

Evidence updates on risk factors for occupational noise-induced hearing loss (ONIHL)

Update 3: genetic factors

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Author	Amanda Bowens, ACC Research
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Contents

Executive summary	2
1 Introduction	3
1.1 Background.....	3
1.2 Purpose.....	3
2 Methods	3
3 Findings	3
3.1 Genetic factors associated with noise-induced hearing loss	3
3.2 Nonsyndromic hearing loss	4
3.3 Other inherited conditions associated with hearing loss.....	5
4 Conclusions	7
References.....	8

Executive summary

This evidence update briefly reviews the literature on genetic risk factors associated with both noise-induced hearing loss (NIHL) and susceptibility to hearing loss more generally. It is a partial update of ACC's 2010 epidemiological review of risk factors for hearing loss.

The update focuses on three areas:

1. **Recent research on genetic factors associated with NIHL:** the evidence base has grown since the 2010 review. An additional 24 primary studies on the role of genetic mutations were identified. All the studies used cross-sectional or case-control designs. Meta-analyses have suggested possible associations between susceptibility to NIHL and variants in several genes, for example heat shock protein 70.
2. **Nonsyndromic hearing loss:** around 70-80% of genetic hearing loss is estimated to be nonsyndromic. There are four main types depending on inheritance pattern. Age of onset, severity and progression vary between and within types. Autosomal recessive forms are more common, but autosomal dominant forms may be more likely to arise in adulthood and progress with age. Some forms are therefore difficult to distinguish from age-related hearing loss.
3. **Other inherited conditions associated with hearing loss:** a range of syndromes, for example mitochondrial disorders, are characterized by hearing loss alongside other signs and symptoms. Syndromes with adult onset tend to be rare. However, research suggests that some more common disorders that may have an inherited component, such as diabetes, are associated with an increased risk of hearing loss.

1 Introduction

1.1 Background

Noise-induced hearing loss (NIHL) results from a complex interaction of genetic and environmental factors. Some researchers estimate that inherited factors may account for up to 50% of hearing loss variability following exposure to noise[1].

ACC carried out a review of hearing loss risk factors in 2010[2] to inform the first edition of its NIHL assessment guide[3]. At the time, research on genetic aspects of NIHL was at an early stage. The number of available studies was small and several were based on the same population sample. The studies all had cross-sectional or case-control designs. ACC's review concluded that the genetic markers investigated up to that point were not strong risk factors for NIHL.

1.2 Purpose

ACC is now updating its 2011 NIHL assessment guide. The update is being led by the NIHL Expert Advisory Group (EAG). The EAG has asked Research to outline recent evidence on associations between genetic risk factors and hearing loss, focusing on three areas:

1. A brief update of research on genetic factors associated with NIHL.
2. An overview of inherited nonsyndromic hearing loss.
3. A summary of other inherited conditions that may be associated with hearing loss.

2 Methods

This evidence update takes the form of a brief report and literature review. It is based on searches of the following databases and information sources undertaken in June and July 2018:

- Embase on the Ovid platform
- Medline & Medline In-Process on the Ovid platform
- PubMed
- Science Direct
- Google Scholar

Search terms included *hearing loss, noise, risk factors, genetics, genetic predisposition to disease, nonsyndromic hearing loss* and *comorbidity*. Studies were also sourced from members of the EAG.

3 Findings

3.1 Genetic factors associated with noise-induced hearing loss

Primary research

The number of primary studies examining links between genetic factors and NIHL has increased since 2010. A total of 24 cross-sectional and case-control studies published between 2010 and 2017 were identified. Most involved Asian (i.e. Chinese or Taiwanese) populations and a broad range of genetic factors and mutations were investigated. However, no cohort studies were identified. Prospective cohort studies are a more rigorous approach

for investigating interactions between genetic and environmental factors, but are more costly and demanding to carry out than cross-sectional or case-control studies[4].

Secondary research

In addition to the primary studies, three recent meta-analyses and a literature review were also identified. Their findings are summarised as follows:

- Based on studies carried out in Polish, Swedish and Chinese populations, a 2013 literature review found that the following genes may be associated with susceptibility to NIHL: two genes encoding potassium ion channels (KCNQ4 and KCNE1), catalase (CAT), protocadherin 15 (PCDH15), myosin 14 (MYH14) and heat shock protein 70 (HSP70)[5].
- A 2017 meta-analysis found the C47T polymorphism of the manganese superoxide dismutase gene (SOD2) was associated with increased risk of NIHL in Chinese, but not in European, study populations[6].
- Two 2017 meta-analyses found that two polymorphisms of the heat shock protein 70 (HSP70) gene were associated with susceptibility to NIHL; some associations were stronger in Caucasians[7, 8].

There is currently no reliable genetic test to distinguish between people who are susceptible or resistant to NIHL[9].

3.2 Nonsyndromic hearing loss

Nonsyndromic hearing loss is an inherited partial or total loss of hearing that is not associated with other signs or symptoms[10]. The causes are complex; research has identified over 90 genes with mutations associated with nonsyndromic hearing loss. Inherited hearing loss can occur in people with no history of the condition in their families.

Classification

Nonsyndromic hearing loss is classified into four main types according to inheritance pattern. The degree and characteristics of hearing loss vary within and between types. Losses range from mild to severe and may show distinctive patterns affecting particular frequencies. Losses can be bilateral or unilateral and may worsen with age.

The four main types of nonsyndromic hearing loss:

1. Most cases (75-80%) are inherited in an **autosomal recessive (DFNB)** pattern. DFNB1, associated with the GJB2 gene, is the most common form. DFNB1 hearing loss is generally prelingual (i.e. apparent before language develops at about one year of age), non-progressive and severe to profound[11, 12]; however, hearing loss can be progressive where there is late onset[13].
2. A smaller percentage of cases (20-25%) is inherited in an **autosomal dominant (DFNA)** pattern. DFNA hearing loss tends to be post-lingual (onset often spans early adulthood to middle age[12]) and progressive[14, 15]. Etiology and presentation are generally more variable than with DFNB.
3. **X-linked (DFNX)** forms of nonsyndromic hearing loss are rare (1-2%).
4. **Mitochondrial** forms of the condition are rare (<1%)[10]; incidence is slightly higher in east Asians than in western populations[16].

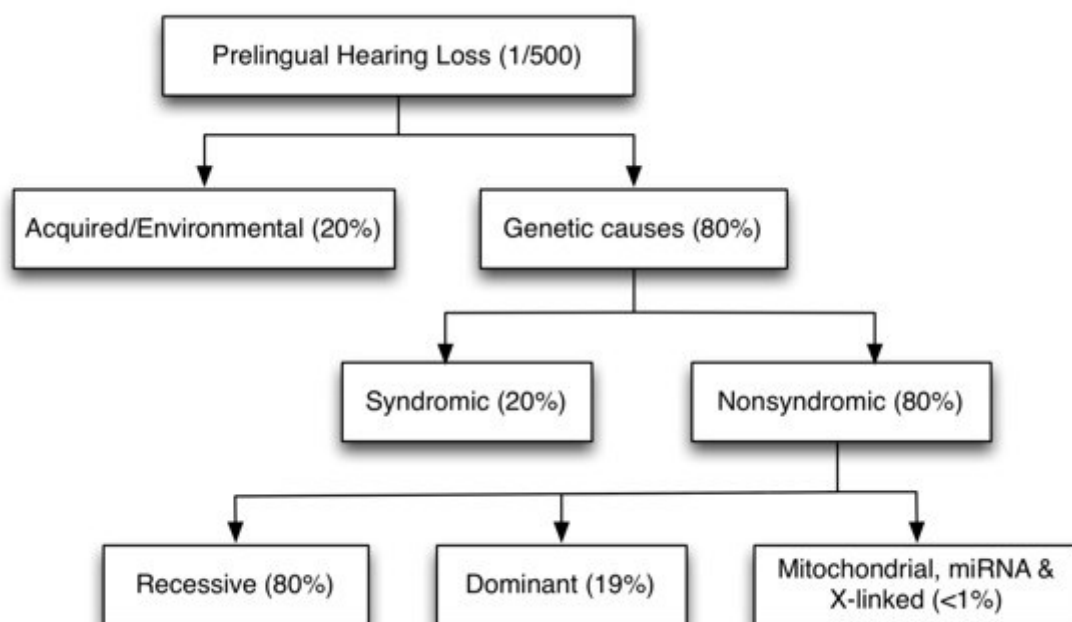
Studies have shown that some genes linked with nonsyndromic hearing loss, particularly DFNA types, may also be associated with increased susceptibility to age-related hearing impairment[17]. As the pathological processes of age-related hearing loss can mimic those of late onset DFNA losses, distinctions between the two are not always clear[12].

Mitochondrial nonsyndromic hearing loss is maternally inherited and variable in onset and severity. Some pathogenic variants in mitochondrial genes can make carriers susceptible to hearing damage caused by aminoglycoside antibiotics[18].

Epidemiology

Estimates of incidence and prevalence of nonsyndromic hearing loss vary according to geography, population and the availability of testing and screening services. As a rough guide, it has been estimated that two to three of every 1,000 babies born in the United States have hearing loss and that up to 80% of such cases result from genetic causes[18]. Some estimates place the percentage of genetic causes lower, at around 50-60%[19, 20]. Around 70-80% of genetic hearing loss is likely to be nonsyndromic[16].

Figure 1: Cases of prelingual hearing loss in developed countries. From Shearer et al.[18]



The approximate prevalence of recessive DFNB1 pattern hearing loss in the general population is 14:100,000[11]. The percentage of inherited hearing impairments associated with DFNB1 varies according to geography; a range of 18-41% has been reported for Europe, Australia, North America, the Middle East and East Asia[13].

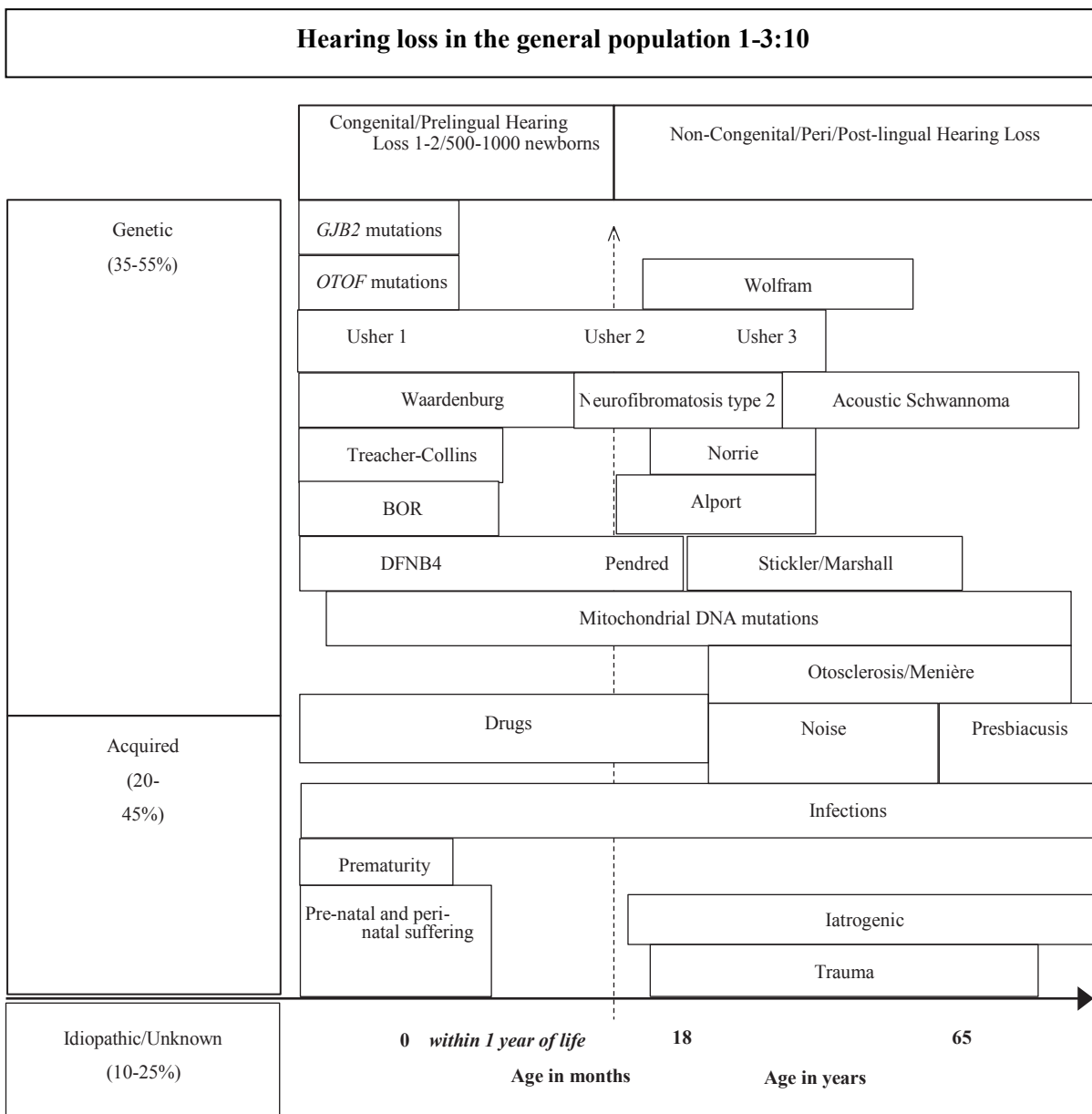
3.3 Other inherited conditions associated with hearing loss

Syndromic hearing loss

In contrast with nonsyndromic hearing loss, syndromic hearing loss occurs with signs and symptoms that affect other parts of the body[18]. Causes of syndromic hearing loss with post-lingual or adult onset tend to be rare and include:

- Mitochondrial disorders: these have been linked with a variety of disorders that may present at any age. Overall prevalence of all mitochondrial disorders in adults and children is estimated to be at least 11.5:100,000[14]. Mitochondrial syndromic hearing impairment is accompanied by problems affecting other organ systems.
- Stickler syndrome: a connective tissue disorder characterized by distinctive facial features and vision and joint abnormalities. Hearing loss varies in severity and can be progressive. Prevalence is around 13.5:100,000 [20].
- Neurofibromatosis type 2: involves the development of noncancerous tumors affecting the nervous system. The most common tumors are known as acoustic neuromas or vestibular schwannomas. Symptoms including hearing loss and tinnitus usually appear in adolescence or early twenties. Prevalence is around 0.5:100,000[20].
- Alport syndrome: leads to kidney disease and progressive hearing loss. It occurs in approximately 1 in 50,000 newborns[21]. Symptoms are more severe in affected males than in females.

Figure 2: Etiology and epidemiology of hearing loss in the general population, with age of symptom onset. From Castiglione et al.[20]



Associations with other disorders

A comprehensive 2016 literature review by Lie and colleagues identified several studies that reported associations between hearing loss and cardiovascular disease, some cardiovascular risk factors (e.g. high blood pressure, high levels of cholesterol or triglycerides) and type 2 diabetes[9]. A 2009 US study based on national cross-sectional surveys 2-3 decades apart found that people with diabetes had a higher prevalence of hearing impairment[22]. A 2017 systematic review and meta-analysis concluded that type 1 diabetes was linked with an increased risk of developing mild or subclinical hearing impairment[23]. Other meta-analyses have found: significantly higher prevalence of hearing impairment in diabetics compared to non-diabetics, independent of age and noise exposure[24]; and significantly higher incidence of at least mild hearing loss in people with type 2 diabetes compared to controls[25].

Some sources have reported that hearing loss may be associated with obesity and chronic inflammation[19]. A large (n=16,554) Korean study found links with chronic kidney disease and metabolic syndrome (the latter in women only)[26].

4 Conclusions

Genetic factors associated with noise-induced hearing loss

The evidence base has grown since 2010. An additional 24 primary studies investigating genetic factors and mutations potentially associated with susceptibility to noise-induced hearing loss (NIHL) were identified. All the studies had cross-sectional or case-control designs. No cohort studies were found. Secondary research in this area is also starting to starting to accumulate. Three meta-analyses and a literature review were identified, the findings of which suggest possible associations between susceptibility to NIHL and a range of genetic factors including variants of heat shock protein 70.

Nonsyndromic hearing loss

Around 70-80% of genetic hearing loss is estimated to be nonsyndromic. It is classified into four main types according to inheritance pattern. Age of onset, severity and degree of progression vary both within and between types. The autosomal recessive form is most common (75-80%), but the autosomal dominant form (20-25%) is more likely to present in adulthood and worsen over time. It can therefore be difficult to distinguish from age-related hearing loss.

Other inherited conditions associated with hearing loss

There is a broad range of inherited syndromes, including mitochondrial disorders, that lead to hearing loss along with other signs and symptoms. Causes of syndromic hearing loss with adult onset tend to be rare. In addition, research suggests that several other conditions which may have an inherited component, such as diabetes and cardiovascular risk factors, may be associated with an increased risk of hearing loss.

Gaps in current knowledge and research

Of all risk factors, increasing age is by far the most strongly associated with hearing loss. Hereditary factors may explain the high degree of variation between individuals. Group studies can identify potential associations with risk factors (e.g. inheritance, noise exposure), but on an individual level it is not currently possible to distinguish between hearing loss caused by ageing, noise or genetic susceptibility.

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