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ORIGINAL ARTICLE

Molecular analysis of hearing loss associated with enlarged vestibular aqueduct in the mainland Chinese: a unique *SLC26A4* mutation spectrum

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Abstract It has been shown that mutations in the *SLC26A4* gene are involved in syndromic deafness characterized by congenital sensorineural hearing impairment and goitre (Pendred's syndrome), as well as in congenital isolated deafness (DFNB4), both of which are associated with enlarged vestibular aqueduct (EVA). The prevalence of *SLC26A4* mutations in Pendred's syndrome is clearly established in many ethnic groups, but the data from Mainland Chinese patients with deafness and EVA remain poor. In this report, 15 patients from 13 unrelated Chinese families with deafness and EVA were analyzed for *SLC26A4* using direct sequencing. A total of 15 pathogenic mutations were observed in 11 unrelated families, 4 of which were novel. One mutation, IVS7-2A>G, was most common, accounting for 22.3% (5/22) of all the mutant alleles, and H723R was infrequent. To date, a total of 23 mutations have been reported among the Chinese, 13 of which were unique. In conclusion, EVA could be a radiological marker for *SLC26A4* analysis among Mainland Chinese hearing-loss patients, and the *SLC26A4* mutation spectrum in the Chinese was different from other reported populations.

Keywords Enlarged vestibular aqueduct · Molecular analysis · *SLC26A4* mutations · Chinese

Introduction

Profound hearing loss affects one in 1000 newborns, and about a half of cases are attributed to genetic factors in western countries (Morton 1991). To date, over 100 non-syndromic hearing loss (NSHL) loci have been mapped, and 41 genes responsible for NSHL have been identified (Van Camp 2006). Among them, the gap junction protein beta 2 (*GJB2*) gene plays a major role in the occurrence of autosomal recessive NSHL, and its mutated protein accounts for up to half of NSHL in some ethnic populations (Kenneson et al. 2002). Mutations in mtDNA could be another important cause of NSHL (Fischel-Ghodsian 1999; Guan 2004) and the incidence of its A1555G mutation is ~2.9% among the Chinese pediatric population with NSHL (Li et al. 2005).

Homozygous mutations in the *SLC26A4* gene cause Pendred's syndrome (PS, OMIM 274600) characterized by sensorineural hearing loss and goiter (Everett et al. 1997), or DFNB4 (OMIM 600791), as well as another automsomal recessive non-syndromic hearing loss without goiter (Li et al. 1998). Taken together, DFNB4 and PS are estimated to account for 5–10% of congenital hearing loss, and

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hearing loss in both disorders is prelingual (Reardon et al. 1999) and frequently associated with enlarged vestibular aqueduct (EVA). Much work has revealed the relationship between EVA and *SLC26A4* mutations (Everett et al. 1997; Coyle et al. 1998; Campbell et al. 2001; Yong et al. 2001; Park et al. 2003). A finding in the murine that *Foxi1* is a gene regulator of pendrin suggests that human *FOXI1* could be another gene causative for human hearing loss with EVA (Hulander et al. 2003), but no causative mutation of *FOXI1* was revealed among EVA patients without *SLC26A4* mutations. To date, more than 100 *SLC26A4* mutations spanning the entire coding region have been described (http://www.medicine.uiowa.edu/pendredandbor/listed_mutations.htm), and 13 of them were observed in the Chinese (Yong et al. 2001; Park et al. 2003; Hu et al. 2005a; Wu et al. 2005; Yang et al. 2005). Previous studies revealed different ethnic groups have unique mutation spectra (Coyle et al. 1998; Campbell et al. 2001; Tsukamoto et al. 2003; Wu et al. 2005). In the Chinese, IVS7-2A>G was most common, accounting for 84% of mutations (Wu et al. 2005). Most of the published work dealt with Chinese patients in Taiwan and Singapore, but data from the mainland of China have still been poor.

To know the distribution and frequencies of *SLC26A4* mutations in mainland Chinese, we investigated in this study a total of 15 patients with hearing loss and with EVA from 13 Chinese families, among which the *GJB2*, mtDNA 12s rRNA and the *FOXI1* were also screened.

Subjects and methods

Subject selection

Fifteen prelingual hearing-loss patients (from 13 unrelated families) with an age range of 2–23 years, and some of their family members, were enrolled. One hundred randomly selected normal-hearing individuals were also included. Informed consent was obtained from all these participants prior to the study, in accordance with the Institutional Review Board and Ethical Committee of Xiangya Hospital of Central South University. Two (DF003 and DF008) of the 15 patients were those reported previously (Hu et al. 2005a, b). Two families were multiplex. In one family (NDF6) where parents were consanguineous, only the proband (a daughter, DF007) was assessed. All the 13 families come from the Central South Area of China. Comprehensive family history was taken, especially with regard to the previous use of aminoglycosides or other drugs, any diseases and their treatments, the age of onset, and any possible genetic factors related to their hearing loss. EVA was defined here when enlargement of the vestibular aqueduct was >1.5 mm at midway between the endolymphatic sac and the vestibule. Perchlorate discharge test was not performed on the patients.

Age-appropriate audiological examinations were performed, which included pure-tone audiometry (PTA), immittance testing and transiently evoked otoacoustic emissions (TEOAE). If PTA was unavailable for young patients, auditory brainstem response (ABR) was done. PTA was calculated from the sum of audiometric thresholds at 500, 1,000, and 2,000 Hz. The severity of hearing loss was classified into the following five grades: (a) mild (20–39 dB), (b)moderate (40–54 dB), (c) moderate severe (55–69 dB), (d) severe (70–90 dB), and (5) profound hearing-loss (>90 dB). Hearing loss was considered as ''progressive'' when the patients lost more than 8 dB in the PTA thresholds when comparing two reliable audiometric tests carried out at least 5 years apart, and as ''fluctuant'' when the mean hearing level had risen by more than 10 dB between two successive audiograms.

Mutation screening

Genomic DNA was extracted from peripheral blood leukocytes with the standard procedures. Polymerase chain reaction (PCR) amplification of all 21 exons of the *SLC26A4* gene was performed as described previously (Everett et al. 1997; Coyle et al. 1998; Prasad et al. 2004; Hu et al. 2005a), and PCR products were directly sequenced after removal of unincorporated dNTPs and primers. Sequencing results were analyzed using the DNASTAR^{TM} software program package (DNASTAR Inc., WI, USA). The data were subsequently compared with the wild-type *SLC26A4* sequence in Genbank [accession number: NT_007933 (gDNA), NM_000441 (cDNA)]. All samples were also screened for mutation in the *GJB2* gene, and for the A1555G mutation in mtDNA as previously described (Li et al. 2004; Hu et al. 2005b). *FOXI1* gene was screened using the following primers, which were designed for 2 exons including their flanking intronic sequences (sequence accession number: NM_012188): FX1AF: 5′-GCCAAGCCCTAGGGGTATAA-3′, FX1AR: 5′-AGCTTCATCAGCTCCTCCTG-3′, FX1BF: 5′-CAACCCCTACCTCTGGTTCA-3′, FX1BR: 5′-GGGAGGAAGGAAGTGAGTC-3′, FX2AF: 5′-TTCCTGCATCTGTCACCTTG-3′, FX2AR: 5′-CTCAGTCCTGGTGTGACCAA-3′, FX2BF: 5′-CATCTTGGATGGAGCCTCAC-3′, FX2BR: 5′-TGCTTATGTCTGGGCAGTT-3′.

Results

Clinical presentaton

All 15 patients complained of prelingual hearing loss. Among them, ten children were found to have bilateral

profound hearing loss by ABR, and six (DF001, DF003, DF005, DF008, DF010 and DF012) of them received cochlear implants in Xiangya Hospital. Five adult patients had bilateral severe hearing loss with a little hearing fluctuation but not progressive. High-resolution computed tomography (HRCT) of the temporal bone revealed that all the 15 patients had EVA—14 with bilateral EVA and one (DF010) unilateral. One patient (DF007) had goiter in the 2nd decade of her life.

Mutation analysis

The mutation screening in the 15 patients revealed no pathogenic alterations in *GJB2* or in the mitochondrial 12s rRNA gene. *SLC26A4* mutation study revealed 15 mutations in 11 of the 13 families examined, but no pathogenic mutations in families NDF3 and NDF9. Genotypes and phenotypes of the 15 patients are shown in Table 1. Among the alterations detected, IVS7-2A>G was most common, accounting for 22.3% (5/22) of the mutant alleles. None of these alterations was detected in 200 alleles of the normal Chinese controls, except one T410M mutant allele. Since hearing loss due to *SLC26A4* mutations is autosomal recessive, if T410M is pathogenic, the carrier frequency for this mutation is 0.5% (1/200). Both of the two intronic mutations, IVS7-2A>G and IVS10-12T>A, were expected to lead to aberrant splicing, according to computer-assisted analysis on the database for Neural Network at Berkeley Drosophila Genome Project (http://www.fruitfly.org/seq_tools/splice.html). As all the 11 missense mutations are predicted to change amino acid residues at evolutionarily conserved domains of pendrin in human, mouse, and rat, they are likely true mutations rather than benign polymorphisms. Other base alterations were also detected in normal Chinese controls (Table 2), although they were hitherto undescribed.

Discussion

SLC26A4, encompasses 21 exons and contains a 2343-bp open reading frame. Its gene product, pendrin, is expressed in the inner ear, thyroid gland and kidney (Everett et al. 1997; Royaux et al. 2001). It was demonstrated that pendrin transports chloride and iodine, and mediates the exchange of chloride and formate (Scott et al. 2000; Royaux et al. 2001). There have been more than 100 different *SLC26A4* mutations reported. The appearance of EVA by HRCT was demonstrated to be a reliable radiological sign for the diagnosis of PS (Phelps et al. 1998). These molecular and radiological findings indicated that PS and the hearing-loss with EVA fall into one clinical spectrum caused by *SLC26A4* mutations, i.e., hearing loss with EVA with/without goiter (Tsukamoto et al. 2003).

Mutation analysis of *SLC26A4* performed in 54 Chinese EVA families (including an area of Mainland China, Taiwan and Singapore) identified 23 different mutations (Yong et al. 2001; Dai et al. 2005; Wu et al. 2005; Yang et al. 2005; present study), viz., 14 missense mutations, two nonsense mutations, five intronic nucleotide changes and two deletions (Table 3). Seven of them were found in more

Table 1 Phenotype and genotype of 15 patients with hearing loss and EVA

Subject No.	Family	Gender	Age at test (years)	EVA	Goiter	Level of hearing impairment	*SLC26A4* genotype	
							Allele 1	Allele 2
DF001	NDF1	M	9	B	–	P	IVS7-2A>G	1975G>C/V659L
DF002	NDF1	F	6	B	–	P	IVS7-2A>G	1975G>C/V659L
DF003	NDF2	F	23	B	–	S	1174A>T/N392Y	1343C>A/S448X
DF004	NDF3	M	4	B	–	P	wt	wt
DF005	NDF4	M	5	B	–	P	754T>C/S252P	1229C>T/T410M
DF006	NDF5	M	13	B	–	S	IVS7-2A>G	IVS7-2A>G
DF007	NDF6	F	23	B	+	S	IVS4_IVS6del	IVS4_IVS6del
DF008	NDF7	M	2	B	–	P	IVS7-2A>G	IVS10-12T>A
DF009	NDF7	M	7	B	–	P	IVS7-2A>G	IVS10-12T>A
DF010	NDF8	M	2	R	–	P	1343C>T/S448L	2168A>G/H723R
DF011	NDF9	M	7	B	–	P	wt	wt
DF012	NDF10	F	10	B	–	P	2T>C/M1T	269C>T/S90L
DF013	NDF11	F	23	B	–	S	1226G>C/R409H	1229C>T/T410M
DF014	NDF12	M	16	B	–	S	697G>C/V233L	1229C>T/T410M
DF015	NDF12	F	10	B	–	P	IVS7-2A>G	2162C>T/T721M

+ *or* – presence or absence, *M* male, *F* female, *B* bilateral, *R* right, *P* profound, *S* severe, *wt* wild-type

Table 2 Six variations in *SLC26A4* observed in normal Chinese controls

Nucleotide change	Amino acid change	Site	Effect	References
147G>C	S49R	Exon 2	Pathogenic	This study
IVS5-17 T>C	–	Intron 5	Polymorphism	This study
1229C>T	T410M	Exon 10	Pathogenic	This study; Coyle et al. (1998)
IVS11+47T>C	–	Intron 11	Polymorphism	This study
1905G>A	G635	Exon 17	Polymorphism	This study
2009T>C	V670A	Exon 17	Pathogenic	This study

than one family. Among these recurrent mutations, IVS7-2A>G was reported to be most frequent, and accounted for 69.1% (76/110) of all mutant alleles in the Chinese, suggesting a founder effect of this intronic mutation (Park et al. 2003; Wu et al. 2005; Yang et al. 2005). In the present study, IVS7-2A>G was still the most frequent mutant allele, but accounted for only 22.3% (5/22) of all mutant alleles detected. Haplotype analysis also favored the derivation of IVS7-2A>G from a common ancestor (data not shown). Another mutation, H723R, the predominant mutation among the Japanese, accounting for 53% of mutant alleles (Tsukamoto et al. 2003), was rarely seen among the Mainland Chinese. Only one H723R mutant allele was detected in our 15 EVA patients (1/22 alleles), and none in 100 normal Chinese controls (0/200 alleles) in this study. These findings suggest a distinct mutation spectrum in Chinese patients, since, apart from the aforesaid, 13 of 23 mutations reported in the Chinese have never been described in other ethnic groups (Table 3), whereas only five mutations (M1T, R409H, T410M, T721M, H723R) have been described in populations except for Asians (Coyle et al. 1998; Van Hauwe et al. 1998; Usami et al. 1999; Prasad et al. 2004; Shears et al. 2004).

In the present study, we did not find any *SLC26A4* mutations in two of 13 families with EVA. This may be explained by a possible occurrence of EVA due to other

Table 3 *SLC26A4* gene mutations identified in the Chinese

Mutation site	Mutation	No. of mutations detected	References
2	M1T	1	This study
3	S90L	1	This study
3	K77I[a]	1	Wu et al. (2005)
5, 6	IVS4_IVS6del1.8kb[a]	2	This study
6	V233L[a]	1	This study
6	S252P[a]	2	This study; Park et al. (2003)
7	G316X[a]	1	Dai et al. (2005)
IVS 7	IVS7-2A>G	76	This study; Dai et al. (2005); Hu et al. (2005b); Park et al. (2003); Wu et al. (2005); Yong et al. (2001)
9	A372V	1	Wu et al. (2005)
10	E387V[a]	1	Wu et al. (2005)
10	N392Y	3	This study; Hu et al. (2005a); Park et al. (2003)
10	S394del[a]	1	Yong et al. (2001)
10	R409H	1	This study
10	T410M	4	This study; Wu et al. (2005)
IVS 10	IVS10-12T>A[a]	1	This study
12	S448X[a]	1	This study; Hu et al. (2005a)
12	S448L[a]	2	This study; Wu et al. (2005)
IVS 13	IVS13+9C>G[a]	1	Yong et al. (2001)
IVS 15	IVS15+5G>A	2	Yang et al. (2005)
IVS 16	IVS16-6G>A[a]	1	Yang et al. (2005)
17	V659L[a]	1	This study
19	T721M	2	This study; Wu et al. (2005)
19	H723R	3	This study; Yong et al. (2001)

[a] Mutations were observed only in the Chinese, and those underlined are novel mutations observed in this study

unknown aetiology. Alternatively, *SLC26A4* mutations may have lain in activate cryptic splice sites in introns or in the promoter region, which was not analyzed in this study. A finding in the murine that *Foxi1* is a gene regulator of pendrin suggests that human *FOXI1* could be another gene causative for human hearing loss with EVA (Hulander et al. 2003). Although we performed mutation analysis of *FOXI1* in all the probands with EVA, no pathogenic mutation was detected (data not shown).

In summary, we have reported on a mutation screening of *SLC26A4* in 13 families with hearing loss and EVA from Central Southern China. Consequently, a spectrum of *SLC26A4* mutations was different from that in the previously reported Chinese cohort in Taiwan and Singapore (Wu et al. 2005; Yang et al. 2005), suggesting the presence of allelic heterogeneity among Chinese patients with hearing-loss and EVA. Further studies of a larger cohort are needed to support this assumption.

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