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Review Article

EYA1-related disorders: Two clinical cases and a literature review

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ABSTRACT

Objectives: To delineate the diagnostic and rehabilitative aspects of syndromes that have overlapping features, we present the cases of two unrelated Caucasian males affected by hearing impairment, preauricular pits and cervical fistulae. Specific findings that are helpful in the diagnosis and management of *EYA1*-related disorders are highlighted.
Methods: Genetic, otologic, imaging, eye and renal evaluations were conducted to achieve a detailed and comprehensive assessment, leading to the most accurate diagnosis and appropriate treatment. A literature review was also carried out.
Results: Diagnostic criteria indicated that the two patients were affected by BOS1 (Branchio-Otic Syndrome 1). We also identified a novel sporadic missense mutation in the *EYA1* gene: p.G533R (c.1597G > A, NM_000503.4), a highly conserved, heterozygotic amino acid substitution. In the other case, we identified the p.X593QextX6 (c.1777T > A, NM_000503.4) substitution. Both variants lead to isoform 1 (EYA1B and EYA1C) which is composed of 592 amino acids. Clinical and in silico evidence suggests a pathogenic role for the new mutations. Imaging evaluation revealed a complex pathology, characterized by external, inner and middle ear malformations, without renal anomalies.
Conclusions: Our results demonstrate the importance of considering the imaging evaluation and the complete DNA sequencing of the *EYA1* gene for the differential diagnosis of deafness and related branchio-oto-renal disorders.

Contents

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1. Introduction

Branchio-oto-renal (BOR), Branchio-otic (BO), Branchio-oto-ureteral (BOU) and Oto-Facio-Cervical (OFC) syndromes are dominant disorders characterized by variable hearing impairment (HI) and branchial defects [1–3]. BOR and BOU syndromes include additional kidney and urinary tract anomalies. All of these syndromes are genetically heterogeneous and caused by mutations in the *EYA1*, *SIX1*, and *SIX5* genes [3,4]. The involvement of different genes was conducted to define different syndrome subtypes, without wide clinical variations (Table 1). It was also reported that DFNA23, a locus for non-syndromic hearing impairment, is due to mutations in *SIX1* [5]. Nevertheless, mutations in the same gene can lead to different syndromes even if it is unclear why some *EYA1* mutations are associated with kidney abnormalities and others are not. It was also previously thought that *EYA1* mutations may be responsible for Branchio-Oculo-Facial (BOF) syndrome (MIM#113620) because of the presence of overlapping features; it is now clear that BOF syndrome is due to mutations in the *TFAP2A* gene (Table. 1) [6].

Approximately 40 percent of people with BO, BOR, BOU or OFC syndromes have mutations in the *EYA1* gene. The prevalence of *EYA1*-related disorders is approximately 2.5:100,000 newborns and require a multidisciplinary approach in diagnosis, management and treatment (Tables 2–4) [7].

The *EYA1* (Eyes absent homolog 1) gene is the human homologue of the Drosophila *Eya1* gene, which is essential for eye development in that species. In humans, it consists of 16 coding exons and has been localized to chromosome 8q13.3 [1–3]. To date, at least 4 different isoforms are known (EYA1A, EYA1B, EYA1C, EYA1D) and are composed of 559 amino acids (AA), 592 AA, 592 AA and 557 AA, respectively. However, the general acceptance of these isoforms remains lacking because of additional transcriptional variants and an inconsistent definition in specialized online databases. It should be noted that isoforms B and C have the same length; however, they could be considered different variants because of change in amino acidic composition. Some authors grouped and named variants B and C as isoform 1, which is composed of 592 AA. Isoform 3 is composed of only 557 AA, is the shortest isoform and corresponds to the variant EYA1D. Isoform 2 is reported to be composed of 559 amino acids and is widely known as variant EYA1A. This classification is not clear or helpful in the definition and collection of *EYA1* mutations. Additionally, many allelic variants or polymorphisms are consistently reported during clinical practice and have been supported by genetic investigations. To avoid misunderstandings, it would be helpful to directly refer to the amino acidic length of the different isoforms or variants.

To date, more than 160 pathologic mutations in the *EYA1* gene have been reported in the literature. The EYA1 protein may be required for the normal development of branchial arches, ears and kidneys. The expression pattern of the murine EYA1 ortholog, Eya1, suggests a role in the development of all components of the

Table 2
Estimated prevalence of *EYA1*, *SIX1* and *SIX5* mutations.

Prevalence of Branchio-oto-renal spectrum disorders	
2–3% of profoundly deaf children	30–40% with *EYA1* mutations ≈5% with *SIX5* mutations <1% with *SIX1* mutations

Table 3
Appropriate phenotypic criteria for *EYA1* testing in BOR Syndrome: affected individuals must have at least three major criteria, two major criteria and at least two minor criteria, or one major criteria and an affected first-degree relative who meets the criteria for BOR (Chang et al., 2004).

Major criteria	Minor criteria
- Branchial anomalies - Hearing loss - Preauricular pits - Renal anomalies	- External ear anomalies - Middle ear anomalies - Inner ear anomalies - Preauricular tags - Facial asymmetry - Palate abnormalities

Table 4
Phenotypic features of BO/BOR syndrome (Chen et al., 1995).

Phenotypic features of BOR syndrome	
Major features (>20%)	Minor features (<20%)
- Hearing loss (93%) - Preauricular pits (82%) - Renal anomalies (67%) - Branchial fistulae (49%) - Pinnae deformities (36%) - External auditory canal stenosis (29%)	- Preauricular tags - Facial asymmetry - Facial nerve paresis - Palate abnormalities - Lacrimal duct aplasia - Euthyroid goitre - Non-rotation of the gastrointestinal tract - Pancreatic duplication cyst - Temporoparietal linear nevus

Table 1
Syndromes with similar phenotypes and overlapping findings; mutations in the *EYA1* gene are responsible for three subtypes of those syndromes: BOR1, BO1 and OFC1. Although these syndromes are often considered to be three different entities, many authors suggest that they should be considered different expressions of the same syndrome. Genes: *EYA1*, Eyes Absent 1 (drosophila), homolog of; *SIX1*, SINE OCULIS HOMEOBOX 1 (drosophila), homolog of; *SIX5*, SINE OCULIS HOMEOBOX 5, drosophila, homolog of; *PAX1*, Paired box gene 1; *TFAP2A*, Transcription FACTOR AP2-Alpha. Syndromes: BOR, Branchio-oto-renal syndrome; BO, Branchio-otic syndrome; OFC, Oto-Facio-Cervical syndrome; BOF = Branchio-Oculo-Facial syndrome.

Syndrome	Molecular genetics			Phenotype					
Name	Gene	Locus	MIM number	Inheritance pattern	Branchial defects	Ear defects	Kidney defects	Eye defects	MIM number
BOR									
BOR 1	*EYA1*	8q13.3	601653	Dominant	+	+	+	±	113650
BOR 2	*SIX5*	19q13.32	600963	Dominant	+	+	+	±	610896
BOR 3 (?)	*SIX1*	14q23.1	601205	Dominant	+	+	±	+	
BO									
BO1	*EYA1*	8q13.3	601653	Dominant	+	+	–	–	602588
BO2	*?*	1q31	–	Dominant	+	+	–	–	120502
BO3	*SIX1*	14q23.1	601205	Dominant	+	+	–	–	608389
OFC1	*EYA1*	8q13.3	601653	Dominant	+	+	–	–	166780
OFC2	*PAX1*	20p11.22	167411	Recessive	+	+	–	±	615560
BOF	*TFAP2A*	6p24.3	107580	Dominant	+	±	±	+	113620