

High Density Gene-Centric Deletion and Amplification Array CGH (Test # 600)

Brief Description and Rationale: Array Comparative Genomic Hybridization (aCGH) enables the detection of deletion and amplification (mostly duplication) mutations of single and multiple exons within a given gene (Tayeh et al. Genet Med 11:232-240, 2009). PreventionGenetics' high density gene-centric (HDGC) aCGH is a custom designed oligonucleotide array with 720K probes. Our test targets a large set of genes (560 genes; see list of genes on page 2 and 3) involved in autosomal recessive, autosomal dominant and X-linked disorders. PreventionGenetics currently offers DNA sequencing tests for these genes. Our array will be periodically expanded to cover new genes that are added to our sequencing menu. *This Test involves analysis only of the specific gene(s) of interest for each patient. This Test is NOT a Chromosome Microarray (CMA) aCGH test.*

PreventionGenetics' aCGH is designed with very high density probe coverage within each gene. The average probe spacing within each exon is 24 bp with a total of 103,533 overlapping probes covering all targeted exons. The average probe spacing within each intron, 5'UTR and 3'UTR is 99 bp with a total of 436,178 overlapping probes covering all targeted introns, 5'UTR and 3'UTR. Therefore, PreventionGenetics' aCGH enables the detection of partial gene deletion and amplification mutations as small as ~100bp as well as deletion and amplification mutations of entire genes.

Deletion and amplification mutation frequency varies among genes, yet it represents a significant fraction of the total pathogenic mutations in essentially every gene (Tayeh et al. 2009). This fraction ranges from values as low as 5% (*ACADM* gene; Andresen et al. Am J Hum Genet. 68:1408-1418, 2001) up to 80% (*NHP1* gene; Konrad et al. Hum Mol Genet 5:367-371, 1996). In cases where the majority of the reported mutations in a gene can be detected by DNA sequencing, then PreventionGenetics' aCGH is an excellent complementary test when DNA sequencing fails to identify the causative mutation(s). In cases where the majority of the reported mutations in a gene are deletion and amplification mutations, then PreventionGenetics' aCGH should be considered as a primary test even before DNA sequencing. The availability of both DNA sequencing and PreventionGenetics' HDGC custom aCGH significantly improves the sensitivity of molecular clinical testing at PreventionGenetics.

Methods: Equal amounts of genomic DNA (1 ug) from each patient and from a gender matched reference sample are amplified and labeled with Cy3 and Cy5 dyes, respectively. Each labeled product is purified and quantified, then 31 µg of the patient product is combined with 31 µg of reference product. To prevent any sample cross contamination, a unique sample tracking control is added to the combined labeled products. The DNA is loaded onto the designated array and allowed to hybridize for at least 40 hours at 42° C. Arrays are then washed and scanned immediately with 2.5 µM resolution. The generated images are analyzed with multiple averaging windows.

Indications for Test: Candidates for this test are:

- Patients with genetic disorders mainly caused by deletion and amplification mutations.
- Patients with autosomal dominant disorders where no mutation has been identified by DNA sequencing.
- Patients with autosomal recessive disorders with one or no mutations have been identified by DNA sequencing.
- Patients with autosomal recessive disorders where one or more amplicons within the gene fails to PCR amplify.
- Male patients with X-linked disorders where no mutation has been identified by DNA sequencing, or PCR fails.
- Female patients with X-linked disorders with one or no mutations have been identified by DNA sequencing.
- Patients with gross genomic imbalances in a region harboring one or multiple genes targeted on PreventionGenetics' HDGC aCGH, to confirm involvement of such gene(s).

Sensitivity of Test: The prevalence of deletion and amplification mutations varies among genes with an estimated range from near 0 to 80% (see www.genetests.org). PreventionGenetics' HDGC custom designed aCGH enables the detection of relatively small deletion and amplification mutations (down to ~100 bp) within a single exon of a given gene or deletion and amplification mutations encompassing the entire gene. Undocumented intronic and noncoding region deletion or amplification variants will require additional functional and/or family studies to determine clinical significance.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 3-4 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Prices: Allele copy number analysis of one gene \$ 990
 Allele copy number analysis of two genes \$ 1190
 Allele copy number analysis of three or more genes \$ 1290 + \$100 for every additional gene
 Reanalysis of existing aCGH for additional genes (up to 5 genes) \$ 690

CPT Codes:

Sample Ascertainment	83890	\$ 30	DNA Isolation	83891	\$ 40
Amplification x1	83898	\$ 300	aCGH x1	88386	\$ 510
Interpretation/Report	83912	\$ 110			

Accreditation: CLIA ID:52D1027685 (expires 1/18/13) CAP ID:7185561, AU ID:1407125 (expires 12/20/12)

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Alphabetical list of genes targeted on the PreventionGenetics' HDGC custom aCGH, Version 3.0:

<i>A4GALT</i>	<i>ABCA4</i>	<i>ABCC8</i>	<i>ABCC9</i>	<i>ABO</i>	<i>ACADM</i>	<i>ACADS</i>	<i>ACADVL</i>	<i>ACTA1</i>
<i>ACTC1</i>	<i>ACTN2</i>	<i>ACVRL1</i>	<i>ADAMTS13</i>	<i>ADAR</i>	<i>ADSL</i>	<i>AGL</i>	<i>AGPAT2</i>	<i>AGRN</i>
<i>AHI1</i>	<i>AIPL1</i>	<i>ALG12</i>	<i>ALG2</i>	<i>ALG3</i>	<i>ALG6</i>	<i>ALG8</i>	<i>ALMS1</i>	<i>ALPL</i>
<i>ALS2</i>	<i>AMH</i>	<i>ANG</i>	<i>ANK1</i>	<i>ANO5</i>	<i>AP3B1</i>	<i>APC</i>	<i>AR</i>	<i>ARG1</i>
<i>ARL13B</i>	<i>ARL6</i>	<i>ARSA</i>	<i>ARSB</i>	<i>ARX</i>	<i>ASAH1</i>	<i>ASPA</i>	<i>ASS1</i>	<i>ATL1</i>
<i>ATM</i>	<i>ATP7A</i>	<i>ATP7B</i>	<i>AUH</i>	<i>AURKC</i>	<i>AUTS2</i>	<i>AVPR2</i>	<i>AXIN2</i>	<i>BAG3</i>
<i>BBS1</i>	<i>BBS10</i>	<i>BBS12</i>	<i>BBS2</i>	<i>BBS4</i>	<i>BBS5</i>	<i>BBS7</i>	<i>BBS9</i>	<i>BCHE</i>
<i>BCKDHA</i>	<i>BCKDHB</i>	<i>BEST1</i>	<i>BLM</i>	<i>BLOC1S3</i>	<i>BMP15</i>	<i>BMPR2</i>	<i>BRAF</i>	<i>BRCA1</i>
<i>BRCA2</i>	<i>BRIP1</i>	<i>BSCL2</i>	<i>BTD</i>	<i>BTK</i>	<i>C14orf104</i>	<i>C7</i>	<i>CA4</i>	<i>CACNA1H</i>
<i>CACNA1S</i>	<i>CAPN3</i>	<i>CAV3</i>	<i>CBS</i>	<i>CC2D2A</i>	<i>CCBE1</i>	<i>CCM2</i>	<i>CDH23</i>	<i>CDKN1B</i>
<i>CEP290</i>	<i>CERKL</i>	<i>CFL2</i>	<i>CFTR</i>	<i>CHAT</i>	<i>CHD7</i>	<i>CHRNA1</i>	<i>CHRNB1</i>	<i>CHRND</i>
<i>CHRNE</i>	<i>CHRNA1</i>	<i>CHST6</i>	<i>CLRN1</i>	<i>CNGA3</i>	<i>CNGB1</i>	<i>CNGB3</i>	<i>CNTNAP2</i>	<i>COL18A1</i>
<i>COL1A1</i>	<i>COL1A2</i>	<i>COL2A1</i>	<i>COL3A1</i>	<i>COL4A5</i>	<i>COL6A1</i>	<i>COL6A2</i>	<i>COL6A3</i>	<i>COL7A1</i>
<i>COL9A1</i>	<i>COL9A2</i>	<i>COL9A3</i>	<i>COLQ</i>	<i>COMP</i>	<i>CPS1</i>	<i>CRB1</i>	<i>CRBN</i>	<i>CRX</i>
<i>CRYAB</i>	<i>CSNK1D</i>	<i>CSRP3</i>	<i>CTH</i>	<i>CTSC</i>	<i>CUL4B</i>	<i>CUL7</i>	<i>CXorf1</i>	<i>CYB5R3</i>
<i>CYBB</i>	<i>CYLD</i>	<i>DAG1</i>	<i>DBT</i>	<i>DCTN1</i>	<i>DCX</i>	<i>DDB2</i>	<i>DDR2</i>	<i>DES</i>
<i>DFNB31</i>	<i>DHCR7</i>	<i>DLD</i>	<i>DLL3</i>	<i>DMD</i>	<i>DNAH11</i>	<i>DNAH5</i>	<i>DNAI1</i>	<i>DNAI2</i>
<i>DNMT3B</i>	<i>DOK7</i>	<i>DPM1</i>	<i>DPM3</i>	<i>DRD2</i>	<i>DSC2</i>	<i>DSG2</i>	<i>DSP</i>	<i>DSPP</i>
<i>DYM</i>	<i>DYSF</i>	<i>EBP</i>	<i>ECM1</i>	<i>EHMT1</i>	<i>EIF2B1</i>	<i>EIF2B2</i>	<i>EIF2B3</i>	<i>EIF2B4</i>
<i>EIF2B5</i>	<i>ELANE</i>	<i>EMD</i>	<i>ENG</i>	<i>ENPP1</i>	<i>ERCC3</i>	<i>ERCC4</i>	<i>ERCC5</i>	<i>EVC</i>
<i>EVC2</i>	<i>EXT1</i>	<i>EXT2</i>	<i>F7</i>	<i>F9</i>	<i>FAH</i>	<i>FANCA</i>	<i>FANCB</i>	<i>FANCC</i>
<i>FANCE</i>	<i>FANCF</i>	<i>FANCG</i>	<i>FANCI</i>	<i>FANCL</i>	<i>FANCM</i>	<i>FBN1</i>	<i>FBN2</i>	<i>FBP1</i>
<i>FGFR3</i>	<i>FKRP</i>	<i>FKTN</i>	<i>FLNC</i>	<i>FLT4</i>	<i>FMO3</i>	<i>FOXC2</i>	<i>FOXH1</i>	<i>FSCN2</i>
<i>FSHB</i>	<i>FSHR</i>	<i>FUS</i>	<i>FUT1</i>	<i>FUT2</i>	<i>G6PC</i>	<i>G6PC3</i>	<i>G6PD</i>	<i>GAA</i>
<i>GALNS</i>	<i>GALT</i>	<i>GAMT</i>	<i>GARS</i>	<i>GATA1</i>	<i>GATM</i>	<i>GBE1</i>	<i>GCDH</i>	<i>GCH1</i>
<i>GALC</i>	<i>GCK</i>	<i>GDF6</i>	<i>GHR</i>	<i>GHSR</i>	<i>GJB1</i>	<i>GJB2</i>	<i>GJC2</i>	<i>GLA</i>
<i>GLB1</i>	<i>GLI2</i>	<i>GLI3</i>	<i>GLIS2</i>	<i>GM2A</i>	<i>GNAT2</i>	<i>GNE</i>	<i>GNPTAB</i>	<i>GNPTG</i>
<i>GNS</i>	<i>GP1BA</i>	<i>GP1BB</i>	<i>GP9</i>	<i>GPC3</i>	<i>GPI</i>	<i>GPR56</i>	<i>GPR98</i>	<i>GRIK2</i>
<i>GUCA1A</i>	<i>GUCA1B</i>	<i>GUCY2D</i>	<i>GUSB</i>	<i>GYS2</i>	<i>HAX1</i>	<i>HEXA</i>	<i>HEXB</i>	<i>HGSNAT</i>
<i>HLCS</i>	<i>HMBS</i>	<i>HMGCL</i>	<i>HNF1A</i>	<i>HPRT1</i>	<i>HPS1</i>	<i>HPS3</i>	<i>HPS4</i>	<i>HPS5</i>
<i>HPS6</i>	<i>HRAS</i>	<i>HSD17B3</i>	<i>HSPB1</i>	<i>HSPB8</i>	<i>HYAL1</i>	<i>IDUA</i>	<i>IGHMBP2</i>	<i>IMPDH1</i>

Alphabetical list of genes targeted on the PreventionGenetics' HDGC custom aCGH, Version 3.0 (continued):

<i>IL1A</i>	<i>IL1B</i>	<i>IL2RG</i>	<i>IMPDH1</i>	<i>INPP5E</i>	<i>INVS</i>	<i>IQCB1</i>	<i>ITGA7</i>	<i>IVD</i>
<i>JAG1</i>	<i>JUP</i>	<i>KCNH2</i>	<i>KCNQ1</i>	<i>KCNV2</i>	<i>KIT</i>	<i>KRAS</i>	<i>KRIT1</i>	<i>L1CAM</i>
<i>LAMA2</i>	<i>LAMP2</i>	<i>LARGE</i>	<i>LDB3</i>	<i>LDLR</i>	<i>LFNG</i>	<i>LHX4</i>	<i>LIPA</i>	<i>LMAN1</i>
<i>LMBRD1</i>	<i>LMNA</i>	<i>LPIN1</i>	<i>LRAT</i>	<i>LRP2</i>	<i>LRRC50</i>	<i>LYST</i>	<i>MAP2K1</i>	<i>MAP2K2</i>
<i>MASTL</i>	<i>MATN3</i>	<i>MATR3</i>	<i>MCCC1</i>	<i>MCCC2</i>	<i>MECP2</i>	<i>MED12</i>	<i>MEN1</i>	<i>MERTK</i>
<i>MESP2</i>	<i>MITF</i>	<i>MKKS</i>	<i>MKS1</i>	<i>MLH1</i>	<i>MLH3</i>	<i>MMAA</i>	<i>MMAB</i>	<i>MMADHC</i>
<i>MPDU1</i>	<i>MPI</i>	<i>MPL</i>	<i>MSH2</i>	<i>MSH6</i>	<i>MTHFR</i>	<i>MTM1</i>	<i>MTR</i>	<i>MTRR</i>
<i>MTTP</i>	<i>MUSK</i>	<i>MUT</i>	<i>MUTYH</i>	<i>MYBPC3</i>	<i>MYH3</i>	<i>MYH6</i>	<i>MYH7</i>	<i>MYH9</i>
<i>MYL2</i>	<i>MYL3</i>	<i>MYO7A</i>	<i>MYOT</i>	<i>NAGLU</i>	<i>NAGPA</i>	<i>NAGS</i>	<i>NEK8</i>	<i>NF1</i>
<i>NF2</i>	<i>NHS</i>	<i>NKX2-1</i>	<i>NLGN3</i>	<i>NPC1</i>	<i>NPC2</i>	<i>NPHP1</i>	<i>NPHP3</i>	<i>NPHP4</i>
<i>NR0B1</i>	<i>NR2E3</i>	<i>NRAS</i>	<i>NRL</i>	<i>NRXN1</i>	<i>NSD1</i>	<i>NT5C3</i>	<i>OCA2</i>	<i>OFD1</i>
<i>OPHN1</i>	<i>OPTN</i>	<i>OTC</i>	<i>PAFAH1B1</i>	<i>PAH</i>	<i>PALB2</i>	<i>PARK2</i>	<i>PAX3</i>	<i>PAX6</i>
<i>PCCA</i>	<i>PCCB</i>	<i>PCDH15</i>	<i>PDCD10</i>	<i>PDE6A</i>	<i>PDE6B</i>	<i>PDE6C</i>	<i>PER2</i>	<i>PFKM</i>
<i>PHEX</i>	<i>PHKA2</i>	<i>PHKB</i>	<i>PHKG2</i>	<i>PKHD1</i>	<i>PKLR</i>	<i>PLN</i>	<i>PLP1</i>	<i>PMM2</i>
<i>PMS1</i>	<i>PNKD</i>	<i>POLH</i>	<i>POMGNT1</i>	<i>POMT1</i>	<i>POMT2</i>	<i>PPARG</i>	<i>PRF1</i>	<i>PRKAG2</i>
<i>PRNP</i>	<i>PROC</i>	<i>PROM1</i>	<i>PRPF3</i>	<i>PRPF31</i>	<i>PRPF8</i>	<i>PRPH2</i>	<i>PRSS12</i>	<i>PSAP</i>
<i>PSEN1</i>	<i>PTCH1</i>	<i>PTEN</i>	<i>PTPN11</i>	<i>PYGL</i>	<i>PYGM</i>	<i>RAB27A</i>	<i>RAF1</i>	<i>RAI1</i>
<i>RAPSN</i>	<i>RB1</i>	<i>RDH12</i>	<i>RDH5</i>	<i>RELN</i>	<i>RET</i>	<i>RGR</i>	<i>RHO</i>	<i>RLBP1</i>
<i>RMRP</i>	<i>RPGRIP1L</i>	<i>ROM1</i>	<i>ROR2</i>	<i>RP1</i>	<i>RPE65</i>	<i>RS1</i>	<i>RSPH4A</i>	<i>RSPH9</i>
<i>RUNX1</i>	<i>RUNX2</i>	<i>RYR1</i>	<i>RYR2</i>	<i>SCN1A</i>	<i>SCN5A</i>	<i>SDCCAG8</i>	<i>SEMA4A</i>	<i>SEPNI</i>
<i>SERPINA7</i>	<i>SERPINC1</i>	<i>SERPING1</i>	<i>SETX</i>	<i>SGCA</i>	<i>SGCB</i>	<i>SGCD</i>	<i>SGCG</i>	<i>SGSH</i>
<i>SHANK3</i>	<i>SHH</i>	<i>SHOC2</i>	<i>SHOX</i>	<i>SIX3</i>	<i>SLC24A1</i>	<i>SLC26A2</i>	<i>SLC26A4</i>	<i>SLC2A2</i>
<i>SLC35C1</i>	<i>SLC37A4</i>	<i>SLC39A4</i>	<i>SLC45A2</i>	<i>SLC4A11</i>	<i>SLC5A1</i>	<i>SLC9A6</i>	<i>SMAD4</i>	<i>SMPD1</i>
<i>SOD1</i>	<i>SOS1</i>	<i>SOX18</i>	<i>SPAST</i>	<i>SPRED1</i>	<i>SPTA1</i>	<i>SPTB</i>	<i>STK11</i>	<i>STX11</i>
<i>STXBP2</i>	<i>SUMF1</i>	<i>SYNE1</i>	<i>TARDBP</i>	<i>TAZ</i>	<i>TBX5</i>	<i>TCAP</i>	<i>TGFB1</i>	<i>TGFB3</i>
<i>TGFBR1</i>	<i>TGFBR2</i>	<i>TGIF1</i>	<i>TH</i>	<i>TIMP3</i>	<i>TMEM216</i>	<i>TMEM43</i>	<i>TMEM67</i>	<i>TNNC1</i>
<i>TNNI2</i>	<i>TNNI3</i>	<i>TNNT1</i>	<i>TNNT2</i>	<i>TNNT3</i>	<i>TOPORS</i>	<i>TOR1A</i>	<i>TP53</i>	<i>TPM1</i>
<i>TPM2</i>	<i>TPM3</i>	<i>TPMT</i>	<i>TRAPPC9</i>	<i>TRIM32</i>	<i>TSC1</i>	<i>TSC2</i>	<i>TSEN2</i>	<i>TSEN34</i>
<i>TSEN54</i>	<i>TTC8</i>	<i>TTN</i>	<i>TTR</i>	<i>TUBA1A</i>	<i>TULP1</i>	<i>TUSC3</i>	<i>TXNDC3</i>	<i>TYRP1</i>
<i>UBE3A</i>	<i>UNC13D</i>	<i>USH1C</i>	<i>USH1G</i>	<i>USH2A</i>	<i>VAPB</i>	<i>VCL</i>	<i>VHL</i>	<i>VIPAR</i>
<i>VPS13B</i>	<i>VPS33B</i>	<i>WAS</i>	<i>WDR35</i>	<i>WDR62</i>	<i>WFS1</i>	<i>XPNPEP3</i>	<i>YWHAE</i>	<i>ZFPM2</i>
<i>ZIC2</i>	<i>ZMPSTE24</i>							