COMMENT

Deafness—family matters

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Knowledge on the genetics of hearing loss has spectacularly progressed over the last 30 years, as over 120 genes are today causally implicated in Non-Syndromic Hearing Loss (NSHL). This genetic heterogeneity is further increased by over 400 forms of syndromic sensorineural HL [1]. Knowing the genetic etiology of HL provides benefits for the patient regarding the disease course, as well as monitoring for other potential clinical features. It also helps to estimate the recurrence risk of the condition within a given family. Genetic testing is now included in the global monitoring of hearing loss.

This edition dedicated to the genetics of NSHL features several articles that explored affected families to (i) identify four novel candidate genes, (ii) confirm the causality of a candidate gene, and (iii) better study alterations in well-characterized HL genes.

Publishing candidate genes on their own with limited data is becoming impossible, as many editorial policies require substantial additional evidence. However, such data is still valuable as it is highly informative for the scientific community. Genmatcher is an alternative to publication but it is not used widely enough. As most of the HL genes that remain to be identified will be rarely implicated, it is only by cumulating bodies of evidence that their causality will be confirmed. In the paper from Bharadwaj et al. [2], the authors have identified 4 candidate genes in four different consanguineous families in which profound HL segregates. For each of the genes, a missense variant in the homozygous state was identified. Although these genes are expressed in neurosensory hair cell of the organ de Corti or in the spiral ganglion cells, their function is still unclear. Two of these genes are known to be involved in other diseases. In addition, as the variants identified in each of the families are all missense alterations, their causality remains to be proven. It is clear that, at this stage, the genes are tagged and additional clues should now come from the identification of other variants of interest in additional families, functional studies or animal models showing a real impact on hearing.

An example of a long-standing candidate gene is *COL4A6*, which is possibly involved in X-linked HL. A missense variant c.177G>A (p.Gly591Ser) was shown to segregate in a single family with HL in 2014 [3] but the subsequent lack of identification of other families with *COL4A6* variants have raised questions as to the causality of this gene. O'Brien and colleagues [4] report the identification of two additional *COL4A6* variants segregating in two different affected families. In the first family, a novel maternally inherited splicing *COL4A6* variant could explain the HL in the mother and a more severe phenotype in the proband, who also carries a paternally-inherited dominant *GJB2* deleterious variant. In the second family, two affected male patients presenting with severe HL carry a novel missense variant. It is important to note that the latter variant has an allele frequency of 0.1% in the Latino/Admixed American population and that 9 hemizygotes have been identified (genomAD). As a consequence, this variant should remain unclassified. This report mainly highlights the complexity of studying so-called "familial HL" as there could be several underlying etiologies, which may potentially overlap. Also audiograms are highly recommended for facilitating data interpretation. Unfortunately, the identification of the novel *COL4A6* missense variant has not resolved the origin of the HL in this family, and WES or WGS would definitely provide further insights.

In the paper from Bueno et al. [5], the authors demonstrate that in 3% of patients presenting with late onset autosomal dominant NSHL, the disease is linked to a specific variant in the *MYO3A* gene. This percentage is particularly high if one considers that it is quite difficult to identify the etiology of late-onset HL. The authors show how important it is to consider the frequency of a variant in a particular population as it has a direct impact on screening and genetic counseling. In addition, elucidating the origin of a variant is always exciting, as it can trace common ancestors between continents.

Very recently, in a previous issue, Maya et al. [6], addressed a very interesting point by raising the question of whether to report a carrier state for a recessive disorder whilst performing a microarray analysis. This question can be extended to any incidental pathogenic sequence variant identified by WES or WGS. As a pilot study, the authors used three well-known HL genes, selected with respect to their mutational spectrum, the associated phenotypes, and because their implication is not restricted to any particular ethnicity. As they underline, currently there is a lack of uniformity in recommendations and country regulations as to whether these incidental findings should be reported. The authors explicitly explain why there cannot be a uniform policy and suggest that any reporting should be based on a detailed evaluation of origin-specific variants for each gene. Additional questions are raised: (i) Should there be a cut-off in the frequency and, if so, how should it be defined? (ii) Should there be a cut off in the severity of the disease (for example, *STRC* deletions are never responsible for profound HL)? (iii) What are the implications of reporting incidental findings for the patients, their families, the genetic counseling and the laboratories performing the tests? It is not only patient care matters or ethical considerations, but also the associated costs that should be taken into consideration by public health programs. It will be most interesting to address these considerations again in a few years when the real cost of genetic testing will be better appreciated and the evolution of techniques stabilized.

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We hope you will enjoy the variety of the papers, all of which share the common purpose of improving patient testing and care.

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COMPETING INTERESTS

The author declares no competing interests.

ADDITIONAL INFORMATION

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