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CASE REPORT

Novel *EYA1* mutation in a Korean branchio-oto-renal syndrome family

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Summary Branchio-oto-renal (BOR) syndrome is an autosomal dominant disorder that is characterized by branchial cysts or fistulae, external ear malformations and/or preauricular pits, hearing loss and renal anomalies. Recent advances in molecular genetics have shown a human homologue of the Drosophila 'eyes absent' gene (*EYA1*) on chromosome band 8q13.3 to be the most common cause of BOR syndrome. Several mutations have been identified in the *EYA1* gene in patients with BOR syndrome worldwide. Here, we report a second Korean family with BOR syndrome with a novel nonsense *EYA1* mutation.

1. Introduction

Branchio-oto-renal (BOR) syndrome (OMIM 113650) is an autosomal dominant disorder that is associated with cervical branchial cleft cysts or fistulae, external ear malformations and/or preauricular pits or sinuses, hearing loss and renal anomalies. BOR syndrome was first described by Melnick et al. [1], and is one of the most common forms of autosomal dominant syndromic hearing loss [2], with an incidence of approximately 1:40,000 in the general population, accounting for 2% of profoundly deaf children [3]. The phenotype for BOR syndrome varies considerably [4—6]. Hearing loss is the most constant feature of BOR syndrome, and is detected in more than 90% of affected individuals [3]. The hearing loss can be sensorineural, conductive or mixed due to an otic anomaly of the outer, middle or inner ear.

In the early 1990s, the gene responsible for BOR syndrome was mapped to the chromosome band 8q12-22 (OMIM 601653) [7—9]. Positional cloning

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was used to identify the causative human homologue of the Drosophila 'eye absent' gene (*EYA1*) [10]. Up to now, several mutations including single nucleotide substitutions, small duplications and deletions as well as complex genomic rearrangements have been identified in the *EYA1* gene in patients with BOR syndrome [10–17]. The majority of *EYA1* mutations, approximately 80%, can be detected in the coding sequence of the *EYA1* gene, and chromosomal rearrangements contribute ~20% to the cause in the BOR syndrome.

Although many mutations have been reported in other populations, there is only one report of BOR syndrome with an *EYA1* gene mutation in Koreans [17]. We report another Korean family with BOR syndrome with a novel *EYA1* mutation as a causative factor.

2. Subjects and methods

The Korean family described in this study spanned four generations with 26 members (Fig. 1). The proband (IV:1) underwent a complete physical examination with special attention being paid to the presence of hearing loss, preauricular pits and ear-lobe anomalies, cervical branchial fistulae and renal abnormalities. Audiological studies were carried out including pure tone audiometry, tympanometry and the auditory brainstem response. A renal ultrasound examination was performed in five affected individuals (II:3, III:1, III:4, IV:1 and IV:3). The distribution of the four clinical features is shown alongside the pedigree (Fig. 1).

After obtaining informed consent, five living family members were examined for any *EYA1* mutations by direct DNA sequencing analysis. The genomic DNA was extracted from the blood using a Wizard genomic DNA purification kit (Promega, Madison, WI, USA). Each of the 16 exons of the *EYA1* gene was amplified by a polymerase chain reaction (PCR) using the appropriate intronic primer sets reported previously [17]. Cycle sequencing was carried out using a BigDye Terminator Cycle Sequencing Ready Reaction kit (Applied Biosystems, Foster City, CA, USA) on an ABI3100 Genetic Analyzer (Applied Biosystems).

3. Results

3.1. Clinical findings

Fig. 1 shows the presence or absence of each of the four major features of the BOR syndrome (hearing loss, preauricular pits, cervical-branchial fistulae and renal abnormalities) for every family member according to the pedigree.

The first generation of this large family had passed away. However, subject I:2 had cervical-branchial fistulae and suffered from hearing loss early in her life. She had seven children with three being affected (II:1, II:3, II:8). None of the family members in the second generation reported any renal disease.

The five affected individuals (II:3, III:1, III:4, IV:1 and IV:3) underwent a clinical evaluation according to their phenotype. All the affected individuals had

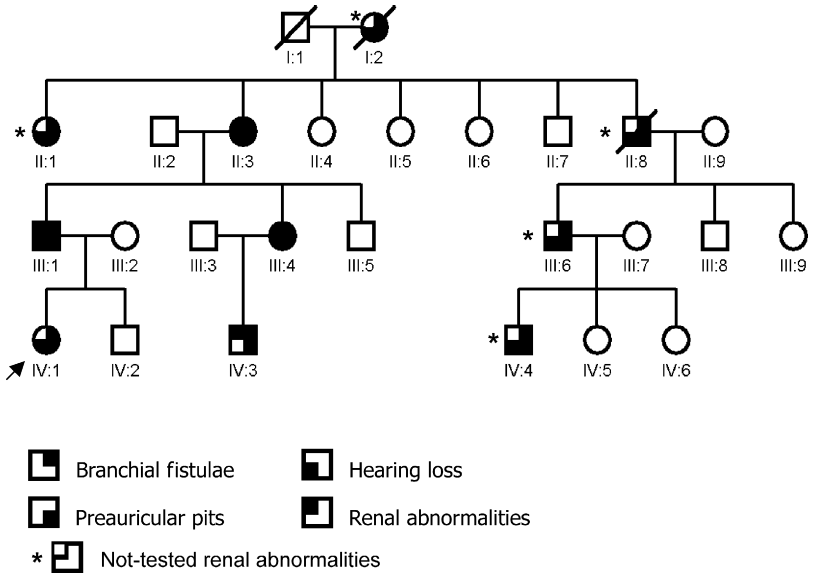

Fig. 1 Pedigree of the family with BOR syndrome. All the affected individuals did not undergo renal ultrasonography. Evaluated family II:3 showed mainly renal hypoplasia (4/5).