# Letter to the Editor

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## Reply to López-Bigas et al.

*To the Editor*:

This timely letter from López-Bigas et al. dramatically illustrates the complexity of hearing loss associated with mitochondrial mutations. In a relatively large sample of 209 families with deafness, they identified 42 families with the A1555G mutation in the *12S rRNA* gene. They demonstrate a 50% penetrance for the phenotype of deafness in all individuals who were positive for the mutation, with a wide range in the age at onset of deafness. A history of aminoglycoside exposure was noted in only 20% of their deaf subjects who were also positive for the mutation. Analysis of 42 unrelated patients with the A1555G mutation for additional mitochondrial variants, such as the G7444A substitution in the *tRNA ser* (*UCN*) gene, or for mutations in the nuclear *Connexin 26* gene were negative. Although their results clearly exclude mutations at these two loci as epistatic modifiers of the A1555G phenotype in Spain, it remains to be determined whether the G7444A mutation(s) account for variation in other populations, such as Mongolia, where a substantial proportion of patients with the A1555G substitution appear to carry the double mutation. Preliminary work in individuals who test positive for the A1555G mutation in the Chinese population has failed to reveal a mutation in the *tRNA ser* (*UCN*) gene. Another phenotypic difference in students with the A1555G/G7444A double mutation is the presence of hearing loss by age 2 years in most of our probands, compared with the later onset of deafness in the Spanish individuals who have no exposure to aminoglycosides. With widespread use of aminoglycoside antibiotics in certain developing nations, a negative history of exposure may not always be reliable. We agree that there is a need to evaluate the possible role of other compounds as well as to consider the implications of oral absorption of aminoglycosides (Kunin et al. 1960; Breen et al. 1972) in carriers of the A1555G mutation who have heightened sensitivity to ototoxicity. In a population such as Spain, where the A1555G mutation is such a frequent cause for deafness, phenotypic comparisons within even a few sets of twins could provide critical evidence of the extent to which inherited differences in nuclear or cytoplasmic modifier genes do, in fact, contribute to variation in the A1555G phenotype.

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## References

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