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Review

Central auditory function of deafness genes

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ABSTRACT

The highly variable benefit of hearing devices is a serious challenge in auditory rehabilitation. Various factors contribute to this phenomenon such as the diversity in ear defects, the different extent of auditory nerve hypoplasia, the age of intervention, and cognitive abilities. Recent analyses indicate that, in addition, central auditory functions of deafness genes have to be considered in this context. Since reduced neuronal activity acts as the common denominator in deafness, it is widely assumed that peripheral deafness influences development and function of the central auditory system in a stereotypical manner. However, functional characterization of transgenic mice with mutated deafness genes demonstrated gene-specific abnormalities in the central auditory system as well. A frequent function of deafness genes in the central auditory system is supported by a genome-wide expression study that revealed significant enrichment of these genes in the transcriptome of the auditory brainstem compared to the entire brain. Here, we will summarize current knowledge of the diverse central auditory functions of deafness genes. We furthermore propose the intimately interwoven gene regulatory networks governing development of the otic placode and the hindbrain as a mechanistic explanation for the widespread expression of these genes beyond the cochlea. We conclude that better knowledge of central auditory dysfunction caused by genetic alterations in deafness genes is required. In combination with improved genetic diagnostics becoming currently available through novel sequencing technologies, this information will likely contribute to better outcome prediction of hearing devices.

1. Introduction

Perception of sensory information results from signal transduction in the sensory endorgan and processing of this information in the central nervous system. Proper formation and function of both components is therefore necessary to achieve optimal performance. It is now well recognized that a combination of genetically encoded programs and neural activity are prerequisites for the development and maintenance of sensory systems (reviewed in Flavell and Greenberg, 2008; Loebrich and Nedivi, 2009; Wolfram and Baines, 2013). The importance of genetic information in sensory perception is demonstrated by the many genes that are involved in sensory impairments. Currently, mutations in more than 60 genes are known to cause hearing loss (reviewed in Brown et al., 2008; Lenz and Avraham, 2011; Angeli et al., 2012) and more than 180 genes are involved in visual impairment (reviewed in Hamel, 2013; Daiger, 2006). Similarly, dysfunctions in other sensory systems such as those for nociception (Mogil et al., 2000; Akopian, 2013), taste (Drayna, 2005), and olfaction (Karstensen and Tommerup, 2012) have a genetic background, albeit much less is currently known about the underlying genetic programs.

Neuronal activity plays a key role in shaping and maintaining sensory circuits after their initial formation and establishing the terminal gene batteries (reviewed in Reid, 2012; Johnston et al., 2005; Hobert, 2011; Fishell and Heintz, 2013; Wolfram and Baines, 2013). The importance of neuronal activity in development was first analyzed in great detail in the visual system, in which eye closure during critical periods leads to anatomical and physical alterations (reviewed in Hubel and Wiesel, 1964, 1965, 2005). Similar observations were later reported for other senses

Abbreviations: ABR, auditory brainstem response; AVCN, anterior ventral cochlear nucleus; CNC, cochlear nucleus complex; DCN, dorsal cochlear nucleus; IHC, inner hair cell; LSO, lateral superior olive; MNTB, medial nucleus of the trapezoid body; OHC, outer hair cell; PVCN, posterior ventral cochlear nucleus; r, rhombomere; SOC, superior olivary complex; SPN, spiral ganglion neuron; TF, transcription factor

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as well (reviewed in Kirkby et al., 2013; Blankenship and Feller, 2010; Katz and Shatz, 1996). In fact, a study of Rita Levi-Montalcini in the auditory system was amongst the first to describe the dependence of central sensory systems on input from the periphery (Levi-Montalcini, 1949). Her experiments in the auditory brainstem of chicken revealed that extirpation of the otic placode resulted in strong hypotrophy of cochlear nuclei. This ground-breaking work was followed by an impressive wealth of data, demonstrating the importance of both spontaneous and experience-driven activity for normal maturation and function of the auditory system (reviewed in Friauf and Lohmann, 1999; Walmsley et al., 2006; Tollin, 2010; Rubel et al., 2004; Kral, 2013). As most forms of deafness result in reduced synaptic input to the auditory nerve, central auditory consequences of hearing impairment were often assumed to be stereotyped, simply reflecting the lack of activity. However, recent analyses mainly from transgenic mice suggest that genetically caused deafness is associated with a larger variety of central auditory defects than previously thought. Here, we will summarize current knowledge on the diverse central auditory functions of deafness genes, provide a mechanistic explanation for a shared genetic program between the peripheral and central auditory system, and discuss the implications of the data for auditory rehabilitation.

2. Central auditory function of deafness genes

2.1. Transcription factors

Mutations in multiple transcription factors (TFs) have been associated with hearing impairment (Dror and Avraham, 2010). Among them, several TFs were reported to function as well in the central auditory system. Mutations in the homeodomain TF HOXA1[1] are associated with the autosomal recessive Athabaskan brain dysgenesis syndrome (ABDS), observed in some Native American tribes, and the Bosley-Salih-Alorainy syndrome (BSAS), reported in Saudi Arabian and Turkish families (Tischfield et al., 2005; Bosley et al., 2008). Both syndromes are characterized by horizontal gaze restriction, delayed motor development, and sensorineural deafness due to aplasia of the cochlea. Ablation of *Hoxa1* in mice resulted in severe abnormalities throughout the ear, including lack of middle ear ossicles and the cochlea (Chisaka et al., 1992; Lufkin et al., 1991). Beyond the ear, the auditory nerve was absent and the superior olivary complex (SOC), the first binaural processing center in the auditory brainstem, was not visible in coronal sections at embryonic day (E)18 (Chisaka et al., 1992) (Table 1). In contrast, the cochlear nucleus complex (CNC) appeared normal (Chisaka et al., 1992). *Hoxa1* is expressed in the developing hindbrain in rhombomeres (r)4 to r7 (Carpenter et al., 1993; Lufkin et al., 1991), which give rise to the posterior ventral cochlear nucleus (PVCN), the dorsal cochlear nucleus (DVCN) (Farago et al., 2006), and large parts of the SOC (Maricich et al., 2009; Rosengauer et al., 2012; Marrs et al., 2013) (Fig. 1). The expression pattern of *Hoxa1* is thus in agreement with a disrupted SOC in *Hoxa1* null mice. Quantitative alterations in the CNC might have escaped detection, as *Hoxa1* null mice die at birth (Chisaka et al., 1992; Lufkin et al., 1991). This renders quantitative analysis of auditory brainstem structures difficult, since they become visible just shortly before birth (Hoffpauir et al., 2009, 2010).

[1] Research in humans is indicated by italicized gene symbols with all letters in uppercase. Mouse research is indicated by italicized gene symbols with only the first letter in uppercase and the remaining letters in lowercase. Protein symbols are not italicized and all letters are uppercase for both species.

Missense or nonsense mutations in the related gene *HOXA2* results in an another autosomal-recessive disorder characterized by microtia, hearing impairment, and cleft palate (Alasti et al., 2008; Brown et al., 2013). Ears in these persons are characterized by small, malformed external ears and variable abnormalities of the ossicular chain, such as absence of the anterior crus of the stapes and the stapedial tendon, or the presence of a rigid ossicular chain. Similar observations were made in constitutive *Hoxa2* null mice. These animals lacked the pinna, the tubotympanic recess, and the stapes; instead they showed a duplication of the malleus and tympanic bones, and a hyperplastic tympanic ring with altered ossification (Gendron-Maguire et al., 1993). These homeotic transformations likely reflect the replacement of skeletal elements from the second branchial arch by those of the first branchial arch (Gendron-Maguire et al., 1993). In the brainstem, the CNC was considerably reduced at birth (Gavalas et al., 1997), presumably due to disturbed r2 and r3 identities (Gavalas et al., 1997) (Table 1). These two rhombomeres give rise to the anteroventral cochlear nucleus (AVCN) (Farago et al., 2006; Maricich et al., 2009; Rosengauer et al., 2012). In addition, lack of *Hoxa2* resulted in the innervation of the ipsilateral instead of the contralateral medial nucleus of the trapezoid body (MNTB) by AVCN neurons (Di Bonito et al., 2013) (Table 1). This abnormal circuitry is presumably caused by down-regulation of the Rig1 axon guidance receptor (Di Bonito et al., 2013). Postnatal alterations of auditory structures could not be analyzed, as the transgenic mice used in these studies die perinatally (Rijli et al., 1993; Di Bonito et al., 2013; Gendron-Maguire et al., 1993).

Within the context of *HOX* genes and their importance for the auditory system, it is of note that another family member, *Hoxb2*, is expressed both in the hindbrain and the inner ear (Szeto et al., 2009). In the hindbrain, *Hoxb2* null mice experience ectopic projections from the PVCN to the MNTB (Table 1). This is likely due to a transformation of the molecular identity of the PVCN to that of the AVCN, as indicated by the increased expression of *Atoh7* in PVCN neurons (Di Bonito et al., 2013). So far, functional consequences of *Hoxb2* mutations for development of the inner ear have not been investigated.

Another TF important for the auditory system is the zinc finger protein GATA3. Mutations in the corresponding gene cause the autosomal-dominant human HDR syndrome (aka Barakat syndrome), characterized by hypoparathyroidism (H), congenital sensorineural deafness (D), and renal insufficiency (R) (van Esch et al., 2000; Nesbit et al., 2004; Muroya et al., 2001). Heterozygote $Gata3^{+/-}$ mice showed a progressive 30 dB shift in hearing thresholds caused by the degeneration of hair cells and supporting cells in the cochlea (van der Wees et al., 2004). Homozygous deletion of *Gata3* affected early inner ear morphogenesis (Karis et al., 2001; Haugas et al., 2012) by causing massive cell death during development of the cochlear duct (Luo et al., 2013). Furthermore, formation of the prosensory domain, which gives rise to the organ of Corti, is disturbed (Luo et al., 2013). Beyond the cochlea, lack of GATA3 caused significantly increased loss of spiral ganglion neurons (SGNs) between embryonic days (E) 12.5 and 14.5 (Luo et al., 2013). In a *Bhlhb5::Cre;Gata3*$^{fl/fl}$ mouse line with specific ablation of *Gata3* in the SGNs, peripheral projections made highly aberrant trajectories to hair cells in the cochlea, whereas projections to the CNC were normal (Appler et al., 2013) (Table 1). The TF GATA3 thus plays an important role for survival and peripheral wiring of SGNs. *Gata3* is also expressed throughout the central auditory brainstem from the CNC up to the inferior colliculus (Zhao et al., 2008; Karis et al., 2001). Detailed characterization of the projections of the efferent olivocochlear bundle, a feedback system running from the SOC back to the cochlea, revealed that GATA3 is essential for innervation of the inner ear. In the absence of GATA3,

Table 1

Protein	Central auditory function in human disorders or mouse models	Reference
Transcription factors		
HOXA1	• Constitutive deletion	
	- Absence of the auditory nerve and SOC at E18	Chisaka et al., 1992
	→ HOXA1 serves as essential factor during embryonic formation of central auditory structures	
HOXA2	• Constitutive deletion	
	- Reduction of CNC due to disturbed r2 and r3 identities	Gavalas et al., 1997
	- Abnormal innervation of the ipsilateral MNTB by AVCN neurons	Di Bonito et al., 2013
	→ HOXA2 required for normal formation and proper wiring of auditory brainstem structures	
HOXB2	• Constitutive deletion	
	- Ectopic projections from PVCN to MNTB	Di Bonito et al., 2013
	→ HOXB2 potentially involved in forming molecular identities of auditory brainstem structures	
GATA3	• Constitutive deletion	Luo et al., 2013
	- Loss of SGNs during embryogenesis	Karis et al., 2001
	- Abnormal wiring of the olivocochlear bundle	Duncan et al., 2011
	• Targeted deletion in SGNs	
	- Aberrant efferent projections from SGNs to the inner ear	Appler et al., 2013
	→ GATA3 important for survival of SGNs and pathfinding of efferent neurons that innervate the cochlear	
ATOH1	• Constitutive deletion	
	- Reduction of CNC and lack of excitatory neurons	Fujiyama et al., 2009
	• Targeted deletion posterior to r3	
	- Loss of PVCN and DCN	Maricich et al., 2009
	• Targeted deletion in r3 and r5 derived cells	
	- Altered ABR	Maricich et al., 2009
	- Near absence of AVCN, reduction of PVCN and DCN	
	- Loss of VGLUT2 positive neurons in LSO and MSO	
	→ ATOH1 essential for formation of the ascending auditory pathway and development of excitatory auditory brainstem neurons	
NEUROD1	• Constitutive deletion	
	- SGNs largely missing	Liu et al., 2000
	- Absence of DCN	
	→ NEUROD1 required for neurogenesis of the SGNs and DCN	
CHD7	• Human mutations (CHARGE syndrome)	
	- Absence of the auditory nerve	Morimoto et al., 2006
	• *Wheels* mutation in CHD7	
	- Ectopic expression of TF KROX-20 in r4 and of HOXB1 in r3 and r5	Alavizadeh et al., 2001
	→ CHD7 seems to be important for definition of segmental boundaries in the developing hindbrain and mutations will therefore likely affect formation of auditory brainstem nuclei	
Signaling molecules		
BMP4	• Ablation of BMP receptors BMPR1a and BMPR1b	
	- Smaller calyces of Held at P8	Xiao et al., 2013
	- Multiple innervation of MNTB neurons	
	→ BMP signaling required for maturation of the calyx of Held	
$Ca_v1.3$	• Constitutive deletion	
	- Volume reduction of all auditory brainstem nuclei	Hirtz et al., 2011
	- Abnormal firing pattern of LSO neurons	
	- No synaptic refinement of the MNTB − LSO projection	Hirtz et al., 2012
	• Targeted deletion in the auditory brainstem	
	- Volume reduction of SOC nuclei	Satheesh et al., 2012
	- Altered ABR	
	→ Essential on-site role of $Ca_v1.3$ in the auditory brainstem for neuronal survival	
IGF1	• Constitutive deletion	
	- Altered ABR with progressively increased peak latencies along the auditory brainstem	Cediel et al., 2006
	→ Particular role in the auditory brainstem requires further investigations	
Miscellaneous proteins		
VGLUT3	• Constitutive deletion	
	- Impaired topographical reorganization and refinement of the inhibitory MNTB − LSO projection	Noh et al., 2010
	→ VGLUT3-assisted glutamatergic neurotransmission is required for refinement	
UCN	• Constitutive deletion	
	- Elevated auditory threshold	Vetter et al., 2002
	- Reduced DPOAE amplitudes	
	→ UCN required for development of normal cochlear mechanics and cochlear amplification	
KCNQ4	• Constitutive deletion	
	- Altered ABR waves I and II	Kharkovets et al., 2006
	→ Particular role in the auditory brainstem requires further investigations	

many projections failed to cross the midline to reach the contralateral ear and instead rerouted with the ipsilateral facial branchial motoneurons and the greater petrosal nerve (Karis et al., 2001; Duncan et al., 2011) (Table 1).

The basic helix-loop-helix TF ATOH1 (aka MATH1) is a close homolog of the *Drosophila* proneural TF atonal, which contributes to Johnston's organ, a chordotonal organ important for hearing. Absence of atonal caused lack of mechanoreceptors progenitors in this organ (Jarman et al., 1993). In mice, targeted ablation of *Atoh1* impaired the generation of hair cells albeit the primordium was formed (Bermingham et al., 1999; Chonko et al., 2013). This lack of hair cells was caused by increased apoptosis, which started at the

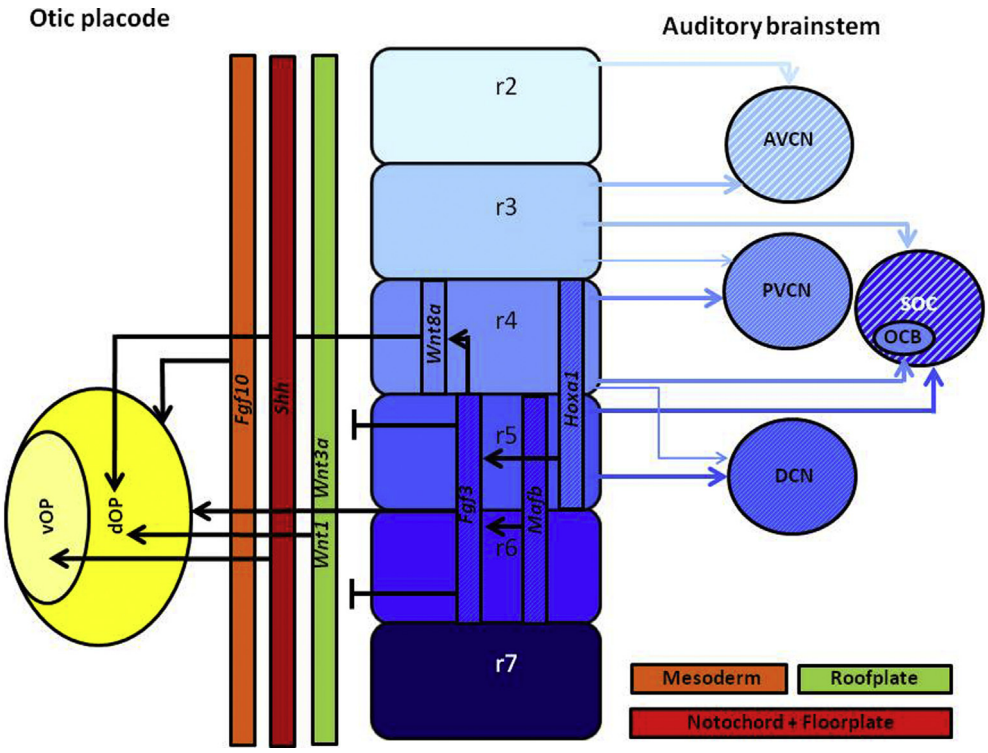

Fig. 1. Shared genetic program during development of the peripheral and central auditory system. Expression of *Hoxa1* in rhombomeres (r) 4 and r5 and of *Mafb* in r5 and r6 are required for the correct expression of *Fgf3* in r5 and r6. *Fgf3* expression in r5 and r6, together with the expression of *Fgf10* in the mesoderm, in turn, is necessary for the induction of the otic placode (OP). *Fgf3* is also essential for the expression of *Wnt8a* in r4 and for preventing a ventral expansion of *Wnt3a* in the hindbrain. *Wnt1*, *Wnt3a* and *Wnt8a* are involved in the specification and maintenance of the dorsal otic placode (dOP). In contrast, expression of *Shh* in the notochord and floorplate is responsible for the patterning of the ventral otic placode (vOP). The anteroventral cochlear nucleus (AVCN) originates mainly from r2 and r3, whereas the posteroventral cochlear nucleus (PVCN) is mainly derived from r4 and from a smaller portion of r3. The dorsal nucleus (DCN) is mostly derived from r5 with a minor fraction from r4. The superior olivary complex (SOC) consists of cells derived from r3 and r5, whereas the neurons of the olivocochlear bundle (OCB) originate from r4. Arrows describe positive regulations and bars negative regulations. Anterior is to the top.

base of the cochlear duct at E15.5 and at the apex at E17.5. This time course parallels the base-to-apex timing of hair cell differentiation in wild-type mice, thus indicating an important role of ATOH1 in differentiation (Chen et al., 2002; Chonko et al., 2013). To study the role of ATOH1 in the central auditory system, mice with constitutive *Atoh1* deletion or brainstem-restricted deletion of the TF were generated. In the latter case, two Cre-driver mouse lines were used, the *Erg2*::*Cre* (aka *Krox-20*::*Cre*) driver line, which ablates *Atoh1* only in r3 and r5 derived cells, or the *Hoxb1*::*Cre* driver line deleting the TF posterior to r3 (Maricich et al., 2009). Constitutive *Atoh1* null mice had a strongly reduced CNC and lacked excitatory neurons throughout the CNC, as demonstrated by the lack of *in situ* hybridization signals with a *Slc17a6* probe. The *Slc17a6* gene encodes the vesicular glutamate transporter VGLUT2 (Fujiyama et al., 2009) (Table 1), which loads synaptic vesicles with glutamate (reviewed in El Mestikawy et al., 2011; Fremeau et al., 2004). In contrast, inhibitory neurons in the CNC such as cartwheel cells and D-stellate cells were still present (Fujiyama et al., 2009). In *Erg2*::*Cre;Atoh*$^{fl/fl}$ mice, altered auditory brainstem responses with fewer peaks and increased threshold were observed, indicating disturbed signal propagation along the ascending auditory pathway (Maricich et al., 2009) (Table 1). Histological examination of adult mice revealed the lack of large parts of the AVCN and reduced sizes of the PVCN and DCN. In addition, SOC neurons lost VGLUT2 positive neurons in the lateral superior olive (LSO) and the medial superior olive (Maricich et al., 2009) (Table 1). This extends the importance of ATOH1 for the development of excitatory auditory brainstem neurons to third order nuclei of the SOC. In *Hoxb1*::*Cre;Atoh*$^{fl/fl}$ mice, the AVCN was normal, but DCN and PVCN were lost (Maricich et al., 2009) (Table 1). The strongly reduced CNC in both constitutive and conditional knockout mice is in agreement with the expression of *Atoh1* in r2 – r5 (Akazawa et al., 1995; Wang et al., 2005), the origin of most neurons of the CNC (Farago et al., 2006; Rosengauer et al., 2012; Wang et al., 2005). Together, the data demonstrate an essential role of ATOH1 for differentiation of inner hair cells and formation of the ascending auditory pathway.

Alike ATOH1, NEUROD1 belongs to the class of basic helix-loop-helix TF. Homozygous missense mutations resulting in a truncated protein were identified in two persons with early onset permanent diabetes, learning disabilities, cerebellar aplasia, myopia, retinal dystrophy, as well as profound sensorineural deafness (Rubio-Cabezas et al., 2010). Detailed analyses of *NeuroD1* null mice revealed that the TF is required for proper formation of the inner ear and neurogenesis of SGNs. In the absence of NEUROD1, the cochlear duct was shortened, additional inner and outer hair cell (IHC and OHC) rows were observed, and 95% of SGNs were missing due to a delamination defect of the neuroblasts from the otic wall, accompanied by increased apoptosis (Liu et al., 2000) (Table 1). In the auditory brainstem of young adult mice, the DCN was absent, whereas the PVCN, another target of SGNs, was still present (Liu et al., 2000) (Table 1). The different effects on target areas of the auditory nerve indicate that disruption of the DCN is caused by a specific role of NEUROD1 in this auditory nucleus and is not merely reflecting lack of innervation.

CHARGE syndrome is characterized by coloboma (C), heart disease (H), atresia choanae (A), retarded growth and development (R), genital hypoplasia (G), and ear anomalies (E) (Tellier et al., 1998; Pagon et al., 1981; Sanlaville and Verloes, 2007). Malformation of the ear is observed in all three segments of the ear, starting with asymmetrically formed pinnae at the outer ear. In the middle

ear, the stapedius muscle and the oval window are sometimes absent, and the stapes and incus are hypoplastic. In the inner ear, cochlear dysplasia, such as lack of cochlear partitioning, is observed (Sanlaville and Verloes, 2007; Castillo et al., 1997; Huang et al., 2012; Lemmerling et al., 1998). As a consequence of these ear anomalies, ~90% of patients exhibit conductive, sensorineuronal, or a mixed hearing impairment (Hang et al., 2012; Huang et al., 2012). Genetic analyses identified mutations in *CHD7*, encoding the chromodomain helicase DNA-binding protein 7, as the underlying cause (Vissers et al., 2004). Beyond the cochlea, computer tomography revealed cochlear aperture atresia in the majority of patients, indicating frequent absence of the auditory nerve (Morimoto et al., 2006) (Table 1).

Mutational analyses in humans and mice demonstrated that the *CHD7* gene locus is highly mutable (Bosman et al., 2005). In one allelic mouse line, the so-called *wheels* mouse, several anomalies were detected in r3 to r5 (Alavizadeh et al., 2001). At E8.5, *Egr2*, encoding the zinc finger transcription factor Krox-20, a specific marker for r3 and r5 (see above) (Wilkinson et al., 1989), was also expressed in r4 (Table 1). In addition, expression analysis of the homeodomain TF HOXB1 demonstrated narrowing of the r4 segment and ectopic expression of this gene along the axial midline of r3 and r5 (Alavizadeh et al., 2001) (Table 1). Taken together, these data indicate abnormal segmental boundaries in this hindbrain area. Since large parts of the CNC and SOC are derived from r3 to r5 (Fig. 1), the auditory brainstem architecture will likely be disturbed. *Wheels* mice die between E10.5 and E11.5 (Alavizadeh et al., 2001) and therefore, conclusive evidence of auditory brainstem malformation is still missing. It will therefore be important to study other allelic mouse variants of *CHD7* in more detail along the ascending and descending auditory pathway.

2.2. Signaling molecules

In addition to TF, signaling molecules prominently orchestrate the development of the auditory system. The bone morphogenetic protein BMP4 is a secreted protein of the TGF-beta gene family (Kitisin et al., 2007). In humans, the gene is located on chromosome 14q22-q23 and a patient with sensorineuronal hearing loss was reported to display an interstitial deletion in this region including *BMP4* (Bakrania et al., 2008). The protein was identified as an early sensory marker of the inner ear (Wu and Oh, 1996). Since *Bmp4* null mice die between E6.5 and E9.5 (Winnier et al., 1995), culture systems were used to examine its function during inner ear development. These studies revealed the involvement of BMP4 in signaling between the otic epithelium and the underlying periotic mesenchyme to induce chondrogenesis of the otic capsule. *Bmp4*-specific antisense oligonucleotides suppressed chondrogenesis in culture and the effect could be rescued by the addition of BMP4 (Liu et al., 2003). Furthermore, BMP4 signaling is important for the commitment of progenitor cells to become sensory epithelium, and for subsequent differentiation of hair cells (Li et al., 2005). The importance of BMP signaling was more recently confirmed in compound mutant mice with ablation of the BMP4 receptors Alk3 and Alk6 (Ohyama et al., 2010).

In the central auditory system, a transcriptome analysis of SOC nuclei in the mouse revealed significantly increased expression of *Bmp4* and *Bmp5* in the MNTB compared to the LSO at postnatal day (P)3 (Xiao et al., 2013). Ablation of the BMP receptors BMPR1a and BMPR1b in transgenic mice demonstrated that BMP signaling is important for functional maturation of the calyx of Held, the giant presynaptic terminal of bushy cells of the AVCN, terminating on MNTB neurons (Xiao et al., 2013) (Table 1). At P8, the calyces were smaller and contained fewer docked vesicles in compound *Bmpr1a/1b* knockout mice. Furthermore, postnatal functional refinement of the projection failed, since single MNTB neurons of *Bmpr1a/1b* null mice still received multiple innervations and displayed smaller excitatory postsynaptic currents than control littermates (Xiao et al., 2013) (Table 1).

Ca^{2+} represents another important signaling factor in neurons, and L-type voltage-gated Ca^{2+} channels act as important entry gates for this cation (Catterall, 2011; Cohen and Greenberg, 2008; Dolmetsch et al., 2001; Bito et al., 1997). In patients with SANDD syndrome (SinoAtrial Node Dysfunction and Deafness), an insertional mutation in *CACNA1D* was identified. This gene encodes the $Ca_v1.3$ pore-forming subunit of L-type Ca^{2+} channels and the mutation renders the channel nonconductive (Baig et al., 2010). Similar symptoms were observed in a *Cacna1d* null mouse model (Platzer et al., 2000; Dou et al., 2004). Deafness is due to the unusual role of $Ca_v1.3$ in the cochlea, where the protein is localized to the basal site of inner hair cells (IHCs), mediating the Ca^{2+} entry required for neurotransmitter release. The channel is therefore essential for transmission of acoustic information to the central auditory pathway. Beyond the cochlea, *Cacna1d* null mice have a disturbed anatomy of all auditory brainstem nuclei, as the CNC, the SOC, the nuclei of the lateral lemniscus, and the inferior colliculus were significantly reduced in size (Hirtz et al., 2011) (Table 1). Notably, the volume of the entire brainstem, or other brain structures such as the neocortex, tectum, or cerebellum were unchanged (Hirtz et al., 2011). These results point to a unique function of $Ca_v1.3$ in auditory neurons. Functionally, neurons of the LSO demonstrated abnormal firing patterns (Hirtz et al., 2011), and further electrophysiological and anatomical experiments demonstrated disrupted synaptic refinement of the inhibitory projections from the MNTB to LSO neurons (Hirtz et al., 2012) (Table 1).

$Ca_v1.3$ is expressed both in IHCs (Platzer et al., 2000) and the auditory brainstem (Jurkovicova-Tarabova et al., 2012). This raised the question to what extent the central auditory anomalies in constitutive *Cacna1d* null mice reflected the lack of peripheral activity or rather an important on-site role of the channel in auditory nuclei (Hirtz et al., 2011). To clarify this issue, an auditory brainstem specific knock-out of *Cacna1d* was generated using a floxed *Cacna1d* allele and the *Egr2::Cre* driver mouse line (Satheesh et al., 2012). In these conditional mice, a considerable volume reduction of SOC nuclei was seen as early as P4. This was accompanied by aberrant auditory brainstem responses (ABR), with strong alterations of the peaks corresponding to neuronal activity in the CNC and SOC (Satheesh et al., 2012) (Table 1). These results demonstrate an essential on-site role of $Ca_v1.3$ in the auditory brainstem, thereby extending the previously reported requirement of L-type Ca^{2+}-channel mediated signaling for survival of auditory brainstem slice cultures (Lohmann et al., 1998) to the *in vivo* tissue.

In the brain, two pore-forming subunits of the L-type Ca^{2+}-channels are expressed, $Ca_v1.2$ and $Ca_v1.3$, encoded by *CACNA1C* and *CACNA1D*, respectively (Hell et al., 1993; Sinnegger-Brauns et al., 2009). In most areas of the brain, functional expression of $Ca_v1.2$ by far exceeds that of $Ca_v1.3$. Radioligand binding assays revealed that $Ca_v1.2$ channels represent 85% of binding sites compared to ~11% for $Ca_v1.3$ (Sinnegger-Brauns et al., 2009). Intriguingly, this relation is inversed in auditory neurons. In whole cell patch-clamp recordings, LSO neurons showed a higher contribution of $Ca_v1.3$ (30%) to the total Ca^{2+} current compared to $Ca_v1.2$ (~15%) (Jurkovicova-Tarabova et al., 2012). This might explain the prominent volume decrease of auditory brainstem structures compared to other brain areas in constitutive *Cacna1d* null mice (Hirtz et al., 2011). Together with the unusual presynaptic role of $Ca_v1.3$ in the inner ear, these data reveal a striking recruitment of the channel to the auditory sensory system.

The insulin-like growth factor (IGF1) is a secreted protein with high sequence similarity to insulin and plays an important role in

development, growth, and metabolism (Varela-Nieto et al., 2003). Homozygous mutations in the insulin-like growth factor 1 gene (*IGF1*) result in prenatal and postnatal growth failure, mental retardation, and profound sensorineural deafness (Woods et al., 1996; Bonapace et al., 2003; Walenkamp et al., 2005). Constitutive ablation of *Igf1* in mice resulted in a 34% reduction of the cochlear volume at P20, altered synaptic innervation of hair cells, and physical attachment of the tectorial membrane to the organ of Corti throughout development (Camarero et al., 2001). Furthermore, the cochlear ganglion showed a 22% loss of cell numbers and decreased myelination (Camarero et al., 2001). *Igf1* is also expressed throughout the postnatal auditory brainstem (Bondy, 1991), which prompted an investigation of its function in the central auditory system. ABR recordings of *Igf1* knockout mice revealed a normal pattern of five peaks, but an increase in latencies was noted (Cediel et al., 2006) (Table 1). Detailed analysis demonstrated a progressive increase in the absolute latency from peak I to peak IV and thus longer interpeak latencies (Cediel et al., 2006). These results indicate that the dysfunction of the central nervous system contributes to the observed hearing impairment (Cediel et al., 2006). The increased delay in ABR response along the auditory brainstem is likely caused by hypomyelination and reduced axon diameters (Beck et al., 1995; Gao et al., 1999). However, IGF1 was also shown to potentiate the function of $Ca_v1.3$ by causing a more rapid activation of the channel (Gao et al., 2006). The increased Ca^{2+} influx resulted in a massive increase in phosphorylated CREB (Gao et al., 2006), which was previously shown to promote neuronal survival in activity-deprived neurons of the CNC (Zirpel et al., 2000). IGF1 might therefore also assist $Ca_v1.3$ in its survival promoting function in the central auditory brainstem and further studies should address this issue.

2.3. Miscellaneous proteins

In addition to $Ca_v1.3$, the vesicular glutamate transporter VGLUT3 has been shown to play a unique role in the auditory system. The protein is one of three proteins that load synaptic vesicles with glutamate, a prerequisite for subsequent neurotransmitter release at the synapse (reviewed in El Mestikawy et al., 2011; Fremeau et al., 2004; Takamori et al., 2006). Whereas VGLUT1 and VGLUT2 transporters are widely present in brain areas of known glutamatergic synapses, VGLUT3 expression is mainly observed in neuronal populations known to release transmitters other than glutamate (El Mestikawy et al., 2011; Fremeau et al., 2004). Surprisingly, VGLUT3 is the only vesicular glutamate transporter expressed in mature (P21) inner hair cells (Seal et al., 2008). Consequently, deletion of the murine *Slc17a8* gene, which encodes VGLUT3, resulted in peripheral deafness, as glutamate release from the IHCs is eliminated (Seal et al., 2008). In humans, mutations in *SLC17A8* were shown to underlie DFNA25, an autosomal-dominant form of progressive, high-frequency nonsyndromic hearing-loss (Ruel et al., 2008). The recruitment of VGLUT3 to IHC might reflect its distinct type of trafficking. In contrast to the other two family members, VGLUT3 can be trafficked to dendrites (Fremeau et al., 2002; Harkany et al., 2004), which might correspond to the basolateral part of epithelial cells such as IHCs (Seal et al., 2008). The presence of VGLUT1 in retinal photoreceptors and bipolar cells, which form ribbon synapses similar to IHCs (Johnson et al., 2003; Sherry et al., 2003), argues against a general requirement of VGLUT3 for the highly specialized ribbon synapse.

Slc17a8 is highly expressed in the central auditory pathway during early postnatal development of MNTB neurons (Blaesse et al., 2005; Gillespie et al., 2005), which additionally co-release glycine and GABA during this period (Nabekura et al., 2004; Friauf et al., 1999). In the auditory brainstem, VGLUT3 thus conforms to its typical role by providing a glutamatergic co-phenotype to neurons that also express other neurotransmitters. Functional analyses revealed that the perinatal release of glutamate is required for refinement of the inhibitory projection of MNTB principal cells to LSO neurons. In the absence of VGLUT3, both the tonotopic reorganization of the projections as well as the functional strengthening of single inputs were abrogated (Noh et al., 2010) (Table 1). This was not due to the peripheral deafness in the *Slc17a8* null mouse, as *otoferlin* null mice, which also lack cochlear-driven activity, demonstrated normal refinement (Noh et al., 2010).

Urocortin (UCN) belongs to the corticotropin-releasing factor family of neuropeptides. These peptides bind to G-protein coupled receptors and are involved in stress modulation (Graham et al., 2011). *Ucn* is expressed in the part of the olivocochlear bundle that runs to the IHC region (Vetter et al., 2002), where UCN-positive fibers make synapses with spiral ganglion afferent terminals (Kaiser et al., 2011). *Ucn* null mice revealed an elevated auditory threshold at 3 and 6 months by 10–20 dB, depending on the test frequency (5.6 kHz–32 kHz), as well as reduced distortion product otoacoustic emission amplitudes (Vetter et al., 2002) (Table 1). In addition, OHCs were significantly smaller in size (Vetter et al., 2002). These data indicate that *Ucn* expression in the central auditory system is required for the development of normal cochlear mechanics and cochlear amplification.

Mutations in the gene encoding the voltage-gated potassium channel KCNQ4 cause autosomal dominant DFNA2A, which is characterized by a non-syndromic progressive high frequency sensorineural hearing loss (Kubisch et al., 1999). In the ear, KCNQ4 is exclusively present at the basal membrane of OHCs. Functional analyses in mice lacking the channel or harboring a dominant negative mutation indicate that KCNQ4 participates in K^+-efflux (Kharkovets et al., 2006). The OHCs of these mice showed resting potentials that were depolarized by about 10–17 mV (Kharkovets et al., 2006). Likely as a consequence of chronic depolarization, OHC slowly degenerated. Within 1 year, the basal turn of the cochlea was almost completely devoid of OHCs, corresponding well with the progressive high frequency loss observed in humans (Kharkovets et al., 2006). OHCs in the apical turn and IHC were apparently unaffected. Expression analyses in the brainstem revealed a striking recruitment of the channel to auditory nuclei (Kharkovets et al., 2000). KCNQ4 is abundant in the AVCN, the PVCN, and the nuclei of the lateral lemniscus, and moderately expressed in several nuclei of the SOC and the inferior colliculus. Only few other brainstem areas such as the spinal trigeminal nucleus were also stained and the authors noted that most of these neuronal populations maintain connections to auditory nuclei (Kharkovets et al., 2000). The precise role of KCNQ4 in the auditory brainstem awaits further functional analyses, but ABR recordings indicate altered processing of auditory information in the brainstem of channel-deficient mice. Whereas the positive peak of wave I is smaller, due to increased hearing thresholds, the positive peak II, mainly reflecting activity of the CNC, is elevated compared to wild-type mice (Kharkovets et al., 2006) (Table 1).

2.4. Candidate deafness genes for central auditory function

The data presented so far demonstrate central auditory function of numerous deafness genes (Table 1). A comparative large-scale microarray-based gene expression analysis of the SOC and the entire brain at P4 and P25 in rat provided compelling evidence that this number will increase in the future (Ehmann et al., 2013). In this analysis, 138 probes of the microarray matched to transcripts associated with hearing impairment. Twenty-six of them (19%) were significantly up-regulated in the SOC in at least one pairwise comparison with the brain. In contrast, only 11 transcripts

associated with hearing impairment showed increased expression in the entire brain. This difference in numbers was significant, indicating SOC-related enrichment of deafness-associated genes (Ehmann et al., 2013). The 26 SOC-related transcripts correspond to 22 genes: *Hoxa2, Ednrb, Gata3, Esrrb, Mitf, Sox10, Fgfr3, Grm7, Igf1, Prkra, Col2a, Eps8, Slc12a7, Slc17a8, Rdx, Myo6, Aqp4, Myh14, Pmp22, Ucn, Tjp2*, and *Slc12a2*. Five of these genes, namely *Hoxa2, Gata3, Igf1, Slc17a8*, and *Ucn* have already been analyzed in the central auditory system. Of note, all five have a clearly confirmed central auditory function (Table 1), suggesting an important role of the other 17 genes beyond the cochlea as well. The known functions of several of these genes support such a notion. Fgfr3, for example, which shows higher expression in the P4-SOC compared to age-matched brain tissue, was shown to be involved in regulating cell survival and patterning in the developing midbrain and hindbrain (Saarimäki-Vire et al., 2007). Furthermore, a known target of Fgfr3 is Bmp4 (Puligilla et al., 2007; Naski et al., 1998), which is important for postnatal maturation of the calyx of Held (Xiao et al., 2013) (Table 1). Finally, mutations in *Sox10, Ednrb*, and *Mitf* all cause Waardenburg syndrome, indicating a functional interaction of these 3 TF (Bondurand et al., 2000). These genes might thus represent a gene regulatory module with an important role in the central auditory system as well.

Taken together, these data demonstrate that many deafness genes have essential functions beyond the cochlea and that this list will likely be extended by further investigations. As the observed abnormalities in the central auditory system are gene-specific, a large variety of defects in auditory processing might be expected. The CNC, for instance, is the sole entry gate to all ascending auditory pathways and any disruption of its structure will therefore affect auditory processing in the entire system. In contrast, the SOC participates in sound localization, which is involved in auditory stream segregation (Middlebrooks and Onsan, 2012; Middlebrooks, 2013). Patients with mutations in deafness genes with central auditory functions will therefore present with different processing deficits in the central auditory pathway. As a consequence, hearing devices used for auditory rehabilitation will feed electric activity into rather different neuronal systems. This will likely influence the post-implantation benefit. It will therefore become important to gain further insight into central auditory functions of deafness genes, in order to better tailor personalized devices. Magnetic resonance imaging has already been proven to detect abnormalities in the auditory nerve (Hang et al., 2012), but disrupted central auditory pathways have so far escaped detection. To shed light on these central dysfunctions, a systematic dissection of the role of deafness genes in the peripheral and central auditory system is required. Likely, this can best be achieved by carefully designed experiments in animal models. This research will largely benefit from the increasing collection of conditional alleles currently generated by the International Knockout Mouse Consortium (KOMP, EUCOMM, NorCOMM, TIGM) (Collins et al., 2007). In combination with established Cre driver mouse lines for the central auditory system such as *Bhlhb5::Cre*, *Egr2::Cre*, *Math5::Cre, Wnt1::Cre, Hoxb1:Cre* and *Ent1::Cre* (Feng et al., 2010; Saul et al., 2008; Jalabi et al., 2013; Marrs et al., 2013), these mouse models will provide a rich resource for tackling this issue.

This approach of spatially restricted gene ablation will also be extremely useful for dissecting the precise central auditory function of various proteins mentioned above, such as KCNQ4, CHD7, or IGF1. The experimental data listed in Table 1 clearly support a central auditory function for these proteins, but some of the observed deficits might nevertheless reflect a mixture of on-site roles in the brain and consequences of peripheral deafness. Central auditory specific ablation of these genes will unambiguously disentangle these two effects. Furthermore, this approach will open new avenues to gain further insight into functional deficits by applying methods such as ABRs or behavioral tests (Jalabi et al., 2013; Allen and Ison, 2012).

3. Shared genetic program during developmental of sensory and neuronal cells in the auditory system

What might be the mechanistic explanation of the widespread expression of deafness genes both in the peripheral and central auditory system? On average, mammalian neurons express ~13,000 protein encoding genes (Subkhankulova et al., 2008), which is more than 50% of the total repertoire of ~21,000 protein encoding genes (Frazer, 2012). Overlapping transcriptomes between sensory cells and sensory information processing neurons might therefore be expected and merely reflect the general genetic complexity of these cells. However, experimental data suggest an intimate molecular crosstalk between the gene regulatory networks governing development of the peripheral and central auditory system (Fig. 1).

In mammals, otic placodes form adjacent to r5 and r6 (Anniko and Wikström, 1984; Rinkwitz et al., 2001), well within the 100 μm distance for target areas of diffusible signaling factors such as Wnts, which emanate from these rhombomeres (Megason and McMahon, 2002; Riccomagno et al., 2005) (Fig. 1). Indeed, the ear does not develop in isolation or in a foreign tissue environment (Waddington, 1937; Yntema, 1939; Jacobson, 1966), and surgical experiments, as well as studies in transgenic mice, demonstrated multiple and essential roles of hindbrain signaling for induction and morphogenesis of the ear (reviewed in Baker and Bronner-Fraser, 2001; Kiernan et al., 2002; Torres and Giraldez, 1998; Whitfield et al., 2002; Choo, 2007; Angeli et al., 2012; Liang et al., 2010; Fritzsch et al., 1997).

Extending early transplantation experiments (Yntema, 1950; Kaan, 1938; Zwilling, 1941), microsurgical rotation of the chicken hindbrain along its horizontal axis resulted in ventralization of the dorsal otic tissue, as indicated by altered expression of marker genes such as *Gbx2*, *NeuroD*, *Lfng*, *Six1*, and *Otx2* (Bok et al., 2005). Removal of r5 affected the size of the cochlear duct, and r6 removal resulted in shortened cochlear ducts without curvature or entire absence of the cochlear duct (Liang et al., 2010). Mice with mutations in rhombomere-expressed genes support the importance of signals emanating from the hindbrain for inner ear development (Fig. 1). As mentioned above, ablation of *Hoxa1* resulted in a lateral and rostral displacement of the otic vesicle and failure of the cochlear duct to differentiate (Chisaka et al., 1992; Lufkin et al., 1991). Similarly, *kreisler* mice with abolished expression of the basic domain leucine zipper TF MAFB in r5 and r6 displayed gross inner ear malformation, without an organized cochlea (Hertwig, 1944; Vazquez-Echeverria et al., 2008; Deol, 1964). Since expression of *Hoxa1* and *MafB* was not detected in the inner ear (Cordes and Barsh, 1994; Mark et al., 1993; Besmer et al., 1986), malformation of the ear was attributed to the disruption of hindbrain signals such as FGF3, which is necessary for inner ear patterning (see next paragraph). A recent analysis of a *Hoxa1-IRES-Cre* mouse line, paired with various reporter lines, observed a *Hoxa1* lineage in the inner ear as well, raising the possibility that Hoxa1 might also play a direct role in ear development (Makki and Capecchi, 2010). Further studies have therefore to clarify whether the strong inner ear phenotype in *Hoxa1* null mice is caused by hindbrain anomalies or rather reflects an important on-site role of the TF in the otic ectoderm. In addition, it is currently unclear whether mispatterning of the hindbrain changes the positional specification of the otic placode, or whether TF such as HOXA1 and MAFB are required to induce hindbrain signals important for inner ear development (Makki and Capecchi, 2010).

Several diffusible signaling factors that are released from the hindbrain and play an important role for the otic placode have been identified (Fig. 1). A well-established secreted factor is FGF3 (aka int-2). Hypomorphic expression of *Fgf3* and *Fgf8* in rhombomeres resulted in loss of or severe size reduction in the otocyst in zebrafish (Maroon et al., 2002; Phillips et al., 2001) and similar results were obtained for *Fgf3* and *Fgf10* in mice (Wright and Mansour, 2003; Hatch et al., 2007; Vazquez-Echeverria et al., 2008; Represa et al., 1991; Alvarez et al., 2003; Urness et al., 2010). Furthermore, FGF3 is essential for expression of *Wnt8a* in r4 (Urness et al., 2010) and likely required to limit the effects of Wnt signaling to the dorsal otic placode (dOP) (Hatch et al., 2007), where WNT1, WNT3a, and WNT8a (or its chicken ortholog WNT8c) are involved in specification and maintenance of this structure (Ohyama et al., 2006; Riccomagno et al., 2005; Vendrell et al., 2013) (Fig. 1). Of note, correct FGF3 signaling requires expression of *Hoxa1* in r4 and r5, and of *Mafb* in r5 and r6 (Carpenter et al., 1993; Frohman et al., 1993; Mckay et al., 1996; Pasqualetti et al., 2001) (Fig. 1). Finally, together with the notochord, the hindbrain floorplate represents an important source of Sonic Hedgehog (Shh) signaling to the ventral inner ear (Jessell, 2000) (Fig. 1). Lack of this factor results in failure of ventral patterning, including complete absence of the cochlear duct in mice (Riccomagno et al., 2002; Liu et al., 2002) or the basilar papilla in chicken (Bok et al., 2005).

In summary, these data reveal an intimate link in the gene regulatory networks governing development of the peripheral auditory endorgan and the hindbrain, which gives rise to central auditory structures (Fig. 1). The TFs in the hindbrain and the diffusible factors released from this region would be in a perfect location to orchestrate joint development of the peripheral and central auditory system. If true, this will support the emerging hypothesis that both the sensory endorgan as well as the neuronal populations in the central nervous system necessary for processing of auditory information, evolved jointly through a shared genetic program (Duncan and Fritzsch, 2012; Fritzsch et al., 2006).

4. Implication of central auditory function for auditory rehabilitation

A peculiarity of the auditory system compared to other sensory systems is the success of electronic devices such as cochlear implants (CI) to ameliorate severe-to-profound sensorineural deafness (reviewed in Eshraghi et al., 2012; Russell et al., 2013; Carlson et al., 2012). CI compensates for lost hair cell function by directly stimulating the auditory nerve. Since its first application some 50 years ago, impressive advances in microelectronics, signaling processing algorithms, and surgical procedures now enable many of the more than 200,000 recipients worldwide to achieve high standard speech recognition in quiet environments. In practice, this allows these persons to listen to conversations and phone calls. Furthermore, the technique even improves spoken language skills in prelingual deaf persons (reviewed in Eshraghi et al., 2012; Russell et al., 2013; Carlson et al., 2012).

However, a major clinical problem is the persistent variability in post-implantation benefit (Geers, 2006; Eshraghi et al., 2012; Hang et al., 2012). Several factors have been shown to influence auditory rehabilitation. Among them are the extent of cochlear nerve hypoplasia, age of intervention and onset of hearing loss, duration of deafness, and cognitive abilities (Geers, 2006; Lazard et al., 2012; Hang et al., 2012). The manifold functions of established deafness genes beyond the cochlea and the molecular link in the genetic program of the peripheral and central auditory system indicate that central auditory functions of deafness genes will also affect post-implantation outcome. Knowing the genetic cause should therefore improve outcome prediction and guide pre-implantation decisions.

Genome-wide clinical molecular diagnostics with single nucleotide resolution was unachievable even a few years ago and only few deafness loci were routinely analyzed in patients with deafness. However, the emergence of low cost massive parallel sequencing techniques substantially changed the diagnostics toolbox (Yan et al., 2013; Katsanis and Katsanis, 2013; Idan et al., 2013). Whole-genome sequencing, whole-exome sequencing, or targeted next generation sequencing have recently been successfully used to identify the underlying genetic causes in many patients with hearing loss (Walsh et al., 2010; Yan et al., 2013; Baek et al., 2012; Diaz-Horta et al., 2012; Brownstein et al., 2013; Miyagawa et al., 2013). These results demonstrate that affordable clinical molecular diagnostics on the genomic level is well within reach. This advance will provide unprecedented insight into disease-causing mechanisms. In combination with increased understanding of the functional consequences of these genetic defects in both the peripheral and central auditory system, and novel speech coding strategies in CIs, these data will improve outcome prediction and auditory rehabilitation by personalized devices. Support for this idea comes from a recent study that evaluated 55 CI users and related their genetic status to their cognitive, language and reading abilities (Bauer et al., 2003). Twenty-two children who were tested positive for mutations in connexin 26 achieved significantly higher scores in reading comprehension and on a standardized block design task compared to children with other etiologies. Obviously, mutations associated with hypoplasia or aplasia of the auditory nerve or central auditory structures will indicate poor benefit from CIs (Morimoto et al., 2006; Huang et al., 2012; Hang et al., 2012). Consequently, improved auditory brainstem or midbrain implants will likely become an interesting option (Lim et al., 2009). The potential benefit of such a strategy is illustrated by a recent study on 21 children with suspected aplasia of the auditory nerve (Colletti et al., 2013). Initial treatment with CIs failed to improve hearing abilities. Subsequent exchange of CIs by brainstem implants resulted in significantly improved auditory performance.

In conclusion, genetic analyses, in combination with a comprehensive knowledge of genetically related defects in the central auditory pathway, will likely improve post-implantation outcome prediction and provide important clues for tailored electronic devices improving auditory rehabilitation.

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