Genetic testing for Deafness
Prevalence

Hearing loss (HL) is the most common sensory disorder. It is found in 1 of 500 newborns. In developed countries, over 80% of all cases of congenital deafness are of genetic origin. In most cases, inherited HL is monogenic. In about 70% of cases of presumably genetic hearing impairment, there are no other distinguishing physical findings (non-syndromic hearing loss, NSHL). In the remaining 30%, the hearing deficit is accompanied by other physical findings (= syndromic). HL is a feature in more than 400 syndromes; Usher syndrome (with retinitis pigmentosa), Pendred syndrome (with hypothyroidism) and Jervell and Lange-Nielsen syndrome (with impaired cardiac conduction) are the most frequent [1].

The identification of the molecular cause of HL in a patient is desirable – especially in order to distinguish non-syndromic from syndromic forms. The latter can present as isolated hearing impairment before additional – in case of Jervell and Lange-Nielsen syndrome potentially life-threatening – complications occur. The knowledge about the mutation is therefore crucial for diagnostic and therapeutic/preventive management.

With approximately 50 causative genes known to date (and just as many genes still to be identified), NSHL is an extremely heterogeneous condition and therefore a challenge for genetic testing.

Time- and cost-efficient genetic testing

- We provide **stepwise analysis** for the genes that cover a substantial fraction of autosomal dominant, autosomal recessive and X-linked hearing loss.
- **The presence of specific phenotypic features allows for targeted analysis** of the genes that are associated with these features.
- We offer **linkage analysis** where applicable (samples available from several family members; recessive deafness families with parental consanguinity) for prioritization of genes to be tested.

As a general rule, we provide molecular testing for every HL gene.

Please contact us in any case of questions.

Automosomal recessive non-syndromic hearing loss (ARNSHL)

ARNSHL accounts for 80% of cases and is – with the exception of three genes – typically prelingual and profound.

According to their prevalence as deafness-causing genes and recognizable phenotypic features associated with specific genes, we conduct stepwise analysis of ARNSHL genes:

<table>
<thead>
<tr>
<th>ARNSHL without specific phenotypic features or linkage data:</th>
<th>Gene(s)</th>
<th>fraction of ARNSHL</th>
<th>Turnaround time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>GJB2, GJB6 (342 kb deletion)</td>
<td>30-50%</td>
<td>1-4 weeks</td>
</tr>
<tr>
<td>2</td>
<td>SLC26A4, hot spots (3 exons)</td>
<td>5-10%</td>
<td>4 weeks</td>
</tr>
<tr>
<td>3</td>
<td>SLC26A4, remaining exons</td>
<td></td>
<td>4 weeks</td>
</tr>
<tr>
<td>4</td>
<td>TMC1</td>
<td>up to 3%</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td>5</td>
<td>DFNB59, TMIE, ESRRB, up to 5%</td>
<td>6 weeks</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>LHFPL5, COMT2, TRIC CDH23</td>
<td>up to 5%</td>
<td>6 weeks</td>
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<td>Other genes on request</td>
<td></td>
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</table>

Progressive ARNSHL:

Progressive ARNSHL is rare, and only four genes have been described for this phenotype. The observation of this course of ARNSHL therefore allows for targeted molecular testing.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Gene(s)</th>
<th>Turnaround time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DFNB59</td>
<td>4 weeks</td>
</tr>
<tr>
<td>2</td>
<td>SERPINB6</td>
<td>4 weeks</td>
</tr>
<tr>
<td>3</td>
<td>MYO3A</td>
<td>6 weeks</td>
</tr>
<tr>
<td>4</td>
<td>LOXHD1</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

Auditory neuropathy:

Most genes involved in ARNSHL cause dysfunction confined to the cochlea (peripheral HL). In contrast, auditory neuropathy (AN) affects inner hair cells, the auditory nerve, the synapse, or neurons of the auditory pathway. AN is characterized by distorted/ absent auditory brainstem responses (ABRs) and preserved otocoustic emissions (OAEs).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Gene(s)</th>
<th>Turnaround time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DFNB59</td>
<td>2-4 weeks</td>
</tr>
<tr>
<td>2</td>
<td>OTOF</td>
<td>6-8 weeks</td>
</tr>
</tbody>
</table>
Autosomal dominant non-syndromic hearing loss (ARNSHL)
ARNSHL accounts for 20% of cases and is typically postlingual and progressive. For some genes, there are specific phenotypic features that can be used for targeted testing.

<table>
<thead>
<tr>
<th>ADNSHL without specific phenotypic features:</th>
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<tbody>
<tr>
<td>Stage</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
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<thead>
<tr>
<th>Prelingual low-frequency ADNSHL:</th>
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<tbody>
<tr>
<td>ADNSHL associated with WFS1 mutations is very characteristic: only affects low frequencies, normal hearing preserved in high frequencies. At older age, hearing in high frequencies is lost.</td>
</tr>
<tr>
<td>WFS1</td>
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<thead>
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<th>Prelingual ADNSHL:</th>
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<tr>
<td>Stage</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>1</td>
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<td>2</td>
</tr>
</tbody>
</table>

X-linked non-syndromic hearing loss (XNSHL)
X-linked hearing loss is extremely rare, accounting for less than 1% of all NSHL cases. Only two causative genes, PRPS1 and POU3F4, are known. We offer molecular testing for both genes.

<table>
<thead>
<tr>
<th>Specimen Requirement</th>
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<tbody>
<tr>
<td>Sample preparation</td>
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<td>DNA or 2-10 ml of EDTA blood</td>
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References