REVIEW

The genetic bases for non-syndromic hearing loss among Chinese

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Deafness is an etiologically heterogeneous trait with many known genetic, environmental causes or a combination thereof. The identification of more than 120 independent genes for deafness has provided profound new insights into the pathophysiology of hearing. However, recent findings indicate that a large proportion of both syndromic and non-syndromic forms of deafness in the Chinese population are caused by defects in a small number of genes. Studies of the genetic epidemiology and molecular genetic features revealed that there is a clear relevance of genes causing deafness in Chinese deaf patients as well as a unique spectrum of common and rare deafness gene mutations in the Chinese population. This review is focused on the genetic aspects of non-syndromic and mitochondrial deafness, in which unique molecular genetic features of hearing impairment have been identified in the Chinese population. The current China population is approximately 1.3 billion. It is estimated that 30 000 infants are born with congenital sensorineural hearing loss each year. Better understanding of the genetic causes of deafness in the Chinese population is important for accurate genetics counseling and early diagnosis for timely intervention and treatment options.

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INTRODUCTION

Hearing loss (HL) is a common congenital disorder and one of the most distressing disorders affecting humanity. Deafness can result from a mutation in a single or a combination of mutations of genes; environmental causes, such as medical problems, environment exposure, trauma and medications, or interactions between genetic and environmental factors.^{1,2} Worldwide, congenital deafness occurs in 1 in 1000 live births, and more than half of these cases are hereditary.^{2,3} Of the estimated minimum of 50% of cases with inherited hearing loss, 70% of these are non-syndromic and 80% of these are autosomal recessive.⁴ Non-syndromic hearing loss (NSHL) is most often sensorineural. It can be divided into DFNA (autosomal dominant deafness, 15–20%), DFNB (autosomal recessive deafness, 80%), DFN (X-linked deafness, 1%), and mitochondrial deafness of at least 1%.^{4,5} To date, 121 deafness loci have been reported, 54 DFNA loci and 67 DFNB loci. More than 40 genes for monogenetic NSHL and even more for syndromic HL have been cloned (<http://webhost.ua.ac.be/hhh/>).⁶

Despite the genetic heterogeneity of deafness, there is evidence that a large proportion of non-syndromic forms of hearing loss in Chinese populations is caused by a limited number of recurrent mutations resulting from common founders or a mutational hot spot. It is well known that there are racial and ethnic differences in the causes, expression, and prevalence of various Mendelian diseases and it is

not surprising that groups with a common ancestry also share genetic risk factors for particular human disorders.^{7,8} Some recessive diseases could become prevalent in a population either because the heterozygous state is associated with a selective advantage and/or because there was a change in frequency of the mutant allele caused by genetic drift or loss of the beneficial allele.⁹ Thus, knowledge of a person's ancestral origin can be informative for the provision of health care, including testing, diagnosis and treatment when genetic factors are involved.¹⁰ A series of studies have revealed genes responsible for Chinese deafness patients, and the differences in mutation spectrum between Chinese (probably other Asian populations) and populations with European ancestry.

According to the China Disabled Persons' Federation website, China has approximately 21 million people with hearing loss out of the 60 million disabled. Although there has been a significant advance in the knowledge of the molecular basis of hereditary deafness in recent years, there have been few studies in China to evaluate the effects of genetic etiologic factors. The magnitude of the problem in China remains largely undefined. State-of-the-art molecular testing is now available for the most common causes of hereditary hearing loss. However, only with knowledge of prevalent population-specific mutations, can an effective strategy for detecting deafness genes and an appropriate genetic counseling be developed. The importance of

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identifying the genetic basis for deafness among Jews and Japanese population have been reported earlier.^{11,12} Here, we focus on the implications of identifying the molecular genetic features in the largest population in the world for patient care, molecular diagnosis and better genetic counseling.

Non-syndromic recessive deafness (DFNB)

DFNB1 (*GJB2*/*GJB6*). Connexin 26 has been found to be the most common cause of deafness in many ethnic populations around the world. *GJB2* encodes a gap junction protein expressed in the cochlea and is thought to be important for recycling potassium ions that flow into sensory hair cells as part of the transduction current. Mutations of *GJB2*, which is responsible for DFNB1 and DFNA3, are the most frequent cause of inherited hearing loss.^{13–15} More than 100 different mutations in *GJB2* have been identified in patients with non-syndromic deafness and a significant difference in the frequency and distribution of the mutations have been observed in different populations (<http://davinci.crg.es/deafness/>). They are responsible for approximately half the cases in the United States, Europe, Australia, and Israel, and have been reported in other populations as well. Most interestingly, a single mutation, 35delG, accounts for up to 70% of Northern and Southern European, as well as American Caucasian populations, with a carrier frequency ranging from 1.3 to 2.8%.^{16,17} Another *GJB2* mutation, the 167delT, accounts for 40% of the pathologic alleles in the Jewish deaf population¹⁸ and has a 4% carrier frequency among Ashkenazi Jews.¹⁹ The 235delC mutation is the most prevalent in Eastern Asian (Japanese, Chinese and Korean) populations, R143W has been described as a recessive cause of deafness in Ghana and the W24X, the most common *GJB2* mutation in India, has also been found in high prevalence in Slovak and Spanish gypsies (www.gendef.org). A series of reports have described genotype–phenotype correlations for most *GJB2* genotypes, enabling, to a certain extent, to predict the phenotype expression on the basis of the genotype. However, for the majority of these genotypes, a certain degree of phenotypic variability was still observed, which was most striking for 35delG homozygous patients. Hearing loss of 35delG homozygous patients ranges from mild to profound.^{20,21} There was inter- and intrafamilial phenotypic variability and the hearing loss ranged from mild (least often) over moderate to severe and profound (most frequent).

More than twenty *GJB2* mutations have been reported in Chinese patients (Figure 1). Mutation screening of *GJB2* in Chinese deaf probands revealed that the deletion of cytosine at position 235 (235delC) mutation was the most prevalent mutation (20.3% of alleles), accounting for 81% of the pathologic alleles in multiplex cases and 67% in simplex cases.²² We further confirmed that 235delC is the most common pathologic mutation in inherited deafness attributed to *GJB2* in the Chinese population.²³ We screened DNA samples from 3004 patients with non-syndromic hearing impairment from 26 regions of China and found that the 235delC allele frequency varies from 0.9 to 19.5%. These results indicate that mutations in *GJB2* are a major cause of inherited and sporadic congenital deafness in the Chinese population. We have recently sequenced the coding region of *GJB2* gene from 2063 unrelated probands with non-syndromic deafness and identified a total of 24 mutations (Figure 1 and Table 1) (Dai *et al.*, unpublished data). Eight of these mutations have not been previously reported. The novel mutations include six frame shifts (c.99delT, c.155_158delTCTG, c.311_324del14, c.388_397del10, c.512_515insAACG and c.605_651ins46), a single amino acid deletion (c.424_426delTCC/del142F), and one nonsense mutation (p.W3X). The two most prevalent mutations including

Figure 1 Schematic representation of the relative linear location of the mutations of *GJB2* gene in the Chinese population. Novel mutations are in bold letters (Dai *et al.*, unpublished data). The structural motifs of connexins are NT: amino-terminus; M1-M4: transmembrane domains 1–4; E1/E2: extracellular domains; CL: cytoplasmic loop; CT: carboxyl-terminus.

c.235delC and c.299_c.300delAT account for 82% of all mutant alleles identified.

The status of the 235delC mutation, which seems to be a unique mutation in Asian populations, is comparable to the 35delG mutation in Caucasian populations. Patients with homozygous or compound heterozygous 235delC mutation exhibit a comparative phenotype varying from mild to profound loss of hearing. The high frequency of the 35delG *GJB2* allelic variant in the white population has been shown to be the result of a founder effect, rather than a mutational hot spot.⁴¹ The 167delT mutation present in Ashkenazi Jews has also been attributed to a founder effect.¹⁹ Both 35delG and 167delT mutations are absent or exceptionally low in Asian populations, in whom, the 235delC is the most prevalent, with carrier rates ranging from 1.0 to 1.3%. This mutation accounts for up to 80% of pathogenic *GJB2* alleles among Japanese,^{14,42,43} and Koreans.⁴⁴ Interestingly, the 235delC has not been detected in South Asian populations from India, Pakistan, Bangladesh and Sri Lanka, in whom the prevalent *GJB2* mutations are W24X and W77X.^{45,46} The high frequency of the 235delC mutation in East Asian populations has subsequently been

Table 1 Mutations underlying non-syndromic hearing loss in Chinese population

<i>Gene</i>	<i>Protein</i>	<i>Chromosomes location (locus)</i>	<i>Mutation</i>	<i>References</i>
GJB2	Connexin 26	13q11-12 (DFNB1)	W3X	Dai <i>et al.</i> unpublished data
			G4D	Dai <i>et al.</i> unpublished data
			35delG	Dai <i>et al.</i> unpublished data
			35iinsG	Dai <i>et al.</i> unpublished data
			R32C	Dai <i>et al.</i> unpublished data
			V37I	Dai <i>et al.</i> unpublished data
			99delT	Dai <i>et al.</i> unpublished data
			E47K	Dai <i>et al.</i> unpublished data
			E47X	Dai <i>et al.</i> unpublished data
			155_158delTCTG	Dai <i>et al.</i> unpublished data
			176_191del16	Dai <i>et al.</i> unpublished data
			235delC	Dai <i>et al.</i> unpublished data
			S85P	Dai <i>et al.</i> unpublished data
			T86R	Dai <i>et al.</i> unpublished data
			299_300delAT	Dai <i>et al.</i> unpublished data
			311_324del14	Dai <i>et al.</i> unpublished data
			R127H	Dai <i>et al.</i> unpublished data
			388_397del10	Dai <i>et al.</i> unpublished data
			S139N	Dai <i>et al.</i> unpublished data
			424_426delTCC	Dai <i>et al.</i> unpublished data
			R143W	Dai <i>et al.</i> unpublished data
			Y152X	Dai <i>et al.</i> unpublished data
			512_515insAACG	Dai <i>et al.</i> unpublished data
			605_650ins46	Dai <i>et al.</i> unpublished data
				24
			IVS3-2A>G	24
			3596_3597ins T	24
			M1T	25
			E37X	26
			P76 L	26
			K77I	27
MYO7A	Myosin VIIA	11q13.5 (USH1B)	R244P	
SLC26A4	Pendrin	7q31 (DFNB4)		

Table 1 Continued

<i>Gene</i>	<i>Protein</i>	<i>Chromosomes location (locus)</i>	<i>Mutation</i>	<i>References</i>
GJB3		13q12 (DFNA2)	S90 L	25
			T94I	26
			P112S	26
			H135R	Our unpublished data
			349delC	26
			387delC	26
			M147V	28
			G197R	26
			IVS4_IVS6del1.8 kb	25
			G204V	26
			V233 L	25
			S252P	25
			D271G	26
			916-917insG	26
			IVS7-2A>G	29
			G316X	30
			IVS10-12T>A	25
			A387V	26
			N392Y	25
			1181_1183delTCT	27
			R409H	25
			T410M	25
			Q421P	26
			K440X	26
			Q446X	26
			448X	25
			Q514X	26
			1555_6delAA	Our unpublished data
			I529S	26
			V545A	Our unpublished data
			S532R	26
			IVS13+9C>G	31
			IVS14-1G>A	32
			IVS14+1G>A	33
			1687_92delA	Our unpublished data
			N558I	26
			IVS15+5G>A	34
			IVS16-6G>A	34
			D573Y	26
			1746delG	26
			V659 L	26
			2082delA	Our unpublished data
			L676Q	32
			R685I	26
			H723R	31
Mitochondrial genome	12S rRNA		R180X	35
			E183K	35
			423delATT	36
			I141V	36
tRNA ^{Leu} (UUR)			A827G	37
			961C insertion	37
			T1005C	37
			T1095C	37, 38
			A1116G	37
			C1494T	37
			A1555G	39
			3243A>G	40

shown to be the result of a founder effect, rather than a mutational hot spot, and 235delC among all East Asian populations was derived from a common ancestral founder.^{47,48}

A role for *GJB6*, the gene adjacent to *GJB2* on chromosome 13, was first suggested in 1999. The most common mutation in *GJB6* is a 342-kb deletion, which causes NSHL when homozygous, or when present in trans with a recessive *GJB2* mutation. The *GJB6* deletion may account for 10% of all *DFNB1* alleles with an extremely wide range based on ethnic origin. *GJB2* and *GJB6* genes are expressed in the cochlea where they can combine to form multi-unit hemichannels in the cell membrane, and function as an integral component of the potassium regulation in the inner ear. The 342-kb deletion (*GJB6*-D13S1830) mutation is most frequent in Spain, France, the United Kingdom, Israel and Brazil (5.9–9.7% of all *DFNB1* alleles); it is less frequent in the USA, Belgium and Australia (1.3–4.5% of all *DFNB1* alleles), and is very rare in Southern Italy,⁴⁹ but has been found, present in Northern Italy and in Germany at frequencies similar to those of other European countries.^{50,51} The deletion was not found in Austria⁵² Turkey^{53,54} and China.^{55–58}

DFNB2 (*MYO7A*). Myosin VIIA, located at 11q13.5, is an unconventional myosin that has been implicated in recessively inherited USH1B,⁷ recessively inherited atypical USH,^{59,60} non-syndromic autosomal recessive hearing impairment (*DFNB2*)²⁴ and autosomal dominant hearing impairment (*DFNA11*).⁶¹ Mutations in *MYO7A*, are associated with Usher syndrome type 1B in many populations, and more than one hundred different mutant alleles of *MYO7A* have been reported (www.hgmd.cf.ac.uk/ac/gene.php?gene=MYO7A). We have previously shown that three recessive alleles (pR2444P, IVS3nt-2a→g and val1199insT) of the *MYO7A* gene cause *DFNB2* in families from China.²⁴ In a recent study of 24 consanguineous Pakistani families segregating deafness as a recessive trait by Riazuddin *et al.*⁶² a total of 23 of these families were found to segregate USH1B whereas one family segregated *DFNB2*. Data of functional analyses of *MYO7A* mutations is consistent with the hypothesis that *DFNB2*-causative mutations lead to a less severe phenotype than the *USH1B*-associated mutations because the resulting proteins retain some degree of normal activity.

DFNB4 (*SLC26A4*). Pendred syndrome is an inherited disorder that accounts for as much as 10% of hereditary deafness.⁶³ The syndrome is characterized by congenital severe-to-profound sensorineural hearing loss (SNHL) and euthyroid goiter. Goiter is not present at birth and develops in early puberty (40%) or adulthood. Vestibular function is abnormal in the majority of affected persons. Recessive mutations of the *SLC26A4* (*PDS*) gene on chromosome 7q can cause sensorineural deafness with goiter⁶⁴ or NSHL without goiter.⁶⁵ Mutations in the *SLC26A4* gene are identified in about 50% of multiplex families. These mutations disrupt *in vitro* transmembrane anion/base exchange activity of the *SLC26A4* polypeptide, pendrin.⁶⁶ So far, more than 100 mutations causing Pendred syndrome and non-syndromic (EVA) sensorineural hearing loss have been reported in the *PDS* gene (<http://www.healthcare.uiowa.edu/labs/pendredandbor/slcMutations.htm>). Moreover, a significant difference in the frequency and distribution of the mutations has been observed in different populations.

To date, more than 40 mutations have been reported among the Chinese deaf patients (Figure 2). The IVS7-2A>G mutation was the most common form accounting for 22.3–57.62% of all the mutant alleles in Chinese patients with hearing loss associated with enlarged vestibular aqueduct (EVA) or both EVA and Mondini dysplasia.^{25,26}

Among Asian populations, a distinct spectrum of *SLC26A4* mutations in patients associated with EVA with highly prevalent founder mutations has been observed, such as p.H723R in Japan and Korea and IVS7-2A>G in Taiwan and mainland China.^{67,32,68,69,34} Park *et al.*³² performed a mutation screening of the seven exons of the *SLC26A4* gene in 274 East Asians and 318 South Asians deaf probands with sporadic or familial severe-to-profound prelingual deafness, including 86 Chinese affected subjects. They demonstrated mutations in *SLC26A4* about 5.5% of both groups and identified three mutations (S252P, IVS7-2 A>G, N392Y) in 5 out of 86 (5.8%) Chinese probands. Tsukamoto *et al.*²⁸ reported causative mutations have been identified in 90% of typical Pendred families in Japan, 78% among them had sensorineural hearing loss associated with EVA and 53% of mutations were the H723R mutation. Campbell *et al.*⁷⁰ stated that L236P, T416P and IVS8+1G>A were the three frequent mutations in the Caucasian population.⁷⁰ In the Spanish population the most frequent mutation is Q514K (17%).⁷¹

The IVS7-2A>G mutation was first reported in a Turkish family⁷² and subsequently detected in deaf subjects from Japan, Korea and China.^{32,28,73,74} IVS7-2A>G has not been found in western populations, including deaf patients in the United States,^{70,73,75,76} <http://www.genetests.org/>,⁷⁷ We have recently reported a comprehensive study of the prevalence of IVS7-2A>G mutation in an analysis of 3271 deaf subjects from 27 regions of 24 provinces of China. The detection rate was found to range from 28% to below 1% based on ethnicity. The results showed that the genetic test for the IVS7-2A>G mutation alone would identify the molecular cause in up to 8–12% of deaf patients in few eastern and central regions of China. However, the IVS7-2A>G mutation occurs at a much lower frequency (0.000–0.019) among ethnic groups in the southwest and northwest regions of China.⁷⁸ The data suggest that for subjects that are negative for the IVS7-2A>G mutation, further mutational analysis of the full *SLC26A4* gene or other deafness-related genes will be necessary.

Non-syndromic dominant hearing loss (DFNA)

DFNA2 (*GJB3*). The Connexin 31 gene (*GJB3*) mapped to chromosome 1p33–p35 encodes for a protein that is 270 amino acids long. Mutations in the *GJB3* gene have been reported to be responsible for both *DFNA* and *DFNB*.^{45,35,36} More than 10 different mutations have been found in patients with deafness from Chinese, Brazilian and Spanish populations.^{74,36,79,80} However, the pathogenicity of most of these sequence alterations still remains questionable. Mutations in *GJB3* have originally been shown to underlie an autosomal dominant form of non-syndromic deafness (*DFNA2*) in Chinese patients; a missense mutation (E183K) and a nonsense mutation (R180X) of *GJB3* were found to be associated with high-frequency hearing loss.³⁶ We subsequently showed that mutations in *GJB3* also underlie recessive non-syndromic form of deafness in this population.⁷⁹ These findings indicate that *GJB3* variations are common in non-syndromic hearing loss patients in the Chinese population. In contrast, the studies described so far have shown that variations in *GJB3* have no or a low genetic relevance in European and Caucasian populations in general. Extensive sequence analysis of the coding region and the 5' UTR of *GJB3* in all five first *DFNA2* families originating from Indonesia, the United States, Belgium and the Netherlands^{81,82} revealed no mutations.⁸³ Nonetheless, the dominant D66del mutation in *GJB3* linked to neuropathy and deafness was identified in one Spanish deaf patient.⁷⁴ The failure in finding HL causing mutations in *GJB3* in a screening of sporadic cases with NSHL performed in California and in Austria further confirms population relevance of *GJB3* mutations in the Chinese population.^{84,85}

Figure 2 Schematic representation of the relative linear location of the mutations of *SLC26A4* gene in the Chinese population. Novel mutations were bold in italic showing above the exons (Our *et al.*, unpublished data).

In a screening of 108 *GJB2* heterozygous Chinese patients with non-syndromic deafness without obvious dominant inheritance patterns, we recently showed that mutations in *Cx26* and *Cx31* genes can interact to cause hearing loss in digenic heterozygotes in humans. Direct physical interaction of *Cx26* with *Cx31* is supported by data showing that *Cx26* and *Cx31* have overlapping expression patterns in cochlea and by the detection of heteromeric *Cx26/Cx31* connexons, using coimmunoprecipitation of mouse cochlear membrane proteins. Furthermore, *in vitro* cotransfection of the two-tagged connexin proteins showed that they were able to co-assemble *in vitro* in the same junction plaque Liu *et al.*⁸⁶

DFNA5. DFNA5 was originally mapped to chromosome 7p15 in an extended Dutch kindred with autosomal dominant progressive hearing loss starting in the high frequencies. With increasing age the middle and low frequencies also became affected.⁸⁷ To date, five mutations have been reported in the DFNA5 gene. Four of them caused skipping of exon 8, resulting in premature termination of the open reading frame. All four mutations segregated with late-onset non-syndromic hearing impairment in the families.^{88–90} Among the mutations identified, a CTT deletion in the polypyrimidine tract of intron 7 and an IVS8+4A→G transition in the splice-donor site of intron 8 have been described in Chinese families with non-syndromic deafness, indicating that mutations in DFNA5 may be major known causes of hereditary hearing loss in Chinese patients.⁸⁹ A truncating mutation, c.640insC, in exon 5 of DFNA5 was recently reported in an Iranian family. Interestingly, the mutation is not a disease-causing mutation, and was even found present in normal-hearing subjects in this family.⁹¹ This finding may be regarded as support to the previously formulated hypothesis that only exon 8 skipping can lead

to DFNA5-associated hearing loss. Recent studies suggest that DFNA5 belongs to a novel GSDMDC family. As different mutations in the DFNA5 gene have been shown to result in hearing loss, it is tempting to speculate that this gene may play some crucial role in the physiological process of hearing.

DFNA9. The DFNA9 locus on chromosome 14q12–q13 is known to be associated with vestibular dysfunction.⁹² The cochlin, encoded by *COCH* is an extracellular matrix protein that contains a region homologous to a domain in factor C of Limulus, also known as LCCL domain and two von Willebrand factor A-like domains (vWFA1 and 2).⁹³ Interestingly, the majority of the previously described *COCH* mutations are missense point mutations located within the LCCL domain of cochlin.^{94–99} They have been associated with progressive hearing loss and concomitant vestibular symptoms. Street *et al.*¹⁰⁰ reported a p.C542F mutation in an American DFNA9 family with hearing loss as well as oculomotor and vestibular disturbances. This mutation located within the vWFA2 domain of cochlin, representing the first reported DFNA9 mutation outside of the LCCL domain. We subsequently identified a different mutation, p.C542Y, at the same location in vWFA2 domain in a large Chinese family with late-onset autosomal dominant non-syndromic progressive sensorineural hearing loss. In addition, a heterozygous missense mutation (p.M512T) at an evolutionarily conserved methionine residue was also identified in the vWFA2 domain in a small family.¹⁰¹ More importantly, none of the C542F, C542Y and M512T mutation carriers had vestibular complaints (dizziness, vertigo, head movement-dependent oscillopsia and instability in the dark) in their lifetime.^{100,101} A genotype–phenotype correlation could thus be established when comparing the vestibular involvement between the

DFNA9 families harboring mutations in the LCCL domain and in the vWFA2 domain.

DFNA11. Mutations in Myosin VIIA have been found to be responsible for the DFNA11 deafness. Initially, an in-frame 9-bp deletion in exon 22 of *MYO7A* was identified to cause DFNA11 in a Japanese family.⁶¹ The affected members suffered from postlingual, bilateral, non-syndromic sensorineural hearing loss, with gradual progression at all frequencies and minor vestibular problems. No evidence was found for retinitis pigmentosa.¹⁰² So far, the DFNA11 families have been identified in other populations including USA, Italy, Dutch and Germany.¹⁰³ Recently, a DFNA11 family with late-onset hearing loss ranging from 20 to 47 years old was reported, involving the high-frequency first. The locus was mapped in a Chinese pedigree with an autosomal dominant non-syndromic hearing loss. A maximum two point LOD score of 5.71 at $\theta=0.05$ on chromosome 11q, was obtained for marker D11S937. The analysis of recombinant haplotypes mapped the locus between markers (D11S165–D11S1874).¹⁰⁴ A missense mutation at the motor region has been recently identified in this Chinese DFNA11 family (Yuan *et al.*, unpublished data). Interestingly, all mutations involved in the DFNA11 families are located at the motor domain of the Myosin VIIA protein.

DFNA39. Xiao *et al.*¹⁰⁵ described two Chinese DFNA39 families, characterized by the combination of bilateral progressive high-frequency sensorineural hearing loss, with dentinogenesis imperfecta-1 (DGI1). DGI1 is an autosomal dominant dental disease associated with abnormal dentin production and mineralization. Distinct mutations within the dentin sialophosphoprotein gene have been found responsible for the clinical manifestations of Dentinogenesis imperfecta 1 with or without DFNA39.

Mitochondrial DNA mutations

Mitochondrial (mt) pathology has been implicated in both inherited and acquired hearing loss. Sensorineural hearing loss (SNHL) is present in 42–70% of individuals with mt cytopathies and can be syndromic and non-syndromic.^{106–108} Mutations in mtDNA have also been found to be associated with both aminoglycoside-induced and non-syndromic deafness.^{108,109} The matrilineal transmission of aminoglycoside-induced deafness in the Chinese population was first reported in isolated pedigrees in the early 1990s and mutations in the mtDNA were suggested as the likely cause.^{30,110} The most commonly used ototoxic drugs in China are aminoglycoside antibiotics including streptomycin, gentamycin and kanamycin. Aminoglycoside antibiotics were widely, and in many cases over-used nationwide in China from the 1960s to 1980s, as they were considered cost-effective in controlling infections by a wide spectrum of bacteria. Despite the large number of reports on aminoglycoside-induced hearing loss in China and in other countries, aminoglycosides and a few new synthetic derivatives from traditional aminoglycosides, such as amikacin, netilmicin, etimicin, isepamicin, are still being used in clinics all over China, especially in low-income areas including mountainous regions. Different prevalences of these predisposing mutations might contribute to the high incidence of aminoglycoside ototoxicity in certain regions of China. The incidence of aminoglycoside-induced deafness has increased in recent years in China. Some studies of deaf-school populations have indicated that aminoglycoside antibiotics may account for 13–66% of profound deafness with a prevalence of 0.035%.¹¹¹ Our data shows that 88% of severe-profound mtDNA deafness carrying the homoplasmic A1555G mutation had exposure to aminoglycosides.¹¹²

The mitochondrial 12S rRNA (MTRNR1) appears to be a hot spot for mtDNA mutations. The MTRNR1 mutations likely alter the secondary structure of the 12S rRNA molecule to make it more similar to its bacterial counterpart, the 16S rRNA, the target of aminoglycoside.¹¹³ This might explain the use of aminoglycosides and the cumulating effect of these MTRNR1 mutations. Sequence analyses of the mitochondrial genome in patients with aminoglycoside ototoxicity have led to the identification of several ototoxic mtDNA mutations in the 12S rRNA gene. The homoplasmic A1555G and mutations at position 961 of the 12S rRNA gene have been implicated with aminoglycoside-induced and non-syndromic hearing loss in many families of different ethnic origins.^{29,114–117,30,110,118,119,37,120} Similarly, the homoplasmic C1494T mutation in the highly conserved decoding site of the same gene has been associated with aminoglycoside-induced and non-syndromic hearing loss in a large Chinese family.¹²¹ Furthermore, the 961 C-insertion and the A827G mutation have been reported to be linked to aminoglycoside ototoxicity or non-syndromic hearing loss,^{30,110,119,37,120} and possibly the T1005C and A1116G mutations can contribute to ototoxic hearing loss.¹¹¹ Another mutation, the T1095C in the 12S rRNA gene has been associated with hearing impairment in several genetically unrelated families including Italian^{122,123} and Chinese deaf patients.^{111,121}

In the familial cases of aminoglycoside ototoxicity, these known predisposing mutations in the 12S rRNA gene account for a significant proportion of cases.^{111,114} The A1555G mutation has been found in high frequency compared to other mutations in the sporadic populations with aminoglycoside ototoxicity. The prevalence of the A1555G mutation varies in hearing-impaired populations from different ethnic origins. The incidence of A1555G mutation in non-syndromic deafness is much lower compared with those with aminoglycoside ototoxicity. In Asian non-syndromic hearing-impaired patients, the prevalence of the A1555G mutation seems to be higher than in Caucasians: 2.9% in Chinese,¹¹¹ 3% in Japanese,¹²⁴ and 5.3% in Indonesian.¹²⁵ There was variation in the incidence of the A1555G mutation in Caucasian deaf populations: 0.6% in Cincinnati white patients,^{30,110} 1.8 and 0.7% in Hungarian and Germany populations, respectively,¹²⁶ 1.8% in Turkish pediatric population,¹²⁷ 2.4% in a Danish cohort¹²⁸ and 2.5% in a UK cohort.¹²⁹ Li *et al.*¹³⁰ conducted a systematic mutational screening of the mitochondrial 12S rRNA gene in a Chinese pediatric population with sporadic aminoglycoside-induced and NSHL.¹³¹ They showed that aminoglycoside ototoxicity is responsible for 48% of cases. Mutations at position 961 in the MTRNR1 gene accounted for ~1.7 and 4.4% cases of aminoglycoside-induced and NSHL, respectively in this Chinese clinical population. The frequency of the A1555G mutation is ~13 and ~2.9% in these Chinese pediatric subjects with aminoglycoside-induced and non-syndromic hearing loss, respectively. Our recent study shows that the mtDNA A1555G is responsible for deafness for a large proportion of NSHL, accounting for 15.5% of SNHL cases from the special clinics for deaf in China.¹¹²

The A1555G mutation is thought to be a susceptibility mutation, which needs the combined action of environmental factors and/or nuclear modifying genes to cause hearing impairment.^{130,132–135} Variants in mitochondrial tRNA^{Glu} A14693G, tRNA^{Thr} T15908C, tRNA^{Arg} T10454C, tRNA^{Ser(UCN)} G7444A and tRNA^{Cys} G5821A may influence the phenotypic manifestation of deafness-associated 12S rRNA A1555G mutation.^{110,118,136,38,137} Interestingly, the tRNA^{Cys} T5802C, tRNA^{Thr} A15924C and ND5 T12338C alterations have been shown to have a potential modifier role in increasing the penetrance and expressivity of the deafness-associated 12S rRNA A1555G mutation in Han-affected Chinese patients.¹³⁸ Furthermore, Liao *et al.*¹³⁹

reported that the ND4 G11696A mutation may act in synergy with the primary deafness-associated 12S rRNA A1555G mutation in a four-generation Chinese family, thereby increasing the penetrance and expressivity of hearing loss in this Chinese pedigree.

The mitochondrial tRNA^{Ser(UCN)} (MTTS1) appears to be another hot spot for mtDNA mutations associated with NSHL. Five deafness-associated mutations, A7445G,^{107,140,141} A7445C¹⁴² 7472insC,^{143,144} T7510C¹⁴⁵ and T7511C^{146,147} have been identified in this gene.

Non-syndromic loci with unknown specific genes DFNA41/42/53

There are also genes for autosomal dominant and recessive as well as X or Y-linked hereditary deafness that is yet to be cloned in the Chinese population. We have previously reported the mapping of the DFNA41 and DFNA53,^{148–150} located on chromosome 12q24-qter and on 14q11.2–q12 respectively, in large multi-generational Chinese families. Another locus (DFNA42) for autosomal dominant non-syndromic hearing loss identified at 5q31.1–32 has also been reported in a Chinese pedigree.¹⁵¹ Finally, an X-linked recessive deafness syndrome with muteness as well as Y-linked inheritance of non-syndromic hearing impairment has also been described in Chinese deaf families.^{152,153}

CONCLUDING REMARKS

We have described in this review genes and spectrum of the mutations found in the Chinese deafness population. So far, mutations in *GJB2*, *GJB3*, *Myo7A*, *SLC26A4* and the A1555G mitochondrial mutation were found to be the major causes of hearing loss in Chinese deaf patients. It has been shown that the 235delC mutation in the *GJB2* gene and IVS7-2A>G (c.919-2A>G) in the *SLC26A4* gene are common founder mutations, thus explaining their frequency. Mutations in the *SLC26A4* gene are second to *GJB2* mutations as a currently identifiable genetic cause of SNHL in China.^{23,78} Differences in spectrum of the *GJB3* and *Myo7A* mutations have also been described in Chinese cases of SNHL. Genetic testing is now available for a number of genes involved in hearing loss. However, only with the knowledge of prevalent population-specific mutations, can an appropriate and effective strategy for detecting deafness genes be developed. This will facilitate precise clinical diagnosis, accurate genetic counseling and will provide a framework for the implementation and assessment of any future gene therapy.

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