# Letters

OBSERVATION

## A Patient With *DNMT1* Gene Mutation Presenting With Polyneuropathy, Hearing Loss, and Personality Changes

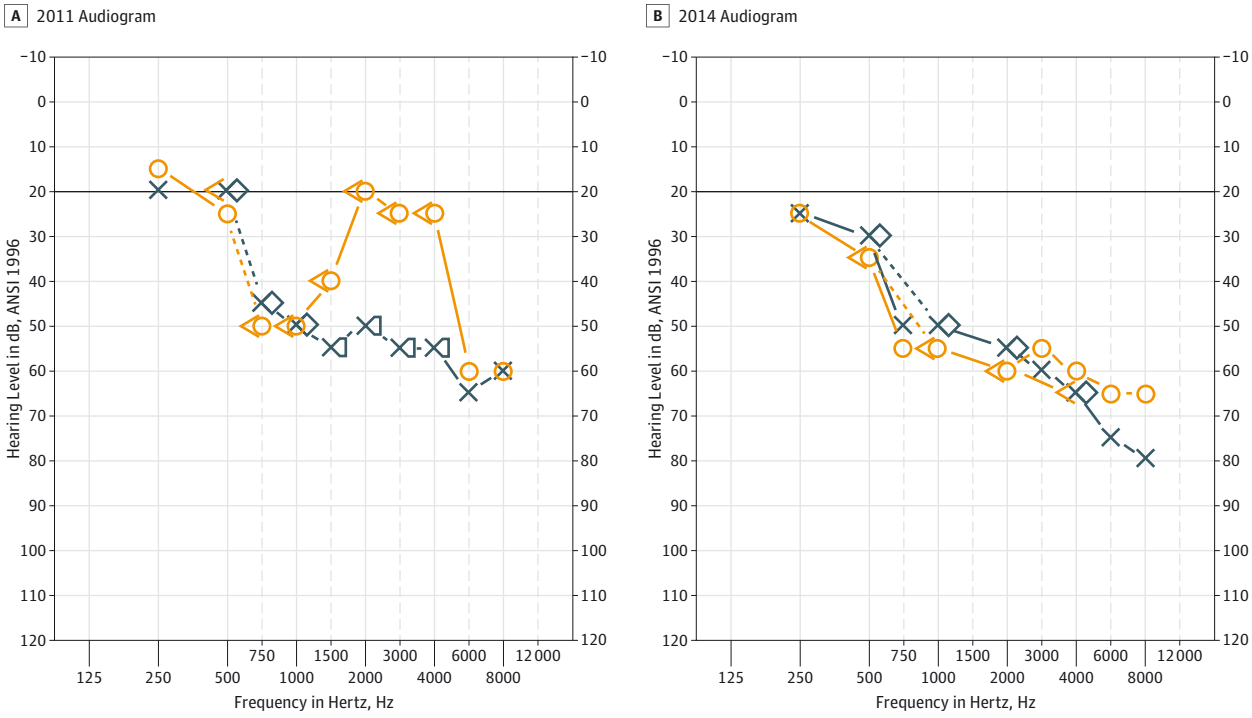
Hereditary sensorineural hearing loss can be syndromic or nonsyndromic. Genetic causes of hearing loss must be distinguished from acquired causes for purposes of genetic counseling. Next-generation sequencing (NGS) panels are now used widely in clinical settings to try to identify genetic causes of hearing loss.

**Report of a Case** | A woman in her 40s was initially referred to our neuromuscular clinic for polyneuropathy and hearing loss. On examination, she was inappropriately happy and indifferent. Her neurologic examination was notable for clinically significant sensory loss to pinprick, vibration, and position sensation distally in the upper and lower extremities and symmetric hyporeflexia. A nerve conduction study showed severe sensory neuropathy, with absent potentials in upper and lower extremity. Common causes of neuropathy, such as inflammatory, vitamin deficiencies, diabetes mellitus, alcoholism, and paraneoplastic and immune-mediated causes, were considered and excluded by appropriate studies.

An otolaryngology consultation was obtained for her associated hearing loss. She reported a 5-year history of hearing loss and denied having significant noise exposure or family history of hearing loss. A hearing test performed at onset of her hearing loss demonstrated right-ear mid-frequency moderate sensorineural hearing loss between the frequencies of 500 and 2000 Hz. In the left ear there was moderately severe mid- and high-frequency hearing loss. Asymmetry between the ears was noted in the high frequencies between 1500 and 4000 Hz with the left ear having 30-dB HL worse hearing loss. (**Figure 1**A)

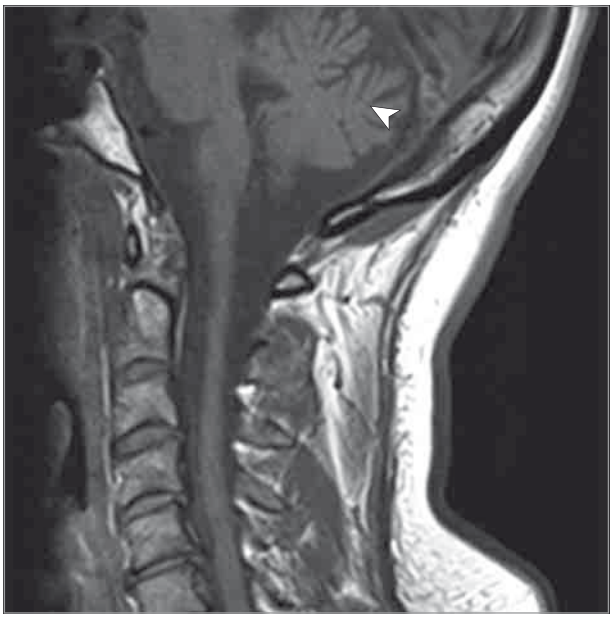
Progressive and asymmetric hearing loss in adulthood led to consideration of autoimmune inner ear disease or a retrocochlear lesion. Results from a workup for autoimmune inner ear disease were negative. Magnetic resonance imaging of the head was negative for a retrocochlear lesion but showed cerebellar atrophy (**Figure 2**). At the time of her initial hearing test, the audiometric configuration in her right ear demonstrated mid-frequency sensorineural hearing loss or "cookie

Figure 1. Audiograms




A, The audiogram from 2011 demonstrates asymmetric mid- and high-frequency hearing loss in left ear (blue) worse than right ear (yellow). B, The audiogram from 2014 demonstrates worsening of right ear (yellow) hearing loss to match left ear (blue) hearing loss.

Figure 2. Brain Magnetic Resonance Image Demonstrating Cerebellar Atrophy



The arrowhead indicates the cerebellar atropy.

bite," which suggests a potential genetic cause of hearing loss (Figure 1A). At the last evaluation, her hearing loss had progressed to symmetrical mid- and high-frequency sensorineural hearing loss (Figure 1B), necessitating use of bilateral hearing aids.

To summarize, our patient, a woman in her 40s, presented with a 5-year history of slow, progressive sensory loss; aberrant affect; and early-onset progressive sensorineural hearing loss. Hereditary sensory and autonomic neuropathies (HSANs) were considered as a potential explanation of her symptoms.

Genetic testing for Hereditary Neuropathy Panel (GeneDx) confirmed the presence of a known pathogenic mutation in the *DNMT1* gene (c.1532 A>G p.Tyr511Cys), consistent with hereditary sensory and autonomic neuropathy with dementia and hearing loss (HSAN type 1E [HSAN1E]). Absence of family history of similar complaints suggested a de novo mutation.

**Discussion** | HSAN1E is an autosomal dominant disorder characterized by progressive dementia, sensory polyneuropathy, autonomic dysfunction (including sudomotor loss), and sensorineural hearing loss. It is caused by *DNMT1* mutation.[1,2] DNA methyltransferase 1 (DNMT1) is a molecule needed for DNA methylation, and individuals with pathogenic mutation in HSAN1E have been found to have global hypomethylation of DNA.[3] Individuals with mutations are typically normal in young age and progress to have severe sensory loss, sensorineural hearing loss, and dementia (similar to frontotemporal dementia) by the fourth decade of life.[3,4]

Our patient presented initially with a classic mid-frequency hearing loss suggesting a genetic cause of hearing loss.[5] This case report highlights the pattern of hearing loss of patients with HSAN1E. In a case series by Klein et al,[2] 11 of 18 patients initially presented with hearing loss alone and subsequently developed other clinical symptoms. Therefore, otolaryngologists and audiologists, when presented with patients with early-onset hearing loss with a genetic pattern, should be vigilant for symptoms that may distinguish patients who could have this rare cause of hearing loss with a poor prognosis.

Treatment of HSAN1E is based on symptoms. Because it is inherited in an autosomal dominant manner, children of affected individuals have a 50% chance of inheriting the pathologic mutation.

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**Published Online:** January 7, 2016. doi:10.1001/jamaoto.2015.3137.

**Conflict of Interest Disclosures:** None reported.

1. Baets J, Duan X, Wu Y, et al. Defects of mutant *DNMT1* are linked to a spectrum of neurological disorders. *Brain*. 2015;138(pt 4):845-861.

2. Klein CJ, Botuyan MV, Wu Y, et al. Mutations in *DNMT1* cause hereditary sensory neuropathy with dementia and hearing loss. *Nat Genet*. 2011;43(6):595-600.

3. Sun Z, Wu Y, Ordog T, et al. Aberrant signature methylome by *DNMT1* hot spot mutation in hereditary sensory and autonomic neuropathy 1E. *Epigenetics*. 2014;9(8):1184-1193.

4. Willems PJ. Genetic causes of hearing loss. *N Engl J Med*. 2000;342(15):1101-1109.

5. Shah RK, Blevins NH, Karmody CS. Mid-frequency sensorineural hearing loss: aetiology and prognosis. *J Laryngol Otol*. 2005;119(7):529-533.

## COMMENT & RESPONSE

## Repetitive Transcranial Magnetic Stimulation and Tinnitus—Still a Noisy Issue

**To the Editor** Regarding the recently published, randomized clinical trial by Folmer et al,[1] using 1-Hz repetitive transcranial magnetic stimulation (rTMS) applied to the temporal cortex in patients with tinnitus for 10 days compared with placebo, the authors[1] reported a significant reduction in tinnitus symptoms, the primary outcome measure. However, rTMS for tinnitus is still not significantly beneficial, so we have some considerations to share:

1. Most of the randomized, sham controlled studies on rTMS for chronic tinnitus used similar, short protocols: low-frequency stimulation to the temporal cortex for 10 days or less (5 days), with some benefit in tinnitus severity and an-