Published in final edited form as:
J Vestib Res. 2008 ; 18(1): 51–58.

Vestibular function in families with inherited autosomal dominant hearing loss

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Abstract

The inner ear contains the developmentally related cochlea and peripheral vestibular labyrinth. Given the similar physiology between these two organs, hearing loss and vestibular dysfunction may be expected to occur simultaneously in individuals segregating mutations in inner ear genes. Twenty-two different genes have been discovered that when mutated lead to non-syndromic autosomal dominant hearing loss. A review of the literature indicates that families segregating mutations in 13 of these 22 genes have undergone formal clinical vestibular testing. Formal assessment revealed vestibular dysfunction in families with mutations in ten of these 13 genes. Remarkably, only families with mutations in the *COCH* and *MYO7A* genes self-report considerable vestibular challenges. Families segregating mutations in the other eight genes do not self-report significant balance problems and appear to compensate well in everyday life for vestibular deficits discovered during formal clinical vestibular assessment. An example of a family (referred to as the HL1 family) with progressive hearing loss and clinically-detected vestibular hypofunction that does not report vestibular symptoms is described in this review. Notably, one member of the HL1 family with clinically-detected vestibular hypofunction reached the summit of Mount Kilimanjaro.

Keywords

Non-sydromic deafness (DFN); calorics; ocular motor; vestibulo-ocular reflex; velocity step test; cervico-ocular reflex; computerized dynamic posturography; vestibular evoked myogenic potential

1. Introduction

Given the common embryonic origins and biology of the auditory and vestibular systems within the inner ear, it might be anticipated that single gene mutations known to cause inherited hearing loss would also lead to vestibular dysfunction. Hearing loss is classified as either syndromic or non-syndromic. When hearing loss is coupled with diagnoses affecting body systems other than the inner ear (e.g. diabetes, retinitis pigmentosa, heart arrhythmias) the hearing impairment is considered syndromic. More commonly, hearing loss is found as a single entity and therefore referred to as non-syndromic.

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Genes underlying non-syndromic deafness (*DFN*) can be inherited in an autosomal dominant (*DFNA*), autosomal recessive (*DFNB*), or X-linked (*DFN*) manner. A number following the *DFNA, DFNB,* or *DFN* designation indicates the order in which the genetic locus was discovered (e.g. *DFNA1*, *DFNA2*) and each locus refers to a specific chromosomal location. Non-syndromic hearing loss can also be inherited maternally due to mitochondrial mutations. The vast majority of deafness genes have been discovered by collaborating with large hearing impaired human pedigrees where the inheritance pattern of the hearing loss in the family is compared to the segregation pattern of genetic markers in DNA from these same individuals. Twenty-two different genes have been discovered that lead to non-syndromic autosomal dominant hearing loss.

In this reveiw, we describe a human pedigree (the HL1 family) segregating non-syndromic autosomal dominant sensorineural hearing loss. Clinical testing in the HL1 family revealed vestibular hypofunction, however the family appears to have adapted well to this lack of vestibular information from their inner ears. In an effort to interpret the HL1 vestibular findings in the context of other DFNA pedigrees we conducted a review of the DFNA vestibular literature.

2. The HL1 family

2.1 Autosomal dominant inheritance of progressive hearing loss

The HL1 family is an American pedigree of Irish decent (Fig. 1). Written informed consent was obtained from the HL1 family members for all study procedures under a protocol approved by the Institutional Review Board of the University of Washington. Linkage to the X-chromosome was excluded by genetic marker analysis as male-to-male transmission was not observed in the pedigree. We also analyzed the segregation pattern of genetic markers tightly flanking the *COCH* (*D14S1021-COCH-D14S54*) and *MYO7A* (*D11S1314-MYO7A-D11S937*) genes in the HL1 family. These markers did not co-segregate with hearing loss in the HL1 family. Mitochondrial inheritance from the mother can not be ruled out as father-to-child transmission has not been observed in the HL1 pedigree. However, the HL1 family members do not have mutations in the two mitochondrial genes, 12S rRNA (bp 648-1601) and tRNASer (UCN) (bp 7446-7516), known to harbor alterations associated with non-syndromic hearing impairment. In addition, the auditory findings in the HL1 family are not consistent with mitochondrial inheritance which is correlated generally with a variable phenotype due to heteroplasmy. Therefore, the auditory phenotype in the HL1 family most likely segregates as an autosomal dominant trait. The gene mutation in the HL1 family has not yet been discovered. Affected HL1 family members demonstrate progressive hearing loss with a tendency for a notch at 2000 Hz (Fig. 1). All molecular genetic and auditory analyses were conducted as described previously [29].

2.2 Vestibular hypofunction

Based on the hearing and balance questionnaires and discussions with the HL1 family members, complaints of significant vestibular problems were not elicited. To determine if clinical vestibular problems could be detected, testing was conducted with two HL1 family members that both demonstrated hearing loss, female II-4 (at the age of 56 years) and her son, male III-3 (at the age of 32 years). Vestibular test parameters and normal values have been described previously [29]. Oculomotor and caloric test results are not available for female II-4. Oculomotor testing was normal for male III-3.

Computerized dynamic posturography

Sensory organization and motor control testing: Male III-3 generated an overall normal sensory organization test (SOT) composite score of 84. During the test, the COG (center of

gravity) alignment indicated that male III-3 put more weight on his left than right foot. This uneven weight distribution may have impacted the motor control test (MCT) results which scored prolonged latencies on the backward translations on the right side. Female II-4 gave an overall abnormal SOT composite score of 65 with her poorest performance under platform condition 6. Her COG alignment favored weight to her left foot, but not to the extent of her son. On the MCT, a prolonged latency was scored on the backward translation on the left side.

Rotational testing

Velocity Step Test: For the velocity step test, the mother and son pair displayed abnormal gain and response time constants under almost all conditions (Table 1).

Sinusoidal oscillation test: During the oscillation test, male III-3 demonstrated abnormal gains across all frequencies (Fig. 2A) with a phase angle lag at 0.04 and 0.08 Hz (Fig. 2B). Female II-4 displayed abnormal gains across all frequencies except 0.64 Hz (Fig. 2A) and a phase lag at 0.08 Hz (Fig. 2B).

Caloric testing: Caloric testing in male III-3 detected a 30% unilateral weakness in the right ear indicating that male III-3 is receiving more vestibular information from his left inner ear than his right.

3. Vestibular literature review for known DFNA gene mutations

To appreciate how often vestibular symptoms and/or abnormal findings from formal clinical vestibular assessment are reported for families with mutations in known *DFNA* genes, we conducted a review of the DFNA literature.

3.1 Compensation for vestibular dysfunction in families with DFNA mutations

Families with alterations in 13 of the 22 *DFNA* genes had undergone formal clinical vestibular testing (Table 2) consisting of one or more of the following evaluations: calorics, ocular motor, vestibulo-ocular reflex (VOR) in most cases by the rotary chair velocity step test, cervico-ocular reflex (COR), computerized dynamic posturography (CDP), and vestibular evoked myogenic potential (VEMP). Caloric testing was the most common type of vestibular assessment in these families. Formal vestibular testing yielded abnormal results in at least some family members for 10 of these 13 *DFNA* genes. For two of these 10 genes, *COCH* and *MYO7A*, abnormal clinical vestibular tests manifested as vestibular symptoms in at least some family members. This is particularly evident in families with *COCH* mutations where Meniere-like features are not unusual (Table 2). Therefore, genetic screening of *COCH* and *MYO7A* is clearly indicated in families with abnormal clinical vestibular test results. Families segregating mutations in the other eight *DFNA* genes yield at yeast some abnormal clinical vestibular test results, but these family members either do not complain of vestibular problems or the problems are considered mild and may also be found in a random sample of individuals. In most cases, family members affected by a *DFNA* mutation seem to compensate for their clinically-detected vestibular loss fairly well in everyday life.

3.2 Notes regarding Table 2

A few points of clarification regarding Table 2 follow. The article reference indicates where the vestibular data was presented, not necessarily where mutation findings were first documented for the family. The “affected individual” notation in Table 2 refers to the finding of hearing loss, but not necessarily vestibular dysfunction in those individuals. In most reports, family members with normal hearing are not included in the vestibular testing. If an article could not be located describing clinical vestibular testing, the cloned DFNA locus was not listed in Table 2, for example DFNA genes GJB3 (DFNA2), GJB6 (DFNA3), EYA4

(DFNA10), POU4F3 (DFNA15), MYH9 (DFNA17), MYO6 (DFNA22), TFCP2L3 (DFNA28), TMC1 (DFNA36), and MYO1A (DFNA48). The two DFNA5 mutations leading to skipping of exon 8 are different genomic alterations. The three p.W276S KCNQ4 mutations are thought to be from unrelated families as is the case for the two p.T669M WFS1 alterations. The ESPN gene study [11], indicated that routine vestibular tests were conducted including one or more of the following tests: caloric, rotatory, optokinetic, swinging torsion, statokinesimetric, and vestibulo-vegetative. Some of the abnormal vestibular findings may be specific to a particular mutation within the *DFNA* gene. The DFNA9 family segregating the p.C542F cochlin alteration demonstrated abnormal central oculomotor test results, suggesting the need for a study addressing cochlin expression in the human central nervous system.

4. Summary

As seen in the HL1 family, the DFNA literature review indicates that in most cases vestibular symptoms are not a major complaint of families with mutations in the known *DFNA* genes even if a vestibular loss is detected in these individuals through formal clinical evaluation. Therefore, the lack of self-reported vestibular symptoms may not accurately convey the amount of vestibular information contributed by the inner ear to families segregating *DFNA* mutations. The HL1 family members do not self-report vestibular problems perhaps because they have adapted to a lack of vestibular information from their inner ears from an early age. Female II-4 and male III-3 appear to compensate well for their clinically-detected vestibular loss in every-day life. This is evident particularly in male III-3 who demonstrated vestibular hypofunction with caloric and rotary chair testing, but generated normal SOT scores on the balance platform and during the same year as these vestibular evaluations reached the summit of Mount Kilimanjaro.

Acknowledgements

We are grateful to the HL1 family for their cooperation. The HL1 family data presented in this review has not been published previously. This work was funded by NIH grants DC04945 (V.A.S), DC006901 (V.A.S.) and P30 DC04661 (V. M. Bloedel Core).

References

1. Abe S, Katagiri T, Saito-Hisaminato A, Usami S, Inoue Y, Tsunoda T, Nakamura Y. Identification of CRYM as a candidate responsible for nonsyndromic deafness, through cDNA microarray analysis of human cochlear and vestibular tissues. Am J Hum Genet 2003;72:73–82. [PubMed: 12471561]
2. Akita J, Abe S, Shinkawa H, Kimberling WJ, Usami S. Clinical and genetic features of nonsyndromic autosomal dominant sensorineural hearing loss: KCNQ4 is a gene responsible in Japanese. J Hum Genet 2001;46:355–361. [PubMed: 11450843]
3. Bischoff AM, Luijendijk MW, Huygen PL, van Duijnhoven G, DeLeenheer EM, Oudesluijs GG, Van Laer L, Cremers FP, Cremers CW, Kremer H. A novel mutation identified in the DFNA5 gene in a Dutch family: a clinical and genetic evaluation. Audiol Neurootol 2004;9:34–46. [PubMed: 14676472]
4. Bischoff AM, Pennings RJ, Huygen PL, Luijendijk MW, Van Wijk E, Cruysberg JR, Kremer H, Cremers CW. Cochleovestibular and ocular features in a Dutch DFNA11 family. Otol Neurotol 2006;27:323–331. [PubMed: 16639269]
5. Bolz H, Bolz SS, Schade G, Kothe C, Mohrmann G, Hess M, Gal A. Impaired calmodulin binding of myosin-7A causes autosomal dominant hearing loss (DFNA11). Hum Mutat 2004;24:274–275. [PubMed: 15300860]
6. de Kok YJ, Bom SJ, Brunt TM, Kemperman MH, van Beusekom E, van der Velde-Visser SD, Robertson NG, Morton CC, Huygen PL, Verhagen WI, Brunner HG, Cremers CW, Cremers FP. A Pro51Ser mutation in the COCH gene is associated with late onset autosomal dominant progressive sensorineural hearing loss with vestibular defects. Hum Mol Genet 1999;8:361–366. [PubMed: 9931344]

7. DeLeenheer EM, Huygen PL, Coucke PJ, Admiraal RJ, van Camp G, Cremers CW. Longitudinal and cross-sectional phenotype analysis in a new, large DFNA2/KCNQ4 family. Ann Otol Rhinol Laryngol 2002;111:267–274. [PubMed: 11915881]
8. DeLeenheer EM, van Zuijlen DA, Van Laer L, Van Camp G, Huygen PL, Huizing EH, Cremers CW. Clinical features of DFNA5. Adv Otorhinolaryngol 2002;61:53–59. [PubMed: 12408063]
9. Di Leva F, D'Adamo P, Cubellis MV, D'Eustacchio A, Errichiello M, Saulino C, Auletta G, Giannini P, Donaudy F, Ciccodicola A, Gasparini P, Franze A, Marciano E. Identification of a novel mutation in the myosin VIIA motor domain in a family with autosomal dominant hearing loss (DFNA11). Audiol Neurootol 2006;11:157–164. [PubMed: 16449806]
10. Donaudy F, Snoeckx R, Pfister M, Zenner HP, Blin N, DiStazio M, Ferrara A, Lanzara C, Ficarella R, Declau F, Pusch CM, Nurnberg P, Melchionda S, Zelante L, Ballana E, Estivill X, Van Camp G, Gasparini P, Savoia A. Nonmuscle myosin heavy-chain gene MYH14 is expressed in cochlea and mutated in patients affected by autosomal dominant hearing impairment (DFNA4). Am J Hum Genet 2004;74:770–776. [PubMed: 15015131]
11. Donaudy F, Zheng L, Ficarella R, Ballana E, Carella M, Melchionda S, Estivill X, Bartles JR, Gasparini P. Espin gene (ESPN) mutations associated with autosomal dominant hearing loss cause defects in microvillar elongation or organisation. J Med Genet 2006;43:157–161. [PubMed: 15930085]
12. Elfenbein JL, Fisher RA, Wei S, Morell RJ, Stewart C, Friedman TB, Friderici K. Audiologic aspects of the search for DFNA20: a gene causing late-onset, progressive, sensorineural hearing loss. Ear Hear 2001;22:279–288. [PubMed: 11527035]
13. T.V.U.H.D.S. Group. Dominantly inherited low-frequency hearing loss. Arch Otolaryngol 1968;88:242–250. [PubMed: 5663381]
14. Iwasaki S, Harada D, Usami S, Nagura M, Takeshita T, Hoshino T. Association of clinical features with mutation of TECTA in a family with autosomal dominant hearing loss. Arch Otolaryngol Head Neck Surg 2002;128:913–917. [PubMed: 12162770]
15. Kemperman MH, De Leenheer EM, Huygen PL, van Duijnhoven G, Morton CC, Robertson NG, Cremers FP, Kremer H, Cremers CW. Audiometric, vestibular, and genetic aspects of a DFNA9 family with a G88E COCH mutation. Otol Neurotol 2005;26:926–933. [PubMed: 16151339]
16. Kemperman MH, DeLeenheer EM, Huygen PL, van Wijk E, van Duijnhoven G, Cremers FP, Kremer H, Cremers CW. A Dutch family with hearing loss linked to the DFNA20/26 locus: longitudinal analysis of hearing impairment. Arch Otolaryngol Head Neck Surg 2004;130:281–288. [PubMed: 15023833]
17. Khetarpal U. DFNA9 is a progressive audiovestibular dysfunction with a microfibrillar deposit in the inner ear. Laryngoscope 2000;110:1379–1384. [PubMed: 10942145]
18. Kunst H, Huybrechts C, Marres H, Huygen P, Van Camp G, Cremers C. The phenotype of DFNA13/COL11A2: nonsyndromic autosomal dominant mid-frequency and high-frequency sensorineural hearing impairment. Am J Otol 2000;21:181–187. [PubMed: 10733181]
19. Kunst H, Marres H, Huygen P, Van Camp G, Joosten F, Cremers C. Autosomal dominant non-syndromal low-frequency sensorineural hearing impairment linked to chromosome 4p16 (DFNA14): statistical analysis of hearing threshold in relation to age and evaluation of vestibulo-ocular functions. Audiology 1999;38:165–173. [PubMed: 10437687]
20. Lalwani AK, Jackler RK, Sweetow RW, Lynch ED, Raventos H, Morrow J, King MC, Leon PE. Further characterization of the DFNA1 audiovestibular phenotype. Arch Otolaryngol Head Neck Surg 1998;124:699–702. [PubMed: 9639482]
21. Marres H, van Ewijk M, Huygen P, Kunst H, van Camp G, Coucke P, Willems P, Cremers C. Inherited nonsyndromic hearing loss. An audiovestibular study in a large family with autosomal dominant progressive hearing loss related to DFNA2. Arch Otolaryngol Head Neck Surg 1997;123:573–577. [PubMed: 9193215]
22. Melchionda S, Bicego M, Marciano E, Franze A, Morgutti M, Bortone G, Zelante L, Carella M, D'Andrea P. Functional characterization of a novel Cx26 (T55N) mutation associated to non-syndromic hearing loss. Biochem Biophys Res Commun 2005;337:799–805. [PubMed: 16226720]

23. Mirghomizadeh F, Bardtke B, Devoto M, Pfister M, Oeken J, Konig E, Vitale E, Riccio A, DeRienzo A, Zenner HP, Blin N. Second family with hearing impairment linked to 19q13 and refined DFNA4 localisation. Eur J Hum Genet 2002;10:95–99. [PubMed: 11938438]
24. Nagy I, Horvath M, Trexler M, Repassy G, Patthy L. A novel COCH mutation, V104del, impairs folding of the LCCL domain of cochlin and causes progressive hearing loss. J Med Genet 2004;41:e9. [PubMed: 14729849]
25. Pauw RJ, Collin RW, Huygen PL, Hoefsloot LH, Kremer H, Cremers CW. Clinical characteristics of a Dutch DFNA9 family with a novel COCH mutation, G87W. Audiol Neurootol 2007;12:77–84. [PubMed: 17264471]
26. Pauw RJ, Huygen PL, Collin RW, Cruysberg JR, Hoefsloot LH, Kremer H, Cremers CW. Phenotype description of a novel DFNA9/COCH mutation, I109T. Ann Otol Rhinol Laryngol 2007;116:349–357. [PubMed: 17561763]
27. Pennings RJ, Bom SJ, Cryns K, Flothmann K, Huygen PL, Kremer H, Van Camp G, Cremers CW. Progression of low-frequency sensorineural hearing loss (DFNA6/14-WFS1). Arch Otolaryngol Head Neck Surg 2003;129:421–426. [PubMed: 12707188]
28. Plantinga RF, de Brouwer AP, Huygen PL, Kunst HP, Kremer H, Cremers CW. A novel TECTA mutation in a Dutch DFNA8/12 family confirms genotype-phenotype correlation. J Assoc Res Otolaryngol 2006;7:173–181. [PubMed: 16718611]
29. Street VA, Kallman JC, Robertson NG, Kuo SF, Morton CC, Phillips JO. A novel DFNA9 mutation in the vWFA2 domain of COCH alters a conserved cysteine residue and intrachain disulfide bond formation resulting in progressive hearing loss and site-specific vestibular and central oculomotor dysfunction. Am J Hum Genet A 2005;139:86–95.
30. Tamagawa Y, Ishikawa K, Ishikawa K, Ishida T, Kitamura K, Makino S, Tsuru T, Ichimura K. Phenotype of DFNA11: a nonsyndromic hearing loss caused by a myosin VIIA mutation. Laryngoscope 2002;112:292–297. [PubMed: 11889386]
31. Todt I, Hennies HC, Basta D, Ernst A. Vestibular dysfunction of patients with mutations of Connexin 26. Neuroreport 2005;16:1179–1181. [PubMed: 16012344]
32. Toth T, Pfister M, Zenner HP, Sziklai I. Phenotypic characterization of a DFNA6 family showing progressive low-frequency sensorineural hearing impairment. Int J Pediatr Otorhinolaryngol 2006;70:201–206. [PubMed: 16043233]
33. Usami S, Takahashi K, Yuge I, Ohtsuka A, Namba A, Abe S, Fransen E, Patthy L, Otting G, Van Camp G. Mutations in the COCH gene are a frequent cause of autosomal dominant progressive cochleo-vestibular dysfunction, but not of Meniere's disease. Eur J Hum Genet 2003;11:744–748. [PubMed: 14512963]

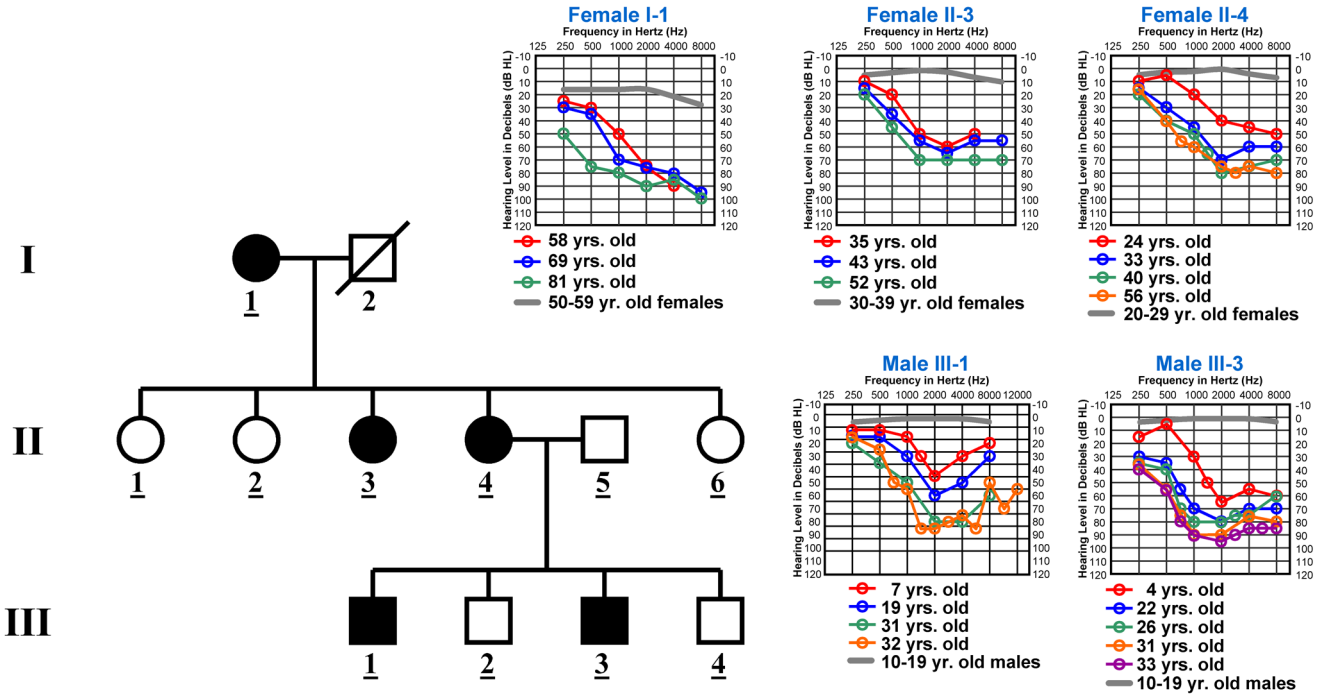

Fig. 1.

Audiologic and haplotype characterization of the HL1 Pedigree. (A) Each individual in the pedigree is assigned a number by generation. Underlined numbers indicate that auditory evaluations were performed for that person. Affected individuals are denoted by blackened symbols, males are denoted by squares, females are denoted by circles, and deceased persons are indicated by a diagonal line through the symbol. Symmetrical hearing loss was detected in all affected HL1 family members and therefore only right ear threshold values are plotted on the audiogram. Frequency in Hertz (Hz) is plotted on the x-axis and hearing level in decibels (dB HL) on the y-axis. Plotted on each audiogram (gray line) are the average pure-tone air conduction thresholds for a person with normal hearing matched in age to the earliest audiogram collected for the family member.

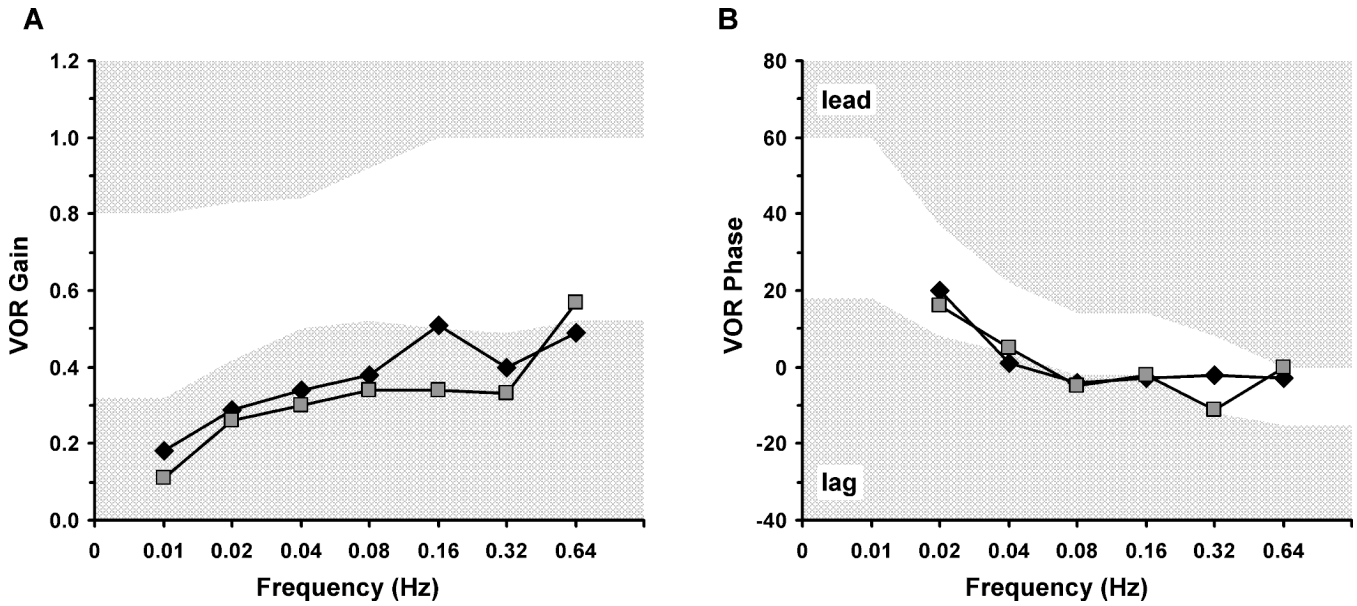

Fig. 2.

Sinusoidal Oscillation Test Results. The mother (II-4) and son (III-3) are plotted with a square and diamond, respectively. For both graphs (A, B) the frequency in Hertz (Hz) is shown on the x-axis. For both graphs the abnormal response range defined by cutting scores (2SD) is denoted by hatched light gray regions. (A) The gain (peak eye velocity/peak head velocity) is plotted on the y-axis. (B) The phase relationship between chair stimulus and eye response is plotted on the y-axis. An abnormal phase angle would be a lag or lead in degrees between eye velocity and chair velocity. VOR = vestibule-ocular reflex.

Table 1

Velocity Step Test

Subject	Velocity Step Test							
	CW		CW stop		CCW		CCW stop	
	Gain	RTC (sec)	Gain	RTC (sec)	Gain	RTC (sec)	Gain	RTC (sec)
II-4	0.41	6*	0.35*	8*	0.17*	5*	0.26*	3*
III-3	0.22*	7*	0.22*	3*	0.26*	4*	0.28*	8*

* indicates abnormal response

Normal gain (>0.40), normal RTC (≥10 sec)

CW, clockwise

CCW, counter clockwise

RTC, response time constant

Table 2

Vestibular Findings in Families with Known *DFNA* Gene Mutations

Locus/Gene	Reference	Mutation	Testing Method & # of Individuals Tested	Findings	Author Conclusion/Comment
CRYM	1	p.K314T, p.X315Y	Caloric on 1 affected person with the X315Y mutation.	Normal caloric.	No vestibular involvement for all affected individuals.
ESPN	11	p.S719R p.D744N p.delK848	Routine vestibular tests. 1–2 individuals tested per mutation.	No vestibular involvement.	No vestibular involvement.
DFNA1, DIAPH1	20	Splice donor, gt-to-gg, FS	Caloric, VAT, & oculomotor. 3 affected individuals tested.	All normal, except 1 person with unilateral caloric weakness.	None of the affected members report vestibular disturbances.
DFNA2, KCNQ4	21	p.W276S	Caloric, VST, & oculomotor. 37 affected individuals tested.	3 of 37 showed unilateral caloric weakness. 13 of 37 showed VOR hyperactivity, 4 of these 13 reported motion sickness, 1 of these 13 reported transient vertigo. 1 of the other 37 also reported transient vertigo. Oculomotor normal except for 1 of 37.	Vestibular system was functional throughout life of these patients. No bilateral caloric weakness. VOR hyperactivity is puzzling, may be a central abnormality.
	2	p.W276S	Caloric. 5 affected individuals tested.	1 of 5 showed unilateral caloric weakness. 2 of 5 reported vertigo. 1 of 5 reported an epilepsy episode.	Further discussion needed to reach a conclusion as whether epilepsy is component of *KCNQ4* mutation.
	7	p.W276S	Caloric & VST. 11 affected individuals tested.	3 of 11 showed VOR hyperactivity, 2 of 3 reported motion sickness. 2 of 11 showed VOR hypoactivity but had normal calorics.	VOR hyperactivity may be explained by release from central inhibition. In mice, *KCNQ4* is expressed in vestibular nuclei.
DFNA3, GJB2	31	5 different mutations	Caloric & VEMP. 1 person w/each mutation tested	Normal calorics, 3 of 5 with absent VEMP, 1 of these 3 reported unsteadiness.	In most cases, saccular defect is well compensated for by patient.
	22	T55N	Caloric & VEMP. 6 affected individuals tested.	5 of 6 with abnormal caloric. 4 of 6 with abnormal VEMP.	Vestibular dysfunction associated with Cx26 mutation for first time.
DFNA4, MYH14	23	p.S120L	Caloric. 5 generation family.	Normal caloric findings.	Normal caloric findings.
	10	p.G376C, p.R726S, p.L976F	Do not indicate testing method. Individuals from 3 different families.	Hearing loss without vestibular involvement.	Hearing loss without vestibular involvement.
DFNA5	8	Exon 8 skip, premat. stop	Caloric & VST. 4 affected individuals tested.	Response parameter values of 4 patients were normal w/few exceptions.	No vestibular symptoms.
	3	Exon 8 skip, premat. stop	VOR. 6 affected individuals tested.	Vestibular symptoms not self reported. 1 of 6 with hyperactive VOR.	Vestibular function was generally normal.
DFNA6/14, WFS1	13	p.L829P	Caloric & oculomotor. 4 generation family.	Oculomotor & caloric tests did not show any consistent deficits.	No significant abnormalities.
	19	p.T699M	Caloric, VST, & oculomotor. 20 affected family members.	19 of 20 w/normal oculomotor, 15 of 17 w/ normal caloric, 1 of 15 w/VOR hyporeflexia, 6 of 15 showed VOR hyperreflexia.	With few exceptions, vestibular function was intact.
	27	p.G674V	Caloric, VST, & oculomotor. 2 affected family members.	Normal oculomotor and vestibular responses.	No substantial vestibular symptoms.

Locus/Gene	Reference	Mutation	Testing Method & # of Individuals Tested	Findings	Author Conclusion/Comment
	32	p.T699M	Caloric & oculomotor. 4 affected individuals tested.	Normal oculomotor and caloric responses.	Normal vestibular responses.
DFNA8/12, TECTA	14	p.R2021H	Caloric. 4 affected individuals tested.	All affected members had normal vestibular function.	All affected members had normal vestibular function.
	28	p.R1890C, p.T83M	VST & oculomotor. 4 affected individuals tested.	Intact horizontal VOR, 2 people w/long time constant. Normal oculomotor. No vestibular symptoms.	Given TECTA is expressed in otolith membrane, otolith-testing paradigms should be considered.
DFNA9, COCH	6	p.P51S	Do not indicate testing method. 6 affected individuals tested.	Vestibular tests disclosed complete areflexia in 5 individuals & severe hyporeflexia in 1.	Patients experienced instability esp in dark & head movement-dependent oscillopsia.
	17	p.V66G	Caloric, 3 affected individuals.	2 with absent bithermal caloric responses. 1 with unilaterally absent caloric responses.	Vestibular complaints.
	33	p.A119T	Caloric, 1 affected individual.	Bilateral decreased response.	Recurrent dizziness & vertigo.
	24	p.V104del	Do not indicate testing method. 1 affected individual.	Total cochleovestibular areflexia in both ears.	Patient reports severe vertigo, nausea, & vomiting.
	15	p.G88E	Caloric, oculomotor, VST. 10 affected individuals.	2 showed vestibular areflexia, 1 showed bilateral caloric weakness, 1 showed asymmetric responses to caloric testing.	Instability especially in dark, vertigo, & tendency to fall.
	29	p.C542F	Caloric, oculomotor, VST, SOT, VEMP, CDP 3 affected individuals tested.	Central oculomotor dysfunction, progressive vestibular hypofunction, absent VEMP responses.	Vestibular symptoms not noticed until after the 4th decade of life.
	25	p.G87W	Caloric, oculomotor, VST. 12 affected individuals.	2 of 10 affected individuals showed vestibular areflexia.	Instability especially in dark, vertigo, & tendency to fall.
	26	p.I109T	Caloric, oculomotor, VST. 7 affected individuals.	1 of 7 showed complete vestibular areflexia.	Instability especially in dark, vertigo, & tendency to fall.
DFNA11, MYO7A	30	del p.A886, K887, K888	Caloric & spontaneous nystagmus. 5 affected individuals tested.	3 of 5 showed caloric hyporeflexia. 3 of 5 showed spontaneous nystagmus.	No vestibular symptoms.
	5	p.R853C	Do not indicate testing method. 5 affected individuals tested.	Mild vestibular dysfunction found in 1 of 5 patients.	Mild vestibular dysfunction found in 1 of 5 patients.
	4	N458I	Caloric & VST. 6 affected individuals tested.	Vestibular symptoms and dysfunction reported & found in 4 of 6 patients.	Vestibular dysfunction not fully penetrant & likely progressive.
	9	p.A230V	Do not indicate testing method. 3 affected individuals tested.	Vestibular bilateral areflexia in all 3 patients.	Minor vestibular problems.

Locus/Gene	Reference	Mutation	Testing Method & # of Individuals Tested	Findings	Author Conclusion/Comment
DFNA13, COL11A2	18	p.G323E	Caloric & VST. 17 affected individuals tested.	Abnormal caloric in 8 of 17, 4 of 17 w/VOR hyperactivity, all w/normal oculomotor.	No substantial vestibular impairment symptoms.
DFNA20/26, ACTG1	12	p.T89I	Interview & neurologic exam.	No evidence of vestibular dysfunction was observed during neurologic exam.	Neither proband nor relatives report vestibular problems.
	16	p.T278I	Caloric, VST, oculomotor, COR. 7 affected individuals.	Normal calorics, 2 people with VOR hyporeflexia, 1 with enhanced COR.	No or very limited vestibular involvement.

FS, frameshift; VAT, vestibular autorotation; VST, vestibular step test; VOR, vestibulo-ocular reflex; VEMP, vestibular evoked myogenic potential; Cx26; connexin-26; Premat., premature; SOT, sinusoidal oscillation test; CDP, computerized dynamic posturography; COR, cervico-ocular reflex