

GeneDx accession #:	000000	Patient name:	DOE, Girl
Date specimen obtained:	11-01-2007	Date of birth:	01-01-2005
Date specimen received:	11-02-2007	Gender:	Female
Date of report:	11-??-2007	Specimen type:	Blood in EDTA
		Submitter ID #:	1234567

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TEST INDICATION: Female with developmental delay, short stature, hypotonia, swallowing difficulty, outer ear abnormalities, atrial septal defect, and dysmorphic facial features; Normal 46,XX karyotype, FISH 22q11 and subtelomere studies.

RESULT:

arr cgh 8q12.1q12.2(61,424,674-62,001,209)x1
Sex: female

ABNORMAL (POSITIVE); SEE INTERPRETATION

This patient harbors a *de novo* interstitial 576-kb deletion within a region of 8q12 that is associated with CHARGE syndrome.

CONFIRMATION:

Quantitative PCR analysis with primers targeted to a gene (CHD7) located within the deleted interval confirmed the presence of a heterozygous deletion of this region in the patient. Analysis of DNA samples from both parents yielded normal results.

INTERPRETATION:

This patient carries an interstitial deletion of approximately 576-kb on the long arm of chromosome 8, extending from cytogenetic band 8q12.1 to 8q12.2. The deleted interval contains two genes, CHD7 and RAB2A. While the clinical relevance of haploinsufficiency for the gene encoding the RAS associated protein 2A is unknown, heterozygous mutations in CHD7 (OMIM 608892) are associated with autosomal dominant CHARGE syndrome (OMIM 214800)¹. The majority of pathogenic mutations in CHD7 are small intragenic mutations identifiable by gene sequencing. However, whole and partial heterozygous deletions of CHD7 also have been reported.^{2,3,4}

CHARGE syndrome is a well-defined genetic disorder in which most cases occur *de novo*, as is the case in this child. Major diagnostic criteria include ocular coloboma, choanal atresia/stenosis, cranial nerve abnormalities, and characteristic ear anomalies; minor clinical features consist of developmental delay, growth deficiency, distinctive facial features, cardiovascular malformation, genital hypoplasia, facial cleft, and tracheoesophageal fistula. As with any contiguous gene deletion syndrome, the phenotype in this patient may be more complex due to the loss of more than one gene within the deleted segment.

RECOMMENDATION

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Clinical correlation between this result and the patient's phenotype is recommended. Genetic counseling is recommended to discuss the implications of this report.

REFERENCES:

1. Online Mendelian Inheritance in Man. www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM
2. Vissers, LE. et al. *Nat Genet.* 36:955-7, 2004.
3. Udaka, T. et al. *Am J Med Genet A.* 143:721-6, 2007
4. Human gene mutation database (HGMD) at www.hgmd.cf.ac.uk/ac/index.php

METHOD: Whole-genome array-based comparative genomic hybridization (aCGH) was performed using the GenomeDx microarray, v1.0. The array contains ~44,000 oligonucleotide probes spaced at an average distance of 80 kb based on the most recent build of the human genome sequence (hg18). Physical genomic intervals may be viewed by entering the sequence coordinates from the results section above into the UCSC genome browser at <http://genome.ucsc.edu/cgi->



GenomeDx Report

High-resolution oligonucleotide array CGH

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bin/hgGateway. The GenomeDx array is designed to detect copy number variation ≥ 50 kb in more than 100 targeted regions (microdeletion/duplication loci, pericentromeric, and subtelomeric regions) and ≥ 300 -500 kb in other areas of the genome. The GenomeDx protocol employs a dye-reversal hybridization strategy to assess DNA copy number in the patient sample in relation to a same-sex reference diploid DNA sample. If applicable, confirmation by quantitative polymerase chain reaction (PCR) involves fluorescence detection of amplicon quantities that correlate with initial template copy number. A gene within the deleted/duplicated region is tested along with a separate normal locus that is used as an internal standard. Results from the patient sample are compared to a reference sample that contains two copies of the tested locus and, in this case, to parental samples.

DISCLAIMER: This oligonucleotide microarray was developed and its performance determined by GeneDx for the sole purpose of identifying gain or loss of DNA segments within the genome. The microarray will detect chromosomal aneuploidy in addition to deletions and duplications (segmental aneusomy) within the entire human genome. As with any genomic array CGH platform, the GenomeDx array does not detect balanced chromosomal aberrations, including Robertsonian translocation, reciprocal translocations, inversions, and balanced insertions, and it is limited in its ability to detect mosaicism. The GenomeDx array will also not detect imbalances in genomic regions that are not represented on the microarray. Normal findings do not rule out the diagnosis of any disorder since some genetic abnormalities may be undetectable with this assay. Clinical implications of some copy number alterations may be unknown at the time of analysis. Consultation with a genetic professional is recommended for test interpretation. This test is used for clinical purposes only. It has not been cleared or approved by the FDA. The FDA has determined that such clearance or approval is not necessary. Pursuant to the requirements of CLIA '88, this laboratory has established and verified the test's accuracy and precision. Genetic testing using the methods applied at GeneDx is expected to be highly accurate. However, the chance of a false positive or false negative result due to laboratory errors incurred during any phase of testing cannot be completely excluded. CLIA ID#: 21D0969951. MD License 953.

Director, Clinical Microarray Services

Medical Director or Clinical Director or Senior
Genetic Counselor

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