

ELECTRONIC LETTER

Y-linked inheritance of non-syndromic hearing impairment in a large Chinese family

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J Med Genet 2004;41:e80 (<http://www.jmedgenet.com/cgi/content/full/41/6/e80>). doi: 10.1136/jmg.2003.012799

Hearing impairment is a common condition responsible for communication disorders affecting one in 1000 newborns.^{1,2} A national poll by the China Association of the Handicapped in 1987 showed that 20.57 million people in the country were affected by auditory or speech disorders, accounting for 34% of the 60 million disabled or 1.58% of the total Chinese population (1.3 billion) (www.cdpf.org.cn). Hearing impairment is caused by environmental and hereditary factors. Environmental factors include perinatal infection, acoustic or cerebral trauma affecting the cochlea, and ototoxic drugs such as aminoglycoside antibiotics.^{3,4} Genetic factors contribute to 50% of deafness cases including syndromic (30%) and non-syndromic (70%) hearing impairment.^{1,5} Recent times have witnessed rapid progress in the field of genetic studies of hereditary hearing impairment, especially non-syndromic hearing impairment. Transmission of non-syndromic hearing impairment can be autosomal recessive (77%), autosomal dominant (22%), X-linked (1%), or matrilineal (mitochondrial inheritance, about 1%).⁴ More than 70 genetic loci have been characterised—that is, 37 for autosomal dominant, 34 for autosomal recessive, and 4 for X-linked forms of non-syndromic hearing impairment. A total of 36 genes (34 nuclear and two mitochondrial) have so far been identified.^{6,7} To date, there has not been any report on Y-linked inheritance of hearing impairment.

Recently, the Institute of Otolaryngology of the Chinese People's Liberation Army (PLA) General Hospital has initiated a national network for collecting pedigrees of hereditary hearing loss. By collaborating with organisations for disabled people throughout China, many pedigrees with hereditary hearing loss have been identified and studied for deafness related genes.^{8,9} This paper describes a highly unusual finding of an extended seven-generation Chinese pedigree with hearing impairment clearly vertically inherited through males. The inheritance characteristics in this family cannot be explained by the four transmission mechanisms mentioned above. A Y-linked inheritance pattern is thus proposed based upon the data of pedigree analysis, segregation analysis and linkage analysis with 382 autosomal microsatellite markers at the spacing of an average of 8.6 cM throughout the genome.

SUBJECTS AND METHODS

Pedigree recruitment and phenotypic evaluation

Details of a seven generation Chinese family (fig 1) were ascertained from the Department of Otolaryngology, Head, and Neck Surgery, at the Institute of Otolaryngology, PLA General Hospital. Informed consent, blood samples, and clinical evaluations were obtained from all participants of this family according to the protocols approved by the PLA General Hospital Institution Review Board. Members of this pedigree were extensively interviewed by experienced ear, nose, and throat doctors and physicians to identify either personal or family medical evidence of hearing impairment,

Key points

- We report here the clinical and genetic characterisation of a very large Chinese family (129 members in seven generations) with non-syndromic hearing impairment.
- The striking feature in this family is the extremely high penetrance (91%) in the patrilineal relatives, but almost no penetrance in the matrilineal relatives. Deafness was bilateral, symmetrical, sensorineural, postlingual, and progressive.
- Complex segregation analysis indicates that a putative major gene was segregating in the pedigree ($p=0.014$), but it does not follow autosomal Mendelian inheritance ($p=0.001$).
- Two point and multipoint model based linkage analysis showed that there is no genome wide significant lod score at 382 microsatellite markers covering 22 autosomal chromosomes to implicate an autosomal locus.
- Y-linked inheritance is thus proposed to be the genetic mode of transmission of the hearing impairment within this family.

tinnitus, vestibular symptoms, use of aminoglycosides, and other clinical abnormalities. The proband and his relations were then given physical examinations of the hair, skin, sclera, iris, mouth, maxilla, mandible, eyes, interocular distance, spine, and extremities. Otolaryngological examinations focused on the auricle, external auditory meatus, and tympanic membrane.

Audiometric evaluations of the proband and other members of this family were performed, including pure tone audiometry (Madsen 502, Denmark), EAR-3A insert earphones (USA), tympanometry and acoustic reflexes using a Madsen 901 (Denmark), and auditory brainstem responses using SmartEP (USA). The audiological data were evaluated based on the recommendations of the EU HEAR project, as described by Stephens.¹⁰ Sensorineural hearing impairment was defined as an air/bone gap <15 dB hearing loss averaged over 0.5, 1, and 2 kHz. The severity of hearing impairment was applied to the better hearing ear, averaged over 0.5, 1, 2, and 4 kHz and was categorised as follows: mild = 20–40 dB hearing loss; moderate = 41–70 dB hearing loss; severe = 71–95 dB hearing loss; and profound >95 dB hearing loss. Frequency ranges were defined: low frequencies ≤ 0.5 kHz; mid frequencies >0.5 kHz ≤ 2 kHz; high frequencies

Abbreviation: df, degrees of freedom

>2 kHz ≤ 8 kHz; extended high frequencies >8 kHz. In this family, individuals were considered as having inherited sensorineural hearing impairment if the hearing deficit occurred before the third decade. To investigate if chromosomal aberrations could be a putative genetic cause for the phenotypic manifestations, standard karyotype analysis was performed on some family members as well.

Segregation analysis

Before the model based genome wide linkage analysis of the large and extended pedigree with non-syndromic hereditary hearing loss, with a total of 129 members, segregation analysis was performed to investigate the presence of major type effects and segregation patterns within the pedigree using the newly developed S.A.G.E. program SEGREG for binary phenotypes.¹¹ Three married-in members without offspring were excluded from the segregation analysis due to unrelatedness. This unique pedigree contains seven generations with 40 sibships (mean sibship size of 2.1) and is with about equal numbers of both sexes and 33 members affected with non-syndromic hereditary hearing loss. According to the classification of relative pairs in the pedigree, it contains 264 first degree relative pairs (parent-offspring and sibling pairs), 459 second degree relative pairs (grandparent-grandchild and avuncular pairs) and 360 third degree relative pairs (cousin pairs). Because of the characteristic of fairly uniformly early age at onset (7–27), we did not fit variable age at onset distribution for this analysis.

Regressive multivariate logistic models for binary traits were used to investigate the segregation pattern within the pedigree.¹² These assume, on the basis of the major phenotypical characteristics of any individual belonging to one or other of two nuclear families, that the two families are likely to be independent.¹¹ In this model, the marginal probability (called susceptibility) that any pedigree member has a particular phenotype is the same for all members who have the same values of any covariates in the model and is given by the cumulative logistic function:

$$\gamma = \frac{e^{\theta_i y_i}}{1 + e^{\theta_i}}$$

where y_i is the trait value for the i th individual and is 1 for an affected individual and 0 for an unaffected individual; and θ_i is the logit of the susceptibility for the i th individual, which depends on the major type ($u = AA$ or AB or BB) and covariates $x_{i1}, x_{i2}, \dots, x_{ip}$:

$$\theta_u(i) = \beta_u + \xi_1 x_{i1} + \dots + \xi_p x_{ip}$$

The nuclear familial residual association parameter (ρ), which is analogous to the correlation parameter in regressive models for continuous traits,¹³ is a second order correlation and is incorporated into the models to account for residual polygenic and common environment effects. We assumed no spouse correlation and equal parent-offspring and sib-sib correlation throughout the analyses. Ascertainment bias was corrected by modelling the simplex sampling scheme from which the pedigree was recruited.

Four criteria proposed for inferring a major gene¹⁴ were used to test the specific hypothesis: *a*) rejection of the hypothesis of no major effects; *b*) rejection of the hypothesis of no transmission of major effects; *c*) failure to reject the hypothesis of Mendelian transmission; and *d*) rejection of the hypothesis of any particular Mendelian inheritance models (dominant, recessive, and general Mendelian models). Hypotheses were assessed by the likelihood ratio test, under the assumption that the negative of twice the difference in natural logarithms for hierarchical models follows a χ^2 distribution.¹⁵

The S.A.G.E. program SEGREG estimates following parameters:

- q_A , the frequency of the putative disease allele (A);
- τ_{AA} , τ_{AB} , and τ_{BB} , the probability that an individual of type AA , AB , or BB transmits the A allele to an offspring (for the Mendelian case, these correspond to 1.0, 0.5, and 0.0, respectively);
- $Susc_{AA}$, $Susc_{AB}$, and $Susc_{BB}$, the susceptibility on the logit scale that major type AA , AB , or BB confers a specific risk that an individual with that type develops non-syndromic hereditary hearing loss; and
- ρ , the first degree second moment familial correlation coefficient measuring residual multifactorial (polygenic and common environment) effects.

Linkage analysis

Genomic DNA was isolated from whole blood of 43 of 50 family members, who received clinical auditory evaluations. Three hundred and eighty two microsatellite markers spanning the 22 autosomes were obtained from Perkin-Elmer Applied Biosystems (ABI Prism Linkage Mapping Sets, version 2). These markers have an average population heterozygosity of ≈ 0.79 and are spaced by an average of 8.6 cM throughout the human genome. Multiplex PCR was

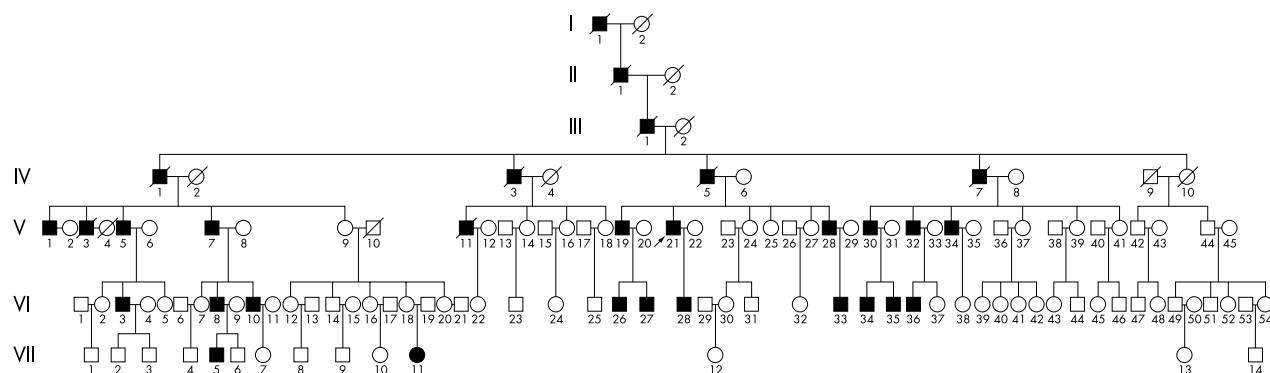


Figure 1 A Chinese pedigree with Y-linked inheritance of non-syndromic hearing impairment. Affected individuals are indicated by the filled symbols. Generations are indicated on the left by Roman numerals, and the numbers under the individuals represent identification numbers for each generation. The proband is identified by an arrow.

performed with PE9600 thermocyclers (Applied Biosystems), producing a final volume of 5 μ l reaction mixture containing 30 ng of genome DNA, 1 \times PCR buffer, 0.2 mM of each dNTP, 3.0 mM MgCl₂, 80 pmol of each of the forward and reverse primers, and 0.2 units of Gold Ampli Taq Polymerase. Reactions were performed based on the instructions provided by the manufacturers and the products were loaded onto a 6% denaturing polyacrylamide gel (7 M urea) and visualised on an ABI 377 sequencer. Alleles were analysed with Genescan analysis software (version 3.0) and Genotyper software (version 2.1).

Two point lod scores between the disease locus and markers were calculated by the MILNK program of the LINKAGE software package.¹⁶ The disease was hypothesised to be an autosomal dominant trait with a disease allele frequency of 0.0001. The allele frequencies for each marker and for each sex were assumed to be equal. We assumed 90% penetrance for lod score calculation instead of 100% because of the possible misinterpretation of the phenotype in some cases. The values for the maximum lod score (Z_{max}) were

calculated by the ILINK program of the LINKAGE package. Multipoint lod scores were calculated using GENEHUNTER software for efforts to fully utilise partial information along the nearby markers and to verify the putative linkage regions identified from the two point model based linkage analysis.¹⁷ In the multipoint analyses, we assumed a trait locus of dominant inheritance and 90% penetrance, the parametric settings for the maximum lod scores attainable for the two point linkage analysis.

RESULTS

Clinical description

The family originated from Jiangxi Province in southeastern China. Most of the family members have been living in the same region for over 200 years. As shown in fig 1, this family history is consistent with patrilineal inheritance. Very strikingly, none of the femal offspring of deaf fathers, except an affected female VII-11, who received gentamicin (0.75 g/day for 3 days) repeatedly for pneumonia at the age of 3 years, had a hearing impairment. On the contrary, 29 out

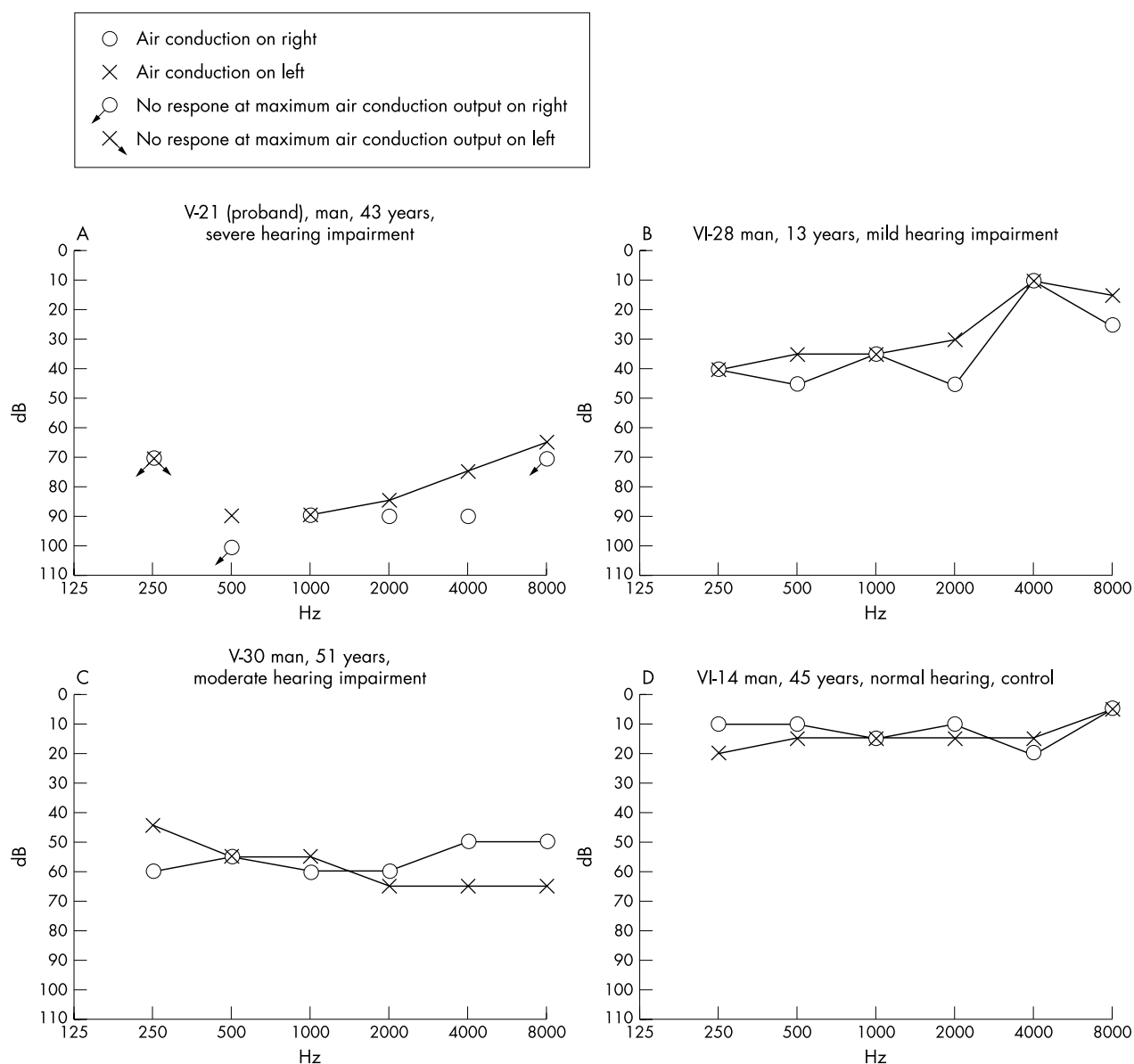


Figure 2 Audiograms of three affected individuals and one matrilineal male control. V-21 (proband) showed severe hearing impairment (A); VI-28 suffered mild hearing impairment (B); V-30 showed moderate hearing impairment (C); and VI-14, as a control, exhibited normal hearing (D).

Table 1 Summary of clinical data for some patrilineal members in the Chinese pedigree

Subject	Sex	Age of test (years)	Age of onset (years)	Pure tone audiometry (dB hearing loss), right	Pure tone audiometry (dB hearing loss), left	Hearing impairment
V-1	Male	71	7	85	80	severe
V-5	Male	55	22	75	67	moderate
V-7	Male	63	12	78	78	severe
V-19	Male	54	8	70	63	moderate
V-21	Male	45	27	90	85	severe
V-30	Male	51	20	56	60	moderate
V-32	Male	48	8	78	77	severe
V-34	Male	42	9	79	74	severe
VI-3	Male	24	7	84	73	severe
VI-8	Male	32	7	76	75	severe
VI-10	Male	35	20	73	80	severe
VI-26	Male	23	18	76	78	severe
VI-27	Male	22	8	64	60	moderate
VI-28	Male	13	13	35	28	mild
VI-34	Male	26	8	58	64	moderate
VI-35	Male	22	18	65	60	moderate
VI-36	Male	11	9	80	79	severe
VII-5	Male	9	7	83	75	severe
VII-2	Male	<1	—	not applicable	not applicable	normal
VII-3	Male	2	—	not applicable	not applicable	normal
VII-6	Male	4	—	not applicable	not applicable	normal

of 32 patrilineal relatives exhibited bilateral, symmetric, and sensorineural hearing impairment as a sole clinical phenotype. These subjects did not have a history of exposure to aminoglycosides or of other causes known to account for the hearing impairment.

The proband (V-21) began suffering hearing impairment at the age of 27 years. His hearing got worse when he had severe tinnitus at the age of 37. At the age of 45, he was evaluated by the ear, nose, and throat doctors from Chinese PLA General Hospital. Auditory evaluation, including pure tone audiometry, immittance, and auditory brainstem response, revealed that he had severe hearing impairment. As shown in fig 2A, the audiometric graph was U-shaped for the left ear but flat for the right ear. He had high tone hearing loss and continuous tinnitus. However, he had no other significant medical history.

As displayed in table 1 and figs 2A, B, and C, audiometric studies showed a variable severity of hearing impairment. Of 18 patrilineal relatives who received audiometric evaluation, 11 subjects, such as V-21, exhibited severe hearing impairment (fig 2A), only subject VI-28 suffered mild hearing impairment (fig 2B), and six subjects, including V-30,

showed moderate hearing impairment (fig 2C). Three young individuals, VII-2, VII-3, and VII-6, with ages of <1, 2, and 4 years, respectively, had normal hearing. The matrilineal sons (for example, VI-14) also showed normal hearing (fig 2D). Interestingly, patrilineal relatives of this family exhibited postlingual onset or progressive, but not congenital hearing impairment. In this family, the ages of onset in the patrilineal relatives ranged from 7 to 27 years with an average of 12.7 (6.4) years. Furthermore, three of the 18 affected relatives also suffered from tinnitus. Individual VI-34 developed tinnitus at the age of 10 years, while V-19 and V-21 had tinnitus at the age of 50 and 37 years, respectively. There was no obvious vestibular dysfunction among all the patrilineal relatives.

Comprehensive examination of the family medical history of these individuals did not identify other clinical syndromes, such as cardiovascular disorders, diabetes, visual problems, or neurological diseases. Also, examinations by genome wide karyotype analysis on individuals of V-30, V-34, VI-3, VI-8, VI-10, VI-34, and V-31 (the wife of V-30) and a computed tomogram of temporal bones on the seven individuals did not show any abnormal evidence (data not shown).

Table 2 Multivariate logistic maximum likelihood estimates of segregation models for inheritance of non-syndromic hereditary hearing impairment

	Multifactorial only	Multifactorial+ commingled	Multifactorial+ Mendelian	Multifactorial+ free τ 's	Multifactorial+ dominant	Multifactorial+ recessive
qA	(1.0)	1.0	1.0	0.85	1.0	1.0
τ_{AA}	(1.0)	1.0	(1.0)	(1.0)
τ_{AB}	(0.5)	0.0	(0.5)	(0.5)
τ_{BB}	(0.0)	0.0	(0.0)	(0.0)
S_{USCAA}	-1.64	-1.75	-1.62	*	-1.65	-1.67
S_{USCAB}	...	-1.75	-1.53	-1.61	-1.65	-1.67
S_{USCBB}	...	-1.75	-1.35	-1.61	-1.60	-1.67
P_{Presid}	7.37	7.93	6.12	7.21	7.15	7.49
-2LnL	83.41	82.35	87.98	71.72	84.15	83.00
Akaike's AIC	87.41	90.35	95.98	83.72	90.15	91.00

Test H_{01} : no major gene effect, $\chi^2 = 4.57$, $df = 3$, $p = 0.116$

Test H_{02} : no transmission of major gene effect, $\chi^2 = 10.63$, $df = 3$, $p = 0.014$

Test H_{03} : Mendelian transmission, $\chi^2 = 16.26$, $df = 3$, $p = 0.001$

Test H_{04} : Mendelian transmission and dominant inheritance, $\chi^2 = 3.83$, $df = 1$, $p = 0.050$

Test H_{05} : Mendelian transmission and recessive inheritance, $\chi^2 = 4.98$, $df = 1$, $p = 0.026$

*This parameter estimator did not converge well, but the hypotheses can still be tested by comparing the models.

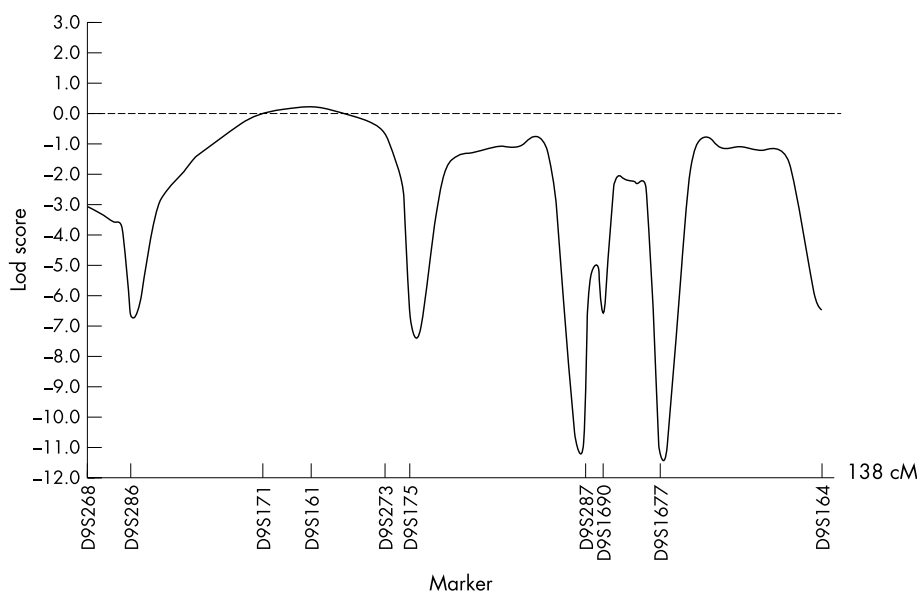


Figure 3 Multipoint lod score analysis of non-syndromic hearing impairment. Genotypes at D9S288, D9S286, D9S171, D9S161, D9S273, D9S175, D9S287, D9S1690, D9S1677, and D9S164 were used to determine the multipoint lod scores at chromosome 9q21. D9S288 is arbitrarily plotted at 0 cM at abscissa. Other microsatellite markers embracing the 9q21 are indicated along the abscissa from telomere to centromere. Multipoint lod score is plotted on the ordinate.

Segregation analysis

Complex segregation analysis was employed to investigate the inheritance pattern within the pedigree. Parameter estimates for six different models are shown in table 2. The null hypothesis of no major type effect was assessed by comparing the model containing multifactorial inheritance alone (H_{01} : $q_A = 1$) with that containing both a Mendelian major gene and multifactorial inheritance (H_{A1} : $0 < q_A < 1$; $\tau_{AA} = 1.0$, $\tau_{AB} = 0.5$, $\tau_{BB} = 0.0$). The model with both effects has three additional parameters (q_A and two susceptibilities), so the likelihood ratio statistic (χ^2) has three degrees of freedom (df). The null hypothesis of no transmission of major gene effects was tested by comparing the commingled model (H_{02} : $q_A = \tau_{AA} = \tau_{AB} = \tau_{BB}$) with the model in which all transmission probabilities were estimated (H_{A2} : $q_A \neq \tau_{AA} \neq \tau_{AB} \neq \tau_{BB}$, 3 df). The null hypothesis of Mendelian transmission was tested by comparing the mixed Mendelian model (H_{03} : $\tau_{AA} = 1.0$, $\tau_{AB} = 0.5$, $\tau_{BB} = 0.0$) with a model where all transmission probabilities were estimated (H_{A3} : free τ 's, 3 df). The null hypothesis of dominant Mendelian inheritance (H_{04}) was tested by comparing the model of the mixed Mendelian model (the general model) with the mixed model ($Susc_{AA} = Susc_{AB} \neq Susc_{BB}$, 1 df). The null hypothesis (H_{05} :

$Susc_{AA} \neq Susc_{AB} = Susc_{BB}$) of recessive Mendelian inheritance was tested in similar way.

The hypothesis of no major effect was not rejected ($\chi^2 = 4.57$, $df = 3$, $p = 0.116$), but the hypothesis of no transmission of the major effect was rejected ($\chi^2 = 10.63$, $df = 3$, $p = 0.014$). This discrepancy between the two tests might be due to the fact that the two models for H_{01} are not hierarchical with each other and thus the test for H_{01} is less powerful, although such a test was extensively used in the segregation analysis.¹⁴ As expected, the hypothesis of Mendelian transmission was strongly rejected ($\chi^2 = 16.26$, $df = 3$, $p = 0.001$). Not surprisingly, both dominant and recessive Mendelian inheritance models were rejected with $p = 0.05$ and 0.026 , respectively. These results clearly support the conjecture that a putative major gene was segregating in the large and extended pedigree in some manner (like sex linked inheritance) other than autosomal Mendelian inheritance.

Linkage analysis

To gain further evidence for sex linked inheritance and to exclude the possibly autosomal inheritances in this pedigree, we carried out a genome wide scan using genomic DNA derived from 42 individuals (24 males, 18 females) of this

Table 3 Two point lod scores between the disease locus and the chromosome 9 markers

Marker	Lod score* at $\theta =$					Z_{max}	θ_{max}
	0.0	0.1	0.2	0.3	0.4		
D9S288	-7.65	-2.67	-1.14	-0.46	-0.12	0.00	0.51
D9S286	-12.71	-3.59	-1.73	-0.80	-0.28	0.10	0.61
D9S171	0.61	0.63	0.48	0.26	0.07	0.65	0.05
D9S161	-3.47	0.97	0.86	0.59	0.28	0.10	0.98
D9S273	1.37	1.24	0.98	0.66	0.33	1.37	0.00
D9S175	-9.37	-1.40	-0.39	-0.05	0.04	0.04	0.42
D9S287	-12.23	-1.23	-0.42	-0.10	0.01	0.02	0.44
D9S1690	-11.96	-1.16	-0.31	0.02	0.10	0.10	0.39
D9S1677	-21.51	-3.25	-1.48	-0.59	-0.14	0.00	0.50
D9S164	-7.86	-0.97	-0.22	0.04	0.09	0.09	0.38

*Lod scores were computed under an autosomal dominant mode of inheritance. The penetrance of the phenotype is defined to be 90%.

Chinese family. Three hundred and eighty two microsatellite markers spanning the 22 autosomes were used. This analysis showed a weak positive two point lod score at seven markers (D3S1701, D3S1297, D4S1539, D7S519, D8S284, D8S1771, and D9S273), ranging from 0.5 to 1.31 (at recombination rate, $\theta = 0.1$). Of these, the highest lod score was obtained at D9S273 (maximum lod score, $Z_{\max} = 1.37$, $\theta = 0.0$, see table 3). To further confirm or reject the linkage at D9S273 (9q21), we carried out a multipoint linkage analysis using nine markers nearby the peak on chromosome 9, namely D9S288, D9S286, D9S171, D9S161, D9S175, D9S287, D9S1690, D9S1677, and D9S164, as well as the peak itself at D9S273, and the result is shown in fig 3. Because the striking feature in this family is extremely high penetrance (91%) in the patrilineal relatives, but almost no penetrance in the matrilineal relatives, we might well assume that this particular hearing disorder is a sex limited trait with male restricted phenotypic expression (and a null penetrance in females). We tested this hypothesis by performing the above multipoint analysis but with the phenotypes of female siblings set as unknown. The resulting multipoint linkage profile resembles fig 3, and the corresponding linkage peak is too small to implicate a genome wide significant linkage (data not shown). In summary, the multipoint linkage analyses essentially excluded the putative linkage region, thereby supporting our proposition of the Y-linked inheritance in the large and extended pedigree.

DISCUSSION

In this study, we performed clinical and genetic characterisation of a large Chinese family with non-syndromic deafness. The clinical phenotype was only present in the paternal lineage of this seven generation pedigree. This suggests that the Y-linked inheritance is most probably the mode of transmission within this family. All affected individuals share some common features: bilateral, symmetrical, purely sensorineural but not any conductive component. Unlike families in which deafness is transmitted with autosomal dominant, recessive or X-linked modes,³ the striking feature in this family is the extremely high penetrance (91% in patrilineal relatives), although the patrilineal relatives in this Chinese pedigree exhibited phenotypic variability including the severity and age of onset. The severity of hearing impairment in this family ranged from mild to severe, but not to profound. The ages of onset for the patrilineal relatives in this family were from 7 to 27 years.

To determine whether familial aggregation of non-syndromic hereditary hearing loss in this pedigree could reflect the action of a single major gene and the mode of inheritance, we performed a segregation analysis with the S.A.G.E. program SEGREG. The likelihood ratio tests for hypotheses of genetic transmission indicate that a putative major gene was segregating in the pedigree ($p = 0.014$), but it does not follow autosomal Mendelian inheritance ($p = 0.001$). Further segregation analysis excluded both dominant and recessive inheritance models for the pedigree. To gain further evidence for sex linked inheritance and to exclude the possible autosomal inheritance, we carried out a genome-wide scan using 382 microsatellite markers spanning the 22 autosomes. Two point and multipoint linkage analysis showed that there is not any significant lod score large enough to implicate an autosomal inheritance locus. Cross validations by comprehensive medical investigation, complex segregation analysis, and model based linkage analysis agree with each other and strongly support the notion that Y-linked inheritance is the mode of genetic transmission within this family.

One possibility might be that a chromosomal translocation involving the Y long arm segregates in this family. However,

we were able to exclude any conspicuous chromosomal rearrangement since the karyotypes analysed in seven members (six affected males and one unaffected female) were normal. Therefore, a mutation in a putative Y chromosome linked gene is likely to account for the inheritance pattern. A Y-specific gene without a homologue on the X chromosome, would be expressed in males only, hence would have to be required for normal hearing in males but not in females. In all likelihood, the disease gene may rather have a functional counterpart on the X chromosome. The gene could thus be located in the pseudo-autosomal region, close to the boundary with the male specific region of the Y containing the SRY sex determining gene (otherwise the probability would be high that the hearing impairment also affects some females in this family). Alternatively, the gene is located in the male specific region of the Y.¹⁸ Of 78 protein coding genes identified in this region, we suggest that PCDH11Y, encoding a protocadherin, is an attractive candidate on the following grounds. Firstly, it has a functional homologue, PCDH11X, on the X chromosome.¹⁹⁻²⁰ Secondly, two other members of the cadherin family, protocadherin15 and cadherin23, have been involved in syndromic and non-syndromic deafness forms.²¹⁻²³

ACKNOWLEDGEMENTS

We thank two anonymous reviewers for their helpful comments on an early version of the manuscript. We also thank the patients and their families for their cooperation during this work, the China Association of the Handicapped for their assistance in our investigations and Dr Yuehui Liu at the Second Affiliated Hospital of Jiang Xi Medical College for his help during pedigree investigations.

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This work was supported by grants from the Beijing Natural Science Foundation (Grant No 7011004), the National High Tech Development Project (Grant Nos 2001AA221092 and 2002AA222052), the National Natural Science Foundation of China (Grant Nos 30170515 and 39970397), and Beijing Science and Technology Innovation Project (Grant No H010210160119).

Conflicts of interest: none declared.

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