Age-Related Hearing Loss

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Age-related hearing loss (ARHL) is the most prevalent sensory deficit in the elderly. This progressive hearing impairment leads to social isolation and is also associated with comorbidities, such as frailty, falls, and late-onset depression. Moreover, there is a growing evidence linking it with cognitive decline and increased risk of dementia. Given the large social and welfare burden that results from ARHL, and because ARHL is potentially a modifiable risk factor for dementia, there is an urgent need for therapeutic interventions to ameliorate age-related auditory decline. However, a prerequisite for design of therapies is knowledge of the underlying molecular mechanisms. Currently, our understanding of ARHL is very limited. Here, we review recent findings from research into ARHL from both human and animal studies and discuss future prospects for advances in our understanding of genetic susceptibility, pathology, and potential therapeutic approaches in ARHL.

Age-related hearing loss (ARHL), also known as presbycusis, is a complex disorder that results from the cumulative effects of aging on the auditory system. It is defined as a progressive, bilateral, symmetrical age-related sensorineural hearing loss, which is most pronounced at the higher frequencies. ARHL is the most prevalent chronic sensory deficit experienced by older adults, with approximately half of adults in their seventh decade showing hearing loss that is severe enough to affect communication (Agrawal et al. 2008), and is the third-most-common health condition affecting older adults after heart disease and arthritis (Collins 1997). Although not life-threatening, this condition is associated with significant psychological and medical morbidity, including social isolation, frailty, depression, and cognitive decline (Lin et al. 2011a, 2013; Kamil et al. 2016; Rutherford et al. 2018). In addition to the health burden, there is also a significant economic cost associated with ARHL. Stucky et al. (2010) estimated that in the year 2002 alone the combined direct medical and lost productivity costs attributable to hearing loss in adults aged ≥65 years in the United States was ∼$9.5 billion. Taking into account the expected increases in life expectancy, it is estimated that the annual cost will increase to ∼$60 billion by 2030 (Stucky et al. 2010). As such, the health, societal, and economic costs of ARHL are vast and ever-increasing. However, compared with congenital and early-onset hearing loss, our understanding of the biochemical processes and molecular biology underlying this condition are limited. Historically, this may reflect an underappreciation of the condition

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owing to the now outmoded assumption that ARHL is an unavoidable effect of aging, but it is also because of the practical considerations and difficulties associated with studying this chronic condition in older human patients.

ARHL PATHOLOGY AND EPIDEMIOLOGY

Historical studies of postmortem human temporal bones suggest that ARHL involves a number of auditory structures: degeneration of the mechanotransducing cochlear inner and outer hair cells (sensory presbycusis); reduced function within the stria vascularis (SV) (strial presbycusis, also known as metabolic presbycusis); and degeneration of the auditory nerve (neural presbycusis) (Schuknecht 1955; Schuknecht and Gacek 1993; Ohlemiller 2004). However, in reality, it is likely most people with presbycusis will show a "mixed" pathology. In addition to peripheral lesions it is also likely there will be changes occurring in central auditory pathways that contribute to the development and progression of ARHL. In this article, we will predominantly focus on what is known about the effects of aging in the peripheral auditory system. Although degenerative changes within the cochlea arise as a consequence of cellular aging, they also reflect the cumulative effects of additional extrinsic factors throughout the life of the individual. As such, ARHL is considered a multifactorial disorder with underlying risk factors that can be divided into several categories: biological age, gender, ethnicity, environment (e.g., noise exposure, ototoxic medications), lifestyle (e.g., smoking, drinking, diet), health comorbidities (e.g., hypertension, diabetes), and genetic predisposition (Yamasoba et al. 2013). Information pertaining to the epidemiology of ARHL has mostly arisen from large cohort studies, in which audiometric testing has been undertaken as part of the evaluation (Brant and Fozard 1990; Gates et al. 1990; Cruickshanks et al. 2003; Agrawal et al. 2008; Gopinath et al. 2009). However, although it is often difficult to directly compare data across these studies, owing to differences in cohort demographics and definitions of hearing loss, it is generally accepted that prevalence doubles with every decade of life from the second through to the seventh decade. Males are more likely to experience hearing loss than females of the same age, and African-Americans show a decreased risk compared with White or Hispanic-Americans (Lin et al. 2011b). Although these ethnic differences in hearing sensitivity are not fully understood, it is thought they might relate to differential lifetime exposure to noise or other environmental risk factors, or differences in melanin levels. Indeed, a study undertaken in albino mice reported that absence of strial melanin coincided with age-associated loss of marginal cells and endocochlear potential (EP) decline when compared with coisogenic pigmented mice (Ohlemiller et al. 2009).

Although noise exposure and ototoxic medications are able to independently cause hearing loss in an individual of any age, they are also extrinsic factors that can exacerbate progression of ARHL (Yang et al. 2015). In modern society, it can be difficult to avoid exposure to environmental noise, whether this is in the workplace, for example, factory workers and armed forces, or with the dramatic increase in the use of personal music devices. Moreover, if you are prescribed ototoxic antibiotics, or require cisplatin-based anticancer therapy, these risks are unavoidable. Conversely, lifestyle is an ARHL risk factor that is amenable to change. In a recent cross-sectional analysis, using 164,770 adults aged between 40 and 69 years of age from the U.K. Biobank Resource, it was found that smoking and passive smoking were associated with increased odds of hearing loss, odds ratio (OR) 1.15 (95% confidence interval [CI], 1.09–1.21), and 1.28 (95% CI, 1.21–1.35), respectively (Dawes et al. 2014). The investigators of this study suggest the higher OR for passive smoking compared with smoking can be explained by smokers being compared with nonsmokers, which will include passive smokers and therefore may underestimate the effects of smoking. However, moderate alcohol consumption was associated with reduced odds of hearing loss, OR 0.61 (95% CI, 0.57–0.65) (Dawes et al. 2014), which is in alignment with previous studies reporting an association between moderate alcohol intake with better hearing (Popelka et al. 2000; Fransen et al. 2008; Gopinath et al. 2010).

In a European multicenter study using 4083 subjects between 53 and 67 years, in addition to smoking, they also found that high body mass index (BMI) correlated with hearing loss (Fransen et al. 2008). However, in a similar-sized study undertaken in Korea, low BMI was found to be associated with hearing loss in adults (Lee et al. 2015). Another larger study investigating the weighted prevalence and associated factors of hearing impairment in ~16,000 Korean adults found that individuals with cardiovascular risk factors (e.g., hypertension, diabetes, smoking, increased serum cholesterol) are at risk of developing hearing impairment (Hong et al. 2015). Moreover, the Australian Blue Mountains Hearing Study found type 2 diabetes was associated with prevalent hearing loss in older adults, OR 1.55 (95% CI, 1.11–2.17) after adjusting for multiple risk factors (Mitchell et al. 2009). A meta-analysis of the effect of either type 1 or type 2 diabetes on hearing found an increased prevalence of hearing loss in diabetics compared with nondiabetics, OR 2.15 (95% CI, 1.72–2.68) and this relationship was not related to the age of participants (n = 20,194) (Horikawa et al. 2013). Although detecting associations between hearing loss and particular lifestyle choices or medical comorbidities can be revealed using large population cohorts, it can be difficult to disentangle the direct contribution of individual risk factors from indirect effects on general health, and therefore establish a causal link. However, taken together, these data suggest that a healthy lifestyle, which includes moderate alcohol intake, may afford some protection against ARHL.

Last, heritability studies among twins and longitudinal studies of family cohorts have shown that genetic predisposition forms a large and important risk factor for ARHL. Various studies report heritability indices of between 0.35 and 0.55 (Karlsson et al. 1997; Gates et al. 1999; Christensen et al. 2001). Hence, given the difficulties of accessing human cochlear tissue for biochemical studies, and as with congenital deafness, it is a genetic approach that is the most likely to provide insights into the molecular mechanisms that result in age-related decline in hearing. Here, we summarize and discuss the progress in our understanding of ARHL genetics based on recent studies undertaken in humans and animals and highlight future perspectives.

INSIGHTS INTO ARHL PATHOLOGY FROM RECENT RESEARCH: HUMAN GENETICS

As a common sensory disorder and a complex disease with a mixture of genetic and environmental components ARHL is resistant to genetic analysis by traditional linkage analysis in families. In a disorder with high heterogeneity, small-to-moderate genetic risk variants, and a significant environmental impact a familial genetic approach is of limited use. Since the first successful genome-wide association study (GWAS) conducted in age-related macular degeneration was published in 2005 (Klein et al. 2005), much hope was raised that this cohort-based approach rather than family-based analysis could reveal the genetic susceptibilities underlying common complex diseases including ARHL. Several GWAS into adult hearing status or ARHL have now been published (summarized in Table 1) (Friedman et al. 2009; Van Laer et al. 2010; Girotto et al. 2011; Nolan et al. 2013; Wolber et al. 2014; Fransen et al. 2015; Vuckovic et al. 2015; Hoffmann et al. 2016), and although many candidates have been linked to ARHL a lack of genome-wide findings that are significant and a poor replication of findings across these studies has limited their impact. One interpretation of these studies is that the heritability of ARHL has been overestimated or, alternatively, that there are thousands of rare variants in the population of small effect on ARHL risk, which would be impossible to detect by GWAS (Fransen et al. 2015).

There are, however, explanations for why common ARHL risk variants in the population may not have been detected in these studies. The power of GWAS to detect genetic risk factors relies primarily on two factors (Manolio et al. 2009; Eichler et al. 2010; Ku et al. 2010). First, it is necessary to have a good phenotyping measure, which is able to clearly delineate between patients and controls; ideally, the measure would also stratify patients into subphenotypes

Table 1. Summary of genome-wide association studies into age-related hearing loss (ARHL)

Study reference	Candidate genes highlighted by investigators[a]	Study design	Sample size	Ethnicity	Hearing phenotype	Age (yr)	Functional validation	Independent cohort replication[b]
Friedman et al. 2009	GRM7 (metabotropic glutamate receptor 7); CDH13 (cadherin 13)	Ca:Co	846 Ca 846 Co	European	*Z*-score based on PTA	53–67	Grm7 expression in HC and SGN	GRM7: several other studies; CDH13: one study
Van Laer et al. 2010	IQGAP2 (IQ motif-containing GTPase-activating-like protein); GRM7 (glutamate receptor 7)	QTA	347	Finnish Saami	Principal component analysis based on PTA	50–75	None	GRM7 (see above)
Girotto et al. 2011	DCLK1 (doublecortin-like kinase 1); PTPRD (protein tyrosine phosphatase receptor-type delta); GRM8 (metabotropic glutamate receptor 8); CMIP (c-Maf inducing protein)	QTA	3417	European	Principal component analysis based on PTA	>18	Expression studies in a subsequent study	GRM8 in Fransen et al. (2015)
Nolan et al. 2013	ESRRG (estrogen-related receptor γ)	QTA	3900	British	Logistic regression analysis of hearing thresholds at 1 and 4 kHz	44–45	Esrrg in HC, SC; Esrrg$^{-/-}$ mice have a mild hearing loss	Variable replication within study
Fransen et al. 2015	ACVR1B (activin receptor type-1B); CCBE1 (collagen and calcium-binding epidermal growth factor (EGF) domains 1)	QTA	2161	Belgian	Principal component analysis based on PTA	53–67	None	None to date
Wolber et al. 2014	**SIK3 (salt-inducible kinase 3)**	Meta	4939	European Silk Road	Principal component analysis based on PTA	18–98	Expression of Sik3 in stria, HC and SGN	None to date
Vuckovic et al. 2015	**PCDH20 (protocadherin 20); SLC28A3 (solute carrier family 28 member 3)**	Meta	2636	Italian Silk Road	Logistic regression analysis based on PTA	18–89	PCDH20 and SLC28A3 expression in HC and cochlea	Nominal replication within study
Hoffmann et al. 2016	**ISG20 (interferon-stimulated gene 20 kDa protein)**; TRIOBP (TRIO and F-actin binding protein); ILDR1 (immunoglobulin-like domain-containing receptor 1); EYA4 (EYA transcriptional coactivator and phosphatase 4)	Ca:Co	6527 Ca 45,882 Co	White-American (non-Hispanic)	Diagnosis of ARHL-related phenotype in electronic health records	18–100	SHIELD database supports expression in the inner ear	Within study replication

PTA, pure tone audiogram; HC, hair cell; SC, supporting cell; SGN, spiral ganglion neuron; Ca:Co, case control; QTA, quantitative trait analysis; Meta, meta-analysis.

[a]Genome-wide significance indicated in bold, defined here as $p < 5 \times 10^{-8}$.

[b]Replication of association at gene level, not necessarily at SNP level.

that are a result of the same underlying pathology. Second, GWAS require very large cohorts involving sample sizes in the thousands and tens of thousands (Spencer et al. 2009; Gibson 2010; Hong and Park 2012). For hearing as a phenotype this is problematic; a pure tone audiogram is the gold standard measure but this requires a trained audiologist, a quiet environment, and a significant amount of time. Extrapolate that out to a sample size of 10,000, and then it becomes extremely expensive to collect these data. Although it may be possible to collect large numbers of ARHL patients from clinics, the recruitment of age-matched controls with "good hearing" is more difficult. A compromise therefore often has to be made between the quality of the hearing data collected and the sample size. This explains why many of the large, population-based, publicly funded genetic cohorts have either not included hearing in the phenotypes collected, or have only collected self-reported questionnaire-based data. This has meant that hearing GWAS cohort collections have had to be initiated from individual research groups, which inevitably has limited the number and scale of the studies undertaken.

Different approaches have been taken to defining a hearing phenotype in the GWAS performed to date. Some studies have performed a quantitative population-based analysis, others used a case-control design. Various phenotype measures used include defined frequency thresholds, speech-in-noise tests, and public health records for evidence of hearing aid prescription to define the phenotype (see Table 1). The cohorts also differ greatly in the age range studied. Given these varied parameters, it is perhaps unsurprising that there is a lack of replication between individual GWAS. Compared with the samples sizes of recent successful GWAS in other disorders (see ebi.ac.uk/gwas), the studies also have reduced power because of the smaller samples caused by the difficulties in collecting large datasets as discussed above.

Despite these issues, the GWAS performed have identified a set of candidates for further analysis, providing a first step toward knowledge of ARHL pathogenesis. The strongest of these candidates is *GRM7*, the gene-encoding glutamate metabotropic receptor 7, a finding that has been replicated in several independent cohorts although not in all populations tested (Friedman et al. 2009; Van Laer et al. 2010; Newman et al. 2012; Luo et al. 2013). It is a G-coupled receptor activated by L-glutamate and its activation is associated with reduced release of the neurotransmitter. Because *GRM7* is expressed in hair cells and spiral ganglion neurons, Friedman et al. (2009) suggested that a genetic variant in *GRM7* might alter ARHL susceptibility caused by increased glutamate release at the synaptic connection between inner hair cells and auditory neurons, which could accumulate to toxic levels. A decline in the number and quality of synaptic connections between the sensory hair cells and auditory neurons is also thought to underlie "hidden hearing loss," an effect in which individuals with normal hearing thresholds still struggle to hear when in a noisy environment (Schaette and McAlpine 2011; Liberman 2015; Viana et al. 2015; Liberman and Kujawa 2017). Based on evidence from mice, it has been suggested that this synaptopathy is a primary pathology in noise-induced hearing loss (NIHL) and ARHL (Viana et al. 2015; Liberman and Kujawa 2017). The OR for the *GRM7* variant most strongly linked to ARHL was 2.56, although the overall haplotype effect was estimated at 12.01 (Friedman et al. 2009).

Single-nucleotide polymorphisms (SNPs) at two other genetic loci were recently reported to be associated at genome-wide significant levels in a study using electronic health records from 6527 patients with a diagnosis of an ARHL-related phenotype (Hoffmann et al. 2016). One variant is a missense SNP in *TRIOBP*, a gene-encoding TRIO and F-actin binding protein, an actin cytoskeleton regulator. Nonsense and frameshift mutations in this gene underlie autosomal recessive deafness-28 (DFNB28, MIM #609823), which present as a severe to profound deafness with a prelingual onset (Riazuddin et al. 2006; Shahin et al. 2006). In addition, characterization of *Triobp* isoform-specific knockout mice identify a role for TRIOBP in the formation of cochlear hair cell stereocilia rootlets, which are required to provide mechanical rigidity to the stereocilia bundle (Kitajiri et al. 2010). The

second variant is intergenic, between the *ISG20* and *ACAN* genes encoding proteins involved in interferon signaling and an extracellular matrix component, respectively. In both cases, the SNPs identified had only a very modest effect on risk of ARHL with an OR below 1.2 despite the genome-wide significance (Hoffmann et al. 2016).

Given the lack of genome-wide significance in many of the studies performed to date, researchers have sought to find the true associations among the background of false associations below this statistical threshold by a variety of strategies. These have included pathway analysis to identify enrichment of genes from pathogenic pathways, prioritizing hits in known deafness genes, investigation of gene function in mutant mouse models, and meta-analysis of data across cohorts. These methods have helped strengthen evidence for *ESRRG*, encoding estrogen-related receptor γ (Nolan et al. 2013) (mouse model), *PCDH20* encoding protocadherin 20 (Vuckovic et al. 2015), *SLC28A3* encoding the nucleoside transporter, solute carrier family 28 member 3 (Vuckovic et al. 2015), and *SIK3* encoding salt-inducible kinase 3 (Wolber et al. 2014) (all meta-analysis) as having a role in adult hearing loss. However, given the known heterogeneity involved in congenital deafness (Bowl et al. 2017), the expectation is that variants in hundreds of genes contribute to ARHL. Therefore, there is still a great need for much larger genetic studies using GWAS or whole-exome or whole-genome sequencing with greater power to detect the relatively subtle effects.

INSIGHTS INTO ARHL PATHOLOGY FROM RECENT RESEARCH: ANIMAL MODELS

Given the difficulties described above of studying presbycusis in human cohorts, researchers have taken to using animal models to help determine the pathogenesis and genetics associated with ARHL. Although no one model organism faithfully displays all aspects of human presbycusis, insights relating to molecular and cellular determinants of cochlear aging have been obtained from studies undertaken in several species including chinchilla, gerbil, rat, and mouse. For example, studies in aged Mongolian gerbils have shown that from 36 months of age they show a mild (15–35 dB) threshold shift, which is most pronounced at the higher frequencies (Mills et al. 1990). Moreover, an identified decline in EP with little sensory hair cell and neuron loss, led to them being classified as a model for a strial-based ARHL (Tarnowski et al. 1991; Schmiedt et al. 2002). The decline in EP was shown to correlate with strial capillary loss and changes to the structure of the marginal cells (Gratton and Schulte 1995; Gratton et al. 1997; Spicer and Schulte 2005). In particular, it is thought that oxidative damage to mitochondria within the strial marginal cells causes reduced ATP production, which in turn reduces Na^+,K^+ ATPase activity, leading to a reduced EP and elevated auditory thresholds (Spicer and Schulte 2005).

ARHL studies in the rat have used the inbred Fischer 344 (F344) albino strain, of which there are two substrains (DuCrl and NHsd). The age-related hearing function and pathology showed by these two substrains are mostly similar, but there are some differences (Syka 2010). F344 rats of both substrains develop a fast, progressive high-frequency hearing loss beginning at 1 year of age, which extends to the lower frequencies by 18 months of age (Popelar et al. 2003). In addition, these rats show a gradual decline in DPOAE amplitudes beginning in young animals, such that by 12 to 18 months of age DPOAEs are no longer present (Popelar et al. 2006). However, old F344 rats have good preservation of inner and outer hair cells (except at the very apical and very basal regions of the cochlea) (Popelar et al. 2006; Bielefeld et al. 2008). They do show markedly reduced labeling for collagen fibers in the lateral wall (SV and spiral ligament [SL]) and fewer type IV fibrocytes in the SL when compared with younger F344 (Buckiova et al. 2006, 2007). Similar to the Mongolian gerbils, aged F344 rats have a less vascularized SV and show degenerative changes within the marginal cell layer of the SV. A more recent study of outbred Wistar albino rats show they also develop a hearing loss similar in progression and magnitude to F344 (Alvarado et al. 2014).

Similar to gerbils and rats, certain mouse strains also show age-related cochlear pathologies that correspond to a "strial-type" of human presbycusis suggested by Schuknecht (Schuknecht 1955; Schuknecht and Gacek 1993; Ohlemiller 2004).

MOUSE AS A MODEL FOR ARHL

The mouse has become a robust and reliable mammalian model for aging research (Vanhooren and Libert 2013). The reasons for this include the ability to strictly control both intrinsic and extrinsic factors, for example, genetic background, diet, environment, and health status. In addition, mice have a short life span, meaning the effects of age become apparent within a contracted time period.

Some of the earliest research using mice to investigate the genetics of ARHL involved the use of inbred strains. Certain strains have long been reported as having "good" hearing into old age (e.g., CAST, CBA/CaJ, CBA/J, C3H/HeH), whereas others show a progressive decline in auditory function (e.g., BALB, C57BL/6, DBA/2J). Subsequent genetic mapping studies have defined ~20 loci that influence ARHL in laboratory strains of mice, and for four of these the underlying genetic lesions have been identified, designated as *ahl* alleles, that is, $Cdh23^{753A}$ (*ahl*, cadherin-23), $Cs^{rs29358506\text{-}A}$ (*ahl4*, citrate synthase), $Gipc3^{343A}$ (*ahl5*, GIPC PDZ domain-containing family member), and $Fscn2^{R109H}$ (*ahl8*, fascin actin-bundling protein 2, retinal) (Noben-Trauth et al. 2003; Shin et al. 2010; Charizopoulou et al. 2011; Johnson et al. 2012; Ohlemiller et al. 2016).

The commonly used C57BL/6 strains develop progressive high-frequency hearing loss caused by a hypomorphic mutation within the cadherin 23 (*Cdh23*) gene, which encodes a component of the stereocilial tip-link required for gating of the mechanoelectrical transducer channel (Noben-Trauth et al. 2003; Siemens et al. 2004; Kazmierczak et al. 2007). C57BL/6J mice show cochlear pathological changes that match the sensory, neural, and strial prebycusis subtypes proposed by Schuknecht. Consistent with the hearing loss, which is evident from as early as 3 months of age, these mice progressively lose sensory hair cells (inner and outer) in an age-dependent manner proceeding from cochlear base to apex. They also show loss of basal spiral ganglion cells, loss of SL fibrocytes and thinning of the SV, although no progressive EP decline is observed at >24 months of age (Hequembourg and Liberman 2001; Ohlemiller 2006, 2009). However, although this strain has been labeled as a model of ARHL, currently there is no convincing evidence associating variants in human *CDH23* with ARHL (Yang et al. 2015).

Used in forward genetic screens, the mouse has been an invaluable model organism for the discovery of genes required for hearing function, and mutations leading to congenital and early-onset hearing loss (Hrabe de Angelis et al. 2000; Nolan et al. 2000; Clark et al. 2004; Bowl et al. 2017). Similar hypothesis-generating approaches would likely yield important insights to genes involved with ARHL, but such programs require large numbers of mice to be bred, aged, and phenotyped, and are therefore prohibitively expensive for an individual research group to undertake. Recently, at the MRC Harwell Institute, a large-scale phenotype-driven screen for genes associated with age-related disease was undertaken in mice. Using the chemical mutagen ENU, pedigrees of mutagenized mice were generated and subject to recurrent screens for phenotypes as they aged (Potter et al. 2016). Importantly, the phenotyping pipeline included clickbox and auditory brainstem response (ABR) tests to assess hearing function. From ~150 pedigrees tested, 27 were found to show late-onset phenotypes, including several that displayed late-onset progressive hearing loss. Of these, three were reported to be caused by ENU-induced mutations within novel hearing loss genes (*Slc4a10*, *Wars2*, and *Zfyve26*, encoding solute carrier family 4 member 10, mitochondrial tryptophanyl transfer RNA [tRNA] synthetase 2 and zinc finger FYVE-type containing 26, respectively). This shows phenotype-driven screens have the capacity to identify models of progressive and/or late-onset hearing loss, and the potential to elaborate on the genetics of this condition.

The mouse is the predominant model organism for studying mammalian auditory function (Bowl and Dawson 2015). In particular, the genetic concordance for mutations causing congenital and early-onset hearing loss is very high, in that genetic lesions identified in patients when modeled in the mouse cause hearing loss, and "hearing" genes discovered in the mouse are often found to harbor mutations in human deafness patients. At present, the concordance for ARHL genes is not so high. In a recent review, Ohlemiller et al. (2016) list ~50 mouse and 20 human candidate genes that have been proposed to influence ARHL and/or NIHL. Interestingly, only around one quarter of the proposed human ARHL genes overlap with proposed mouse ARHL genes. This could mean the remaining candidate human genes are not required for age-related auditory function in the mouse or, more likely, the mouse models for these genes may not have been fully characterized into old age. To fully elaborate on the requirement of these genes, mice would not only need to be sufficiently aged, but they may also need to be challenged (e.g., with noise or secondary genetic alleles) to induce an auditory phenotype. Additionally, the genetic variants that increase risk of ARHL, unlike many of those that cause congenital deafness, may need to be studied in "knockin" models of the human mutation, rather than knockout models. These concerns are particularly relevant for the validation of candidate genes arising from GWAS, the vast majority of which have not yet been followed up in mouse models (Table 1). A more integrated approach is required to both validate ARHL GWAS hits in animal models and also provide insights into the mechanisms underlying ARHL (see Fig. 1).

As additional mouse and human ARHL susceptibility alleles are identified, it will be interesting to observe whether they are "mild" alleles of genes reported for congenital/early-onset, hearing loss, or whether they are novel genes not previously linked with hearing loss. In particular, one might expect that ARHL susceptibility genes are likely to encode structural and homeostatic proteins normally required for maintaining auditory cellular structure and function into old age, and that hypomorphic alleles of these genes will provide less resilience to environmental or lifestyle ARHL risk factors. Indeed, genes linked to metabolism of reactive oxygen species, antioxidant systems, and mitochondrial function have been reported as ARHL susceptibility genes (McFadden et al. 1999; Ohlemiller et al. 2000; Van Eyken et al. 2007; Someya et al. 2008). These genes are not inner-

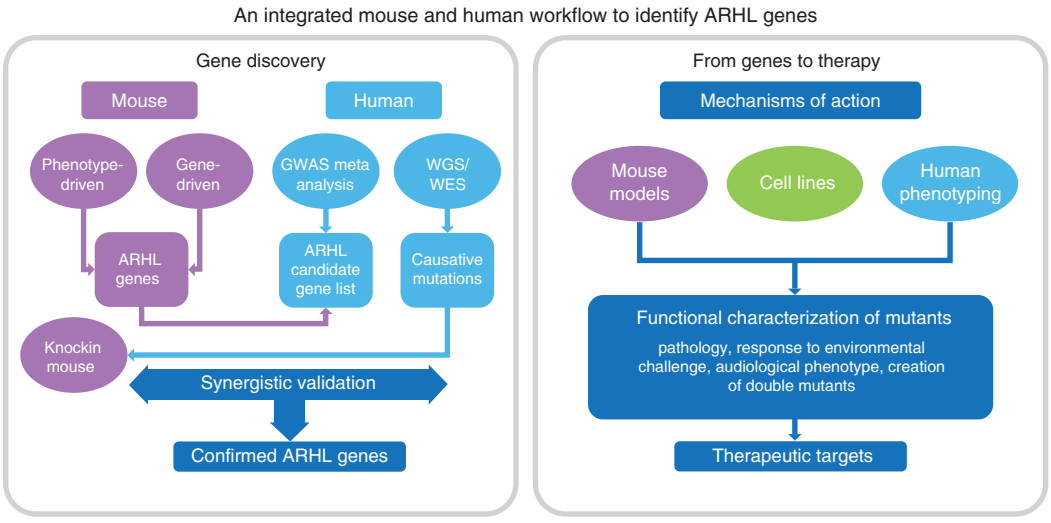

Figure 1. An integrated mouse and human workflow to identify age-related hearing loss (ARHL) genes. GWAS, genome-wide association studies; WES, whole-exome sequencing; WGS, whole-genome sequencing.

ear specific, but instead have widespread expression and function in many cells throughout the body. Identifying why the ear is so susceptible to loss of these genes will be important for the design of therapeutic interventions.

FUTURE PERSPECTIVES

Rapid technical developments in genetics are providing researchers with more advanced tools applicable to common disease research. Whole-genome sequencing or whole-exome sequencing capture all variants present so, unlike GWAS, these approaches will be able to identify whether there are many rare variants in genes that confer ARHL susceptibility. However, even with these new tools, there is still a need of large cohorts to have sufficient power to detect ARHL genes. The U.K. Biobank study is a population-based study involving more than 500,000 people between 40 and 69 years of age, which recently released genotype data imputed to 90 million variants (Sudlow et al. 2015). Self-reported hearing data is available from all participants and a speech-in-noise test was completed in a subset of 188,000 participants (Dawes et al. 2014). Completion of this U.K. Biobank GWAS analysis in such a large cohort should determine whether there are common variants within the population that play a role in ARHL. Certainly, failure to detect any such associations in a study with such great power would indicate that either there are many thousands of very rare variants responsible, or that the heritability of ARHL has been greatly overestimated.

To date, the mouse has been underutilized as a model organism for the study of human presbycusis. However, this likely reflects the paucity of strong candidate genes arising from human association studies together with the cost of aging cohorts of mice to detect late-onset effects rather than the mouse not being a good model organism. As more genes/alleles are identified through GWAS and familial sequencing studies, future endeavors will certainly involve the generation and longitudinal phenotyping of mouse mutants carrying these exact genetic lesions. Recent advances in genome-editing technologies such as CRISPR/Cas9 that now allow the generation of mice carrying specific point mutations without leaving a "footprint" is a rapid, highly efficient, and relatively inexpensive approach to take. Validation of human ARHL-causing mutations in the mouse, or other organisms, will provide a genetic diagnosis, but equally importantly these models will also provide the opportunity to study disease progression and ascertain the pathological changes occurring within the aging cochlea, something that is not possible in humans. This understanding is a prerequisite for the design of therapeutic interventions to ameliorate age-related auditory decline. In addition, validated models can also be used for preclinical studies to test the efficacy of new therapeutic approaches. However, before embarking on the generation of a genome-edited knockin, it is important to consider the effect of the candidate human mutation in the context of the human sequence. Moreover, careful consideration should also be given to which inbred or outbred mouse strain is used to model a human genetic lesion, as a given knockin mutation on one particular genetic background may or may not show penetrance compared with when tested on a different background. Indeed, it may be that the allele should be trialed on several backgrounds.

ARHL AND DEMENTIA

One of the most significant developments in our knowledge of ARHL etiology over the last decade has been the emergence of hearing loss as a risk factor for developing dementia. A large number of studies have found a link between ARHL and cognitive decline, dementia, and Alzheimer's disease with the hearing loss predating and predicting subsequent clinical diagnosis of dementia (Lin et al. 2013; Gurgel et al. 2014; Wei et al. 2017; Jayakody et al. 2018). There are several possible explanations for this association between the two morbidities and the resulting implications for our understanding of the mechanisms underlying the two diseases. The most widely proposed model suggests that the lack of auditory input and subsequent social isolation accelerates loss of cognitive function. Alternatively, it could be that in some individuals with ARHL, the hearing loss itself is an early mani-

festation of a preclinical cognitive decline; it is known that patients with dementia show pathological signs of decline for decades before a clinical diagnosis of dementia. Third, there may be common pathological pathways involved in causing both disorders. Plausible pathways that have been linked to both pathologies include oxidative damage, inflammation, vascular function, mitochondrial dysfunction, glutamate excitotoxicity, and RNA granule dysregulation (Towers et al. 2011; Wong and Ryan 2015; Ganguly et al. 2017; Maziuk et al. 2017; Du et al. 2018; Jayakody et al. 2018; Ridge and Kauwe 2018). It is also possible that more than one of these models is relevant and that, as well as common causative factors underlying hearing loss and cognitive decline with age, the resulting lack of auditory input accelerates the psychological consequences and hence the clinical impact of the pathology. Pertinent to this question, some studies have found that treatment of hearing loss with hearing aids is able to prevent or lessen the speed of cognitive decline (Dawes et al. 2015; Mamo et al. 2017; Maharani et al. 2018), although further studies are required to establish this as a preventative strategy. A positive side effect of recent publicity about the link between midlife hearing loss and the risk of dementia is that it will raise the profile of research into ARHL with research funding bodies (Livingston et al. 2017).

THERAPEUTIC APPROACHES TO TREATING OR PREVENTING ARHL

Given there is currently an insufficient understanding of the mechanisms involved in ARHL, it is unsurprising that very few clinical trials to prevent or treat ARHL have taken place. In the absence of clear biological targets for drug development, pharmaceutical companies are reluctant to invest in expensive translational research despite the size of the potential market for an ARHL therapy. In addition, the design of clinical trials to assess efficacy of therapies for ARHL is problematic. The identification of a drug that could prevent or ameliorate further progression of a mild-to-moderate hearing loss is currently a more realistic prospect than a drug or therapy, which can improve an existing hearing loss. However, to detect a significant effect on hearing loss clinical trials may need to follow participants for months or years making them long and consequently expensive to undertake. Despite these difficulties, a number of clinical and preclinical trials with pharmacological therapies for adult hearing loss are underway. The results of these early trials, even if unsuccessful at identifying an efficacious therapy, will be important in informing the design of future ARHL clinical trials. The first reported clinical trial designed to treat ARHL with a pharmacological agent was conducted by Pfizer and completed in 2013 using PF-04958242, a positive allosteric modulator of the AMPA receptor, an ionotropic glutamate receptor (Bednar et al. 2015). The study was undertaken with 44 participants with ARHL over the age of 50, and no improvement in hearing thresholds was detected 1 and 5 hours after a single dose. In the CLARITY-1 study sponsored by Autifony Therapeutics and completed in 2016, the effect of a modulator of voltage-gated potassium channels, AUT 00063, on the hearing of people over the age of 50 who had been diagnosed with ARHL was assessed (see clinicaltrials.gov/ct2/show/NCT02345031). After a 4-week treatment period, no improvement in hearing as assessed by a speech-in-noise test was identified ($n = 37$) compared with the placebo group ($n = 39$) at the end of the study. A much larger study involving 550 participants is going to be completed in 2021, assessing the effect of the acetylcholinesterase inhibitor, Huperzine A on hearing function and cognitive decline over a 3-year period (see clinicaltrials.gov/ct2/show/NCT03101722). A number of other clinical trials are underway to investigate the effect of various therapies on mild-to-moderate hearing loss, including a Novartis Pharmaceuticals phase I and II study using a gene therapy approach to deliver the pro–hair cell transcription factor ATOH1 to participants with severe-to-profound hearing loss, in an attempt to improve hearing by promoting regeneration of hair cells from supporting cells (see clinicaltrials.gov/ct2/show/NCT02132130). There is some evidence this approach has been able to restore hearing in

animal models of hearing loss (Izumikawa et al. 2005). Furthermore, studies with modulators of metabotropic glutamate receptor 7 in animal models of NIHL conducted by Pragma Therapeutics have shown proof-of-concept and are progressing to preclinical trials. Although these and other studies are not specifically recruiting ARHL patients, the results are likely to have implications for all types of acquired hearing loss.

CONCLUDING REMARKS

Compared with the major advances in the understanding of the genes and pathological mechanisms involved in congenital deafness our knowledge of ARHL is still limited. There are many challenges that remain in this field, but it should also be acknowledged that some advances have been made, including the identification of some strong candidate genes implicated in ARHL susceptibility. Progress is also signified by the first clinical trials for progressive adult hearing loss being undertaken. Although whole-genome sequencing is becoming increasingly affordable and will be used in ARHL, a lack of adequate research funding to undertake studies with sufficient power is probably still the major barrier to further progress in ARHL.

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