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C57BL/6-derived mice and the *Cdh23*^{ahl} allele – Background matters

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ABSTRACT

C57BL/6-derived mice are the most utilised mice in biomedical research, and yet actually there is no such thing as a generic C57BL/6 mouse. Instead, there are more than 150 C57BL/6-derived sub-strains recognised by the Mouse Genome Informatics (MGI) database, each of which carry sub-strain-specific fixed genetic differences that can potentially lead to phenotypic differences affecting a single, or multiple biological systems. One of the most widely known strain-specific alleles is the *Cdh23*^{ahl} allele, a single nucleotide change that predisposes C57BL/6-derived mice to a progressive hearing loss that starts in the high-frequency region. As such, this allele is of particular relevance to auditory researchers. However, a recent study, comparing C57BL/6NTac mice with a co-isogenic strain in which the *Cdh23*^{ahl} allele has been 'repaired' using genome editing, suggests that the *Cdh23*^{ahl} allele may have a broader effect on phenotype expressivity of mouse mutants impacting not just the auditory system, but other organ systems as well. Here, using the *Cdh23*^{ahl} allele as an exemplar, we discuss the importance of knowing, understanding and reporting the genetic background of mouse mutants.

1. The rise of C57BL/6-derived mice in research

In the early 1900's, C.C. Little purchased a female mouse (designated C57) from Abbie Lathrop and by 1921 starting from this one animal he had generated the inbred C57BL strain (the product of >20 generations of sibling matings). Subsequently, in 1937 strain 6 was separated from the C57BL colony and bred at The Jackson Laboratory, becoming the C57BL/6J inbred strain. In 1951, these mice were imported to the US National Institutes of Health (NIH) to form a new inbred strain of mice, C57BL/6N. These two strains, and their derived sub-strains, are the most recognised and cited in biomedical research. However, genetic drift when breeding mice means that if kept as a closed colony, separated from the original inbred strain for ≥20 generations, that colony becomes a new sub-strain of the original inbred strain. Examples of this include C57BL/6C (also known as C57BL/6CrSlc, maintained by Japan SLC) and C57BL6NTac (maintained by Taconic Farm) which were each established from the C57BL/6N inbred strain in 1972 and 1991, respectively. Currently, there are 187 C57BL/6-derived sub-strains recognised by the mouse informatics database (MGI) (See Table 1 and supplementary file 1).

There are several reasons why C57BL/6-derived mice have become the mainstay of biomedical research; they are good breeders, produce moderate-size litters, are long-lived, and have a low incidence of tumours with age (Festing and Blackmore, 1971; Rowlatt et al., 1976). A practical reason for their adoption is their coat colour. Classic gene targeting strategies involve the injection of modified embryonic stem cells (ES cells) into a fertilised mouse blastocyst taken from a second genetic background. The resulting offspring will be chimaeras, with cells derived from both the ES donor and the host blastocyst. The dark, black coat of C57BL/6-derived mice made them a popular choice from which to obtain ES cells as when these were injected into blastocysts derived from an albino line, the degree of chimerism could be visually estimated from the proportion of black versus white in the offspring's coat. From this, mice exhibiting the highest degrees of black patches of coat colour, which is indicative of the inclusion of ES cells, would be selected as breeders to maximise the chance of propagating the targeted allele through the germ line. For these reasons, C57BL/6-derived mice have become the predominant background for the generation of genetically engineered mouse mutants. Moreover, given that it is costly, in terms of time and money, to backcross an engineered mutation from one background strain to a different strain, researchers tend to maintain and study their mutation of interest on the background it was first generated; in many cases this would be a C57BL/6-derived background.

Importantly, each C57BL/6-derived sub-strain is unique and should not be considered genetically identical to another sub-strain as, during the process of becoming inbred, random nucleotide changes will likely become fixed in the genome of that specific sub-strain. For instance, while the many C57BL/6-derived sub-strains appear very similar,

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Table 1
Top 25 most utilised C57BL/6-derived sub-strains, based on the number of references associated with the strain on the Mouse Genome Informatics (MGI) database. This number is not a true reflection of the number of research papers using these sub-strains as many publications do not link to the respective MGI ID. For a full list of the 187 C57BL/6-derived sub-strains recognised by the MGI, see supplementary file 1.

Strain Name	MGI ID	Synonyms	Refs
C57BL/6J	MGI:3028467	B6|B6J|Black 6|C57 Black	5618
C57BL/6JEiJ	MGI:2160528		614
C57BL/6NCrl	MGI:2683688	C57BL/6NCrlBr|C57BL/6NCrlBR	236
C57BL/6N	MGI:2159965		115
C57BL/6NJ	MGI:3056279	B6N|Black 6N|C57BL/6NCrJ	102
C57BL/6JRj	MGI:2670020		91
C57BL/6NTac	MGI:2164831	C57BL/6Tac|C57BL/6Tac	83
C57BL/6JOlaHsd	MGI:2164189	C57BL/6HUK|C57BL/6S	70
C57BL/6JJcl	MGI:3055581		62
C57BL/6NHsd	MGI:2161078		44
C57BL/6ByJ	MGI:2159783	B6|B6 Bailey|B6 Bailey J|B6By|Black 6 Bailey|C57 Bailey	42
C57BL/6JJmsSlc	MGI:5488963		41
C57BL/6By	MGI:2159895	B6 Bailey|B6By|Black 6 Bailey	29
C57BL/6NRj	MGI:6236253		27
C57BL/6NCrSlc	MGI:5295404	57BL/6C	25
C57BL/6JBomTac	MGI:4939906		22
C57BL/6NNia	MGI:6275033		21
C57BL/6Ros	MGI:2159744		20
C57BL/6JArc	MGI:5425110		19
C57BL/6Pas	MGI:2160096		19
C57BL/6JCrl	MGI:3775640		18
C57BL/6NJcl	MGI:2160139		18
C57BL/6NCr	MGI:2160593		16
C57BL/6JRccHsd	MGI:6156915		14
C57BL/6JRos	MGI:2159764		13

behavioural differences have long been noted (Bryant et al., 2008; Matsuo et al., 2010; Simon et al., 2013). Moreover, there are sub-strain-specific genetic variants that are known to be confounding factors when studying particular biological systems. For example, C57BL/6N derived sub-strains carry the *Crb1*^{rd8} allele, which causes a mild retinal degeneration (Mehalow et al., 2003; Aleman et al., 2011; Mattapallil et al., 2012; Pritchett-Corning et al., 2012), and the *Cyfip2*^{S968F} allele, which alters the effect of amphetamines (Kumar et al., 2013). Conversely, the C57BL/6J sub-strain carries the *Nnt*$^{C57BL/6J}$ allele, which impacts insulin secretion and glucose tolerance (Freeman et al., 2006; Ronchi et al., 2013). In fact, a number of metabolic differences have been noted when directly comparing C57BL/6J and C57BL/6NCrl mice (Nemoto et al., 2022).

The observed differences between C57BL/6-derived sub-strains also extend to the auditory system with C57BL/6J mice showing a greater susceptibility to noise when compared to C57BL/6NHsd (Kendall and Schacht, 2014). Conversely, C57BL/6NHsd mice appear to have a faster rate of high-frequency hearing loss compared with C57BL/6J (Kendall and Schacht, 2014); although this did not appear to be the case when comparing C57BL/6J with C57BL/6NJ (Kane et al., 2012) or C57BL/6NTac (Simon et al., 2013).

In 2013, a large-scale phenotypic comparison was made between C57BL/6J and C57BL/6NTac mice, leveraging data collected from the International Mouse Phenotyping Consortium (IMPC) programme (Simon et al., 2013). Here, they found a number of significant phenotypic differences between the two sub-strains that were replicated between different mouse phenotyping centres. The most striking of these differences was in the Morris water maze and Rotarod motor learning performance tests, where the C57BL/6NTac mice performed notably worse than C57BL/6J in both. These apparent differences in motor learning could impact behavioural assessments of auditory sensitivity where training is required. Alongside phenotypic comparisons, the genomes of C57BL/6J and C57BL/6NTac mice were also compared, which identified 51 genes that carry sequence or structural variants predicted to affect gene function. As such, it is imperative that researchers know, understand, and report the genetics of the mice they are using in their research.

2. C57BL/6-derived mice and hearing research

The wide availability of mouse models (e.g. knockouts, knock-ins, etc) generated on C57BL/6-derived backgrounds means that many of the mouse models used in auditory research are maintained on a C57BL/6-derived genetic background. However, all C57BL/6-derived sub-strains develop a progressive hearing loss that is first evident for high-frequency hearing thresholds by 3-months of age, but which progresses to profound hearing impairment affecting all frequencies by 15-months of age (Hunter and Willott, 1987; Li and Borg, 1991; Kane et al., 2012). The cause of this accelerated "age-related" hearing loss is a strain-specific single nucleotide variant within the *Cadherin-23* (*Cdh23*) gene (*Cdh23*$^{c.753A}$), commonly referred to as the *Cdh23*^{ahl} allele (Johnson et al., 2000; Noben-Trauth et al., 2003). This hypomorphic allele causes in-frame skipping of the seventh coding exon (exon 9) of the *Cdh23* gene. In addition to the C57BL/6-derived sub-strains, this allele is also present in 27 other commonly used inbred mouse strains, including CD-1, BALB/cBy, DBA/1J, and DBA/2J (http://www.informatics.jax.org/allele/MGI:3028349). So, while *Cdh23*^{ahl}-containing strains are not ideal for studying genes implicated in susceptibility to age-related hearing loss, they are commonly used for the study of genes required for the development and early maintenance of the auditory system, including those linked to congenital deafness and early-onset hearing loss.

Cadherin-23 (Cdh23), also known as Otocadherin, is an atypical member of the Cadherin superfamily, which along with Protocadherin-15 (Pcdh15) forms filamentous tip-links between the tips of the stereocilia present on the apical surface of the sensory cells of the inner ear, namely inner and outer hair cells. In the cochlea, Cdh23 (comprising 27 extracellular cadherin (EC) repeats) forms the upper part of the tip-link, while Pcdh15 (comprising 11 EC repeats) forms the base of the tip-link and is connected to mechanoelectrical transducer (MET) channels (Beurg et al., 2009; Kazmierczak et al., 2007a). When soundwave-induced mechanical energy deflects the stereocilia, this generates mechanical tension in the tip-links which opens the MET channels allowing the influx of K^+ and Ca^{2+} ions, depolarisation of the hair cell, and subsequent neurotransmitter release onto the auditory nerve (Zheng and Holt, 2021). The interaction between Cdh23 and Pcdh15 involves domains EC1 and EC2 of both proteins and is stabilised by Ca^{2+} to form a strong, but flexible bond (Sotomayor et al., 2012; Mulhall et al., 2021). Under excessive force, such as that which occurs with exposure to loud noise, these tip-links can break, but they are able to reform rapidly (Zhao et al., 1996).

In humans, nonsense, frameshift, or splice-site mutations of *CDH23* typically cause Usher syndrome type ID (USH1D), a syndromic condition characterised by the presence of congenital sensorineural hearing loss, vestibular dysfunction, and progressive retinitis pigmentosa (Smith et al., 1994; Oshima et al., 2008; Okano et al., 2019). Whereas, missense mutations of *CDH23* tend to be associated with non-syndromic sensorineural hearing loss, DFNB12 (Bork et al., 2001; Astuto et al., 2002; de Brouwer et al., 2003; Wagatsuma et al., 2007; Schultz et al., 2011). In both conditions, the phenotypic presentation can be variable, likely reflecting the nature of the underlying mutation and the effect it has on the function of the encoded protein (Becirovic et al., 2008; Oshima et al., 2008; Okano et al., 2019; Wagatsuma et al., 2007). In both USH1D and DFNB12 hearing loss is early onset, and is often identified at pre-lingual timepoints (Usami et al., 2022).

More recently, *CDH23* variants have been identified that do not

cause USH1D or DFNB12, but instead are associated with either noise-induced hearing loss (Kowalski et al., 2014; Wu et al., 2022) or age-related hearing loss (Wells et al., 2019; Usami et al., 2022). Interestingly, some *CDH23* variants associated with late-onset, age-related hearing loss have also been found in a small subset of patients with early-onset or congenital hearing loss (Usami et al., 2022), suggesting that in these cases additional contributing genetic and/or environmental interactions may influence the phenotype expressivity. Taken together, these genotype-phenotype correlations indicate that: the most damaging *CDH23* variants lead to a syndromic hearing loss (USH1D); less damaging variants lead to non-syndromic hearing loss (DFNB12); and, mild variants that do not immediately impact protein function act as susceptibility alleles that require an additional insult(s) such as age, noise, or a second interacting genetic variant to elicit a phenotype. Indeed, the *Cdh23*^{ahl} allele should likely be considered a susceptibility allele, and that C57BL/6-derived mice are a good model to investigate the molecular and cellular mechanisms of the *Cdh23*^{ahl} allele interaction with age, noise, and additional genetic loci. Such studies would provide valuable insight into the biology of *Cdh23*-associated progressive hearing loss, which may identify common downstream effector pathway(s) responsible for the age-related decline of the mammalian auditory system.

In humans, age-related hearing loss reflects the cumulative effects of ageing on the auditory system, which includes environmental insults, lifestyle choices, and genetic susceptibility. Regarding presentation, ARHL is characterised by progressive, bilateral sensorineural hearing loss that initially affects high-frequency hearing and progresses to lower frequencies with age. In seminal work by Schuknecht, the primary pathological causes of age-related hearing loss are attributed to: the loss of hair cells (sensory presbyacusis); degeneration of spiral ganglion neurons (neural presbyacusis); or, degeneration of the stria vascularis (strial presbyacusis). A fourth category attributed to alterations to basilar-membrane mechanics (conductive presbycusis) was also proposed (Schuknecht, 1964; Schuknecht and Gacek, 1993). However, it is likely that in most cases there will be a mixed pathology.

Consistent with Schuknecht's post-mortem pathological findings in humans, C57BL/6-derived mice homozygous for the *Cdh23*^{ahl} allele progressively lose both inner- and outer- hair cells in an age-dependent manner, starting at the base of the cochlea and progressing to the apex. In addition to the loss of the inner hair cells, longitudinal observations showed that C57BL/6J mice also have a notable loss of basal spiral ganglion neurons, loss of type IV fibrocytes of the spiral ligament, and thinning of the stria vascularis with age (Hequembourg and Liberman, 2001). Interestingly, despite the observed atrophy within the lateral wall, the endocochlear potential is not reduced even at 12 months of age (Yang et al., 2013).

Given these phenotypic similarities, C57BL/6-derived mice that carry the *Cdh23*^{ahl} allele are considered a good model of age-related hearing loss. However, 20 years after the allele was first identified we still do not understand the biological mechanism whereby this proposed hypomorphic allele confers susceptibility to ARHL. As mentioned earlier, the encoded CDH23 protein is an essential component of the hair cell tip-link that is critical for mechano-electrical transduction and as such loss-of-function mutations in *Cdh23* cause congenital hearing loss. It has been proposed that the *Cdh23*^{ahl} allele causes the production of a CDH23 protein that is less stable than wild-type CDH23. However, a large proportion of C57BL/6-derived mice that carry the *Cdh23*^{ahl} allele have normal ABR thresholds up to ~3-months of age, which must mean that tip-links are 'functional' in these mice. As to why the high-frequency hearing of these mice progressively worsens from around 3-months of age is currently unknown; changes to auditory sensitivity cannot be attributed to loss of hair cells alone, as hair cell loss is thought to occur after the loss of auditory sensitivity (Henry and Chole, 1980), although damage to the stereocilia can already be evident (Hultcrantz and Li, 1993a). Perhaps the *Cdh23*^{ahl} allele produces a suboptimal CDH23 protein, leading to low-grade stress in the sensory hair cells that can only be withstood for a certain period, and it is the metabolically more active basal hair cells that succumb first. However, more research is required to determine the exact biology of the auditory decline exhibited by these mice.

With the advent of CRISPR/Cas9-mediated genome editing, we and others have generated C57BL/6-derived mice in which the *Cdh23*^{ahl} allele has been specifically corrected back to the wild-type sequence (Mianné et al., 2016; Yasuda et al., 2020). We find that our co-isogenic 'corrected' C57BL/6NTac (C57BL/6NTac.*Cdh23*$^{c.753A>G}$) mice exhibit good high-frequency hearing thresholds up to at least 18-months of age (Figure 1A). Interestingly, these mice still develop a late-onset (from ~12-months) low-frequency hearing impairment, albeit to a lesser degree than that seen in standard C57BL/6NTac mice (Figure 1A). By comparing C57BL/6-derived mice with their equivalent co-isogenic 'corrected' mice it has been possible to demonstrate definitively that the *Cdh23*^{ahl} allele is the primary driver of age-related hearing loss in the C57BL/6-derived background (Mianné et al., 2016; Yasuda et al., 2020). However, it is important to note that Kane et al. (2012) found that breeding of the *Cdh23*^{ahl} allele onto a CBA/CaJ background, via linkage backcrosses, was not sufficient to induce the same accelerated hearing loss as observed in C57BL/6-derived strains (Figure 1B). These findings suggest that additional genetic factors within the C57BL/6-derived background contribute to *Cdh23*^{ahl}-mediated accelerated hearing loss, but they are not sufficient to cause hearing loss in isolation.

Originally, the corrected C57BL/6NTac.*Cdh23*$^{c.753A>G}$ line was generated to enable the use of the knockout mouse models generated by the IMPC programme for age-related hearing studies. Given that all IMPC knockout models are generated on C57BL/6-derived backgrounds, utilisation of the corrected C57BL/6NTac.*Cdh23*$^{c.753A>G}$ line allows the *Cdh23*^{ahl} allele to be bred out of the knockout model in just two generations while maintaining the integrity of their genetic background. In addition, the corrected C57BL/6NTac.*Cdh23*$^{c.753A>G}$ mice allow, through direct comparison with C57BL/6NTac mice, the investigation of the physiological consequence of the *Cdh23*^{ahl} allele on the auditory system. For example, the age-related reinnervation of efferent synapses at the inner hair cell was originally proposed to be a consequence of *Cdh23*^{ahl}-mediated progressive hearing loss in C57BL/6-derived mice (Lauer et al., 2012). Indeed, when compared to age-matched C3H/HeJ mice that do not carry the *Cdh23*^{ahl} allele, both C57BL/6NTac and C57BL/6J mice have more efferent synapses to their inner hair cells. However, the corrected C57BL/6NTac.*Cdh23*$^{c.753A>G}$ mice exhibit a similar number of efferent connections compared to C57BL/6NTac mice, indicating that efferent rewiring of aged inner hair cells is not directly related to *Cdh23*^{ahl}-mediated progressive hearing impairment (Jeng et al., 2021). Similarly, many of the age-associated differences in the biophysical properties of cochlear sensory hair cells and non-sensory supporting cells that are observed between C57BL/6NTac and C3H/HeJ mice, could not be attributed to the presence of the *Cdh23*^{ahl} allele. Specifically, young C57BL/6-derived mice with or without the *Cdh23*^{ahl} allele have more synaptic ribbons that are more broadly distributed in inner hair cells, as well as showing an increase in ribbon volume with age, compared with C3H/HeJ mice. Additionally, ATP-induced Ca^{2+} currents in the greater epithelial ridge (GER) appear greater in older C57BL/6-derived mice with or without the *Cdh23*^{ahl} allele compared with age-matched C3H/HeJ mice (Hool et al., 2023; Jeng et al., 2021, 2020a, 2020b). Importantly, for these types of comparisons to be meaningful strict breeding strategies are required to ensure that the corrected C57BL/6NTac.*Cdh23*$^{c.753A>G}$ mice remain co-isogenic with C57BL/6NTac.

3. The use of C57BL/6 in noise challenge

Age-related hearing loss and noise-induced hearing loss share many of the same pathological features, including loss of cochlear synapses preceding the loss of hair cells, as well as degeneration of spiral ganglion neurons and lateral wall (Liberman, 2017). Indeed, there have now been

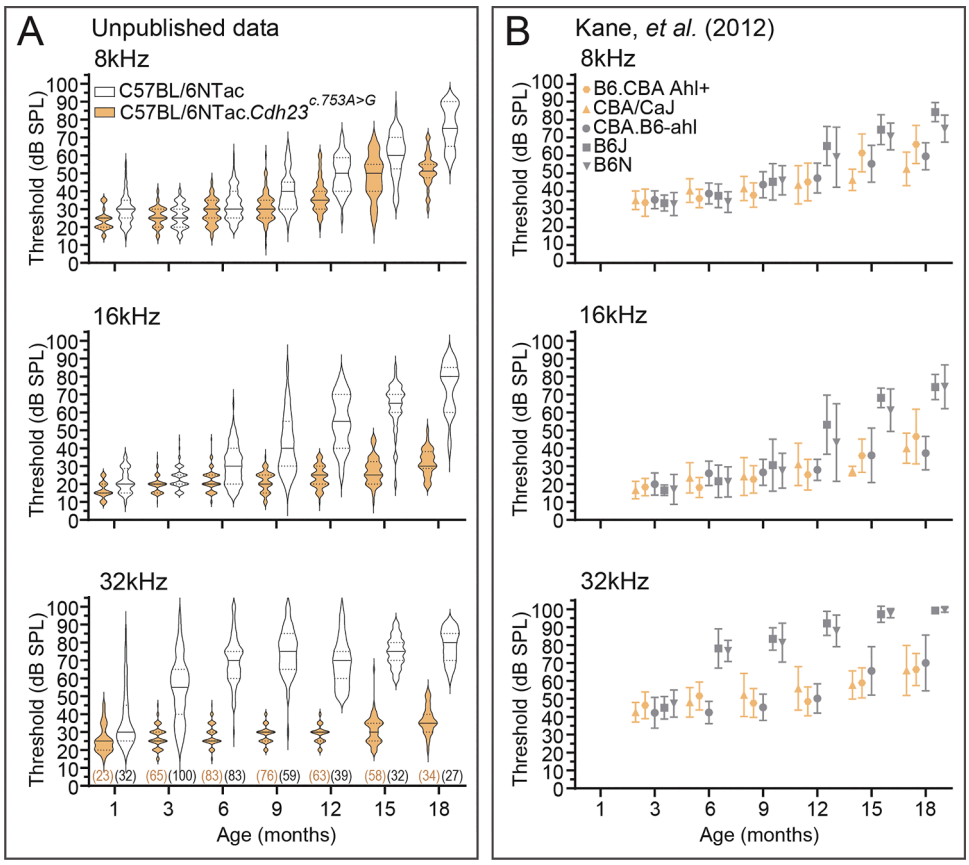

Fig. 1. Auditory thresholds with respect to age in multiple background strains. **(A)** Longitudinal ABR phenotyping of standard C57BL/6NTac and corrected C57BL/6NTac.*Cdh23*$^{c.753A>G}$ mice between 1- and 18-months of age. Violin plots of ABR thresholds recorded for low- (A, 8kHz), mid- (B, 16kHz), and high-frequency stimuli (C, 32kHz). All data recorded at our laboratory between 2016 – 2023. The number of mice recorded is shown in brackets below the 32kHz plot. Some of these data have been published previously (Aguilar et al., 2024; Mianné et al., 2016). **(B)** Longitudinal phenotyping data adapted from Kane et al. (2012) showing recorded ABR thresholds of three inbred strains C57BL/6J (B6J), C57BL/6N (B6N) and CBA/CaJ, and two speed congenic strains with (CBA.B6-ahl) or without (B6.CBA Ahl+) the *Cdh23*^{ahl} allele.

several studies indicating that exposure of young mice to noise accelerates their age-related hearing loss (Fernandez et al., 2015; Jensen et al., 2015; Fetoni et al., 2022), which may be indicative of a shared molecular pathway. This would seem to make sense in a real-world setting, as the cochlea is subject to many varied environmental challenges over the lifespan, including exposure to noise. As such, in the laboratory setting, a noise challenge is sometimes used alongside ageing when investigating genetic susceptibility to progressive hearing loss (Yan et al., 2013; Ingham et al., 2020; Tan et al., 2021). However, as with ageing similar problems arise with using C57BL/6-derived mice that carry the *Cdh23*^{ahl} allele, as they are more vulnerable to permanent threshold shifts following exposure to levels of noise that only cause temporary threshold shifts in other commonly used inbred strains, such as the CBA/Ca and CBA/CaJ sub-strains (Shone et al., 1991; Li, 1992; Hultcrantz and Li, 1993b; Myint et al., 2016). Through comparison of C57BL/6-sub-strains with other strains that do, or do not, carry the *Cdh23*^{ahl} allele, it has been suggested that the presence of the *Cdh23*^{ahl} allele is the primary cause of the increased vulnerability to noise-induced hearing loss (Ohlemiller et al., 2000; Davis et al., 2001; Harding et al., 2005). However, these comparisons cannot exclude the possibility of other strain-specific genetic differences being involved in the response to noise in each of these different inbred strains.

To date, most of what we know about the physiological consequence of noise over-exposure on the murine cochlea comes from research undertaken using CBA/CaJ mice (e.g.: Wang et al., 2002; Hirose and Liberman, 2003; Hirose et al., 2005; Kujawa and Liberman, 2006, 2009; Furman et al., 2013). It may be tempting to assume that correction of the *Cdh23*^{ahl} allele in a C57BL/6-derived mouse would render their physiological response to noise similar to that of CBA/CaJ mice. However, this is unlikely to be true, especially as it has been noted that differences in response to noise exposure is even evident between different CBA sub-strains (Ohlemiller et al., 2011; Versteegh et al., 2022). Thus, in order to fully ascertain the influence of the *Cdh23*^{ahl} allele on noise-induced hearing loss, more research is needed to compare the biological response to noise in C57BL/6NTac, C57BL/6NTac.*Cdh23*$^{c.753A>G}$, and CBA/CaJ mice.

4. Genetic interactions of *ahl*

Despite the presence of the *Cdh23*^{ahl} allele in C57BL/6-derived sub-strains, these mice are still widely used in auditory research, due to the widespread production of genetically manipulated models on these genetic backgrounds. To mitigate against the effect of the *Cdh23*^{ahl} allele, auditory researchers typically restrict their studies to early adulthood, before 3-months of age, assuming that auditory physiology in C57BL/6-derived mice is normal before this time point.

However, there is increasing evidence that the presence of the *Cdh23*^{ahl} allele has consequences prior to the onset of progressive age-related hearing loss in C57BL/6-derived mice. Genetic interactions between the *Cdh23*^{ahl} allele and mutations in the genes *Superoxide dismutase* (encoding SOD1) (Johnson et al., 2010), *Atp2b2* (encoding PMCA2) (Watson and Tempel, 2013), and *Neuroplastin* (encoding NPTN) (Newton et al., 2022), suggest that mice homozygous for the *Cdh23*^{ahl} allele are particularly sensitive to dysregulation of calcium and

oxidative stress. The production of reactive oxygen species (ROS) and oxidative stress is a common mechanism involved in various cochlear pathologies, including ototoxicity, noise-induced damage, and age-related degeneration (Henderson et al., 2006; Böttger and Schacht, 2013; Wong and Ryan, 2015). In C57BL/6-derived mice, administration of mitochondrial antioxidants, or the genetic manipulation of genes involved in oxidative and ER stress pathways, modifies their age-related hearing loss phenotype (Someya et al., 2009; Johnson et al., 2010; Fu et al., 2018; Chen et al., 2024), implicating oxidative stress as a key contributing factor to age-related auditory decline. However, this is not limited to C57BL/6-derived mice carrying the *Cdh23*^{ahl} allele, but has also been observed in the Senescence Accelerated Mouse (SAMP8) mouse, which also has an accelerated aging phenotype (Marie et al., 2017). In SAMP8 mice, oxidative stress drives the degeneration of multiple cell types in the cochlea (Menardo et al., 2012; Benkafadar et al., 2019). While the initial driver of ROS generation in SAMP8 and C57BL/6-derived mice is likely very different, the phenotypic similarities suggest that oxidative stress is a possible generalised cochlear aging mechanism that could be targeted therapeutically to mitigate against age-related hearing loss in the human population.

Recently, we have demonstrated a genetic interaction between *Cdh23*^{ahl} and *Embigin* (*Emb*), which encodes a fibronectin-binding type I transmembrane receptor that belongs to the basigin family of neural cell adhesion molecules. When an *Embigin* null allele is maintained on a standard C57BL/6NTac background the mice exhibit an early-onset progressive hearing loss, which becomes evident from around 6-weeks of age, as well as developmental defects in the brain and heart, causing peri-natal mortality in a proportion of the homozygous mutants. However, when the same *Embigin* null allele is maintained on the corrected C57BL/6NTac background (C57BL/6NTac.*Cdh23*$^{c.753A>G}$) the mice do not exhibit hearing loss, nor brain or heart defects, and are not sub-viable (Newton et al., 2023). Despite being expressed in a wide array of different tissues (Sannigrahi et al., 2019; Balan et al., 2021; "The Human Protein Atlas," n.d.), *Cdh23* is largely considered a cochlear gene. As such, a functional impact of the *Cdh23*^{ahl} allele outside of the aging cochlea is largely ignored. Our finding that the *Cdh23*^{ahl} allele genetically interacts with *Embigin* in the neonatal brain and heart strongly highlights that the *Cdh23*^{ahl} allele has notable effects in organs other than the auditory system. There is now good evidence that homophilic trans-binding of the full-length extracellular component of the CDH23 protein forms potent cell-cell bonds that strongly inhibit cellular migration (Kazmierczak et al., 2007b; Sannigrahi et al., 2019; Singaraju et al., 2019). Although not tested, *Cdh23*^{ahl}-induced skipping of the 7th coding exon, which encodes part of the 3rd extracellular cadherin repeat (EC3), could impact the strength of these bonds. In the brain, *Cdh23* expression in the auditory cortex has been shown to be required for interneuron development, an effect that is independent of peripheral auditory impairment (Libé-Philippot et al., 2017); although, the hypomorphic *Cdh23*^{ahl} allele has no effect on either interneuron development or maintenance (Rogalla and Hildebrandt, 2020). Moreover, *Cdh23* expression has been shown to be increased in several regions of the brain following low-level repetitive blast exposure in rats (De Gasperi et al., 2023), which could indicate a role in neuroplasticity. Indeed, CDH23 variants have been found in cohorts of patients with schizophrenia (Karagyaur et al., 2024; Tesolin et al., 2023), a condition associated with dysplasticity (Morishita and Vinogradov, 2019). Interestingly, mice with the *Cdh23*^{ahl} allele have been shown to exhibit increased pre-pulse inhibition (PPI) responses, which is contrary to what one might expect of mice with hearing deficits (Balan et al., 2021). Moreover, mice heterozygous for the *Cdh23*^{ahl} allele, which therefore do not exhibit age-related hearing loss, have deficits in amplitude modulation following responses (AMFR, also known as envelope following response) independent of auditory threshold response (Burghard et al., 2019), which in humans has been linked with deficits in auditory temporal processing and reduction in speech intelligibility.

The identification of genetic interactions with the *Cdh23*^{ahl} allele has important implications for genetic research using mouse models maintained on C57BL/6-derived backgrounds. Importantly, this is not just restricted to auditory-based research, but is also relevant for research investigating non-auditory systems in which the *Cdh23*^{ahl} allele has wrongly long been considered "inert". Furthermore, the finding that for certain mutant lines the co-presence of the *Cdh23*^{ahl} allele acts to potentiate their hearing loss is important as it means that all auditory phenotyping data generated from mouse models maintained on C57BL/6-derived backgrounds need to be interpreted as such. An identified hearing loss may not be evident, or be much less severe, if bred on a non-*Cdh23*^{ahl} background.

5. Conclusion

It has been 20-years since the *ahl* allele was identified as the genetic cause behind the progressive hearing loss phenotype observed in many commonly utilized inbred strains, However, two decades on we are only just beginning to elaborate upon the effects of this well known, but often ignored, allele. While several genetic interactions have been reported for the *ahl* allele, which manifest as hearing loss phenotypes that are more severe than observed for either allele alone. It is likely this is just the tip of the iceberg, given there has not been a large-scale systematic assessment of mouse models of hearing impairment maintained on both an *ahl*-positive and an *ahl*-negative genetic background. Moreover, the recent finding of an *ahl* genetic interaction causing heart and brain defects clearly indicates that this allele needs to be considered as a potential variable of phenotype expressivity across other organ systems and not just the auditory system. Indeed, the presence or absence of *ahl* in the genetic background of mouse mutants could be an underlying contributor to the failure of reproducibility that continues to plague mouse studies. As such, it is critically important for researchers to know and report the genetics of their models. However, despite improvements made by the implementation of the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines, information provided in publications reporting animal research is often incomplete in regard to genetic background. It is not uncommon to read a paper reporting research that involved the use of mice and find there is no mention of the genetic background of the models used. Furthermore, it is also not uncommon for authors to state that they have used C57BL/6 mice in their studies, even though no such inbred strain exists. To combat this, a new Laboratory Animal Genetic Reporting (LAG-R) framework has been proposed, designed to complement the ARRIVE guidelines by standardising the genetic information included in scientific publications (Teboul et al., 2024). Increasing scientific rigour is a responsibility of all researchers, but is arguably more pertinent for those that use model organisms. Moreover, the identification of additional genetic interactions involving the *ahl* allele, both within and outside of the auditory system, will help provide insight into the biology of this very interesting and enigmatic allele.

CRediT authorship contribution statement

Sherylanne Newton: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Carlos Aguilar:** Writing – review & editing, Investigation, Formal analysis. **Michael R. Bowl:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that no competing interests exist.

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Supplementary materials

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Data availability

Data will be made available on request.

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