I read with interest the recent article by Yelverton and colleagues\(^1\) that profiles a large group of patients with hearing loss and mitochondrial mutations. The authors should be commended for the size and scope of this study; however, I feel that the study’s limitations may lead to misconceptions among some readers about this interesting and important patient group.

The authors note some limitations to their retrospective study, including a lack of controls, selection bias, and incomplete clinical information. However, they do not mention that their selective screening of only MTTS1 and MTRNR1 genes may also result in bias, especially in light of a poorly defined cohort. While I agree with the authors’ assertions that these 2 genes have so far accounted for the majority of mitochondrial nonsyndromic hearing loss, it is not clear that the study’s broad inclusion criteria have excluded those with syndromic features. This has implications not only for genetics research but also for clinicians considering a mitochondrial cause for a patient with deafness. Even if the authors had excluded syndromic cases, some have argued that focusing only on MTTS1 and MTRNR1 genes may hinder the discovery of novel variants. Other approaches have uncovered at least 5 new mitochondrial genes implicated in nonsyndromic hearing loss.\(^2\)

For the clinician, identification of additional clinical features (blindness, diabetes, ophthalmoplegia, migraine, muscle weakness) associated with mitochondrial syndromes may prompt the screening of several other mitochondrial genes.\(^3\) These features may or may not be present when the patient first develops hearing loss, resulting in a blurring of clinical boundaries between “syndromic” and “nonsyndromic” cases. Second, do the authors have any explanations for the lack of matrilineal inheritance in several cases? Given the well-established inheritance pattern of mitochondrial disease, could it be that these simplex or multiplex families represent sporadic cases? Or perhaps other factors are at play, as the authors allude to in their discussion of phenotypic variability in patients harboring the A1555G mutation. Could these findings be partly explained by variable penetrance or additional mitochondrial (or autosomal) mutations not identified by this study?\(^4\)

The role of nuclear modifiers, which would not follow a matrilineal inheritance model and alter the penetrance of mitochondrial mutations, may affect the genetic approach to diagnosis. Perhaps future studies could focus on whether the hearing loss in these patients can be attributed to mitochondrial dysfunction rather than specific mitochondrial mutations alone.

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