SickKids | Genome Diagnostics

HEREDITARY HEARING LOSS:

COMMON AND NON-SYNDROMIC HEARING LOSS

Hearing loss has an incidence of 1 in 500 births, with approximately 50% of cases of isolated childhood hearing loss having a genetic etiology, with many genes involved. Hereditary hearing loss may be conductive, sensorineural (SNHL) or a combination of both. Conductive hearing loss results from abnormalities of the external ear and/or the ossicles of the middle ear. SNHL results from malfunction of inner ear structures. Hearing loss can be either syndromic, having malformations of the external ear or other organs and/or medical problems involving other organ systems, or it can be non-syndromic (NSHL) where there are no other associated anomalies. The majority of NSHL can be attributed to mutations in the GJB2 gene. The rest of NSHL is characterized by genetic heterogeneity and indistinguishable phenotypes. Syndromic hearing loss makes up approximately 30% of genetic prelingual (present before speech develops) SNHL but its relative contribution to all deafness is much smaller, reflecting the occurrence and diagnosis of postlingual (after language develops) deafness. Clinical features of syndromic SNHL may include: pigmentary, renal and eye anomalies (retinitis pigmentosa), cleft palate, as well as other organ involvement.

GENETICS

The genetics of hearing loss are complex and different modes of inheritance (autosomal dominant, autosomal recessive, X-linked) have been described. The common and non-syndromic hearing loss targeted Next- Generation Sequencing (NGS) panel at our laboratory includes genes associated with all these modes of inheritance.

TEST METHODS

Complete sequencing of the coding region and flanking intron/exon boundaries of the genes listed in the table. This is done via NGS of a targeted panel of genes associated with syndromic and non-syndromic hearing loss. Please refer to our "A Guide to Next Generation Sequencing" information sheet available on our website, for further details.

Dosage analysis for the genes on this panel is also available. Please note this includes the STRC gene, which is associated with autosomal recessive non-syndromic sensorineural hearing loss (OMIM: 603720; PMID: 24963352). This assay will also detect the recurrent contiguous gene deletion involving the CKMT1B, STRC and CATSPER2 genes associated with autosomal recessive deafness and male infertility syndrome (DIS, OMIM: 611102).

INTERPRETATION OF TEST RESULTS

Genetic testing may reveal one or more variants in the NGS hearing loss targeted gene panel, which should be interpreted in the context of the suspected clinical diagnosis, inheritance pattern, clinical findings, family history and other experimental data. Please refer to our "A Guide to Interpreting Sequence Variations" information sheet available on our website, for further details.

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MODE OF INHERITANCE	LIST OF GENES ON THE NGS PANEL
Autosomal recessive	**ADGRV1, *CDH23*, *CIB2*, CLDN14, DFNB59, ESPN, ESRRB, GIPC3, GJB2, GJB6, GPSM2, GRXCR1, HGF, ILDR1, LHFPL5, LOXHD1, LRTOMT, *KCNE1*, *KCNQ1*, MARVELD2, MYO15A, MYO3A, MYO6, MYO7A, OTOA, OTOF, OTOG, OTOGL, *PCDH15*, *PDZD7*, PTPRQ, RDX, SERPINB6, *SLC26A4*, STRC, TECTA, TMC1, TMIE, TMPRSS3, TPRN, TRIOBP, *USH2A*, *WFS1*, *WHRN***
Autosomal dominant	**ACTG1, *CHD7*, COCH, DFNA5, DIAPH1, EYA1, EYA4, GJB2, GJB6, GRHL2, KCNQ4, MYH14, *MYH9*, MYO6, MYO7A, POU4F3, PTPRQ, *SIX1*, SLC17A8, TECTA, TMC1, *WFS1***
X-linked	***POU3F4*, PRPS1, SMPX**

Genes that are underlined can cause both syndromic and non-syndromic hearing loss.

CDH23, CIB2, PCDH15, PDZD7, USH2A, WHRN—Usher syndrome
SLC26A4—Pendred syndrome
KCNE1, KCNQ1-Jervell & Lange-Nielson syndrome
WFS1—Wolfram syndrome
CHD7—CHARGE syndrome
MYH9—Mary-Hegglin anomaly, Fechtner sydrome, Sebastian syndrome
SIX1—Branchootic syndrome
POU3F4—Choroideremia

WHO SHOULD BE TESTED?

-Individuals clinically suspected of being affected with hereditary hearing loss.

-Relatives of a proband with identified pathogenic variant(s) in a hearing loss associated gene.

-Pregnancies at increased risk due to a family history of a known type of hereditary hearing loss.

For More Information

GeneReviews: Deafness and Hereditary Hearing Loss Overview: http://www.ncbi.nlm.nih.gov/books/NBK1434/

Genome Diagnostics Laboratory: www.sickkids.ca/genome-diagnostics

To locate a genetics center near you:

Canadian Association of Genetic Counsellors (CAGC): www.cagc-accg.ca

National Society of Genetic Counselors (NSGC): www.nsgc.org

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1. A negative result after NGS testing does not rule out the presence of a deletion or duplication. Deletion/duplication testing is available through our laboratory. If clinically indicated, please contact us to discuss this testing.

2. The clinical course or severity of symptoms cannot be predicted by molecular analysis.

3. Test results should be interpreted in the context of clinical findings, family history and other laboratory data.

4. Current molecular testing may not detect all possible mutations for this disease. A negative test does not rule out the possibility of hereditary hearing loss.

5. This test was developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.

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