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Government-funded universal newborn hearing screening and genetic analyses of deafness predisposing genes in Taiwan

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ABSTRACT

Objective: To investigate the association of eight connexin genes (*GJB2*, *GJB4*, *GJA1P1*, *GJB6*, *GJB3*, *GJA1*, *GJB1*, and *GJC3*) and the *SLC26A4* gene with congenital hearing impairment among infants in a universal newborn hearing screening program.
Method: From September 2009 to October 2013, the consecutive neonates born in all six branches of Taipei City Hospital were enrolled. Infants who failed the newborn hearing screening and were diagnosed with hearing impairment underwent the genetic analyses.
Result: 15,404 neonates were born at Taipei City Hospital, and 15,345 neonates underwent newborn hearing screening. Among them, 32 infants were diagnosed with unilateral or bilateral hearing impairment. 26 of them underwent analyses of the connexin genes and the *SLC26A4* gene. Of the connexin genes, two infants carried a *GJB3* mutation (heterozygous c.580G>A and heterozygous c.520G>A, respectively). Only one infant carried a *GJB2* mutation (homozygous c.235delC). One infant carried a *GJA1P1* mutation (heterozygous c.929delC) and another carried a *GJB4* mutation (heterozygous c.302G>A). Additionally, one infant carried a *GJA1P1* novel variant (heterozygous c.1081C>T). Another infant carried a *GJA1* novel variant (heterozygous c.1-33C>G). Of the *SLC26A4* gene, one infant carried heterozygous c.919-2A>G mutation and a novel variant (heterozygous c.164+1G>C), and high-resolution computed tomography (HRCT) of the temporal bone revealed bilateral enlarged vestibular aqueducts. One infant carried heterozygous c.919-2A>G mutation and no inner ear anomalies were demonstrated by HRCT of the temporal bone. Another infant carried a novel variant (heterozygous c.818C>T).
Conclusion: These results provide a genetic profile of the connexin genes and *SLC26A4* gene among infants with hearing impairment detected by a universal newborn hearing screening program in Taiwan. Further studies and long-term follow up of this cohort are warranted to determine the pathogenicity of each variants and the long-term hearing consequence.

1. Introduction

Congenital hearing impairment is the most common birth defect in developed countries [1]. The prevalence of congenital bilateral hearing impairment of moderate or greater degree range from 1 in 900 to 1 in 2500 [2]. Congenital hearing impairment leads to delayed language development, difficulties with behavior and psychosocial interaction, and poor academic performance.

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Intervening early with speech and language therapy and amplification improves language outcomes [3]. Universal newborn hearing screening programs, which identify congenital hearing impairment at an early age and allow for early intervention, are therefore recommended.

Congenital hearing impairment, either syndromic or nonsyndromic, is caused by genetic factors in more than half of the cases [4,5]. Mutations in the connexin genes are the most commonly identified genetic causes of congenital hearing impairment in different populations around the world [6,7]. The connexins are the protein subunits that comprise the gap-junction channel, one of the most critical pathways for intercellular communication that mediates the ionic and metabolic coupling of adjacent cells. More than 20 different connexin proteins have been identified in mammals. They all share a common structure, but each of them has its own tissue distribution specificity, electrophysiological characteristics, and regulatory properties [8].

Pendred syndrome (MIM #274600), the most common syndromic form of congenital hearing loss, is characterized by sensorineural or mixed hearing impairment, inner ear anomalies (ranging from isolated enlargement of the vestibular aqueducts to Mondini dysplasia), and development of thyroid goiter in late childhood to early adulthood. Non-syndromic autosomal recessive deafness-4 (DFNB4, MIM #600791) is characterized by sensorineural or mixed hearing impairment and inner ear anomalies. Thyroid goiters are not characteristic of DFNB4. Mutations in *SLC26A4* gene, which encodes an anion transporter known as pendrin, are the major genetic causes of Pendred syndrome and DFNB4 [9–11], and might be the second most commonly identified cause of congenital hearing impairment worldwide.

In the majority of studies which researched the mutations associated with prelingual hearing impairment in the Taiwanese population, the hearing-impaired subjects were mainly recruited from students of the rehabilitation schools for the deaf [12–15]. Some of the studies purely focused on the *GJB2* gene [12,13], or targeted only a few deafness-associated mutations [16].

In view of the lack of broader genetic information of other connexin genes and the *SLC26A4* gene among the population of infants who fail the newborn hearing screening and are diagnosed with congenital hearing impairment in Taiwan, we surveyed eight connexin genes (*GJB2*, *GJB4*, *GJA1P1*, *GJB6*, *GJB3*, *GJA1*, *GJB1*, and *GJC3*) and the *SLC26A4* gene among infants with hearing impairment identified in a government-funded universal newborn hearing screening program.

2. Materials and methods

From September 2009 to October 2013, consecutive neonates born in all six branches of Taipei City Hospital were enrolled in the study. Special classes were provided to educate physicians, audiologists, hospital staff, and related personnel before starting the program. The Department of Health, Taipei City Government and the Health Promotion Administration, Ministry of Health and Welfare in Taiwan paid the cost of each hearing screening. Parents were informed of the availability of newborn hearing screening when they were admitted to the hospital for the birth.

In this study, we used an automated auditory brainstem response (AABR) system (ALGO3; Natus Medical, Inc., San Carlos, CA) with a threshold of 35-dB nHL to screen all of the newborns. The screening procedure was performed by a well-trained nurse in the neonatal nursery when the newborn was sleeping or at the end of feeding. An otolaryngologist checked the ears of the newborn before performing the hearing screening test and cleared any fluid in the external ear canal. The first AABR test was performed 24–36 h after birth. A second AABR test was repeated within 36–60 h if a newborn failed the initial screening.

All newborns who failed the second hearing screening before discharge underwent a distortion product otoacoustic emission (DPOAE) test (ILO 292; Otodynamics Inc., Herts, UK) as well as an AABR test in the outpatient department at the age of 1 month. Infants who failed any of these tests would then undergo a comprehensive diagnostic workup for confirmation of hearing impairment. The workup included DPOAE, tympanometry, auditory brainstem response (ABR), auditory steady-state response (ASSR), and cross-check by behavioral audiometry. The hearing level, calculated by four-tone averages (500, 1000, 2000, and 4000 Hz), was labeled as mild (20–40 dB HL), moderate (41–70 dB HL), severe (71–95 dB HL), or profound (>95 dB HL) hearing loss.

Universal newborn hearing screening procedures were performed according to previously published methods [17]. The flowchart of universal newborn hearing screening and genetic analyses is illustrated in Fig. 1. Infants who received a diagnosis of unilateral or bilateral hearing impairment were subjects for genetic analyses of the connexin gene family (including the *GJB2*, *GJB4*, *GJA1P1*, *GJB6*, *GJB3*, *GJA1*, *GJB1*, and *GJC3* genes) and the *SLC26A4* gene.

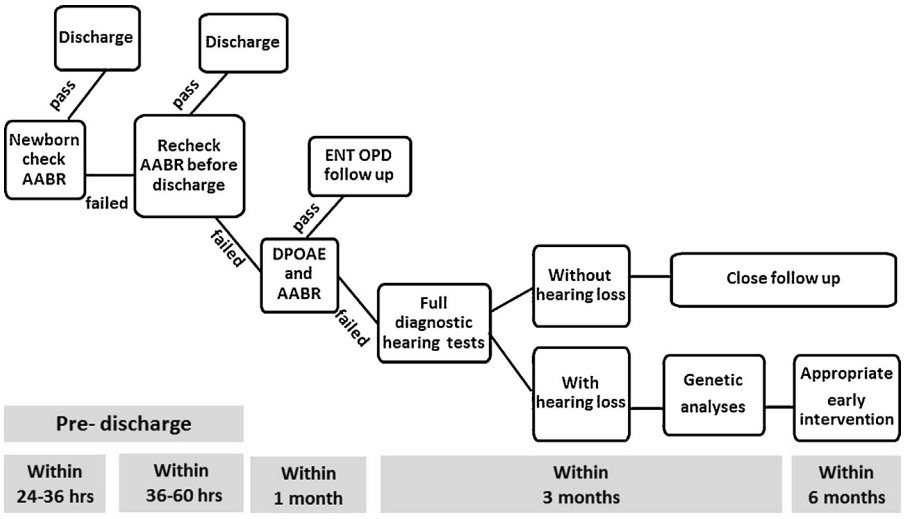

Fig. 1. Flowchart of universal newborn hearing screening and genetic analyses. AABR = automated auditory brainstem response; DPOAE = distortion product otoacoustic emission; ENT = ear, nose, and throat; OPD = outpatient department.