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Inheritance patterns of progressive hearing loss in laboratory strains of mice

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Abstract

Positional cloning of mouse deafness mutations uncovered a plethora of proteins that have important functions in the peripheral auditory system in particular in the cochlear organ of Corti and stria vascularis. Most of these mutant variants follow a monogenic form of inheritance and are rare, highly penetrant, and deleterious alleles. Inbred and heterogenous strains of mice, in contrast, present with non-syndromic hearing impairment due to the effects of multiple genes and hypomorphic and less penetrant alleles that are often transmitted in a non-Mendelian manner. Here we review hearing loss inheritance patterns as they were discovered in different strains of mice and discuss the relevance of candidate genes to late-onset progressive hearing impairment in mouse and human.

Keywords

Hearing loss; inbred strains; heterogeneous strains; presbycusis

1. Genetic diversity

The genomes of the common laboratory strains of mice are genetic mosaics composed of contributions from four *Mus musculus* subspecies – *M. m. domesticus*, *M. m. musculus*, *M. m. castaneus*, and *M. m. molossinus* (which likely arose by natural hybridization between *musculus* and *castaneus*). These four subspecies are endogenous to discrete geographic regions in the northern hemisphere. In depth sequence analyses of twelve classic inbred strains (C57BL/6J, DBA/2J, A/J, AKR/J, BALB/cByJ, NOD/LtJ, FVB/NJ, NZW/LacJ, 129S1/SvImJ, C3H/HeJ, BTBR T+tf/J and KK/HIJ) and four wild-derived strains representing each of the four subspecies (CAST/Ei-*castaneus*, MOLF/Ei-*molossinus*, PWD/PhJ-*musculus*, and WSB/EiJ-*domesticus*), demonstrated that 68 percent of the genome of classical inbred strains originated from the *M. m. domesticus* subspecies with additional contributions of *M. m. molossinus* (10%), *M. m. musculus* (6%), and *M. m. castaneus* (3%) (Frazer et al., 2007; Yang et al., 2007).

Genetic heterogeneity among the laboratory strains is the result of changes in the nucleotide sequence, which are caused by single nucleotide substitutions, deletions and insertions, segmental duplications, and copy-number variations. Single-nucleotide polymorphisms (SNP) occur at a rate of 1 SNP per 756 base pairs among the laboratory strains and with a rate of 1 in 397 bp among wild-derived strains (Frazer et al., 2007). With an estimated SNP discovery rate of 43%, it was estimated that there are a total of 8 million SNPs among classical inbred

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strains. The frequency at which these SNPs occur in coding exons needs to be determined, but in humans an individual's exome (the set of all exons in a genome) can harbor up to 10,413 synonymous and 10,389 non-synonymous SNPs of which >80% are common alleles (Ng et al., 2008).

Mice of the same inbred strain may not be completely isogenic throughout their entire genome. Although inbreeding greatly minimizes genetic diversity in a population, a small degree of variation can persist even in extensively inbred strains because of newly occurring mutations, as evidenced by the copy number variation that was detected in mice of the C57BL/6 strains and the C57BL/6J sub-strain (Watkins-Chow et al., 2008) (Egan et al., 2007). This within-strain genetic variation, however, is far less than the degree of genetic variation observed among inbred strains.

2. Phenotypic diversity

Response to a loud sound can be detected in a mouse by the Preyer reflex (ear flick), but this simple behavioral method detects only supra-threshold responses. More informative, quantitative assessments of hearing function in mice on a large scale are currently performed using electrophysiological methods: auditory-brain stem response (ABR) measurements and distortion-product-otoacoustic-emission (DPOAE) testing (Kermany et al., 2006; Martin et al., 2007; Schwander et al., 2007). ABR waveforms are recorded from the activity of the cochlear nerve and brainstem nuclei in response to an acoustic stimulus of defined frequency and amplitude and represent a measurement of the activity of all cellular structures involved in acoustic signal receiving, processing, amplification, and transmission. DPOAEs, in contrast, are produced directly by the sensory outer hair cells. Measurement of DPOAEs thus can be an informative secondary screen of mice with hearing impairment detected by ABR, to specifically assess outer hair cell function.

A large scale ABR screen of 80 inbred strains that represent most of the phylogenetic diversity of the laboratory mouse identified 35 strains with various levels of hearing loss with respect to onset, degree, and progression (Zheng et al., 1999). Among those hearing impaired strains, 19 strains showed profound hearing loss before twelve weeks of age and exhibited 10–20 decibel (dB) increases in hearing thresholds as early as three weeks of age. Sixteen strains developed hearing loss at ages much older than 12 weeks. In addition to threshold variations, inbred strains also show remarkable differences with respect to amplitude of ABR wave forms and peak latencies (Zhou et al., 2006). Hearing loss among many inbred strains of mice has been further differentiated by DPOAE measurements (Jimenez et al., 1999; Martin et al., 2007). Because all of the strains assessed for hearing impairment are inbred and reared in similar environments, the observed phenotypic differences should largely be accounted for by genetic factors, suggesting that a large number of hearing loss variants are segregating among strains of mice.

3. Inheritance patterns

Hearing differences among inbred strains of mice have long been noted. Initial studies by Kocher (1960) showed that mice of the C57BL/6 strain exhibit an impaired Preyer's reflex by three months of age (Kocher, 1960). Morphology revealed a base-to-apex progression of degeneration of cochlear hair and supporting cells as well as the spiral ganglion neurons. In one-year old hearing-impaired mice a thinning of the stria vascularis was also present. F1 hybrids between C57BL/Gr and CBA mice showed perfectly normal Preyer's reflexes up to one year of age, but interestingly, a backcross to C57BL/Gr produced progeny with normal and impaired hearing in a 1:1 ratio suggesting the presence of one recessive allele in the C57BL/Gr strain (Kocher, 1960). Using a behavioral test paradigm, Mikaelian and colleagues demonstrated that the hearing loss in C57BL/6 mice progresses from high-to-low frequencies

and is accompanied by a base-to-apex degeneration of the organ of Corti (Mikaelian et al., 1974). Electrophysiological recordings by Henry and colleagues showed decreased amplitudes of summation potentials and decreased cochlear microphonics in C57BL/6 compared to CBA/J mice at seven weeks of age that continued to decrease with increasing age (Henry et al., 1978; Henry et al., 1980). Henry extended the auditory comparisons to a diverse panel of six inbred strains identifying a remarkable range of hearing loss (Henry, 1982). According to Henry, SJL/J and AU/SsJ mice showed a loss of hearing that resembled closely the hearing loss observed in the human population; mice of the AKR/J strain best modeled sensorineural presbycusis; and A/J, LP/J and C57BR/cdJ strain mice showed audiograms that were reminiscent of effects due to single-gene mutations.

To assess the genetic architecture that underlies hearing impairment in C57BL/6J and other inbred strains, Erway and colleagues measured ABR thresholds in aged mice of the CBA/H-T6J, DBA/2J, C57BL/6J, BALB/cByJ, and WB/ReJ strains, and all combinations of their F1 hybrids (Erway et al., 1993). The data suggested that recessive alleles at three distinct genetic loci control most of the hearing loss, with a recessive susceptibility allele at one locus being present in the C57BL/6J, BALB/cByJ, and WB/ReJ strains and recessive susceptibility alleles at all three loci present in the DBA/2J strain. Subsequent genetic studies of hearing loss in mouse strains have employed linkage backcrosses and intercrosses, recombinant inbred strains, and congenic strains. These and other strategies for mapping and identifying genes underlying quantitative traits have been described in detail elsewhere (Flint et al., 2005). Below and in Table 1 we summarize inheritance patterns and genetic mapping results from hearing loss studies of C57BL/6J, NOD/LtJ, A/J, DBA/2J, Black Swiss, 101/H, and BUB/BnJ mice.

2.1. C57BL/6J

To test the one-locus recessive inheritance model of hearing loss in the C57BL/6J strain, Johnson and colleagues used segregation and linkage analyses of a (C57BL/6J × CAST/Ei) × C57BL/6J backcross (Johnson et al., 1997). The wild-derived CAST/Ei strain was used as a linkage outcross strain because of its associated good hearing phenotype and its genetic distinctness. ABR measurements of 18-month-old N2 backcross mice revealed a bimodal distribution of thresholds clearly distinguishing mice with thresholds below 75 decibels sound pressure level (dB SPL) from those with thresholds greater than 85 dB SPL. Genome-wide linkage analyses identified a locus (named *ahl*) with a very high LOD score of 24.5 associated with the *D10Mit5 – D10Mit31* interval on Chromosome (Chr) 10.

The common origins of most inbred strains and the similarities with respect to their hearing phenotypes suggested that the *ahl* allele may be shared with a wider spectrum of strains. To test this proposition, ABR thresholds of progeny from backcrosses involving a series of hearing impaired strains and the CAST/Ei strain were tested for linkage with Chr 10 markers. It was found that the *ahl* allele is a major predisposing factor to hearing loss not only in the C57BL/6J strain but also in strains such as A/J, BALB/cByJ, BUB/BnJ, C57BR/cdJ, DBA/2J, NOD/LtJ, SKH/2J, and 129P1/ReJ (Johnson et al., 2000).

The combined information from recombinants from these backcrosses together with recombinants from additional mapping crosses involving the modifier of deaf waddler (*mdfw*) locus – which is allelic with *ahl* – delimited the genetic interval to an 830 kb region on Chr 10 (Noben-Trauth et al., 2003; Zheng et al., 2001). Sequencing of all four genes in this interval identified a functional polymorphism (G753A) in the coding sequence of cadherin 23 (*Cdh23*). This single nucleotide polymorphism (SNP) occurs at the last position of exon 7 and alters the consensus splice site leading to in-frame skipping of exon 7. The G753A SNP was highly correlated with hearing function in 50 inbred strains ($p=10^{-5}$; chi square test). The G753A variant is distributed across the phyolgenetic tree of inbred strains but is not found in

any of the wild-derived strains, suggesting that it is a founder mutation in several lineages of laboratory mice.

The genetic mapping of the *ahl* locus led to the development of a C57BL/6J congenic strain (B6.CAST-*Ahl*) in which the C57BL/6J-derived *ahl* allele conferring susceptibility to hearing loss was replaced by the resistant CAST-derived *Ahl* allele. ABR measurements accompanied by cochlea histopathology of this congenic strain provided an indirect measure of the isolated effect of the *ahl* locus on the hearing pathology of C57BL/6J mice and revealed evidence for additional hearing loss loci in this strain. In particular, although hearing thresholds in 24-month-old B6.CAST-*Ahl* mice were significantly elevated compared to the normal hearing wildtype CAST/Ei mice, they were still lower than in age-matched C57BL/6J mice (Keithley et al., 2004).

ABR analyses of a set of C57BL/6J consomic (chromosome substitution) strains, in which individual C57BL/6J chromosomes were replaced by the homologous chromosomes from the MSM strain (derived from *M. m. molossinus*), provided evidence for such an additional hearing loss locus (Nemoto et al., 2004). Whereas mice of the MSM strain retained normal hearing up to 17 months of age, and C57BL/6J mice showed elevated thresholds of 70 dB SPL, mice of the B6-Chr17^{MSM} consomic strain showed intermediate thresholds, suggestive of an additional age-related hearing loss (AHL) locus on Chr 17. Subsequent linkage analyses mapped this locus (named *ahl3*) near marker *D17Mit119*, located at the middle of Chr 17. Refined congenic strain analysis indicated that *ahl3* is located within a 14-Mb region between *D17Mit274* and *D17Mit183* (Morita et al., 2007).

2.2. NOD/LtJ

The NOD strain was developed by selection for diabetes in a substrain that traces its origin to an outbred colony of ICR mice (Makino et al., 1980). NOD/LtJ mice exhibit very early onset hearing loss, showing 30 dB threshold elevations at 3 weeks of age, which progresses rapidly to near complete deafness by nine weeks of age (Zheng et al., 1999). Backcross analysis of (NOD × CAST) F1 hybrids to NOD mice showed that the Chr 10 *ahl* locus contributes to the hearing loss of NOD mice, but does not explain the much earlier onset compared with C57BL/6J mice, which have the same *ahl* allele (Johnson et al., 2000; Noben-Trauth et al., 2003). Genetic linkage analyses of 290 N2 backcross progeny from a (C57BL/6J × NOD) × NOD backcross identified a hearing loss locus (named *ahl2*) associated with a significant LOD score of 5.5 with marker *D5Mit309* on Chr 5 (Johnson et al., 2002). Because NOD/LtJ mice also carry the recessive *ahl* allele on Chr 10, the (NOD × CAST) × NOD backcross was evaluated to ascertain potential epistatic interactions between *ahl* and *ahl2*. ABR measurements showed that only mice with *ahl/ahl ahl2/ahl2* or *ahl/ahl* +/*ahl2* genotypes showed elevated thresholds, whereas mice with the +/*ahl ahl2/ahl2* genotype showed normal hearing. This result suggests that *ahl2* alone has no or very little effect on hearing loss, but requires the sensitizing effect of two recessive *ahl* alleles to show its effect. Backcross mice and NOD/LtJ mice with the *ahl/ahl ahl2/ahl2* genotype mice develop hearing loss much earlier than backcross mice or C57BL/6J mice with the *ahl/ahl* +/+ genotype. These results suggest that the *ahl2* locus exacerbates the effects of the *ahl* locus, resulting in earlier onset and more rapid progression of hearing loss.

2.3. A/J

The A strain, developed in 1921, has been widely used in cancer and immunology research. Mice of the A/J substrain exhibit an early-onset progressive hearing loss that was first reported in 1982 (Henry, 1982). They exhibit elevated ABR thresholds by 25 days of age, and hearing loss progresses to near deafness by three months of age (Zheng et al., 1999; Zheng et al., 2008). Linkage analysis of progeny from a backcross of (A/J × CAST) F1 hybrids to A/J mice

showed that the *ahl* locus contributes to the age-related hearing loss of A/J mice, as it does in several other mouse strains (Johnson et al., 2000). Hearing loss of A/J mice occurs earlier and is more severe than that of C57BL/6J mice even though they share the same *ahl* allele (Noben-Trauth et al., 2003); therefore, additional genetic factors must be involved.

A mitochondrial contribution to the hearing loss of A/J mice was analyzed by measuring ABR thresholds of backcross progeny produced from reciprocal (A/J × CAST) F1 hybrids (Johnson et al., 2001). Maternally-derived A/J mitochondria were shown to exert a significant detrimental effect on hearing when compared with maternally-derived CAST mitochondria, but the mitochondrial effect was limited to backcross mice with predisposing *ahl/ahl* genotypes. Sequencing of the mitochondrial genome revealed a single nucleotide insertion in the tRNA-Arg gene (*mt-Tr*) that is likely responsible for the phenotypic effect.

The effect of the *ahl* locus combined with the mitochondrial effect is still not enough to account for the full extent of hearing loss exhibited by A/J mice, therefore, additional studies were undertaken to map other contributing loci. AXB and BXA recombinant inbred strains, B6.A chromosome substitution strains, and an (A/J × CAST) × A/J linkage backcross were used to map yet another age-related hearing loss locus (named *ahl4*) to the distal region of Chr 10 (Zheng et al., 2008). As was the case with mitochondria, the *ahl4* effect on hearing loss was limited to backcross mice with predisposing *ahl/ahl* genotypes. The *ahl4* locus could explain about 40% of the ABR threshold variation in these mice.

2.4. DBA/2J

The DBA (dilute brown agouti) inred strain was developed in 1909 by Clarence Little and is the oldest of all inbred strains. Mice of the DBA/2J sub-strain develop various tumors but are probably best known for their susceptibility to audiogenic seizures. While the genetic cause of this predisposition is unknown, DBA/2J mice develop early-onset hearing loss. This hearing loss is profound but not quite as pronounced as in NOD/LtJ mice; hearing thresholds at three weeks of age are elevated by 15–20 dB and reach near deafness levels by 14 weeks (Zheng et al., 1999). The hearing loss is paralleled by degeneration of the organ of Corti and spiral ganglia (Willott et al., 1984; Willott et al., 2005).

The BXD set of recombinant inbred (RI) strains is a valuable resource for the genetic analysis of quantitative trait differences between the parental C57BL/6J and DBA/2J inbred strains (Williams et al., 2001). As both parental strains harbor hearing loss alleles, analysis of a sufficient number of BxD RI strains could reveal the underlying genetic factors and their map locations. In an early study, Willott and colleagues evaluated ABR threshold measurements and spiral ganglia morphometrics in mice from 25 BXD RI strains but were unable to find statistically significant linkage with any chromosome region (Willott et al., 1998). A subsequent analysis of ABR thresholds of mice from 31 BXD RI strains was able to demonstrate linkage of elevated thresholds with a locus (named *ahl8*) on distal Chr 11 (Johnson et al., 2008). F1 hybrids between the parental strains (B6D2F1) exhibited normal hearing thresholds suggesting recessive inheritance. A backcross of B6D2F1 hybrids to DBA/2J mice confirmed linkage and refined the location of *ahl8* to the distal-most 10 Mb region of Chr 11. Interestingly, a backcross using the CAST/Ei strain demonstrated an epistatic interaction between *ahl* and *ahl8*. The effects of *ahl8* on the hearing loss phenotypes of backcross mice were manifested only in mice with *ahl/ahl* genotypes.

2.5. Black Swiss

Heterogeneous (genetically diverse) stocks of mice with varying degrees of hearing loss provide the opportunity to study a spectrum of phenotypes in a relatively small (n=20) sample size. A recent survey of six heterogenous stocks identified five strains (Swiss Webster, ICR,

NIH Swiss, Black Swiss, and CF-1) with varying degrees and time courses of hearing loss (Drayton et al., 2006). Mice of the NMRI strain showed normal hearing thresholds up to one year of age.

The hearing loss in Black Swiss mice is of early-onset, progresses slowly and is sensorineural in origin. Quantitative trait loci (QTL) linkage analyses of backcross and intercross progeny, derived from a cross with the CAST/Ei strain, identified two QTL that explain most of the phenotypic variation in the crosses. A strong QTL named *ahl5* (61% effect size) with a genome-wide LOD score of 8.9 associated with *D10Mit20* on distal Chr 10, and a second weaker QTL named *ahl6* (effect size: 32%) with a LOD score of 3.8 was linked to Chr 18. Both loci account for approximately 90% of the phenotypic variation. Statistical analyses of the individual and combined QTL effects showed that the *ahl6* locus increases the *ahl5* effect on hearing thresholds (Drayton et al., 2006).

2.6. 101/H

Mice of the 101/H strain show hearing loss starting at around 7 weeks of age and progressing to severe hearing impairment at 10 months with compound action potential (CAP) thresholds around 100 dB SPL for frequencies of 12 kHz and greater (Mashimo et al., 2006). Hearing loss proceeds from high-to-low frequencies and the presence of normal endocochlear potentials indicates that the hearing impairment in 101/H mice is of sensorineural origin. Interestingly, the morphology of the stereociliary hair bundle at the time of hearing loss appears normal suggesting a pathology downstream of the initial mechanotransduction.

Intercrosses using the MAI and MBT strains as outcross partners were used to detect quantitative trait loci that underlie hearing loss in 101/H mice. Linkage analyses of 66 F2 progeny identified two loci, named progressive hearing loss 1 (*Phl1*) and *Phl2. Phl1* localizes to Chr 17 near marker *D17Mit113* with a highly significant LOD score of 6.7. *Phl2* mapped to Chr 10 near *D10Mit115* with a LOD score of 5.3. For both loci, the associations between markers and elevated CAP thresholds were conferred by the 101/H alleles. Alleles at the *Phl1* locus had a codominant effect on CAP thresholds. Statistical analyses of individual and combined effects demonstrated a genetic interaction between *Phl1* and *Phl2*, such that *Phl2*, having no or little effect on its own, influences the CAP thresholds that are determined primarily by *Phl1* genotypes.

2.6. BUB/BnJ

BUB/BnJ mice develop early-onset hearing loss, exhibiting 30–40 dB ABR threshold elevations by three weeks of age and become almost deaf by eight weeks (Zheng et al., 1999). Ten-month-old N2 progeny from a backcross of (BUB/BnJ × CAST/Ei) F1 hybrids to BUB/BnJ mice showed significant linkage of ABR thresholds with the *ahl* locus on Chr 10 (Johnson et al., 2000). Linkage analyses of the same N2 progeny at three months of age showed significant association with markers on Chr 13 (Johnson et al., 2005). There was no epistatic interaction between these two loci; each locus contributed additively to the phenotypic variation and together they account for almost all of the genetic variation in the backcross. The Chr 13 locus accounted for most of the hearing loss variation in young mice and the *ahl* locus had a greater effect in old mice.

The BUB/BnJ strain like the Frings (RB/1) strain is derived from Swiss albino mice. Both strains undergo early-onset hearing loss and are susceptible to audiogenic seizures, suggesting a common underlying genetic cause (Klein et al., 2005). The audiogenic seizure locus (*Mass1*) was mapped to Chr 13 and identified as a frame-shift mutation in the G protein-coupled receptor (*Gpr98*) gene (Skradski et al., 2001). This frame-shift mutation also is present in the BUB/BnJ strain. F1 hybrids between BUB/BnJ and Frings mice retain their susceptibility to

audiogenic seizures. The coinciding Chr 13 map locations of the early-onset hearing loss locus of BUB/BnJ mice with the *Gpr98* gene and the allelism between the audiogenic seizure locus of BUB/BnJ and Frings mice argue that the frame-shift mutation in *Gpr98* causes both the hearing loss and seizure susceptibility of BUB/BnJ mice.

In developing cochlear hair cells *Gpr98* was immuno-localized to the ankle-link region of the hair bundle and shown to form a component of the ankle link complex (Goodyear et al., 1999; McGee et al., 2006; Michalski et al., 2007). Hence, loss of *Gpr98* function causes abnormally formed stereociliary hair bundles that lack cohesive firmness such that stereocilia appear disconnected and detached from each other (Johnson et al., 2005; McGee et al., 2006; Yagi et al., 2007).

Each of the strains discussed presents with its own characteristic hearing phenotype owing to the presence of a unique combination of hearing loss alleles (Table 1). In the predominant form of inheritance, two variants epistatically interact in a manner by which a major effect component (such as *ahl, ahl5, or Phl1*) is either timely and/or quantitatively exacerbated by a second minor effect allele (such as *ahl2, ahl6, or Phl2*). However additive ($Gpr98^{Mass1}$ and $Cdh23^{ahl}$) and co-dominant (*Phl1*) forms of inheritance are also found.

The finding of a distinguishing hearing phenotype in inbred and heterogeneous strains suggests the presence of an analogous assortment of genetic variants in these strains. The rapidly advancing next-generation sequencing technology combined with a map location derived from a medium-scale genetic cross will significantly facilitate the identification of these genetic variants.

4. Complex diversity

Although existing inbred strains are an ideal tool to study single- and multi-gene effects, their genetics does not necessarily reflect the complexity of common diseases in humans. To overcome this limitation a Collaborative Cross was established to generate 1000 RI lines derived from eight inbred strains carefully selected to maximize genetic diversity (Churchill et al., 2004). Among the eight founder strains are the C57BL/6J, A/J, and NOD/LtJ strains, which exhibit sensorineural hearing loss. Once completed, each of these new 1000 RI lines will represent a unique combination of alleles, generating an unprecedented degree of phenotypic and genetic diversity while fully preserving the advantages of an inbred strain. It is expected that each of these lines will be genotyped for thousands of SNPs and that the genomes of the eight founder strains will be fully sequenced generating a publicly available resource of unique accuracy and precision. Phenotyping a small set of RI strains (100–200 strains) for any particular trait, such as ABR thresholds, DPOAE and cochlear microphonics levels, mechanotransduction, and hair cell patterning may instantly reveal the chromosomal location of a genetic variant(s) controlling this trait. Phenotyping the remainder of the 1000 RI lines will provide a genetic resolution of 0.1cM – equivalent to approximately 200kb of genomic sequence containing an estimated 3–4 genes.

A recent study investigating the segregation of 90 physiological traits in chromosomal substitution strains revealed a complex genetic architecture of complex traits and an unexpected degree of epistasis (Shao et al., 2008). Likewise it is expected that some hearing phenotypes in the Collaborative Cross will be genetically complex and influenced by epistatic interactions.

5. Genes underlying progressive hearing loss in mice

So far, a single gene variant ($Cdh23^{ahl}$) and a mitochondrial DNA variant (*mt-Tr*) are the only genetic factors contributing to progressive hearing loss in inbred strains of mice that have been molecularly characterized, although at least eight additional genetic loci have been mapped

(Table 1). The *Gpr98*^{frings} mutation listed in Table 1, by itself, causes a congenital rather than progressive hearing loss. It is the additive effect of this mutation with the *Cdh23*^{ahl} variant that results in the progressive hearing loss of BUB/BnJ mice. Recent evidence indicates that CDH23 is a component of the stereocilia tip links and thus has a direct role in mechanical gating of the transducer current entering hair cells (Kazmierczak et al., 2007). As previously mentioned, the hearing loss susceptibility variant of *Cdh23*, which is found in many inbred strains, causes in-frame skipping of exon 7. Loss of this exon is predicted to shorten the ectodomain region of the protein, which could potentially weaken tip links and increase the likelihood of their breakage. Alternatively, the misfolded protein may be retained in the endoplasmic reticulum, causing a constitutive shortage of functional cadherin 23. Recurring loss of tip links could lead to cellular stress and hair cell degeneration, which over time would result in a progressive hearing loss. The *Cdh23*^{ahl} variant was shown to interact with a variant of the mitochondrial *mt-Tr* gene to affect hearing loss in backcrosses involving the A/J strain mice. This same mtDNA variant was later shown to cause an increase in reactive oxygen species (ROS) production in a study of cell lines carrying four different common mouse mtDNA haplotypes in an identical nuclear background (Moreno-Loshuertos et al., 2006). Excess ROS production caused by this mtDNA variant could exacerbate the stressful effects of the *Cdh23* variant and increase the rate of hair cell degeneration, which could explain how these two factors might interact to affect progressive hearing loss in A/J mice.

The complex nature of progressive hearing loss in mouse strains, caused by multiple genes (some with small effects) and environmental influences, makes molecular identification of responsible genes more difficult than is the case with monogenic mutations that have large phenotypic effects. Genetic loci contributing to hearing loss in inbred strains (often measured by elevations in ABR thresholds) can be treated as quantitative trait loci (QTLs). New methods have greatly improved capabilities for QTL gene identification (Arbilly et al., 2006; Flint et al., 2005), and it is therefore likely that the genes underlying the eight progressive hearing loss loci listed in Table 1, and others yet to be mapped, will eventually be identified. Although genetic analysis of inbred strains is challenging, the underlying multigenic nature of their hearing loss and its late onset make inbred strains better models for human presbycusis than are mice with mutations of single genes. Single-gene mutations, however, identify candidate genes that later can be tested for their involvement in more genetically complex disorders.

Many genes whose dysfunction causes progressive hearing loss have been identified from studies of mice with spontaneous and targeted mutations. Table 2 lists some of these genes, the auditory pathologies proposed to be caused by their mutations, and representative references. The genes function in the maintenance or repair of hair cells, spiral ganglion cells, fibrocytes, and extracellular matrix components of the cochlea, in hair bundle integrity and regulation of hair cell depolarization, in endolymph ion homeostasis, and in oxidative stress response mechanisms and energy metabolism. An interesting case of digenic inheritance of age-related hearing loss was demonstrated in mice doubly heterozygous for spontaneous deactivating mutations of *Cdh23* and *Pcdh15*, which encode cadherins thought to be constituents of the stereociia tip links (Kazmierczak et al., 2007) (Zheng et al., 2005). As previously stated, over time weakened tip links could lead to cumulative hair cell degeneration and eventual hearing loss.

6. Genes underlying age-related hearing loss in human populations

Genes proposed to underlie age-related hearing loss in human populations are listed in Table 3. It has been suggested that milder allelic forms of genes underlying monogenically inherited, progressive hearing impairment (such as *ACTG1*, *COCH*, and *DFNA5*) may also contribute to presbycusis and recently this relationship has indeed been demonstrated for the genes underlying two monogenic hearing disorders (Fransen et al., 2003). The *KCNQ4* gene, which

encodes a potassium channel expressed in outer hair cells, underlies *DFNA2* and was tested as a candidate gene for age-related hearing impairment (ARHI) in two independent human populations (Van Eyken et al., 2006). Results of this study showed that SNPs within the *KCNQ4* gene are positively associated with ARHI at a statistically significant level. Another genetic study, which involved population samples from 7 European countries, examined a set of 70 candidate genes and identified a statistically significant linkage of ARHI with SNPs in intron 1 of the *GRHL2* gene, also known as *TFCP2L3* (Van Laer et al., 2008). A mutation of this gene, which encodes a transcription factor in epithelial cells lining the cochlear duct, previously was shown to underlie the monogenic progressive hearing disorder *DFNA28* (Peters et al., 2002). *NAT2*, which encodes an enzyme important in the metabolism of reactive oxygen species, is another candidate gene that has been shown to be positively associated with ARHI (Unal et al., 2005;Van Eyken et al., 2007). Recently, a large-scale genome-wide association study, without reference to particular candidate genes, identified a highly significant association of ARHI with a SNP in the *GRM7* gene (Friedman et al., 2008). *GRM7* encodes metabotropic glutamate receptor type 7, and it was postulated that the linked SNP may confer a greater susceptibility to glutamate exciotoxicity.

Age-related hearing loss or presbycusis is the most common sensory deficit in elderly individuals and thus is a major human health concern. It is becoming increasingly clear that genetic factors play a substantial role in determining presbycusis susceptibility, but the late onset of the hearing loss and its underlying complex interactions of multiple environmental and genetic risk factors greatly complicate the identification of responsible genes. Because of the close similarities of the human and mouse auditory systems, genetic studies of hearing loss in inbred strains of mice provide a valuable approach for the identification of the genes and molecular pathways that underlie complex cases of age-related hearing loss in human populations (Vrijens et al., 2008). A comparison of Tables 2 and 3 shows that variants of the *KCNQ4* and *COCH* genes and mtDNA variants have been shown to contribute to progressive hearing loss in both humans and mice. Many more such examples are likely to follow as genetic and molecular methods for genetic mapping and gene identification become more refined.

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Abbreviations

Ahl
: age-related hearing loss

Phl
: progressive hearing loss

QTL
: quantitative trait locus

SNP
: single-nucleotide polymorphism

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Table 1

Mode of inheritance of hearing loss in common mouse strains

Strain	Locus	Chr	cM position	Reference
epistatic inheritance				
NOD/LtJ	*Cdh23*^{ahl}	10	30	(Johnson et al., 1997; Noben-Trauth et al., 2003)
	ahl2	5	40–55	(Johnson et al., 2002)
A/J	*Cdh23*^{ahl}			
	ahl4	10	70–80	(Zheng et al., 2008)
	mt-Tr	mito		(Johnson et al., 2001)
DBA/2J	*Cdh23*^{ahl}			
	ahl8	11	70–80	(Johnson et al., 2008)
Black Swiss	*ahl5*	10	35–42	(Drayton et al., 2006)
	ahl6	18	38–44	(Drayton et al., 2006)
additive inheritance				
C57BL/6J	*Cdh23*^{ahl}	10		
	ahl3	17	20–45	(Nemoto et al., 2004)
BUB/BnJ	*Cdh23*^{ahl}	10		
	Gpr98^{frings}	13	40	(Johnson et al., 2005)
co-dominant and epistatic inheritance:				
101H	*Phl1*	17	5–20	(Mashimo et al., 2006)
	Phl2	10	30–40	(Mashimo et al., 2006)

Table 2

Genes with mutations that cause progressive hearing loss in mice

Gene	Mutation	Proposed Gene Function	Reference
Atp1a1, Atp1a2, Slc12a2	targeted knockout (haploinsufficiency)	endocohlear potential, potassium homeostasis	(Diaz et al., 2007)
Barhl1	targeted knockout	maintenance of hair cells	(Li et al., 2002)
Cdh23	straiin variant	hair bundle integrity, tip link	(Noben-Trauth et al., 2003)
Cdh23, Pcdh15	*v* and *av* double heterozygotes	hair bundle integrity, tip link	(Zheng et al., 2005)
Cdkn2d	targeted knockout	hair cell re-entry into cell cycle	(Chen et al., 2003)
Chrnb2	targeted knockout	spiral ganglion cell maintenance	(Bao et al., 2005)
Coch	targeted knock-in	extracellular matrix?	(Robertson et al., 2008)
Col9a1	targeted knockout	integrity of tectorial membrane	(Suzuki et al., 2005)
Fbxo2, Skp1	targeted knockout	protein quality control in cochlea	(Nelson et al., 2007)
Gabr-a5,b2,b3	targeted knockout	hair cell and neuron maintenance	(Maison et al., 2006)
Kcnma1	targeted knockout	regulate OHC depolarization	(Ruttiger et al., 2004)
Kcnq4	targeted knockout	regulate OHC depolarization	(Kharkovets et al., 2006)
mt-Tr (mtDNA)	strain variant	energy metabolism, oxidative stress	(Johnson et al., 2001)
Nfrkb	targeted knockout	survival of spiral ganglion cells	(Lang et al., 2006)
Ngfr	targeted hypomorph	survival of spiral ganglion cells	(Sato et al., 2006)
Otos	targeted knockout	fibrocyte integrity	(Delprat et al., 2005)
Polg	targeted knock-in	accumulation of mtDNA mutations, oxidative stress	(Kujoth et al., 2005)
Smad5	targeted knockout (haploinsufficiency)	hair cell apoptosis	(Yang et al., 2009)
Sod1	targeted knockout	oxidative stress	(McFadden et al., 1999)
Vasp	targeted knockout	pillar cells actin cytoskeleton?	(Schick et al., 2004)

Table 3

Genes proposed to underlie age-related hearing loss in humans

Gene	Mutation	Proposed Gene Function	Reference
ACTG1	DFNA20/26	hair cell maintenance and repair	(Zhu et al., 2003)
COCH	DFNA9	extracellular matrix	(de Kok et al., 1999)
DFNA5	DFNA5	unknown	(Van Laer et al., 2002)
GRHL2	DFNA28 intron 1 SNP	cochlear epithelial cell maintenance?	(Van Laer et al., 2008)
GRM7	SNPs	susceptibility to glutamate excitotoxicity	(Friedman et al., 2008)
KCNQ4	DFNA2 SNPs	potassium recycling, regulation of OHC depolarization	(Kubisch et al., 1999; Van Eyken et al., 2006)
mtDNA genes	several	energy metabolism, oxidative stress	(Fischel-Ghodsian, 1999)
NAT2	SNPS	detoxification of reactive oxygen species	(Unal et al., 2005; Van Eyken et al., 2007)