

This finding is consistent with a lack of penetrance of the mutation in this cohort.

On the basis of a mutation frequency of 0.19% in this population, genetic screening before aminoglycoside administration is cost-effective when balanced against the costs of lifelong deafness or the need for cochlear implantation.⁵ In this issue of the *Journal*, a letter by Vandebona et al.⁶ reports a prevalence of 0.21% for the m.1555A→G mutation in an aging population of European descent, but the prevalence of the mutation in non-European populations is unknown. Clearly, robust studies involving other ethnic groups are required to determine whether screening is appropriate.

On the basis of our findings, we recommend that elective genetic testing be performed on a case-by-case basis to prevent hearing loss, although in an acute, life-threatening situation, the best interests of the patient may require the administration of aminoglycosides before the results of genetic testing are available. Children with leukemia and patients with tuberculosis could be tested at diagnosis, and those allergic to beta-lactam antibiotics could be tested in the surgical outpatient department. Universal screening of neonates would not be effective in preventing 100% of deafness related to m.1555A→G, since admission to a neonatal intensive care unit usually occurs before such screening could take place. Screening all pregnant women for the mutation would be an alternative approach, since the mutation is maternally inherited and is almost al-

ways homoplasmic. Such an approach would not detect low levels of heteroplasmy.

Maria Bitner-Glindzicz, F.R.C.P., Ph.D.
 Marcus Pembrey, F.R.C.P., F.Med.Sci.
 Andrew Duncan, Ph.D.

UCL Institute of Child Health
 London WC1N 1EH, United Kingdom
 mbitnerg@ich.ucl.ac.uk

Jon Heron, Ph.D.
 Susan M. Ring, Ph.D.
 Amanda Hall, Ph.D.

University of Bristol
 Bristol BS8 1TH, United Kingdom

Shamima Rahman, F.R.C.P.C.H., Ph.D.
 MRC Centre for Neuromuscular Diseases
 London WC1N 3BG, United Kingdom

Supported by a grant from Sparks, the Children's Medical Research Charity. The U.K. Medical Research Council, the Wellcome Trust, and the University of Bristol provide core support for ALSPAC.

1. Hu DN, Qui WQ, Wu BT, et al. Genetic aspects of antibiotic induced deafness: mitochondrial inheritance. *J Med Genet* 1991; 28:79-83.
2. Hutchin T, Haworth I, Higashi K, et al. A molecular basis for human hypersensitivity to aminoglycoside antibiotics. *Nucleic Acids Res* 1993;21:4174-9.
3. Estivill X, Govea N, Barceló E, et al. Familial progressive sensorineural deafness is mainly due to the mtDNA A1555G mutation and is enhanced by treatment of aminoglycosides. *Am J Hum Genet* 1998;62:27-35.
4. Jones RW, Ring S, Tyfield L, et al. A new human genetic resource: a DNA bank established as part of the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC). *Eur J Hum Genet* 2000;8:653-60.
5. Bitner-Glindzicz M, Rahman S. Ototoxicity caused by aminoglycosides. *BMJ* 2007;335:784-5.
6. Vandebona H, Mitchell P, Manwaring N, et al. Prevalence of mitochondrial 1555A→G mutation in adults of European descent. *N Engl J Med* 2009;360:642-4.

Prevalence of Mitochondrial 1555A→G Mutation in Adults of European Descent

TO THE EDITOR: Sensorineural hearing loss is the most common type of sensory impairment worldwide.¹ We have found that pathogenic mitochondrial DNA (mtDNA) mutations, such as the m.3243A→G mutation associated with mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), are prevalent and can cause sensorineural hearing loss in adults of European descent.² Polymorphisms within mtDNA can modify a patient's risk of hearing loss.³ The m.1555A→G mutation, which is located in the 12S ribosomal RNA gene of the mitochondrial ge-

nome, is known to cause hearing loss, especially after exposure to aminoglycoside antibiotics.⁴

We prospectively collected audiologic data and DNA from blood and hair-follicle samples from 2856 subjects over the age of 49 years who were noninstitutionalized permanent residents of two suburban areas west of Sydney (known as the Blue Mountains Hearing Study cohort)² and screened them for the m.1555A→G mutation, using polymerase-chain-reaction-restriction-fragment-length polymorphism techniques. We also carried out mitochondrial DNA haplogroup

analysis (for details, see the Supplementary Appendix, available with the full text of this letter at NEJM.org).

Of the 2856 subjects, 6 had homoplasmic m.1555A→G mutations, providing a population prevalence of 0.21% (95% confidence interval, 0.08 to 0.46). According to family history obtained by interview, none of the mutation carriers were related to one another, either genetically or by marriage. Two of them belonged to mtDNA haplogroup U, two to mtDNA haplogroup J, and one to mtDNA haplogroup H. The haplotype on which the mutation of the sixth carrier occurred could not be determined. All six carriers had audiologic evidence of sensorineural hearing loss in at least one ear (Fig. 1, and tables in the Supplementary Appendix). All carriers reported having had no exposure to aminoglycosides.

We performed multiple linear regression analysis with adjustment for age, sex, and other risk factors for hearing loss, such as a family history of hearing loss, occupational noise exposure, and a history of type 2 diabetes. Mean auditory thresholds were calculated for each ear, given that two mutation carriers had asymmetrical hearing loss, a feature typical of mitochondrial hearing loss.⁵ After adjustment for these variables, mean auditory thresholds were significantly higher in three of the six carriers than in the general population (Fig. 1, and the Supplementary Appendix). The subject who was exposed to ototoxic drugs (quinine and furosemide) had the earliest age of onset (58 years) and the longest duration of hearing loss (>20 years).

We conclude that the m.1555A→G mutation affects about 1 in 500 subjects in our population-based cohort and independently causes sensorineural hearing loss. The population prevalence of the m.1555A→G mutation in our sample is nearly identical to that reported in this issue of the *Journal* in a letter by Bitner-Glindzicz et al.,⁶ who genotyped British children of European descent. The population prevalence of the m.1555A→G mutation is similar to that of the MELAS m.3243A→G mutation,² for a combined prevalence of about 1 in 250. These data indicate that mtDNA mutations may be a common genetic cause of sensorineural hearing loss in persons of European descent.

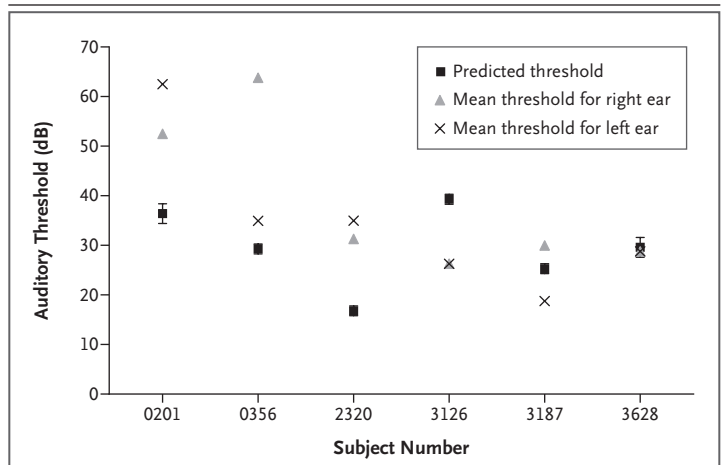


Figure 1. Mean Auditory Thresholds for Six Subjects with the m.1555A→G Mutation, as Compared with Predicted Thresholds.

Predicted values were calculated from the estimated regression equation for the general population. The variables that were included in the regression model were age, sex, a family history of hearing loss, occupational noise exposure, and a history of type 2 diabetes. The error bars indicate 95% confidence intervals. Three of the six carriers of the m.1555 A→G mutation (Subjects 0201, 0356, and 2320) show a significant increase in the auditory threshold for both ears, as compared with the predicted mean auditory thresholds.

Himesha Vandebona, Ph.D.

University of Sydney Kolling Institute for Medical Research
Sydney, NSW 2065, Australia

Paul Mitchell, M.D., Ph.D.

University of Sydney Centre for Vision Research
Sydney, NSW 2145, Australia

Neil Manwaring, Ph.D.

Kate Griffiths, B.Sc.

University of Sydney Kolling Institute for Medical Research
Sydney, NSW 2065, Australia

Bamini Gopinath, Ph.D.

Jie Jin Wang, M.Med., Ph.D.

University of Sydney Centre for Vision Research
Sydney, NSW 2145, Australia

Carolyn M. Sue, M.B., B.S., Ph.D.

University of Sydney Kolling Institute for Medical Research
Sydney, NSW 2065, Australia
csue@med.usyd.edu.au

Supported by grants (302166, 975159, 991047, and 211069) from the Australian National Health and Medical Research Council and the Australian Brain Foundation.

Dr. Mitchell reports receiving consulting fees from Novartis, Pfizer, and Solvay Pharmaceuticals, lecture fees from Novartis and Solvay Pharmaceuticals, and grant support from Pfizer. No other potential conflict of interest relevant to this letter was reported.

1. Bitner-Glindzic M. Hereditary deafness and phenotyping in humans. *Br Med Bull* 2002;63:73-94.
2. Manwaring N, Jones MM, Wang JJ, et al. Population prevalence of the MELAS A3243G mutation. *Mitochondrion* 2007;7:230-3.
3. Manwaring N, Jones MM, Wang JJ, et al. Mitochondrial DNA haplogroups and age-related hearing loss. *Arch Otolaryngol Head Neck Surg* 2007;133:929-33.
4. Prezant TR, Agopian JV, Bohlman MC, et al. Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness. *Nat Genet* 1993;4:289-94.
5. Sue CM, Lipsett LJ, Crimmins DS, et al. Cochlear origin of hearing loss in MELAS syndrome. *Ann Neurol* 1998;43:350-9.
6. Bitner-Glindzic M, Pembrey M, Duncan A, et al. Prevalence of mitochondrial 1555A→G mutation in European children. *N Engl J Med* 2009;360:640-2.

Correspondence copyright © 2009 Massachusetts Medical Society.

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication, subject to editing and abridgment, provided they do not contain material that has been submitted or published elsewhere. Please note the following:

- Letters in reference to a *Journal* article must not exceed 175 words (excluding references) and must be received within 3 weeks after publication of the article. Letters not related to a *Journal* article must not exceed 400 words. All letters must be submitted over the Internet at authors.NEJM.org.
- A letter can have no more than five references and one figure or table.
- A letter can be signed by no more than three authors.
- Financial associations or other possible conflicts of interest must be disclosed. (Such disclosures will be published with the letters. For authors of *Journal* articles who are responding to letters, this information appears in the published articles.)
- Include your full mailing address, telephone number, fax number, and e-mail address with your letter.

Our Web site: authors.NEJM.org

We cannot acknowledge receipt of your letter, but we will notify you when we have made a decision about publication. Letters that do not adhere to these instructions will not be considered. Rejected letters and figures will not be returned. We are unable to provide prepublication proofs. Submission of a letter constitutes permission for the Massachusetts Medical Society, its licensees, and its assignees to use it in the *Journal's* various print and electronic publications and in collections, revisions, and any other form or medium.