

Branchiootorenal (BOR/BOS) Spectrum Disorder Panel

Genes Tested

<i>EYA1</i>	<i>SIX1</i>	<i>SIX5</i>
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Disorder: Branchiootorenal (BOR/BOS) spectrum disorder is characterized by malformations of the external, middle and/or inner ear, branchial clefts or cysts, hearing loss which may be of sensorineural, conductive or mixed types, and, in some patients, renal malformations of varying severity. Over 90% of patients with BOR have hearing loss of some degree. Onset of hearing loss ranges from childhood to young adulthood. Progressive hearing loss occurs in about 30% of patients and may be associated with enlarged vestibular aqueducts (EVA).

Branchiootorenal spectrum disorder has an estimated prevalence of 1/40,000, and is inherited as an autosomal dominant condition. This condition is highly variable, even among family members.

Indications: Patients with physical manifestations of branchiootorenal spectrum disorder

Specimen: At least 5 mLs whole blood in purple top (EDTA) tube. Label each tube with patient's name, birth date, and date of collection.

Testing Methodology: This test is performed by enrichment of the exons, flanking intronic and un-translated regions (5' and 3') of the genes specified above using microdroplet PCR technology followed by next-generation sequencing with > 20 fold coverage at every target base. All pathogenic and novel variants, as well as variants of unknown (indeterminate) significance, as determined bioinformatically, are confirmed by Sanger sequencing.

If the Branchiootorenal Spectrum Disorder Panel test result is normal, reanalysis of the remaining genes on the **OtoSeq® Hearing Loss Panel** may be requested.

Alternately, you may opt to order the **OtoSeq® Hearing Loss Panel**, which detects mutations in these genes as well as 20 other genes which cause hearing loss, in lieu of the Branchiootorenal Spectrum Disorder Panel.

PCR and bidirectional sequence analysis of the coding regions and exon/intron boundaries of the *EYA1* gene is also orderable as an individual test.

Test Sensitivity: Approximately 40% of individuals with BOR/BOS have an identified mutation in *EYA1*. Approximately 10% of individuals with BOR/BOS will have a chromosomal rearrangement in the region of the *EYA1* gene, which will not be detected by our test methodology. FISH and deletion duplication analysis may be indicated in the presence of normal sequencing results when the index of clinical suspicion remains high. Mutations in *SIX5* and *SIX1* each account for 2-3% of symptomatic individuals. Other, as of yet, unidentified genes may be responsible for BOR/BOS in some families.

The sensitivity of next-generation sequencing is over 99% for the detection of nucleotide base changes, small deletions and insertions in the regions analyzed. Mutations in regulatory regions or other untranslated regions are not detected by this test. Large deletions



Human Genetics

Molecular Genetics Laboratory

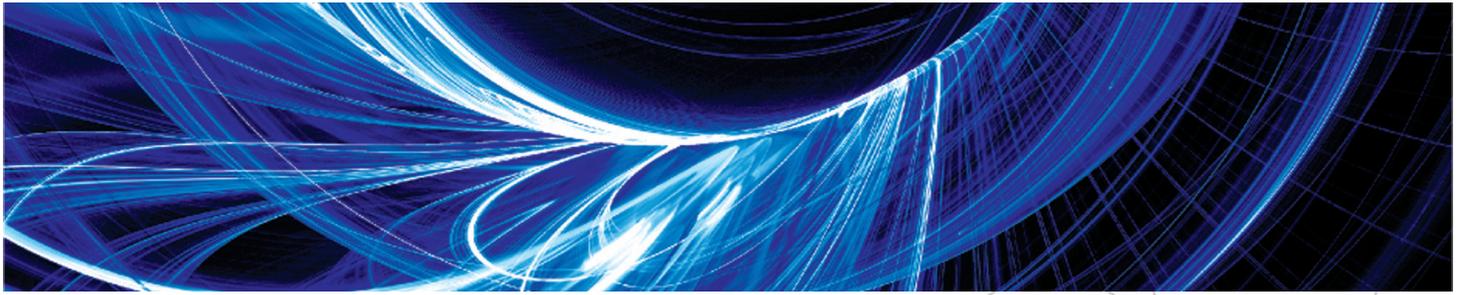
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www.cchmc.org/hearing-loss



involving entire single exons or multiple exons, large insertions and other complex genetic events are quite common in *EYA1* and will not be identified using this methodology. Rare primer site variants may lead to erroneous results.

Note: Single gene sequencing is available for all genes in the panel.

Turn-Around Time:

- 56 days for NGS of the panel
- Up to 42 days for analysis of any gene by Sanger sequencing
- Additional 42 days for reanalysis of remaining genes on the **OtoSeq® Hearing Loss Panel** (if requested).

Cost: Please call 1-866-450-4198 for current pricing, insurance precertification, or with any billing questions.

CPT Codes:

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|---|------------------|
| • BOR/BOS panel | 81406, 81479(x2) |
| • Single gene sequencing of <i>EYA1</i> | 81406 |
| • Single gene sequencing of <i>SIX1</i> , <i>SIX5</i> | 81479 |
| • OtoSeq® reanalysis (if requested) | 81479 |

Results: Each test report includes a detailed interpretation of the genetic findings, the clinical significance of the result, and specific recommendations for clinical management and additional testing, if warranted. Results will be reported to the referring physician or health care provider as specified on the test requisition form.

References:

Chang, E. H., M. Menezes, et al. (2004). "Branchio-oto-renal syndrome: the mutation spectrum in *EYA1* and its phenotypic consequences." *Hum Mutat* 23(6): 582-589.

Hoskins, B. E., C. H. Cramer, et al. (2007). "Transcription factor *SIX5* is mutated in patients with branchio-oto-renal syndrome." *Am J Hum Genet* 80(4): 800-804.

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Krug, P., V. Moriniere, et al. (2011). "Mutation screening of the *EYA1*, *SIX1*, and *SIX5* genes in a large cohort of patients harboring branchio-oto-renal syndrome calls into question the pathogenic role of *SIX5* mutations." *Hum Mutat* 32(2): 183-190.

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Patrick, A. N., B. J. Schiemann, et al. (2009). "Biochemical and functional characterization of six *SIX1* Branchio-oto-renal syndrome mutations." *J Biol Chem* 284(31): 20781-20790.

Ruf, R. G., P. X. Xu, et al. (2004). "*SIX1* mutations cause branchio-oto-renal syndrome by disruption of *EYA1-SIX1-DNA* complexes." *Proc Natl Acad Sci U S A* 101(21): 8090-8095.

Smith, R. J. H. (1993). *Branchiootorenal Spectrum Disorders*. GeneReviews. R. A. Pagon, T. D. Bird, C. R. Dolan, K. Stephens and M. P. Adam. Seattle (WA).

Additional information and test requisitions are available at: www.cchmc.org/hearing-loss

Shipping Instructions

Please enclose a completed **test requisition, audiogram and MRI/CT report, if available** with the sample. **All information must be completed before the sample can be processed.** Place samples in Styrofoam mailer and ship at room temperature by overnight Federal Express to arrive Monday through Friday.

Ship to:

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