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Vestibular Dysfunction in DFNB1 deafness

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Abstract

Mutations of *GJB2* and *GJB6* (connexin-26 and 30) at the DFNB1 locus are the most common cause of autosomal recessive, nonsyndromic deafness. Despite their widespread expression throughout the vestibular system, vestibular dysfunction has not been widely recognized as a commonly associated clinical feature. The observations of vertigo accompanying DFNB1 deafness in several large families prompted our hypothesis that vestibular dysfunction may be an integral, but often overlooked, component of DFNB1 deafness. Our aim was to define the prevalence of vestibular dysfunction in Cases of DFNB1 deafness and Controls with other forms of deafness. We developed and used a survey to assess symptoms of vestibular dysfunction, medical, and family history was distributed to Cases with deafness due to pathogenic *GJB2* and/or *GJB6* mutations and deaf Controls without DFNB1 deafness. Our results showed: Surveys were returned by 235/515 Cases (46%) with DFNB1 mutations and 121/ 321 Controls (38%) without these mutations. The mean age of Cases (41) was younger than Controls (51; $p<0.001$). Vestibular dysfunction was reported by 127 (54%) of Cases and was present at significantly higher rates in Cases than in deaf Controls without DFNB1 deafness ($p< 0.03$). Most (63%) had to lie down in order for vertigo to subside, and 48% reported that vertigo interfered with activities of daily living. Vertigo was reported by significantly more Cases with truncating than non-truncating mutations and was also associated with a family history of dizziness. We conclude that vestibular dysfunction appears to be more common in DFNB1 deafness than previously recognized and affects activities of daily living in many patients.

Keywords

Vertigo; Vestibular Dysfunction; Connexin; DFNB1; Deafness

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INTRODUCTION

Hearing loss (HL) is a common neurosensory impairment affecting up to 3 of every 1,000 children at birth and nearly doubling in frequency by the age of 10 years [Morton and Nance, 2006]. At least 60% of deafness in infancy and childhood is genetically determined [Marazita et al., 1993; Morton and Nance, 2006], and more than 100 loci for either syndromic or nonsyndromic forms have been mapped or sequenced (http://webhost.ua.ac.be/hhh/). A remarkable feature of the genetic epidemiology of deafness was the discovery that recessive mutations at a single locus (DFNB1) account for 30–40% of all probands with deafness in many, but not all, populations [Denoyelle et al., 1999; Zelante et al., 1997]. DFNB1 is located at 13q11-q12 [Guilford et al., 1994] and includes the *GJB2* and *GJB6* genes, which encode the connexin 26 (Cx26) and connexin 30 (Cx30) proteins, respectively. More than 100 mutations have been discovered in the *GJB2* gene, ranging from a very common mutation, 35delG [Cryns et al., 2004] to “private” mutations found only in single families. Digenic interactions with deletion mutations involving the *GJB6* gene (Cx30) are a frequent explanation for the hearing loss in some individuals heterozygous for a single *GJB2* mutation [del Castillo et al., 2003] while approximately 18 *GJB2* mutations exhibit dominant transmission.

Cx26 and 30 are structurally related subunits of a gap junction protein, which aggregate to form homomeric or heteromeric connexons [Kumar and Gilula, 1996], which facilitate the passage of ions and small molecules between cells. Histologic studies have shown that the Cx26 and 30 proteins are both widely distributed in the functional compartments of the cochlea and the vestibular sensory epithelia [Forge et al., 2003; Kikuchi et al., 1994]. Cx26 is also the major gap junction protein expressed in the melanocytes of the human vestibular dark cell area, where it may play a pivotal role in the passive movement of ions between the endolymph and perilymph [Masuda et al., 2001]. Animal studies demonstrate that gap junction channels in both the auditory and vestibular regions of the cochlea are comprised mainly of connexin 26 and 30 subunits [Qu et al., 2007]. Additionally, there is extensive expression of connexin proteins in the ampulla, utricle and the nonsensory epithelia of the saccule accompanied by specific saccular hair cell loss in connexin 30 knockout mice [Qu et al., 2007; Forge et al., 2003].

The spectrum of phenotypic features seen in DFNB1 deafness has continued to expand and is influenced by several factors including the type of mutation, as well as other genetic and environmental modifiers. Originally, the DFNB1 phenotype was characterized as an isolated congenital, stable, bilateral, profound sensorineural hearing loss. Several studies now indicate that the hearing loss can vary from mild to profound, even within the same family [Murgia et al., 1999; Denoyelle et al., 1999; Loffler et al., 2001; Lerer et al., 2000; Mueller et al., 1999; Sobe et al., 2000; Azaiez et al., 2004; Cryns et al., 2004]. A few reports have documented the progression of hearing loss, as well as sudden hearing loss and losses confined to the high frequencies [Janecke et al., 2002; Wilcox et al., 2000]. Chain-termination mutations, which result in a truncated defective protein, are generally associated with greater degrees of hearing loss than non-truncating mutations, which lead to amino acid substitutions but no change in protein size [Snoeckx et al., 2005; Azaiez et al., 2004]. Finally, although DFNB1 deafness was originally considered to be invariably congenital in onset, it is now recognized that perhaps as many as 4%–8% of affected infants could have normal hearing at birth and then develop a later-onset hearing loss ([Norris et al., 2006; Orzan and Murgia, 2007; Schimmenti et al., 2008]). These infants would escape detection by newborn hearing screening programs and result in a later age of identification and treatment. These studies are consistent with animal studies that found a gradual postnatal deterioration in the outer hair cells in the cochlea [Cohen-Salmon et al., 2002] and suggest that newborn hearing screening does not identify all children with prelingual hearing loss.

Earlier reports on associated inner ear malformations based largely on visual inspection showed no conspicuous abnormalities of the temporal bones on CT imaging [Cohn et al., 1999; Denoyelle et al., 1999]. However, recent data suggests that anomalies are common in *GJB2* deafness when the cochlear and vestibular architecture is precisely measured with electronic calipers [Propst et al., 2006]. In this study at least one temporal bone anomaly was found in 72% (38/53) of the participants (more than 50% of ears) with 47% (18/38) of them having bilateral anomalies. The detected abnormalities have included dilated endolymphatic fossa, hypoplastic modiolus, enlarged vestibular aqueduct (EVA), hypoplastic lateral semicircular canals, and hypoplastic cochlea [Propst et al., 2006]. It is of interest, and possible relevance, that dilation of the endolymphatic fossa, which has been reported in 1/3 of patients with *GJB2* deafness, has also been associated with vertigo in patients with Meniere's disease [Propst et al., 2006; Krombach et al., 2005]. In addition, Kenna et al [2007] found that 18% of children with biallelic GJB2 mutations had additional clinical manifestations apart from hearing loss, including structural ear abnormalities as well as vertigo [Kenna et al., 2007].

Despite the widespread expression of the *GJB2* and *GJB6* genes throughout the inner ear, vestibular dysfunction has not been commonly associated with DFNB1 deafness in previous reports [Cohn and Kelley, 1999; Denoyelle et al., 1999] as it has been with some forms of autosomal dominant deafness, like DFNA9, caused by mutations of the cochlin protein within the inner ear [Robertson et al., 1998]. Epidemiologic studies of vestibular vertigo in the general population have shown a point prevalence of 1.5% and a lifetime incidence of 8% with female gender, self reported depression, tinnitus, hypertension, and dyslipidemia having independent effect on the incidence in multivariate analyses [Neuhauser et al., 2005]. Previous studies of dizziness suggest that the lifetime prevalence may be as high as 20 to 30% of the general population, but most studies suffer from a lack of standardization and difficulty quantitating the perceived severity [Neuhauser and Lempert, 2009; Kroenke and Price, 1993; Hannaford et al., 2005; Yardley et al., 1998].

Anecdotal evidence of associated vestibular dysfunction in a large family where both parents, and all nine of their offspring were deaf was the impetus for this study. *GJB2* testing in the parents and four of the nine children revealed that all were homozygous for the 35delG mutation (Fig 1). The father and six of the nine deaf offspring also reported symptoms of vertigo. While it was clearly possible that the hearing loss and vertigo were unrelated, this family prompted us to examine the prevalence of vertigo and in a large sample of deaf probands with *GJB2* deafness in an effort to determine the frequency of this association.

METHODS

After obtaining appropriate IRB approval, we designed an internet-based survey instrument (Supplement 1) which was distributed to deaf subjects who had been tested for mutations in *GJB2* and *GJB6* through the North American Repository of deaf individuals [Pandya et al., 2003] or as part of a study of the alumni of Gallaudet University [Arnos et al., 2008]. The survey link was sent by electronic mail to those subjects aged 18 and above and for whom we had a valid address. In cases where a valid e-mail address was not available or had expired, a paper copy of the survey with a return envelope was mailed. A reminder notice was sent to all non-responders one to two months later.

The questionnaire sought information on the presence, characteristics, age of onset, duration, frequency, and length of episodes of vertigo and/or tinnitus, as well as the past medical and/or a family history of vertigo, migraine, and other medical conditions. The survey also sought specific information regarding severity of vertigo, including need for medications,

emergency room visits, and interference with activities of daily living, requiring bedrest, and /or associated nausea and vomiting. We designed this survey instrument to establish the presence and severity of vertigo based upon published validated neurotologic data on the epidemiology of vestibular vertigo in the general population obtained through structured interviews [Neuhauser et al., 2005]. The responses were entered into an Excel database, and statistical analyses were performed using JMP Software version 6.0.0 (SAS Institute, Cary, NC). Summary statistics were calculated, and inferential tests, including contingency analyses with Fisher's Exact Test and Chi-Square test and logistic regression, were performed.

RESULTS

The response rate for the 515 Cases with *GJB2/6* mutations was 46%, with 235 completed surveys. The mean age of the Cases was 41.7 years (range 18–84 years). Of these respondents, 127 (54%) reported vertigo, and 111 (47%) reported tinnitus while 73 (31%) reported both symptoms. The median age of onset of vertigo was 31, with a mean of 34.7 years. Sixty-two percent of respondents were female, and 86% reported being of Caucasian ancestry. Surveys were also sent to 321 deaf Controls from the same North American Deafness Repository who were also sequenced and did not carry *GJB2/6* mutations, and responses were obtained from 121 (38% response rate). Of these, we analyzed responses from 61 subjects who had either autosomal recessive inheritance of deafness (based on a family history of an affected sibling) or an unknown cause of deafness. Responses from subjects who were documented or suspected to have autosomal dominant forms of deafness were not analyzed in order to decrease the confounding effect of autosomal dominant forms of hearing loss, which can be associated with vertigo. The mean age of Controls was older than the *GJB2/6* Cases at 51 (range 22–84; $p<0.001$). Of the Controls, there were an equal number (62%) of female respondents compared with Cases, and 90% of Controls were of Caucasian ancestry. Significantly fewer Controls (25/61 or 41%) reported vertigo ($p<0.03$). The mean age of onset of vertigo in the Control group was 26.4 years. A comparable percentage of Controls (47%) reported baseline tinnitus, and 30% of Controls reported both tinnitus and vertigo.

Descriptive Data: Tables I and II summarize the reported clinical features of vertigo in both study groups. For Cases in the *GJB2/6* group, of those reporting vertigo, symptoms were intermittent in 96% and had a positional component in 68%. Among the Controls, symptoms were intermittent in 92%; but much less likely to include a positional component (36%; $p<0.0005$). Of the *GJB2/6* Cases, vertigo episodes were described as a spinning sensation (70%) a well as feelings of lightheadedness (74%) with (44%) noting disequilibrium. In the Control group, 60% reported spinning, 52% lightheadedness, and 52% imbalance. Thirty-six percent of the DFNB1 Cases reported that vertigo lasted only minutes, while 48% reported that the episodes lasted minutes to hours. For Controls, vertigo episodes were of shorter duration; 68% reported that episodes lasted less than one minute. In the Control group, the episodes of vertigo were of significantly shorter duration, lasting less than 1 minute in most subjects, while most of the Cases reported duration of minutes to hours or hours to days (Chi Square 10.544, 2df, $p=0.005$). Seventy-one percent in the *GJB2/6* Cases and 78% of the Controls experienced more than three lifetime episodes of vertigo

Most (63%) Cases in the *GJB2/6* group had to lie down in order for the vertigo to subside, and 48% reported that vertigo interfered with activities of daily living. In contrast, 46% of Controls had to lie down ($p<0.05$) and 28% reported interference with activities of daily living ($p<0.03$). Nausea and vomiting associated with vertigo were reported by 38% of *GJB2/6* Cases and 36% of Controls. Baseline tinnitus was present in 57% of Cases with vertigo and 72% of Controls with vertigo. In those with tinnitus and vertigo, tinnitus was

reported to worsen with vertiginous spells in 23% of the *GJB2/6* Cases and in 28% of the Controls. Medications for vertigo, most commonly meclizine or diuretics, were used by 27% of the *GJB2/6* Cases and 25% of the Controls. Emergency room visits due to vertigo were present in 14% of Cases and 20% of Controls.

Tables III and IV outlines relevant past medical and family history data in Cases and Controls with and without vertigo. Table III demonstrates that 40% of Cases with vertigo reported other medical conditions, including hypertension, type II diabetes, mitral valve prolapse, hypothyroidism and gastroesophageal reflux disease. This finding did not differ from the Cases without vertigo, in which 35% reported similar additional medical conditions. Similarly, in Table IV, 24% of Controls with vertigo as well as 50% of Controls without vertigo reported other chronic conditions. Thus, overall the total reporting of other medical conditions in Cases and Controls was 75% and 74%. Eighteen Cases (14%) with vertigo in the *GJB2/6* group had undergone prior ear surgery, most frequently cochlear implantation (44% of this subgroup) or myringotomy with tube placement (22% of this subgroup). This was not significantly different from the Controls, in which 32% of those with vertigo reported prior ear surgery, most commonly cochlear implantation (38%) or tube placement (25%). In the *GJB2/6* Cases without vertigo, 13 respondents (12%) had undergone prior ear surgery, again, most frequently cochlear implantation (54%) or tube placement (38%). Similarly, 11% of the Controls without vertigo had undergone prior ear surgery, most commonly cochlear implantation (50%).

A family history of vertigo was reported in 40% of *GJB2/6* Cases with vertigo, but in only in 20% of Cases without vertigo ($p<0.05$). In contrast, a family history of vertigo was reported in 29% of Controls with vertigo and in 21% of Controls without vertigo. Overall, dizzy subjects were more likely to report a family history of dizziness ($p<.005$); but there was no significant difference between the Cases and Controls in this regard.

The phenotypic effects of truncating and nontruncating mutations on the presence of vertigo in Cases with *GJB2/6* deafness were compared using a contingency analysis and chi square test. Table V presents the genotypes of the 127 Cases in the *GJB2/6* group reporting vertigo in comparison with the Cases without vertigo. Ninety three percent of those with vertigo carried two truncating mutations in comparison to 86.1% among those without vertigo ($p<0.03$). A chi square analysis revealed a significant association between the presence of vertigo in the subject and several personal and family history variables as summarized in Table III. Perhaps somewhat surprisingly, there was no significant association between the presence or absence of vertigo and prior ear surgery.

DISCUSSION

The results of our study indicate that dizziness appears to be an integral feature of the connexin deafness phenotype as indicated by the frequency and duration of vertigo, the presence of associated symptoms, and the use of medications to mitigate the effects of vertigo on activities of daily living. The reported prevalence of dizziness (54%) in Cases with *GJB2/6* deafness far exceeds the reported prevalence and lifetime incidence of vestibular vertigo in the general population [Neuhauser et al., 2005; Neuhauser and Lempert, 2009], and also exceeded the frequency observed in a Control group composed of subjects with other recessive or unknown causes of deafness.

Our findings are consistent with recent radiologic evidence documenting the frequent presence of subtle cochlear and vestibular malformations on fine cut temporal bone CT scans in patients with DFNB1 deafness [Propst et al., 2006], and suggest that these small changes may have clinical relevance. Our data differs from most older studies of connexin

deafness that have not documented a substantial frequency of symptoms attributable to vestibular dysfunction on rotary chair and caloric testing [Cohn and Kelley, 1999; Denoyelle et al., 1999]. This may have been due in part to the compensatory mechanisms which mitigate insult to the vestibular system, which makes abnormal responses intermittent.

However, newer studies incorporating Vestibular Evoked Myogenic Potentials (VEMP), indicate that a more substantial percentage of those with deafness, and specifically connexin deafness, may have vestibular abnormalities than previously recognized [Kasai et al., 2010; Tribukait et al., 2004; Zagolski 2007; Shinjo et al., 2007; Zhou et al., 2009]. The VEMP is a "short latency electromyogram that is evoked by high-level acoustic stimuli (either click or tone burst) and recorded from surface electrodes over the tonically contracted sternocleidomastoid muscle" and examines the saccule and inferior vestibular nerve, whereas traditional vestibular testing examines the lateral semicircular canal and superior vestibular nerve [Akinet al., 2003; Colebatch et al., 1994; Welgampola et al., 2003; Murofushi et al., 1996; Murofushi et al., 1995]. The VEMP response can be obtained on people with any degree of sensorineural hearing loss (SNHL) [Colebatch et al., 1994; Murofushi et al., 1998; Robertson and Ireland, 1995; Ackley, 2004] as long as there is no conductive component, making it applicable to the deaf population.

Our data were originally described in Dodson et al. [2006] and are in agreement with recent investigations of vestibular dysfunction in subjects with connexin deafness [Kasai et al., 2010]. This study demonstrated that the percentage of vestibular dysfunction, as measured by VEMPs and caloric testing, was statistically higher in *GJB2* deafness than in patients with congenital deafness not caused by *GJB2* mutations or in healthy controls. In 2007, Zagolski reported on vestibular studies in which VEMP and calorics were performed on 40 normal hearing children, and 18 children with nonsyndromic hereditary hearing loss, of which five had biallelic GJB2 mutations. Of these children with biallelic *GJB2* mutations, three had no response to either VEMPs or caloric testing, while the remaining two had normal studies [Zagolski, 2007].

In our survey, *GJB2/6* Cases who reported vertigo were significantly ($p<0.03$) more likely to have two truncating mutations. This is consistent with a previous study which found that the presence of two truncating mutations is associated with more severe audiologic phenotypes [Snoeckx et al., 2005]. We also found significant associations between the presence of vertigo and tinnitus, aural fullness, and a family history of dizziness in our Cases with DFNB1 deafness. In agreement with another study of vertigo [Neuhauser et al., 2005], female gender and a history of migraine were also significantly associated with vertigo. Future studies may well identify other genetic modifiers that interact with DFNB1 mutations to increase the risk of these symptoms.

The strengths of the current study include the investigation of vestibular complaints in deaf Cases who were all homozygous for recessive *GJB2/6* mutations, compared to deaf Controls who did not have DFNB1. We found that self reported dizziness and vertigo was more frequent in the Cases than Controls and more severe in those Cases who were homozygous for chain terminating mutations. As with any survey in which the response rate is less than 100%, the potential responder bias must be considered. However, even if every non-respondent in the *GJB2/6* group had not experienced vertigo, the observed prevalence in our sample would have been more than twice the reported prevalence of vestibular vertigo in the general population. In addition, responder bias cannot explain the effects we observed of truncating mutations on the severity of vestibular symptoms since the details of the molecular structure of the mutations were unknown to the participants. Detailed clinical, vestibular and radiologic studies of symptomatic and non-symptomatic *GJB2/6* patients who

are homozygous for truncating and non-truncating mutations respectively could provide objective support for our findings.

As data emerges regarding the vestibular dysfunction in individuals with *GJB2* and *GJB6* mutations, it will permit a greater appreciation by physicians and patients of the full range of symptoms that may be associated with connexin deafness. This in turn should improve the clinical management of a patient population that has often been underserved in the past [Harmer, 1999].

CONCLUSION

Symptoms of vestibular dysfunction are more frequent in patients with DFNB1 deafness than previously recognized. Vertigo appears to be a common feature of this form of genetic deafness, especially cases with truncating mutations, and in those with tinnitus, aural fullness, and a family history of dizziness. Further investigation into the genetics and pathophysiology of vertigo in DFNB1 utilizing VEMPs, is clearly warranted, and should lead to the increased recognition and treatment of these sometimes disabling symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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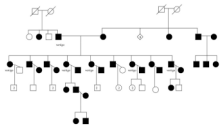

Figure 1.
35delG/35delG DFNB1 family with vestibular dysfunction. Shading represents deafness.

Table I

Comparison of Survey Results in Cases and Controls with Vertigo

Vertigo Characteristics	***GJB2/6* Respondents (N=127)**	**Control Respondents (N=25)**
Presence of Vertigo	127/235 (54%)	25/61 (41%)*(P<0.03)
Characteristics		
➢ Spinning vertigo	70%	60%
➢ Lightheadedness	74%	52%
➢ Dysequilibrium	44%	52%
Positional Component	68%	36%*(P<0.0005)
Intermittent	96%	92%
Duration		
➢ Less than 1 minute	36%	68%
➢ Minutes to Hours	48%	16%
➢ Hours to Days	16%	16%
> 3 lifetime episodes	71%	78%

Table II

Summary of Survey Results in Cases and Controls with Vertigo

Vestibular Dysfunction Characteristics	GJB2/6 Respondents (N=127)	Control Respondents (N=25)
Vertigo Requires Bedrest to Resolve	63%	46%*(P<0.05)
Vertigo Interferes with Activities of Daily Living	48%	28% *(P<0.03)
Associated Nausea/Vomiting	38%	36%
Vertigo Requires Chronic Medication Use	27%	25%
Baseline Tinnitus	57%	72%
Tinnitus Which Worsens During Vertigo Spell	23%	28%
Emergency Room Visits Due to Vertigo	14%	20%
Aural Fullness	27%	29%
Headaches	29%	24%

Table III

Comparison of Past Medical, Family History, and Associated Factors Between Cases with and without vestibular dysfunction

Associated Factors	GJB2/6 Respondents (Cases) with Vertigo (N=127)	GJB2/6 Respondents (Cases) without Vertigo (N=108)
Baseline Tinnitus	57%	35% *(P<0.05)
Other Medical Conditions	40%	35%
Prior Ear Surgery	14%	12%
Cochlear Implantation	6%	6%
Female Gender	70%	53%*(P<0.05)
Biallelic Truncating Mutations	95%	86%*(P<0.05)
Personal Hx of Migraine	38%	23% *(P<0.05)
Family Hx of Dizziness	40%	20%*(P<0.05)
Family Hx of Migraine	59%	37%

Table IV

Comparison of Past Medical, Family History, and Associated Factors Between Controls with and without vestibular dysfunction

Associated Factors	Control Respondents with Vertigo (N=25)	Control Respondents without Vertigo (N=36)
Baseline Tinnitus	72%	29% *(P<0.0009)
Other Medical Conditions	24%	50%
Prior Ear Surgery	32%	11%
Cochlear Implantation	12%	6%
Female Gender	68%	60%
Personal Hx of Migraine	42%	20% * (P<0.05)
Family Hx of Dizziness	29%	21%
Family Hx of Migraine	46%	34%

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Table V

Frequency of *GJB2* and *GJB6* mutations in Study Participants with and without vertigo*

	With Vertigo		Without Vertigo	
Genotype	***n***	**%**	***n***	**%**
GJB2 Truncating/Truncating (T/T):				
35delG/31del38	1	0.79		
35delG/35delG	91	71.65	69	64.49
35delG/167delT	5	3.94	6	5.61
35delG/235delC			1	0.93
35delG/289insA			1	0.93
35delG/310del14	4	3.15	1	0.93
35delG/312del14			3	2.80
35delG/333-334delAA	2	1.57		
35delG/408insA	1	0.79	1	0.93
35delG/E47X	3	2.36	2	1.87
35delG/Q57X	2	1.57		
167delT/167delT	3	2.36	4	3.74
GJB6 309 kbdel/-, *GJB2* 167delT/-	5	3.94	1	0.93
GJB6 309 kbdel/-, *GJB2* 35delG/-	4	3.15	2	1.87
GJB6 309 kbdel/-, *GJB2* 312del14/-			1	0.93
GJB6 309 kbdel/*GJB6* 309 kbdel			1	0.93
Total T/T Genotypes	**121**	**95.28**	**93**	**86.92**
GJB2 Truncating/Nontruncating(T/NT):				
35delG/delE120			1	0.93
35delG/G130V			1	0.93
35delG/K15T			1	0.93
35delG/L90P			1	0.93
35delG/M34T			1	0.93
35delG/N206S			1	0.93
35delG/R143W	1	0.79	1	0.93
35delG/R184P			2	1.87

	With Vertigo		Without Vertigo	
Genotype	***n***	**%**	***n***	**%**
35delG/S139N	1	0.79	1	0.93
35delG/V37I			1	0.93
35delG/W77R			1	0.93
167delT/R184P	1	0.79		
269insT/H100Y			1	0.93
310del14/R32C	1	0.79		
Total T/NT Genotypes	**4**	**3.15**	**13**	**12.15**
TOTAL (with T/NT mutations vs total)				
GJB2 Nontruncating/Nontruncating (NT/NT):				
I81M/V95M			1	0.93
M34T/H100Y	1	0.79		
R143W/E147K	1	0.79		
Total NT/NT Genotypes	**2**	**1.57**	**1**	**0.93**
TOTAL All Genotypes	**127**		**107**	

* one individual heterozygous for a dominant *GJB2* mutation (W44R) not included