

HEREDITARY HEARING LOSS: SYNDROMIC FORMS OF HEARING LOSS

Alport syndrome is a genetic disorder characterized by cochlear, kidney and ocular involvement. Individuals frequently develop sensorineural hearing loss during late childhood or early adolescence. Affected individuals may also have misshapen lenses in the eyes and abnormal coloration of the retina; which seldomly lead to vision loss. Individuals experience progressive loss of kidney function with hematuria and proteinuria, often resulting in end-stage renal disease.

Norrie syndrome is an X-linked condition characterized by sensorineural hearing loss, abnormal retinal development leading to congenital blindness and developmental delay. Most affected males develop progressive asymmetrical sensorineural hearing loss starting in childhood. Hearing loss may be severe and bilateral by mid-adulthood. Developmental delay is found in about 30% of patients. Some have cognitive and psychosocial behavioral disorders, including psychosis.

Treacher-Collins syndrome is a genetic condition that affects the development of facial bones and other tissues of the face. The features of this disorder vary greatly, ranging from almost unnoticeable to severe. About 50% of individuals have conductive hearing loss due to the malformation of the ossicles and hypoplasia of the middle ear cavities. Other less common abnormalities include cleft palate and choanal stenosis or atresia. Most individuals have normal intelligence.

Waardenburg syndrome (WS) is a group of genetic conditions that can cause congenital sensorineural hearing loss and pigmentation changes of the skin, hair (white forelock or early graying of the scalp hair) and eyes (heterochromia iridium). There are four types of WS; type I & II have very similar features, type III includes abnormalities of the upper limbs and type IV includes Hirschsprung disease.

GENETICS

These four forms of syndromic hearing loss can be inherited in autosomal dominant (AD), autosomal recessive (AR) or X-linked fashion. The targeted Next-Generation-Sequencing (NGS) panel described below include genes associated with all three modes of inheritance.

WHO SHOULD BE TESTED?

- Individuals clinically suspected of being affected with one of these four syndromic forms of hearing loss.
- Relative of a proband with identified pathogenic variant(s) in a gene associated with one of these four syndromic forms of hearing loss.
- Pregnancies at increased risk due to a family history of one of these four forms of syndromic hearing loss.

TEST METHODS

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

INTERPRETATION OF TEST RESULTS

Genetic testing may reveal one or more variants in one of these nine genes, 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.

Syndromic form of hearing loss	Gene	Inheritance Pattern
Alport syndrome	COL4A3	Autosomal Dominant & Recessive
Alport syndrome	COL4A4	Autosomal Dominant & Recessive
Alport syndrome	COL4A5	X-linked
Norrie Syndrome	NDP	X-linked
Treacher Collins Syndrome	TCOF1	Autosomal Dominant
Waardenburg Syndrome, Type 1 & 3	PAX3	Autosomal Dominant & Recessive
Waardenburg Syndrome, Type 2a	MITF	Autosomal Dominant
Waardenburg Syndrome, Type 4a	EDNRB	Autosomal Dominant & Recessive
Waardenburg Syndrome, Type 4b	EDN3	Autosomal Dominant & Recessive
Waardenburg Syndrome, Type 4c	SOX10	Autosomal Dominant

For More Information

Alport syndrome: <http://www.ncbi.nlm.nih.gov/books/NBK1207/>

Norrie Syndrome: <http://ghr.nlm.nih.gov/condition/norrie-disease>

Treacher-Collins Syndrome: <http://www.ncbi.nlm.nih.gov/books/NBK1532/>

Waardenburg Syndrome: <http://ghr.nlm.nih.gov/condition/waardenburg-syndrome>

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

To locate a genetics center near you:

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

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



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 these forms of syndromic hearing loss.

5. This test was developed and its performance characteristics validated by the Molecular Genetics 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.