



## Genomic Alterations, Postnatal, ClariSure™ CGH

Test code: 16135X

### Clinical Use

- Differential diagnosis of developmental delay, mental retardation, autism, and congenital anomalies
- Confirm or exclude the diagnosis of known chromosomal syndromes
- Assist in clinical management and genetic counseling

### Clinical Background

The etiology of disorders characterized by developmental delay, mental retardation, autism, and dysmorphic features overlaps in that a specific disorder may manifest with more than one of these characteristics. Furthermore, many of the disorders are attributed to unbalanced chromosomal aberrations, ie, those with a net gain or loss of genetic material. Thus, the laboratory evaluation used to help determine the etiology of these symptoms is quite similar. Such a laboratory evaluation includes the use of high resolution chromosome analysis, fluorescence in situ hybridization (FISH), and molecular techniques such as polymerase chain reaction (PCR) coupled with gel electrophoresis. Owing to limitations of the methods, however, the underlying cause of the disorder is too often not determined.

Microarray-based comparative genomic hybridization (array CGH, aCGH) is another technique that can be employed to help determine the etiology. aCGH can detect unbalanced chromosomal aberrations including microdeletions, microduplications, aneuploidy, unbalanced translocations, and subtelomeric and pericentromeric copy number alterations. Unlike chromosome analysis, aCGH can detect deletions and duplications smaller than 5 megabases (Mb) and, in contrast to FISH, can scan for multiple aberrations simultaneously when clinical symptoms do not point to a specific disorder.

This postnatal-targeted aCGH assay is an expanded version of that reported by Chan et al.<sup>1</sup> It uses bacterial artificial chromosomes (BACs), containing known regions of the human genome, printed on coated glass slides. This array includes over 3000 BACs per slide, which equates to an average of 1 BAC/Mb across the genome, exceeding even the highest G-banded chromosome analysis that has 850 bands/genome resolution. Additionally, BAC coverage is enriched at subtelomeric and pericentromeric regions and in close proximity to regions associated with specific dosage abnormality syndromes. Refer to Table 1 for a list of gene

targets and associated disorders.

The American College of Medical Genetics practice guidelines recommend CGH be used as an adjunct to chromosome analysis and FISH testing when evaluating patients with developmental delay, mental retardation, and/or congenital anomalies.<sup>2</sup> Studies have shown aCGH can detect clinically relevant genomic aberrations undetected by chromosomal analysis or FISH studies,<sup>3-7</sup> thus improving etiology determination by roughly 3% to 14%.

### Individuals Suitable for Testing

- Individuals with an unexplained abnormal phenotype but normal karyotype or FISH studies

### Specimen Requirements

10 mL room-temperature whole blood (sodium-heparin, green-top tube); 5 mL minimum

### Method

- Extraction of patient DNA from whole blood
- Array-CGH
  - Random priming amplification with differential labeling of patient and reference DNA; samples tested in duplicate
  - Hybridization of patient and reference DNA to a microarray containing over 3000 individual BACS (each in duplicate)
  - Comparison of reference and patient DNA fluorescence signals to determine copy number ratios
- Verification of duplications or deletions with specific FISH assays
- Results reported: description of any genomic gains or losses detected, along with a clinical interpretation
- Analytical sensitivity: >97%
- CPT codes\*: 88386; 83891; 83892; 83898

### Interpretive Information

Genomic gains and losses are reported according to International System Cytogenetic Nomenclature (ISCN).<sup>8</sup> The presence of specific chromosomal alterations previously associated with DD/MR indicates that these rearrangements are the cause of DD/MR. Parental testing and FISH verification of aberrations detected with array-CGH should rule out false-positive results.

This assay does not detect genetically balanced translocations, low-level mosaicism, or genomic alterations outside the regions represented in the array. Thus, negative results do not rule out the possibility of chromosomal abnormalities.

Additional assistance in interpretation of results is available from our Genetic Counselors by calling 1-866-GENE-INFO (1-866-436-3463).

Table 1. Genes Targeted in the Genomic Alterations, Postnatal, ClariSure™ CGH Assay

OMIM #	Disorder	Gene Target	Gene Map Locus
607872	1p36 deletion syndrome	Multiple	1p36
612474	1q21.1 deletion syndrome	Multiple	1q21.1
274000	1q21.1 deletion syndrome (thrombocytopenia-absent radius [TAR] syndrome)	Multiple	1q21.1
612475	1q21.1 duplication syndrome	Multiple	1q21.1
612513	2p16.1-p15 deletion syndrome	Multiple	2p16.1-p15
612313	2q32-q33 deletion syndrome	Multiple	2q32-q33
609425	3q29 microdeletion syndrome	Multiple in 3q29, including <i>PAK2</i> and <i>DLG1</i>	3q29
612001	15q13.3 microdeletion syndrome	Multiple	15q13.3
610443	17q21.31 microdeletion syndrome	<i>MAPT, CRHR1</i>	17q21.31
608363	22q11.2 microduplication syndrome	Duplication of 3-Mb region in 22q11	22q11.2
611867	22q11.2 deletion syndrome, distal	Multiple	22q11.2
606232	22q13.3 deletion syndrome	<i>SHANK3</i>	22q13.3
610253	9q34.3 deletion syndrome	<i>EHMT1</i>	9q34.3
300200	Adrenal hypoplasia, congenital	<i>NROB1</i>	Xp21.3-p21.2
118450	Alagille syndrome	<i>JAG1</i>	20p12
203200	Albinism, oculocutaneous, type II	<i>OCA2</i>	15q11.2-q12
	All unique subtelomeric regions	Multiple	41 subtelomeres
	All unique pericentromeric regions	Multiple	43 pericentromeric regions
141750	Alpha-thalassemia/mental retardation syndrome, deletion type	<i>HBA1, HBA2, SOX8</i>	16pter-p13.3
104760	Alzheimer disease-1, APP-related	<i>APP</i>	21q21
	Aneuploidy	Multiple	All chromosomes
105830	Angelman syndrome	<i>UBE3A</i>	15q11.2-q13
106210	Aniridia, type II	<i>PAX6</i>	11p13
607941	Atrial septal defect 2	<i>GATA4</i>	8p23.1-p22
608636	Autism susceptibility	Duplication of 15q11-q13	15q11
611913	Autism susceptibility	Multiple	16p11.2
300495	Autism, X-linked, susceptibility	<i>NLGN4X</i>	Xp22.33
400003 400026 400027	Azoospermia factors (a, b, and c)	<i>DAZ 1-4</i>	Yq11
209900	Bardet-Biedl syndrome 14	<i>CEP290</i>	12q21.3
602522	Bartter Syndrome, infantile, with sensorineural deafness	<i>BSND</i>	1p31
109400	Basal cell nevus syndrome (Gorlin syndrome)	<i>PTCH1</i>	9q22.3
130650	Beckwith-Wiedemann syndrome	<i>CDKN1C, H19, KCNQ10T1</i>	11p15.5
110100	Blepharophimosis, ptosis, and epicanthus inversus	<i>FOXL2</i>	3q23
600430	Brachydactyly-mental retardation syndrome	Deletion 2q37	2q37

continued

<b>OMIM #</b>	<b>Disorder</b>	<b>Gene Target</b>	<b>Gene Map Locus</b>
113650	Branchiootorenal syndrome 1	<i>EYA1</i>	8q13.3
300300	Bruton agammaglobulinemia tyrosine kinase	<i>BTK</i>	Xq21.3-q22
166700	Buschke-Ollendorff syndrome	<i>LEMD3</i>	12q14
114290	Campomelic dysplasia	<i>SOX9</i>	17q24.3-q25.1
115470	Cat eye syndrome		22q11
118220	Charcot-Marie-Tooth disease, demyelinating, type 1A	<i>PMP22</i>	17p11.2
214800	CHARGE syndrome	<i>CHD7</i>	8q12.1
119600	Cleidocranial dysplasia	<i>RUNX2</i>	6p21
122470	Cornelia de Lange syndrome	<i>NIPBL</i>	5p13.1
123450	Cri-du-chat syndrome	Multiple	5p15.2
176450	Currarino syndrome	<i>HLXB9</i>	7q36
220200	Dandy-Walker syndrome	<i>ZIC4, ZIC1</i>	3q24
142340	Diaphragmatic hernia, congenital	<i>CHD2, NR2F2</i>	15q26.1
188400 192430	DiGeorge/Velocardiofacial syndrome 1	<i>HIRA, TBX1</i>	22q11.2
601362	DiGeorge/Velocardiofacial syndrome 2	Unknown	10p14-p13
300018	Dosage-sensitive sex reversal	<i>NROB1</i>	Xp21.3-p21.2
190685	Down syndrome critical region	Multiple	21q22.3
300672	Epileptic encephalopathy, early infantile, 2	<i>CDKL5</i>	Xp22
175100	Familial adenomatous polyposis (FAP)/Gardner syndrome	<i>APC</i>	5q21-q22
164280	Feingold syndrome	<i>MYCN</i>	2p24.1
175700	Greig cephalopolysyndactyly syndrome	<i>GLI3</i>	7p13
162500	Hereditary neuropathy with pressure palsies (HNPP)	<i>PMP22</i>	17p11.2
306955	Heterotaxy, visceral, X-linked	<i>ZIC3</i>	Xq26.2
236100	Holoprosencephaly 1	<i>TMEM1</i>	21q22.3
157170	Holoprosencephaly 2	<i>SIX3</i>	2p21
142945	Holoprosencephaly 3	<i>SHH</i>	7q36
142946	Holoprosencephaly 4	<i>TGIF</i>	18p11.3
609637	Holoprosencephaly 5	<i>ZIC2</i>	13q32
610828	Holoprosencephaly 7	<i>PTCH1</i>	9q22.3
142900	Holt-Oram syndrome	<i>TBX5</i>	12q24.1
307030 300474	Hyperglycerolemia (glycerol kinase deficiency)	<i>GK</i>	Xp21.3-p21.2
146255	Hypoparathyroidism, sensorineural deafness, renal disease (HDR)	<i>GATA3</i>	10p15
147791	Jacobsen	Deletion 11q23; many genes	11q23
608629	Joubert syndrome 3	<i>AHI1</i>	6q23.3
610188	Joubert syndrome 5	<i>CEP290</i>	12q21.3
308700	Kallmann syndrome 1	<i>KAL1</i>	Xp22.3
	Klinefelter (XXY male)		
150230	Langer-Giedion syndrome (trichorhinophalangeal syndrome)	<i>TRPS1, EXT1</i>	8q24.11-q24.13
127300	Leri-Weill dyschondrosteosis	<i>SHOX</i> <i>SHOXY</i>	Xpter-p22.32 Ypter-p11.2

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<b>OMIM #</b>	<b>Disorder</b>	<b>Gene Target</b>	<b>Gene Map Locus</b>
169500	Leukodystrophy, demyelinating, adult-onset, autosomal dominant	<i>LMNB1</i>	5q23.3-q31.1
151623	Li-Fraumeni syndrome 1	<i>TP53</i>	17p13.1
257320	Lissencephaly 2, Norman-Roberts type	<i>RELN</i>	7q22
300067	Lissencephaly, X-linked	<i>DCX</i>	Xq22.3-q23
609192	Loeys-Dietz syndrome, type 1A	<i>TGFBR1</i>	9q22
154700	Marfan syndrome	<i>FBN1</i>	15q21.1
300419	Mental retardation, X-linked	<i>ARX</i>	Xp22.13
300706	Mental retardation, X-linked, syndromic, Turner type	<i>HUWE1</i>	Xp11.2
300123	Mental retardation, X-linked, with isolated growth hormone deficiency	<i>SOX3</i>	Xq26.3
206900	Microphthalmia, syndromic 3	<i>SOX2</i>	3q26.3-q27
247200 607432	Miller-Dieker lissencephaly syndrome	<i>LIS1</i>	17p13.3
235730	Mowat-Wilson syndrome	<i>ZEB2</i>	2q22
161200	Nail-patella syndrome	<i>LMX1B</i>	9q34.1
256100	Nephronophthisis 1	<i>NPHP1</i>	2q13
162200	Neurofibromatosis type I	<i>NF1</i>	17q11.2
101000	Neurofibromatosis type II	<i>NF2</i>	22q12.2
163950	Noonan syndrome 1	<i>PTPN11</i>	12q24.1
610733	Noonan syndrome 4	<i>SOS1</i>	2p22-p21
312080	Pelizaeus-Merzbacher disease	<i>PLP1</i>	Xq22
601313	Polycystic kidney disease 1	<i>PKD1</i>	16p13.3-p13.12
610883	Potocki-Lupski syndrome	<i>RAI1</i>	17p11.2
601224	Potocki-Shaffer syndrome	<i>EXT2, ALX4</i>	11p11.2
176270	Prader-Willi	<i>SNRPN</i> <i>NDN</i>	15q12 15q11-q13
176270	Prader-Willi-like phenotype	<i>SIM1</i>	6q16.3-q21
137920	Renal cysts and diabetes syndrome	<i>HNF1B</i>	17q12
180200	Retinoblastoma	<i>RB1</i>	13q14.1-q14.2
312750	Rett syndrome	<i>MECP2</i>	Xq28
180500	Rieger syndrome, type 1	<i>PITX2</i>	4q25-q26
180849	Rubinstein-Taybi syndrome	<i>CREBBP</i>	16p13.3
101400	Saethre-Chotzen syndrome	<i>TWIST1</i>	7p21
607208	Severe myoclonic epilepsy of infancy	<i>SCN1A</i>	2q24
184757	Sex reversal, XY, with or without adrenal failure	<i>NR5A1</i>	9q33
606606	Short stature, pituitary and cerebellar defects, and small sella turcica	<i>LHX4</i>	1q25
270400	Smith-Lemli-Opitz syndrome	<i>DHCR7</i>	11q12-q13
182290	Smith-Magenis syndrome	<i>RAI1</i>	17p11.2
117550	Sotos	<i>NSD1</i>	5q35
183600	Split hand/foot malformation 1	<i>SHFM1</i>	7q21.2-q21.3
600095	Split hand/foot malformation 3	<i>SHFM3</i>	10q24
605289	Split hand/foot malformation 4	<i>TP73L</i>	3q27

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OMIM #	Disorder	Gene Target	Gene Map Locus
606708	Split hand/foot malformation 5	<i>DLX1, DLX2</i>	2q31
308100	Steroid sulfatase deficiency (ichthyosis, X-linked)	<i>STS</i>	Xp22.32
108300	Stickler syndrome, type 1	<i>COL2A1</i>	12q13.11-q13.2
186000	Synpolydactyly 1	<i>HOXD</i> gene cluster	2q31-q32
190350	Trichorhinophalangeal 1	<i>TRPS1</i>	8q24.12
107480	Townes-Brock syndrome	<i>SALL1</i>	16q12.1
605284	Tuberous sclerosis 1	<i>TSC1</i>	9q34
191092	Tuberous sclerosis 2	<i>TSC2</i>	16p13.3
181450	Ulnar-mammary syndrome	<i>TBX3</i>	12q24.1
119300	van der Woude syndrome	<i>IRF6</i>	1q32-q41
193510	Waardenburg syndrome, type IIA	<i>MITF</i>	3p14.1-p12.3
194072	WAGR syndrome	<i>WT1</i>	11p13
609757	Williams-Beuren region duplication syndrome	<i>ELN, LIMK1</i>	7q11.23
194050	Williams-Beuren syndrome (7q11.23 deletion)	<i>ELN, LIMK1</i>	7q11.23
194190	Wolf-Hirschhorn	165kb critical region contains <i>FGFR3</i>	4p16.3

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TS2157-HS 02/2009



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