International Journal of Pediatric Otorhinolaryngology 75 (2011) 202–206

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

The audiological characteristics of a hereditary Y-linked hearing loss in a Chinese ethnic Tujia pedigree

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ARTICLE INFO

Article history:
Received 28 August 2010
Received in revised form 29 October 2010
Accepted 30 October 2010
Available online 3 December 2010

Keywords:
Hearing loss
Pedigree
Chinese
Y-linked inheritance

ABSTRACT

Objective: To investigate audiometric characteristics of hearing loss in a large Chinese ethnic Tujia family and determine its hereditary type.
Methods: Total 76 live individuals were investigated in the notable 84 members of this family. The detailed audiometric evaluations were undertaken for the proband and his 47 family members. The degrees of sensorineural hearing impairment were defined as an air/bone gap <15 dB hearing loss averaged over 0.5, 1 and 2 kHz. The severity of hearing loss was established based on the hearing ability of the better ear, averaged over 0.5, 1, 2 and 4 kHz, and classified into four categories: mild, moderate, severe and profound.
Results: Nineteen patrilineal relatives of the 76 live members had hearing impairment. The age of onset ranged from 7 to 21 years old with the average of 13.2 years. The audiometric defect was described by auditory curves of a high frequency in 47% of the patients. Affected members in this family demonstrated a non-syndromic, late onset, bilateral, symmetrical, postlingual and sensorineural hearing loss.
Conclusions: The audiometric configuration in males of the pedigree is consistent with the hereditary Y-linked hearing loss. Thus we speculate that a putative gene on the Y chromosome could contribute to the cause of the disease.

1. Introduction

Hearing impairment is the most common sensory deficit and one of the most distressing disorders affecting humanity. Approximately half of these cases are genetic origin [1]. Of the estimated minimum of 50% of cases with inherited hearing impairment, 70% of these are non-syndromic. Non-syndromic hearing impairment (NSHI) can be divided into autosomal dominant deafness (15–20%), autosomal recessive deafness (80%), X-linked deafness (1%), and mitochondrial deafness (at least 1%) [2]. In the past two decades, rapid progress has been made on the study of genetic deafness in developed countries as well as in china. Hu et al. [3] analyzed 36 pedigrees with a positive family history of aminoglycoside antibiotic induced deafness and ascertained in a population of 483,611 in Shanghai suburb. The results showed that the susceptibility to antibiotic ototoxicity was transmitted by females exclusively, indicating mitochondrial inheritance. Other groups studied the molecular basis of aminoglycoside-induced hearing loss in Chinese family [4,5]. Liu et al. [6] explored the audiological and genetic features of the mitochondrial DNA (mtDNA) mutations and found that the hearing loss was post-lingual, bilateral, sensorineural, and symmetric, and the main audiogram shapes were sloping. For many populations, the most common cause for non-syndromic autosomal recessive hearing loss is mutation on GJB2 gene which encodes connexin 26, a gap junction protein [7]. Liu et al. [8] reported that the audiogram in the majority of individuals with the GJB2 mutations was residual/sloping or flat and rarely U-shaped, similar to what seen in persons with hearing impairment without GJB2 mutations. In addition, they found no difference in the audiogram shapes between Chinese cases with the 235delC mutation and cases with other GJB2 mutations. Xia et al. [9] cloned the GJB3 gene encoding human gap junction protein β-3 and revealed that mutations in GJB3 may be responsible for bilateral high-frequency hearing impairment. A DFNA11 family with late-onset hearing loss ranging from 20 to 47 years old was reported and the locus was mapped in a Chinese pedigree with an autosomal dominant non-syndromic hearing loss [10]. A missense mutation at the motor region has been recently identified in this Chinese DFNA11 family. Liu et al. reported the mapping of the DFNA41 and DFNA53, located on chromosome

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doi:10.1016/j.ijporl.2010.10.035

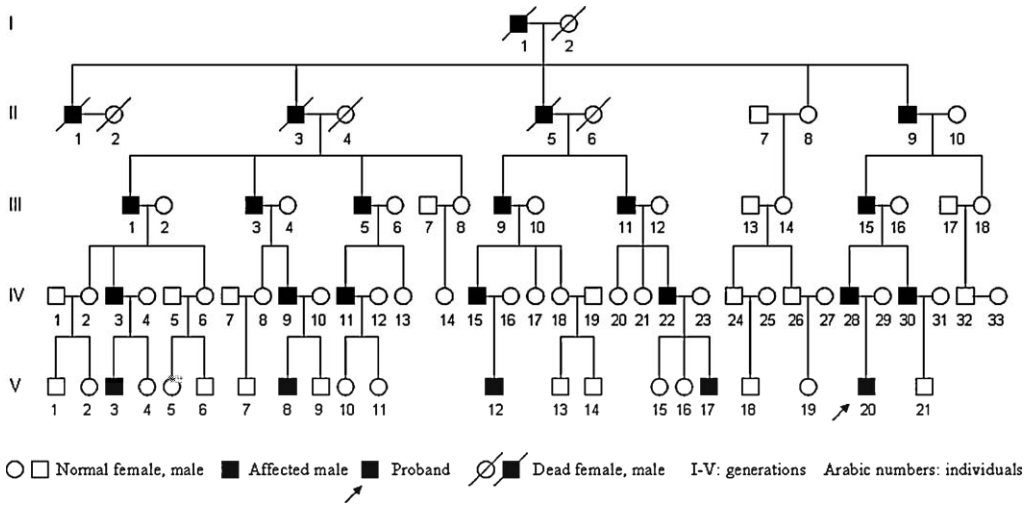

Fig. 1. A pedigree of non-syndromic hearing impairment from 84 members of a Chinese ethnic Tujia family. All affected individuals are patrilineal males, indicating the Y-linked inheritance pattern.

12q24–qter and 14q11.2–q12 respectively, in large multi-generational Chinese families [11,12]. Another locus (DFNA42) for autosomal dominant non-syndromic hearing loss was identified on 5q31.1–32 in a Chinese pedigree [13]. Wang et al. [14] reported an X-linked recessive Chinese family with well-characterized familial subjects affected with congenital profound sensorineural hearing impairment (CPSHI) which is associated with a founder mutation in the POU3F4 gene. Finally, a Y-linked inheritance of non-syndromic hearing impairment has also been described in Chinese deaf families [15,16]. In the present study, we reported a rare Chinese family and described the audiometric characteristics of the affected members since audiometric configuration has been considered to be helpful in indicating a hearing loss of genetic origin [17]. The aims of the present study were to: (1) evaluate the audiometric characteristics of hearing loss in a large Chinese ethnic Tujia family and analyze the pattern of inheritance of this family; (2) compare the audiometric configuration of this family with the DFNY1 family and determine the most possible pattern of inheritance of this family.

2. Subjects and methods

2.1. Ethical considerations

The study protocol has been reviewed and approved by the Research Ethics Committee of Huazhong University of Science and Technology, Wuhan, China. Informed consent before clinical evaluations was obtained from all participants.

2.2. Participants

The effected family (Fig. 1) is from a Chinese ethnic minority, Tujia. The Tujia population has been living in the west of Hunan and Hubei Province of China for two thousand years. The family in this study originated from Changyang ethnic Tujia Autonomous County in Hubei Province. Most of the family members have been living in the same village for over 150 years. The oldest member of the family has been keeping a genealogical record of the family's history and this tradition has continued up to now. Details of the pedigree were verified through study of the family records and interviews with the elders in the family. The proband was a 7-year-old male. His immediate relatives were interviewed and investigated in May 2009 by otolaryngologists from the Tongji Hospital of the Tongji Medical College, the Huazhong University of Science and Technology. The investigation was then extended to 84 family members from five generations of which 76 members were interviewed. Forty-seven members were given detailed physical examinations and audiometric evaluations. All effected individuals had no history of taking ototoxic drugs.

2.3. Audiometric evaluations

The audiometric evaluations included pure-tone audiometry using EAR-3A insert earphones (Aearo Company, US), and/or auditory brainstem responses using SmartEP (Intelligent Hearing Systems, US). The description of hearing impairment was recorded according to recommendations included in the EU HEAR project as described by Stephens [18]. The degrees of sensorineural hearing loss were defined as an air/bone gap $<$15 dB HL (hearing loss) averaged over 0.5, 1 and 2 kHz. The severity of hearing loss, according to the better hearing ear and averaged over 0.5, 1, 2 and 4 kHz, was categorized as follows: mild (20–40 dB HL), moderate (41–70 dB HL), severe (71–95 dB HL) and profound ($>$95 dB HL). The frequencies were ranged as low ($<$0.5 kHz), mild (0.5–2 kHz), high (2–8 kHz) and extreme high ($>$8 kHz). Audiometric scales were defined as (1) upward sloping: $>$15 dB HL from the most impaired low frequency to high frequency; (2) U-shaped: $>$15 dB HL difference between the worst result in the mid-frequency range and those at either end; (3) gentle sloping: 15–29 dB HL difference between the mean of 0.5 and 1 kHz and the mean of 4 and 8 kHz, or steep sloping: $>$30 dB HL difference between the above frequencies; (4) flat: $<$15 dB HL difference between the mean of 0.25 and 0.5 kHz, the mean of 1 and 2 kHz, and the mean of 4 and 8 kHz.

3. Results

3.1. The distribution of the disease in the family

According to the family record the first member with hearing impairment (I-1, the founder) was born on 21 April 1875 and died on 19 May 1928. Table 1 showed the distribution of affected members in the family. Of 21 live patrilineal males, 18 were diagnosed with hearing loss, one already had hearing loss, and two were too young to be diagnosed at the time of examination. The age of onset ranged from 7 to 21 years, with a mean of 13.2 years. Among the 22 patrilineal females, none was found to have hearing loss (Table 1). There was no hearing loss among matrilineal males either. The patrilineal females of the family produced 9 male

Table 1
Distribution of affected live members in the family.

Lineage	Number	Diagnosed as affected	Survey as affected	Undiagnosed
Patrilineal males	21	18	1	2
Consanguineous females	22	0	0	0
Matrilineal males	9	0	0	0

Table 2
Age of onset, PTA and ABR in patrilineal males of the family.

Subject	Age at test	Age at onset	PTA (dB HL[a])		Hearing loss	ABR[b] (ms)	
			Right ear	Left ear		Right ear	Left ear
II-9	74	8	86	81	Severe	No response	No response
III-1	65	15	74	66	Moderate	4.11	4.12
III-3	62	20	79	79	Severe	No response	no response
III-5	59	12	71	64	Moderate	3.87	4.21
III-9	63	7	89	86	Severe	No response	No response
III-11	60	9	78	76	Severe	3.97	4.13
III-15	53	18	58	60	Moderate	4.32	4.20
IV-3	36	8	79	77	Severe	3.84	4.20
IV-9	35	21	85	74	Severe	No response	4.40
IV-11	35	13	76	76	Severe	3.93	4.00
IV-15	40	20	74	81	Severe	3.84	No response
IV-22	36	19	73	80	Severe	3.65	No response
IV-28	30	18	65	61	Moderate	4.36	4.13
IV-30	27	8	79	80	Severe	No response	No response
V-3	13	11	82	76	Severe	No response	3.97
V-8	12	9	58	63	Moderate	3.71	3.93
V-12	17	13	72	79	Severe	4.12	No response
V-17	15	14	77	73	Severe	3.94	4.38
V-20	7	7	35	30	Mild	4.18	4.25
V-9	5	–	15	19	Normal	–	–
V-21	4	–	11	18	Normal	–	–

[a] Hearing loss.
[b] Inter-peak latency (ms) of waves I–V with sound stimuli at 100 dB nHL (normal hearing level).

offspring through non-consanguineous marriage. None of the male offspring exhibited any sign of hearing loss (Table 1).

3.2. The audiometric results of patrilineal male patients

The PTA data demonstrated bilateral, symmetrical, and sensorineural hearing loss in 19 out of 21 males; 2 male children were normal by hearing tests (may be too young for the onset). Among these 19 males, the hearing loss was classified as 'severe' for thirteen, 'moderate' for five, and 'mild' for one. Nine patients (9/19, 47%) had descending profile with high frequencies hearing loss; 7 (37%) were depressed in all frequencies and 3 (16%) had U-shaped readings (data not shown). ABR tests revealed no responses at both ears at 100 dB normal hearing level (nHL) in four (II-9, III-3, III-9 and IV-30) of the 19 affected (21%); five patients (IV-9, IV-15, IV-22, V-3 and V-12) showed no response at only one ear (the other ear was normal). The remaining 10 patients (53%) showed normal waves and interpeak latency (Table 2). Comparing the PTA data with the ABR data, we found that patients who showed no response in ABR tended to have severe high frequency (>2000 Hz) hearing loss, which was consistent with the pure-tone audiometric test data.

3.3. Audiometric results for wives of patrilineal males

To exclude shared household environments as a reason for hearing impairment shown in this pedigree or the possibility of introduction of an X-linked or mutated mitochondrial gene for hearing impairment by the wives, we investigated 14 live spouses (II-10, III-2, III-4, III-6, III-10, III-12, III-16, IV-4, IV-10, IV-12, IV-16, IV-23, IV-29 and IV-31) of the affected males in the family. Table 3 showed the PTA results for these females. Individuals II-10 (75 years old), III-2 (65 years old) and III-4 (61 years old) had mild hearing loss, which might be age-related. The rest of the 14 spouses had normal hearing. Of the 14 spouses, 2 were from the same village, 4 from the neighboring villages, 5 from non-agricultural regions and 4 from other provinces. The fact that they came from such wide geographical regions would exclude the possibility that they all carried the same defective X-linked or mitochondrial gene and introduced it into the pedigree. Since hearing impairment was only observed in the males, adverse household environment could not be the causative factor for hearing loss we observed.

Table 3
PTA results for the wives of affected males in the family.

Subject	Age	PTA (dB HL)[a]	
		Right ear	Left ear
II-10	75	23	25
III-2	65	25	29
III-4	61	26	38
III-6	56	25	10
III-10	61	19	63
III-12	58	20	19
III-16	52	15	38
IV-4	35	11	10
IV-10	34	13	14
IV-12	32	10	15
IV-16	41	16	23
IV-23	36	14	18
IV-29	28	15	10
IV-31	26	5	16

[a] Pure tone averages were shown.

Table 4
PTA results for the patrilineal females and their male offspring.

Subject	Gender	Age	PTA (dB HL)[a]	
			Right ear	Left ear
II-8	Female	76	17	20
III-14	Female	53	25	19
III-18	Female	51	18	13
IV-2	Female	38	16	18
IV-8	Female	37	15	14
IV-13	Female	28	11	15
IV-18	Female	36	16	13
IV-21	Female	37	18	18
IV-24	Male	32	11	11
IV-32	Male	28	16	10
V-1	Male	19	5	13
V-13	Male	12	11	10

[a] Pure tone averages were shown.

3.4. Audiometric results for patrilineal females and their male offspring

Twenty-one patrilineal female members in the family were identified and 8 received audiometric evaluations. No hearing impairment was found among them. Of the 9 male descendants from the patrilineal females, four received audiometric evaluations and all were normal (Table 4).

4. Discussion

In the present study, we reported a Chinese ethnic Tujia family with gender-limited expression of moderate to severe hearing loss with sloping, flat or U-shape auditory curves. Theoretically, father–son inheritance over five generations in this family excluded mitochondrial, X-linked and autosomal recessive modes of inheritance. The possibility of autosoma1 dominant inheritance was calculated as follows. The probability that a son of an affected father will be affected is 0.5 and the probability of a daughter being normal is 0.5. Nineteen male members in this family were affected and all sixteen daughters of affected males were unaffected. Thus, the probability of autosomal dominant inheritance is 1:235. Such a small probability makes it unlikely that the defect can be attributed to an autosomal dominant gene. In addition, phenotypically, the audiometric configuration in males of the pedigree is similar to the reported hereditary Y-linked hearing loss [15,16]. Therefore, we speculate that a putative gene on the Y chromosome could contribute to the cause of the disease. Phenotypes are known to be influenced by the genes, the environment and the interactions between them. Phenotypes of non-syndromic hearing loss include but not limited to the age of onset, the severity, and audiometric configuration. For example, DFNB1-related hearing impairment is usually bilateral, symmetric, non-progressive, and has flat audiograms [19]. DFNA2 families show progressive hearing impairment starting in the high frequencies [20,21]. DFNA9 families usually exhibit progressive sensorineural hearing loss associated with vestibular dysfunction [22]. In contrast, DFNA6/14 families show low frequency sensorineural hearing loss [23]. mtDNA deafness is moderate to severe generally. Hearing loss is bilateral, mild to profound, with a symmetric pattern and is more severe with aminoglycoside exposure. Audiograms associated with mtDNA deafness are usually sloping [24]. Based on the analysis of phenotypic characteristics and the comparison with the DFNY1 family [15,16], we could establish a Y-linked inheritance in this family. The gene responsible for the audiological characteristics must have high penetrance (90.5%, 19 out of 21) in patrilineal males who exhibited 95% of moderate to severe hearing loss. Audiometric readings indicated that 47% of the patients had a high frequency and sloping auditory curve while 41% had a flat curve, suggesting that additional genetic (e.g. modifiers) or environmental factors might have modified the expression of this trait. To our knowledge, the pedigree we reported in this study could be the second family with Y-linked gene that contributes to hearing impairment. It has certain characteristics and expression pattern distinct from other deafness of autosomal, mitochondrial or X-linked inheritance. Although the first Y-linked gene locus was approved by Human Genome Organization Nomenclature Committee [15], the deaf gene on Y chromosome has not yet been identified. Members of this pedigree could be the subjects for a new study to locate the "deaf" gene on Y chromosome. Whether the same gene on Y chromosome contributes to hearing impairment in the two Chinese families remain to be studied further.

The past two decades have witnessed significant progress in the field of hereditary hearing loss. To date, more than 137 genes/loci for non-syndromic hearing loss have been mapped to the human genome (http://webh01.ua.ac.be/hhh/). Further molecular genetic studies will hopefully lead to the discovery of a wide variety of molecules that are implicated in the pathogenesis of hearing impairment and a better understanding of the development of deafness. These will facilitate the prenatal screening and diagnosis of deafness and guide the treatment such as cochlear implantation to dramatically improve the quality of life for patients [25–27].

Conflict of interest

None.

Acknowledgements

We thank all the family members for their kind participation in the study. We thank Dr. Yingqun Wang for his suggestions and editorial assistance. This work was supported by the Special Fund from the Central Collegiate Basic Scientific Research Bursary (Grant No. 0109510019).

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