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Phenotype-Genotype Correlations in Otosclerosis: Clinical Features of OTSC2

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Abstract

As part of the GENDEAF consortium, a European multi-centre otosclerotic database is under construction to collect the clinical data of as many otosclerotic patients as possible. Otosclerosis represents a heterogeneous group of heritable diseases in which different genes may be involved regulating the bone homeostasis of the otic capsule. The purpose of the GENDEAF otosclerosis database is to explore the otosclerotic phenotype more in depth. Subtle phenotypic differences otherwise not visible, may become statistically relevant in a large number of patients. Their identification can lead towards the discovery of new genes involved in the pathway of abnormal bone metabolism in the human labyrinth. As soon as one of the otosclerotic genes is identified, it would allow us to identify genotype-phenotype correlations. From other deafness genes, it is known that different mutations in the same gene may cause similar phenotypes of varying severity. Also the variability in treatment outcomes after surgery or fluoride therapy may result not only from differences in practice or surgical skill among physicians, but also on the nature of the underlying disorder. Screening large numbers of patients would make it possible to undertake clinical trials comparing different treatments. Identifying a genetic susceptibility would allow us to dissect out possible environmental factors that prevent the expression of clinical otosclerosis in those that carry the mutated gene and yet retain normal hearing.

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Otosclerosis is a disorder in which both genetic and environmental etiological factors are involved [1]. Although a limited number of large autosomal dominant families have been described, most patients occur in small families

with unclear inheritance pattern or have no prominent familial character, pointing to a complex etiology in these cases. Clinical otosclerosis has a reported prevalence of 0.3% among white adults, making it the single most common cause of hearing impairment in this population [2]. Histological otosclerosis even has a prevalence of 3.5% among white adults [3].

Otosclerosis represents a heterogeneous group of genetic diseases in which different genes may be involved regulating the bone homeostasis of the otic capsule. It is hypothesized that in response to various gene variants and environmental factors, the physiologic inhibition of bone turnover in the otic capsule is overruled resulting in a localized bone dysplasia known as otosclerosis [3]. Many different environmental factors have been implicated in the etiology of otosclerosis, including infectious causes such as measles virus, hormones (related to puberty, pregnancy and menopause), and nutritional factors (fluoride intake) [4, 5].

Large autosomal dominant otosclerosis families have been used for gene identification studies, but the first gene responsible for otosclerosis has yet to be cloned. However, five genetic loci, OTSC1–OTSC5, have been published to date, supporting the hypothesis that mutations in any of a number of genes may be capable of causing the otosclerosis phenotype. OTSC1 was mapped to chromosome 15q25–q26 in an Indian family in which hearing loss began in childhood [6]. The OTSC2 locus was mapped to a 16 cM region on chromosome 7 (7q34–36) in a large Belgian family [7]. More recently, the OTSC3 locus has been mapped to chromosome 6 in a large Cypriot family (6p21.3–22.3) [8]. The defined OTSC3 interval covers the human leukocyte antigen (HLA) region, consistent with reported associations between HLA-A/HLA-B antigens and otosclerosis. The localization of OTSC4 in an Israeli family has also recently been reported [9]. A fifth locus for otosclerosis (OTSC5) was mapped to chromosome 3q22–24 in a large Dutch family [10]. Such genetic heterogeneity has been well demonstrated for nonsyndromic sensorineural hearing loss [11].

Materials and Methods

Hearing thresholds obtained in patients from two previously published OTSC2 families were collected. Only patients with a haplotype consistent with the linkage were included. Data from 34 genotypically affected members from two families with a linkage to OTSC2 were included to investigate the phenotype-genotype correlations more in depth. The mean age of the affected members was 52 years ranging between 24 and 89 years. The male/female ratio was 15/24. All subjects had undergone a general otorhinolaryngological examination to exclude nonhereditary causes of hearing impairment. Audiograms were recorded using standard procedures. Both air and bone conduction threshold levels were recorded. Last-visit preoperative audiograms were included. To recognize the maximal effect of the disease on

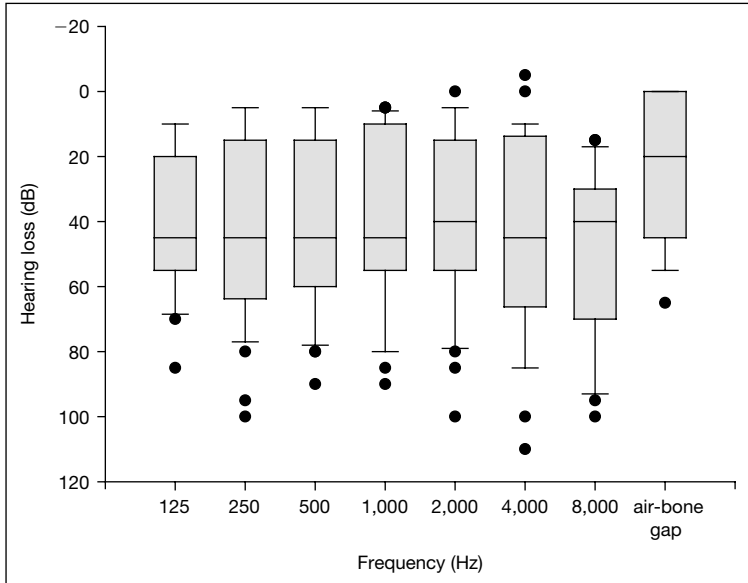


Fig. 1. Box-and-whisker plot: air conduction versus air-bone gap at 500 Hz.

hearing, only the thresholds of the worst ear were used in the statistical analysis. Pure-tone hearing thresholds were analyzed in relation to age (linear regression analysis) to construct age-related typical audiograms (ARTA) both for bone and air conduction pertaining to age 20, 30, 40, 50, 60, 70 and 80 years. Also age-related air-bone gaps (ARAB) were plotted: the air-bone gap was recalculated from the ARTA by subtracting bone from air conduction. Statistical analysis was performed with the SPSS 11.5.1 software.

Results

Data from 34 genotypically affected persons from two families were included. Linear regression analysis demonstrated only weak correlations between hearing loss and age (R^2 values for air conduction: between 0.09–0.32; R^2 values for bone conduction: between 0.05–0.31).

The air conduction thresholds per frequency as well as the air-bone gap at 500 Hz are illustrated with a box-and-whisker plot (fig. 1). Overall, the audiometric configuration was quite variable resulting in mean hearing thresholds from 250 to 8,000 Hz that were not statistically significantly different.

Figure 2 shows the ARTA for bone and air conduction as well as the ARAB. The ARTA for air conduction had a configuration that was rather flat between 250 and 4,000 Hz. The ARTA for bone conduction demonstrated a

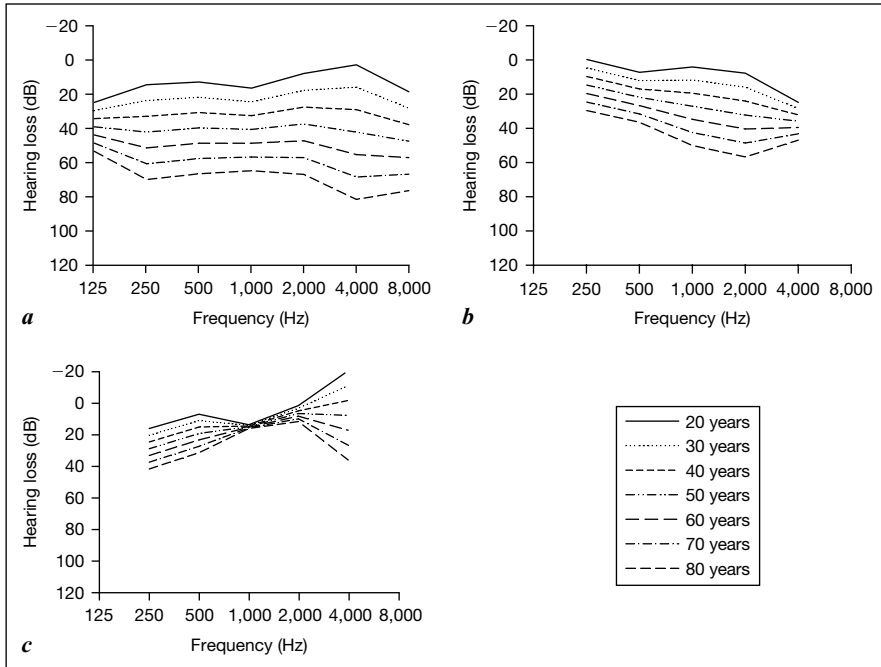


Fig. 2. ARTA and ARAB of OTSC2 patients. *a* ARTA (air conduction). *b* ARTA (bone conduction). *c* ARAB.

slight slope towards higher frequencies with a maximal deterioration/year at 2,000 Hz. Yearly deterioration was minimal at 500 Hz.

Also the annual threshold deterioration was calculated for each frequency between 250 and 4,000 Hz. The annual threshold deterioration indicated a progression of 0.37–0.82 dB/year for bone conduction and 0.81–1.32 dB/year for air conduction. On the ARAB plots, the maximal air-bone gap was situated at 500 and 4,000 Hz and the Carhart notch at 1–2 KHz was also clearly visible. The air-bone gap deterioration at 500 Hz amounted to 0.41 dB/year.

Discussion and Conclusion

The pooled data from two families segregating with the OTSC2 locus demonstrated quite variable audiometric configurations with only a limited contribution of age. Even in this monogenic form of otosclerosis, it seems that other modifying factors are implicated in the mechanism that triggers the osseous change. These results clearly illustrate the complexity of the otosclerotic disease:

the mechanism of removal of normal bone followed by its replacement by otosclerotic bone remains as yet unknown. It is hypothesized that these modifying factors may be both genetic and environmental. Further refinement of the phenotype-genotype correlation will become available as soon as the OTSC2 gene for otosclerosis is cloned and specific mutations recognized.

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