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The bewitched ear: State of the art genomics research on tinnitus

By Royce E. Clifford[a,b,c]

[a] Division of Otolaryngology – Head and Neck Surgery, School of Health Sciences, University of California San Diego, La Jolla, CA, USA
[b] Department of Research, Veteran Administration Hospital San Diego, CA, USA
[c] Visiting Scientist, Department of Environmental Science, Harvard School of Public Health, Boston MA, USA

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Whether the historical record for tinnitus dates back to a "bewitched ear" as described in a 17th Dynasty Egyptian papyrus, or to *Corpus Hippocraticum* of the 3rd century BC [1], the current quest for the mechanism, characterization, and treatment of ringing in the ears is ongoing and intense. A recent publication in *EBioMedicine*, "Burden of rare variants in synaptic genes in patient with severe tinnitus: an exome based extreme phenotype study", is the first research to use whole exome sequencing (WES) to identify genes and variants associated with tinnitus [2]. Not only does it provide researchers with new genes to replicate and explore, it augments the growing literature on the genomics of tinnitus by providing a framework for looking at rare variants and insertions-deletions (indels) in the human genome.

Tinnitus, defined as noise perceived in the absence of external sound, has a world-wide prevalence estimated at 11•9%-30•9% [3]. Even when it is not bothersome, tinnitus is comorbid with hearing loss, cognitive dysfunction, depression including the risk of suicide, neuroticism, sleep disorders, and/or anxiety, in at least half of tinnitus patients [4]. Societal costs include loss of productivity, missed days of work, time lost due to health care visits, expense of palliative treatments such as cognitive behavioural therapy, and equipment for relief from the persistent phantom sound [5]. Yet despite its pervasiveness around the world, no objective biomarker nor treatment eliminates the persistent or recurrent internal sound.

Tinnitus is a complex polygenic trait, indicating that it is associated with multiple genes each with a small, but cumulative, effect [6]. Human genomic research into tinnitus can be broadly divided into "bottom up" studies, consisting of whole genome sequencing (WGS) or WES as seen here, and "top down" studies, including genome-wide association studies (GWAS). The first technique focuses on a small area of the genome chosen because of its relevance to the pathology. In this case, the authors have begun by considering genes in the synaptome, seen to be applicable to tinnitus in brain imaging [1,7]. Using WES, they have surveyed rare gene variants and insertion-deletions with a mean allele frequency (MAF) of less than 0•05 in the population. *Amanat, et al.,* then perform fine-mapping to identify specific gene alleles associated with tinnitus in diverse aetiologies with relatively small populations of patients.

In contrast, GWAS, although able to survey the entire genome in an unbiased fashion, does not pinpoint the exact pathologic allele or alleles and because of its large sample size requirements, cannot capture rare variants, or those with MAF $<$ 0•01-0•05%. GWAS consists of a "sampling" of markers of MAF $>$ 0•01 to identify blocks of DNA that may be associated with a disorder. For a polygenic disorder such as tinnitus, where the effect size of each allele can be less than 0•01, GWAS requires hundreds of thousands of cases and controls to identify statistically significant genes. Subsequent fine-mapping in WGS or WES of the loci is then necessary to identify specific genes and alleles that have an effect on the disorder and to bring the research findings closer to the relevant clinical level of treatment and cure.

Research in the field is hampered by tinnitus' subjective nature and elusive source of generation/perception [6]. Further complicating the picture, hearing loss is thought to directly relate to cochlear sensory damage, while this phantom sound appears to be associated with multiple central neural changes in response to peripheral neural deafferentation [8]. Here the authors have highlighted the idea that tinnitus may be an end-stage of multiple etiologies, i.e. age-related and/or noise-induced in the general population, or as an endpoint to the less common Meniere's Disease. By using an "extreme phenotype," i.e. those whose lives are more severely affected by the ringing in their ears, they have identified putative genes, ANK2, AKAP9, and TSC2, associated with cytoskeleton scaffolding, axonal branching, and connectivity in neurons.

The "extreme phenotype" consists of study participants whose lives are severely affected by the noise in their ears. The Tinnitus Handicap Inventory, one of a few standardized means of assessing tinnitus, asks questions about the emotional aspects of the disorder. Questions include the effect of tinnitus on anger, confusion, cognition, desperation, loss of control, frustration, anxiety, and depression, among others [9]. Structural MRI data indicates increased connectivity between the auditory cortex and amygdala/parahippocampal regions, important in emotional memory encoding, and enhanced connectivity between Heschl's gyrus and bilateral pre-frontal lobes, crucial to executive control and regulation of emotion [10]. It will be important going forward to separate genes associated with the sound of tinnitus with its emotional and cognitive context.

E-mail address: r2clifford@health.ucsd.edu

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Ultimately, in order to complete the entire picture of the genetic architecture of tinnitus, both top-down and bottom-up approaches will be required, then further proof-of-concept evidence in the laboratory. We have our work cut out for us.

Contributions

Royce E. Clifford, MD, MPH, solely wrote this commentary, from conceptualisation and visualisation, up to and including all writing from original draft, through review, and editing.

Declaration of Competing Interests

Dr. Clifford previously was a consultant for Decibel Tx and has no other conflicts of interest.

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References

[1] Dietrich S. Earliest historic reference of 'tinnitus' is controversial. J Laryngol Otol 2004;118:487–8.
[2] Amanat S, Gallego-Martinez A, Sollini J, Perez-Carpena P, Espinosa-Sanchez JM, Aran I, et al. Burden of rare variants in synaptic genes in patients with severe tinnitus: an exome based extreme phenotype study. EBioMedicine 2021. doi: 10.1016/j.ebiom.2021.103309.
[3] McCormack A, Edmondson-Jones M, Somerset S, Hall D. A systematic review of the reporting of tinnitus prevalence and severity. Hear Res 2016;337:70–9.
[4] Shargorodsky J, Curhan GC, Farwell WR. Prevalence and characteristics of tinnitus among US adults. Am J Med 2010;123:711–8.
[5] Stockdale D, McFerran D, Brazier P, Pritchard C, Kay T, Dowrick C, et al. An economic evaluation of the healthcare cost of tinnitus management in the UK. BMC Health Serv Res 2017;17:1–9.
[6] Clifford RE, Maihofer AX, Stein MB, Ryan AF, Nievergelt CM. Novel risk loci in tinnitus and causal inference with neuropsychiatric disorders among adults of European ancestry. JAMA Otolaryngol Head Neck Surg 2020;146:1015–25.
[7] Pirooznia M, Wang T, Avramopoulos D, Valle D, Thomas G, Huganir R, et al. SynaptomeDB : an ontology-based knowledgebase for synaptic genes. Bioinformatics 2012;28:897–9.
[8] Elgoyhen AB, Langguth B, De Ridder D, Vanneste S. Tinnitus: perspectives from human neuroimaging. Nat Rev Neurosci 2015;16:632–42.
[9] Newman C, Jacobson G, Spitzer J. Development of the tinnitus handicap inventory. Arch Otolaryngol Neck Surg 1996;122:143–8.
[10] Lin X, Chen Y, Wang M, Song C, Lin B, Yuan X, et al. Altered topological patterns of gray matter networks in tinnitus: a graph-theoretical-based study. Front Neurosci 2020;14:1–12.