The SLC26A4 Gene Mutations in Children With Deafness and Large Vestibular Aqueduct Syndrome

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Objective
Large vestibular aqueduct syndrome (LVAS) is the common inner ear deformity in Sensorineural hearing loss of children and adolescents. A large number of studies at home and abroad show that ERA is closely related to SLC26A4 gene mutation. The mutation of SLC26A4 gene is the pathogenic factor of autosomal recessive nonsyndromal deafness caused by GJB2 mutation. Wang et al. found that the mutation rate of SLC26A4 gene in large vestibular patients in China was 97.9%.

In this study, 4 LVAS families and 153 patients with distributed deafness were collected. PCR combined with DNA sequencing method was used to detect SLC26A4 gene mutation, and genetic counseling was provided for their deafness because of deafness families, and the basis was provided for clinical establishment of LVAS genetic diagnosis method.

Methods
The objects of this study were 165 cases of deafness in 4 deaf families, some family members and distributed deafness patients in the otologyngology department of Wuhan children’s hospital. Peripheral blood samples were collected. The onset age of the patients ranged from 6 months to 10 years, with an average age of 4.8±4.5 years and a median age of 3.5 years. 150 patients with normal hearing and no significant abnormalities in other systems were selected as normal controls, including 78 males and 72 females, aged 3~34 years, with an average age of 17.4±11.9 years and a median age of 4.1 years. The idea is that the auditory hearing is measured in pure tone and the auditory brain-stem response (ABR) is detected in the deaf patients. The idea is that the patient is diagnosed as LVAS in the temporal bone CT (CT), which is larger than 1.5mm in diameter from the total foot of the semicircular canal to 1/2 of the exit of the vestibular aqueduct. Genomic DNA was extracted and all 21 exons of SLC26A4 gene were amplified. Direct positive and negative Sanger sequencing was performed.

Results
CT examination of the temporal bone showed LVAS without any other inner ear malformation. Partial hearing loss of LVAS patients is shown in table 2. Fifteen patients with LVAS were aged from 6 months to 10 years old, male and female. In this study, 4 LVAS patients and their relatives in the family were tested for SLC26A4 gene, and two types of mutations were found, namely c. 919-2a >g and H723R. Genotypes of family members are shown in table 1. Among 153 sporadic cases, 7 patients were found to be homozygous mutations of c. 919-2a >G, 2 patients were homozygous mutations of c. 919-2a >G/H723R, in addition, 1 patient was homozygous mutations of H723R, 1 patient was homozygous mutations of c. 919-2a >G/N392Y, 1 patient was homozygous mutations of c. 919-2a >G/S532R, 1 patient was homozygous mutations of c. 919-2a >G/D669V, 1 patient was homozygous mutations of K440X/H723R, and 1 patient was homozygous mutations of G197R. The 303 patients presented ivs18-48inscaa /V609G complex hybrid mutation.

Conclusion
SLC26A4 gene is located at 7q31, belonging to the ion transporter family. SLC26A4 gene has various mutations, distributed in various exons or their flanks. Among the mutations detected in this study, c. 919-2a >g and H723R are the most common mutations in Chinese patients with LVAS. In E002 families, the hearing test results of proband ii-1 showed severe sensorineural deafness, and SLC26A4 gene was a complex hybrid mutation of c. 919-2a >G/H723R, which was the cause of deafness in patients. In this study, 153 patients with deafness and 15 patients with LVAS were included, including 12 patients with c. 919-2a >g mutation, with a mutation rate of 7.84% in all patients. Mutation rate of H723R was 2.61% in 4 cases. C. 919-2a >g homozygous mutation in 7 patients, accounting for about 4.58% of all patients. In addition, the genetic mutation type of patient 303 is extremely rare, that is, ivs18-48inscaa /V609G complex hybrid mutation, and the hearing examination results showed moderate sensorineural deafness, while CT showed no enlargement of the vestibular aqua. SLC26A4 gene mutation is the common cause of LVAS, and clinical detection of SLC26A4 gene mutation will be helpful for the diagnosis of LVAS. There are ethnic differences in the relationship between SLC26A4 mutation and phenotype. For example, the c. 919-2a >g mutation is often manifested as Pendred syndrome in Europeans, while most Chinese patients are not accompanied by thyroid dysfunction. Therefore, a large number of clinical data on SLC26A4 genotype and phenotype should be collected to provide a data basis for further understanding of the pathogenesis of SLC26A4 at the molecular level.