International Journal of Pediatric Otorhinolaryngology 78 (2014) 1513–1516

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

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

Mutation analysis of seven consanguineous Uyghur families with non-syndromic deafness

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ARTICLE INFO

Article history:
Received 23 April 2014
Received in revised form 12 June 2014
Accepted 14 June 2014
Available online 23 June 2014

Keywords:
Uyghur
Consanguineous marriage
Deafness
Mutation
SLC26A4

ABSTRACT

Objective: To investigate the genetic causes of consanguineous Uyghur families with nonsyndromic deafness.
Method: Seven consanguineous Uyghur families with nonsyndromic deafness were recruited in this study and characterized for their audiometric phenotype. Mutation analysis of common deafness genes *GJB2*, *SLC26A4* and *MT-RNR1* was performed in all families by direct sequencing.
Result: Bi-allelic mutations in *SLC26A4*, including p.N392Y/p.N392Y, p.S57X/p.S57X and p.Q413R/p.L676Q, were detected in three families as the pathogenic causes for the deafness. No mutations were identified in *GJB2* and *MT-RNR1*.
Conclusion: Mutations in *SLC26A4* was the most common causes of the Uyghur consanguineous deaf families.

1. Introduction

Hereditary deafness is the most common neurosensory disorder in humans [1]. Among them, approximately 70% of cases are non-syndromic without other distinctive clinical abnormalities [1]. Mutations in three genes, *GJB2*, *SLC26A4* and *MT-RNR1*, were commonly found in non-syndromic deaf patients. In Chinese Hans, for example, bi-allelic *GJB2* mutations were reported in 19.1% of the patients with non-syndromic deafness, followed by bi-allelic *SLC26A4* mutations in 12.1% and the mitochondrial m.A1555G mutation of *MTRNR1* in 1.6% [2–4]. These genes have been routinely screened during genetic testing and counseling of deafness.

Uyghur was one of the biggest ethnic minorities in northwest China with a population of over 9.87 millions. Unlike that in Chinese Hans, the molecular etiology study of deafness in Uyghurs has been rare. In one study, nine mutations, including c.35delG, c.176_191del16, c.235delC and c.299_300delAT in *GJB2*, c.538C>T in *GJB3*, c.919-2A>G and p.H723R in *SLC26A4* and m.1555A>G and m.1494C>T in *MT-RNR1*, were screened using a micro array-based detection method in Uyghur patients with non-syndromic deafness [5]. The four aforementioned mutations in *GJB2* were found in 9.05% of the patients, followed by the two *SLC26A4* mutations in 2.01%. To date, sequencing of the entire deafness genes in Uyghurs has not been reported yet.

The consanguineous marriage remains frequent in certain regions of Uyghur population. In a deaf–mute School in Xinjiang, China, we recruited seven consanguineous Uyghur families with non-syndromic deafness. Sequencing of *GJB2*, *SLC26A4* and *MT-RNR1* was performed to investigate the genetic causes of deafness in those families.

2. Methods

2.1. Subjects and ethics statement

In a total of 230 students from the deaf–mute School of Kashgar, Xinjiang, China, we identified and recruited seven deaf probands whose parents were consanguineously married. Other family members, including the parents and the siblings of the probands

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http://dx.doi.org/10.1016/j.ijporl.2014.06.023
0165-5876/

were recruited subsequently. All subjects gave written and informed consent to participate in this study. This study was approved by the ethics committee of the Shanghai Jiaotong University School of Medicine, Xinhua Hospital and was in compliance with the Declaration of Helsinki.

2.2. Clinical evaluations

Complete medical history inquiry and detailed physical examination were performed in all deaf subjects to exclude the possibility of environmental or syndromic hearing impairment. Auditory evaluations included otoscopic examination, otoacoustic emission and pure tone audiometry. The hearing threshold was determined as the average of the hearing levels at 0.5, 1.0, 2.0 and 4.0 kHz for the better ear. The severity of hearing impairment was defined as mild (20–40 dB), moderate (41–70 dB), severe (71–95 dB) and profound (>95 dB).

2.3. Mutation analysis

Genomic DNA was extracted from the whole blood samples using the Blood DNA kit (Tiangen Biotech, Beijing, China). Mutations screening of m.A1555G and m.C1494T of *MT-RNR1* were performed in all probands by the PCR amplification and bidirectional sequencing as previously described [6]. For all probands, exon 2 of *GJB2*, twenty-one exons of *SLC26A4* and flanking introns of both were also sequenced. Segregation of the detected mutations was subsequently confirmed in all the family members.

3. Results

3.1. Clinical characterization

The pedigrees and the representative audiograms of the seven consanguineous deaf families were shown in Fig. 1. All deaf subjects had prelingual, bilateral, severe-to-profound sensorineural deafness and none of them complained of the vestibular symptom. No other abnormalities were identified in the patients.

3.2. Mutation analysis of GJB2, SLC26A4 and MT-RNR1

Sequencing of *GJB2* and *MT-RNR1* revealed no pathogenic mutations in probands of the seven consanguineous deaf families. In contrast, bi-allelic mutations in *SLC26A4* including p.N392Y/p.N392Y, p.S57X/p.S57X and p.Q413R/p.L676Q were detected in 3 probands KLX8-1, KLX77-1, and KLX207-1, respectively (Figs. 1 and 2). All four *SLC26A4* mutations have been reported previously for deaf patients in Asia [7,8].

4. Discussion

In this study, we performed a mutation analysis of *GJB2*, *SLC26A4* and *MT-RNR1* in seven consanguineous Uyghur deaf families. Due to the cultural customs, consanguineous deaf families were relatively common in the Uyghur deaf population. Our studies therefore may provide important information regarding to the genetic testing and counseling of genetic hearing loss in Uyghurs.

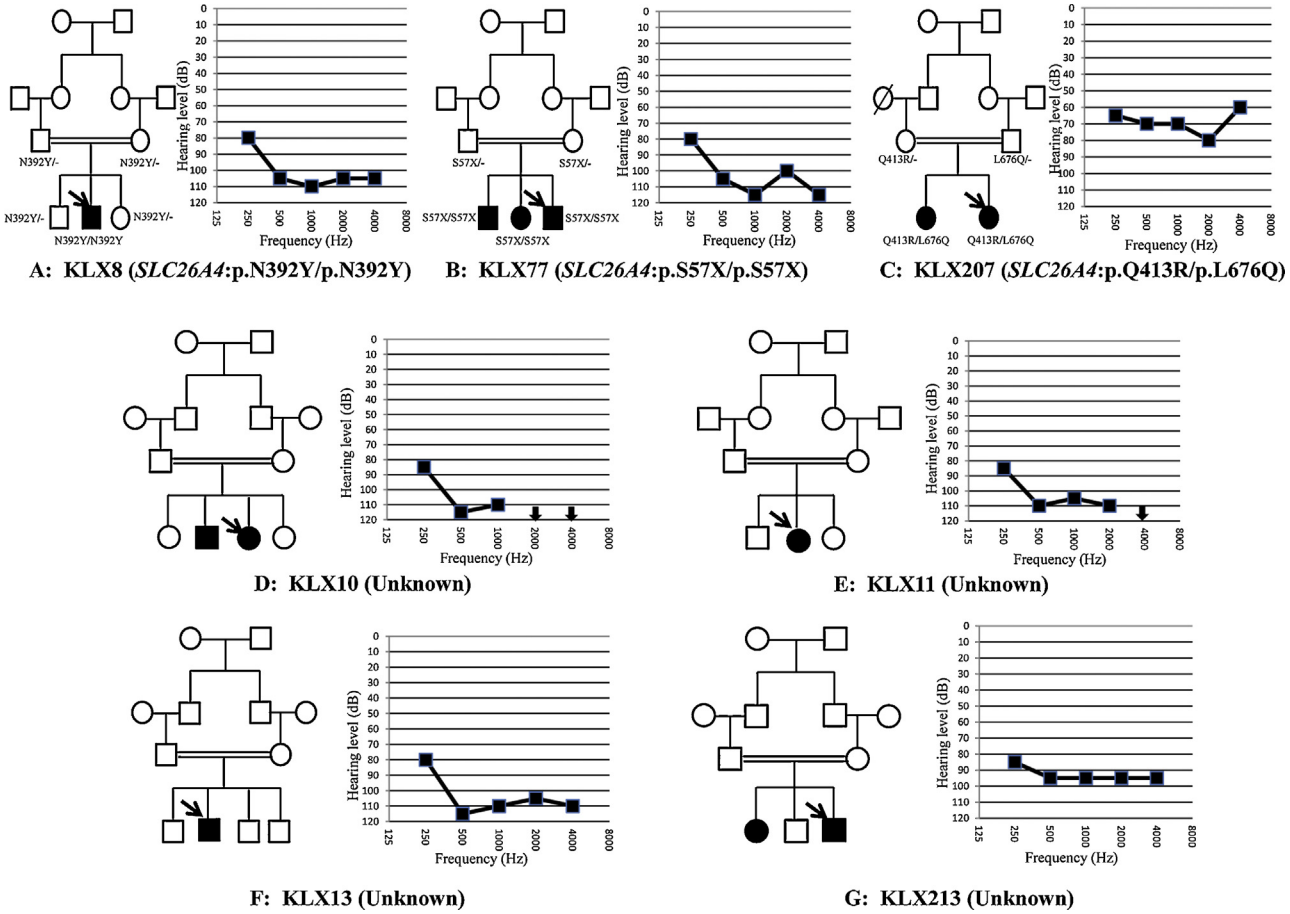

Fig. 1. Pedigrees, genotypes and phenotypes of the seven consanguineous deaf families. Audiograms of representative probands (arrows) were shown on the right.