LETTER TO JMG

Genetic homogeneity and phenotypic variability among Ashkenazi Jews with Usher syndrome type III

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Usher syndrome (USH) is an autosomal recessive disorder comprising of bilateral sensorineural hearing loss, progressive loss of vision due to retinitis pigmentosa (RP), and variable vestibular dysfunction. It is the most frequent cause of deafness and concurrent blindness in schools for the deaf-blind,[1] with a prevalence of 1/16 000 to 1/50 000 in various populations.[2] The majority of Usher syndrome cases can be clinically classified into three subtypes.[3 4] USH type I (USH1; OMIM 276900, 276903, 276904, 601067, 602097, 602083 and 606943) is characterised by profound prelingual sensorineural hearing loss, vestibular areflexia, and prepubertal onset of RP. USH type II (USH2; OMIM 276901, 276905 and 605472) is characterised by moderate to severe hearing impairment, no vestibular impairment, and onset of RP in the first or second decade of life. USH type III (USH3; OMIM 276902) is characterised by progressive, post-lingual hearing loss, variable onset and severity of RP, with or without vestibular dysfunction. Atypical forms of Usher syndrome associated with mutations in *USH1B* and *USH1D* have also been reported.[5–7] There is progression of hearing loss in some of these atypical cases, making them potentially difficult to clinically distinguish from USH3.

USH3 was originally thought to be very rare, accounting for at most a few percent of the total USH population, until Pakarinen and coworkers found that up to 40% of the USH cases in Finland were consistent with USH3.[4] Difficulty in accurately detecting the progression of hearing loss may account for the lower frequency of reported USH3 cases outside of Finland. In the Finnish USH3 cohort, hearing loss was diagnosed before the age of 10 years in most patients, but up to the age of 40 years in some patients, with moderate to severe hearing threshold elevations at the time of detection. The mean hearing threshold (80 dB HL) in the USH3 cohort was lower than that in USH1 but higher than in USH2. The rate of progression varied greatly, with 42% of patients having final hearing thresholds greater than 90 dB HL (profound), and the time interval since onset of hearing loss significantly correlated with the final hearing level.[4 8] Vestibular function was abnormal in 50% of the patients.[4 8] Average age of diagnosis of RP in the Finnish cohort ranged from 3 to 51 years (mean 17 years) with both visual fields and visual acuity reaching minimal levels by 40 years of age and progression of visual acuity loss not significantly differing from the other USH types.[8] Similarly, visual findings are not useful for differentiating between USH1 and USH2.[9] It thus appears that progression of hearing loss is the key discriminatory feature between USH3 and USH1 or USH2.

One USH3 locus, *USH3A* on chromosome 3q25, has been identified.[10] *USH3A* expression has been detected in the cochlea and retina, although its function is unknown.[11 12] Nine mutations causing disease have so far been identified in *USH3A*.[10–12] Y176X (also referred to as Fin$_{major}$) is a nonsense mutation responsible for most of the USH3 cases among

Key points

- Usher syndrome type III (USH3) is an autosomal recessive disorder characterised by progressive hearing loss, retinitis pigmentosa, and variable peripheral vestibular dysfunction.

- Sixteen (40%) of a cohort of 40 Ashkenazi Jewish subjects with Usher syndrome were clinically classified as USH3, all of whom were homozygous for the N48K mutation of *USH3A*.

- The carrier frequency of N48K was 0.7% (95% CI 0 to 1.6%) among Ashkenazi Jews from the New York area, with a predicted USH3 prevalence of 1.2 per 100 000.

- N48K homozygotes displayed a wide range of phenotypic severities.

- Genetic testing for N48K in Ashkenazi Jews will prove helpful in diagnosing USH3 in infants and young children and in distinguishing it from other forms of Usher syndrome.

Finns, and haplotype analysis suggests that it is a founder mutation in the Finnish population.[10 12] Other mutant alleles of *USH3A* include missense, deletion, and insertion mutations. 143T→G, a mutation in codon 48 that causes the substitution of lysine for asparagine (N48K), disrupts the only N glycosylation consensus site of the *USH3A* translation product, clarin-1.[11] N48K has been detected in 12 Ashkenazi Jewish USH3 patients from 10 unrelated families; eleven patients were homozygotes and the twelfth proband was a compound heterozygote.[11 12] Haplotype analysis suggested that N48K is a founder mutation,[11 12] and it was found in one of 221 control chromosomes from Ashkenazi Jews.[11] The aim of our study was to evaluate the clinical phenotype and genetic basis of USH3 in the Ashkenazi Jewish population.

MATERIALS AND METHODS
Subjects
Ashkenazi Jewish subjects with Usher syndrome were ascertained through the National Institute on Deafness and Other Communication Disorders (NIDCD), Mount Sinai School of Medicine, Sackler School of Medicine at Tel Aviv University, and the Center for Deaf-Blind Persons in Israel as part of an IRB approved study of Usher syndrome in the

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Abbreviations: RP, retinitis pigmentosa; USH, Usher syndrome

Ashkenazi Jewish population (NINDS/NIDCD joint IRB, 97-DC-0180; Mount Sinai, 01-0124 HG; Helsinki Committee of Tel Aviv University). Informed consent was obtained from all participants. Affected individuals or their parents completed a questionnaire and an interview by one of the investigators (SLN, TB, ACM, or AB) and, when possible, provided medical records.

Individuals were classified as USH1, USH2, or USH3 according to standard diagnostic criteria.[3][4] The USH3 classification was based upon medical history or audiometric evidence of progression of hearing loss that was not consistent with age related progression, and a diagnosis of RP reported by the patient or in medical records. Audiograms were classified according to the European Working Group on Genetics of Hearing Impairment.[13]

Genomic DNA was extracted from antecubital venous blood samples (PUREGENE reagents, Gentra Systems, Inc, Minneapolis, MN, USA) or buccal mucosal cells obtained by a swab.[14] Normal controls were anonymised DNA samples that had been previously prepared from 419 Ashkenazi Jewish individuals presenting for Tay-Sachs disease carrier screening in the New York city area. Family histories of hearing loss or RP were not available from these individuals, who had provided consent for the use of their DNA samples in additional genetic studies.

Mutation analysis

The first exon (nt 129–545, GenBank accession NM_174879) of *USH3A* was PCR amplified from genomic DNA as previously described.[11] 143T→G (N48K) was detected in affected subjects by direct sequencing of PCR products. Control DNA samples were screened for N48K by restriction endonuclease digestion, based upon the observation that 143T→G creates a *Stu*I digestion site.[11]

RESULTS

USH3A genotype

Sixteen (40%) of 40 USH subjects, from 11 of 30 unrelated Ashkenazi Jewish families, were classified as USH3 (fig 1). Subjects with USH3 ranged in age from 26 to 70 years old. DNA samples were obtained from 14 of these individuals, as well as from 17 unaffected family members. Two affected individuals (LMG 198/II-3 and LMG214/II-1) were interviewed but no DNA was obtained. These two individuals were assumed to have the same genotype as their affected siblings (fig 1), who were found to be homozygous for N48K. Eleven of the USH3 subjects were female and three were male. An initial screening for the N48K mutation of *USH3A*[11][12] demonstrated that all 14 affected subjects were homozygous for this mutation. All unaffected family members tested were either heterozygous or homozygous for the wild type allele. N48K was not detected in five USH2 individuals from three unrelated families.

We found an N48K carrier frequency of 3/419 (0.7%; 95% CI 0–1.6%) among Ashkenazi Jews from the New York area. The corresponding allele frequency (3/838 chromosomes; 0.35%) is not significantly different (p = 0.608) from that reported for Ashkenazi Jews from Israel (1/221 chromosomes; 0.45%).[11]

Auditory phenotype

The age of detection of hearing loss in USH3 subjects ranged from infancy to greater than 35 years, with the majority of cases being diagnosed by the age of 10 years (table 1). The hearing loss was progressive in all cases. The severity of hearing loss at the time of the most recent audiogram ranged from mild to profound, with eight patients having profound loss at some frequencies (table 1, fig 2). Hearing loss was symmetrical in all cases except two (LMG181/ III-1; LMG191/

II-1). One subject was reported to have had profound loss by 8 years of age, while hearing loss was only mild to moderate in the better ear of one 49 year old subject. The audiometric configuration was downsloping in most cases (fig 2). All subjects used oral–auditory communication, with three subjects also using sign language. Thirteen subjects wore hearing aids and two subjects previously used hearing aids but now have cochlear implants. One subject never had hearing aids because her hearing loss was considered too severe, and she has never received a cochlear implant. One subject who received a cochlear implant (LMG214/II-3) reported significant improvement in speech discrimination and another implant recipient (LMG187/III-3) is now capable of oral telephone conversation. Pre- or post-implant performance scores were not available for these subjects.

Ocular phenotype

All subjects reported the diagnosis of RP by an ophthalmologist. Reported onset of either night blindness or tunnel vision ranged from 4 years of age "early childhood" to 18 years of age "late teens" (table 1). Six subjects reported the onset of visual symptoms occurred prior to the onset of auditory symptoms. Five subjects, all 50 years of age or older, reported either minimal vision or total blindness. Current visual fields ranged from 20° in a 26 year old to complete blindness at 38 years of age. Best corrected visual acuity, when available, ranged from 20/40 to no light perception. Ten subjects (62.5%) reported having cataracts, consistent with the high frequency of cataracts previously described in USH1 and USH2, as well as in RP in general.[9][15–18]

Vestibular phenotype

Only three subjects reported balance difficulties, which were all subjectively mild in severity (table 1). One of these three subjects also reported possible early motor developmental delay (LMG198/II-1). One of the subjects with balance symptoms had caloric reflex testing as measured by electronystagmography (ENG), which was normal at 14 years of age (LMG195/II-2). Two subjects without vestibular complaints also had ENG/caloric tests, which were both normal. Additional evaluations (rotary chair testing) with potentially increased sensitivity for detecting subtle vestibular dysfunction were not performed.

Intrafamilial variation

Five study families had more than one affected USH3 individual. In most of these cases, the intrafamilial visual and auditory phenotypic variability was significant and approximated the interfamilial variability we observed among our USH3 cohort. For example, subjects III-1 and II-3 in LMG181 are first cousins once removed (fig 1): II-3 had a mild to moderate hearing loss at 38 years of age, while III-1 already had a moderate to profound loss at 29 years (fig 2). Subjects II-2 and II-3 in LMG195 are siblings (fig 1): II-2 had a moderate to profound hearing loss at 25 years of age, while II-3 had mild to moderate loss for only the mid to high frequencies at the same age (fig 2). Furthermore, II-2 has a visual field of 15° at 44 years of age, while II-3 has a visual field of less than 5° at 41 years (table 1).

DISCUSSION

We previously reported a founder mutation in the *GJB2* gene (167delT) that is carried by 4% of Ashkenazi Jews and is a major cause of autosomal recessive nonsyndromic hearing loss in this population.[19] We also recently described a founder mutation in *PCDH15* (R245X) that is the major cause of USH1 in the same population.[20] Our current results are consistent with those of other studies, and indicate that the N48K mutation of *USH3A* accounts for a large proportion of USH3
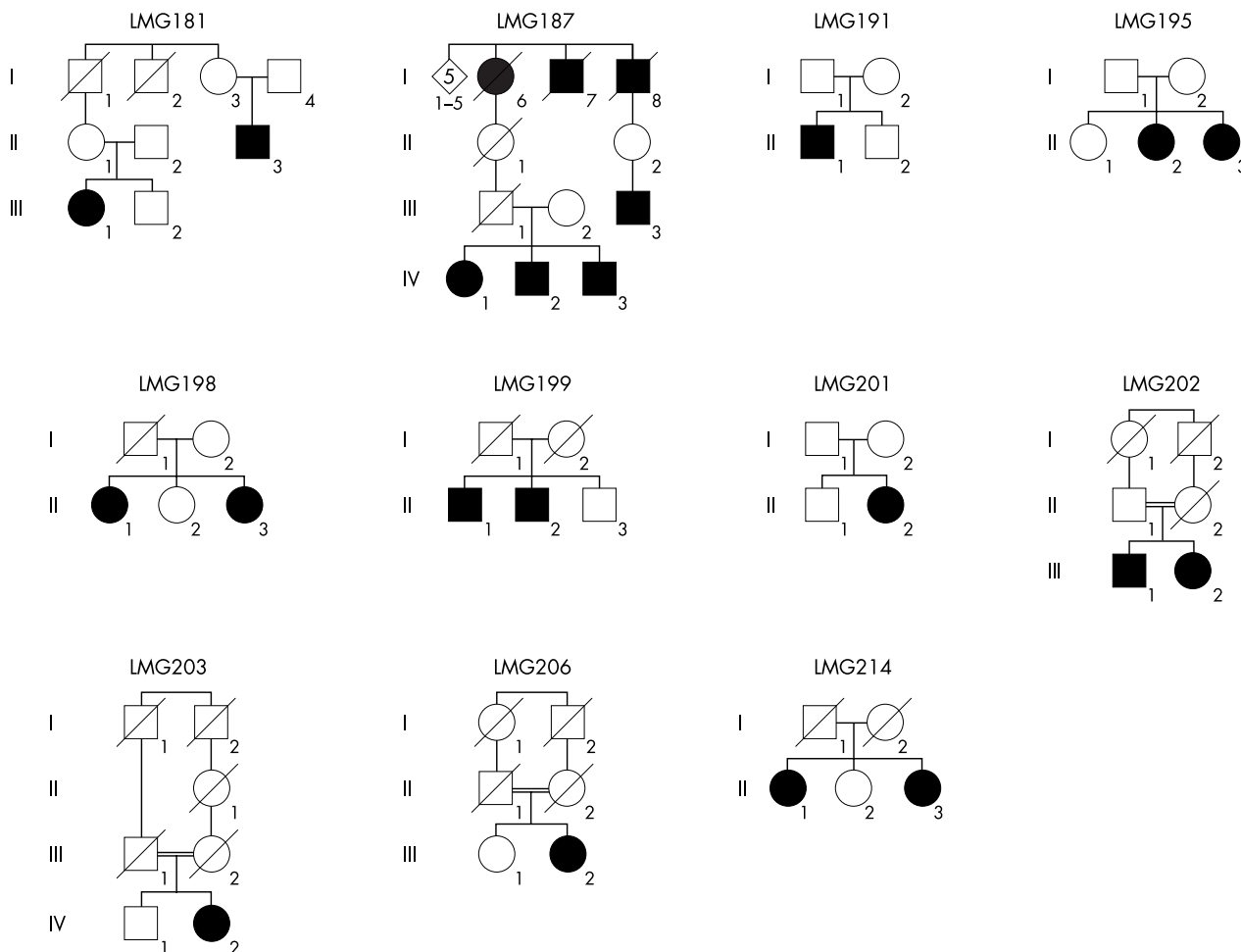
Figure 1 Pedigrees for the USH3 study families. All affected subjects who underwent molecular testing were homozygous for the N48K mutation.

in Ashkenazi Jews,[11] [12] and is thus another prevalent founder mutation causing hearing loss in this population.

It is of interest that sixteen (40%) of our 40 USH subjects had USH3. USH3 has previously been considered to be a rare type of Usher syndrome, comprising only a few percent of the total cases, although no systematic studies are available to support this claim.[4] The high proportion of USH3 in the Finnish and Ashkenazi Jewish populations suggests that only populations with a genetic history permitting the wide spread of a founder mutation will display an increased frequency of USH3. A similar situation, in which mutational events at a locus are uncommon, also exists for DFNB1 deafness caused by *GJB2* mutations in Ashkenazi Jews.[19] [21] [22]

We classified 44% of the subjects in our larger cohort as USH1, consistent with the results of other studies, whereas 11% were classified as USH2, which is a much lower proportion than previously reported for the general population.[23–26] The comparatively increased proportion of USH3 and decreased proportion of USH2 in our cohort may be due to ascertainment bias, as our subjects were recruited primarily through deaf-blind centres and organisations, and through the internet. Larger cohorts will be needed to determine if our findings accurately reflect the epidemiology of Usher syndrome in the Ashkenazi Jewish population.

We identified an N48K carrier frequency of 0.7% in Ashkenazi Jewish control DNA samples. Assuming Hardy–Weinberg equilibrium, the predicted prevalence of USH3 due to N48K is 1.2 per 100 000. If USH3 accounts for 40% of all types of Usher syndrome among Ashkenazi Jews, the

predicted overall prevalence of Usher syndrome is 3 in 100 000 in this population. This is within the published estimates of the prevalence of Usher syndrome in the general population (1/16 000 to 1/50 000).[2] These results indicate that there is not necessarily a greater prevalence of Usher syndrome among Ashkenazi Jews, in whom N48K and the R245X mutation of *PCDH15* account for approximately 67% of cases.[20]

None of the 17 unaffected USH3 family members we tested were homozygous for N48K, suggesting that this mutation is likely to be fully penetrant in homozygotes. Although N48K mutation testing will be an excellent diagnostic tool for USH3 in Ashkenazi Jews, it will be less useful for predicting clinical prognosis due to the highly variable expressivity that we observed. Our findings and those of Pakarinen and co-workers[4] [8] indicate that genetic, environmental, or stochastic factors may modify the USH3 phenotype.

Progression of hearing loss is a consistent finding in USH3 patients. Indeed, our clinical classification based upon reported or audiometric evidence of hearing loss progression was 100% concordant with the molecular diagnosis of USH3 in our Usher syndrome cohort. The wide range of severity and age of onset of visual impairment in our subjects and in the Finnish cohort indicates that the ocular phenotype will not be useful in differentiating USH3 from other types of Usher syndrome. Thus, progression of hearing loss is a key clinical criterion for distinguishing USH3 from USH1 and USH2. Reports of hearing loss progression in USH2 are unconvincing due to either the absence of genetic confirmation of the

Table 1 Demographic and phenotypic data for N48K homozygotes

Family	Subject	Gender	Age (years)	Auditory phenotype			Ocular phenotype		Vestibular symptoms (ENG result)	Notes
				Age at onset (years)	Most recent HL severity	Communication; rehabilitation	Age at onset (years)	Vision impairment		
LMG181	III-1	F	30	6	Moderate to profound	Oral; HA	10-11	Good CV; 15° VF	Mild	1. Endolymphatic shunt 2. Asymmetric hearing loss 3. Cataract surgery
	II-3	M	52	5–6	Mild to moderate	Oral; HA	9-10	Light perception, gross objects; minimal VF	None	1. Cataract surgery
LMG187	III-3	M	48	7–8	Profound	Oral; CI	4	NA	None	1. Mumps encephalitis at 4 years
LMG191	II-1	M	50	Late teens	Moderate to profound	Oral; HA	5	Totally blind since 38 years	None	1. Asymmetric hearing loss
LMG195	II-3	F	41	9–10	Mild to severe	Oral; HA	10	20/60; good CV; <5° VF	None (normal)	1. Cataract surgery 2. Otospongiosus at 20-30 years
	II-2	F	44	3	Severe to profound	Oral; HA	12	20/70; good CV; 15° VF	Mild (normal at 14 years)	1. Cataract surgery 2. Endolymphatic shunt at ~20 years
LMG198	II-3	F	40	9–10	Severe	Oral; HA	Late teens	Good CV; limited VF	None	1. Cataract surgery
	II-1	F	46	7	Severe to profound	Oral; HA	18	Good CV; limited VF	Mild	1. Cataract surgery
LMG199	II-1	M	49	33	Mild to severe	Oral; HA	Teens	20/40; can read; VF 5° OS, 15° OD	None	
	II-2	M	56	Teens	Moderate	Oral; HA	11	Can't read; VF <5°	None	1. MD and glaucoma OD 2. Cataract surgery
LMG201	II-2	F	26	18	Moderate to severe	Oral; HA	15	Good CV; 20° VF	None	
LMG202	III-2	F	56	1-2	Moderate to severe	Oral; HA	Early childhood	No useful vision	None	1. Ichthyosis; affected brother has USH and ichthyosis
LMG203	IV-2	F	56	>35	Moderate to severe	Oral; HA	Early childhood	No useful vision	None	
LMG206	III-2	F	54	6	Severe to profound	Sign + oral; HA	Early childhood	Can read large print; very limited VF	None	1. Cataract surgery
LMG214	II-3	F	60	5	Profound	Sign + oral; CI	9	20/200; can read large print; VF <5°	None (normal)	1. Cataract surgery
	II-1	F	70	Infancy	Profound	Sign + oral; no HA or CI	17	Light perception, gross objects	None	

HL, hearing loss; HA, hearing aids; VF, visual field; CV, central vision; CI, cochlear implant; NA, not available; MD, macular degeneration; OD, right eye; OS, left eye.
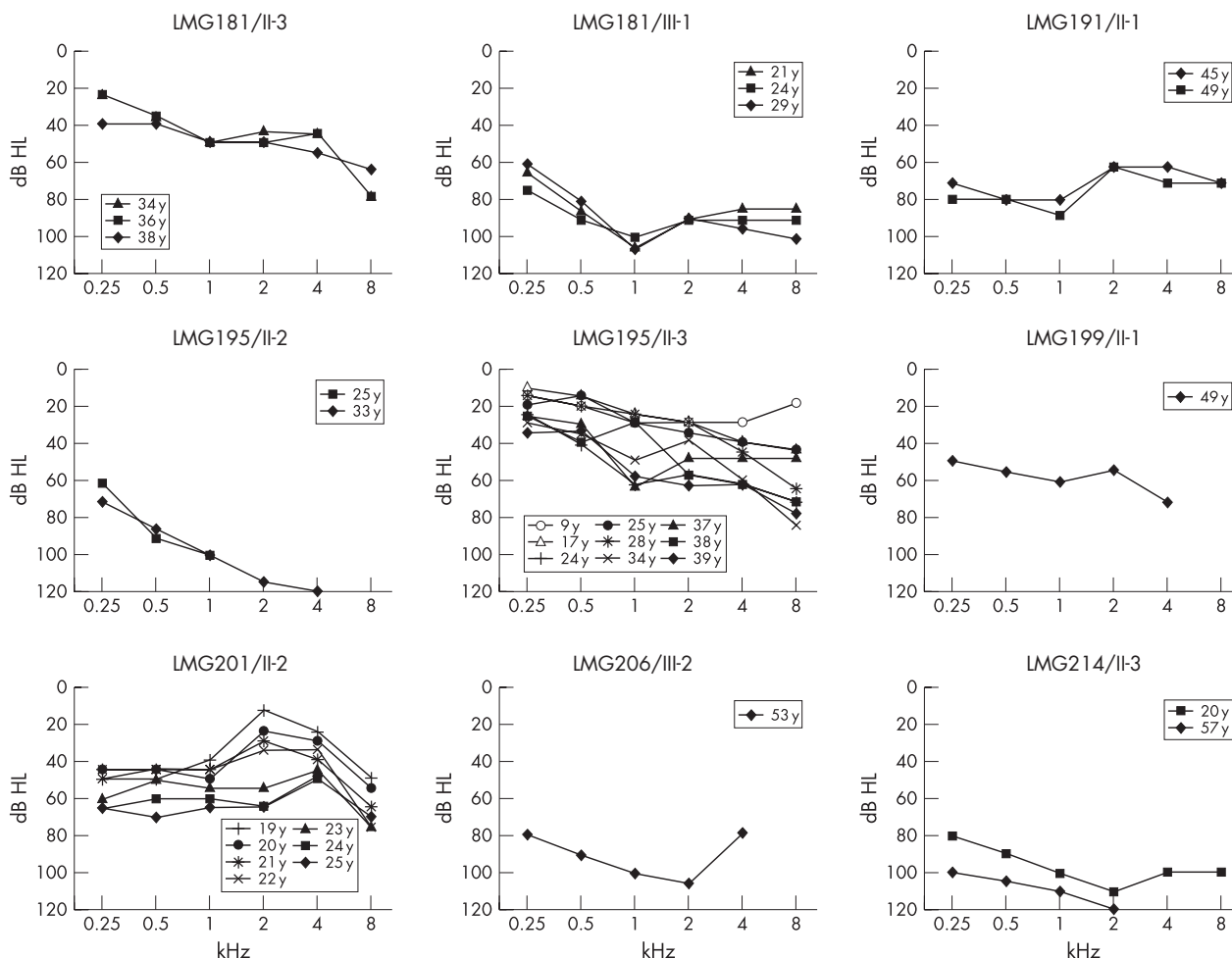
Figure 2 Pure tone air conduction audiometric thresholds for the better hearing ears of USH3 subjects.

USH2 diagnosis[27] [28] or a lack of longitudinal documentation of progression.[28] [29] However, there are atypical forms of USH1 with documented progression of hearing loss due to mutations in *USH1B* and *USH1D*.[5–7] Because of these rare cases and to confirm the diagnosis, it is important to perform molecular testing in all cases of USH3 in Ashkenazi Jews to distinguish it from atypical USH1. The rate of progression may also eventually be a useful criterion to distinguish between the two. However, this study cannot address that question because too few of our subjects had serial audiometric data with enough residual hearing over a sufficiently long time interval to derive quantitative conclusions about rates of hearing loss progression associated with N48K.

Little is known about the initial hearing status and onset of hearing loss in USH3, although the development of normal speech indicates that the onset of functionally significant loss is post-lingual. This is consistent with the late detection of hearing loss in many USH3 patients. Although the congenital hearing status of USH3 patients has not been reported, it is possible that many of these individuals will pass universal newborn hearing screening or even subsequent childhood screens. This information could potentially be used to distinguish USH3 clinically from USH1 and USH2.

USH3 presents differently from USH1 and USH2, and the onset of visual symptoms may precede the onset of auditory symptoms. Atypical forms of USH caused by some mutations in *MYO7A* or *CDH23* may also have a delayed onset of symptoms.[5–7] The perception of USH as a childhood disease may lead to diagnostic errors in populations where USH3 or

atypical phenotypes are more prevalent. Ashkenazi Jewish and Finnish patients presenting with progressive sensorineural hearing loss should undergo ophthalmological evaluation, and those presenting with RP should undergo an audiological evaluation. Molecular testing can be helpful in both situations, especially in Ashkenazi Jews where a high proportion of USH3 is due to a single mutation. Genetic testing of infants at risk for Usher syndrome could prove especially helpful in cases where sedation would otherwise be required for an electroretinogram to detect RP. The applicability of this paradigm to other ethnic groups will depend upon the prevalence and genetic basis of USH3 in those populations.

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