THE UNIVERSITY OF CHICAGO | Genetic Services Laboratories

Oculodentodigital dysplasia (ODDD) Testing: Mutation Analysis of *GJA1*

Clinical Features:

Oculodentodigital dysplasia [ODDD, MIM# 164200] is characterized by a typical facial appearance and variable involvement of the eyes, fingers and dentition. Ocular features include bilateral microphthalmia, microcornea and ocular hypotelorism. Digital malformations typically include fifth finger camptodactyly, syndactyly of the fourth and fifth fingers and missing phalanges of the toes. Teeth are typically small and carious. Neurologic features can include spastic quadriparesis, progressive spastic paraparesis, and abnormal white matter changes in brain MRI (1). Intrafamilial variability of the major phenotypic characteristics is not uncommon.

Molecular Genetics:

Mutations of the *GJA1* [OMIM #121014] gene have been identified in patients with ODDD. *GJA1* has 2 coding exons and is located at 6q22.31. Paznekas et al, (2003) identified mutations in *GJA1* in 100% (17/17) patients with ODDD (2). The majority of mutations identified in *GJA1* are missense mutations (1). *GJA1*, or connexin 43, like other gap junction genes are expressed by virtually all cells of the body and play a vital role in providing an intercellular pathway for passage of ions and small molecules.

Inheritance:

Mutations in *GJA1* are generally autosomal dominant with high penetrance but variable expressivity. Autosomal recessive inheritance has also been reported by Richardson et al, (2006) in which a homozygous nonsense mutation in *GJA1* was identified in a consanguineous patient with ODDD (3).

Test Methods:

We offer full gene sequencing of all coding exons and intron/exon boundaries of *GJA1* by direct sequencing of amplification products in both the forward and reverse directions. Our CNV detection algorithm was developed and its performance determined for the sole purpose of identifying deletions and duplications within the coding region of the gene(s) tested. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by this methodology. Regions of high homology and repetitive regions may not be analyzed. This methodology will not detect low level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of our deletion/duplication assay may be reduced when DNA extracted by an outside laboratory is provided.

GJA1 sequencing and deletion/duplication analysis

Sample specifications:	3 to 10cc of blood in a purple top (EDTA) tube
Cost:	$540
CPT codes:	81403, 81404
Turn-around time:	4 weeks

Results:

Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

1. Paznekas WA, Karczeski B, Vermeer S et al. GJA1 mutations, variants, and connexin 43 dysfunction as it relates to the oculodentodigital dysplasia phenotype. Hum Mutat 2009: 30: 724-733.
2. Paznekas WA, Boyadjiev SA, Shapiro RE et al. Connexin 43 (GJA1) mutations cause the pleiotropic phenotype of oculodentodigital dysplasia. Am J Hum Genet 2003: 72: 408-418.
3. Richardson RJ, Joss S, Tomkin S et al. A nonsense mutation in the first transmembrane domain of connexin 43 underlies autosomal recessive oculodentodigital syndrome. J Med Genet 2006: 43: e37.

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