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Gradual Symmetric Progression of DFNA34 Hearing Loss Caused by an *NLRP3* Mutation and Cochlear Autoinflammation

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Abstract

Objective—To characterize the audiometric phenotype of autosomal dominant DFNA34 hearing loss (HL) caused by a missense substitution in the *NLRP3* gene. *NLRP3* encodes a critical component of the NLRP3 inflammasome that is activated in innate immune responses.

Study Design—This study was conducted under protocol 01-DC-0229 approved by the NIH Combined Neurosciences IRB. We performed medical and developmental history interviews and physical and audiological examinations of affected individuals with DFNA34 HL caused by the p.Arg918Gln mutation of *NLRP3*. We retrospectively reviewed audiological reports, when available, from other health care centers.

Setting—Federal biomedical research facility.

Subjects—Eleven members of a North American family segregating p.Arg918Gln.

Main Outcome Measures—Pure-tone thresholds, rates of pure-tone threshold progression, and speech discrimination scores.

Results—Eight subjects had bilateral sensorineural HL with an onset in the late 2nd to 4th decade of life. Slowly progressive HL initially primarily affected high frequencies. Low and middle frequencies were affected with advancing age, resulting in moderate HL with a downsloping audiometric configuration. The average annual threshold deterioration was 0.9 to 1.5 dB/year. Speech recognition scores ranging from 60–100% were consistent with cochlear, but not retrocochlear, etiology. Three subjects (16, 22, and 32 years old) had normal hearing thresholds.

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CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

Conclusions—DFNA34 HL has an onset during early adulthood and progresses approximately 1.2 dB/year.

Keywords

Cryopyrin-associated periodic syndromes; DFNA34; Hearing loss; Innate immunity; Interleukin-1 β ; *NLRP3*

INTRODUCTION

The *NLRP3* gene encodes NLRP3 protein also referred to as cryopyrin, a key component of the NLRP3 inflammasome whose activation results in secretion of the proinflammatory cytokine interleukin-1 β (IL-1 β) (1). Gain-of-function mutations of *NLRP3* are known to cause autosomal dominant systemic autoinflammatory disease, termed cryopyrin-associated periodic syndromes (CAPS), by constitutive activation of the NLRP3 inflammasome leading to increased IL-1 β production and secretion (2-4). CAPS include three clinical disorders: neonatal-onset multisystem inflammatory disease (NOMID), Muckle-Wells syndrome (MWS) and familial cold autoinflammatory syndrome (FCAS). These disorders share a number of common symptoms and signs, including recurrent fevers, urticaria, headache, conjunctivitis, arthralgia and arthritis, with different levels of severity and duration of episodes. Hearing loss and aseptic meningitis are features of NOMID and MWS, but are rarely observed in FCAS (5, 6). Although the details of the pathogenesis of HL in NOMID or MWS patients remain unknown, there is pathologic enhancement of the cochlea on post-contrast magnetic resonance imaging with fluid-attenuation inversion recovery (MRI-FLAIR). This result has been interpreted to reflect cochlear inflammation as a result of constitutive activation of the NLRP3 inflammasome (5, 7). Anakinra, a non-glycosylated recombinant version of the human IL-1 receptor antagonist, significantly improves clinical symptoms and inflammatory markers in patients with NOMID, MWS and FCAS (7-9).

Recently, we reported that a gain-of-function mutation, c.2753G>A (p.Arg918Gln), in *NLRP3* causes nonsyndromic DFNA34 HL in North American Caucasian family LMG113 (10). On post-contrast MRI-FLAIR, pathologic enhancement of the cochlea was identified in an affected individual, similar to but less severe than that observed in the patients with NOMID or MWS. These findings indicated that DFNA34 HL was caused by cochlear autoinflammation. There were also asymptomatic low-grade elevations of serologic markers of inflammation. The purpose of this study was to characterize the auditory phenotype associated with this novel variant of CAPS.

SUBJECTS AND METHODS

This study included 11 members from four generations of family LMG113 carrying the p.Arg918Gln mutation of *NLRP3*. This study was approved by the Combined Neurosciences Institutional Review Board of the National Institutes of Health, Bethesda, Maryland. A written informed consent for this study was obtained from the participants or their parents or guardians. The details for the audiometric examination and data analyses are described in Supplementary Information.

RESULTS

Otologic history and examination

Eight heterozygous carriers of p.Arg918Gln from the second and third generations, ranging in age from 32 to 74 years old, reported gradual, symmetric and progressive HL. The reported ages of onset of HL varied from the late 2nd to 4th decade of life. All affected individuals used auditory-verbal communication. Hearing aids were reported to provide significant subjective benefit for their auditory and speech perception. None of the individuals had received a cochlear implant. There were no external or middle ear abnormalities detected by otoscopy.

Auditory evaluation

All of the 8 affected subjects (1192, 1301, 1236, 1191, 1285, 1189, 1183 and 1194) from the second and third generations, except for subject 1189, had bilateral, symmetric sensorineural HL (Fig. 1). High-frequency HL was observed with a down-sloping audiometric configuration in younger subjects, 1192 and 1236, whereas a flat audiometric configuration was observed in an older subject, 1183. Pure-tone audiometry did not reveal a significant air-bone gap in any affected individuals. Acoustic immittance was within normal ranges in all tested ears. The acoustic reflex was elicited, even when the averaged hearing thresholds were more than 50 dB HL, supporting a probable cochlear origin of HL. Distortion product otoacoustic emissions (DPOAEs) were absent in subject 1189, consistent with a cochlear origin of HL. For the other affected subjects, DPOAEs were not examined.

The fourth generation of LMG113 included nine individuals. Three of these individuals (subjects 1196, 1239 and 1238), ranging from 16 to 32 years of age, had p.Arg918Gln. All 3 individuals had normal hearing (Fig. 1).

Air-conduction pure tone thresholds of the 11 heterozygous carriers of p.Arg918Gln were plotted separately for each stimulus frequency to generate a linear regression line representing the progression rate (dotted line in Fig. 2), designated as annual threshold deterioration (ATD). The calculated ATD was 0.9 dB/year for 0.25 and 0.5 kHz, 1.2 dB/year for 1 and 2 kHz, 1.4 dB/year for 4 kHz, and 1.5 dB/year for 8 kHz. The ATD of the pure-tone average (0.5/1/2/4 kHz) was 1.2 dB/year.

The age-related typical audiogram (ARTA) was derived from the trend curve (broken line in Fig. 2) obtained by applying non-linear regression analysis to the plotted pure tone thresholds (Fig. 3A). The threshold values for low-frequency stimuli showed greater progression than those for high frequencies at older ages.

Speech discrimination scores (SDSs) of the 8 affected individuals were plotted in relation to age to establish a linear regression line representing the deterioration rate (dashed line in Fig. 4A). The age at onset of deterioration, defined as the age at SDS=90%, was 35 years with a deterioration rate of 0.4%/year. Speech discrimination scores plotted relative to the pure-tone averages (1/2/4 kHz) were within a boundary (broken) line encompassing 98% of SDSs examined in 324 individuals with cochlear HL (11), indicating a probable cochlear origin of HL (Fig. 4B).

DISCUSSION

Here we describe the auditory characteristics of DFNA34 HL caused by the p.Arg918Gln mutation of *NLRP3*. The age at onset of HL varied from the late 2nd to 4th decade of life with $ATD_{0.5/1/2/4 \text{ kHz}}$ of 1.2 dB HL/year. These findings indicate that DFNA34 HL has a late onset and moderate rate of progression in comparison with DFNA phenotypes. High frequency HL can be caused by mutations in a number of different DFNA genes including *KCNQ4* (DFNA2), *DFNA5* (DFNA5), *COCH* (DFNA9), *POU4F3* (DFNA15), *ACTG1* (DFNA20/26) and *TMC1* (DFNA36) (12-17). The calculated $ATD_{0.5/1/2/4 \text{ kHz}}$ of these DFNA HL are as the followings: DFNA2, 0.7 dB HL/year; DFNA5, 1.0 dB HL/year; DFNA9, 1.6 dB HL/year; DFNA15, 1.2 dB HL/year; DFNA20/26, 1.7 dB HL/year; DFNA36, 1.9 dB HL/year (calculated from audioprofiles in AudioGene) (18).

A study of 57 individuals with all types of CAPS disorders found that sensorineural was the most common type of HL as opposed to conductive or mixed; high frequency thresholds are typically affected; HL progressively declined with the age; and hearing thresholds in NOMID patients were worse than those in MWS patients (5). Another study of 33 MWS individuals showed that 22 patients had bilateral progressive sensorineural HL that initially affected primarily high frequencies, although rates of progression of HL varied in groups of patients depending on their *NLRP3* mutations (9). A recent report described the auditory characteristics of a Dutch family (W07-1001) with MWS caused by a heterozygous substitution, p.Tyr859His, in *NLRP3*. The affected individuals showed bilateral symmetric progressive sensorineural HL initially affecting the high frequencies. The age at onset of HL varied from 4 to 25 years of age, with an ATD of 1.3 to 1.8 dB/year. The ARTA of W07-1001 is shown in Fig. 3B (19). In combination with the auditory characteristics of DFNA34, HL associated with *NLRP3* mutations has been characterized by bilateral progressive sensorineural HL initially affecting the high frequencies, although the age at onset and the severity have been variable.

CONCLUSION

DFNA34 HL is caused by a mutation in the *NLRP3* gene, encoding a critical protein for the function of the NLRP3 inflammasome and innate immunity. DFNA34 HL has an onset during early adulthood and progresses approximately 1.2 dB/year.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.
Pure-tone thresholds for LMG113 members carrying the p.Arg918Gln mutation of *NLRP3*.
Air-conduction hearing thresholds are shown for the better-hearing ear.

Fig. 2.

Collective longitudinal and cross-sectional air-conduction hearing thresholds for each stimulus frequency. Hearing thresholds for individuals are shown with distinctive symbols and connected with unbroken lines. Dotted lines represent the cross-sectional linear regression lines. Broken lines represent the cross-sectional regression curves fitted to hearing thresholds of each individual.

Fig. 3.

Age-related typical audiograms (ARTAs) of family LMG113 with DFNA34 HL and family W07-1001 with Muckle-Wells syndrome (19). (A) In family LMG113, data was only available for subjects in the 2nd decade of life and older. Hearing loss progressed with an annual threshold deterioration (ATD) of 0.8 to 1.5 dB/year. The ARTA of family LMG113 was derived from cross-sectional regression curves in Fig. 2. (B) In family W07-1001, HL progressed with an ATD of 1.3 to 1.8 dB/year (19).

Fig. 4. Maximum speech discrimination scores (SDSs) of the 8 affected members of LMG113 plotted as a function of age and of pure tone average (1/2/4 kHz). (A) The age at onset of deterioration, defined as the age at SDS=90%, was 35 years with a deterioration rate of 0.4%/year. The SDS for each individual is shown by different symbols. Broken line represents cross-sectional regression line. (B) The SDSs plotted against the pure-tone averages were located within a boundary (broken) line encompassing 98% of SDSs examined in 324 individuals with cochlear HL (11), indicating the probable cochlear origin of HL in DFNA34.