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Branchiootorenal Spectrum Disorder

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Summary

Clinical characteristics

Branchiootorenal spectrum disorder (BORSD) is characterized by malformations of the outer, middle, and inner ear associated with conductive, sensorineural, or mixed hearing impairment, branchial fistulae and cysts, and renal malformations ranging from mild renal hypoplasia to bilateral renal agenesis. Some individuals progress to end-stage renal disease (ESRD) later in life.

Extreme variability can be observed in the presence, severity, and type of branchial arch, otologic, audiologic, and renal abnormality from right side to left side in an affected individual and also among individuals in the same family.

Diagnosis/testing

The diagnosis of branchiootorenal spectrum disorder is based on clinical criteria. The diagnosis is established in a proband with the clinical features and/or heterozygous pathogenic variants in *EYA1*, *SIX1*, or *SIX5* identified on molecular genetic testing.

Management

Treatment of manifestations: Excision of branchial cleft cysts/fistulae, fitting with appropriate aural habilitation, and enrollment in appropriate educational programs for the hearing impaired are appropriate. A canaloplasty should be considered to correct an atretic external auditory canal. Medical and surgical treatment for vesicoureteral reflux may prevent progression to end-stage renal disease (ESRD). ESRD may require renal transplantation.

Surveillance: Semiannual examination for hearing impairment and annual audiometry to assess progression of hearing loss; monitoring of renal function to prevent progression to ESRD; semiannual/annual examination by a nephrologist and/or urologist, as indicated.

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Agents/circumstances to avoid: Nephrotoxic medications.

Evaluation of relatives at risk: At-risk relatives should be screened for hearing loss and renal involvement to allow for early diagnosis and treatment.

Genetic counseling

BORSD is inherited in an autosomal dominant manner. The offspring of an affected individual are at a 50% risk of inheriting the pathogenic variant. Once the pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

GeneReview Scope

Branchiootorenal Spectrum Disorder: Included Phenotypes
• Branchiootorenal (BOR) syndrome • Branchiootic syndrome (BOS)

For synonyms and outdated names see Nomenclature.

Diagnosis

Branchiootorenal spectrum disorder comprises branchiootorenal (BOR) syndrome and branchiootic syndrome (BOS), two phenotypes that differ only by the presence or absence of renal abnormality. Many affected persons in families with diagnosis confirmed by molecular genetic testing have clinical findings consistent with the diagnosis of BOR syndrome; however, some affected persons in these same families have clinical findings consistent with BOS [Orten et al 2008]. For this reason, these syndromes are best considered as one disorder known as branchiootorenal spectrum disorder.

Suggestive Findings

Branchiootorenal spectrum disorder (BORSD) **should be suspected** in individuals with the following characteristics. See Table 1.

Table 1. Major and Minor Diagnostic Criteria for Branchiootorenal Spectrum Disorder

Major Criteria	Minor Criteria
• Second branchial arch anomalies • Deafness • Preauricular pits • Auricular malformation • Renal anomalies	• External auditory canal anomalies • Middle ear anomalies • Inner ear anomalies • Preauricular tags • Other: facial asymmetry, palate abnormalities

In the absence of a family history, three or more major criteria OR two major and two minor criteria (Table 1) must be present to make the clinical diagnosis of BORSD [Chang et al 2004].

Second branchial arch anomalies

- Branchial cleft sinus tract appearing as a pinpoint opening anterior to the sternocleidomastoid muscle, usually in the lower third of the neck
- Branchial cleft cyst appearing as a palpable mass under the sternocleidomastoid muscle, usually above the level of the hyoid bone

Otologic findings

- Deafness: mild to profound in degree; conductive, sensorineural, or mixed in type (see Deafness and Hereditary Hearing Loss Overview)
- Preauricular pits
- Auricular malformation (lop ear, cupped ear)
- Preauricular tags
- Abnormalities of the external auditory canal: atresia or stenosis
- Middle ear abnormalities: malformation, malposition, dislocation, or fixation of the ossicles; reduction in size or malformation of the middle ear space
- Inner ear abnormalities: cochlear hypoplasia; enlargement of the cochlear and vestibular aqueducts; hypoplasia of the lateral semicircular canal [Ceruti et al 2002, Kemperman et al 2002]

Renal anomalies

- Renal agenesis, hypoplasia, dysplasia
- Uretero-pelvic junction (UPJ) obstruction
- Calyceal cyst/diverticulum
- Calyectasis, pelviectasis, hydronephrosis, and vesicoureteral reflux

Note: Individuals with an affected family member need only one major criterion to make the diagnosis of BORSD [Chang et al 2004].

Establishing the Diagnosis

The diagnosis of a branchiootorenal spectrum disorder **is established** in a proband with the clinical features listed in Suggestive Findings and/or by identification of a heterozygous pathogenic variant in one of the genes listed in Table 2.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of branchiootorenal spectrum disorder is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with atypical features in whom the diagnosis of branchiootorenal spectrum disorder has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of branchiootorenal spectrum disorder the use of a **multigene panel** is recommended.

A multigene panel including *EYA1*, *SIX1*, *SIX5*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the diagnosis of branchiootorenal spectrum disorder is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if exome sequencing is not diagnostic.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in Branchiootorenal Spectrum Disorder (BORSD)

Gene [1, 2]	Proportion of BORSD Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
EYA1	40% [6]	80% [6]	20% [6]
SIX1	2% [7]	100% [7]	Unknown [8]
SIX5	2.5% [9]	100% [9]	Unknown [8]
Unknown [10]	>50%	NA	

1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on allelic variants detected in this gene.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Chang et al [2004], Krug et al [2011]
7. Heterozygous pathogenic variants were identified in 10 (4.0%) of 247 unrelated individuals with BORSD syndrome in whom an *EYA1* or *SIX5* pathogenic variant was not identified [Kochhar et al 2008]. This prevalence implies that *SIX1* pathogenic variants account for approximately 2% of cases of BORSD.
8. No data on detection rate of gene-targeted deletion/duplication analysis are available.
9. Heterozygous pathogenic variants were identified in 5 (5.2%) of 95 unrelated individuals with BORSD in whom an *EYA1* or *SIX1* pathogenic variant was not identified [Hoskins et al 2007]; these data imply a *SIX5* mutation rate of fewer than 2.5% of persons with BORSD syndrome.
10. Brophy et al [2013], Morisada et al [2014]

Clinical Characteristics

Clinical Description

The presence, severity, and type of branchial arch, otologic, audiologic, and renal abnormality in branchiootorenal spectrum disorder (BORSD) may differ from right side to left side in an affected individual and among individuals in the same family.

Second branchial arch anomalies include branchial cleft cyst or sinus tract (cervical fistulae) (50%). Cysts can become infected and sinus tracts can drain.

Otologic findings, found in more than 90% of individuals with BORSD [Chang et al 2004], include:

- **Hearing loss** (>90%) [Stinckens et al 2001]
  - Type: mixed (52%), conductive (33%), sensorineural (29%)
  - Severity: mild (27%), moderate (22%), severe (33%), profound (16%)
  - Non-progressive (~70%), progressive (~30%, correlates with presence of a dilated vestibular aqueduct on computed tomography) [Kemperman et al 2004]
- **Abnormalities of the pinnae**
  - Preauricular pits (82%)
  - Lop ear malformation (36%)
  - Preauricular tags (13%)
- **Abnormalities of the external auditory canal.** Atresia or stenosis (29%)
- **Middle ear abnormalities.** Malformation, malposition, dislocation, or fixation of the ossicles; reduction in size or malformation of the middle ear space
- **Inner ear abnormalities.** Variably present:
  - Cochlear hypoplasia
  - Enlargement of the cochlear and vestibular aqueducts
  - Hypoplasia of the lateral semicircular canal [Ceruti et al 2002, Kemperman et al 2002]

Renal anomalies. Renal malformations can be unilateral or bilateral and can occur in any combination. The most severe malformations result in pregnancy loss (since bilateral renal agenesis can end in miscarriage) or neonatal death; ESRD later in life may necessitate dialysis or transplantation.

Although renal anomalies are common, the true prevalence is difficult to establish because not all affected individuals undergo intravenous pyelography or renal ultrasonography. In a study in which 21 affected individuals had one of these two tests, renal anomalies were noted in 67% [Chang et al 2004] and included the following:

- Renal agenesis (29%), hypoplasia (19%), dysplasia (14%)
- Uretero-pelvic junction (UPJ) obstruction (10%)
- Calyceal cyst/diverticulum (10%)
- Calyectasis, pelviectasis, hydronephrosis, and vesicoureteral reflux (5% each)

Other findings [Chang et al 2004]

- Lacrimal duct aplasia
- Short or cleft palate
- Retrognathia
- Euthyroid goiter
- Facial nerve paralysis
- Gustatory lacrimation

Genotype-Phenotype Correlations

A genotype-phenotype correlation has not been defined for BORSD. In fact, families have been identified segregating *SIX1* pathogenic variants and exhibiting broad intrafamilial phenotypic variability. For example, in one large family all 18 persons with hearing loss carried the p.Tyr129Cys variant in *SIX1*, although six persons also had ear pits, three others had branchial cysts, and two developed a renal carcinoma [Ruf et al 2004]. In a small Tunisian family [Mosrati et al 2011], five persons with moderate-to-profound mixed or sensorineural

hearing loss had the *SIX1* p.Glu125Lys variant. Preauricular pits were present in four persons, but none had other branchial, renal, or temporal bone anomalies. These reports suggest that genetic background and stochastic factors influence intrafamilial phenotypic variability and preclude making genotypic-phenotypic correlations.

Penetrance

Based on careful clinical studies of large pedigrees, branchiootorenal spectrum disorder appears to have 100% penetrance, although expressivity is highly variable [Chang et al 2004].

Nomenclature

BOR syndrome was originally known eponymously as Melnick-Fraser syndrome. While phenotypic descriptions are applied to BOR, BOS, and even branchiootoureteral (BOU) syndrome, these clinical distinctions must be considered in light of the associated molecular genetics. Affected individuals within a single family may have findings of any of the phenotypes. Thus, the term "branchiootorenal spectrum disorder" has replaced the older descriptive phenotype designations.

Prevalence

The prevalence of branchiootorenal spectrum disorder is not known. In 1976, GR Fraser surveyed 3,640 children with profound hearing impairment and found only five (0.15%) with a family history of branchial fistulae and preauricular pits (1:700,000) [Fraser 1976]. Four years later, FC Fraser et al [1980] surveyed 421 children attending schools for the deaf in Montreal for preauricular pits and branchial fistulae, and identified 19 children with preauricular pits; two also had branchial fistulae. The parents of nine children agreed to participate in further investigation, which included audiograms and intravenous pyelograms, and confirmed BORSD segregating in four families, leading the authors to estimate the prevalence of BORSD at 1:40,000, or roughly 2% of profoundly deaf children. Interestingly, Morisada et al [2014] reported that only 250 patients with BORSD (95% confidence interval, 170-320) were identified in clinics in Japan in 2009-2010, suggesting that there are ethnic differences in the prevalence. In the authors' experience at the Molecular Otolaryngology and Renal Research Laboratories (MORL), of 3,379 persons screened for genetic causes of hearing loss (no exclusionary criteria), the diagnostic rate was 42.4% (1,434 persons had an identified genetic cause of hearing loss); 25 of the 1,434 persons (1.7%) had BORSD [Smith, unpublished data].

Genetically Related (Allelic) Disorders

EYA1

- Otofaciocervical (OFC) syndrome (OMIM 166780). This rarely encountered disorder with distinguishing features that include a long face with narrow nose, high arched palate, lop ears, long neck, sloping shoulders and clavicles, winged, low, and laterally set scapulae, tetralogy of Fallot, and hearing loss has been reported to be a contiguous gene deletion syndrome involving *EYA1*, which therefore accounts for the BORSD aspects of the phenotype [Rickard et al 2001]. Estefanía et al [2006], however, described a single individual heterozygous for a canonic splice donor variant in *EYA1* with an OFC syndrome phenotype and concluded that single-nucleotide substitutions in *EYA1* can also lead to OFC syndrome [Estefanía et al 2006]. Given the large number of individuals with BORSD with a wide variety of *EYA1* pathogenic variants who do not have features specific to OFC syndrome, this conclusion should be interpreted with circumspection. Estefanía et al limited their genetic analysis to amplification and sequencing of *EYA1* coding exons, which is an insufficient genetic analysis to support their conclusion.
- Congenital anterior segment anomalies with or without cataract (OMIM 602588). This eye finding has been reported in three persons with pathogenic variants in *EYA1*. In two of these individuals, other

features of BORSD were present, suggesting that congenital eye anomalies may be an occasional feature of BORSD [Azuma et al 2000].

SIX1 has been assigned as the DFNA23 locus (OMIM 605192), which maps to chromosome 14q21-q22. However, in the original family purported to have DFNA23, while a pathogenic variant was found in *SIX1*, the individual in question also had a solitary left hypodysplastic kidney with vesicoureteral reflux and progressive renal failure consistent with the diagnosis of BORSD [Salam et al 2000].

***SIX5*.** No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *SIX5*.

Differential Diagnosis

More than 400 genetic syndromes that include hearing loss have been described [Toriello & Smith 2013, Korver et al 2017]. Although the branchiootorenal spectrum disorder has a distinctive phenotype that is readily appreciated when segregating in large families, the diagnosis can be difficult to establish in small families. See Hereditary Hearing Loss and Deafness Overview.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with branchiootorenal spectrum disorder the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- **Second branchial arch anomalies.** Cervical examination for fistulae; computed tomography of the neck if a mass is palpable under the sternocleidomastoid muscle above the level of the hyoid bone
- **Otologic findings**
  - A complete assessment of auditory acuity using ABR, emission testing, and pure tone audiometry (see Hereditary Hearing Loss and Deafness Overview)
  - Computed tomography of the temporal bones, especially if the hearing impairment fluctuates or is progressive
- **Renal anomalies.** Renal ultrasound examination and/or excretory urography (intravenous pyelography); tests of renal function: BUN and creatinine; urinanalysis
- **Other.** Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Recommended treatment:

- **Second branchial arch anomalies.** Excise branchial cleft cysts/fistulae.
- **Otologic anomalies**
  - Fit with appropriate aural habilitation as indicated.
  - Enroll in an appropriate educational program for the hearing impaired.
  - Consider canaloplasty to correct an atretic canal; however, in individuals with BORSD, associated middle ear anomalies (e.g., a facial nerve overriding the oval window) can preclude a successful result. Evaluate the status of the middle ear preoperatively by obtaining thin-cut CT images of the temporal bones in both the axial and coronal planes.
- Renal anomalies
  - Treat urologic and renal abnormalities in the standard manner.

- If renal anomalies (e.g., vesicoureteral reflux) are present, medical and surgical treatment may prevent progression to end-stage renal disease (ESRD).
- If ESRD develops, consider renal transplantation.

Surveillance

Surveillance for otologic and renal anomalies should be offered as described below.

Otologic anomalies. Serial audiometry to survey for progression of hearing loss:

- Annual examination by a physician who is familiar with hereditary hearing impairment
- Semiannual examination for hearing impairment and annual audiometry to assess stability of hearing loss (more frequent if fluctuation or progression is described by the affected individual)

Renal anomalies. Semiannual/annual examination by a nephrologist and/or urologist may be indicated based on level of renal function and type of renal and/or collecting system malformation.

Agents/Circumstances to Avoid

Individuals with renal abnormalities should use appropriate caution when taking medications (i.e., antibiotics and analgesics) that can impair renal function or require normal renal physiology for clearance.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic relatives at risk for BORSD to determine if a treatable and/or possibly progressive otologic and/or renal abnormality is present. Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known;
- Comprehensive physical examination (to include hearing evaluation and renal imaging and function studies) if the pathogenic variant in the family is not known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Branchiootorenal spectrum disorder (BORSD) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 90% of individuals diagnosed with BORSD have an affected parent.

- A proband with BORSD may have the disorder as the result of a *de novo* *EYA1*, *SIX1*, or *SIX5* pathogenic variant. Approximately 10% of cases are caused by *de novo* pathogenic variants.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing for the pathogenic variant identified in the proband and examination of the parents for hearing loss, preauricular pits, lacrimal duct stenosis, branchial fistulae and/or cysts, and renal anomalies.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, two possible explanations are a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (although no instances of germline mosaicism have been reported, it remains a possibility).
- Although most individuals diagnosed with BORSD have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluation of the parents has been performed.

Sibs of a proband. The risk to the sibs of a proband depends on the clinical/genetic status of the proband's parents:

- If a parent is diagnosed with BORSD, the risk to each sib is 50%. Disease severity in sibs who inherit a pathogenic variant cannot be accurately predicted and is extremely variable even within the same family.
- If the parents are clinically unaffected and the *EYA1*, *SIX1*, or *SIX5* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband

- Each child of an individual with BORSD has a 50% chance of inheriting the *EYA1*, *SIX1*, or *SIX5* pathogenic variant.
- Disease severity cannot be accurately predicted and is extremely variable even within the same family.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected, his or her family members may be at risk.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Fetal ultrasound examination. For fetuses at increased risk for BORSD, prenatal ultrasound examination at 16-17 weeks' gestation should be considered for evaluation of significant renal malformations and/or oligohydramnios.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

While requests for prenatal testing for significant medical conditions such as bilateral renal agenesis are generally accepted, requests for prenatal testing for conditions such as BORSD may be more problematic. Variable expressivity makes it impossible to accurately predict which manifestations of BORSD may occur and how mild or severe they will be. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **American Society for Deaf Children**

  Phone: 800-942-2732 (ASDC)

  Email: info@deafchildren.org

  deafchildren.org

- **BabyHearing.org**

  This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.

  babyhearing.org

- **Children's Craniofacial Association**

  Phone: 800-535-3643

  Email: contactCCA@ccakids.com

  www.ccakids.org

- **Face Equality International**

  United Kingdom

  faceequalityinternational.org

- **Kidney Foundation of Canada**

  Canada

  Phone: 514-369-4806; 800-361-7494

  Email: info@kidney.ca

  www.kidney.ca

- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org
- **National Kidney Foundation (NFK)**
  Phone: 855-NKF-CARES; 855-653-2273
  Email: nkfcares@kidney.org
  www.kidney.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Branchiootorenal Spectrum Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
EYA1	8q13.3	Eyes absent homolog 1	EYA1 database	EYA1	EYA1
SIX1	14q23.1	Homeobox protein SIX1	SIX1 database	SIX1	SIX1
SIX5	19q13.32	Homeobox protein SIX5	SIX5 database	SIX5	SIX5

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Branchiootorenal Spectrum Disorder (View All in OMIM)

113650	BRANCHIOOTORENAL SYNDROME 1; BOR1
600963	SIX HOMEOBOX 5; SIX5
601205	SIX HOMEOBOX 1; SIX1
601653	EYA TRANSCRIPTIONAL COACTIVATOR AND PHOSPHATASE 1; EYA1
602588	BRANCHIOOTIC SYNDROME 1; BOS1
608389	BRANCHIOOTIC SYNDROME 3; BOS3
610896	BRANCHIOOTORENAL SYNDROME 2; BOR2

Molecular Pathogenesis

The vertebrate Eya gene family comprises four transcriptional activators that interact with other proteins in a conserved regulatory hierarchy to ensure normal embryologic development.

The vertebrate orthologs of *so* are members of the *Six* gene family and similarly bind with Eya proteins, inducing nuclear translocation of the resultant protein complex. *Six1* and *Six5* function as transactivators and transcriptional repressors, depending on their cofactors, and are involved in regulation of organogenesis [Silver et al 2003, Li et al 2004, Bricaud & Collazo 2006, Hoskins et al 2007].

Eya proteins have intrinsic phosphatase activity, enabling it to serve as a promoter-specific transcriptional coactivator. It is part of the Six-Eya-Dach regulatory network that defines a molecular mechanism by which a recruited coactivator with phosphatase function (in this case, Eya) derepresses target genes. Six1 acts as a repressor or as an activator of gene transcription based, at least in part, on the recruitment of opposing cofactors. The recruitment of Dach is associated with corepressor activity, while the recruitment of Eya is associated with coactivator activity. The coactivator activity of Eya is based on its phosphatase activity, which reverses the corepressor activity of Dach and permits the recruitment of other coactivators [Li et al 2003].

EYA1

Gene structure. *EYA1* consists of 16 coding exons that extend over 156 kb. It has at least four alternatively spliced transcripts. For a detailed summary of gene and protein information, see Table A, **Gene**.

The 5' exons (exon -1 and the 3' end of exon 1) produce an open reading frame (ORF) that could add more than 156 amino acids to the amino terminal of *EYA1*; however, it is not known whether this sequence is translated. The 17 introns of *EYA1* vary in size from 0.1 to 27.5 kb [Orten et al 2008].

Pathogenic variants. More than 80 different pathogenic variants of *EYA1* that result in BORSD have been identified [Kumar et al 1998]. These include nonsense [Kumar et al 1998], missense, frameshift [Kumar et al 1998], and splice site variants and large deletions and insertions of both coding sequence and upstream regulatory elements. A large deletion of ~2.7 Mb that includes *EYA1* has been reported as a relatively common cause of BORSD. The breakpoints of this deletion are in long terminal repeat elements of the ERV1 retrovirus family [Sanchez-Valle et al 2010, Brophy et al 2013]. Deletions affecting only upstream regulatory elements are less frequently identified but are likely to become an increasingly recognized cause of BORSD [Sanggaard et al 2007, Ishihara et al 2008, Maharana et al 2017].

All of these pathogenic variants affect at least two *EYA1* isoforms. In addition, the presence of pathogenic variants in exon 12, which is skipped in the shortest transcript EYA1D (NM_172059.3), indicates that the longer isoforms are necessary for EYA1 function [Orten et al 2008].

Normal gene product. The proteins encoded by the transcript variants EYA1A (NP_742057.1; 559 amino acids) and EYA1B (NP_742055.1; 592 amino acids) differ only in their N-terminal region. EYA1C (NM_000503.5) has two overlapping open reading frames (ORFs). One of the predicted ORFs is identical to that of EYA1B; however, for this ORF, the first stop codon is an additional 369 nucleotides upstream. 5' UTR variations and alternate splicing are consistent with multifaceted control of *EYA1* gene expression, which is particularly relevant because the protein encodes products important for inner ear, kidney, and branchial arch development [Ishihara et al 2008, Maharana et al 2017].

The structure of the EYA1 proteins includes a highly conserved 271-amino-acid carboxy terminus called the eya-homologous region (eyaHR) and a more divergent proline-serine-threonine (PST)-rich (34%-41%) transactivation domain at the amino terminus (eya variable region, eyaVR) [Zhang et al 2004].

Abnormal gene product. Some pathogenic variants in *EYA1* generate mutated proteins that are rapidly degraded, implying that haploinsufficiency can cause BORSD [Zhang et al 2004]. These data are also consistent with the presence of large deletions of one allele of *EYA1* in some families with BORSD. Based on data derived from in vivo studies of the *Drosophila* developmental system, other pathogenic missense variants affect either phosphatase or transcription function [Mutsuddi et al 2005]. These different types of mutational effects are predicted to lead to differences in phenotype.

SIX1

Gene structure. *SIX1* has a transcript of 1,376 bp and two exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Eight *SIX1* pathogenic variants have been reported [Ruf et al 2004, Ito et al 2006, Kochhar et al 2008]. One of these, c.328C>T, was detected in six unrelated families from multiple ethnic groups [Kochhar et al 2008].

Table 3. *SIX1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.50T>A	p.Val17Glu	NM_005982.3 NP_005973.1
c.317T>G	p.Val106Gly	
c.328C>T	p.Arg110Trp	
c.334C>T	p.Arg112Cys	
c.373G>A	p.Gly125Lys	
c.386A>G	p.Tyr129Cys	
c.397_399delGAG	p.Glu133del	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *SIX1* is one of six members of the SIX gene family *(SIX1-SIX6)* in humans. Like each of the transcribed proteins in this family, homeobox protein SIX1 has both a conserved SIX domain and homeodomain, which are required for DNA binding. Expression of SIX1 is necessary for normal development of the inner ear, nose, thymus, kidney, and skeletal muscle. Mice with a targeted deletion of the ortholog *Six1* have been shown to have abnormalities of these organs [Ando et al 2005].

Abnormal gene product. Functional characterization of several *SIX1* pathogenic variants has shown that they appear to have one of the following consequences [Ohto et al 1999, Ruf et al 2004, Patrick et al 2009]:

- Abolish SIX1-EYA1 complex formation, thus preventing nuclear localization (i.e., p.Val17Glu); or
- Abrogate DNA binding of the SIX1-EYA1 complex (i.e., p.Val106Gly, p.Arg110Trp, p.Arg112Cys, p.Tyr129Cys, p.Glu133del)

To date, no loss-of-function variants have been reported in association with the BORSD phenotype [Ruf et al 2004]. This observation is consistent with intolerance to loss of function, as indicated by its pLI score (Exome Aggregation Consortium [ExAC]). A pLI (probability of loss-of-function intolerance) score reflects the probability that a gene is intolerant to a loss-of-function variant [Samocha et al 2014].

SIX5

Gene structure. *SIX5* has a transcript of 3,145 bp and three exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Based on the identification of pathogenic variants in *SIX5* in five of 95 unrelated individuals with BORSD syndrome, at least four pathogenic variants are known [Hoskins et al 2007]. Of note, Krug et al [2011] reported the p.Thr552Met variant segregating with the BORSD phenotype in a small family of three affected persons; each person, however, also carried a partial deletion of *EYA1*, confounding interpretation of the effect (if any) of the *SIX5* variant (see Table 4).

Table 4. *SIX5* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.472G>A	p.Ala158Thr	NM_175875.3 NP_787071.2
c.886G>A	p.Ala296Thr	
c.1093G>A	p.Gly365Arg	
c.1655C>T	p.Thr552Met	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The homeobox protein SIX5 has 739 amino acid residues and a high degree of homology to SIX1, and is known to interact directly with EYA1. However, unlike SIX1, SIX5 has an additional activation domain (AD) at the C terminus [Hoskins et al 2007].

Abnormal gene product. Disease-associated variants have been shown to result in reduced protein function. In vitro data from a yeast two-hybrid system suggest that both p.Ala158Thr and p.Thr552Met residues of SIX5 may be required for efficient binding with EYA1 as measured by *lacZ* expression [Hoskins et al 2007]. The p.Ala158Thr and p.Thr552Met variants show a significant reduction in *lacZ* expression. The p.Ala296Thr and p.Gly365Arg pathogenic variants result in a slight reduction in *lacZ* expression

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Chapter Notes

Author Notes

Molecular Otolaryngology and Renal Research Laboratories web page

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