22	5	42.6
RP11-79E13	5	44.1
RP11-91M6	5	45.4
RP11-19F12	5	45.6
AC027339.3	5	48.4
RP11-551B22	5	49.1
RP11-17H13	5	52.4
RP11-143O12	5	53.9
AC034244.6	5	54.6
AC016635.8	5	60.2
RP11-19I19	5	61.7
RP11-79C4	5	63.5
RP11-89N5	5	63.5
RP11-79C20	5	65.7
RP11-480H11	5	66
RP11-91C10	5	68.1
RP11-88J2	5	70.1
RP11-91M11	5	71.4
RP11-91E18	5	71.5
RP11-79I10	5	73.9
RP11-90A9	5	78.7
RP11-90M19	5	80.3
RP11-80D2	5	82.6
RP11-275E14	5	83.2
RP11-258M21	5	85
RP11-90J17	5	86.1
AC005406.2	5	89.9
AC104125.1	5	90.3
RP11-88D22	5	94.3
RP11-89C2	5	99.6
RP11-115L24	5	101.1
RP11-277N18	5	103.3
RP11-252I13	5	103.7
RP11-88L16	5	108.1
RP11-89L24	5	110
RP11-91G9	5	110.6
RP11-64F17	5	111.4
RP11-58G19	5	112.4
RP11-81L23	5	113.8
RP11-47L19	5	118.1
RP11-81C5	5	120.5
RP11-79K4	5	121.6
RP11-90A15	5	123
RP11-90G5	5	123.9

TABLE 2-continued

clone_id	chromosome	linear
RP11-265M23	5	124.7
RP11-42M12	5	129
AC004038.1	5	130.2
AC005178.1	5	133.5
RP11-21C10	5	134.5
AC027305.4	5	134.8
CTD-2004C12	5	137.5
RP11-89G4	5	137.9
AC008667.7	5	141.2
RP11-115I4	5	142
RP11-15J20	5	143
RP11-55M16	5	143.1
CTB-60P23	5	144.7
RP11-124B12	5	149
AC011352.4	5	149.8
RP11-89F1	5	151.9
RP11-79I6	5	153.9
RP11-86C20	5	155
RP11-91G17	5	156.3
AC010603	5	158.2
RP11-79I9	5	159.1
RP11-89J5	5	159.9
RP11-90N23	5	161.1
RP11-31B18	5	164.8
CTB-4E7	5	165.7
RP11-134N14	5	166.7
AC010254.5	5	167.1
AC091921.1	5	169.7
RP11-94L2	5	171
RP11-13H20	5	172.6
RP11-90C21	5	173.2
AC011384.3	5	174.5
RP11-14K9	5	175
RP11-15F10	5	175.6
AC011387.4	5	177.7
RP11-626B22	5	182.4
RP1-136B1	6	0.1
AL035696.14	6	0.4
RP11-91F13	6	1.7
RP3-380B8	6	3.7
RP1-80N2	6	4.3
RP11-177C16	6	5.2
RP3-470K1	6	6.2
RP1-103M22	6	7.2
RP3-416J7	6	7.9
RP1-20B11	6	8.3
RP11-79M24	6	9.4
RP11-90P11	6	9.5
RP11-91C13	6	10.5
RP3-398A12	6	10.8
RP11-421M1	6	11.6
RP11-304M10	6	12.7
RP3-441J1	6	13.7
RP1-257A7	6	14.3
RP11-90I11	6	15.4
RP3-365E2	6	15.5
RP1-147M19	6	16.7
RP1-273P12	6	18.9
RP11-90M17	6	19.3
RP1-298J15	6	19.7
RP1-209A6	6	21.3
RP11-91H17	6	22.2
RP3-369A17	6	22.9
RP1-242N11	6	23.8
RP1-130G2	6	25.2
RP1-52M20	6	26.3
RP1-224B21	6	27.8
AL0201917.3	6	28.8
RP5-874C20	6	30.6
RP11-88D2	6	30.8
RP5-974I11	6	31.6
RP3-377H14	6	32.1
RP11-79J17	6	35.2
RP11-79J23	6	37.1

TABLE 2-continued

clone_id	chromosome	linear
RP3-329A5	6	37.5
RP3-524E15	6	38.4
RP1-50J22	6	38.6
RP11-91E11	6	39.7
RP3-460D19	6	40.7
RP11-505E17	6	42.1
RP11-81F7	6	43.9
RP11-79I2	6	44.3
RP5-973N23	6	45.9
RP11-121G20	6	47.1
RP3-449H6	6	47.4
RP1-244F24	6	48.3
RP3-447E21	6	48.9
RP11-90H17	6	49.3
RP1-306F2	6	51.1
RP11-79F13	6	52
RP4-753D5	6	53.7
RP3-357H1	6	54.7
RP11-90K15	6	55.2
RP1-27K12	6	56.3
RP11-7H16	6	56.4
RP11-146B10	6	58.5
RP11-79O24	6	59.2
RP3-496N17	6	60.4
RP1-271N20	6	65.5
AL133459.9	6	66
RP11-448N11	6	66.6
RP11-79F21	6	67.7
RP11-88N6	6	68.1
RP3-442I1	6	68.4
RP5-819L10	6	69.5
RP1-129L7	6	70.1
RP11-80L16	6	70.4
RP1-304O5	6	71.6
RP1-46B1	6	73.3
RP3-376F14	6	74.8
RP1-104A17	6	75.5
RP11-90G9	6	76.4
RP5-1046G13	6	76.9
RP11-374I18	6	77.6
RP11-28P18	6	79
RP1-238D15	6	79.8
RP1-134M13	6	80.5
RP11-343P23	6	81.9
RP11-79L15	6	82.8
RP1-136A11	6	83.4
RP11-217L13	6	83.5
RP1-232L24	6	84.6
RP1-159G19	6	84.9
RP1-279A18	6	85.5
RP5-1046E21	6	86.1
RP11-801I18	6	87.2
AL049699.8	6	88.3
RP4-676J13	6	89.1
RP1-33L1	6	90
RP11-43O2	6	91.5
RP1-102H19	6	92.5
RP3-486L4	6	93.2
RP4-570O12	6	93.8
RP1-131H7	6	94.8
RP1-154G14	6	96
RP3-433F14	6	97.2
RP1-149C7	6	97.9
RP11-538A16	6	98.5
RP11-79F23	6	100
RP1-104O17	6	101.6
RP11-22L21	6	102.6
RP3-453D15	6	103.9
RP11-79G15	6	104.6
RP1-121G13	6	105.8
RP11-79K22	6	106.6
RP11-90O11	6	106.8
RP11-79O12	6	107.1
RP3-514B11	6	108.8

TABLE 2-continued

clone_id	chromosome	linear
RP11-284O5	6	109.8
RP3-454N4	6	110.9
RP3-429G5	6	113.6
RP1-128O3	6	113.7
RP1-70A9	6	115.1
RP1-261K5	6	115.9
RP3-487J7	6	117.1
RP11-506B6	6	117.9
RP11-91B17	6	118.7
RP11-367G18	6	119.4
RP1-124O9	6	120.2
Z95329.1	6	120.5
RP1-136O14	6	122.1
RP1-94G16	6	123.5
RP3-344F17	6	124.2
RP1-193N13	6	125.3
RP11-411H20	6	126
RP1-224E15	6	126.6
RP3-438G17	6	128
RP3-425C14	6	128.7
RP11-80B14	6	129.4
RP3-329N18	6	129.9
RP1-249H1	6	130.1
RP11-138M12	6	131.5
RP1-312L17	6	133.3
RP3-480J14	6	134.1
RP1-86D1	6	134.8
RP1-69D17	6	136.2
RP3-353O9	6	137.7
RP1-215F14	6	138.7
RP11-435E4	6	139.4
RP11-368O13	6	140.4
RP11-557H15	6	141.3
RP1-38C16	6	142.4
RP11-89G8	6	142.6
RP11-91G15	6	143.7
RP3-372K1	6	144.2
RP11-133O15	6	145
RP1-225E12	6	145.9
RP5-899B16	6	147
AL357080.13	6	148
RP11-89A10	6	148.5
RP3-468K18	6	150.9
RP11-43G16	6	152.3
RP11-545I5	6	153
RP1-69B13	6	153.6
RP3-434O8	6	155
RP1-281H8	6	156.6
RP1-12G14	6	156.7
RP11-291C6	6	157.7
RP3-358E10	6	159.9
RP11-535A9	6	160.4
RP1-278N12	6	161.6
RP1-257I9	6	162.7
RP11-91I3	6	164.4
RP11-266C7	6	165.3
RP11-88B24	6	166.4
RP3-393E18	6	166.9
RP3-428L16	6	168.3
RP11-81H13	6	168.4
RP1-119H20	6	169.1
RP1-51J12	6	171
RP11-104N13	6	172.2
RP3-345E4	6	173.5
RP1-167A14	6	174.6
RP1-125N5	6	175.9
RP11-351J23	6	176.7
RP1-182D15	6	177.5
RP1-140C12	6	178.1
AC073957.7	7	0.7
RP11-90J23	7	3.8
RP11-42B7	7	3.9
RP11-2K20	7	4.7
RP11-161C7	7	6.1

TABLE 2-continued

clone_id	chromosome	linear
RP11-79G16	7	7.6
RP11-79O21	7	9.3
RP11-451C12	7	10.9
RP11-89B15	7	15.1
RP11-123E5	7	17.1
RP11-70K3	7	17.8
RP11-91A24	7	19.4
CTB-23M10	7	21.1
RP11-79G17	7	21.5
RP11-79D17	7	22.8
CTB-119H12	7	23.6
AC010677.4	7	27.1
RP11-81F15	7	28
RP11-88B20	7	29
RP11-80J6	7	29.9
RP11-242I4	7	30.5
RP11-90J13	7	32.1
AC018648.5	7	33
RP11-89N17	7	34
RP11-115G23	7	35.4
AC083876.2	7	36.7
RP11-75O22	7	37.5
RP11-115G1	7	39
RP11-64I2	7	40
RP11-112L4	7	40.1
AC005027.2	7	42.3
RP11-100C21	7	43.3
RP11-449D13	7	44.2
RP11-52M17	7	45.2
RP11-109N2	7	46.9
AC073341.9	7	48.1
RP11-11D14	7	48.4
RP11-15L23	7	51.8
RP11-91C9	7	53.2
RP11-90N11	7	54.6
AC073347.3	7	56.5
RP11-90O18	7	61
RP11-45N18	7	61.9
RP11-35P20	7	65.5
AC006319.3	7	66
RP11-41F23	7	67.7
RP11-89D15	7	67.8
RP11-88H20	7	68.5
RP11-114E12	7	69.2
RP11-90B1	7	69.6
RP11-137E8	7	72.5
RP11-89A20	7	74.8
RP11-451M14	7	75.5
RP11-88H22	7	76.8
RP11-60N2	7	78
RP11-91E1	7	78.4
RP11-89L18	7	78.9
AC005064.3	7	80.5
RP11-90N9	7	83.2
RP11-22M18	7	84.7
RP11-88D24	7	85
RP11-46O13	7	87.7
AC000059.1	7	89.6
RP11-90H9	7	91.8
RP11-79O7	7	93.2
RP11-91M13	7	93.8
RP11-10D8	7	99.1
RP11-80P24	7	99.4
RP11-72J24	7	105
RP11-80L6	7	106.9
RP11-89M2	7	107.6
RP11-77E2	7	108.5
AC002487.1	7	109.2
RP11-12L9	7	112.3
CTB-22K14	7	113.2
RP11-90N13	7	113.4
RP11-88J20	7	114.3
RP11-89O20	7	115.1
RP11-78C11	7	116.5

TABLE 2-continued

clone_id	chromosome	linear
RP11-110C11	7	117.5
RP11-51M22	7	117.9
CTB-133K23	7	119.2
RP11-140O21	7	122.6
RP11-3L10	7	123
RP11-112P4	7	123.6
RP11-81B7	7	129.3
RP11-80N8	7	129.9
RP11-66F23	7	131.3
RP11-35B6	7	131.9
AC007938.1	7	132.8
RP11-79E7	7	136.5
RP11-140I14	7	137.7
RP11-88K4	7	139.5
RP11-80J18	7	140.1
RP11-137O4	7	141
AC083883.6	7	141.6
AC004853.1	7	147.4
RP11-79M8	7	148.1
RP11-79K23	7	151
RP11-89P11	7	151.3
RP11-91P1	7	152.3
RP11-43L19	7	155.6
RP11-79K9	7	157.4
RP11-80J22	7	157.8
RP11-58F7	7	160.8
RP11-91J19	8	0.2
AF188030.3	8	1.5
RP11-11P7	8	2.7
RP11-121F7	8	3.3
RP11-45M12	8	4
RP11-89I12	8	4.6
RP11-1K11	8	4.8
RP11-90J21	8	7.4
RP11-79E11	8	7.8
RP11-79I19	8	9.3
RP11-252K12	8	11.5
RP11-80B8	8	11.6
RP11-90O17	8	12.9
RP11-23H1	8	15.5
AC010656.7	8	16
RP11-90I3	8	17.1
RP11-89M16	8	17.8
RP11-51C1	8	20
RP11-89O4	8	21.5
RP11-110I16	8	22.3
RP11-89M8	8	23.6
RP11-76B12	8	25.7
RP11-90M13	8	26.7
RP11-70L1	8	27.7
RP11-138J2	8	28.4
RP11-116F9	8	29.3
RP11-662B19	8	29.8
RP11-279J6	8	30.9
RP11-173D10	8	31.9
RP11-139G9	8	32.2
RP11-57I3	8	33.7
RP11-2I13	8	34.6
RP11-91P13	8	34.9
RP11-79H13	8	36.1
RP11-237M13	8	37.4
RP11-89M20	8	37.8
RP11-113G10	8	39.4
RP11-90P5	8	39.5
RP11-262I23	8	40.5
AC015649.6	8	42.2
RP11-89A4	8	43.3
RP11-12L15	8	46
RP11-113H14	8	47.9
RP11-10H3	8	49
RP11-11C20	8	51.6
AC090814.2	8	52.7
RP11-105K5	8	53.4
RP11-767C6	8	54

TABLE 2-continued

clone_id	chromosome	linear
RP11-99M6	8	54.5
RP11-172D2	8	54.7
AC046176.7	8	55.9
RP11-16M8	8	56.2
AC021393.5	8	58.4
RP11-91I20	8	58.8
RP11-24L2	8	60.2
AC019357.5	8	61.5
AC023533.6	8	62.5
RP11-89A16	8	63.2
AC087768.3	8	64.3
RP11-79G22	8	67.5
RP11-11K9	8	69.9
RP11-114M5	8	71.2
RP11-148M7	8	73.2
RP11-359N14	8	73.7
RP11-117N14	8	74.3
RP11-88N8	8	75.1
RP11-65J24	8	76.3
RP11-89H1	8	77.4
RP11-80F24	8	78.3
RP11-90B7	8	79.1
RP11-15K1	8	79.9
RP11-89I14	8	80.5
RP11-93E11	8	81.6
RP11-257P3	8	82.2
RP11-90F1	8	85.5
RP11-90O15	8	85.7
RP11-96G1	8	86.5
RP11-91K2	8	87
RP11-80P18	8	87.7
RP11-90G19	8	88.6
RP11-88J22	8	89.6
RP11-88J8	8	91
RP11-89F14	8	91.9
RP11-27I15	8	94.1
RP11-90N3	8	95.2
RP11-80P10	8	96.1
RP11-90D11	8	98.8
RP11-30J11	8	100
RP11-91O11	8	102.2
RP11-79F7	8	107
RP11-79J9	8	108
RP11-81B5	8	109.2
RP11-80D8	8	109.8
RP11-79C21	8	109.9
RP11-91K1	8	110.8
RP11-79C18	8	111.2
RP11-3A12	8	113.6
RP11-89I16	8	115.3
RP11-30P9	8	119
RP11-89P19	8	119.5
RP11-88J18	8	121.8
AC037486.2	8	122.6
RP11-89P9	8	125.8
RP11-91M23	8	127.3
RP11-65D17	8	127.7
RP11-89K10	8	128.1
RP11-79E8	8	131.1
RP11-94M13	8	133.3
RP11-184M21	8	134.7
AF186190.3	8	135.1
RP11-45B19	8	135.9
RP11-21H16	8	136.2
RP11-17M8	8	137.9
RP11-449D3	8	138.2
RP11-489O18	8	139.1
RP11-13A18	8	141.7
RP11-642A1	8	141.7
RP11-349C2	8	144.7
RP5-1124C13	8	145.2
RP11-31M2	9	0.7
AL136231.12	9	1.2
RP11-140C18	9	1.9

TABLE 2-continued

clone_id	chromosome	linear
RP11-207C16	9	2.4
RP11-79M14	9	3
RP11-79K3	9	4.3
RP11-376O21	9	5
RP11-91E3	9	6.5
RP11-32D4	9	8.5
RP11-130C19	9	10.6
RP11-88P16	9	11.6
RP11-125B21	9	12.3
RP11-32F11	9	13.1
RP11-328C23	9	14.1
RP11-382H24	9	14.6
RP11-79B9	9	15.7
RP11-490C5	9	16.8
RP11-109M15	9	17.8
RP11-340N12	9	18.9
RP11-163F8	9	19.3
RP11-81B11	9	20.5
RP11-87O1	9	20.7
RP11-399M15	9	21.1
RP11-89C6	9	21.7
RP11-408N14	9	24.2
AL391117.7	9	24.9
RP11-332M12	9	26.9
AL139235	9	27.1
RP11-381K22	9	28.4
RP11-57P14	9	29.2
RP11-64M21	9	30.1
RP11-159L16	9	31.5
RP11-29M23	9	32.1
RP11-630H9	9	32.6
RP11-70F16	9	33.3
RP11-52I10	9	34
RP11-79E21	9	34.4
RP11-54K16	9	35.3
RP11-395N21	9	37.6
RP11-327L3	9	38.2
RP11-12P15	9	39
RP11-203L2	9	59.2
RP11-16N10	9	59.7
RP11-129O15	9	60.8
RP11-89K20	9	61.2
RP11-63P12	9	62.8
RP11-54O21	9	63.6
RP11-174B4	9	65.5
RP11-323A7	9	66.5
RP11-158I5	9	67.5
AL445684	9	69.1
RP11-79G7	9	70.7
RP11-91M2	9	71.6
RP11-79J13	9	72.7
RP11-22C13	9	73.7
RP11-80F16	9	73.7
RP11-80H20	9	74.9
RP11-65C15	9	76.9
RP11-79I21	9	77.7
RP11-65B23	9	78.7
RP11-88J16	9	79.6
RP11-406A20	9	80.4
RP11-563G12	9	81
RP11-95G21	9	81.5
RP11-89K14	9	82.1
RP11-62C3	9	83.4
RP11-19J3	9	83.8
RP11-30L4	9	84.8
RP11-173G21	9	87.1
RP11-89L5	9	88
RP11-80J10	9	88.2
RP11-79A20	9	88.3
RP11-23B15	9	89.2
RP11-69F21	9	90.7
AL356798.17	9	91.9
RP11-80H12	9	92.7
RP11-91L19	9	94.2

TABLE 2-continued

clone_id	chromosome	linear
RP11-318L4	9	95.4
RP11-217O12	9	96.4
RP11-80N14	9	96.9
RP11-80F13	9	99.6
RP11-505C13	9	100.4
RP11-115J22	9	101.3
RP11-81P13	9	102.6
RP11-104M22	9	103.2
RP11-4O1	9	104.4
RP11-408O19	9	105.4
RP11-9H12	9	105.7
RP11-88F16	9	107.5
RP11-45A16	9	109
RP11-451E16	9	111
RP11-98E22	9	111.5
RP11-57K1	9	112.4
RP11-342H3	9	114
RP11-297L11	9	114.7
RP11-74E13	9	115.7
RP11-142K22	9	115.8
RP11-116C10	9	117.2
RP11-91G7	9	117.9
RP11-282P20	9	118.8
RP11-1M19	9	119.8
RP11-339B21	9	121.1
RP11-98H23	9	121.8
RP11-17O4	9	122.5
RP11-89P10	9	123.4
RP11-81P5	9	125.3
RP11-326L24	9	126
RP11-153P4	9	127.1
AL354671.10	9	127.7
RP11-92B21	9	128.5
RP11-145E17	9	129.3
RP11-100C15	9	129.8
RP11-417A4	9	131.3
AL590627.18	9	132.2
RP11-10D13	10	0.2
RP11-164C1	10	0.7
RP11-809C18	10	0.7
RP11-38M7	10	0.9
RP11-90D7	10	1
RP11-89B19	10	1.2
RP11-74N14	10	1.7
RP11-80D10	10	2.6
RP11-118K6	10	3.1
RP11-89J3	10	4.5
RP11-90M21	10	7
RP11-79C22	10	7.6
RP11-42I17	10	8.6
RP11-91K20	10	8.8
AL136319.8	10	11.2
RP11-89C21	10	12.1
RP11-796C22	10	13.5
RP11-24J20	10	13.8
AL157392.11	10	14.2
RP11-22K18	10	15.1
RP11-271M1	10	15.7
RP11-149I8	10	16.3
RP11-394I23	10	16.7
RP11-337F21	10	17.8
RP11-576H16	10	18.8
RP11-91D9	10	19.3
RP11-60J16	10	20.5
RP11-108B14	10	22.6
RP11-89J6	10	23.4
RP11-90F7	10	23.6
RP11-176P2	10	24.9
RP11-80K21	10	26
RP11-79D7	10	27.5
RP11-91A23	10	28.7
RP11-89I20	10	29.4
RP11-89D1	10	30
RP11-15H10	10	30.6

TABLE 2-continued

clone_id	chromosome	linear
RP11-125C10	10	33.1
RP11-33I16	10	33.4
RP11-79K19	10	34.5
RP11-174P15	10	35.9
RP11-365P10	10	37.1
RP11-155G16	10	37.3
RP11-393J16	10	38.4
RP11-109N22	10	39.4
RP11-22B24	10	41
RP11-80J20	10	41.2
RP11-48O11	10	43.9
RP11-20J15	10	44.6
RP11-42B19	10	47.4
AL390716.26	10	49.1
RP11-71N21	10	49.7
RP11-27P22	10	50.3
RP11-92I18	10	51.4
RP11-75M12	10	52.3
RP11-133C15	10	53
RP11-319F12	10	53.9
RP11-449J3	10	55.1
RP11-394D15	10	55.5
RP11-88B18	10	56.6
RP11-373P23	10	59
RP11-79A2	10	61.1
RP11-91H19	10	62.3
RP11-166B18	10	63.4
RP11-267O2	10	64.3
RP11-90E17	10	65.5
RP11-351O1	10	66.5
RP11-428G2	10	68.4
RP11-344A5	10	70.2
RP11-474D14	10	71.2
RP11-86K9	10	71.9
RP11-135E4	10	72.3
RP11-6P16	10	73
RP11-52K17	10	73.4
RP11-91A1	10	74.2
RP11-472K8	10	75.8
RP11-354E23	10	76.9
RP11-390A15	10	78
RP11-90D9	10	79
RP11-89A18	10	79.3
RP11-399K21	10	79.8
RP11-79M9	10	80.8
RP11-19C18	10	81.8
RP11-157J13	10	82.8
RP11-90J7	10	83.5
RP11-93O23	10	85.4
RP11-175M21	10	86.4
RP11-315E23	10	87.1
RP11-185K11	10	87.8
RP11-124L5	10	88.9
RP11-90O7	10	90.3
RP11-52G13	10	91.7
RP11-57C13	10	92.2
RP11-79A15	10	92.7
RP11-129G17	10	93.3
AL157394.14	10	94
RP11-248C1	10	94.9
RP11-152G7	10	96.5
AC079844.3	10	96.6
RP11-366I13	10	97.8
RP11-91M16	10	99.7
RP11-80J24	10	99.8
RP11-90J1	10	100.1
RP11-79M5	10	101.1
RP11-90O1	10	102
RP11-123G19	10	103.4
CTD-2022D20	10	104.6
RP11-483F11	10	105.8
RP11-316M21	10	106.3
RP11-108L7	10	107.2
RP11-68M5	10	107.9

TABLE 2-continued

clone_id	chromosome	linear
RP11-89G15	10	108.5
RP11-416N2	10	110.3
RP11-541N10	10	110.5
RP11-202C2	10	111.8
RP11-89G20	10	112.8
RP11-432B10	10	114.1
RP11-626C11	10	115.1
RP11-90K19	10	115.9
RP11-469M11	10	117.3
RP11-271I13	10	118
RP11-431P18	10	119.9
RP11-89C18	10	120.2
RP11-106N20	10	121.5
RP11-89H7	10	123
RP11-96N16	10	124.7
CTB-54O2	10	125.6
RP11-140G2	10	126.2
RP11-354M20	10	126.7
RP11-51G15	10	127.6
RP11-79M19	10	128
RP11-140B17	10	129
RP11-95I16	10	129.8
RP11-500G22	10	130.9
RP11-101I20	10	131.9
RP11-8O10	10	133.1
RP11-16P8	10	133.9
RP11-42K2	10	135.3
RP11-88B12	10	135.7
RP11-48A2	10	135.9
RP11-90O13	10	137.6
RP11-122K13	10	138.1
RP11-408L20	10	139.2
RP11-142I8	10	139.6
AL392043.10	10	140.6
RP11-288G11	10	141.2
RP11-90B19	10	141.4
RP11-108K14	10	141.8
RP11-371C18	11	1.5
RP11-89O6	11	5.8
RP11-21N2	11	7
RP11-79E12	11	9.4
RP11-170F20	11	9.9
RP11-206L19	11	10.9
RP11-98J9	11	12.5
RP11-21L19	11	13.1
RP11-7O20	11	13.8
RP11-89P13	11	14.6
RP11-166E15	11	16
RP11-108J18	11	16.9
RP11-81D23	11	17.2
RP11-80B10	11	18.3
RP11-11A11	11	19
AC016904.4	11	21.4
AC009638.4	11	24.4
RP11-16H3	11	26
RP11-79M22	11	26.8
RP11-79E9	11	29.1
RP5-859D17	11	29.6
RP1-296L11	11	31
AC027548	11	31.8
RP1-187A11	11	33.2
RP11-90F13	11	33.9
RP1-22J9	11	34.1
RP11-91G22	11	35.6
AC026970.4	11	36.1
RP11-72A10	11	36.6
RP11-219O3	11	37.2
RP11-36H11	11	37.9
RP11-89G12	11	39.3
AC013488.6	11	40.9
RP11-220C23	11	41.4
RP11-150D18	11	42.4
RP11-79O11	11	44
RP11-12C11	11	45.6

TABLE 2-continued

clone_id	chromosome	linear
AP002509.1	11	48.3
RP11-79A4	11	48.6
RP11-56E13	11	51.5
RP11-77M17	11	53.9
RP11-135H8	11	54.6
AC090309.4	11	57.6
RP11-205I14	11	59.1
RP11-729B4	11	59.4
RP11-5F17	11	61
RP11-49D19	11	62.4
RP11-15L8	11	64.3
RP11-607L20	11	64.4
RP11-203N8	11	67.7
AP000405.3	11	68
RP11-20K4	11	68.8
RP11-730K20	11	69.7
RP11-80B24	11	71.2
RP11-8D13	11	71.4
RP11-44J5	11	72.7
RP11-548G17	11	73.6
RP11-115O9	11	74.5
RP11-168B13	11	75.6
RP11-102M18	11	77.4
RP11-91P18	11	78.2
RP11-483P13	11	78.6
AP002343.1	11	79.3
RP11-79B7	11	80.2
RP11-7H7	11	81
AP001557.3	11	82
RP11-91A3	11	82.9
RP11-1E8	11	84.7
RP11-90K17	11	86.5
RP11-89M14	11	87.2
RP11-19P3	11	87.8
RP11-80P16	11	88.7
RP11-80F20	11	89.4
RP11-876F8	11	91.2
RP11-30C9	11	92.7
RP11-372E19	11	94.7
RP11-163O18	11	96.6
RP11-91O4	11	96.9
RP11-16K5	11	99.1
RP11-267L1	11	101.3
RP11-775E2	11	103.8
RP11-88H18	11	106.4
RP11-33F6	11	106.6
RP11-179B7	11	108.1
RP11-51M23	11	108.6
RP11-648J7	11	109.9
AP003057.1	11	110.9
RP11-56J3	11	112.4
RP11-209E9	11	112.6
RP11-2F21	11	114.1
RP11-89O8	11	114.4
RP11-163A13	11	116.1
RP11-79I17	11	117.6
AP003463.1	11	119.5
RP11-356E17	11	121.2
RP11-35P15	11	122.2
RP11-45N4	11	123.2
RP11-112I9	11	123.7
RP11-62A14	11	124.6
RP11-89H13	11	125.6
RP11-89P5	11	126.2
RP11-344F5	11	127.5
RP11-164B14	11	128.1
RP11-87O12	11	129.2
RP11-11C15	11	129.4
RP11-164A10	11	130.2
RP11-10N17	11	131.2
RP11-50B3	11	132.4
RP11-20M1	11	132.8
RP11-41K5	11	133.2
RP11-112M22	11	134.7

TABLE 2-continued

clone_id	chromosome	linear
AP003482.1	11	136
AC023429	11	136.9
RP11-354O3	11	137.6
RP11-77C9	11	138.6
RP11-17M17	11	139.6
AP000903.5	11	139.7
RP11-27H17	11	140.9
RP11-469N6	11	141.4
RP11-598F7	12	0.1
RP11-283I3	12	0.2
RP11-359B12	12	1
RP11-79K20	12	1
RP11-543P15	12	3.1
RP11-88D16	12	3.3
RP11-74M9	12	4.2
RP11-388F6	12	4.4
RP11-91B13	12	4.6
RP11-319E16	12	5.2
RP11-451H11	12	5.9
RP11-433J6	12	6.7
RP11-277E18	12	8.3
RP11-13C13	12	10.2
RP11-144O23	12	11.1
RP11-434C1	12	12
RP11-4N23	12	13.4
RP11-59H1	12	13.8
RP11-96K24	12	14.5
RP11-502N13	12	15
RP11-91B19	12	16.3
RP11-1018J8	12	17.2
AC087311.22	12	17.7
RP11-871F6	12	18.7
RP11-489N6	12	20.1
RP11-206D16	12	21.3
RP11-956A19	12	22.7
RP11-460N10	12	23.4
RP11-12D15	12	24.7
RP11-80N2	12	25
RP11-729I10	12	26.1
RP11-90K13	12	28.3
RP11-89L4	12	29.3
RP11-64J22	12	30.1
RP11-1060J15	12	31.7
RP11-780A5	12	34
RP11-100P18	12	34.3
AC011324.22	12	35.6
RP11-56J24	12	36.6
RP11-152M7	12	40.4
RP11-91K15	12	42.3
RP11-90I21	12	44.4
RP11-624G19	12	45.6
RP11-490D11	12	46.7
RP11-139E19	12	46.9
RP11-79K1	12	49.1
RP11-89H19	12	49.5
RP11-25K5	12	51.5
RP11-91L17	12	53
RP11-79O1	12	53.9
RP11-97N16	12	55.1
RP11-101H10	12	55.8
RP11-972K6	12	56.5
RP11-681G7	12	57.2
RP11-548L8	12	57.9
RP11-183H16	12	58.9
RP11-91I15	12	59.3
RP11-799O6	12	60.1
RP11-39G24	12	60.8
RP11-90P21	12	62.9
RP11-35G5	12	63.4
RP11-80D18	12	64.2
RP11-88F24	12	64.2
RP11-88F18	12	64.4
RP11-91H3	12	64.5
RP11-631N16	12	65.2

TABLE 2-continued

clone_id	chromosome	linear
RP11-196H14	12	66.2
RP11-1022B3	12	66.4
AC025603.1	12	68.8
RP11-596J18	12	69.9
RP11-91K23	12	71
RP11-90G3	12	73.7
RP11-89P15	12	75.3
RP11-89M22	12	75.9
RP11-92P22	12	77.2
RP11-81H3	12	78.4
RP11-96F19	12	81
RP11-90C1	12	82.4
RP11-530C5	12	83.8
RP11-230I13	12	85.3
RP11-362A1	12	86.1
RP11-79B17	12	90.8
RP11-88N10	12	91.4
RP11-900F13	12	92.8
AC083808.9	12	93.8
RP11-89F16	12	94.9
RP11-141N1	12	95.8
AC073655.26	12	97.5
RP11-282G15	12	98.4
AC069263.8	12	99.5
RP11-510I5	12	100.5
RP11-79K8	12	102
RP11-81D15	12	102.3
RP11-90E9	12	102.8
RP11-91M8	12	107.4
RP11-443B14	12	109.4
RP11-91M22	12	109.6
RP11-110L13	12	111.2
RP11-90N16	12	112
RP11-81H23	12	112.4
RP11-951I11	12	113.5
RP11-91I24	12	114.3
AC007570.23	12	115.3
RP11-426H24	12	117.4
RP11-90D13	12	118
RP11-90F3	12	118.2
RP11-100B17	12	119
RP11-91M21	12	120.4
RP11-119J23	12	121.2
RP11-101P14	12	122.5
RP11-110J12	12	124
RP11-3L23	12	125.1
RP11-665J20	12	127.3
RP11-87C12	12	128.7
RP11-512M8	12	129.1
RP11-486O12	12	130.9
RP11-526P6	12	135.5
RP11-91B1	12	136.2
RP11-81G12	12	137.7
RP11-119J21	12	138.1
RP11-89F23	12	138.5
AC048343.14	12	146.5
RP11-408E5	13	17.3
RP11-110K18	13	18.1
RP11-26D3	13	19
RP11-347L8	13	20.2
RP11-316G23	13	20.6
RP11-300N13	13	22.9
RP11-90M15	13	23.6
RP11-111G7	13	24.2
RP11-91C24	13	25.4
RP11-89J10	13	25.9
RP11-35M5	13	26.8
RP11-90M5	13	28.6
RP11-63C16	13	29.5
RP11-367C11	13	30.3
CTD-2037D17	13	31.4
RP11-141M1	13	32.4
RP11-87G1	13	32.5
RP11-269G10	13	33.5

TABLE 2-continued

clone_id	chromosome	linear
RP11-90F5	13	33.9
RP11-91K18	13	35.4
RP11-495J3	13	36.4
RP11-186J16	13	38.6
RP11-83P2	13	40.1
RP11-13I8	13	41.3
RP11-117I13	13	42
RP11-160G19	13	43.2
RP11-71C5	13	43.7
RP11-80H2	13	45.4
RP11-457D13	13	46.2
RP11-480G1	13	47.6
RP11-189B4	13	48.2
RP11-94N9	13	49
RP11-90K7	13	50.5
RP11-185C18	13	51.3
RP11-91J7	13	52.3
RP11-456B18	13	54.7
RP11-100C24	13	56.8
RP11-81D19	13	57.5
RP11-142D16	13	59.1
RP11-218B22	13	59.5
RP11-282D7	13	63.2
RP11-91F3	13	63.7
RP11-37I8	13	64.6
RP11-23B16	13	66.6
AL138958.18	13	68.1
RP11-1G3	13	69.2
RP11-14B2	13	70.3
RP11-81D9	13	71.4
RP11-79I4	13	72
RP11-132L12	13	73.3
RP11-29G8	13	73.9
RP11-138D23	13	74.9
RP11-298H15	13	75.8
AL359257.8	13	77.2
RP11-318G21	13	78.2
RP11-25J23	13	79.9
RP11-80N10	13	81.2
RP11-89A14	13	83.4
RP11-118K20	13	84.7
RP11-29C8	13	86.1
RP11-30L8	13	86.6
RP11-753M10	13	87.5
RP11-29P20	13	88.1
RP11-27D9	13	89.2
RP11-114G1	13	89.9
RP11-79H7	13	90.8
RP11-51B13	13	91.6
RP11-121J7	13	91.9
RP11-165N12	13	92.9
RP11-80B16	13	94.2
RP11-210E23	13	95
RP11-74A12	13	95.6
RP11-79A16	13	96.6
RP11-83D23	13	97
RP11-122A8	13	99.8
RP11-366N24	13	100.4
RP11-151A6	13	101.2
RP11-90C11	13	101.8
AL391122.9	13	102.5
RP11-36L18	13	103.6
RP11-202O6	13	104.5
RP11-100K21	13	106.1
RP11-25E13	13	107.2
RP11-207D10	13	107.7
AL445649.15	13	108.5
RP11-330C15	13	109.4
RP11-107H21	13	110
RP11-90L1	13	111.5
RP11-91C11	13	111.8
RP11-474D23	13	112.4
RP11-75F3	13	113
RP11-98F14	13	114.5

TABLE 2-continued

clone_id	chromosome	linear
RP11-245B11	13	114.8
RP11-391H12	13	117.7
RP11-98N22	14	17
RP11-89F2	14	17.4
RP11-71E6	14	18.5
RP11-566I2	14	18.6
RP11-65O3	14	20
RP11-81F9	14	20.3
RP11-89K22	14	22.2
RP11-529E4	14	25.5
RP11-125A5	14	26.4
RP11-369O9	14	27
RP11-91K19	14	29
RP11-91C17	14	29.4
RP11-54H22	14	29.9
RP11-557O15	14	30.5
RP11-26M6	14	32.2
RP11-465B6	14	33.4
RP11-88D14	14	34.8
RP11-91H1	14	35.3
RP11-305B23	14	36.4
RP11-88N14	14	37.8
RP11-89D19	14	38.6
RP11-89H24	14	40.5
RP11-435L2	14	41.2
RP11-453F20	14	43.1
RP11-91J1	14	43.6
RP11-52O23	14	45.8
RP11-94K16	14	46.7
RP11-90K14	14	47.7
RP11-368A1	14	48.9
RP11-262M8	14	50.4
RP11-12P7	14	51.8
RP11-172G1	14	53.2
AL359234.4	14	54.6
RP11-571J17	14	56.1
RP11-2L22	14	57.3
RP11-79M1	14	57.8
RP11-471N20	14	58.9
RP11-79I3	14	59.9
RP11-445J13	14	61.6
RP11-44K16	14	62.7
RP11-63G22	14	63.1
RP11-156E22	14	65.7
RP11-79B13	14	66.6
AL160191.3	14	68.4
CTD-3014H8	14	69.1
RP11-325N20	14	70.8
RP11-89B22	14	71.5
RP11-382O4	14	73.1
CTD-2317F5	14	74.2
RP11-81O20	14	74.9
RP11-463C8	14	75.9
RP11-63D17	14	76.7
RP11-232C2	14	77.5
RP11-80L10	14	78.8
RP11-114N19	14	79.7
AL133279.7	14	87.1
RP11-79J20	14	88.3
RP11-99C24	14	89.4
RP11-90H21	14	90.4
RP11-90P19	14	90.4
RP11-28G16	14	91.3
RP11-374H13	14	92.1
RP11-160P21	14	93.4
RP11-80F23	14	95.1
RP11-88L4	14	98.1
RP11-431B1	14	98.4
RP11-89J8	14	99.3
RP11-90G22	14	100
RP11-365N19	14	102.7
RP11-454M12	14	102.8
RP11-73M18	14	103.6
RP11-894P9	14	103.6

TABLE 2-continued

clone_id	chromosome	linear
AL049840.8	14	104
RP11-80H14	15	17.1
AC090983.2	15	21.1
RP11-339C21	15	21.8
AC079090.3	15	23.9
AC021360.4	15	24.9
RP11-420B6	15	26
RP11-303I17	15	26.7
AC011938.4	15	28.4
RP11-81N9	15	28.7
RP11-194H7	15	29.4
RP11-462A2	15	30.3
RP11-79A5	15	33
RP11-62L9	15	34.3
RP11-521C20	15	35.1
CTD-2339L15	15	35.7
RP11-328J12	15	36.4
RP11-79O13	15	38.4
RP11-88J10	15	38.7
RP11-329C22	15	40.3
RP11-88D20	15	40.9
RP11-81G13	15	42.2
AC066615	15	42.8
RP11-89O12	15	43.2
RP11-154J22	15	44
RP11-295H24	15	45
RP11-416K5	15	45.9
RP11-105D1	15	46.8
RP11-313P18	15	47.5
RP11-23N2	15	48.4
RP11-316P21	15	48.8
RP11-390M11	15	50.2
RP11-548M13	15	51.2
RP11-80N16	15	51.7
RP11-139H15	15	52.7
RP11-79C5	15	53.3
CTD-2330J20	15	54.3
CTD-2280O8	15	55
RP11-79J15	15	55.4
RP11-90A19	15	57.2
RP11-89A6	15	59.2
RP11-53H4	15	61.3
RP11-70A7	15	62.6
RP11-54P3	15	62.8
RP11-85E15	15	63.8
AC048383	15	66.2
RP11-101C13	15	66.5
RP11-64K10	15	68
RP11-368G21	15	68.3
RP11-500O23	15	69.3
AC023300.6	15	71.1
RP11-79J21	15	73.1
RP11-338C8	15	74.2
RP11-10K12	15	74.9
AC015970.4	15	75.5
RP11-81A1	15	76.3
RP11-558F16	15	77.8
AC011441.4	15	78.2
RP11-152F13	15	78.7
RP11-81L17	15	80.2
RP11-90B9	15	80.7
RP11-91O13	15	80.9
RP11-296P8	15	82.5
RP11-80J8	15	84.1
RP11-91E10	15	85.2
RP11-533L13	15	85.7
AC013787.9	15	86.9
RP11-360F18	15	88.2
RP11-79A7	15	89.4
RP11-369O17	15	90.2
RP11-79C10	15	93
RP11-337N12	15	93.4
RP11-120N1	15	94.7
RP11-80F4	15	95.4

TABLE 2-continued

clone_id	chromosome	linear
RP11-397C10	15	96
RP11-90E5	15	97.3
RP11-14C10	15	98.5
RP11-344L6	16	0.2
RP11-334D3	16	1.3
RP11-417B20	16	1.8
RP11-433P17	16	3.1
RP11-95P2	16	5.1
RP11-89M4	16	5.6
RP11-24M13	16	6.8
RP11-349I11	16	7.5
RP11-79M18	16	8.4
RP11-475D10	16	9.7
RP11-89D3	16	11.3
RP11-490O6	16	12.2
AC007216.2	16	12.6
RP11-165M1	16	13
RP11-81L19	16	15.5
RP11-91M7	16	16.5
RP11-396B14	16	18.1
RP11-81F1	16	18.2
RP11-79I15	16	19.2
RP11-109D4	16	19.6
RP11-141E3	16	22
RP11-450G5	16	22.7
RP11-146J7	16	24.3
RP11-79F19	16	25.1
RP11-167K14	16	26.5
RP11-488I20	16	28.2
CTA-670B5	16	28.4
RP11-85E7	16	30.8
RP11-499D5	16	32.8
RP11-80F22	16	43.2
RP11-79M6	16	44.8
RP11-89O14	16	46.4
RP11-474B12	16	47.4
RP11-1103K14	16	48
RP11-303G21	16	48.8
RP11-98C8	16	49.3
RP11-305A7	16	50
RP11-147B17	16	51
RP11-424K7	16	51.6
RP11-142G1	16	52.7
RP11-79E10	16	53.1
RP11-466N18	16	54
RP11-81D3	16	55
RP11-212I21	16	55.9
RP11-250E14	16	58.8
RP11-79E15	16	59.9
RP11-11E14	16	60.2
RP11-246M14	16	62.4
RP11-89G14	16	63
RP11-3I14	16	64.2
RP11-154N7	16	68.2
RP11-5A19	16	69
RP11-553M22	16	69.8
RP11-89K4	16	73.1
RP11-58M3	16	74.4
RP11-90L19	16	75
AC009054.6	16	78.1
RP11-12H11	16	79.9
RP11-91O9	16	80.8
RP11-118F19	16	85.2
RP11-90J5	16	86.4
RP11-80H6	16	88.4
RP11-309G16	16	89.3
RP11-443M9	16	89.6
RP11-7D23	16	92.1
RP11-79A1	16	92.2
RP4-597G12	16	93.2
AC027455.12	17	0.4
RP11-91C8	17	0.6
RP11-356I18	17	0.7
RP11-26N16	17	0.9

TABLE 2-continued

clone_id	chromosome	linear
RP5-1029F21	17	1.21
RP11-4F24	17	1.8
RP11-380H7	17	2.2
RP11-545O6	17	4.3
RP11-459C13	17	4.4
RP11-457I18	17	5.6
CTB-44J6	17	6.7
RP11-89D11	17	8.9
RP11-405P10	17	9.6
CTB-41I6	17	11.1
RP11-383G9	17	11.7
RP11-385G5	17	14.2
RP11-90G21	17	15.6
RP11-89F21	17	16
RP11-78J16	17	16.9
RP11-89K6	17	17.9
RP11-746E8	17	18.5
RP11-404D6	17	19.3
RP11-79O4	17	24.8
RP11-363P3	17	25
RP11-88B16	17	29.1
RP11-73F15	17	30
RP11-79O9	17	31.7
RP11-79K15	17	32.9
RP11-521P1	17	33.4
RP11-58O8	17	34.9
RP11-81D5	17	39
RP11-19G24	17	39.4
RP11-513C18	17	40.4
RP11-89A22	17	40.8
RP11-29C11	17	41.6
AC016889.11	17	42.7
RP11-266I24	17	43
RP11-436J4	17	44.1
RP11-510P20	17	46.5
RP11-79O18	17	46.9
RP11-110H20	17	49.4
RP11-81D7	17	50.3
CTB-43I4	17	53.2
RP11-42M14	17	54.1
RP11-524I12	17	57.2
RP11-506H21	17	59.7
RP11-481M4	17	61.1
AC040904.2	17	61.9
RP11-561K8	17	63.7
RP11-89H15	17	65.8
RP11-52B5	17	66.9
RP11-89L7	17	68
RP11-387O17	17	69.6
RP11-79K13	17	70.1
RP11-300G13	17	71.2
RP11-90L11	17	71.7
AC087301.3	17	73
RP11-65C22	17	75.4
RP11-91M1	17	75.7
RP11-91O17	17	75.7
RP11-76G4	17	76.7
RP11-89B11	17	77.5
RP11-61B11	17	77.9
RP11-165J13	17	80.9
RP11-46E14	17	81.4
RP11-55N14	18	4.3
RP11-80L18	18	5.7
RP11-102E12	18	6.4
RP11-105C15	18	7.5
RP11-91I8	18	8.1
RP11-102O20	18	11.2
AP001077.4	18	14.4
RP11-151D11	18	15.6
RP11-411B10	18	16.5
RP11-79F3	18	21.6
RP11-90G7	18	26.5
RP11-676D16	18	27.9
RP11-79G13	18	28.8

TABLE 2-continued

clone_id	chromosome	linear
AC021224.7	18	30.5
RP11-63N12	18	33.2
RP11-79G5	18	33.8
RP11-90B5	18	35.2
RP11-104N11	18	36.5
RP11-89M10	18	40.5
RP11-20A13	18	44.9
RP11-91K12	18	45.6
RP11-80P2	18	48
RP11-160B24	18	55
RP11-153B11	18	55.6
RP11-79L5	18	58.7
RP11-4G8	18	59.6
AC067859.3	18	60.2
RP11-91H13	18	61.7
RP11-75O12	18	65.2
RP11-90B3	18	65.8
RP11-89I22	18	65.9
RP11-88B2	18	67.4
RP11-105L16	18	69
RP11-79A24	18	69.2
RP11-90A7	18	69.2
RP11-49H23	18	69.4
RP11-57F7	18	71.5
RP11-90L15	18	73.4
RP11-90L3	18	79
RP11-91C19	18	80.5
RP11-89N1	18	81.5
AP001933.3	18	86.9
RP11-54G9	19	4.2
RP11-268O21	19	4.4
AC027319.5	19	6.8
CTD-3193O13	19	10.1
RP11-79F15	19	11.1
RP11-91O21	19	13.1
RP11-19I2	19	14.6
AC010422.7	19	15.3
RP11-56K21	19	17.2
CTD-2231E14	19	19.2
AC004447.1	19	22.4
RP11-152P7	19	42.7
RP11-46I12	19	43.8
RP11-110J19	19	43.9
RP11-79M11	19	46.4
RP11-91H20	19	46.8
RP11-147D7	19	47.1
AC008555.5	19	49.9
RP11-92J4	19	51
RP11-118P21	19	52.5
RP11-46C6	19	52.9
RP11-208I3	19	57.4
RP11-210C7	19	59.6
RP11-79A22	19	60.3
RP11-21J15	19	60.9
RP11-126L20	19	61.6
RP11-17I20	19	63.8
RP11-510I16	19	66.5
RP11-79A3	19	68.7
RP11-79I16	19	69.4
RP11-35J17	19	70.5
AC005261.1	19	74.3
RP11-420P11	19	75.9
RP5-1103G7	20	0.3
RP5-863C7	20	0.5
AL031665.19	20	1.2
AL031665.19	20	1.3
AL049634.8	20	1.4
RP4-684O24	20	1.9
RP4-816K17	20	2.3
RP11-26F18	20	3.2
RP4-599I11	20	4.7
RP5-1054C24	20	5.7
RP5-859D4	20	6.7
RP5-836E8	20	7.7

TABLE 2-continued

clone_id	chromosome	linear
RP11-79E16	20	8.6
RP5-873P14	20	9.5
RP5-931K24	20	10.3
RP11-90E23	20	11.2
RP11-88P14	20	12.2
RP11-89F13	20	14.5
RP11-91O7	20	15.6
RP11-80N12	20	16.8
RP11-11M17	20	17.8
RP11-91M17	20	19.4
RP11-91G1	20	20.9
RP4-788L20	20	22.5
RP11-218C14	20	23.5
RP11-79K14	20	25
RP11-90H19	20	25.6
RP3-410C9	20	26.2
RP5-1018D12	20	29.8
RP5-857M17	20	30.1
RP5-836N17	20	30.6
RP5-1125A11	20	32.3
RP4-756N5	20	33.5
RP5-901O8	20	34.3
RP3-460J8	20	35.1
RP11-138A15	20	35.9
RP4-564F22	20	36.8
RP4-616B8	20	37.4
RP5-1123D4	20	38.9
RP5-824J5	20	39
RP4-661I20	20	40
RP1-3E5	20	40.9
RP5-970A17	20	41.1
AL031676.3	20	41.5
RP11-169A6	20	43.5
RP3-337O18	20	44.3
RP11-323C15	20	45.3
RP3-453C12	20	45.8
RP1-73E16	20	46.3
RP5-1063B2	20	48.1
RP5-963K23	20	48.3
RP11-5P14	20	49.4
RP5-1185N5	20	50.4
RP4-715N11	20	51.1
RP11-91L1	20	51.8
RP5-885A10	20	54.4
RP4-749H19	20	55.4
RP5-907D15	20	57
RP5-1043L13	20	58.6
RP5-1040G13	20	59.5
RP5-1107C24	20	60.4
RP5-1005F21	20	60.5
RP5-885L7	20	61.5
AL158091.31	20	62.4
RP4-583P15	20	62.4
AL121581.41	20	62.7
RP11-89M24	21	13.5
AL163206	21	14.3
RP11-15E10	21	16.5
RP11-375O2	21	17
RP11-49B5	21	18.1
RP11-49J9	21	18.8
RP11-64I12	21	19.7
RP11-97F14	21	20.5
RP11-80N20	21	21.4
RP11-13J15	21	21.8
RP11-88D18	21	23.1
RP11-15H6	21	24.4
RP11-90A17	21	25.4
RP11-79G23	21	27
RP11-30N6	21	27.5
RP11-191I6	21	29.1
RP11-147H1	21	30
RP11-79D9	21	30.9
RP11-79A12	21	32.3
RP11-17O20	21	33

TABLE 2-continued

clone_id	chromosome	linear
AL163281.2	21	37.9
RP11-114H1	21	38.8
RP11-120C17	21	39.4
RP11-88N2	21	41.3
RP11-91O6	22	15.2
RP11-81B3	22	15.6
RP11-186O8	22	16.8
RP11-22M5	22	19.1
RP11-76E8	22	21.4
RP5-930L11	22	22
RP11-89A2	22	22.9
RP11-91K24	22	24.1
RP11-79G21	22	25
RP11-79G6	22	27.2
RP11-247I13	22	28.7
Z73979.1	22	30.1
RP1-215F16	22	32.3
RP11-89D12	22	33
RP5-1119A7	22	33.6
RP3-327J16	22	35.9
RP3-370M22	22	37
RP5-979N1	22	38.4
RP5-821D11	22	38.9
RP3-323M22	22	40.1
RP1-185D5	22	40.6
RP1-32I10	22	41.5
RP4-695O20	22	42.3
RP11-140I15	22	42.9
RP5-1163J1	22	43.4
RP1-111J24	22	44.4
RP11-262A13	22	45.8
RP3-355C18	22	47.1
U62317.2	22	47.7
U82668.1	X	0.04
LLNOYCO3M"15D10	X	0.05
RP4-617A9	X	0.9
AC079264.23	X	2.6
RP11-366M24	X	3.9
CTB-9P2	X	5.7
RP11-383I22	X	6.7
RP11-451G24	X	7
RP11-89B5	X	8.3
AC005859.1	X	10.3
RP11-90F9	X	11.4
AC095352.5	X	12.6
RP11-143E20	X	14.5
RP11-79B3	X	15.8
RP5-958B3	X	16.8
RP1-245G19	X	17.1
AC017058.4	X	18.2
RP11-497C10	X	19.2
RP11-507P24	X	20
RP11-487M22	X	25.2
RP6-27C10	X	25.8
CTB-229E10	X	27.1
RP11-89L23	X	27.3
RP11-122N14	X	28.1
RP11-124H12	X	28.4
RP5-1147O16	X	29
AL031643.1	X	29.9
RP11-70D7	X	31
RP13-46M24	X	33.2
CTB-227D11	X	34
RP11-91I16	X	34.3
RP11-495K15	X	35.1
RP11-506C6	X	35.8
RP11-258I23	X	37.2
RP11-524P6	X	38.3
RP11-252K10	X	39.3
RP11-561I16	X	40.1
RP4-551E13	X	40.8
AL020989.2	X	42.2
RP1-30G7	X	43
RP1-306D1	X	43.9

TABLE 2-continued

clone_id	chromosome	linear
RP1-212G6	X	44.7
DJ230G1	X	44.9
RP11-107C19	X	45.6
RP11-58H17	X	46.6
RP11-637B23	X	47.8
RP11-363G10	X	48.7
ICRFC100H0164	X	49.2
RP3-501A4	X	49.9
RP11-292J24	X	50.5
RP11-266I3	X	51.2
RP11-465E19	X	52.1
RP3-323P24	X	53.2
ICRFC100G11100	X	53.5
ICRFC104A07135	X	53.8
RP3-344I7	X	54.2
RP11-90N17	X	57
RP11-151A2	X	57.5
RP11-90I7	X	58.7
RP1-80C12	X	60.8
RP11-523P2	X	61.6
RP11-470E22	X	62.8
ICRFC104E01154	X	63.6
RP11-451A4	X	63.6
RP11-177A4	X	64.6
RP11-291O7	X	65.1
RP11-136A22	X	66.2
RP13-260P4	X	66.9
RP13-36G14	X	67.6
RP3-368A4	X	67.9
ICRFC100H0130	X	68
RP11-79C13	X	69.8
RP11-236O12	X	70.7
RP4-570L12	X	71.6
RP11-346E8	X	73.5
ICRFC104B1939	X	74.5
RP11-217H19	X	74.7
RP1-75N13	X	75.9
RP11-405O21	X	76.6
RP11-326A14	X	77.2
RP1-223D17	X	78.9
RP1-287L14	X	80
RP11-192B18	X	80.8
RP11-145I17	X	81
RP3-473J6	X	82.7
RP11-156J23	X	86.8
RP11-88F12	X	87.3
RP11-465C5	X	88.5
RP11-483J19	X	88.9
AL449189.1	X	89.9
RP1-117P19	X	91.1
RP13-75G22	X	92.2
RP11-485F13	X	93.1
RP3-377O6	X	94
RP11-89G18	X	95.1
Z70281	X	95.7
RMCOXP001	X	96.4
RP1-198P4	X	97.6
RP11-572H24	X	99.6
RP1-315B17	X	100.5
RP1-75H8	X	101.9
RP5-1070B1	X	102.6
AL031177.1	X	103.4
RP11-40K1	X	103.9
RP1-302C5	X	105.3
CTB-423D18	X	105.8
RP11-14G9	X	105.9
RP11-80F14	X	106.8
RP11-485M23	X	107.5
RP5-961O8	X	108.2
RP5-964N17	X	109.1
RP11-491C15	X	110.5
RP3-525N14	X	113.4
CTB-281O10	X	114.3
RP1-93I3	X	114.3

TABLE 2-continued

clone_id	chromosome	linear
RP11-566B18	X	116.7
RP6-64P14	X	118.2
RP3-370N13	X	118.4
RP5-1052M9	X	119.6
RP1-96A9	X	120.4
RP1-256K24	X	121.2
RP11-79C15	X	122
RP1-293E14	X	123.5
RP3-454M7	X	124.4
RP5-875H3	X	125.7
RP1-297J13	X	126.2
RP1-197O17	X	126.9
RP1-84F12	X	128.8
CTB-45B24	X	129.5
RP4-809E13	X	130.4
RP11-112K13	X	132.4
RP11-483M22	X	133.2
RP5-833B2	X	134.2
RP13-34G21	X	135.1
CTB-138O16	X	136
RP1-177G6	X	136.1
RP6-232G24	X	137.3
RP1-231L4	X	138.7
RP11-514L15	X	139.3
RP1-145B12	X	140.1
RP1-73A14	X	142.4
RP5-824H1	X	143
RP11-489K19	X	143.5
c31.4	X	143.6
L31948.1	X	145.9
RP11-414C23	Y	2.8
RP11-71M14	Y	15.9
RP11-91A13	Y	17.7
AC009235.4	Y	20

[0214] Substrate Surfaces

[0215] The compilations, or sets, libraries or collections, of nucleic acids, can be immobilized (directly or indirectly, covalently or by other means) to any substrate surface. The arrays of the invention can incorporate any substrate surface, e.g., a substrate means. The substrate surfaces can be of a rigid, semi-rigid or flexible material. The substrate surfaces can be flat or planar, be shaped as wells, raised regions, etched trenches, pores, beads, filaments, or the like. Substrates can be of any material upon which a nucleic acid (e.g., a "capture probe") can be directly or indirectly bound. For example, suitable materials can include paper, glass (see, e.g., U.S. Pat. No. 5,843,767), ceramics, quartz or other crystalline substrates (e.g. gallium arsenide), metals, metalloids, polacryloylmorpholide, various plastics and plastic copolymers, Nylon™, Teflon™, polyethylene, polypropylene, poly(4-methylbutene), polystyrene, polystyrene/latex, polymethacrylate, poly(ethylene terephthalate), rayon, nylon, poly(vinyl butyrate), polyvinylidene difluoride (PVDF) (see, e.g., U.S. Pat. No. 6,024,872), silicones (see, e.g., U.S. Pat. No. 6,096,817), polyformaldehyde (see, e.g., U.S. Pat. Nos. 4,355,153; 4,652,613), cellulose (see, e.g., U.S. Pat. No. 5,068,269), cellulose acetate (see, e.g., U.S. Pat. No. 6,048,457), nitrocellulose, various membranes and gels (e.g., silica aerogels, see, e.g., U.S. Pat. No. 5,795,557), paramagnetic or superparamagnetic microparticles (see, e.g., U.S. Pat. No. 5,939,261) and the like. Reactive functional groups can be, e.g., hydroxyl, carboxyl, amino groups or the like. Silane (e.g., mono- and dihydroxyalkylsilanes, aminoalkyltrialkoxysilanes, 3-aminopropyl-triethoxysilane, 3-aminopropyltrimethoxysilane) can provide a hydroxyl functional group for reaction with an amine functional group.

[0216] Nucleic Acids and Detectable Moieties: Incorporating Labels and Scanning Arrays

[0217] In making and using the compilations, or sets, libraries or collections, of nucleic acids and arrays and practicing the methods of the invention, nucleic acids associated with a detectable label can be used. The detectable label can be incorporated into, associated with or conjugated to a nucleic acid. Any detectable moiety can be used. The association with the detectable moiety can be covalent or non-covalent. In another aspect, the array-immobilized nucleic acids and sample nucleic acids are differentially detectable, e.g., they have different labels and emit difference signals.

[0218] Useful labels include, e.g., ^{32}P, ^{35}S, ^{3}H, ^{14}C, ^{125}I, ^{131}I; fluorescent dyes (e.g., Cy5™, Cy3™, FITC, rhodamine, lanthamide phosphors, Texas red), electron-dense reagents (e.g. gold), enzymes, e.g., as commonly used in an ELISA (e.g., horseradish peroxidase, beta-galactosidase, luciferase, alkaline phosphatase), colorimetric labels (e.g. colloidal gold), magnetic labels (e.g. Dynabeads™), biotin, dioxigenin, or haptens and proteins for which antisera or monoclonal antibodies are available. The label can be directly incorporated into the nucleic acid to be detected, or it can be attached to a probe or antibody that hybridizes or binds to the target. A peptide can be made detectable by incorporating (e.g., into a nucleoside base) predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, transcriptional activator polypeptide, metal binding domains, epitope tags). Label can be attached by spacer arms of various lengths to reduce potential steric hindrance or impact on other useful or desired properties. See, e.g., Mansfield (1995) Mol Cell Probes 9:145-156. In array-based CGH, fluors can be paired together; for example, one fluor labeling the control (e.g., the "nucleic acid of "known, or normal, karyotype") and another fluor the test nucleic acid (e.g., from a chorionic villus sample or a cancer cell sample). Exemplary pairs are: rhodamine and fluorescein (see, e.g., DeRisi (1996) Nature Genetics 14:458-460); lissamine-conjugated nucleic acid analogs and fluorescein-conjugated nucleotide analogs (see, e.g., Shalon (1996) supra); Spectrum Red™ and Spectrum Green™ (Vysis, Downers Grove, Ill.); Cy3™ and Cy5™. Cy3™ and Cy5™ can be used together; both are fluorescent cyanine dyes produced by Amersham Life Sciences (Arlington Heights, Ill.). Cyanine and related dyes, such as merocyanine, styryl and oxonol dyes, are particularly strongly light-absorbing and highly luminescent, see, e.g., U.S. Pat. Nos. 4,337,063; 4,404,289; 6,048,982.

[0219] Other fluorescent nucleotide analogs can be used, see, e.g., Jameson (1997) Methods Enzymol. 278:363-390; Zhu (1994) Nucleic Acids Res. 22:3418-3422. U.S. Pat. Nos. 5,652,099 and 6,268,132 also describe nucleoside analogs for incorporation into nucleic acids, e.g., DNA and/or RNA, or oligonucleotides, via either enzymatic or chemical synthesis to produce fluorescent oligonucleotides. U.S. Pat. No. 5,135,717 describes phthalocyanine and tetrabenztriazaporphyrin reagents for use as fluorescent labels.

[0220] Detectable moieties can be incorporated into sample genomic nucleic acid and, if desired, any member of

the compilation of nucleic acids or array-immobilized nucleic acids, by covalent or non-covalent means, e.g., by transcription, such as by random-primer labeling using Klenow polymerase, or "nick translation," or, amplification, or equivalent. For example, in one aspect, a nucleoside base is conjugated to a detectable moiety, such as a fluorescent dye, e.g., Cy3™ or Cy5™, and then incorporated into a sample genomic nucleic acid. Samples of genomic DNA can be incorporated with Cy3™- or Cy5™-dCTP conjugates mixed with unlabeled dCTP. Cy5™ is typically excited by the 633 nm line of HeNe laser, and emission is collected at 680 nm. See also, e.g., Bartosiewicz (2000) Archives of Biochem. Biophysics 376:66-73; Schena (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Pinkel (1998) Nature Genetics 20:207-211; Pollack (1999) Nature Genetics 23:41-46.

[0221] In another aspect, when using PCR or nick translation to label nucleic acids, modified nucleotides synthesized by coupling allylamine-dUTP to the succinimidyl-ester derivatives of the fluorescent dyes or haptenes (such as biotin or digoxigenin) are used; this method allows custom preparation of most common fluorescent nucleotides, see, e.g., Henegariu (2000) Nat. Biotechnol. 18:345-348.

[0222] In the compilation of nucleic acids, arrays and methods of the invention, labeling with a detectable composition (labeling with a detectable moiety) also can include a nucleic acid attached to another biological molecule, such as a nucleic acid, e.g., a nucleic acid in the form of a stem-loop structure as a "molecular beacon" or an "aptamer beacon." Molecular beacons as detectable moieties are well known in the art; for example, Sokol (1998) Proc. Natl. Acad. Sci. USA 95:11538-11543, synthesized "molecular beacon" reporter oligodeoxynucleotides with matched fluorescent donor and acceptor chromophores on their 5' and 3' ends. In the absence of a complementary nucleic acid strand, the molecular beacon remains in a stem-loop conformation where fluorescence resonance energy transfer prevents signal emission. On hybridization with a complementary sequence, the stem-loop structure opens increasing the physical distance between the donor and acceptor moieties thereby reducing fluorescence resonance energy transfer and allowing a detectable signal to be emitted when the beacon is excited by light of the appropriate wavelength. See also, e.g., Antony (2001) Biochemistry 40:9387-9395, describing a molecular beacon comprised of a G-rich 18-mer triplex forming oligodeoxyribonucleotide. See also U.S. Pat. Nos. 6,277,581 and 6,235,504.

[0223] Aptamer beacons are similar to molecular beacons; see, e.g., Hamaguchi (2001) Anal. Biochem. 294:126-131; Poddar (2001) Mol. Cell. Probes 15:161-167; Kaboev (2000) Nucleic Acids Res. 28:E94. Aptamer beacons can adopt two or more conformations, one of which allows ligand binding. A fluorescence-quenching pair is used to report changes in conformation induced by ligand binding. See also, e.g., Yamamoto (2000) Genes Cells 5:389-396; Smimov (2000) Biochemistry 39:1462-1468.

[0224] Detecting Dyes and Fluors

[0225] In addition to labeling nucleic acids with fluorescent dyes, the invention can be practiced using any apparatus or methods to detect "detectable labels" of a sample nucleic acid, a member of the compilation of nucleic acids, or an array-immobilized nucleic acid, or, any apparatus or methods to detect nucleic acids specifically hybridized to each other. In one aspect, devices and methods for the simultaneous detection of multiple fluorophores are used; they are well known in the art, see, e.g., U.S. Pat. Nos. 5,539,517; 6,049,380; 6,054,279; 6,055,325; 6,294,331. Any known device or method, or variation thereof, can be used or adapted to practice the methods of the invention, including array reading or "scanning" devices, such as scanning and analyzing multicolor fluorescence images; see, e.g., U.S. Pat. Nos. 6,294,331; 6,261,776; 6,252,664; 6,191,425; 6,143,495; 6,140,044; 6,066,459; 5,943,129; 5,922,617; 5,880,473; 5,846,708; 5,790,727; and, the patents cited in the discussion of arrays, herein. See also published U.S. patent applications Nos. 20010018514; 20010007747; published international patent applications Nos. WO0146467 A; WO9960163 A; WO0009650 A; WO0026412 A; WO0042222 A; WO0047600 A; WO0101144 A.

[0226] For example a spectrograph can image an emission spectrum onto a two-dimensional array of light detectors; a full spectrally resolved image of the array is thus obtained. Photophysics of the fluorophore, e.g., fluorescence quantum yield and photodestruction yield, and the sensitivity of the detector are read time parameters for an oligonucleotide array. With sufficient laser power and use of Cy5™ and/or Cy3™, which have lower photodestruction yields an array can be read in less than 5 seconds.

[0227] When using two or more fluors together (e.g., as in a CGH), such as Cy3™ and Cy5™, it is necessary to create a composite image of all the fluors. To acquire the two or more images, the array can be scanned either simultaneously or sequentially. Charge-coupled devices, or CCDs, are used in microarray scanning systems, including practicing the methods of the invention. Thus, CCDs used in the methods of the invention can scan and analyze multicolor fluorescence images. Color discrimination can also be based on 3-color CCD video images; these can be performed by measuring hue values. Hue values are introduced to specify colors numerically. Calculation is based on intensities of red, green and blue light (RGB) as recorded by the separate channels of the camera. The formulation used for transforming the RGB values into hue, however, simplifies the data and does not make reference to the true physical properties of light. Alternatively, spectral imaging can be used; it analyzes light as the intensity per wavelength, which is the only quantity by which to describe the color of light correctly. In addition, spectral imaging can provide spatial data, because it contains spectral information for every pixel in the image. Alternatively, a spectral image can be made using brightfield microscopy, see, e.g., U.S. Pat. No. 6,294,331.

[0228] Data Analysis

[0229] The methods of the invention further comprise data analysis, which can include the steps of determining, e.g., fluorescent intensity as a function of substrate position, removing "outliers" (data deviating from a predetermined statistical distribution), or calculating the relative binding affinity of the targets from the remaining data. The resulting data can be displayed as an image with color in each region varying according to the light emission or binding affinity between targets and probes. See, e.g., U.S. Pat. Nos. 5,324,633; 5,863,504; 6,045,996. The invention can also incorporate a device for detecting a labeled marker on a sample located on a support, see, e.g., U.S. Pat. No. 5,578,832.

[0230] Sources of Genomic Nucleic Acid

[0231] The invention provides methods of detecting a genetic mosaicism in any sample comprising nucleic acid, such as a cell population or tissue or fluid sample, by performing an array-based comparative genomic hybridization (CGH). The nucleic acid can be derived from (e.g., isolated from, amplified from, cloned from) genomic DNA. The genomic DNA can be from any source.

[0232] In one aspect, the cell, tissue or fluid sample from which the nucleic acid sample is prepared is taken from a patient suspected of having a pathology or a condition associated with genetic defects. The causality, diagnosis or prognosis of the pathology or condition may be associated with genetic defects, e.g., with genomic nucleic acid base substitutions, amplifications, deletions and/or translocations. The cell, tissue or fluid can be from, e.g., amniotic samples, chorionic villus samples (CVS), serum, blood, chord blood or urine samples, CSF or bone marrow aspirations, fecal samples, saliva, tears, tissue and surgical biopsies, needle or punch biopsies, and the like.

[0233] Methods of isolating cell, tissue or fluid samples are well known to those of skill in the art and include, but are not limited to, aspirations, tissue sections, drawing of blood or other fluids, surgical or needle biopsies, and the like. A "clinical sample" derived from a patient includes frozen sections or paraffin sections taken for histological purposes. The sample can also be derived from supernatants (of cell cultures), lysates of cells, cells from tissue culture in which it may be desirable to detect levels of mosaicisms, including chromosomal abnormalities and copy numbers.

EXAMPLES

[0234] The following example is offered to illustrate, but not to limit the claimed invention.

Example 1

Making Nucleic Acid Arrays

[0235] The following example demonstrates exemplary protocol for making an array of the invention.

[0236] Making BAC Microarrays:

[0237] BAC clones greater than fifty kilobases (50 kb), and up to about 300 kb, are grown up in Terrific Broth medium. Larger inserts, e.g., clones >300 kb, and smaller inserts, about 1 to 20 kb, are also be used. DNA is prepared by a modified alkaline lysis protocol (see, e.g., Sambrook). The DNA is labeled, as described below.

[0238] The DNA is then chemically modified as described by U.S. Pat. No. 6,048,695. The modified DNA is then dissolved in proper buffer and printed directly on clean glass surfaces as described by U.S. Pat. No. 6,048,695. Usually multiple spots are printed for each clone.

Example 2

Nucleic Acid Labeling and DNase Enzyme Fragmentation

[0239] A standard random priming method is used to label genomic DNA before its attachment to the array, see, e.g., Sambrook. Sample nucleic acid is also similarly labeled. Cy3™ or Cy5™ labeled nucleotides are supplemented together with corresponding unlabeled nucleotides at a molar ratio ranging from 0.0 to about 6 (unlabeled nucleotide to labeled nucleotides). Labeling is carried out at 37° C. for 2 to 10 hours. After labeling the reaction mix is heated up to 95° C. to 100° C. for 3 to 5 minutes to inactivate the polymerase and denature the newly generated, labeled "probe" nucleic acid from the template.

[0240] The heated sample is then chilled on ice for 5 minutes. "Calibrated" DNase (DNA endonuclease) enzyme is added to fragment the labeled template (generated by random priming). "Trace" amounts of DNase is added (final concentration was 0.2 to 2 ng/ml; incubation time 15 to 30 minutes) to digest/fragment the labeled nucleic acid to segments of about 30 to about 100 bases in size.

Example 3

Hybridization of Nucleic Acid Samples to Arrays

[0241] The following example sets forth exemplary methods for pretreating nucleic acid samples and hybridizing these samples to arrays. This exemplary hybridization protocol can be used to determine if a nucleic acid segment, such as a genomic clone, is within the scope of the invention (e.g., is a member of a compilation, library, clone set of the invention).

[0242] Step 1: Pretreat DNA Samples

[0243] Random prime labeling of large sized DNA samples, such as genomic DNA, can be more efficient if the DNA sample is first digested to produce smaller fragments. For every test sample to be analyzed, four genomic DNA digests were performed: two of the test sample and two of an appropriate reference or control sample.

[0244] 1. Restriction enzyme digest of genomic DNA: on ice, pipet the following into an autoclaved microcentrifuge tube:

[0245] DNA X μl for 1 μg

[0246] React 3 10×Buffer 5 μl

[0247] Eco RI 2 μl (20 units)

[0248] Water (orange vial) μl to a final volume of 50 μl

[0249] 2. After addition of the enzyme and DNA, mix briefly by vortexing and recollect samples by brief centrifugation.

[0250] 3. Incubate samples overnight (16 hours) at 37° C.

[0251] 4. Determine the completion of the reaction by removing a 5 μl aliquot from the reaction mix, and analyzing the aliquot by agarose gel electrophoresis (0.8% agarose).

[0252] If the digestion is complete, stop the reaction by incubating in a heating block at 72° C. for 10 minutes. It is recommended to fill the wells of the heating block with water approximately 15 minutes before denaturing the samples so that the tubes are in contact with water at 72° C.

[0253] 5. Re-purify the digested DNA sample (either by phenol/chloroform extraction/EtOH precipitation

or a suitable commercially available 'post-enzyme digestion/PCR clean-up kit' such as Zymo Research's DNA Clean and Concentrator TM-5 Cat No. D4005). Note: It is recommended to requantifying the DNA samples at this juncture to ensure that equitable amounts of the test and reference samples will be labeled in the following step.

[0254] At least 500 ng of digested DNA of each sample were used for labeling.

[0255] Genomic DNA samples adequately digested with a four base pair (4-bp) cutter restriction enzyme, such as EcoRI, should produce a relatively homogenous smear extending from 20 kb to approximately 600 bp.

[0256] Step 2: Differentially Label DNA with Cy3-dCTP and Cy5-dCTP

[0257] The objective in this step is to label the test and reference samples with both Cy-3 and Cy-5 to facilitate the co-hybridization between the Cy-3 labeled test and Cy-5 labeled reference samples, and conversely the Cy-5 labeled test and Cy-3 labeled reference samples.

[0258] 1. To the re-purified DNA samples, add sterile water to bring the total volume to 25 μl. Then add 20 μl of 2.5×random primer/reaction buffer mix (e.g., from Gibco/BRL's BIOPRIME™ labeling kit).

[0259] 2. Mix the samples well and then boil for 5 minutes.

[0260] 3. Immediately place the samples on ice and allow to sit for 5 minutes.

[0261] 4. On ice, add 2.5 μl of SPECTRAL LABELING BUFFER, for use with SPECTRAL CHIP™ (Spectral Genomics, Houston Tex.) to each sample.

[0262] 5. Add 1.5 μl Cy5-dCTP or Cy3-dCTP to the respective test and reference DNA samples (1 mM stocks).

[0263] 6. Finally, add 1 μl Klenow Fragment (from the Gibco/BRL BIOPRIME™ labeling kit) to the samples, mix the sample well by tapping, and recollect by brief centrifugation.

[0264] 7. Incubate the sample at 37° C. for 1½-2 hours. Place the samples on ice and determine the probe size distribution by removing a 5 μl aliquot from the reaction mix, and analyzing the aliquot by agarose gel electrophoresis (0.8% agarose). Note: Optimally, the majority of the probe should range in size between 100-500 bp.

[0265] 8. Stop the reaction by adding 5 μl 0.5 M EDTA pH 8.0 and incubating in a heating block at 72° C. for 10 minutes. Place the samples on ice. The samples can now be used to proceed with hybridization or can be stored at −20° C. until required.

[0266] Optimally the majority of the probe should range in size between 100-500 bp.

[0267] Step 3: Hybridize Labeled DNA to the Array

[0268] At this juncture, there should be four tubes, which should correspond to the Cy-3 and Cy-5 labeled test samples and the Cy-3, and Cy-5 labeled reference samples.

[0269] 1. Combine the Cy3-labeled test DNA sample with the Cy5-labeled reference sample and, conversely, the Cy5-labeled test DNA sample with the Cy3-labeled reference sample. Add 45 μl of SPECTRAL HYBRIDIZATION BUFFER I, for use with SPECTRAL CHIP™ (Spectral Genomics, Houston Tex.) to each of the two tubes.

[0270] 2. Precipitate the two samples by adding 11.3 μl of 5MNaCl and 110 μl of room temperature isopropanol. Mix the samples well and incubate in the dark at room temperature for 10-15 minutes.

[0271] 3. Centrifuge the samples at full speed (10,000 g) for 10 minutes.

[0272] 4. Carefully aspirate the supernatant, avoiding the pellet. Note: The pellets should have a purplish hue, indicating that there are equitable amounts of Cy3 and Cy5 labeled DNA. Too pink or too blue a sample, suggests that the corresponding genomic DNA was not effectively labeled.

[0273] 5. Rinse the pellets with 500 μl of 70% ethanol and allow the pellets to air-dry briefly in the dark at room temperature.

[0274] 6. Add 10 μl of sterile water (orange vial) to the pellets. Let stand at room temperature for 5 minutes and then thoroughly resuspend. After ensuring that the pellets are completely resuspended, add 30 μl of SPECTRAL HYBRIDIZATION BUFFER II, for use with SPECTRAL CHIP™ (Spectral Genomics, Houston Tex.) and mix well by repeated pipetting.

[0275] 7. Denature the samples by incubating in a water bath at 72° C. for 10 minutes. Note: Alternatively, the sample can be denatured in a heating block set at 72° C. We recommend filling the wells of the heating block with water approximately 15 minutes before denaturing the samples so that the tubes are in contact with water at 72° C.

[0276] 8. After the denaturation of the samples, immediately place the tubes on ice for 5 minutes.

[0277] 9. Incubate the samples at 37° C. for 30 minutes.

[0278] 10. Pipette the sample onto the center of the array and cover with a 22×60 cover slip to spread it out. Note: It is imperative that the entire array is covered and that air bubbles are avoided.

[0279] 11. Place the slide in a hybridization chamber. If a microarray hybridization chamber is used, then add 10 μl of 2×SSC, 50% formamide to either side of the chamber. (H_2O works just as well).

[0280] 12. Close the chamber and wrap with aluminum foil. Put the chambers in a Kapak Pouch with wet paper and heat seal the bag. Put the bag in a 37° C. incubator for 16 hours. Note: We recommend using a shaking platform incubator to facilitate and maintain even distribution of the probe on the slide.

[0281] Step 4: Post Hybridization Washes

[0282] While Coplinjars can be used in the post-hybridization washes, it is recommended to wash each slide in individual Petri dishes in a shaking platform incubator.

[0283] 1. Pre-warm the following solutions at 50° C. in individual Petri dishes:

[0284] 2×SSC, 50% deionized Formamide

[0285] 2×SSC, 0.1% NP-40

[0286] 0.2×SSC

[0287] 2. Soak the slide in 2×SSC, 0.5% SDS briefly at room temperature and gently slide off the cover slip using a pair of clean forceps. Avoid peeling off the cover slip by force. (Alternatively, 2×SSC can be used)

[0288] 3. Using a pair of forceps, transfer the slide to pre-warmed 2×SSC, 50% Formamide. Wash the slides by incubating in the shaking incubator at 50° C. for 20 minutes.

[0289] 4. Repeat step 3 using pre-warmed 2×SSC, 0.1% NP-40.

[0290] 5. Repeat step 3 using pre-warmed 0.2×SSC for 10 minutes.

[0291] 6. Briefly rinse the slides with distilled deionized water. This last wash greatly reduces background fluorescence but should not exceed 10 seconds.

[0292] 7. Immediately dry the slides under forced air. Do not air dry the slides. The slides are now ready for scanning.

[0293] A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

What is claimed is:

1. An array for the detection of a chromosomal abnormality or a diagnosis of a syndrome associated with a contiguous gene abnormality, comprising:

a plurality of nucleic acids segments, wherein each nucleic acid segment is immobilized to a discrete and known spot on a substrate surface to form an array of nucleic acids, and each spot comprises a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

2. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 1, locus 1p;36, and the syndrome detected is 1p Deletion Syndrome.

3. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 1, locus 7p11.2, and the syndrome detected is Smith-Magenis syndrome (SMS).

4. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 3, locus 3p25-pter, and the syndrome detected is 3p Deletion Syndrome.

5. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 3, locus 3p21-pter, and the syndrome detected is 3p Duplication Syndrome.

6. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 4, locus 4p16.3, and the syndrome detected is Wolf-Hirschhorn Syndrome.

7. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 4, locus 4p15.2-16.1, and the syndrome detected is 4p Duplication Syndrome.

8. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 5, locus 5p15.2-pter, and the syndrome detected is Cri du Chat Syndrome.

9. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 7, locus 7p13.3, and the syndrome detected is Miller-Dieker Syndrome.

10. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 7, locus 7q11.23, and the syndrome detected is Williams Syndrome.

11. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 8, locus 8q24.1, and the syndrome detected is Langer-Giedion Syndrome (LGS).

12. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 8, locus 8q24.1, and the syndrome detected is Trichorhinophalangeal Syndrome (TRPS).

13. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 8, locus 8q13.3, and the syndrome detected is branchio-oto-renal (BOR) syndrome.

14. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 9, locus 9p, and the syndrome detected is 9p Deletion Syndrome.

15. The array of claim 14, wherein the 9p locus comprises locus 9p22-pter.

16. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 10, locus 10p13-p14, and the syndrome detected is DiGeorge Syndrome II.

17. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 11, locus 11p13, and the syndrome detected is WAGR Syndrome.

18. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 11, locus 11p15.5, and the syndrome detected is Beckwith-Wiedemann Syndrome.

19. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 11, locus 11p11.2, and the syndrome detected is Potocki-Shaffer Syndrome (Multiple Exostoses II Locus).

20. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 13, locus 13q22, and the syndrome detected is Hirschsprung disease and Waardenburg syndrome.

21. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 15, locus 15q12, and the syndrome detected is Angelman Syndrome.

22. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 15, locus 15q12, and the syndrome detected is Prader-Willi Syndrome.

23. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 16, locus distal 16p13.3, and the syndrome detected is Rubinstein-Taybi Syndrome.

24. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 16, pericentromeric region, and the syndrome detected is idiopathic epilepsy and paroxysmal dyskinesia.

25. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 17, locus 17p12, and the syndrome detected is Charcot-Marie-Tooth Disease Type 1A(CMT-1A).

26. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 17, locus 17p12, and the syndrome detected is Hereditary Neuropathy with Liability to Pressure Palsies.

27. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 17, locus 17p13.3, and the syndrome detected is Miller-Dieker Syndrome/Isolated Lissencephaly.

28. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 17, locus 17p11.2, and the syndrome detected is Smith-Magenis Syndrome.

29. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 20, locus 20p11.2-p12, and the syndrome detected is Alagille Syndrome.

30. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 22, locus 22q11.2, and the syndrome detected is Digeorge/Velocardiofacial Syndrome.

31. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp21, and the syndrome detected is Adrenal Hypoplasia Congenita (AHC).

32. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp21, and the syndrome detected is Duchenne/Becker Muscular Dystrophy.

33. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp21, and the syndrome detected is Glycerol Kinase Deficiency.

34. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp22, and the syndrome detected is Pelizaeus-Merzbacher Disease.

35. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp22.3, and the syndrome detected comprises steroid sulfatase deficiency.

36. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp22.3, and the syndrome detected is Leri-Weill syndrome.

37. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome Y, locus SRY locus/Yp, and the syndrome detected comprises abnormalities of the SRY locus.

38. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp22.3, and the syndrome detected is Kallman Disease.

39. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp21, and the syndrome detected is Sex Reversal (DSS).

40. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 17, locus 17p11.2, and the syndrome detected is 17p11.2 Duplication Syndrome.

41. The array of claim 1, wherein a segment of genomic nucleic acid comprises chromosome 17, locus 17p11.2, and the syndrome detected is Smith-Magenis syndrome (SMS).

42. The array of claim 1, further comprising at least one spot comprising a nucleic acid segment acting as a positive control.

43. The array of claim 1, further comprising at least one spot comprising a nucleic acid segment acting as a negative control.

44. The array of claim 1, wherein about 75% of the spots comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

45. The array of claim 44, wherein about 80% of the spots comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

46. The array of claim 45, wherein about 85% of the spots comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

47. The array of claim 46, wherein about 90% of the spots comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

48. The array of claim 47, wherein about 95% of the spots comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome

49. The array of claim 48, wherein about 98% of the spots comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

50. The array of claim 49, wherein 100% of the spots comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

51. The array of claim 1, wherein the array-immobilized genomic nucleic acid segments in a first spot are non-overlapping in sequence compared to the array-immobilized genomic nucleic acid segments in a second spot.

52. The array of claim 51, wherein the array-immobilized genomic nucleic acid segments in a spot are non-overlapping in sequence compared to the array-immobilized genomic nucleic acid segments all of other genomic nucleic acid-comprising spots on the array.

53. The array of claim 1, wherein at least one cloned genomic nucleic acid segment is spotted in duplicate or triplicate on the array.

54. The array of claim 53, wherein the duplicate spot or triplicate spot has a different amount of nucleic acids segments immobilized.

55. The array of claim 53, wherein all the cloned genomic nucleic acid segments are spotted in duplicate or triplicate on the array.

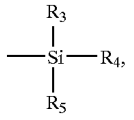
56. The array of claim 1, wherein about 95% of the array-immobilized genomic nucleic acid comprise a detectable label.

57. The array of claim 56, wherein about 98% of the array-immobilized genomic nucleic acid comprise a detectable label.

58. The array of claim 57, wherein 100% of the array-immobilized genomic nucleic acid comprise a detectable label.

59. The array of claim 1, wherein the array-immobilized genomic nucleic acid are covalently bound to the substrate surface.

60. The array of claim 59, wherein the array-immobilized genomic nucleic acid are covalently bound to a compound having the general formula: R_1—X—R_2, wherein R_1 is a cyclic ether, an aldehyde, or a chloromethylphenyl moiety; X is a moiety chemically suitable for linking the R_1 moiety to the R_2 moiety, and the R_2 moiety has the general formula



wherein R_3, R_4 and R_5 comprise identical or different alkoxy group or chloro groups.

61. The array of claim 59, wherein the array-immobilized genomic nucleic acid are covalently bound to a compound having the general formula: R_1—X—R_2, wherein R_1 is an amino group, R_2 is an alkoxysilane group or a chlorohalide group; and X is a moiety chemically suitable for linking the R_1 group and the R_2 group.

62. The array of claim 59, wherein the array-immobilized genomic nucleic acid are covalently bound to a compound having the general formula

$$R_1—X—Si(OR_2)_m(Cl)_n(R)_k,$$

wherein m+k is the integer 3, and n can be 0 if m is greater than 0, or n+k is the integer 3 and m can be 0 if n is greater than 0; X is an inert linker; R1 comprises a group reactive toward the biological molecule; R is an alkyl group; and, R_2 is an alkyl group.

63. The array of claim 1, wherein a cloned nucleic acid segment is cloned in a construct comprising an artificial chromosome.

64. The array of claim 63, wherein the artificial chromosome comprises a bacterial artificial chromosome (BAC).

65. The array of claim 63, wherein the artificial chromosome is selected from the group consisting of a human artificial chromosome (HAC) a yeast artificial chromosome (YAC), a transformation-competent artificial chromosome (TAC) and a bacteriophage P1-derived artificial chromosome (PAC).

66. The array of claim 1, wherein a cloned nucleic acid segment is cloned in a construct comprising a vector selected from the group consisting of a cosmid vector, a plasmid vector and a viral vector.

67. The array of claim 1, wherein the cloned nucleic acid segment is between about 50 kilobases (0.5 megabase) to about 500 kilobases (5 megabases) in length.

68. The array of claim 67, wherein the cloned nucleic acid segment is between about 100 kilobases (1 megabase) to about 400 kilobases (4 megabases) in length.

69. The array of claim 68, wherein the cloned nucleic acid segment is about 300 kilobases (3 megabases) in length.

70. An array for the detection of a chromosomal abnormality or the diagnosis of a syndrome associated with a contiguous gene abnormality, comprising:

a plurality of nucleic acids segments, wherein each nucleic acid is immobilized to a discrete and known spot on a substrate surface to form an array of nucleic acids, and each spot comprises a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome, and the plurality of nucleic acids segments comprise:

chromosome 1, locus 1p36, wherein the syndrome detected is 1p Deletion Syndrome;

chromosome 3, locus 3p25-pter, wherein the syndrome detected is 3p Deletion Syndrome;

chromosome 3, locus 3p21-pter, wherein the syndrome detected is 3p Duplication Syndrome;

chromosome 4, locus 4p16.3, wherein the syndrome detected is Wolf-Hirschhorn Syndrome;

chromosome 4, locus 4p15.2-16.1, wherein the syndrome detected is 4p Duplication Syndrome;

chromosome 5, locus 5p15.2-pter, wherein the syndrome detected is Cri du Chat Syndrome;

chromosome 7, locus 7p13.3, wherein the syndrome detected is Miller-Dieker Syndrome;

chromosome 7, locus 7q11.23, wherein the syndrome detected is William's Syndrome;

chromosome 8, locus 8q24.1, wherein the syndrome detected is Langer-Giedion Syndrome (LGS);

chromosome 8, locus 8q24.1, wherein the syndrome detected is Trichorhinophalangeal Syndrome (TRPS);

chromosome 9, locus 9p, wherein the syndrome detected is 9p Deletion Syndrome;

chromosome 10, locus 10p13-p14, wherein the syndrome detected is DiGeorge Syndrome II;

chromosome 11, locus 11p13, wherein the syndrome detected is WAGR Syndrome;

chromosome 11, locus 11p15.5, wherein the syndrome detected is Beckwith-Wiedemann Syndrome;

chromosome 11, locus 11p11.2, wherein the syndrome detected is Potocki-Shaffer Syndrome (Multiple Exostoses II Locus);

chromosome 15, locus 15q12, wherein the syndrome detected is Angelman Syndrome;

chromosome 15, locus 15q12, wherein the syndrome detected is Prader-Willi Syndrome;

chromosome 16, locus distal 16p13.3, wherein the syndrome detected is Rubinstein-Taybi Syndrome;

chromosome 17, locus 17p12, wherein the syndrome detected is Charcot-Marie-Tooth Disease Type 1A(CMT-1A);

chromosome 17, locus 17p12, wherein the syndrome detected is Hereditary Neuropathy with Liability to Pressure Palsies;

chromosome 17, locus 17p13.3, wherein the syndrome detected is Miller-Dieker Syndrome/Isolated Lissencephaly;

chromosome 17, locus 17p11.2, wherein the syndrome detected is Smith-Magenis Syndrome;

chromosome 20, locus 20p11.2-p12, wherein the syndrome detected is Alagille Syndrome;

chromosome 22, locus 22q11.2, wherein the syndrome detected is Digeorge/Velocardiofacial Syndrome;

chromosome X, locus Xp21, wherein the syndrome detected is Adrenal Hypoplasia Congenita (AHC);

chromosome X, locus Xp21, wherein the syndrome detected is Duchenne/Becker Muscular Dystrophy;

chromosome X, locus Xp21, wherein the syndrome detected is Glycerol Kinase Deficiency;

chromosome X, locus Xp22, wherein the syndrome detected is Pelizaeus-Merzbacher Disease;

chromosome X, locus Xp22.3, wherein the syndrome detected comprises steroid sulfatase deficiency;

chromosome Y, locus SRY locus/Yp, wherein the syndrome detected comprises abnormalities of the SRY locus;

chromosome X, locus Xp22.3, and the syndrome detected is Kallman Disease;

chromosome X, locus Xp21, and the syndrome detected is Sex Reversal (DSS); and,

chromosome 17, locus 17p11.2, and the syndrome detected is 17p11.2 Duplication Syndrome.

71. An array for the detection of a chromosomal abnormality or the diagnosis of a syndrome associated with a contiguous gene abnormality comprising a plurality of nucleic acids segments, wherein each nucleic acid segment is immobilized to a discrete and known spot on a substrate surface to form an array of nucleic acids, and the nucleic acid segments are selected from the group consisting of chromosome 1, locus 1p36; chromosome 3, locus 3p25-pter; chromosome 3, locus 3p21-pter; chromosome 4, locus 4p16.3; chromosome 4, locus 4p15.2-16.1; chromosome 5, locus 5p15.2-pter; chromosome 7, locus 7p13.3; chromosome 7, locus 7q11.23; chromosome 8, locus 8q24.1; chromosome 8, locus 8q24.1; chromosome 9, locus 9p; chromosome 10, locus 10p13-p14; chromosome 11, locus 1p13; chromosome 11, locus 1p15.5; chromosome 11, locus 11p11.2; chromosome 15, locus 15q12; chromosome 16, locus distal 16p13.3; chromosome 17, locus 17p12; chromosome 17, locus 17p13.3; chromosome 17, locus 17p11.2; chromosome 20, locus 20p11.2-p12; chromosome 22, locus 22q11.2; chromosome X, locus Xp21; chromosome X, locus Xp22; chromosome X, locus Xp22.3; and, chromosome Y, locus SRY locus/Yp.

72. The array of claim 71, wherein the array comprises at least two members of the group of nucleic acid segments.

73. The array of claim 72, wherein the array comprises at least five members of the group of nucleic acid segments.

74. The array of claim 73, wherein the array comprises at least ten members of the group of nucleic acid segments.

75. The array of claim 70 or claim 71, further comprising at least one spot comprising a nucleic acid segment to act as a positive control.

76. The array of claim 70 or claim 71, further comprising at least one spot comprising a nucleic acid segment to act as a negative control.

77. A method of detecting a chromosomal abnormality or for diagnosis of a syndrome associated with a contiguous gene abnormality in an individual comprising the following steps:

(a) providing an array as set forth in claim 1;

(b) providing a sample comprising a substantially full complement of genomic DNA from the individual;

(c) contacting the genomic DNA of step (b) or a nucleic acid comprising a sequence equivalent to the genomic DNA of step (b) with the array of step (a) under conditions wherein the nucleic acid in the sample can specifically hybridize to the genomic nucleic acid segments immobilized on the array;

(g) measuring the location and amount of genomic DNA specifically hybridized to the genomic nucleic acid segments immobilized on the array, thereby detecting a chromosomal abnormality or making a diagnosis of a syndrome associated with a contiguous gene abnormality in an individual.

78. The method of claim 77, wherein detecting the chromosomal abnormality in the individual detects a disease or a condition or a syndrome in the individual.

79. The method of claim 77, wherein the individual is a human.

80. The method of claim 77, wherein the individual is an embryo.

81. The method of claim 77, wherein the individual is suspected of having a chromosomal abnormality.

82. The method of claim 77, wherein the individual is suspected of having a disease or condition associated with a karyotype abnormality.

83. The method of claim 77, wherein the disease comprises a cancer.

84. The method of claim 77, wherein the sample comprises a body fluid sample, a cell sample or a tissue sample.

85. The method of claim 84, wherein the sample comprises a cancer cell or a tumor cell sample.

86. The method of claim 77, wherein the sample is a biopsy sample.

87. The method of claim 77, wherein the sample is a blood sample.

88. The method of claim 77, wherein the sample is a urine sample.

89. The method of claim 77, wherein the sample is a cerebral spinal fluid (CSF) sample.

90. The method of claim 77, wherein the sample is an amniotic fluid sample.

91. The method of claim 77, wherein the sample is a chorionic villus sample.

92. The method of claim 77, wherein the sample is an embryonic cell or embryo tissue sample.

93. The method of claim 77, further comprising associating the sample nucleic acid or the nucleic acid immobilized to the array with a detectable label.

94. The method of claim 93, wherein the detectable label is covalently associated with the nucleic acid.

95. The method of claim 93, wherein the detectable label comprises a fluorescent label.

96. The method of claim 95, wherein the fluorescent label comprises Cy5™ or equivalent.

97. The method of claim 95, wherein the fluorescent label comprises Cy3™ or equivalent.

98. The method of claim 95, wherein the fluorescent label comprises a rhodamine, a fluorescein or an aryl-substituted 4,4-difluoro-4-bora-3a, 4a-diaza-s-indacene dye or equivalents.

99. The method of claim 93, wherein labeling of the nucleic acid segments comprises random prime labeling.

100. The method of claim 93, wherein labeling of the nucleic acid segments comprises nick translation labeling.

101. The method of claim 93, wherein about 95% of the array-immobilized genomic nucleic acid comprise a detectable label.

102. The method of claim 101, wherein about 98% of the array-immobilized genomic nucleic acid comprise a detectable label.

103. The method of claim 102, wherein 100% of the array-immobilized genomic nucleic acid comprise a detectable label.

104. The method of claim 93, comprising use of a device that can detect a detectable label.

105. The method of claim 104, wherein the device measures which spots on the substrate surface are associated with a detectable label.

106. The method of claim 104, wherein the device measures how much detectable label is on which spot on the substrate surface.

107. The method of claim 104, wherein the device comprises a charge-coupled device (CCD).

108. The method of claim 104, wherein the device is capable of multicolor fluorescence imaging.

109. The method of claim 104, comprising use of a computer processor to analyze multicolor fluorescence imaging data.

110. The method of claim 104, further comprising use of a computer and a computer program algorithm to interpret data imaged from the array and display results.

111. The method of claim 77, further comprising a washing step, wherein nucleic acid in the sample not specifically hybridized to the genomic nucleic acid segments immobilized on the array are removed.

112. The method of claim 111, wherein the washing step comprises use of a solution comprising a salt concentration of about 0.02 molar at pH 7 at a temperature of at least about 50° C.

113. The method of claim 111, wherein the washing step comprises use of a solution comprising a salt concentration of about 0.15 M at a temperature of at least about 72° C. for about 15 minutes.

114. The method of claim 111, wherein the washing step comprises use of a solution comprising a salt concentration of about 0.2×SSC at a temperature of at least about 50° C. for at least about 15 minutes.

115. The method of claim 77, further comprising steps for a comparative genomic hybridization (CGH), the method further comprising associating the nucleic acid in the first sample of step (b) with a detectable label;

providing a second sample comprising nucleic acid complementary to a substantially complete genome, wherein the nucleic acid comprises a detectable label distinguishable from the detectable label associated with the first sample genomic nucleic acid, and the karyotype of the genome of the second sample is known;

contacting the array with the nucleic acid of the first sample and the nucleic acid of the second sample under conditions wherein the nucleic acid of the samples can specifically hybridize to the array-immobilized nucleic acid;

measuring the location and amount of nucleic acid from the first and second sample specifically hybridized to the genomic nucleic acid segments immobilized on the array, thereby performing a comparative genomic hybridization.

116. The method of claim 115, wherein the nucleic acid from the first and the second sample are from the same species.

117. The method of claim 116, wherein the nucleic acid from the first and the second sample are from a human sample.

118. The method of claim 115, wherein the substantially complete genome of the second sample comprises a wild type genome.

119. A kit comprising the following components:

(a) an array for the detection of a chromosomal abnormality or a diagnosis of a syndrome associated with a contiguous gene abnormality, comprising a plurality of nucleic acids segments, wherein each nucleic acid is immobilized to a discrete and known spot on a substrate surface to form an array of nucleic acids, and each spot comprises a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome; and,

(b) instructions for using the array to detect a chromosomal abnormality.

120. The kit of claim 119, further comprising materials to prepare a sample comprising a genomic nucleic acid for application to the array.

121. The kit of claim 119, further comprising materials to label the sample genomic nucleic acid.

122. The kit of claim 119, further comprising a sample of wild type genomic nucleic acid.

123. The kit of claim 122, wherein the wild type genomic nucleic acid is labeled.

124. The kit of claim 123, wherein the wild type genomic nucleic acid comprises a label different from that used to label the sample genomic nucleic acid.

125. The kit of claim 122, wherein the wild type genomic nucleic acid comprises a human wild type genomic nucleic acid.

126. A compilation of nucleic acids for the detection of a chromosomal abnormality or a diagnosis of a syndrome associated with a contiguous gene abnormality, comprising a plurality of nucleic acids segments, wherein each nucleic acid segment comprises a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

127. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 1, locus 1p;36, and the syndrome detected is 1p Deletion Syndrome.

128. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 1, locus 7p11.2, and the syndrome detected is Smith-Magenis syndrome (SMS).

129. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 3, locus 3p25-pter, and the syndrome detected is 3p Deletion Syndrome.

130. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 3, locus 3p21-pter, and the syndrome detected is 3p Duplication Syndrome.

131. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 4, locus 4p16.3, and the syndrome detected is Wolf-Hirschhorn Syndrome.

132. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 4, locus 4p15.2-16.1, and the syndrome detected is 4p Duplication Syndrome.

133. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 5, locus 5p15.2-pter, and the syndrome detected is Cri du Chat Syndrome.

134. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 7, locus 7p13.3, and the syndrome detected is Miller-Dieker Syndrome.

135. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 7, locus 7q11.23, and the syndrome detected is Williams Syndrome.

136. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 8, locus 8q24.1, and the syndrome detected is Langer-Giedion Syndrome (LGS).

137. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 8, locus 8q24.1, and the syndrome detected is Trichorhinophalangeal Syndrome (TRPS).

138. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 8, locus 8q13.3, and the syndrome detected is branchio-oto-renal (BOR) syndrome.

139. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 9, locus 9p, and the syndrome detected is 9p Deletion Syndrome.

140. The compilation of nucleic acids of claim 126, wherein the 9p locus comprises locus 9p22-pter.

141. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 10, locus 10p13-p14, and the syndrome detected is DiGeorge Syndrome II.

142. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 11, locus 11p13, and the syndrome detected is WAGR Syndrome.

143. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 11, locus 11p15.5, and the syndrome detected is Beckwith-Wiedemann Syndrome.

144. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 11, locus 11p11.2, and the syndrome detected is Potocki-Shaffer Syndrome (Multiple Exostoses II Locus).

145. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 13, locus 13q22, and the syndrome detected is Hirschsprung disease and Waardenburg syndrome.

146. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 15, locus 15q12, and the syndrome detected is Angelman Syndrome.

147. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 15, locus 15q12, and the syndrome detected is Prader-Willi Syndrome.

148. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 16, locus distal 16p13.3, and the syndrome detected is Rubinstein-Taybi Syndrome.

149. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 16, pericentromeric region, and the syndrome detected is idiopathic epilepsy and paroxysmal dyskinesia.

150. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 17, locus 17p12, and the syndrome detected is Charcot-Marie-Tooth Disease Type 1A(CMT-1A).

151. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 17, locus 17p12, and the syndrome detected is Hereditary Neuropathy with Liability to Pressure Palsies.

152. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 17, locus 17p13.3, and the syndrome detected is Miller-Dicker Syndrome/Isolated Lissencephaly.

153. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 17, locus 17p11.2, and the syndrome detected is Smith-Magenis Syndrome.

154. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 20, locus 20p11.2-p1^2, and the syndrome detected is Alagille Syndrome.

155. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 22, locus 22q11.2, and the syndrome detected is Digeorge/Velocardiofacial Syndrome.

156. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp21, and the syndrome detected is Adrenal Hypoplasia Congenita (AHC).

157. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp21, and the syndrome detected is Duchenne/Becker Muscular Dystrophy.

158. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp21, and the syndrome detected is Glycerol Kinase Deficiency.

159. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp22, and the syndrome detected is Pelizaeus-Merzbacher Disease.

160. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp22.3, and the syndrome detected comprises steroid sulfatase deficiency.

161. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp22.3, and the syndrome detected is Leri-Weill syndrome.

162. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome Y, locus SRY locus/Yp, and the syndrome detected comprises abnormalities of the SRY locus.

163. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp22.3, and the syndrome detected is Kallman Disease.

164. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome X, locus Xp21, and the syndrome detected is Sex Reversal (DSS).

165. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 17, locus 17p1.2, and the syndrome detected is 17p1.2 Duplication Syndrome.

166. The compilation of nucleic acids of claim 126, wherein a segment of genomic nucleic acid comprises chromosome 17, locus 17p11.2, and the syndrome detected is Smith-Magenis syndrome (SMS).

167. The compilation of nucleic acids of claim 126, wherein the nucleic acid segments further comprise a cloning vehicle.

168. The compilation of nucleic acids of claim 126, wherein about 75% of the nucleic acid segments comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

169. The compilation of nucleic acids of claim 168, wherein about 80% of the nucleic acid segments comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

170. The compilation of nucleic acids of claim 169, wherein about 85% of the nucleic acid segments comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

171. The compilation of nucleic acids of claim 170, wherein about 90% of the nucleic acid segments comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

172. The compilation of nucleic acids of claim 171, wherein about 95% of the nucleic acid segments comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome

173. The compilation of nucleic acids of claim 172, wherein about 98% of the nucleic acid segments comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

174. The compilation of nucleic acids of claim 173, wherein 100% of the nucleic acid segments comprise a segment of genomic nucleic acid associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome.

175. The compilation of nucleic acids of claim 126, wherein the nucleic acids segments are immobilized onto a surface.

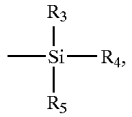
176. The compilation of nucleic acids of claim 175, wherein the nucleic acid segments are immobilized on a surface as an array.

177. The compilation of nucleic acids of claim 126, wherein about 95% of the nucleic acid segments comprise a detectable label.

178. The compilation of nucleic acids of claim 177, wherein about 98% of the nucleic acid segments comprise a detectable label.

179. The compilation of nucleic acids of claim 178, wherein 100% of the nucleic acid segments comprise a detectable label.

180. The compilation of nucleic acids of claim 126, wherein the nucleic acid segments further comprise a compound having the general formula: R_1—X—R_2, wherein R_1 is a cyclic ether, an aldehyde, or a chloromethylphenyl moiety; X is a moiety chemically suitable for linking the R_1 moiety to the R_2 moiety, and the R_2 moiety has the general formula



wherein R_3, R_4 and R_5 comprise identical or different alkoxy group or chloro groups.

181. The compilation of nucleic acids of claim 126, wherein the nucleic acid segments further comprise a compound having the general formula: R_1—X—R_2, wherein R_1 is an amino group, R_2 is an alkoxysilane group or a chlorohalide group; and X is a moiety chemically suitable for linking the R_1 group and the R_2 group.

182. The compilation of nucleic acids of claim 126, wherein the nucleic acid segments further comprise a compound having the general formula

$$R_1—X—Si(OR_2)_m(Cl)_n(R)_k,$$

wherein m+k is the integer 3, and n can be 0 if m is greater than 0, or n+k is the integer 3 and m can be 0 if n is greater than 0; X is an inert linker; R_1 comprises a group reactive toward the biological molecule; R is an alkyl group; and, R_2 is an alkyl group.

183. The compilation of nucleic acids of claim 126, wherein at least one nucleic acid segment is cloned in a construct comprising an artificial chromosome.

184. The compilation of nucleic acids of claim 183, wherein the artificial chromosome comprises a bacterial artificial chromosome (BAC).

185. The compilation of nucleic acids of claim 183, wherein the artificial chromosome is selected from the group consisting of a human artificial chromosome (HAC) a yeast artificial chromosome (YAC), a transformation-competent artificial chromosome (TAC) and a bacteriophage P1-derived artificial chromosome (PAC).

186. The compilation of nucleic acids of claim 126, wherein at least one nucleic acid segment is cloned in a construct comprising a vector selected from the group consisting of a cosmid vector, a plasmid vector and a viral vector.

187. The compilation of nucleic acids of claim 126, wherein the nucleic acid segments are between about 50 kilobases (0.5 megabase) to about 500 kilobases (5 megabases) in length.

188. The compilation of nucleic acids of claim 187, wherein the nucleic acid segments are between about 100 kilobases (1 megabase) to about 400 kilobases (4 megabases) in length.

189. The compilation of nucleic acids of claim 188, wherein the cloned nucleic acid segments are between about 150 kilobases (1.5 megabase) and about 300 kilobases (3 megabases) in length.

190. A compilation of nucleic acids for the detection of a chromosomal abnormality or the diagnosis of a syndrome associated with a contiguous gene abnormality, comprising a plurality of nucleic acid segments associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome, and the plurality of nucleic acids segments comprise:

chromosome 1, locus 1p36, wherein the syndrome detected is 1p Deletion Syndrome;

chromosome 3, locus 3p25-pter, wherein the syndrome detected is 3p Deletion Syndrome;

chromosome 3, locus 3p21-pter, wherein the syndrome detected is 3p Duplication Syndrome;

chromosome 4, locus 4p16.3, wherein the syndrome detected is Wolf-Hirschhorn Syndrome;

chromosome 4, locus 4p15.2-16.1, wherein the syndrome detected is 4p Duplication Syndrome;

chromosome 5, locus 5p15.2-pter, wherein the syndrome detected is Cri du Chat Syndrome;

chromosome 7, locus 7p13.3, wherein the syndrome detected is Miller-Dieker Syndrome;

chromosome 7, locus 7q11.23, wherein the syndrome detected is William's Syndrome;

chromosome 8, locus 8q24.1, wherein the syndrome detected is Langer-Giedion Syndrome (LGS);

chromosome 8, locus 8q24.1, wherein the syndrome detected is Trichorhinophalangeal Syndrome (TRPS);

chromosome 9, locus 9p, wherein the syndrome detected is 9p Deletion Syndrome;

chromosome 10, locus 10p13-p14, wherein the syndrome detected is DiGeorge Syndrome II;

chromosome 11, locus 11p13, wherein the syndrome detected is WAGR Syndrome;

chromosome 11, locus 11p15.5, wherein the syndrome detected is Beckwith-Wiedemann Syndrome;

chromosome 11, locus 11p11.2, wherein the syndrome detected is Potocki-Shaffer Syndrome (Multiple Exostoses II Locus);

chromosome 15, locus 15q12, wherein the syndrome detected is Angelman Syndrome;

chromosome 15, locus 15q12, wherein the syndrome detected is Prader-Willi Syndrome;

chromosome 16, locus distal 16p13.3, wherein the syndrome detected is Rubinstein-Taybi Syndrome;

chromosome 17, locus 17p12, wherein the syndrome detected is Charcot-Marie-Tooth Disease Type 1A(CMT-1A);

chromosome 17, locus 17p12, wherein the syndrome detected is Hereditary Neuropathy with Liability to Pressure Palsies;

chromosome 17, locus 17p13.3, wherein the syndrome detected is Miller-Dieker Syndrome/Isolated Lissencephaly;

chromosome 17, locus 17p11.2, wherein the syndrome detected is Smith-Magenis Syndrome;

chromosome 20, locus 20p11.2-p 12, wherein the syndrome detected is Alagille Syndrome;

chromosome 22, locus 22q11.2, wherein the syndrome detected is Digeorge/Velocardiofacial Syndrome;

chromosome X, locus Xp21, wherein the syndrome detected is Adrenal Hypoplasia Congenita (AHC);

chromosome X, locus Xp21, wherein the syndrome detected is Duchenne/Becker Muscular Dystrophy;

chromosome X, locus Xp21, wherein the syndrome detected is Glycerol Kinase Deficiency;

chromosome X, locus Xp22, wherein the syndrome detected is Pelizaeus-Merzbacher Disease;

chromosome X, locus Xp22.3, wherein the syndrome detected comprises steroid sulfatase deficiency;

chromosome Y, locus SRY locus/Yp, wherein the syndrome detected comprises abnormalities of the SRY locus;

chromosome X, locus Xp22.3, and the syndrome detected is Kallman Disease;

chromosome X, locus Xp2l, and the syndrome detected is Sex Reversal (DSS); and, chromosome 17, locus 17p11.2, and the syndrome detected is 17p11.2 Duplication Syndrome.

191. A compilation of nucleic acids, wherein each nucleic acid segment is associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome, and the nucleic acid segments are selected from the group consisting of chromosome 1, locus 1p36; chromosome 3, locus 3p25-pter; chromosome 3, locus 3p21-pter; chromosome 4, locus 4p16.3; chromosome 4, locus 4p15.2-16.1; chromosome 5, locus 5p15.2-pter; chromosome 7, locus 7p13.3; chromosome 7, locus 7q11.23; chromosome 8, locus 8q24.1; chromosome 8, locus 8q24.1; chromosome 9, locus 9p; chromosome 10, locus 10p13-p14; chromosome 11, locus 11p13; chromosome 11, locus 11p15.5; chromosome 11, locus 11p11.2; chromosome 15, locus 15q12; chromosome 16, locus distal 16p13.3; chromosome 17, locus 17p12; chromosome 17, locus 17p13.3; chromosome 17, locus 17p11.2; chromosome 20, locus 20p11.2-p12; chromosome 22, locus 22q11.2; chromosome X, locus Xp21; chromosome X, locus Xp22; chromosome X, locus Xp22.3; and, chromosome Y, locus SRY locus/Yp.

192. The compilation of nucleic acids of claim 191, wherein nucleic acid segments are immobilized onto a surface substrate.

193. The compilation of nucleic acids of claim 192, wherein the nucleic acid segments are immobilized onto the surface substrate as an array.

194. A method of detecting a chromosomal abnormality or for diagnosis of a syndrome associated with a contiguous gene abnormality in an individual comprising the following steps:

(a) providing an compilation of nucleic acids as set forth in claim 126 or claim 191;

(b) providing a sample comprising a substantially full complement of genomic DNA from the individual;

(c) contacting the genomic DNA of step (b) or a nucleic acid comprising a sequence equivalent to the genomic DNA of step (b) with the compilation of nucleic acids of step (a) under conditions wherein the nucleic acid in the sample can specifically hybridize to the compilation of nucleic acids;

(g) measuring the location and amount of genomic DNA specifically hybridized to the compilation of nucleic acids of step (a), thereby detecting a chromosomal abnormality or making a diagnosis of a syndrome associated with a contiguous gene abnormality in an individual.

195. The method of claim 194, wherein detecting the chromosomal abnormality in the individual detects a disease or a condition or a syndrome in the individual.

196. The method of claim 194, wherein the individual is a human.

197. The method of claim 194, wherein the individual is an embryo.

198. The method of claim 194, wherein the individual is suspected of having a chromosomal abnormality.

199. The method of claim 194, wherein the individual is suspected of having a disease or condition associated with a karyotype abnormality.

200. The method of claim 194, wherein the disease comprises a cancer.

201. The method of claim 194, wherein the sample comprises a body fluid sample, a cell sample or a tissue sample.

202. The method of claim 201, wherein the sample comprises a cancer cell or a tumor cell sample.

203. The method of claim 201, wherein the sample is a biopsy sample.

204. The method of claim 201, wherein the sample is a blood sample.

205. The method of claim 201, wherein the sample is a urine sample.

206. The method of claim 201, wherein the sample is a cerebral spinal fluid (CSF) sample.

207. The method of claim 201, wherein the sample is an amniotic fluid sample.

208. The method of claim 201, wherein the sample is a chorionic villus sample.

209. The method of claim 201, wherein the sample is an embryonic cell or embryo tissue sample.

210. The method of claim 194, further comprising associating the sample nucleic acid or the compilation of nucleic acids of step (a) with a detectable label.

211. The method of claim 210, wherein the detectable label is covalently associated with the nucleic acid.

212. The method of claim 210, wherein the detectable label comprises a fluorescent label.

213. The method of claim 212, wherein the fluorescent label comprises Cy5™ or equivalent.

214. The method of claim 212, wherein the fluorescent label comprises Cy3™ or equivalent.

215. The method of claim 212, wherein the fluorescent label comprises a rhodamine, a fluorescein or an aryl-substituted 4,4-difluoro-4-bora-3a, 4a-diaza-s-indacene dye or equivalents.

216. The method of claim 210, wherein labeling of the nucleic acid segments comprises random prime labeling.

217. The method of claim 210, wherein labeling of the nucleic acid segments comprises nick translation labeling.

218. The method of claim 210, wherein about 95% of the compilation of nucleic acids of step (a) comprises a detectable label.

219. The method of claim 218, wherein about 98% of the compilation of nucleic acids of step (a) comprises a detectable label.

220. The method of claim 219, wherein 100% of the compilation of nucleic acids of step (a) comprises a detectable label.

221. The method of claim 210, further comprising use of a device that can detect a detectable label.

222. The method of claim 221, wherein the device comprises a charge-coupled device (CCD).

223. The method of claim 212, wherein the device is capable of multicolor fluorescence imaging.

224. The method of claim 223, further comprising use of a computer processor to analyze multicolor fluorescence imaging data.

225. The method of claim 224, further comprising use of a computer and a computer program algorithm to interpret imaged data and to display results.

226. The method of claim 194, further comprising a washing step, wherein nucleic acid in the sample not specifically hybridized to the compilation of nucleic acids of step (a) are removed.

227. The method of claim 226, wherein the washing step comprises use of a solution comprising a salt concentration of about 0.02 molar at pH 7 at a temperature of at least about 50° C.

228. The method of claim 226, wherein the washing step comprises use of a solution comprising a salt concentration of about 0.15 M at a temperature of at least about 72° C. for about 15 minutes.

229. The method of claim 226, wherein the washing step comprises use of a solution comprising a salt concentration of about 0.2×SSC at a temperature of at least about 50° C. for at least about 15 minutes.

230. The method of claim 194, further comprising

associating the nucleic acid in the first sample with a detectable label;

providing a second sample comprising nucleic acid complementary to a substantially complete genome, wherein the nucleic acid comprises a detectable label distinguishable from the detectable label associated with the first sample genomic nucleic acid, and the karyotype of the genome of the second sample is known;

contacting the compilation of nucleic acids with the nucleic acid of the first sample and the nucleic acid of the second sample under conditions wherein the nucleic acid of the samples can specifically hybridize to the compilation of nucleic acids;

measuring the location and amount of nucleic acid from the first and second sample specifically hybridized to the compilation of nucleic acids.

231. The method of claim 230, wherein the nucleic acid from the first and the second sample are from the same species.

232. The method of claim 231, wherein the nucleic acid from the first and the second sample are from a human sample.

233. The method of claim 230, wherein the substantially complete genome of the second sample comprises a wild type genome.

234. A kit comprising the following components:

(a) a compilation of nucleic acids comprising a plurality of nucleic acids segments, wherein each nucleic acid is associated with a chromosomal abnormality, a contiguous gene abnormality, a genetically linked disease or a syndrome; and,

(b) instructions for using the compilation of nucleic acids to detect a chromosomal abnormality.

235. The kit of claim 234, further comprising materials to prepare a sample comprising a genomic nucleic acid for application to the compilation of nucleic acids.

236. The kit of claim 234, further comprising materials to label the sample genomic nucleic acid.

237. The kit of claim 234, further comprising a sample of wild type genomic nucleic acid.

238. The kit of claim 237, wherein the wild type genomic nucleic acid is labeled.

239. The kit of claim 237, wherein the wild type genomic nucleic acid comprises a label different from that used to label the sample genomic nucleic acid.

240. The kit of claim 237, wherein the wild type genomic nucleic acid comprises a human wild type genomic nucleic acid.

241. A method for selecting a genomic nucleic acid segment for use as a hybridization target in a comparative genomic hybridization (CGH) reaction for the detection of a chromosomal aneuploidy comprising

(a) selecting a chromosomal segment that hybridizes to a single locus under stringent conditions, wherein the locus comprises a segment of the chromosome comprising the aneuploidy to be detected;

(b) selecting a chromosomal segment having at least about 15% to 25% unique sequence not present in the other regions of the genome such that at least 75% to 85% of the sequence within the chromosomal segment is repetitive, except for chromosomal segments from the X chromosome or Y chromosome, which can have up to 90% to 95% repetitive sequences; and

(c) selecting a clone selected in both step (a) and step (b), thereby selecting a genomic nucleic acid segment for use as a hybridization target in a comparative genomic hybridization (CGH) reaction for the detection of a chromosomal aneuploidy.

242. The method of claim 241 comprising selecting a chromosomal segment having at least about 15% unique sequence not present in the other regions of the genome.

243. An article of manufacture comprising a plurality of nucleic acid segments, wherein each nucleic acid segment comprises the following characteristics:

(a) each nucleic acid segment comprises a genomic nucleic acid sequence that hybridizes to a single locus of the genome under stringent conditions; and

(b) each nucleic acid segment has at least about 15% to 25% unique sequence not present in the other regions of the genome such that at least 75% to 85% of the sequence within the chromosomal segment is repetitive, except for chromosomal segments from the X chromosome or Y chromosome, which can have up to 90% to 95% repetitive sequences.

244. The method of claim 243, wherein the article of manufacture is an array.

245. A library of nucleic acid segments, wherein each member of the library comprises the following characteristics:

(a) each member of the library comprises a genomic nucleic acid sequence that hybridizes to a single locus of the genome under stringent conditions; and

(b) each member of the library has at least about 15% to 25% unique sequence not present in the other regions of the genome such that at least 75% to 85% of the sequence within the chromosomal segment is repetitive in nature, except for chromosomal segments from the X chromosome or Y chromosome, which can have up to 90% to 95% repetitive sequences.

* * * * *

专利名称(译)	核酸和阵列的汇编以及使用它们的方法		
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摘要(译)

在一个方面，本发明提供核酸的编组，制品，例如阵列，以及用于检测染色体异常的方法，例如染色体非整倍性，缺失，扩增等，以及相关综合征的诊断或预后。具有连续的基因异常。还提供套件。