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Review

Contribution of genetic factors to noise-induced hearing loss: A human studies review

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ABSTRACT

Noise-induced hearing loss (NIHL) is a complex disease that results from the interaction of genetic and environmental factors. Over the last 10 years there has been a great increase in association studies trying to identify the susceptibility genes for NIHL in humans. They were conducted based on the candidate gene approach and comprised predominantly the group of oxidative stress genes, inner ear potassium recycling pathway genes and monogenic deafness genes, as well as other genes. So far, the most promising results were obtained for two genes encoding potassium ion channels (*KCNQ4* and *KCNE1*), catalase (*CAT*), protocadherin 15 (*PCDH15*), myosin 14 (*MYH14*) and heat shock protein (*HSP70*), because they were replicated in two (Polish and Swedish) or three (Polish, Swedish and Chinese) populations, and were sufficient in size to yield high power for the detection of a causative allele. Today, the development of high-throughput genotyping methods allows the detection of hundreds and thousands of single nucleotide polymorphisms (SNPs) in a single array which undoubtedly will lead toward identification of new NIHL susceptibility genes. This in turn will contribute to the development of genetics tests that would allow for better protection of noise-exposed individuals and personalized treatment, if necessary.

Contents

1. Introduction

Noise-induced hearing loss (NIHL) is a worldwide leading occupational health risk in industrialized countries and the second most common form of sensorineural hearing impairment, after presbyacusis. According to European Communities estimates (2004), about 20% of European workers are exposed, half or more of their working time, to noise so loud that they have to raise their voice to talk to other people. It has been estimated that worldwide as many as 500 million individuals might be at risk of developing NIHL [1].

Susceptibility to the damaging effects of noise differs remarkably among individuals; after an identical noise exposure not all subjects develop hearing loss. NIHL has been therefore classified as a complex disease, resulting from the interaction of genetic and environmental factors. In order to develop new therapies that prevent NIHL, high priority has been given to research aimed at improvement of scientific knowledge of molecular causes leading to this complex disease.

The genetic basis of NIHL has been clearly demonstrated in animals. Mouse strains (C57BL/6J) exhibiting age-related hearing

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loss (AHL) were shown to be more susceptible to noise than other strains [2–4]. Also, several knockout mice including *SOD1*−/− [5]; *GPX1*−/− [6]; *PMCA2*−/− [7] and *CDH23*+/− [8] were shown to be more sensitive to noise than their wild-type littermates. These studies on knockout mice indicated that there are some genetic deficits that disrupt different pathways and structures within the cochlea and thereby increase the inner ear susceptibility to noise.

Contrary to animal studies, the discovery of human genetic factors predisposing to NIHL has encountered many difficulties. To date, no heritability studies have been performed, since families where all subjects are exposed to identical noise conditions are almost impossible to collect. Another approach has therefore been adopted, where the putative causal variants could be studied in candidate genes, carefully selected on the basis of information regarding their biological function. This has opened the door to further analysis determining whether they do increase susceptibility to NIHL on a population basis, using association studies.

The aim of this paper was to overview human association study results on gene polymorphisms in populations exposed to noise and indicate the first potential susceptibility genes for NIHL. The review includes papers published over the last 10 years in English. Eleven most crucial human association studies were identified by literature search of accessible medical and other databases (PubMed, Embase, Scopus, Bio-Med Central, Web of Science).

Over the last 10 years a great increase in association studies aiming at identification of NIHL susceptibility genes has been observed. Hundreds of single nucleotide polymorphisms (SNPs) have been screened in genes involved in different pathways and structures in the inner ear, for this reason grouped into oxidative stress genes, potassium recycling pathway genes, monogenic deafness genes and heat shock protein genes. Summary of positive human association studies results is presented in Table 1.

1.1. Oxidative stress genes

The cochlea is a metabolically active organ, oxidative stress plays therefore a major role in the pathomechanisms of NIHL. Since hair cells are highly demanding in energy during and after noise overexposure, a local prolonged release of free radicals (reactive oxygen and nitrogen species) takes place, which may lead to cochlear epithelium damage, particularly if the antioxidant defense system is not efficient enough to neutralize them.

There are two groups of antioxidant enzymes that are active in the cochlea. The first group comprises enzymes involved in glutathione metabolism, including glutathione S-transferase (GST), glutathione peroxidase (GPX1), and glutathione reductase (GSR). GST classes comprise *GSTM1* and *GSTT1* genes which show great genetic variability in humans. Up to 50% of the Caucasian population are null genotypes for *GSTM1* gene, and 25–40% of the Caucasian population are null genotypes for the *GSTT1* gene [9]. The second class of antioxidant enzymes includes the enzymes involved in the breakdown of superoxide anions and hydrogen peroxide (catalase–CAT, superoxide dismutase 1–Cu/Zn SOD1, superoxide dismutase 2–mitochondrial SOD2 and serum paraoxonase/arylesterase 2–PON2).

The results of studies on association between variations in oxidative stress genes and susceptibility to NIHL are equivocal. Rabinowitz et al. [9] analyzed *GSTM1* and *GSTT1* deletion polymorphisms in 58 noise-exposed workers. They found that carriers of *GSTM1* gene were protected from NIHL. This association is, however, regarded as a spurious one, as this study lacks sufficient power due to the small sample size. Another study of a limited sample set (94 male workers exposed to noise) analyzed polymorphisms in *PON1*, *PON2* and *SOD2* genes. The last two genes (*PON2* and *SOD2*) revealed significant associations with NIHL; again, however, these results should be interpreted with caution because of the insufficient power to detect a causative gene [10].

In much more comprehensive study performed in the Swedish workers (103 susceptible to noise and 114 resistant to noise workers selected from over 1200 subject database), none of seven oxidative stress genes, namely *GSTM1*, *GSTT1*, *CAT*, *SOD*, *GPX*, *GSR* and *GSTP1*, was shown to be a susceptibility gene for NIHL [11]. However, the same authors have shown that the effect of smoking on susceptibility to NIHL is dependent on the presence of the *GSTM1* deletion, suggesting a substantial interaction of genes and environmental factors in NIHL development [12].

Because of the evidence that oxidative stress may be an underlying mechanism of NIHL, the association of *CAT* and NIHL was re-analyzed in two large independent populations (Swedish and Polish, described above). Besides the 3 original SNPs, 9 additional variants were genotyped in order to more completely cover the gene under study. Additionally, more detailed statistics was applied, taking into account interactions of genotype and noise exposure levels. The authors indicated significant associations for 2 SNPs in both sample sets. This approach suggested that the genotype may have differential effect on noise susceptibility, depending on the noise exposure level [13].

More recent studies support the role of oxidative stress gene polymorphisms in the development of NIHL. *SOD2* SNP in the mitochondrial targeting sequence was shown to be associated with noise-induced hearing loss in Chinese workers, and again this effect was enhanced by higher levels of noise exposure [14]. Also, double blind, crossover study in 53 male workers treated with N-acetyl-cysteine supported the hypothesis that individuals carrying all genotypes with *GSTT1* null, *GSTM1* null, and *GSTP1* Ile(105)/Ile(105) are more susceptible to NIHL [15]. On the other hand, the ototoxicity of aminoglycosides, which seem to involve similar oxidative stress mechanisms, was shown to be independent of *GSTM1* and *GSTT1* gene polymorphisms [16].

1.2. Potassium-recycling pathway genes

The sensory cells of the inner ear are bathed in endolymph, the extracellular fluid rich in potassium ions that fills the scala media. K^+ is the major charge carrier for the sensory transduction and its proper recycling is of great importance for the process of hearing.

Table 1
Summary of positive human association study results on susceptibility genes for noise-induced hearing loss.

Groups of genes	Gene	Population (no.)	References
Oxidative stress genes	*GSTM1 PON2*, *SOD2 CAT*[a]	American (58), Italian (94), Swedish (205) and Polish (685)	Rabinowitz et al. [9], Fortunato et al. [10], Konings et al. [13][b]
Potassium ions recycling genes	*KCNE1*, *KCNQ4*	Swedish (218), Polish (238)	Van Laer et al. [28], Pawelczyk et al. [29]
	KCNQ1, *GJB1*, *GJB2*, *GJB4*, *KCNJ10*	Polish (238)	Pawelczyk et al. [29]
Monogenic deafness genes	*PCDH15*, *MYH14*	Swedish (215) and Polish (238)	Konings et al. [30,38]
Heat shock protein genes	*HSP70*	Chinese (194), Swedish (206), and Polish (238)	Yang et al. [37], Konings et al. [38]

[a] Only when noise exposure level is taken into account.
[b] Previous analysis in a Swedish population was negative (Carlsson et al. [11]).