EYA1 and *SIX1* Gene Analysis in Branchiootorenal (BOR) / Branchiootic (BO) Syndrome

Disorder Also Known As: Branchiootorenal Dysplasia, Melnick-Fraser Syndrome, Eyes absent homolog 1

Clinical Features:
BOR (Branchiootorenal) syndrome, which clinically overlaps with branchiootic syndrome, is characterized by multiple malformations clinically diagnosed by the following major criteria: second branchial arch anomalies, deafness, preauricular pits, auricular deformities and renal anomalies (ranging from mild to severe or complete absence of kidneys). Minor criteria include: external auditory canal anomalies, middle or inner ear anomalies, preauricular tags and others. To be diagnosed there must be 2 affected individuals in the family; or the individual must display 3 or more of the major criteria, or 2 major and 2 minor criteria. Both reduced penetrance and variable expressivity have been observed. The estimated prevalence of BOR syndrome is 1:40,000 in the general population and ~2% among profoundly deaf children. Hearing impairment can be mild to severe and can be conductive, sensorineural or mixed.[2]

Inheritance Pattern/Genetics:
BOR and BO are inherited in an autosomal dominant manner. Approximately 10% of cases are caused by a de novo variant.

More than 100 variants in the EYA1 gene have been associated with BOR Syndrome, including nonsense, missense, splice site variants, small deletions and insertions. Approximately 10-20% of patients with BOR are found to have large deletions of one or more exons, the entire gene, or chromosomal rearrangement involving the EYA1 gene.[1,2,6]

There are very few published cases of BOR/BO syndrome due to variants in the SIX1 gene. Most variants are missense changes affecting the homeodomain region, which is essential for specific Six1-DNA binding.[4,5]

Test Methods:
Analysis is performed by bi-directional sequencing of all coding exons (exons 3-18) and splice sites of the EYA1 gene. Concurrently, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is performed to evaluate for a deletion or duplication of one or more exons of this gene. Additionally, bi-directional sequencing of the coding regions and splice sites of the SIX1 gene (exons 1 and 2) is available. Variants/deletions/duplications found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis, qPCR or another appropriate method.

Test Sensitivity:

Up to 82% of patients meeting the diagnostic criteria listed above will have an EYA1 variant detected by combined full gene sequencing and deletion/duplication testing.[1,6,7] Two studies found that approximately 80% of variants can be identified by sequence analysis of the coding sequence of EYA1, while the remaining 20% represent large deletions or chromosomal rearrangements.[1,6] Deletions/duplications of one or more exons can be detected by targeted array CGH analysis with exon-level resolution (ExonArrayDx). A balanced chromosomal rearrangement involving the EYA1 gene would be missed by our methods. The clinical sensitivity of SIX1 testing has not been established.

References:

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