Molecular and hereditary mechanisms of sensorineural hearing loss with focus on selected endocrinopathies

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Abstract. Hearing loss is one of the most widespread sensory disorders. The incidence of deafness in general population is 1:1000 newborns. About one half of the congenital sensorineural hearing loss (SNHL) cases is inherited. Recessive mutations in the gap junction beta 2 (GJB2) gene are the most common genetic causes of the nonsyndromic SNHL. The GJB2 encodes a protein connexin 26 which forms a subunit of gap junction essential for the correct function of the inner ear. The syndromic SNHL is associated with a wide range of other symptoms, which encompass also dysfunctions of endocrine organs. The Pendred syndrome associated with the hearing impairment is characterized by a prelingual, bilateral sever to profound SNHL, goiter, and iodine organification defect. It is an autosomal recessive disorder, which develops due to mutations in pendrin, an anion channel encoded by SLC26A4 gene. Another important type of syndromic hearing loss is the Maternally Inherited Diabetes and Deafness syndrome, which is caused by several mitochondrial DNA mutations. These mutations are clinically manifested by a hearing impairment with development of the diabetes in the adult age. Hearing impairment occurs during puberty when sensation of high frequency tones is affected following with further progress to profound bilateral sensorineural hearing impairment in the whole frequency range. This review deals with the molecular mechanisms of common genetic causes of the hereditary SNHL along with the selected endocrinopathies emphasizing that the DNA analyses along with the functional studies significantly contribute to the early SNHL diagnosis followed by personalized therapy and genetic counseling.

Keywords: hearing impairment, inner ear, connexin, Pendred syndrome, diabetes

Sensorineural hearing loss

Hearing loss is one of the most common sensory disorders. Based on the World Health Organization's data, over 278 million people suffer from the hearing loss (WHO 2010). The incidence of profound hearing loss is 1:1000 in newborns (Morton 1991); however, the etiology of the hearing disorders is extremely diverse. Approximately half of the congenital sensorineural hearing loss (SNHL) is caused by genetic abnormalities, 25% by environmental factors, and the remaining 25% has unknown origin (Morton 1991; Schrijver 2004).
The hereditary hearing loss is usually manifested by a bilateral damage of the inner ear or auditory pathway—nervus vestibulocochlearis, which is referred as bilateral SNHL. It can be present in a nonsyndromic form (70%), as a single disorder, or syndromic form (30%) associated with dysfunction of other organs (Van Camp et al. 1997; Acmg 2002). The hereditary SNHL is characterized by autosomal recessive (80%), autosomal dominant (15 to 20%), X-linked (1%) or mitochondrial inheritance (1 to 5%) (Pandya et al. 1999; Schrijver 2004). For the normal hearing, correct function of about 300 genes is required (Friedman and Griffith 2003). Concerning the etiology of hearing impairment, the \textit{GJB2} is the most frequently involved gene encoding the protein connexin (Cx) 26. The \textit{GJB2} gene mutations are the most common reasons of the nonsyndromic deafness development in the Caucasoid population (Kelsell et al. 1997; Estivill et al. 1998a). The second most frequent reason of the nonsyndromic SNHL occurrence in some countries is a large deletion in the \textit{GJB6} gene encoding Cx30 (Del Castillo et al. 2003). The connexins forming intercellular connections (gap junction) in the inner ear cochlea play an important role in the transport and recycling of potassium ions, which are necessary for its proper function (Wangemann 2006).

The nonsyndromic or syndromic SNHL connected with the goiter (Pendred syndrome) appears on the basis of the \textit{SLC26A4} gene mutations (Everett et al. 1997). This gene encodes a protein transporter pendrin, which is expressed in several cochlear cell types, follicular cells in thyroid gland, and kidneys. Mutations of the mitochondrial DNA contribute significantly to the hearing impairment etiology and can induce syndromic as well as nonsyndromic hearing loss. Considering that the mitochondrial dysfunctions affect also the inner ear (as the organ with high metabolic activity), the SNHL is a frequent clinical symptom of the mitochondrial diseases (Fischel-Ghodsian 2003).

**SNHL caused by defect of connexins**

\textbf{Connexins (Cxs)} represent protein subunits of an intercellular gap junction. To date, 21 Cx genes have been identified in the human genome (Rackauskas et al. 2010). The genes that encode individual Cxs are named according to sequential homology arranged into
5 groups (α, β, γ, δ and ε) (Pfenninger et al. 2011). Proteins are classified according to their size in kDa. The primary structure and topology of Cxs within the protein subfamily is common. They consist of four alpha-helical transmembrane domains (m1-m4) connected by two extracellular (e1, e2) and one intracellular loop (c1) (Fig. 1a). The transmembrane domains and extracellular loops are highly conserved. The cytoplasmic loop and protein carboxyl terminus are unique for each Cx, differing in the length and composition of the amino acids (Saez et al. 2003; Herve et al. 2004). Six Cx units compose one hemichannel called connexon. The connexons of two adjacent cells dock and constitute a gap junction (Bruzzone et al. 1996). Depending on the composition of the channels, the Cxs can be homomeric, if they consist of one Cx isoform, or heteromeric, if they consist of two different Cx isoforms. The gap junction channels may also be divided into homotypic or heterotypic form, depending on the presence of the Cx types. The homotypic gap junctions are made by one Cx isoform, the heterotypic by two different connexons (Fig. 1b) (Bruzzone et al. 1996).

The gap junctions allow direct passage of ions, small molecules and other metabolites between cells including molecules functioning as second messengers - cAMP, cGMP, IP₃, ATP - or other metabolites up to 1 kDa in size (Saez et al. 2003; Martinez et al. 2009). Voltage-dependent gating of hemichannels composed of Cx26 is affected by the presence of a helical structure in the amino-terminus (N), which is embedded into the lumen of the channel (Maeda and Tsukihara 2011). Each helical structure of N-terminus during voltage equilibrium state interacts with the transmembrane domain 1 of its own Cx molecule. Six helical structures of the hemichannel are directed into a pore creating the narrowest part of the channel entrance called pore funnel. When membrane potential between adjacent cells changes, the N-terminus structures are released from the transmembrane domains into the pore. They gather at the end of the pore and form structures, so called plugs that close the channel (Purnick et al. 2000; Maeda and Tsukihara 2011).

Several isoforms of the Cxs are expressed in the inner ear cochlea. These particularly include the Cx26 and Cx30 and to a lesser extent the Cx31, Cx32, Cx43, and Cx45 (Zelante et al. 1997; Xia et al. 1998; Grifa et al. 1999; Liu et al. 2001). The Cxs play an important role in the recirculation of K⁺ ions. The defects of Cxs in the inner ear result in disruption of K⁺ recirculation leading to hearing loss (Martinez et al. 2009) (for details see Fig. 2).

**SNHL induced by the defect of Cx26** is the most frequent hereditary cause of this disease (Hilgert et al. 2009a). Other Cxs, such as Cx30, Cx31, and Cx43, are only rarely involved in the etiology of the hearing disorders (Liu et al. 2001; Hong et al. 2010). The Cx26 protein is encoded by the GJB2 gene located on the long arm of the chromosome 13 (13q11-q12). The GJB2 gene is composed of 2 exons, one which encodes 5’ untranslated region (5’ UTR) and the another which encodes the complete open reading frame (ORF) and 3’ untranslated region (3’ UTR) (Saez et al. 2003). The protein is composed of 226 amino acids, with a molecular weight of 26 kD.

Currently more than 90 pathogenic mutations in the **GJB2 gene** have been identified with a significant contribution of the frameshift and nonsense mutations (http://davinci.crg.es/deafness/). The frequency of the individual mutations varies within the ethnic groups. In the Caucasian population, the most frequent mutation is c.35delG a recessive deletion of one of the six guanines at the codon position 30 – 35 (Denoyelle et al. 1997; Zelante et al. 1997). This deletion leads to the shifted reading frame, creation of stop codon, and premature termination of the connexin 26 synthesis (Denoyelle et al. 1997). In Ashkenazi Jews, the most frequent mutation is a recessive deletion of the thymine at position 167 (c.167delT) which also causes frameshift and premature stop codon (Zelante et al. 1997). In Asian countries, Japan, China, and Korea, the frameshift mutation c.235delC dominates (Fuse et al. 1999; Park et al. 2000; Liu et al. 2002). Concerning the Indian and Pakistani populations, the recessive nonsense mutation of c.71G>A prevails (Kelsell et al. 1997) which was also found with high frequency in Roma populations in several countries, Slovak Republic, Czech Republic, and Spain (Minarik et al. 2003; Seeman et al. 2004; Alvarez et al. 2005). The pathogenic GJB2 mutations found in Slovakia, Czech Republic, Austria, and Hungary are listed in Table 1.

**The effect of mutations on the protein function** is not completely known due to complexity of the gap junction channels structure (Snoeckx et al. 2005). However, based on the different gap junction defects, mutations in the GJB2 can be divided into several groups (Hoang Dinh et al. 2009).

The first group includes mutations preventing the docking of the gap junction channel. These mutations involve the inhibition of various processes: 1) oligomerisation of the Cxs into hemichannels, 2) transport and incorporation of hemichannels in the membrane or 3) connexons connection between the cells and docking. 

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**Table 1. Frequency of pathogenic mutations in GJB2**

<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Slovak Republic</td>
<td></td>
<td>35%</td>
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<tr>
<td>Czech Republic</td>
<td></td>
<td>23%</td>
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<tr>
<td>Austria</td>
<td></td>
<td>16%</td>
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<tr>
<td>Hungary</td>
<td></td>
<td>7%</td>
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<tr>
<td>Japan</td>
<td></td>
<td>10%</td>
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<tr>
<td>China</td>
<td></td>
<td>5%</td>
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<tr>
<td>Korea</td>
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<td>5%</td>
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<tr>
<td>India</td>
<td></td>
<td>10%</td>
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<tr>
<td>Pakistan</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Slovakia</td>
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<td>35%</td>
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<tr>
<td>Czech Republic</td>
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<td>Austria</td>
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<td>Hungary</td>
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<td>Japan</td>
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<td>China</td>
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<tr>
<td>Korea</td>
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<td>5%</td>
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<tr>
<td>India</td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Pakistan</td>
<td></td>
<td>5%</td>
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</tbody>
</table>
Fig. 2. Upper-left figure shows the cross section of the ear and its individual parts, with highlighted location of inner ear cochlea. Flow directions of potassium ions are visible in the cross section of the cochlea itself. Cochlea is composed of three parts: scala vestibuli, scala tympani, filled with perilymph. Between these two parts there is scala media with a fluid, the endolymph. Potassium cations pass from endolymph to hair cells and then are transported to supporting cells organ of Corti. Among the supporting cells, $K^+$ ions pass through gap junction channels formed by connexins 26 and 30 as far as to the cells of spiral ligament and stria vascula-ris. Potassium ions are actively transported from stria vascularis cells back to endolymph. Potassium cations from supporting cells are also transported to perilymph, from which they pass to cells of spiral ligament and stria vascularis and to endolymph. Revised according to Mammano et al. (2007) and http://www.kids-ent.com/website/pediatric_ent/ear_infections/index.htm.

of the gap junction (Thonnissen et al. 2002; de Zwart-Storm et al. 2008; Maeda and Tsukihara 2011). For instance, these include c.35delG (Zelante et al. 1997), oligomerisation-deficient mutant c.551G>C (Thonnissen et al. 2002) or dominant substitution c.548C>T which prevents hemichannels from joining to form gap junction (de Zwart-Storm et al. 2008).

The second group consists of mutations resulting in the creation of the gap junction channels with no function. The connexons are incorporated into the membrane forming gap junction plaques associated with the loss of the hemichannel activity (Hoang Dinh et al. 2009). For example, the dominant point substitution c.223C>T shows a complete loss of channel voltage sensitivity (Chen et al. 2005; Lee et al. 2009).

The third group includes mutations specifically damaging the biochemical coupling of the gap junction. For example, the recessive substitution c.250G>C selectively decreases the membrane permeability for the inositol trisphosphate (IP$_3$) through gap junction (Beltramello et al. 2005). However, the importance of IP$_3$ for the correct gap junction function in cochlea is not fully understood yet (Hoang Dinh et al. 2009).

The fourth group contains gain of function mutations with abnormal opening of the hemichannels and increased gap junction activity. The examples include dominant mutations, c.134G>A (Gerido et al. 2007), c.34G>C or c.148G>A, leading to an increased channel permeability, and thus resulting in the cell death (Lee et al. 2009).
Mutations in the Cx26 are manifested by nonsyndromic or syndromic SNHL. The nonsyndromic SNHL is mainly caused by mutations with autosomal recessive manner of inheritance (Hilgert et al. 2009a). Almost half of the recessive mutations are frameshift or nonsense type (Pfenniger et al. 2011). They have no specific localization within the protein and can be found in all Cx26 domains (Martinez et al. 2009). Hearing loss phenotype develops in recessive homozygotes or compound heterozygotes GJB2 mutations. The SNHL may also develop in compound heterozygous form of the GJB2 mutation with the second mutation in GJB6 (Cx30) or GJB3 (Cx31) (Liu et al. 2009; Rodriguez-Paris and Schrijver 2009). In the case of compound heterozygote of two genes, the expression of these genes is probably affected (Ortolano et al. 2008) which is not due to digenic inheritance as previously assumed (Lerer et al. 2001). The level of hearing loss in the GJB2/GJB6 carriers may range from mild to profound (Rodriguez-Paris et al. 2011).

<table>
<thead>
<tr>
<th>Nucleotide position</th>
<th>Protein position</th>
<th>Inheritance type</th>
<th>Clinical condition</th>
<th>Found in country</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Substitutions</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>c.1-3201G&gt;A</td>
<td>-</td>
<td>AR</td>
<td>SNHL</td>
<td>SK, CZ</td>
</tr>
<tr>
<td>c.44A&gt;C</td>
<td>p.Lys15Thr</td>
<td>AR</td>
<td>Hearing impairment</td>
<td>CZ</td>
</tr>
<tr>
<td>c.51C&gt;A</td>
<td>p.Ser17Tyr</td>
<td>AR</td>
<td>SNHL</td>
<td>H</td>
</tr>
<tr>
<td>c.56G&gt;C</td>
<td>p.Ser19Thr</td>
<td>AR</td>
<td>Hearing impairment</td>
<td>H</td>
</tr>
<tr>
<td>c.71G&gt;A</td>
<td>p.Trp24*</td>
<td>AR</td>
<td>SNHL</td>
<td>SK, CZ, A, H</td>
</tr>
<tr>
<td>c.101T&gt;C</td>
<td>p.Met34Thr</td>
<td>AR</td>
<td>SNHL</td>
<td>SK, CZ, H</td>
</tr>
<tr>
<td>c.109G&gt;A</td>
<td>p.Val37Ile</td>
<td>AR</td>
<td>SNHL</td>
<td>SK, H</td>
</tr>
<tr>
<td>c.139G&gt;T</td>
<td>p.Glu47*</td>
<td>AR</td>
<td>Hearing impairment</td>
<td>SK, H</td>
</tr>
<tr>
<td>c.154G&gt;C</td>
<td>p.Val52Leu</td>
<td>not determined</td>
<td>SNHL</td>
<td>A</td>
</tr>
<tr>
<td>c.177G&gt;T</td>
<td>p.Gly59Val</td>
<td>not determined</td>
<td>SNHL</td>
<td>H</td>
</tr>
<tr>
<td>c.223C&gt;T</td>
<td>p.Arg75Trp</td>
<td>AD</td>
<td>SNHL</td>
<td>SK</td>
</tr>
<tr>
<td>c.250G&gt;A</td>
<td>p.Val84Met</td>
<td>AR</td>
<td>AN, Hearing impairment</td>
<td>SK</td>
</tr>
<tr>
<td>c.269T&gt;C</td>
<td>p.Leu90Pro</td>
<td>AR</td>
<td>SNHL</td>
<td>SK, CZ, A, H</td>
</tr>
<tr>
<td>c.551G&gt;A</td>
<td>p.Arg184Gln</td>
<td>AR</td>
<td>SNHL</td>
<td>SK</td>
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<tr>
<td><strong>Deletions</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>c.35delG</td>
<td>p.Val12fs</td>
<td>AR</td>
<td>SNHL</td>
<td>SK, CZ, A, H</td>
</tr>
<tr>
<td>c.31_45del</td>
<td>p.Ala11fs</td>
<td>AR</td>
<td>SNHL</td>
<td>H</td>
</tr>
<tr>
<td>c.167delT</td>
<td>p.Arg56fs</td>
<td>AR</td>
<td>SNHL</td>
<td>SK, H</td>
</tr>
<tr>
<td>c.235delC</td>
<td>p.Cys79fs</td>
<td>AR</td>
<td>SNHL</td>
<td>H</td>
</tr>
<tr>
<td>c.313_326del</td>
<td>p.Gly105fs</td>
<td>AR</td>
<td>SNHL</td>
<td>SK, CZ, H</td>
</tr>
<tr>
<td>c.333_334del</td>
<td>p.Glu112fs</td>
<td>AR</td>
<td>Hearing impairment</td>
<td>SK</td>
</tr>
<tr>
<td>c.358_360del</td>
<td>p.Glu119del</td>
<td>not determined</td>
<td>Hearing impairment</td>
<td>CZ, A</td>
</tr>
</tbody>
</table>

SNHL – sensorineural hearing loss, AN – auditory neuropathy, AR – autosomal recessive, AD – autosomal dominant
The **syndromic SNHL** is caused by autosomal dominant mutations, where hearing loss is manifested by a postlingual hearing loss phenotype (Hilgert et al. 2009a). Mutations are mostly found in the region of the N-terminus and the first extracellular protein loop (Martinez et al. 2009). Until now, one dominant mutation has been described in the second extracellular loop (de Zwart-Storm et al. 2008). The SNHL is manifested by hearing impairment associated with skin diseases, for example the KID (Keratitis-Ichthyosis-Deafness) syndrome and palmoplantar keratoderma (Heathcote et al. 2000; Richard et al. 2002). It has been proposed that skin diseases related to the GJB2 mutations are caused by dominant-negative effect of the mutated Cx26, which affects other Cx isoforms, creating heteromeric gap junction channels and thus disrupting their normal function also in the skin. Theory of the dominant-negative effect is supported by several factors. All the syndromic hearing disorders develop as a result of dominant mutations. The mutated Cx26 inhibits the co-expressed wild type Cx26, Cx30 or Cx43 in the exogenous expression systems in a dominant-negative manner (Rouan et al. 2001; de Zwart-Storm et al. 2008; Martinez et al. 2009). The type of skin disease is closely related to the mutation location. The KID syndrome is linked with mutations in the N-terminus and extracellular loop 1. The Palmoplantar keratoderma is linked with mutations in the extracellular loop 1 (Martinez et al. 2009).

The **nonsyndromic and syndromic** hearing loss may develop also due to damage of the Cx30, Cx31, and Cx43 (Hilgert et al. 2009b). The Cx30 is encoded by gap junction beta 6 (GJB6) gene located on the short arm of the chromosome 13, in close proximity to GJB2 (50 kb). The point mutations causing hearing impairment in GJB6 are relatively rare and only few of them have been identified (c.14C>T, c.63delG, c.119C>T, c.175G>C) (Grifa et al. 1999; Gardner et al. 2006; Nemoto-Hasebe et al. 2009; Wang et al. 2011). However, large deletions of this gene, ranging from 131 kb to >920 kb, may occur more frequently. Depending on their size and location, these deletions affect not only GJB6 but also a number of genes including the CRYLI, GJB2, GJA3, and ZMYM2 (Feldmann et al. 2009; Wilch et al. 2010). Recessive deletion of D13S1830 (309 kb) is the most prevalent. In some countries, such as England, France or Spain, this deletion was identified from 20 to 40% of the GJB2 mutation carriers (Del Castillo et al. 2003). Studies from Western Austria (Frei et al. 2004), Czech Republic (Seeman et al. 2005), and Slovakia (Varga et al. 2011) have revealed only rare incidence of this mutation in the Central European countries. The loss of a possible cis-regulatory element located upstream of the GJB6 gene was assumed as a potential mechanism for the developing hearing loss in carriers with GJB6 large deletions along with other GJB2/GJB6 mutations (Rodriguez-Paris and Schrijver 2009). Extensive rearrangements cause a deletion of one or more potential regulatory elements which may lead to a disruption of the GJB2 transcription (Feldmann et al. 2009; Rodriguez-Paris and Schrijver 2009; Wilch et al. 2010; Rodriguez-Paris et al. 2011). The damage of the Cx31 is rare in the nonsyndromic and syndromic SNHL (Hilgert et al. 2009b). The Cx31 is encoded by the gap junction beta 3 (GJB3) gene located on the short arm of the chromosome 1 (1p34). More than 10 GJB3 mutations responsible for hearing loss are known. Syndromic SNHL may be accompanied by a peripheral neuropathy (Lopez-Bigas et al. 2001), but mostly is linked to skin disease, Erythrokeratodermia variabilis (Kelsell et al. 2001). Two mutations in the GJA1 gene (located in chromosome 6), coding Cx43, were associated with SNHL and have been reported in four Afro-American families (Liu et al. 2001). Afterwards, it has been proven that these mutations are localized on the chromosome 5 in the pseudogene of Cx43 (rhoGJA1) (Paznekas et al. 2003). However, identification of three missense mutations in GJA1 and rhoGJA1, as well as their subsequent functional study suggest an association with the hearing loss (Hong et al. 2010).

**SNHL and Pendred syndrome**

The SNHL is connected with more than 400 clinical syndromes (Hilgert et al. 2009b). One of the most frequent is the **Pendred syndrome**, an autosomal recessive disease characterized by bilateral SNHL, goiter, and positive perchlorate discharge test which reflects the iodine organification defect (Reardon and Trembath 1996). The estimated incidence is 7.5:100 000 in the United Kingdom (Fraser 1965; Pryor et al. 2005) and accounts for approximately from 1 to 8% cases of the inborn deafness (Smith and Hone 2003).

The **Pendred syndrome** develops due to mutations in the gene encoding the membrane protein - *pendrin* (Everett et al. 1997). Pendrin is an electroneutral anion channel belonging to the family of SLC26 transporters (Everett et al. 1997). It is composed of 780 amino acids arranged into 11 or 12 transmembrane domains (Everett et al. 1997; Royaux et al. 2000). In the C-terminus region is located a STAS domain (Sulfate Transporter Antagonist of Anti-Sigma Factor) which probably plays an important role in the biosynthesis, function, and regulation of this
transporter (Babu et al. 2010). Based on the sequence homology, the pendrin is closely related to the family of sulphate transporters; however, it does not provide the transport of sulphates (Scott et al. 1999). Pendrin allows the mutual exchange of $I^-$, $Cl^-$, $HCO_3^-$, $HCOO^-$ anions in the inner ear, thyroid gland, and kidneys (Everett et al. 1997; Royaux et al. 2001). Mutations in pendrin-encoding gene may cause syndromic (Pendred Syndrome) or nonsyndromic hearing loss in connection with Enlarged Vestibular Aqueduct – EVA or Mondini Dysplasia (Everett et al. 1997; Usami et al. 1999).

The role of pendrin in the inner ear. Pendrin is expressed in several cell types of the inner ear, e.g. inner and outer hair cells, Deiter’s and Claudius’ cells, spindle-shaped cells of the stria vascularis, prominentia spiralis, and external sulcus cells (Royaux et al. 2003; Wangemann et al. 2004; Yoshino et al. 2003, 2006). In the vestibular apparatus, the pendrin is located in the apical membrane of epithelial cells of the utriculus, saccus, and ampulla as well as ductus and saccus endolymphaticus (Royaux et al. 2003; Yoshino et al. 2004). In the inner ear, it plays a role in the maintaining of the pH value of the endolymph. The endolymph pH is slightly alkaline (Nakaya et al. 2007; Wangemann et al. 2007) and homeostasis is dependent on the concentration of $H^+$ and $HCO_3^-$. The hydrogen anions are actively transported to endolymph by $H^+$-ATPase (Karet et al. 1999). The transport of $HCO_3^-$ is provided by pendrin through the exchange of chlorine anions (Scott et al. 1999). The damaged pendrin leads to the reduction of $HCO_3^-$, and thus increasing the acidity of the endolymph. The endolymph acidity inhibits pH-sensitive TRPV5 and TRPV6 $Ca^{2+}$ channels (Transient Receptor Potential Vanilloid). This subsequently leads to a reduced reabsorption of the calcium ions and their increased concentration in the endolymph. This mechanism probably results in vestibular dysfunction, degeneration of hair cells, and hearing loss (Nakaya et al. 2007; Wangemann et al. 2007).

Role of pendrin in the thyroid gland. In the thyroid gland, the pendrin provides transport of iodine anions to the lumen of thyroid follicles. Iodides are actively cap-

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**Fig. 3.** Transport of iodide ion by NIS iodide pump into a follicular cell and pendrin into the follicular lumen followed by subsequent organicization and binding into T3, T4.

tured from the blood on the basolateral membrane and transferred into the follicular cells via the Na⁺/I⁻ symport (NIS) (Dohan et al. 2003) (Fig. 3). This co-transport of two sodium cations and one iodide is carried out on the basis of electrochemical sodium gradient provided by Na⁺/K⁺-ATPase (Filetti et al. 1999). From the apical cell membrane, iodide is released into the lumen of follicles and in the presence of hydrogen peroxide (H₂O₂) is oxidized by thyreoperoxidase (TPO). The production of H₂O₂ is provided by Ca²⁺ and NADPH-dependent dual oxidases (DUOX1/2) (Dupuy et al. 1999). The organification/iodination of tyrosine residues on the thyroglobulin molecule takes place in the follicular lumen, thus producing monoiodotyrosine (MIT) and diiodotyrosine (DIT). The thyreoperoxidase also catalyses the coupling of MIT and DIT into the triiodothyronine (T₃) and triiodothyronine (T₄/thyroxine), which remain coupled with the thyroglobulin in the colloid of the lumen (Fig. 3). Secretion of T₃ and T₄ is preceded by the thyroglobulin pinocytosis into the follicular cells. Afterwards, T₃ and T₄ are separated from the thyroglobulin and secreted into the bloodstream. The unspent MIT and DIT are enzymatically degraded into the iodtyrosine by dehalogenase 1 (Gnidehou et al. 2004).

Pendrin in the apical membrane of the follicular cells allows an exchange of iodide and chloride anions between the follicular lumen and cells (Yoshida et al. 2004). However, its role, as a single transporter of iodide across the follicular lumen (Fig. 3), is still unclear (Bizhanova and Kopp 2010). Electrophysiological studies have discovered two iodide transporters on the apical side of the follicular cells (Golstein et al. 1992). Channel that could participate in the outflow of iodides or exchange of the Cl⁻/I⁻ ions in follicles, might be a chloride channel ClCn5 located in the apical membrane of the follicular cells. Deficit of this channel leads to the development of goiter in mice (van den Hove et al. 2006).

**Mutation in pendrin encoding gene.** Pendrin is encoded by the SLC26A4 gene (Solute Carrier family 26, member 4), which is located on the long arm of chromosome 7 (7q22.3-q31.1) and contains 21 exons. For this gene more than 170 variants (Dossena et al. 2011b) and approximately 40 pathogenic mutations have been described so far (Hilgert et al. 2009a). Mutations are present in the promoter, exons or introns. The point substitutions are the most widespread, accounting for 64%, followed by deletions, insertions, and splice site mutations, accounting for approximately 13% of the cases (Dossena et al. 2011b). There may also be rare cases of larger deletions, such as 4 kb long deletion (exon 3) found in the East-Asian population (Park et al. 2003). These mutations are characterized by an autosomal recessive inheritance. They cause Pendred syndrome, SNHL associated with goiter (Reardon a Trembath 1996; Campbell et al. 2001) and nonsyndromic SNHL associated with inner ear malformations, such as EV (Enlarged Vestibular Aqueduct) or Mondini Dysplasia (Usami et al. 1999). Pendred syndrome is manifested by biallelic mutations (homozygote/compound heterozygote) (Pryor et al. 2005). It may also occur due to compound heterozygous mutations in SLC26A4 and other genes, such as gene encoding the FOXI1 transcription factor (forkhead box) (Yang et al. 2007) or gene encoding Kir4.1 potassium channel (KCNJ10) (Yang et al. 2009).

In terms of protein structure, mutations in the SLC26A4 often cause retention of pendrin in various cell compartments, thus preventing from reaching plasma membrane and its incorporation. The location of a mutated protein in cell varies according to the individual mutation (Yoon et al. 2008). For example, the most widespread mutation in Caucasoid population (L236P) causes retention of pendrin in the centrosomal region, while other mutation most often found in East Asia (H723R) causes arresting of mutated protein in the endoplasmic reticulum. These mutations mostly lead to an incorrect composition of protein and its subsequent degradation (Yoon et al. 2008). Another mutations do not affect protein composition and the pendrin is incorporated into the plasma membrane, but its transport function is disrupted (Taylor et al. 2002; Choi et al. 2009). Loss of function SLC26A4 mutations causes reduction in the protein activity including aminoacid substitutions and shortening of the protein (Dossena et al. 2011b).

Mutations in the SLC26A4 gene are linked to a wide spectrum of hearing disorders, from mild to profound ones (Azaiez et al. 2007). The Pendred syndrome is characterized by a prelingual severe to profound bilateral SNHL (Reardon et al. 1997). However, in some cases, it may be fluctuating or progressive after a head injury (Reardon et al. 1997; Colvin et al. 2006). For individuals with SLC26A4 mutations, goiter usually appears during puberty, but it may develop at any age or be completely missing in some individuals (Pryor et al. 2005). The function of thyroid gland is variable, from normal to hypothyroidism (Reardon et al. 1999). According to Bizhanova and Kopp (2010), key factor in the development of goiter and hypofunction of thyroid gland in individuals suffering from Pendred syndrome...
is reduced intake of iodine from the food. The euthyroid individuals with biallelic SLC26A4 mutations have been reported in countries with excessive intake of iodine, such as Japan and Korea (Park et al. 2003; Tsukamoto et al. 2003). Additionally, a congenital hypothyroidism has been reported in patients with Pendred syndrome in regions with iodine deficiency (Gonzalez Trevino et al. 2001). However, goiter did not develop in the SLC26A4 knock-out mice, provided iodine-deficient nutrition, which suggests influence of other environmental, epigenetic or genetic factors necessary for goiter and hypothyroidism development in patients with Pendred syndrome (Calebiro et al. 2011; Iwata et al. 2011).

**SNHL on the basis of mitochondrial DNA mutations**

Due to mitochondrial DNA (mtDNA) mutations, syndromic or nonsyndromic SNHL may develop. The mitochondrial DNA mutations account for approximately 5% of the postlingual nonsyndromic SNHL cases (Ballana et al. 2007).

Mitochondrial DNA is double-stranded circular DNA with a length of 16 569 bp encoding 37 genes. The mtDNA is compact, does not include introns and the coding sequences of the adjacent genes are mainly overlapping or separated by at most 1-2 non-coding bases. It is characterized by maternal inheritance, thus a zygote during fertilization obtains mitochondria only from the ovum (DiMauro 2004). Distribution of the mitochondria from a dividing mother cell into the daughter cells during mitosis is generally being random. The human cell contains 100 to 1 000 mitochondria and each mitochondrion contains 1 to 10 copies of mtDNA (Wallace 1999).

mtDNA is characterized by a high incidence of mutations. Since it is present in multiple copies, one individual can be a carrier of both mutated and non-mutated mtDNAs. The occurrence of mixed wild-type and mutant mtDNA is referred as a heteroplasmy, which is reported as percentage of the mutated DNA (Wallace 1999). The heteroplasmy level is higher in cells with slow and lower in tissues with fast cell division. For example, heteroplasmy of the buccal mucosa cells may be even by 20% higher than in blood cells (‘t Hart et al. 1996). Some of the mtDNA mutations are manifested in heteroplasmic while others in homoplasmic form, with cells containing 100% of mutated mtDNA. The homoplasmic mutations are present in all the mtDNA copies of the affected individual (Vilkki et al. 1989).

Nowadays, several hundreds of mtDNA mutations are known which are responsible for the onset of a single disease or multiorgan damage. The point substitutions are the most prevalent mutation types. However, a number of insertions, simple and multiple deletions, as well as a complex of rearrangements and inversions have also been reported (http://mitomap.org/MITOMAP).

Based on a 10-year UK study, the minimal prevalence of pathogenic mtDNA mutations and mitochondrial diseases has been estimated in the ratio of 12.5:100 000 individuals (1:8 000) (Chinnery et al. 2000). However, another UK study reported the presence of a pathogenic mutation that could lead to disease onset even in ratio of 1:200 individuals (Elliott et al. 2008).

The relationship between the genotype and phenotype is highly variable. The same mutation can cause several diseases (Maassen et al. 2005). Clinical manifestations and severity of cells and organs damages depend on several factors. These include sorting of mitochondria during the cell division, rate of mutated mtDNA and energy requirements of the tissue. The mtDNA mutations cause damage predominantly in organs with high energy demands. Due to high energy request and low regeneration ability of hair cells, the inner ear cochlea is sensitive to mitochondrial dysfunction. Thus SNHL is a frequent clinical manifestation of mitochondrial diseases (Fischel-Ghodsian 2003; Kato et al. 2010). Mutations of mtDNA can cause syndromic and nonsyndromic SNHL and some of them may even increase the inner ear hair cells sensitivity to ototoxic drugs (Estivill et al. 1998b; Hendrickx et al. 2006). Hearing loss resulting from mtDNA mutations probably develops due to insufficient ATP production in *stria vascularis* marginal cells. These cells allow the active transport of K+ back to endolymph via voltage-dependent potassium channels. The exact concentration and circulation of potassium ions in individual cells and compartments of cochlea are necessary for function of Corti organ and acoustic signal transmission to the neural pathway (Wangemann 2006; Olmos et al. 2011). List of mtDNA mutations leading to SNHL is given in Table 2.

**Nonsyndromic SNHL and mtDNA mutations.** The mtDNA mutations causing nonsyndromic SNHL are considered as homoplasmic, when the rate of mutated mtDNA is above 85% in the entire mitochondrial genome (Berrettini et al. 2008). Mutations act as a primary factor for the development of the SNHL and they provide predisposition to such disorder (Estivill et al. 1998b). The most frequent mutation leading to the development of nonsyndromic SNHL is m.1555A>G.
Sensorineural hearing loss, MIDD – Maternally Inherited Diabetes and Deafness syndrome is highlighted in bold. MELAS – Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, Stroke – like episodes; MERRF – Myoclonus Epilepsy with Ragged Red Fibres; LHON – Leber’s Hereditary Optic Neuropathy. Data about the homoplasmy and heteroplasmy are taken from http://mitomap.org/bin/view.pl/MITOMAP/MutationsRNA.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Locus</th>
<th>RNA</th>
<th>Clinical condition</th>
<th>Homoplasmy/ Heteroplasmy</th>
<th>References</th>
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<tbody>
<tr>
<td>m.827A&gt;G</td>
<td>MTRNR1</td>
<td>12S rRNA</td>
<td>Nonsyndromic SNHL</td>
<td>+/-</td>
<td>(Ealy et al., 2011)</td>
</tr>
<tr>
<td>m.961delT/insC</td>
<td>MTRNR1</td>
<td>12S rRNA</td>
<td>Nonsyndromic SNHL</td>
<td>++/-</td>
<td>(Kobayashi et al., 2005)</td>
</tr>
<tr>
<td>m.961T&gt;G</td>
<td>MTRNR1</td>
<td>12S rRNA</td>
<td>Nonsyndromic SNHL</td>
<td>+/-</td>
<td>(Tang et al., 2002)</td>
</tr>
<tr>
<td>m.1494C&gt;T</td>
<td>MTRNR1</td>
<td>12S rRNA</td>
<td>Nonsyndromic SNHL</td>
<td>+/-</td>
<td>(Zhao et al., 2004)</td>
</tr>
<tr>
<td>m.1555A&gt;G</td>
<td>MTRNR1</td>
<td>12S rRNA</td>
<td>Nonsyndromic SNHL</td>
<td>+/-</td>
<td>(Estivill et al., 1998b)</td>
</tr>
<tr>
<td>m.3388C&gt;A</td>
<td>MTND1</td>
<td></td>
<td>Nonsyndromic SNHL</td>
<td></td>
<td>(Gutierrez Cortes et al., 2012), (Leveque et al., 2007)</td>
</tr>
<tr>
<td>m.3243A&gt;G</td>
<td>MTTL1</td>
<td>tRNALeu</td>
<td>MIDD, MELAS, MERRF etc.</td>
<td>-/+</td>
<td>(van den Ouweland et al., 1994), (Fabrizi et al., 1996)</td>
</tr>
<tr>
<td>m.3271T&gt;C</td>
<td>MTTL1</td>
<td>tRNALeu</td>
<td>diabetes mellitus, MELAS</td>
<td>-/+</td>
<td>(Tsukuda et al., 1997), (Goto, 1995)</td>
</tr>
<tr>
<td>m.7472insC</td>
<td>MTTS1</td>
<td>tRNAser</td>
<td>SNHL, ataxia, myoclonus</td>
<td>-/+</td>
<td>(Tiranti et al., 1995)</td>
</tr>
<tr>
<td>m.7444G&gt;A</td>
<td>MTCO1</td>
<td></td>
<td>SNHL, LHON</td>
<td>+/-</td>
<td>(Pandya et al., 1999), (Brown et al., 1995)</td>
</tr>
<tr>
<td>m.7445A&gt;G</td>
<td>MTTS1</td>
<td>tRNAser</td>
<td>SNHL, palmoplantar keratoderma</td>
<td>+/-</td>
<td>(Reid et al., 1994), (Sevior et al., 1998)</td>
</tr>
<tr>
<td>m.7510T&gt;C</td>
<td>MTTS1</td>
<td>tRNAser</td>
<td>Nonsyndromic SNHL</td>
<td>-/+</td>
<td>(Hutchin et al., 2000)</td>
</tr>
<tr>
<td>m.7511T&gt;C</td>
<td>MTTS1</td>
<td>tRNAser</td>
<td>Nonsyndromic SNHL</td>
<td>+/-</td>
<td>(Sue et al., 1999b)</td>
</tr>
<tr>
<td>m.8296A&gt;G</td>
<td>MTTK</td>
<td>tRNALys</td>
<td>MIDD, MERRF, MELAS</td>
<td>-/+</td>
<td>(Arenas et al., 1999), (Sakuta et al., 2002)</td>
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<tr>
<td>m.8363G&gt;A</td>
<td>MTTK</td>
<td>tRNALys</td>
<td>SNHL, MERRF, cardiomyopathy</td>
<td>-/+</td>
<td>(Santorelli et al., 1996), (Virgilio et al., 2009)</td>
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<tr>
<td>m.12201T&gt;C</td>
<td>tRNAlis</td>
<td></td>
<td>Nonsyndromic SNHL</td>
<td>-/+</td>
<td>(Yan et al., 2011)</td>
</tr>
<tr>
<td>m.12258C&gt;A</td>
<td>MTTS2</td>
<td>tRNAser</td>
<td>MIDD</td>
<td>-/+</td>
<td>(Lynn et al., 1998)</td>
</tr>
<tr>
<td>m.14535_14536insCC</td>
<td>MTND6</td>
<td></td>
<td>MIDD</td>
<td>-/+</td>
<td>(Bannwarth et al., 2011)</td>
</tr>
<tr>
<td>m.14709T&gt;C</td>
<td>MTTE</td>
<td>tRNAGlu</td>
<td>MIDD/myopathy</td>
<td>+/-</td>
<td>(Perucca-Lostanlen et al., 2002), (McFarland et al., 2004)</td>
</tr>
</tbody>
</table>

SNHL – sensorineural hearing loss, MIDD – Maternally Inherited Diabetes and Deafness syndrome is highlighted in bold. MELAS – Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, Stroke – like episodes; MERRF – Myoclonus Epilepsy with Ragged Red Fibres; LHON – Leber’s Hereditary Optic Neuropathy. Data about the homoplasmy and heteroplasmy are taken from http://mitomap.org/bin/view.pl/MITOMAP/MutationsRNA.

The individuals with this mutation show sudden or delayed onset of hearing loss after administration of aminoglycoside antibiotics (Estivill et al. 1998b; Rahman et al. 2012). The m.1555A>G mutation is located...
at a highly conserved position of the mitochondrial 12S rRNA gene. It causes structural changes to a small subunit of mitochondrial ribosome enabling the binding and impact of aminglycosides (Forge and Schacht 2000; Guan 2011). However, hearing loss may absent in some m.1555A>G mutation carriers, which suggests the presence of another environmental or genetic factor inducing such hearing loss (Rahman et al. 2012). Estimated prevalence of m.1555A>G is about 1:500 (Bitner-Glindzicz et al. 2009). Data from study covering more than 7,000 individuals indicate for a more frequent (1:385) prevalence of this mutation in the Caucasian population (Rahman et al. 2012).

Until 2007, the mtDNA mutations causing nonsyndromic SNHL had only been described in genes for 12S rRNA and tRNA\textsubscript{Ser}\textsuperscript{UCN}. The screening of the entire mitochondrial genome of patients with nonsyndromic hearing loss has revealed several other variants and cell culture studies have confirmed pathogenicity for one of them (m.3388C>A) (Leveque et al. 2007; Gutierrez Cortes et al. 2012). This point substitution is found in a gene encoding the ND1 subunit of complex I of mitochondrial respiratory chain and causes a lower activity of the complex I (Gutierrez Cortes et al. 2012).

**Syndromic SNHL and mtDNA mutations.** Syndromic SNHL, based on the mtDNA mutations, is associated with a wide range of disorders. The impact of sole mutation is often manifested through various phenotypes and syndromes. The most frequent mutation causing syndromic SNHL (m.3243A>G) mainly causes the MELAS syndrome (Mitochondrial myopathy, Encephalopathy, Lactic Acidosis, Stroke – like episodes) or MIDD (Maternally Inherited Diabetes and Deafness) syndrome (van den Ouweland et al. 1994). However, rarely it may cause also MERRF (Myoclonus Epilepsy with Ragged Red Fibres) (Fabrizi et al. 1996), PEO (paternally inherited Progressive External Ophthalmplegia) (Moraes et al. 1993), KSS (Kearns-Sayre syndrome) or Leigh syndrome (Sue et al. 1999a). Mutation m.3243A>G is present in tRNA\textsubscript{Ser}\textsuperscript{UCN} gene, which transports leucine amino acid to mitochondrial ribosomes. This mutation causes several defects in the structure and function of tRNA\textsubscript{Ser}\textsuperscript{UCN}. For example, dysfunction of aminocyclation or reduction of tRNA processing results in a reduction of the tRNA amount and damages its coupling with mitoribosomes which has impact on the translation and decreases the ATP synthesis (Florentz et al. 2003; Olmos et al. 2011). The syndromic SNHL is a result of several mutations present in genes encoding the transfer RNA. Other mutations causing syndromic SNHL are shown in Table 2.

### Maternally Inherited Diabetes and Deafness syndrome

**Maternally Inherited Diabetes and Deafness (MIDD) syndrome** is characterized by the SNHL in connection with the diabetes mellitus. This syndrome appears on the basis of mtDNA mutations and is characterized by maternal inheritance. Six mutations have been described, most of them being heteroplasmic (Table 2). The blood heteroplasmy in individuals with the MIDD syndrome vary between studies in range from 1 to 40%, but it may reach even 80% (van Essen et al. 2000; Maassen et al. 2005; Laloi-Michelin et al. 2009). However, it is still not clear whether 1% heteroplasmy may lead to a diabetic phenotype (Maassen et al. 2005).

Hearing loss associated with the MIDD syndrome is sensorineural, bilateral, and progressive, and usually becomes apparent during adolescence with typical loss in hearing of high frequencies. Gradually it leads to profound hearing loss in all frequencies and progression varies between 1.5 and 7.9 dB per year (Yamasoba et al. 1996; Hendrickx et al. 2006). Diabetes mellitus of the m.3423A>G mutation carriers is manifested in the age of 35 years in average (Maassen et al. 2004). The penetration of this mutation is high. Diabetes develops in approximately 85% of carriers before the age of 70. This type of diabetes is characterized by reduced glucose-induced secretion of insulin, premature aging of beta cells, and absence of insulin resistance (Maassen et al. 2005). However, some studies, concerning the carriers of the m.3423A>G mutation, have confirmed a hepatic dysfunction (Takahashi et al. 2008) or reduced insulin sensitivity of skeletal muscles (Lindroos et al. 2009).

Most attributes indicate that the main pathological influence is directed on the mitochondria particularly in beta cells (Sivitz and Yorek 2010). The mitochondria in the pancreatic beta cells are necessary for ATP production, which plays a crucial role in insulin secretion. The glucose enters the beta cells postprandially by GLUT2 transporters and its glycolysis and mitochondrial metabolism lead to an intracellular ATP increase. The ATP binds to the Kir 6.2 subunit of K\textsubscript{ATP} channel, closes it and leads to depolarization of cell membrane. These results in opening of voltage-dependent Ca\textsuperscript{2+} channels followed by inflow of calcium ions into cells and insulin vesicle exocytosis is initiated (Maechler et al. 1998; Polak and Cave 2007). Decreased ATP production in beta cells probably impairs the glucose-induced insulin release into the blood circulation (Sivitz and Yorek 2010). Another mechanism leading to disruption of insulin secre-
tion is an increased production of free oxygen radicals by mitochondria, which results in oxidative damage of beta cells (Green et al. 2004; Sivitz and Yourek 2010). Diabetes in the MIDD syndrome is caused by the beta cell dysfunction alone compared to the type 2 diabetes where the beta cell dysfunction occurs together with the insulin resistance. Therefore, medicaments targeting the insulin resistance are effective in the type 2 diabetes but not in the MIDD syndrome. In addition, metformin is contraindicated in the MIDD due to higher risk of the lactate acidosis development. The lactate accumulation is caused by mitochondrial damage and metabolism in anaerobic conditions (Murphy et al. 2008). Diet alone or in the combination with the oral antidiabetics is treatments of choice in patients with the newly manifested diabetes in the MIDD syndrome. But progressive failure of beta cells is the cause that most of the MIDD syndrome patients will switch to the insulinotherapy earlier than the patients with type 2 diabetes (Olsson et al. 1998; Maassen et al. 2004).

Conclusions

The most frequent monogenic causes of the nonsyndromic SNHL originate due to mutations located in the connexin genes. Their identification is highly important not only in the term of classification, but particularly for the determination of the genetic risk for mutation carriers’ children. Moreover, the mutation found in the GJB2 gene may bring better prediction of patients hearing skills improvement after cochlear implantation. The syndromic SNHL associated with endocrinopathies occurs less often, but proof of the genetic cause has a large importance in terms of the further diagnosis and treatment. In Pendred syndrome, the hearing impairment mostly precedes clinical manifestation of the thyroid disease. Revealing the SLC26A4 mutation may accelerate the diagnosis assessment of the hypothyreosis. When correct diagnosis is omitted, the hypothyreosis may present a health risk for patient, especially in situation with high demands of the thyroid hormone production. In patients with the MIDD syndrome, the confirmation of the mtDNA mutation is worthy of pharmacogenetic aspects. Diabetes mellitus in the MIDD patients is manifested in the adulthood by a deficiency of the pancreatic antibodies and is often misdiagnosed as the type 2 diabetes. This incorrect diagnosis may be harmful for patient because metformin is the first line of treatment in the type 2 diabetes, whereas in the MIDD it is not only ineffective but even increases the risk of the lactate acidosis development. Taken together, the results from DNA diagnostics of the monogenic hearing loss should progressively come into the routine clinical practice in the selected types of hearing impairments. In Slovakia, the DNA diagnostics of the GJB2, GJB6, and SLC26A4 genes and m.3243A>G mtDNA mutation is available in the DIABGENE Laboratory (diabgene@savba.sk; www.diabgene.sk).

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