GENEReviews

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Branchiootorenal Syndrome

[*BOR Syndrome. Includes: Branchiootorenal Syndrome 1 (BOR1); Branchiootorenal Syndrome 2 (BOR2)*]

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Summary

Disease characteristics. Branchiootorenal (BOR) syndrome 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. The presence, severity, and type of branchial arch, otologic, audiologic, and renal abnormality may differ from right side to left side in an affected individual and also among individuals in the same family. Some individuals progress to end-stage renal disease (ESRD) later in life.

Diagnosis/testing. The diagnosis of BOR is made using clinical criteria. Molecular genetic testing of the *EYA1* gene (BOR1) detects mutations in approximately 40% of individuals with the clinical diagnosis of BOR syndrome. Molecular genetic testing of the *SIX5* gene (BOR2) detects mutations in 5.2% of individuals with the clinical diagnosis of BOR syndrome who do not have an *EYA1* mutation. Such testing is available clinically.

Management. Management of BOR includes excision of branchial cleft cysts/fistulae, fitting with appropriate aural habilitation, and enrollment in appropriate educational programs for the hearing impaired. A canaloplasty can be considered to correct an atretic canal. Medical and surgical treatment for vesicoureteral reflux may be necessary. End-stage renal disease may require dialysis or renal transplantation. Surveillance includes semiannual examination for hearing impairment and annual audiometry to assess stability of hearing loss and semiannual/annual examination by a nephrologist if indicated.

Genetic counseling. BOR syndrome is transmitted in an autosomal dominant manner. Affected individuals have a 50% chance of transmitting the disorder to each child. Extreme clinical variability can be observed in the same family. Prenatal testing for fetuses at risk for an *EYA1* mutation is clinically available for families in which the disease-causing mutation has been identified.

Diagnosis

Clinical Diagnosis

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

Table 1. Major and Minor Diagnostic Criteria for Branchiootorenal Syndrome

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

Second branchial arch anomalies

- Branchial cleft sinus tract appearing as a pin-point 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 deformity (lop-ear deformity)
- 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 anomaly

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

Note: (1) Individuals with an affected family member need only one major criterion to make the diagnosis of BOR syndrome [Chang et al 2004]. (2) In the absence of structural renal anomalies, the clinical diagnosis of branchiooto syndrome (BO syndrome) should be considered.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Genes. Three genes are known to be associated with BOR syndrome:

- ***EYA1***(BOR1). Approximately 40% of individuals with BOR syndrome have mutations in *EYA1* [Chang et al 2004].
- ***SIX5***(BOR2). Approximately 5.2% of individuals with BOR syndrome (who did not have identifiable mutations in *EYA1* or *SIX1*) had mutations in *SIX5* [Hoskins et al 2007].
- ***SIX1*.** A very small percentage of individuals with BOR syndrome have mutations in *SIX1* [Ruf et al 2004].

Other loci. It is probable that mutations in additional genes are causally related to the BOR syndrome phenotype.

Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Clinical testing

- ***EYA1***
  - **Mutation scanning.** The complete *EYA1* coding sequence is screened for allele variations by DHPLC; the specific mutation is then identified by direct sequencing. (Mutation scanning does not detect large insertions or deletions, which are present in the approximately 20% of individuals* with an *EYA1* mutation who have a chromosomal rearrangement.)
  - **Deletion/duplication testing.** Real-time PCR, Southern analysis, or FISH testing of *EYA1*. Approximately 10% of individuals* with a BOR syndrome phenotype have a large chromosomal rearrangement that can be detected with real-time PCR, or the analysis of Southern blots or FISH hybridized with probes corresponding to each of the *EYA1* exons. A semi-quantitative PCR-based screen facilitates the rapid and reliable detection of many of these rearrangements [Chang et al 2004].

    * Approximately 20% of individuals with *EYA1* mutations, but 10% of those with a BOR phenotype, have a large chromosomal rearrangement.
- ***SIX5***
  - **Sequence analysis.** Heterozygous mutations were identified in 5/95 (5.2%) unrelated individuals with BOR syndrome in whom an *EYA1* or *SIX1* mutation was not identified [Hoskins et al 2007].

Research testing

- **Mutations of *SIX1***have been implicated in a small number of individuals with BOR syndrome [Ruf et al 2004]. Testing of this gene is available on a research basis only.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. Molecular Genetic Testing Used in BOR Syndrome

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Gene and Test Method [1]	Test Availability
EYA1	Mutation scanning	Small insertions, small deletions, missense and nonsense mutations in *EYA1*	30%	Clinical Testing
	Duplication/ deletion testing	Partial or whole-gene rearrangements	10%	
SIX5	Sequence anlaysis	Sequence variants	~5% [2]	Clinical Testing
SIX1	Direct DNA [3]	Sequence variants	<1.0%	Research only

1. In individuals with a BOR syndrome phenotype
2. Detection rate of 5.2% in individuals without detectable mutations in *EYA1* and *SIX1* genes
3. Direct DNA methods may include mutation analysis, mutation scanning, sequence analysis, or other means of molecular genetic testing to detect a genetic alteration associated with BOR syndrome.

Interpretation of test results. Failure to detect an *EYA1* or *SIX5* mutation may reflect only the limited extent of the mutation screen and thus does not exclude the diagnosis of BOR syndrome.

Genetically Related (Allelic) Disorders

Branchiooto (BO) syndrome. BO can be caused by allelic variants of *EYA1*. The BO syndrome is characterized by deafness, cup-ear deformity, preauricular pits, and branchial fistulae, but absence of renal anomalies. In two families with BO syndrome and mutations in *EYA1*, affected individuals had sensorineural (25%), mixed (66%), or conductive (9%) hearing loss; branchial fistulae (100%); preauricular pits (80%); and cup-ear deformity (60%) [Abdelhak et al 1997; Vincent et al 1997; Chang et al 2004].

Additional loci for BO syndrome are (1) BOS2 (1q31) [Kumar et al 2000] and (2) BOS3 (14q23.1-24.3) [Ruf et al 2003]. The gene for BOS2 has not been cloned but in the BOS3 interval on chromosome 14, three different mutations in *SIX1* have been identified in four BO/ BOR kindreds [Ruf et al 2004]. In two of these kindreds the BO phenotype segregates with a missense mutation of *SIX1* (p.Tyr129Cys, p.Arg110Trp) and in one kindred in which the phenotype included renal anomalies, an amino acid deletion (p.Glu133del) was present. The remaining family segregates p.Arg110Trp with the disease phenotype, but renal studies were not done [Ruf et al 2004].

Phenotypic differences probably reflect genetic background, protein-protein interactions (EYA1 and SIX1 are part of a complex protein network), or the level of clinical investigation. For example, one individual with a deletion of the entire *EYA1* gene and BO syndrome has been reported [Haan et al 1989, Kalatzis et al 1996], and in two families with BO syndrome, mutations have been identified in exons 4 and 9 [Abdelhak et al 1997; Vincent et al 1997]. However, most mutations in *EYA1* are associated with BOR syndrome.

In the large extended family with BO syndrome linked to BOS2 (1q31), affected individuals have branchial anomalies and hearing loss associated with commissural lip pits [Kumar et al 2000] (see Differential Diagnosis.)

Oto-facial-cervical (OFC) syndrome. Two individuals with *de novo* deletions of the *EYA1* gene and surrounding region had complex phenotypes including features of BOR syndrome [Rickard et al 2001].

Clinical Description

Natural History

The presence, severity, and type of branchial arch, otologic, audiologic, and renal abnormality may differ from right side to left side in an affected individual and between individuals in the same family.

Second branchial arch anomalies include the following:

- 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 BOR syndrome [Chen et al 1995, Chang et al 2004], include the following:

- Hearing loss (>90%)
  - 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) [Stinckens et al 2001, Kemperman et al 2004]
- Abnormalities of the pinnae
  - Preauricular pits (82%)
  - Lop-ear deformity (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; include:
  - Cochlear hypoplasia
  - Enlargement of the cochlear and vestibular aqueducts
  - Hypoplasia of the lateral semicircular canal [Ceruti et al 2002, Kemperman & Koch 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; end-stage renal disease (ESRD) later in life may necessitate dialysis or transplantation [Widdershoven et al 1983, Heimler & Lieber 1986, Ni et al 1994].

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% [Chen et al 1995, 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 [Chen et al 1995, Chang et al 2004]

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

The following are the findings in the four families segregating *SIX1* mutations:

- Family 1. Hearing loss (sensorineural, conductive and/or mixed) was present in all 18 affected individuals; ear pits in six; branchial cysts in three; and lacrimal duct stenosis in three [Ruf et al 2003]. Two affected individuals developed renal carcinoma.
- Family 2. This family of Swiss descent was assumed to be segregating autosomal dominant nonsyndromic hearing loss mapped to the DFNA23 locus [Salam et al 2000]. The only individual described (patient IV:5) had a solitary left hypodysplastic kidney with vesicoureteral reflux and progressive renal failure.
- Family 3. In this family of German descent, the two affected individuals have hearing loss, bilateral ear pits and branchial cysts.
- Family 4. In this family of German/Irish descent, the phenotype includes hearing loss, preauricular pits, cup-ear deformity, and bilateral branchial cysts [Ruf et al 2004].

Genotype-Phenotype Correlations

A genotype-phenotype correlation has not been defined for BOR/BO syndrome. To compare phenotype with genotype, Zhang and colleagues (2004) grouped *EYA1* mutations as inactivating (i.e., splice site mutations, insertions, nonsense mutations, and duplications and deletions of more than 3 bp) or non-inactivating (i.e., missense mutations and 3 bp deletions). They showed that *EYA1* inactivating mutations are not associated with a more severe phenotype (p=0.799).

A parent-of-origin effect does not appear to be present, as renal defects have been reported in six liveborn offspring of affected fathers [Cremers & Fikkers-Van Noord 1980, Carmi et al 1983, Widdershoven et al 1983, Greenberg et al 1988] and four liveborn offspring of affected mothers [Fitch & Srolovitz 1976, Cremers & Fikkers-Van Noord 1980, Widdershoven et al 1983, Chitayat et al 1992].

Penetrance

In studies of large pedigrees, the phenotype appears to have 100% penetrance, although expressivity is highly variable [Chen et al 1995, Chang et al 2004].

Anticipation

Although several investigators have raised the possibility of anticipation (the tendency of some dominant conditions to become more severe in successive generations), this phenomenon has not been confirmed in family studies. In seven three-generation families assessed for anticipation with respect to severity of hearing loss and renal involvement, the degree of hearing loss increased in four families in successive generations, but did not in the remaining three

families. Generational progression in renal disease was present in three families, but in one family, the reverse was observed [Chen et al 1995].

Nomenclature

BOR syndrome is known eponymously as Melnick-Fraser syndrome. Phenotypic descriptions include branchiooto syndrome (BO) and branchiootoureteral (BOU) syndrome, in addition to BOR syndrome.

Prevalence

The prevalence of BOR syndrome 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, in a study by FC Fraser of 421 children in the Montreal School for the Deaf, 2% of the profoundly deaf students had BOR syndrome [Fraser et al 1980]. Using these data, Fraser et al (1980) estimated the prevalence of BOR syndrome at 1:40,000. The true prevalence is probably somewhere between these extremes.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The extreme clinical variability associated with BOR syndrome has suggested to many investigators that the phenotype represents a heterogeneous group of diseases. In support of this possibility, three different conditions have been described:

- **BO syndrome.** Melnick et al (1978) described three families, one with features of BOR syndrome and two with only cup-shaped pinnae and branchial arch fistulae. Neither the renal abnormalities nor the hearing impairment expected with BOR syndrome was present in the latter families; these individuals were classified as having BO syndrome.
- **BOU (branchiootoureteral syndrome.** The issue became more complicated when FC Fraser et al (1983) reevaluated intravenous pyelograms previously interpreted as normal in individuals with BO syndrome (deafness, cup-ear deformity, preauricular pits, branchial fistulae) and documented duplication of the collecting system and bifid renal pelvesin three of four "normal" studies. Whether BOU syndrome is part of the spectrum of BOR syndrome or a separate disorder has not yet been clarified.
- **BO-like syndrome.** In two large families with BO-like syndrome, linkage to the *EYA1* region of chromosome 8q has been excluded [Kumar, Marres et al 1998; Stratakis et al 1998]. Although these data can be interpreted as confirming heterogeneity, in neither of these families is the phenotype classic for BOR syndrome.
  - Affected individuals in the family studied by Kumar, Marres et al (1998) had been examined in detail by Marres & Cremers (1991), who found conductive hearing loss in the lower and middle frequencies (40%), preauricular sinuses (55%), external ear anomalies (60%), and commissural lip pits (40%). Branchial fistulae and renal anomalies were absent.
  - Affected individuals in the family studied by Stratakis et al (1998) had sensorineural hearing loss (40%), cup-ear deformity (27%), preauricular pits (100%), and mandibular asymmetry (20%). Branchial fistulae and renal anomalies were lacking.

- **BOF (branchiooculofacial) syndrome.** Affected individuals have bilateral postauricular and cervical branchial sinus defects with hemangiomas, cleft lip with or without cleft palate, nasolacrimal duct obstruction, low set ears with posterior rotation, nasal malformation with a broad bridge and flattened tip, and occasionally, prematurely grey hair [Trummer et al 2002]. Inheritance is autosomal dominant.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with branchiootorenal (BOR) syndrome, the following evaluations 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 Deafness and Hereditary Hearing Loss 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

Treatment of Manifestations

- **Second branchial arch anomalies.** Excision of branchial cleft cysts/fistulae
- **Otologic anomalies**
  - Fitting with appropriate aural habilitation as indicated
  - Enrollment in an appropriate educational program for the hearing impaired
  - A canaloplasty can be considered to correct an atretic canal; however, in individuals with BOR syndrome, associated middle ear anomalies such as a facial nerve overriding the oval window can preclude a successful result. The status of the middle ear can be evaluated preoperatively by obtaining thin-cut computed tomographic images of the temporal bones in both the axial and coronal planes.
- **Renal anomalies**
  - Urologic and renal abnormalities should be treated in the standard manner.
  - If renal anomalies (such as vesicoureteral reflux) are present, medical and surgical treatment may prevent progression to end-stage renal disease.
  - If end-stage renal disease develops, renal transplantation should be considered.

Surveillance

- **Otologic anomalies**
  - Semiannual examination by a physician who is familiar with hereditary hearing impairment

- 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 if indicated, based on level of renal function and type of renal and/or collecting system malformation

Agents/Circumstances to Avoid

Individuals with BOR syndrome and 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.

Testing of Relatives at Risk

Relatives at risk for BOR syndrome should be screened to determine if a treatable and/or possibly progressive otologic and/or renal abnormality is present.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

BOR syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 90% of individuals diagnosed with BOR syndrome have an affected parent.
- A proband with BOR syndrome may have the disorder as the result of a *de novo* mutation. Approximately 10% of cases are caused by *de novo* mutations.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include examination of the parents for hearing loss, preauricular pits, lacrimal duct stenosis, branchial fistulae and/or cysts, and renal anomalies [Chitayat et al 1992]. An apparently negative family history cannot be confirmed until appropriate evaluation of the parents has been performed.

Note: Although most individuals diagnosed with BOR syndrome have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members.

Sibs of a proband

- The risk to the sibs of a proband depends on the genetic status of the proband's parents.
- If a parent is diagnosed with BOR syndrome, the risk to each sib is 50%.
- Disease severity cannot be accurately predicted and is extremely variable even within the same family [Ni et al 1994].
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If a disease-causing mutation cannot be detected in the DNA extracted from leukocytes of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband

- Each child of an affected individual has a 50% chance of having BOR syndrome.
- Disease severity cannot be accurately predicted and is extremely variable even within the same family [Ni et al 1994].

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

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA particularly if the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk for BOR syndrome caused by an *EYA1* mutation is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

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

No laboratories offering molecular genetic testing for prenatal diagnosis of BOR syndrome caused by mutations in *SIX1* or *SIX5* are listed in the GeneTests Laboratory Directory.

However, prenatal testing may be available for families in which the disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see Testing.

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

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 BOR may be more problematic. Variable expressivity makes it impossible to accurately predict which manifestations of BOR may occur and how mild or severe they will be. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Branchiootorenal Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
EYA1	8q13.3	Eyes absent homolog 1
SIX1	14q23	Homeobox protein SIX1
SIX5	19q13.3	Homeobox protein SIX5

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Branchiootorenal Syndrome

113650	BRANCHIOOTORENAL SYNDROME 1; BOR1
600963	SINE OCULIS HOMEOBOX, DROSOPHILA, HOMOLOG OF, 5; SIX5
601205	SINE OCULIS HOMEOBOX, DROSOPHILA, HOMOLOG OF, 1; SIX1
601653	EYES ABSENT 1; EYA1
610896	BRANCHIOOTORENAL SYNDROME 2; BOR2

Table C. Genomic Databases for Branchiootorenal Syndrome

Gene Symbol	Locus Specific	Entrez Gene	HGMD
EYA1	EYA1	2138 (MIM No. 601653)	EYA1
SIX1		6495 (MIM No. 601205)	SIX1
SIX5		147912 (MIM No. 600963)	SIX5

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic 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

structure of these 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].

Studies in *Drosophila* indicate that the eyaHR mediates interactions with the gene products of *so* (sine oculis) and *dac* (dachshund), and that expression of both *eya* and *so* is initiated by *ey* (eyeless). The vertebrate orthologues of *so* are members of the *Six* gene family and similarly bind with Eya proteins, inducing nuclear translocation of the resultant protein complex. Amino terminal transcriptional activation has been demonstrated for the *Drosophila eya* and murine *Eya1-3* gene products, an additional indication that *Eya* interactions and pathways are conserved across species [Abdelhak et al 1997].

Expression of *Eya* genes is present in a wide variety of tissues early in embryogenesis, and although each gene has a unique expression pattern, extensive overlap exists. For example, murine studies have shown that *Eya1*, *Eya2*, and *Eya4* are all expressed in the presomitic mesoderm and head mesenchyme, but only *Eya1* and *Eya4* are expressed in the otic vesicle [Wayne et al 2001]. *Eya3* expression is restricted to craniofacial and branchial arch mesenchyme in regions underlying or surrounding the *Eya1*-, *Eya2*-, or *Eya4*-expressing cranial placodes [Abdelhak et al 1997].

EYA1

Normal allelic variants: *EYA1* consists of 16 coding exons that extend over 156 kb. It has at least three alternatively spliced transcripts that differ only in their 5' regions *(EYA1A*, *EYA1B*, *EYA1C*).

- An additional exon, exon 1', is contained in *EYA1B* just 3' to exon 1. Translation is initiated using a different start codon and the predicted protein is 592 amino acids long.
- The third isoform, *EYA1C*, uses the same start codon as *EYA1B*, but also contains an additional exon, exon -1, upstream from exon 1 and the 3' portion of exon 1.

These 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 seventeen introns of *EYA1* vary in size from 0.1 to 27.5 kb [Abdelhak et al 1997].

Numerous polymorphisms of *EYA1* have been reported [Abdelhak et al 1997; Abdelhak et al 1997]. When allelic variants are discovered, it is not always clear whether they are disease causing. Since mutations in *EYA1* are **not** found in 60% of people with a BOR syndrome phenotype, caution must be used when interpreting the effect of missense mutations in a single family, especially if rigorous population-based studies have not been performed.

Pathologic allelic variants: Over 80 different disease-causing mutations of *EYA1* that result in either BOR or BO syndrome have been identified [Abdelhak et al 1997; Abdelhak et al 1997; Kumar et al 1997; Vincent et al 1997; Kumar, Kimberling et al 1998]. These mutations include gross deletions of several exons [Abdelhak et al 1997], nonsense mutations [Abdelhak et al 1997; Kumar, Kimberling et al 1998], missense mutations [Abdelhak et al 1997; Kumar et al 1997], frameshift mutations [Abdelhak et al 1997; Vincent et al 1997; Kumar, Kimberling et al 1998], splice site mutations [Abdelhak et al 1997], and gross insertions [Abdelhak et al 1997]. A list of BOR/BO syndrome mutations is maintained at www.medicine.uiowa.edu. (For more information, see Genomic Databases table.)

Normal gene product: The proteins encoded by *EYA1A* (559 amino acids) and *EYA1B* (592 amino acids) differ only in their N-terminal region. *EYA1C* has two overlapping 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. The full extent of the second ORF has not been completely determined. Thus, *EYA1C* could give rise to two distinct proteins or alternatively the two ORFs could be translated into a single protein by ribosomal frame shifting [Abdelhak et al 1997].

The 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 [Abdelhak et al 1997].

The Eya protein has intrinsic phosphatase activity, enabling it to serve as a promoter-specific transcriptional co-activator. It is part of the Six-Eya-Dach regulatory network that defines a molecular mechanism by which a recruited co-activator with phosphatase function (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 co-repressor activity, while the recruitment of Eya is associated with co-activator activity. The co-activator activity of Eya is based on its phosphatase activity, which reverses the co-repressor activity of Dach and permits the recruitment of other co-activators, including CREB-binding protein (CBP) [Li et al 2003].

Abnormal gene product: Some mutations in *EYA1* generate mutant proteins that are rapidly degraded, implying that haploinsufficiency can cause the BOR syndrome phenotype [Zhang et al 2004]. With other mutations, functional analysis of human-derived *EYA* mutations in an in vivo *Drosophila* developmental system suggests that defects in either phosphatase or transcription function occur; these different types of mutational effects are predicted to lead to differences in phenotype [Mutsuddi et al 2005].

SIX1

Normal allelic variants: The *SIX1* gene has a transcript of 1376 bp and two exons.

Pathologic allelic variants: See Table 3. Based on the identification of mutations in *SIX1* in four families segregating BOR syndrome, at least three pathologic allelic variants exist. These three amino acid residues — Arg110, Tyr129, and Glu133 — are essential for the structure or function of the SIX1 protein [Ruf et al 2004]. (For more information, see Genomic Databases table.)

Table 3. *SIX1* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
c.328C>T	p.Arg110Trp	NM_005982.2 NP_005973.1
c.386A>G	p.Tyr129Cys	
c.397_399del	p.Glu133del	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

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 *SIX1* have been shown to have abnormalities of these organs [Ando et al 2005].

Abnormal gene product: The SIX domain mutation p.Arg110Trp of *SIX1* only affects its interaction with *EYA1*, while the two homeodomain mutations p.Tyr129Cys and p.Glu133del affect both this interaction and Six1 binding with DNA. Because these three mutations are missense and not truncating mutations, the respective transcripts are unlikely to be subject to nonsense-mediated decay and the phenotype is unlikely to be the consequence of haploinsufficiency [Ruf et al 2004]. In contrast, some mutations of *EYA1* cause BOR syndrome by haploinsufficieny [Zhang et al 2004].

SIX5

Normal allelic variants: The *SIX5* gene has a transcript of 3145 bp and three exons.

Pathologic allelic variants: Based on the identification of mutations in *SIX5* in five of 95 unrelated patients with BOR syndrome, at least four pathologic allelic variants are known (see Table 4). None of these four allelic variants was observed in 150 healthy control individuals [Hoskins et al 2007].

Table 4. *SIX5* Pathologic Allelic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequence
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	

See Quick Reference for an explanation of nomenclature. *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

Normal gene product: The homeobox protein SIX5 has 739 amino acid residues, 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: In vitro data suggest that both p.Ala158Thr and p.Thr552Met residues of SIX5 may be required for efficient binding with EYA1 [Hoskins et al 2007]. Yeast two-hybrid liquid β-galactosidase assays using GAL4 BD-SIX5 and GAL4 AD-Eya1D constructs cause strong *lacZ* expression as a result of interaction between the two fusion proteins. The p.Ala296Thr and p.Gly365Arg mutations result in a slight reduction in *lacZ* expression, while both p.Ala158Thr and p.Thr552Met show more than a twofold reduction in *lacZ* expression.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

AboutFace International
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Fax: 416-597-8494

Email: info@aboutfaceinternational.org
www.aboutfaceinternational.org

American Society for Deaf Children
3820 Hartzdale Drive
Camp Hill PA 17011
Phone: 800-942-2732 (parent hotline); 717-703-0073 (business V/TTY)
Fax: 717-909-5599
Email: asdc@deafchildren.org
www.deafchildren.org

Children's Craniofacial Association
13140 Coit Road Suite 517
Dallas TX 75240
Phone: 800-535-3643; 214-570-9099
Fax: 214-570-8811
Email: contactCCA@ccakids.com
www.ccakids.com

The Kidney Foundation of Canada
700-15 Gervais Drive
Toronto ON M3C 1Y8
Canada
Phone: 800-387-4474;416-445-0373
Fax: 416-445-7440
Email: kidney@kidneycob.on.ca
www.kidney.on.ca

my baby's hearing
This site, developed with support from the National Institute on Deafness and Other Communication Disorders, provides information about newborn hearing screening and hearing loss.
www.babyhearing.org

National Association of the Deaf
8630 Fenton Street Suite 820
Silver Spring MD 20910
Phone: 301-587-1788 (voice); 301-587-1789 (TTY)
Fax: 301-587-1791
Email: NADinfo@nad.org
www.nad.org

National Kidney Foundation
30 East 33rd Street Suite 1100
New York NY 10016
Phone: 800-622-9010; 212-889-2210
Fax: 212-689-9261
Email: info@kidney.org
www.kidney.org

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

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Chapter Notes

Author Notes

Web: Pendred/BOR Home Page

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- 24 January 2006 (me) Comprehensive update posted to live Web site
- 30 October 2003 (me) Comprehensive update posted to live Web site
- 28 November 2001 (me) Comprehensive update posted to live Web site
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- 6 January 1999 (rjhs) Original submission