Compound heterozygous dominant and recessive GJB2 mutations cause deafness with palmoplantar keratoderma

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ABSTRACT

GJB2 gene mutation is the most common cause of congenital sensorineural hearing loss worldwide. Most GJB2 gene mutations have been associated with autosomal recessive non-syndromic hearing loss (DFNB1), but some are also associated with autosomal dominant non-syndromic hearing loss (DFNA3). In addition, this gene is also associated with skin homeostasis and some GJB2 gene mutations in this gene cause autosomal dominant syndromic hearing loss with skin disorders (Keratitis-ichthyosis-deafness syndrome, Hystrix-like ichthyosis-deafness syndrome, Palmoplantar keratoderma with deafness syndrome, Vohwinkel syndrome and Bart–Pumphrey syndrome). Herein we report a Japanese sensorineural hearing loss patient with palmoplantar keratoderma who carries a rare compound heterozygote of autosomal dominant and autosomal recessive GJB2 gene mutations. This is the first report of GJB2-associated hearing loss with palmoplantar keratoderma caused by compound heterozygous autosomal dominant and autosomal recessive GJB2 gene mutations in a Japanese patient.

Introduction

Sensorineural hearing loss (SNHL) is one of the most common neurosensory disorders in humans. The incidence of SNHL is estimated to be 1 in 500–1000 newborns [1]. The hearing loss in more than half of these patients is associated with genetic causes [1]. This form of hearing loss is extremely heterogeneous, with about 100 genes known to be responsible for non-syndromic hearing loss [2]. The GJB2 gene is the most common cause of non-syndromic hearing loss and more than 300 variants have been reported. Most GJB2 gene mutations are associated with autosomal recessive non-syndromic hearing loss (DFNB1); however, some GJB2 mutations have been reported to be associated with autosomal dominant non-syndromic or syndromic hearing loss (ADHL) [3]. Syndromic hearing loss with GJB2 gene mutations is associated with various skin diseases, such as hystrix-like ichthyosis-deafness (HID) syndrome (OMIM 602540), keratitis-ichthyosis-deafness (KID) syndrome (OMIM 148210), Vohwinkel syndrome (OMIM 124500), Bart–Pumphrey syndrome (OMIM 149200) and palmoplantar keratoderma (PPK) with deafness (OMIM 148350) [4 for review]. With regard to palmoplantar keratoderma with deafness syndrome, the following mutations have been reported: p.E42del, p.N54H, p.G59A, p.G59R, p.H73R, p.R75Q, p.R75W, p.G130V, p.S183F and p.R184Q [4,5]. Compound heterozygotes of an autosomal recessive non-syndromic hearing loss GJB2 mutation with an autosomal dominant syndromic hearing loss GJB2 mutation are quite rare with only a limited number of reports to date. Herein we report a Japanese sensorineural hearing loss patient with palmoplantar keratoderma who carries a rare compound heterozygote of autosomal dominant and autosomal recessive GJB2 gene mutations. This is the first report of GJB2-associated hearing loss with palmoplantar keratoderma caused by compound heterozygous autosomal dominant and autosomal recessive GJB2 gene mutations in a Japanese patient.

Case report

The proband (IV-1; AH 0690) is a 7-year-old boy in a Japanese family with a history of hearing loss.
spanning three generations (Figure 1(A)). Pure-tone audiometry showed bilateral profound hearing loss (Figure 1(B)). He was the first child of deaf parents and showed no particular complications in the perinatal period. His hearing loss was identified through newborn hearing screening on the basis of automated auditory brainstem response (ABR). He was referred to Yokohama City University Medical Center, Department of Otolaryngology and Head and Neck Surgery for further examinations at six months of age, at which time his tympanic membranes were found to be normal. An ABR with click stimuli showed bilateral hearing loss of approximately 100dBnHL in both ears and he was promptly fitted with bilateral hearing aids. His hearing level was unchanged from 1 to 7 years old. He did not have any episodes of dizziness or vertigo attacks. Computed tomography (CT) findings of the middle and inner ear showed no abnormalities. In addition to the hearing loss, he had diffuse hyperkeratosis of the palms and soles from two years of age (Figure 1(C) left and center photos). Although his mother and maternal grandfather also had a history of hearing loss and hyperkeratosis of the palms and soles with onset in infancy (Figure 1(C) right photo shows the mother’s hyperkeratotic palms), his paternal grandfather, paternal grandmother, granduncle and maternal grandmother had a history of hearing loss without any cutaneous hyperkeratosis.

YSS 5103 is a 40-year-old female and mother of the proband. PTA showed bilateral profound sensorineural hearing loss. She demonstrated bilateral congenital non-progressive hearing loss, but did not experience any episodes of vertigo. She also had diffuse hyperkeratosis of the palms and soles, which was present from infancy.

YSS 5104 is a 42-year-old male and father of the proband. PTA showed bilateral profound SNHL. In his medical examination by interview, he demonstrated bilateral congenital non-progressive hearing loss. He didn’t have any episodes of vertigo or any cutaneous hyperkeratosis of the palms and soles.

To identify the genetic cause of hearing loss in this family, molecular diagnosis was performed using genomic DNA extracted from the peripheral blood of the proband and his parents. We performed comprehensive next-generation sequencing analysis for 68 genes reported to cause hearing impairment as described previously [6]. As a result, we identified compound heterozygous mutations, \textit{GJB2}:NM004004.5:c.223C>T:p.R75W and \textit{GJB2}:NM004004.5:c.235delC:p.L79fs, in the proband. We also identified a homozygous \textit{GJB2}:NM004004.5:c.235delC:p.L79fs mutation in the maternal grandmother.
his father and a heterozygous \textit{GJB2}:NM004004.5:c.223C>T:p.R75W in his mother. The identified mutations were confirmed by Sanger sequencing using exon-specific custom primers described elsewhere [7].

\textbf{Discussion}

Autosomal dominant inherited hearing loss associated with \textit{GJB2} mutations has been identified in both non-syndromic and syndromic hearing loss patients. The p.R75W mutation has previously been reported to be responsible for autosomal dominant inherited hearing loss with PPK in an Egyptian family [8]. The same mutation was also identified from patients with autosomal dominant hearing loss with PPK in Chinese [9,10] and Korean [11] families. Interestingly, the same mutation was also identified from a German autosomal dominant inherited hearing loss family without PPK [12], suggesting broad phenotypic variability in this mutation.

Compound heterozygotes of autosomal recessive and autosomal dominant \textit{GJB2} mutations are quite rare and to the best of our knowledge, have only been reported in nine papers [5,10,13–19]. Rouan et al. reported a case of congenital profound hearing loss with PPK who carried compound heterozygous \textit{GJB2} mutations; c.125\_127del for autosomal dominant and c.35delG for autosomal recessive [13]. Löffler et al. reported a case of congenital profound hearing loss with compound heterozygous \textit{GJB2} mutations; p.R143Q for autosomal dominant and p.I90P for autosomal recessive [14], while the proband’s mother carried a heterozygous p.R143Q mutation indicating mild to moderate hearing loss. Welch et al. reported two siblings carrying compound heterozygous \textit{GJB2} mutations; p.W44C for autosomal dominant and p.K15T for autosomal recessive [15]. The audiometric configurations of these siblings were more severe than that of their father, who carried a heterozygous p.W44C mutation. Bonyadi et al. reported a case of congenital profound hearing loss with p.R143Q and c.35delG mutations [16], and Riahi et al. reported a case of congenital profound hearing loss with p.R143Q and p.V37I mutations [17]. It is noteworthy that the proband’s mother in this case, who carried a heterozygous p.R143Q mutation, did not have hearing loss, suggesting either the low penetrance of this mutation or the misclassification of the pathogenicity of this variant. Pang et al. studied the autosomal dominant mutations in the \textit{GJB2} gene in the Chinese population and identified two compound heterozygote families (one for p.R75Q and p.V37I mutations another for p.R75W and c.235delC). Both of these cases have congenital profound hearing loss and PPK [10]. Boushiha et al. reported twin cases with profound hearing loss and PPK who carried p.R75Q and c.35delG mutations [18]. Their grandmother, who carried a heterozygous p.R75W mutation, also showed profound hearing loss with PPK, whereas their mother did not have PPK in spite of carrying the same mutation.

Pavithra et al. reported a congenital profound hearing loss case who carried a compound heterozygote of three mutations; p.R184Q for autosomal dominant and c.\([-23 +1G>A;370C>T]\) for autosomal recessive [5]. All of these reports suggested that the compound heterozygote of autosomal dominant and autosomal recessive \textit{GJB2} mutations shows more severe hearing loss than the heterozygous autosomal dominant mutation carrier, whereas the PPK phenotype varied among the reported cases. In this paper, we reported a case of congenital profound hearing loss with PPK who carried compound heterozygous autosomal dominant and autosomal recessive \textit{GJB2} mutations. In this family, the maternal family members hearing loss and PPK was caused by a p.R75W mutation, whereas the paternal family members hearing loss was caused by a c.35delC mutation inherited in a recessive manner. Interestingly, the p.R75W mutation has been identified in populations with different ethnic backgrounds, including Egyptian, Korean, Chinese, German and Japanese, suggesting a mutation hotspot is involved in the development of this mutation. This hypothesis was also supported by \textit{de novo} mutation identification in Chinese and Egyptian cases [8–10]. The associated skin symptoms for autosomal dominant inherited hearing loss vary among reports and the detailed mechanisms for this difference remain unclear. Rouan et al. demonstrated trans-dominant negative effects of syndromic \textit{GJB2} mutations on connexin 43 function, suggesting a possible mechanism for the associated skin symptoms [13]. However, this hypothesis does not explain the phenotypic variations within the same mutation. Therefore, further study is required to better understand the basic mechanisms for hearing loss and skin symptoms.

\textbf{Conclusion}

In this paper, we report a Japanese sensorineural hearing loss patient with palmoplantar keratoderma who carries a rare compound heterozygote of autosomal dominant and autosomal recessive \textit{GJB2} gene mutations. The maternal family members also carried the same dominant mutation with associated
palmoplantar keratoderma and deafness. This is the first report of GJB2-associated hearing loss with palmoplantar keratoderma caused by compound heterozygous autosomal dominant and autosomal recessive GJB2 gene mutations in a Japanese patient.

Disclosure statement
The authors have no conflicts of interest to declare.

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