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A Canadian Collaboration Identifies the First Causative Gene, FOXL1, for Otosclerosis

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Editor's note: This is a collaboration between Memorial University and Western University researchers.

A long-standing collaboration between Memorial University (Newfoundland and Labrador) and Western University (Ontario) has leveraged the power of interdisciplinary expertise and large families to identify novel hearing loss genes. Dr. Susan Stanton's hearing science research team at the National Centre for Audiology (Western University) provides expertise to Dr. Terry-Lynn Young's genetic research team at Memorial (Faculty of Medicine), contributing to both gene discovery projects and exploration of the effects of the gene throughout the auditory pathway. Clinical expertise has been an integral part of the team's success, including clinical data acquisition and interpretation, and consultation with hearing health providers. This team has also taken the unusual step of hiring a licensed clinical audiologist (Anne Griffin) whose role includes recruitment of families with multiple cases of hearing loss, auditory testing and data interpretation, assessment of clinical implications, and counselling and referral of research participants for hearing and genetic care. The interdisciplinary approach has paid dividends. This Canadian team discovered the first OTSC (otosclerosis) gene and mutation: a 15bp deletion in the *FOXL1* gene which causes autosomal dominant otosclerosis in a seven-generation family from Newfoundland and a 3-generation family from Ontario.[1]

Otosclerosis is a complex condition which presents clinically in various forms, with varied age of onset. The classical form, categorized as a low-frequency conductive hearing loss due to sclerotic bone formation around the stapes resulting in fixation, is present in approximately 0.3-0.4% of the Caucasian population[3] and is the form most readily recognized in the audiology clinical setting. Sclerotic bone formation can disrupt cochlear function as it invades the otic capsule, resulting in sensorineural hearing loss termed "cochlear otosclerosis."[4,5] Sclerotic bone growth may affect both stapes and cochlear function, resulting in mixed hearing loss.[6–9] The toxicity of sclerotic bone in the

cochlea may cause very significant deterioration of hearing to the point where cochlear implantation is the only option to improve hearing.[10-14]

It is estimated that approximately half of otosclerosis cases are heritable in nature[15] and researchers around the world have spent the past several decades investigating genetic contributions to this disorder. To date, 10 distinct genetic regions responsible for heritable forms of otosclerosis have been mapped to specific chromosomes in the human genome, using large pedigrees identified in other countries.[16–23] So far, only the *FOXL1* gene has been identified as causing autosomal dominant otosclerosis, an achievement realized by the team's synergy of genetic, clinical, and hearing science expertise. Audiology expertise was applied to recruit extended relatives and categorize hearing loss profiles from past clinical records and new assessments in both Newfoundland and Ontario. Dr. Stanton's hearing science team used conservative diagnostic criteria to distinguish otosclerosis from hearing loss due to other causes. The genetics team at Memorial was then able to compare genomes between relatives with confirmed otosclerosis and those without to find the genetic alteration shared only by the relatives with otosclerosis. Identification of the first genetic mutation to cause autosomal dominant otosclerosis is a significant breakthrough and has the power to accelerate further discoveries of genetic cause, advance new diagnostics for early detection and inform new treatment options for otosclerosis.

Of particular interest in the clinical setting, the discovery of the *FOXL1* mutation demonstrates that otosclerosis caused by the same gene and specific mutation may vary widely in type and severity of resulting hearing loss, even among members of a single family, ranging from no measurable loss to profound cochlear otosclerosis. It also highlights that family members whose hearing loss does not present as classic otosclerosis and even asymptomatic family members can be carriers and transmitters of the mutation. It is possible that hereditary otosclerosis may be present more often than suspected among clients of hearing health care.

Identification of genes causing hearing loss has the potential to inform and improve patient management, identification, and treatment, translating into huge value for families. Documentation of family history by clinicians can identify that otosclerosis may be familial and provide helpful evidence to support referrals to genetic care or clinical research. Genetic counsellors, accessed by referral according to protocols that vary from province to province, provide families with testing and information to clearly establish familial hearing loss's genetic basis and inheritance and identify family members at risk. This has immediate value for family members who want to know why hearing loss is present, how risk is transmitted and who is genuinely at risk and who is not. Once a genetic cause is discovered, all carriers' family members can be identified through genetic testing regardless of clinical symptoms. Testing for a gene known to cause familial hearing loss can accurately identify carrier status and the risk that familial hearing loss may develop. Only relatives who are genuinely at risk because they have inherited the mutation need to be monitored for the onset and progression of the familial hearing loss, eliminating any need for clinical surveillance of others. Even when the causative gene has not yet been identified, genetic counsellors can identify inheritance patterns in the family history, which helps delineate the risk of inheritance and identify family members who can benefit from future identification of the cause.

The team is committed to ensuring that research participants benefit from the research they make possible and has hired genetic counsellors to expedite genetic care for family members. In addition, the team's audiologist and genetic counsellors have developed single-page summaries of information about each newly discovered gene mutation, including the inheritance pattern and the

hearing loss it causes. These summaries are distributed to family members receiving genetic counselling as a concise tool to help them discuss the familial hearing loss gene with their hearing health clinicians and other family members. These summaries are updated as relevant information about natural history, additional risks, or new treatment becomes available. For example, the genetic summary developed for the otosclerosis gene is shown here.

Genetic-Factors-with-Hearing-LossDownload

This Canadian collaboration provided an opportunity to coordinate audiologic counselling for families with gene identification and genetic counselling and has demonstrated that care provided by audiologists can inform and be informed by genetic care. By documenting patients' hearing loss from onset through every stage of progression, audiologists help identify the natural history of a genetic hearing loss; its characteristic development over time, which is revealed in data assembled from multiple affected relatives at different stages of the lifespan. Access to information on genetic cause, inheritance pattern, and natural history can beneficially influence hearing care planning to ensure timely diagnosis and intervention strategies tailored to known features of familial hearing loss. Though the high variability of onset and presentation of otosclerosis may prevent standardization of monitoring and intervention for family members, audiologists can prepare and empower family members to recognize and access timely care for symptoms if and when they occur.

This collaboration has identified other genes[24,25] and conducted advanced auditory testing on many family members whose genetic cause is known. New collaborations and partnerships have been developed to enable further gene discoveries and study the specific effects of hearing loss genes on auditory and vestibular structure and function. The team strives for new knowledge that improves outcomes for hearing loss, achievable only by mutual contribution and learning of researchers and clinicians at every stage of the continuum from family engagement to research study to clinical care, where the benefit is returned to families.

Though over 140 genes are now known to cause hearing loss, with many more yet to be discovered, knowledge translation necessary to realize benefit for clinical and family management of hearing loss lags behind, perhaps in part because the relevance to clinical care and the value to families has not been widely communicated or appreciated. Considering the high heritability of hearing loss, this is an exciting time for the profession of audiology to consider how clinical knowledge of genetic causes and specific effects on auditory function can benefit person-centered clinical practitioners and their clients and families.

Take-Home Message

An interdisciplinary collaboration of clinicians and researchers has the power to advance our knowledge of hearing and hearing loss and improve the outcome for those experiencing hearing loss, as demonstrated by the discovery of the first otosclerosis gene. Audiologists contribute significantly to hearing loss research by documenting family history, clinical assessments, observations, interpretations, and recommendations and by making families aware of opportunities to participate in relevant research. Families can benefit from the interaction of audiologists with genetic counsellors to coordinate care and support for mutual patients. Clinicians can also have more direct roles in helping research teams to identify genes, develop opportunities for inter-professional collaboration, and translate opportunities for benefit to their patients and clinical practice. Knowledge of genetic causes and natural history can benefit families and clinicians and

create value for person-centered practice.

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