Table 2 (Continued)

ID	Age	Mutation allele 1/allele 2	Age of awareness	Progression	Fluctuation	Tinnitus	Vertigo	Goiter	Threshold (Rt) (dB)[a]	Threshold (Lt) (dB)[a]	Hearing level in the low frequencies[b]
4486	20	p. [1707 + 5G>A]; [1707 + 5G>A]	4	+	+	+	+	+	72.5	95	78.1
4490	25	p. [T410M];[T410M]	0	−	−	+	+	+	87.5	92.5	90.0
4508	29	p. [H723R];[H723R]	5	+	+	−	−	−	85	110	91.9
4518	26	p. [H723R];[919-2A>G]	0	+	+	+	+	−	105	97.5	98.1
4530	5	p. [H723R];[919-2A>G]	0	+	+	−	+	−	67.5	86.25	71.9
4545	12	p. [1707 + 5G>A];[H723R]	4	+	+	+	+	+	86.25	28.75	53.1
4549	13	p. [V659L];[1219delCT]	NA	+	+	+	+	−	38.75	50	38.1
4663	0	p. [1707 + 5G>A];[H723R]	0	−	+	NA	NA	−	68.75	68.75	99.2
4696	0	p. [V659L];[H723R]	0	+	−	NA	NA	−	NA	NA	97.5
4362	26	p. [H723R]; [=]	6	+	−	−	−	−	70	68.75	63.8
4513	34	p. [H723R]; [=]	NA	+	+	+	NA	−	71.25	53.75	61.3
4645	23	p. [919-2A>G]; [=]	14	+	−	+	−	−	96.25	105	93.8
723	NA	p. [H723R]; [=]	NA	NA	NA	NA	NA	NA	NA	NA	NA
724	NA	p. [2111ins5bp]; [=]	NA	NA	NA	NA	NA	NA	NA	NA	NA
742	NA	p. [H723R]; [=]	NA	NA	NA	NA	NA	NA	NA	NA	NA
1975	3	p. [H723R];[H723R]	0	NA	NA	NA	NA	NA	80	70	62.5
2082	2	p. [H723R];[H723R]	0	−	−	−	−	−	NA	NA	NA
4735	9	p. [H723R];[919-2A>G]	0	+	+	+	+	−	107.5	110	103.8
195	20	p. [=];[=]	2	+	+	+	+	−	83.75	83.75	81.9
670	8	p. [=];[=]	3	+	−	+	−	−	26.25	107.5	62.5
1755	16	p. [=];[=]	NA	NA	NA	NA	NA	NA	NA	NA	NA
2607	5	p. [=];[=]	0	−	+	−	−	−	97.5	105	98.8
3851	33	p. [=];[=]	0	+	+	+	−	+	103.75	103.75	100.6
4194	11	p. [=];[=]	NA	+	+	−	−	−	67.5	80	76.3
4215	5	p. [=];[=]	0	+	+	−	−	−	98.75	93.75	93.8
4216	55	p. [=];[=]	NA	+	+	+	+	NA	51.25	78.75	68.8
4258	30	p. [=];[=]	28	NA	−	+	−	−	17.5	7.5	13.8
4281	6	p. [=];[=]	2	−	−	−	−	−	57.5	61.25	63.1
4324	37	p. [=];[=]	6	−	−	−	−	−	10	27.5	22.5
4352	3	p. [=];[=]	0	+	+	−	−	−	86.25	88.75	88.1
4357	6	p. [=];[=]	4	+	+	+	−	−	71.25	72.5	67.5
4397	5	p. [=];[=]	0	−	−	−	−	−	102.5	105	100.6
4402	8	p. [=];[=]	0	+	−	−	−	−	100	90	88.8
4450	12	p. [=];[=]	NA	+	+	+	−	−	NA	NA	NA
4462	8	p. [=];[=]	7	+	−	+	−	−	63.75	20	41.3
4488	1	p. [=];[=]	0	−	−	NA	−	−	97.5	97.5	95.0
4671	2	p. [H723R];[600 + 1G>T]	0	+	−	−	+	−	NA	NA	NA
3253	NA	p. [I529S];[H723R]	NA	NA	NA	NA	NA	NA	NA	NA	NA
4949	0	p. [L727X];[H723R]	0	+	−	−	−	−	NA	NA	51.7
J27	NA	p. [H723R];[S448L]	NA	NA	NA	NA	NA	NA	NA	NA	90.6
3309	5	p. [919-2A>G];[P76S]	0	+	+	+	+	−	106.25	106.25	101.3
J15	0	p. [P123S];[H723R]	0	NA	NA	NA	NA	NA	NA	NA	NA
FUK2004	1	p. [H723R];[T94I]	0	NA	NA	N/A	NA	NA	NA	NA	85.0
1299	NA	p. [S610X];[S657N]	0	NA	NA	NA	NA	NA	NA	NA	NA
SNS5500	42	p. [919-2A>G];[919-2A>G]	4	+	+	+	+	+	70	81.3	64
SNS5503	37	p. [H723R];[1707 + 5G>A]	5	+	+	+	+	+	67.5	70	NA

Abbreviation: EVA, enlarged vestibular aqueduct.
[a]Average of 500, 1000, 2000 and 4000 Hz.
[b]Average of 125, 250 and 500 Hz.

retention of improperly folded Pendrin mutants in the endoplasmic reticulum has been suggested as the major pathological mechanism for Pendred syndrome.[19,20] In this study, we compared not only the difference between the T and NT mutations, but also compared the individual mutations and severity of hearing. However, there were no correlations (data not shown). Indeed, there was great variation regarding hearing loss severity even with the same mutations. For example, in the patients homozygous for the most prevalent mutation, p.–H723R, hearing level at low frequency varied from 61 to 99 dB (Table 2). In addition, many reports have described intrafamilial

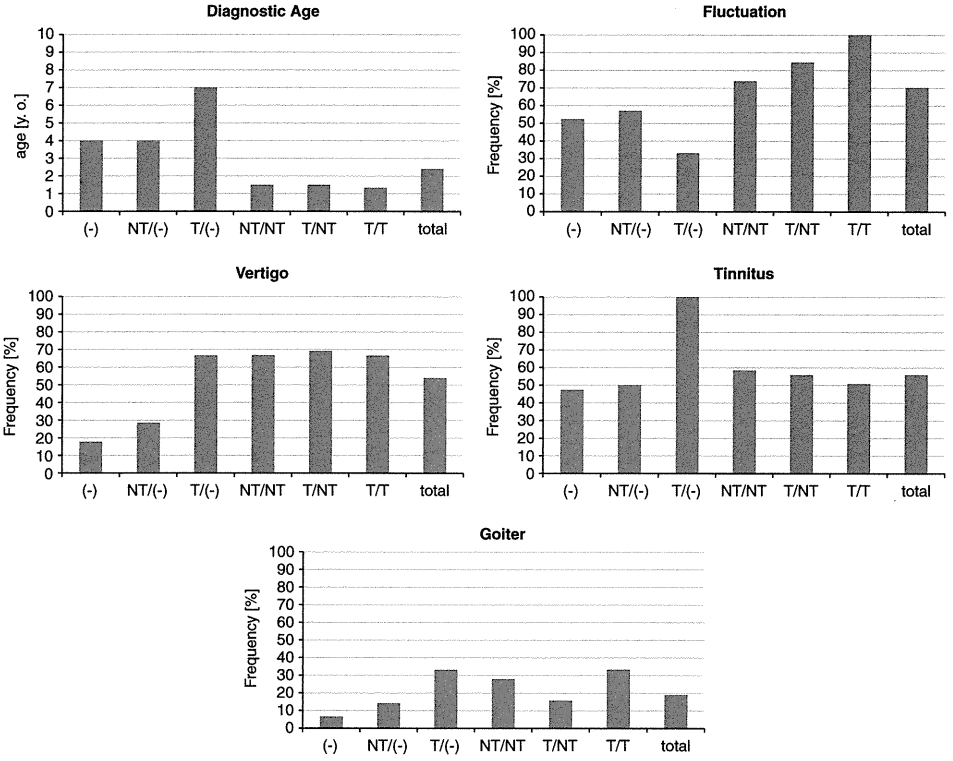

Figure 1 Genotypes and phenotypes (diagnostic age, fluctuation, vertigo, tinnitus and goiter) in the current study. NT/(−), heterozygote of nontruncating mutation; NT/NT, nontruncating/nontruncating; NT/T, nontruncating/truncating; T/(−), heterozygote of truncating mutation; T/T, truncating/truncating; (−), wild type.

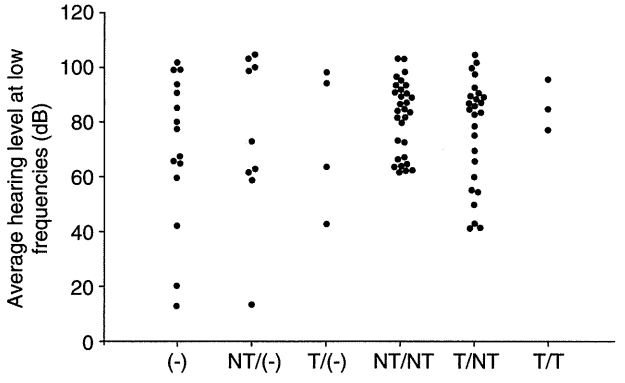

Figure 2 The relationship between hearing level at the lower frequencies and genotype. Hearing level was the average of 125, 250 and 500 Hz. NT/(−), heterozygote of nontruncating mutation; NT/NT, nontruncating/nontruncating; NT/T, nontruncating/truncating; T/(−), heterozygote of truncating mutation; T/T, truncating/truncating; (−), wild type.

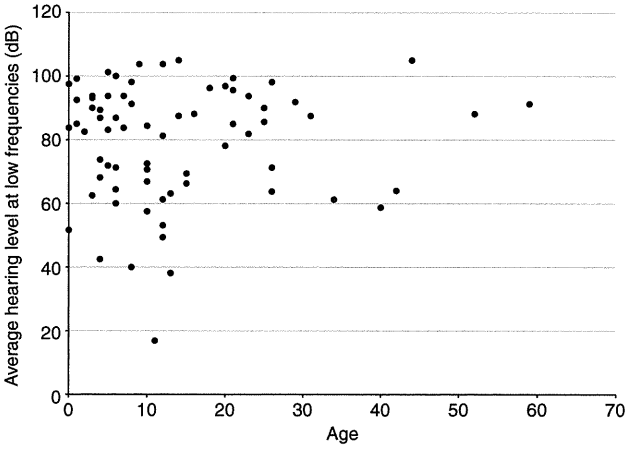

Figure 3 The relationship between hearing level and age in subjects with biallelic *SLC26A4* mutations. Hearing level was calculated as the average of 250, 500, 1000 and 2000 Hz in both sides.

phenotypic variation.[8–12] Therefore, phenotype may be determined not only by *SLC26A4* mutations but also other factors (genetic as well as environmental), contributing to such variability (Figure 2).

Unlike in the case of *GJB2*, phenotype cannot be predicted from the genotype;[6] however, the clarification of clinical features will enable more appropriate genetic counseling and proper medical management for these patients.

The present study confirmed clinical characteristics of 66 patients with EVA caused by biallelic *SLC26A4* mutations. These included congenital (5/63, 7.9%), fluctuated (42/52, 80.8%) and progressive (49/56, 87.5%) hearing loss usually associated with vertigo (35/52, 67.3%) and/or goiter (12/53, 22.6%) during long-term follow-up, in accordance with our previous study.[6] It is known that goiter sometimes becomes apparent between 10 and 20 years of age. The present cohort included young children, and therefore the frequency of goiter may be underestimated. As seen in Figure 3, in 66 patients with biallelic mutations for whom data were available, onset of hearing loss was likely to be early onset, and progressive with age.

CONCLUSIONS

Pendred syndrome and nonsyndromic hearing loss associated with EVA are a continuum of disease characterized as being associated with congenital, fluctuating and progressive hearing loss, and most patients have vertigo and/or goiter. However, in the present study, no genotype–phenotype correlation was found. The results obtained from the present study will facilitate accurate molecular diagnosis and better genetic counseling.

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