# Otosclerosis
## From Genetics to Molecular Biology

Thomas A. Babcock, MD*, Xue Zhong Liu, MD, PhD

**KEYWORDS**

• Otosclerosis • Otic capsule • Genetics • Gene • Pathophysiology

**KEY POINTS**

- Otosclerosis is considered an autosomal dominant disease with reduced penetrance but approximately 40% to 50% of all clinical cases have been reported to be sporadic with a lack of positive family history.
- Many studies propose that otosclerosis is a complex genetic disease, caused by a combination of genetic and environmental factors.
- The genetic factors demonstrated to play a role in the development of otosclerosis are involved in several molecular pathways, including bone remodeling, immunologic pathways, inflammation, and endocrine pathways.

### INTRODUCTION

Hereditary forms of conductive hearing loss consistent with clinical otosclerosis were first described in the late nineteenth century.[1,2] An understanding of the inheritance of otosclerosis was subsequently refined over the course of several years, with later studies demonstrating an autosomal dominant mode of inheritance with incomplete penetrance between 25% and 40%.[3–10] To date, although there are cases of familial clinical otosclerosis with autosomal dominant inheritance, a majority of cases do not follow a clear mendelian autosomal dominant pattern of inheritance, and approximately 40% to 50% of all clinical cases have been reported to be sporadic with a lack of positive family history.[11,12] It has been proposed that this may be due to reduced penetrance, other models of inheritance besides autosomal dominant, new mutations, phenocopies, or complex or multifactorial forms of otosclerosis caused by a combination of environmental and genetic factors.[12,13] Perhaps the most commonly accepted explanation for the development of disease in a majority of cases

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Department of Otolaryngology, University of Miami Miller School of Medicine, 1120 NorthWest 14th Street, 5th Floor, Miami, FL 33136, USA
* Corresponding author.
*E-mail address:* thomas.babcock@bhcpns.org

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is contribution from a combination of various environmental and genetic factors. The concept of a complex disease caused by a spectrum of combined environmental and genetic factors is not unique to otosclerosis; several chronic diseases, such as age-related hearing loss, Alzheimer disease, and coronary artery disease, are believed to develop in a similar fashion.[13] To this effect, over the past several years, extensive research has implicated various environmental and genetic factors in the pathophysiology of otosclerosis (**Fig. 1**). The genetic factors dmonstrated to play a role in the development of otosclerosis are involved in several molecular pathways, including bone remodeling, immunologic pathways, inflammation, and endocrine pathways. This article discusses several environmental and genetic factors that have been demonstrated to contribute to the development of otosclerosis. Chromosomal loci with disease-causing mutations that have been identified using linkage studies in familial cases of otosclerosis with clear mendelian segregation are reviewed.

## EPIDEMIOLOGY

Otosclerosis is most prevalent in white populations of European descent, with a prevalence of approximately 0.3% to 0.4%, although it is rare among African blacks.[11] Ethnic disparities in prevalence of clinical otosclerosis may be a reflection of differences in environmental and genetic factors. There has been a reported decline in the incidence of clinical otosclerosis among white populations over the past several years.[14] Perhaps further genetic and epidemiologic studies will help elucidate the ethnic disparities in disease prevalence and the pathogenesis of otosclerosis.

## BONE REMODELING IN THE OTIC CAPSULE AND OTOSCLEROSIS

The otic capsule has several unique characteristics that may be important features in the context of development of otosclerosis. It consists of an of inner endosteal layer, intermediate endochondral layer, and outer periosteal layer and arises through a process called endochondral ossification during fetal development, a process consisting of initial formation of a cartilaginous structure, which is subsequently replaced by bone.[11] After endochondral ossification, small foci of embryonic remnant called globuli interossei persist in the intermediate endochondral layer and contain quiescent

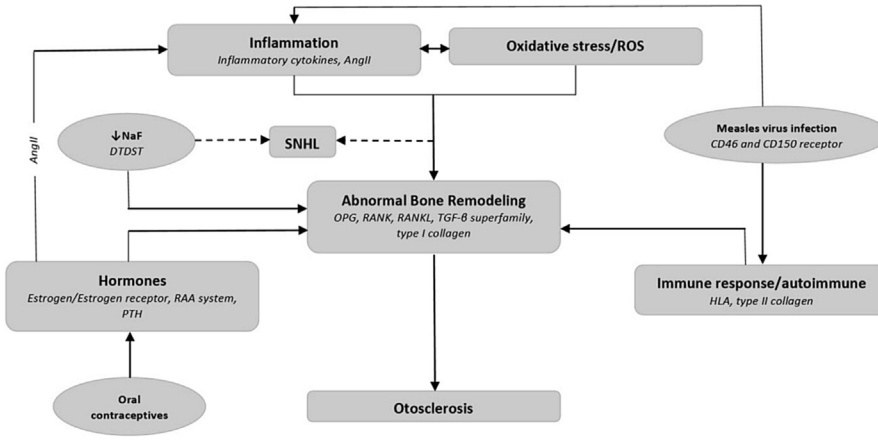


**Fig. 1.** Correlation of various environmental and molecular etiologic factors implicated in the pathogenesis of otosclerosis. AngII, angiotensin II; NaF, sodium fluoride; RAA, renin-angiotensin-aldosterone; ROS, reactive oxygen species; SNHL, sensorineural hearing loss.