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Genetic Aspects Of Otosclerosis: Current Data On Predisposition, Candidate Genes, And Clinical Significance

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Abstract

This article presents an analytical review of current evidence on the genetic aspects of otosclerosis. Otosclerosis is considered a disorder of pathological bone remodeling of the otic capsule that most commonly causes stapes fixation and conductive or mixed hearing loss. The reviewed literature indicates that the disease is characterized by familial aggregation, autosomal-dominant inheritance with incomplete penetrance in a subset of families, and a pronounced polygenic and multifactorial background. The best-studied genetic signals involve RELN, TGFB1, BMP2, BMP4, MEPE, ACAN, SERPINF1, and FOXL1. However, several associations have not been consistently replicated across populations, highlighting substantial genetic heterogeneity. It is concluded that genetic markers cannot yet replace clinical diagnosis, but they are valuable for risk stratification in familial cases, early-onset disease, and bilateral involvement, and they provide a scientific basis for future personalized approaches.

Keywords: *otosclerosis, genetics, RELN, TGFB1, BMP2, BMP4, SERPINF1, FOXL1, ACAN, hearing loss, hereditary predisposition, genetic heterogeneity*

INTRODUCTION

Otosclerosis is a pathological process of bone tissue remodeling of the labyrinthine capsule, affecting primarily the region of the stapes footplate and leading to restricted stapedial mobility. Clinically, the disease most commonly manifests as

progressive conductive hearing loss; however, cochlear involvement may give rise to mixed or sensorineural hearing loss. According to current data, clinical otosclerosis occurs in approximately 0.30–0.38% of individuals of European descent, typically presents in adulthood, and becomes bilateral in 70–80% of patients over time.

Interest in the genetics of otosclerosis is driven by the fact that a family history is identified in approximately 40–60% of patients, and in familial forms the disease has long been regarded as autosomal dominant with incomplete penetrance and variable expressivity. At the same time, contemporary reviews emphasize that otosclerosis cannot be reduced to a single mutation or single pathogenetic pathway: it is most likely a complex disease in which hereditary predisposition, characteristics of bone metabolism, hormonal and inflammatory factors, and population-level genetic heterogeneity all converge.

The aim of the present work is to systematize current data on the genetic aspects of otosclerosis, to identify the most extensively studied genes and loci, to assess the reproducibility of reported associations, and to determine their potential clinical significance.

METHODOLOGY

This work is carried out as an analytical literature review following the IMRAD model. The article draws on contemporary publications concerning the genetics of otosclerosis, including review articles, case-control association studies, genome-wide association studies (GWAS), sequencing data, and papers dedicated to the functional interpretation of genetic variants. Priority was given to studies with clinically or surgically confirmed diagnoses, as well as to publications analyzing the reproducibility of genetic signals and differences between familial and sporadic forms of the disease.

The review encompasses works dedicated to RELN, TGFB1, BMP2, BMP4, MEPE, ACAN, SERPINF1, and FOXL1, as these genes and loci appear most frequently in contemporary genetic publications on otosclerosis. In interpreting the data, account was taken of the fact that positive signals identified in particular populations are not always replicated in other ethnic cohorts and therefore require cautious appraisal from the standpoint of the genetic heterogeneity of the disease.

RESULTS

The results of the analysis indicate that the genetic component of otosclerosis is most convincingly expressed at the level of familial aggregation and polygenic predisposition. Early genetic investigations and clinical reviews repeatedly described familial cases with an autosomal-dominant pattern of inheritance and incomplete penetrance. Subsequently, several susceptibility loci were mapped, and practical guidelines note that the disease has been associated with regions on chromosomes 6p, 9p, 1q, 3q, 6q, 7q, 15q, and 16q. For a long time, however, the causative genes within these loci remained undefined.

The most prominent reproducible signal has been RELN. In 2009, a GWAS identified an association of RELN variants with otosclerosis in European cohorts, and subsequent studies have partially supported the role of this gene. Nevertheless, the biological mechanism through which reelin influences bone remodeling of the otic capsule has remained unclear to date. A major step forward was taken in 2023, when the largest GWAS meta-analysis conducted to date — comprising 3,504 cases and 861,198 controls drawn from three biobanks — identified 27 associated loci, including the previously known RELN signal, signals in TGFB1 and MEPE, and an association in the OTSC7 region. These findings substantially broadened understanding of the hereditary architecture of the disease and confirmed its polygenic nature.

The second most compelling line of evidence concerns genes of the TGF-β signaling pathway. Associations for BMP2 and BMP4 were reported in early studies, followed by those for TGFB1. In 2013, an association between TGFB1 and predisposition to otosclerosis was demonstrated along with altered expression of this gene. In 2014, analysis of a clinically and histologically confirmed cohort again supported a link to TGFB1, although results for other genes were less consistent. In a British population, TGFB1 was shown to be associated primarily with clinically confirmed otosclerosis, whereas RELN appeared more strongly associated with familial forms — once again underscoring the genetic heterogeneity of the disease and the probable existence of several pathogenetic subtypes.

In addition to common variants, the contribution of rare and familial mutations has been discussed in recent years. For SERPINF1, rare heterozygous variants and altered expression were described in 2016 in familial cases of otosclerosis, making this gene a strong candidate. A subsequent study, however, did not confirm its

unambiguous pathogenic role, leaving the clinical interpretation of SERPINF1 contested to this day. Notably, a new study appeared in 2023 again pointing to a possible association of variants and reduced SERPINF1 expression with the disease. The data for this gene should therefore be regarded as conflicting but worthy of further investigation.

Rarer findings also merit considerable attention. In 2022, a pathogenic deletion in FOXL1 was described, interpreted by the authors as the first causative gene identified for otosclerosis in an autosomal-dominant form of the disease. Also situated within this genetic landscape is ACAN: a large study demonstrated that a broad spectrum of protective and predisposing variants in aggrecan influences susceptibility to otosclerosis. These findings are important because they extend the genetic analysis of the disease beyond a few 'classical' genes and point to the involvement of a wider network of regulators of chondrogenesis and osteogenesis.

DISCUSSION

Summarizing the evidence, it may be concluded that otosclerosis should today be regarded as a genetically complex disease with differing architectures in familial and sporadic forms. The most reliably reproduced signals are those associated with RELN and genes of the TGF-β pathway, whereas many other findings are either population-specific or require additional validation. For this reason, any overly categorical assertion about a single 'principal gene' of otosclerosis would at present be methodologically untenable.

From a clinical perspective, genetic data are already meaningful, but for now primarily as a tool for risk stratification rather than routine diagnostics. The presence of a family history, earlier disease onset, bilateral involvement, and the combination with characteristic audiological findings all increase the likelihood of hereditary predisposition. However, no single validated genetic test currently exists for routine healthcare practice that could replace clinical examination, audiometry, and imaging. A more realistic path involves the creation of multifactorial panels that incorporate family history, phenotype, and a combined set of genetic markers rather than a single SNP.

Interpopulation variability deserves particular attention. For example, in a Polish cohort, no significant association was confirmed for the examined RELN and TGFB1 variants, despite their positive results in other cohorts. This demonstrates

that the ethnic composition of the sample, differences in phenotyping, and the size of the study group substantially influence the outcomes of genetic investigations. Consequently, future studies must be multicenter in design, with clear separation of familial and sporadic forms, and must include mandatory functional verification of identified variants.

CONCLUSION

In conclusion, the genetic aspects of otosclerosis are currently described as a combination of familial predisposition, incomplete penetrance, and a polygenic hereditary architecture. The most robust evidence has accumulated for RELN, TGFB1, and TGF-β-related genes, while contemporary GWAS have substantially expanded the number of potentially significant loci. At the same time, the evidence base for certain genes, including SERPINF1, remains ambiguous, and rare findings such as FOXL1 require further confirmation in independent cohorts. The practical conclusion is that genetics is already important for understanding the pathogenesis of otosclerosis and for future personalized medicine, but for the present it should be regarded as a complement to clinical diagnosis rather than its replacement.

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