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Branchiooculofacial Syndrome

Synonym: BOF Syndrome

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Summary

Clinical characteristics

Branchiooculofacial syndrome (BOFS) is characterized by branchial (cervical or infra- or supra-auricular) skin defects that range from barely perceptible thin skin or hair patch to erythematous "hemangiomatous" lesions to large weeping erosions; ocular anomalies that can include microphthalmia, anophthalmia, coloboma, cataract, and nasolacrimal duct stenosis/atresia; and facial anomalies that can include dolichocephaly, hypertelorism or telecanthus, broad nasal tip, upslanted palpebral fissures, cleft lip or prominent philtral pillars that give the appearance of a repaired cleft lip (formerly called "pseudocleft lip") with or without cleft palate, upper lip pits, and lower facial weakness (asymmetric crying face or partial weakness of cranial nerve VII). Malformed and prominent pinnae and hearing loss from inner ear and/or petrous bone anomalies are common. Intellect is usually normal.

Diagnosis/testing

The diagnosis of BOFS is established in a proband with characteristic clinical findings and a heterozygous pathogenic variant in *TFAP2A* identified by molecular genetic testing.

Management

Treatment of manifestations: In general, children with BOFS should be managed by a multispecialty team including craniofacial specialists, plastic surgeons, otolaryngologists, and speech-language therapists. Small, linear, or superficial branchial skin defects may heal spontaneously; however, some require surgical intervention. Treatment of ophthalmic manifestations is per pediatric ophthalmologist. Nasolacrimal duct stenosis or atresia often requires surgery. Anophthalmia or severe microphthalmia may require a conformer (a structure, usually plastic, inserted into the eye socket to encourage its growth). It is recommended that cleft lip be repaired by an experienced pediatric plastic surgeon. Nasal tip abnormalities, lesser forms of cleft lip ("pseudocleft"), and

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malformed pinnae may need surgical correction. Standard treatments for hearing loss, renal malformations, dental manifestations, and congenital heart defects. Treatment of sensory, psychologic, and developmental challenges with supportive therapies.

Surveillance: Ophthalmology examination and vision assessment as recommended by ophthalmologist; audiology evaluation as recommended by otolaryngologist and/or audiologist; at each visit assess for a recurrent urinary tract infection suggestive of vesicoureteral reflux, assess teeth for size, number, carries, and malocclusion, and assess for new cysts; developmental and behavioral assessment annually or as needed; monitor for signs of low self-esteem and other psychological issues at each visit in older children as they enter adolescence.

Genetic counseling

BOFS is inherited in an autosomal dominant manner. *De novo* pathogenic variants are observed in 50%-60% of affected individuals. Each child of an individual with BOFS has a 50% chance of inheriting the pathogenic variant. Once the *TFAP2A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

There are no formal diagnostic guidelines for branchiooculofacial syndrome (BOFS) developed by consensus panels, algorithms using a hierarchy of clinical findings, or evidence-based test standards. Diagnostic criteria have been proposed (see Table I in Milunsky et al [2011]).

Suggestive Findings

BOFS **should be suspected** in probands with findings in two or three of the following categories.

Branchial (cutaneous) defects. Cervical or infra- or supra-auricular **skin defects**:

- Vary from barely perceptible thin skin or hair patch to erythematous "hemangiomatous" lesions to large weeping erosions;
- Are most distinctive when they are bilateral and anterior cervical in location, and may be described as "cutis aplasia" [Wurfbain et al 2023];
- Differ from the punctuate sinus tracts of the branchiootorenal (BOR) syndrome;
- If very mild, may be unrecognized and heal spontaneously, but tend to "weep."

Ocular anomalies

- Microphthalmia, anophthalmia
- Coloboma
- Cataract
- Ptosis
- Nasolacrimal duct stenosis/atresia
- Strabismus

Facial anomalies

- Characteristic appearance with dolichocephaly, hypertelorism or telecanthus, broad nasal tip, and upslanted palpebral fissures (See Figure 1.)
- Cleft lip or prominent philtral pillars (technically known as a lesser-form cleft lip [formerly "pseudocleft lip"]), with or without cleft palate (Isolated cleft palate has not been reported.)
- Upper lip pits

- Lower facial nerve and/or muscle hypoplasia (asymmetric crying face, partial weakness of cranial nerve VII)
- Inner ear and petrous bone anomalies such as cochlear dysplasia, Mondini dysplasia, and enlarged vestibular aqueduct
- Malformed and prominent pinnae
- Hearing loss (conductive, sensorineural, mixed)

Establishing the Diagnosis

The clinical diagnosis of BOFS can be **established** in a proband based on proposed clinical diagnostic criteria [Milunsky et al 2011], or the molecular diagnosis can be established in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *TFAP2A* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (2) Identification of a heterozygous *TFAP2A* variant of uncertain significance does not establish or exclude the diagnosis.

Clinical Diagnosis

All three of the main features are present:

- Branchial (cutaneous) skin defect
- Ocular anomaly
- Facial anomalies (characteristic facial appearance)

OR

Two of the three main features plus one of the following are present:

- Affected first-degree relative, independently diagnosed
- Ectopic thymus (dermal)

Molecular Diagnosis

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see **Option 1**), whereas comprehensive genomic testing does not (see **Option 2**).

Option 1

- **Single-gene testing.** Sequence analysis of *TFAP2A* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *TFAP2A* and other genes of interest (see Differential Diagnosis) may also be considered to identify the genetic cause of the condition 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

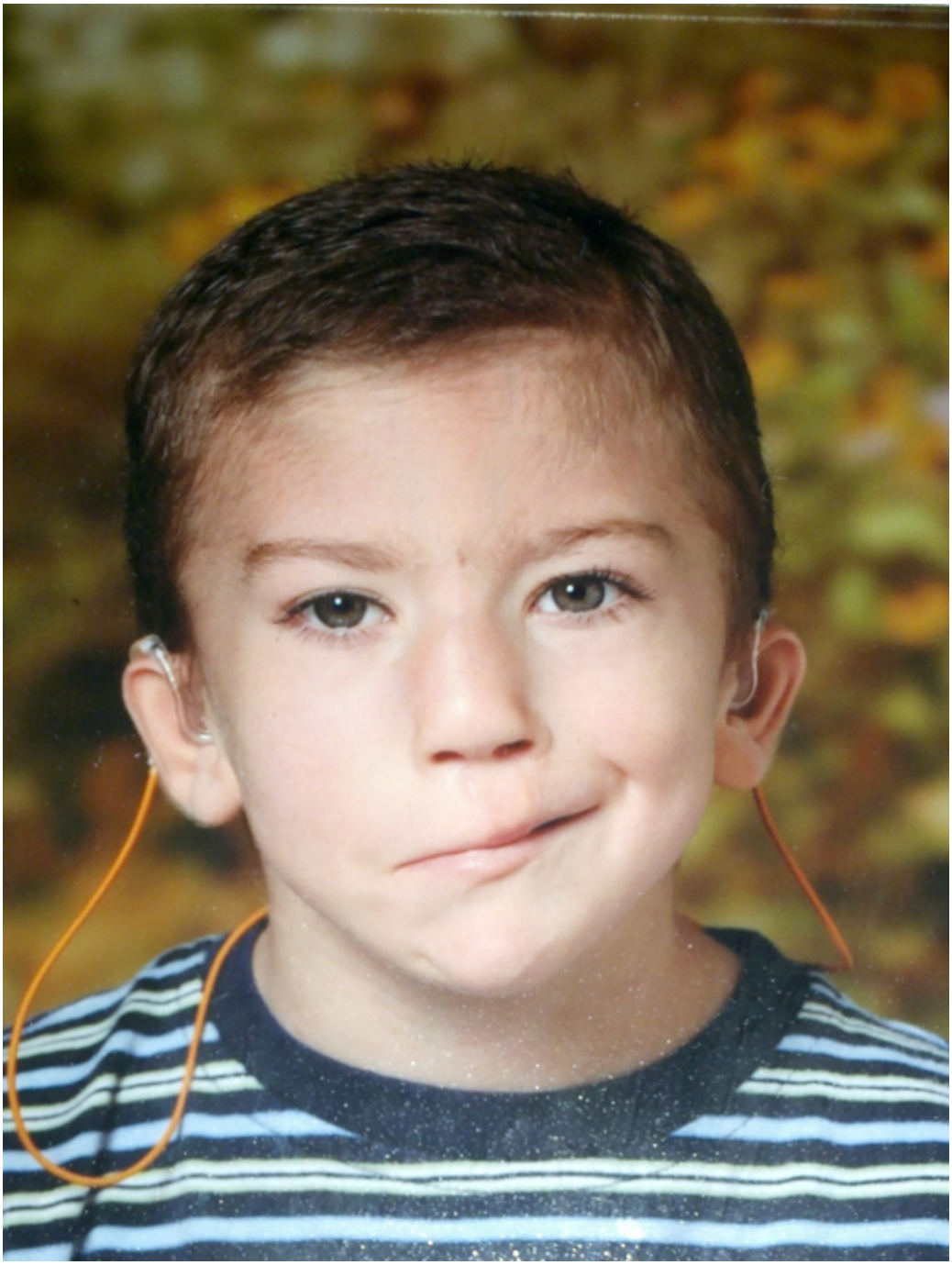

Figure 1. Photo of a boy age five years with branchiooculofacial syndrome syndrome (BOFS). Details of the molecular findings are reported in Milunsky et al [2008] (patient 3, age two years). He has a right-sided cervical cutaneous defect ("B") that was repaired; bilateral nasolacrimal duct stenosis and hypertelorism ("O"); and bilateral "mini-microform" cleft lip and full nasal tip, with mild upslanting palpebral fissures ("F"). Although he has bilateral bone conduction hearing loss, he prefers traditional aids to bone conduction hearing aids. His smile reveals right-sided lower facial nerve weakness. He attends kindergarten, meeting all of his Individualized Educational Plan goals at the learning center for the deaf. He is very sociable, and both speaks English and signs fluently in American Sign Language.

Photo generously provided by this child's mother.

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

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in Branchiooculofacial Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
TFAP2A	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [5]	<5% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. 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.
4. Milunsky et al [2011]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as 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. Milunsky et al [2008], Gestri et al [2009]

Clinical Characteristics

Clinical Description

Most individuals with branchiooculofacial syndrome (BOFS) can be diagnosed in infancy on the basis of their clinical features. Females and males are affected equally. Although the facial features are generally recognizable, some individuals may have subtle differences [Authors, personal observation].

Classic BOFS Findings

Branchial (cutaneous) defects occur in a cervical (90%) or infra- or supra-auricular (60%) location.

- Defects vary from barely perceptible thin skin or hair patch to erythematous "hemangiomatous" lesions to large weeping erosions.
- The mildest defects may be unrecognized and in rare cases heal completely spontaneously. There may be a small residual sinus or tract that may appear to "weep," revealing the patency.

Ocular anomalies include the following:

- Structural eye malformations can include microphthalmia, anophthalmia, coloboma, or cataract.
- Periorbital abnormalities include nasolacrimal duct stenosis/atresia leading to weeping eyes and ptosis.
- Visual concerns include strabismus and significant visual impairment.

- Lam et al [2023] reviewed the ocular findings in 172 previously reported individuals and one additional individual with BOFS; the most common findings included nasolacrimal duct stenosis (57%), coloboma (46%), anophthalmia/microphthalmia (37%), cataract (16%), strabismus (14%), and myopia (12%).

Facial anomalies. Characteristic facial appearance includes dolichocephaly, hypertelorism or telecanthus, broad nasal tip, and upslanted palpebral fissures (see Figure 1). Other findings may include:

- Cleft lip or prominent philtral pillars (technically known as a lesser-form cleft lip [formerly "pseudocleft lip"])
  - Occurring with or without cleft palate (99%)
  - No instances of isolated cleft palate reported
- Upper lip pits
- Lower facial nerve and/or muscle hypoplasia (asymmetric crying face, partial weakness of cranial nerve VII)
- Ear anomalies
  - Malformed and prominent pinnae
  - Inner ear and petrous bone anomalies such as cochlear dysplasia, Mondini dysplasia, and enlarged vestibular aqueduct
  - Hearing loss (70%) (conductive, sensorineural, mixed)
- Broad nose with full nasal tip, which is distinct from the appearance of the nose in other individuals with cleft lip

Additional Findings Observed in BOFS

Immune system. Thymic anomalies (ectopic, dermal) (~35%), typically bilateral with normal thymic function

Renal system

- Structural anomalies (35%) (e.g., dysplastic, absent, multicystic)
- Vesicoureteral reflux

Ectodermal (hair, teeth, nails)

- Premature hair graying, poliosis (forelock or patchy) (35%)
- Hypoplastic teeth
- Dysplastic nails
- Cysts, subcutaneous (dermoid-like, often on the scalp; less commonly other areas of the head and neck)

Psychomotor development (typically normal)

- Visual and hearing handicaps (frequent)
- Autism spectrum disorder, intellectual disability (rare)

Growth restriction. Uncommon

Miscellaneous and rare (<5 individuals each)

- Heterochromia irides
- Congenital heart defect (atrial septal defect, tetralogy of Fallot)
- Polydactyly (bilateral, usually postaxial)
- Medulloblastoma (1 individual) [Milunsky et al 2008]
- Trigonocephaly (1 individual) [Wurfbain et al 2023]

Genotype-Phenotype Correlations

No clear genotype-phenotype correlation exists.

Significant inter- and intrafamilial variability have been observed with the same pathogenic variants [Milunsky et al 2011]. Missense, frameshift, and splicing variants along with more complex rearrangements [Tekin et al 2009, Milunsky et al 2011] throughout the gene result in similar phenotypes.

The majority of individuals with a deletion involving *TFAP2A* appear to have an abnormally prominent philtrum that may be on the spectrum of microform cleft lip [Lin et al 2009]. LeBlanc et al [2013] described an infant and mother with a 593-kb deletion including *TFAP2A* and five additional genes. Neither is reported to have any type of cleft or abnormal philtrum. Otherwise, the marked inter- and intrafamilial variability appear similar to that observed with intragenic pathogenic variants.

Penetrance

BOFS has shown almost complete penetrance. Careful examination of individuals identified in a family with BOFS with a *TFAP2A* pathogenic variant is necessary to reveal subtle findings including premature graying (individuals may have dyed their hair), faint hair on the neck, or heterochromia of the irides.

Prevalence

The prevalence of BOFS is not known. It is a rare condition, with fewer than 150 individuals having a well-described clinical and/or molecular diagnosis. An informal survey of clinical geneticists who attended a 2017 dysmorphology conference identified an additional 27 unpublished individuals (18 with a clinical diagnosis and nine with a molecular diagnosis). While these numbers are insufficient to calculate a population-based prevalence, they support the impression that BOFS remains a rare disorder.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *TFAP2A*.

Differential Diagnosis

The branchiooculofacial syndrome phenotype is distinctive and can typically be differentiated on a clinical basis from disorders with overlapping features (see Table 2).

Table 2. Disorders of Interest in the Differential Diagnosis of Branchiooculofacial Syndrome

Gene(s) / Genetic Mechanism	Disorder	MOI	Features of This Disorder	
			Overlapping with BOFS	Distinguishing from BOFS
22q11.2 deletion	22q11.2 deletion syndrome	AD	• Eye abnormalities • Ear abnormalities • Branchial abnormalities • Renal abnormalities • Orofacial cleft	• Cardiac defects common • No BOFS facial features
CHD7	*CHD7* disorder (incl CHARGE syndrome)	AD	• Eye abnormalities • Ear abnormalities • Orofacial cleft	• No skin defects • No premature gray hair • Frequent posterior segment coloboma & choanal atresia • No BOFS facial features

Table 2. continued from previous page.

Gene(s) / Genetic Mechanism	Disorder	MOI	Features of This Disorder	
			Overlapping with BOFS	Distinguishing from BOFS
EDN3 *EDNRB* *KITLG* *MITF* *PAX3* *SNAI2* *SOX10* *SOX10*	Waardenburg syndrome (See Waardenburg Syndrome Type I.)	AD AR	• Premature graying of hair • Telecanthus • Hearing loss	• No renal abnormalities • No BOFS facial features
EYA1 *SIX5* *SIX1*	Branchiootorenal spectrum disorder	AD	• Ear abnormalities • Branchial abnormalities • Renal abnormalities	• Branchial pits (vs draining sinuses w/overlying skin defects in BOFS) • No BOFS facial features
TP63	Ectrodactyly, ectodermal dysplasia, cleft lip/palate syndrome 3 (See *TP63*-Related Disorders.)	AD	• Orofacial cleft • Ectodermal abnormalities	• Ectrodactyly • No BOFS facial features

AD = autosomal dominant; AR = autosomal recessive; BOFS = branchiooculofacial syndrome; MOI = mode of inheritance

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with branchiooculofacial syndrome (BOFS), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Branchiooculofacial Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Branchial defects	Exam of skin defects by pediatric plastic surgeon	To delineate extent of lesion(s), determine if there is a sinus, &, most importantly, determine if thymic remnant could be present
Eyes	Complete eye exam by pediatric ophthalmologist	To assess for visual limitations, strabismus, & nasolacrimal duct obstruction
	Referral of those w/anophthalmia &/or severe microphthalmia to support services for visually impaired	
Cleft lip/palate	Formal eval of cleft lip/palate & other possible facial abnormalities	By cleft lip/palate team, which often incl clinical geneticist, pediatric plastic surgeon, ENT, audiologist, speech-language therapist, & dental & orthodontic specialist
Hearing	• Hearing eval • CT imaging of temporal bone to anticipate optimal hearing correction [1]	
Kidney	Renal ultrasonography w/referral to nephrologist if renal abnormalities are identified	
Dental	Referral for dental assessment for any dental issues	If not done as part of cleft assessment

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Neurodevelopment/ Behavior	• Developmental assessment particularly for children w/ visual &/or hearing problems • Assessment for depression, attention dysregulation, autism, intellectual disability	
Cardiac	Echocardiogram in those w/murmur or cardiac symptoms	
Genetic counseling	By genetics professionals [2]	To inform affected persons & their families re nature, MOI, & implications of BOFS to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

BOFS = branchiooculofacial syndrome; MOI = mode of inheritance
1. Raveh et al [2000], Stoetzel et al [2009], Tekin et al [2009]
2. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Note: (1) Motor delays are not part of BOFS; thus, physical and occupational therapy is not anticipated. (2) The role of cancer surveillance is not established.

Treatment of Manifestations

Milunsky et al [2011] provided management guidelines that remain clinically useful and have not been updated. In general, children with BOFS and multiple anomalies should be followed in a setting in which multispecialty care can be provided by a team including, for example, craniofacial specialists, plastic surgeons, otolaryngologists, and speech-language therapists (see Table 4). Ideally, multispecialty evaluations and surgery should be performed within a craniofacial clinic.

Table 4. Branchiooculofacial Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Branchial defects	• Most larger skin defects require surgical excision. • Note: Skin defects should not be cauterized.	Branchial or supra-auricular skin defects that are small, linear, or superficial may heal spontaneously.
	Sinus tracts must be dissected by experienced pediatric plastic surgeon.	• Exploration for a thymic remnant may be necessary; such tissue should be sent for histopathologic exam. • If dermal thymic tissue is present, evaluate for mediastinal thymic tissue prior to excision of ectopic thymus.
Ophthalmic manifestations	Management per pediatric ophthalmologist	• Obstruction from nasolacrimal duct stenosis or atresia must be relieved & affected persons monitored for restenosis. • Severe microphthalmia or anophthalmia may be managed by inserting a conformer into the eye socket to encourage its growth.

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Cleft lip/palate	• Surgical treatment by pediatric plastic surgeon experienced in treating cleft lip • In addition to the nasal tip flattening or asymmetry that may be assoc w/cleft lip, a characteristic full, flat nasal tip may need a corrective procedure.	Lesser forms of cleft lip (formerly known as "pseudocleft") may need surgical correction. [1]
Ears/Hearing	• Affected persons may need reconstruction of malformed protruding pinnae. • Hearing loss is treated routinely (see Hereditary Hearing Loss and Deafness Overview).	If diagnosed in early infancy, auricular molding may be indicated.
Renal manifestations	Standard treatment per nephrologist/urologist	
Dental manifestations	Standard treatment per dentist/orthodontist	
Neurodevelopment/ Behavior	Sensory, psychologic, & developmental challenges should be treated w/supportive therapies.	Currently, data are insufficient to recommend requiring more psychologic support for more severely affected persons.
Congenital heart defect	Standard treatment per cardiologist	

Adapted from Milunsky et al [2011], Table IV
1. Lin et al [2009]

Surveillance

To monitor existing manifestations and the individual's response to supportive care, the evaluations summarized in Table 5 are recommended.

Table 5. Branchiooculofacial Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Eyes/Vision	Ophthalmology exam & vision assessment	As recommended by ophthalmologist
Hearing	Audiology eval	As recommended by ENT/audiologist
Renal manifestations	Assess for recurrent urinary tract infections suggestive of vesicoureteral reflux.	At each visit
Dental	Teeth should be monitored for size & number, caries, & malocclusion.	
Skin	Assess for new cysts.	
Neurodevelopment/ Behavior/Psychiatric	Developmental & behavioral assessment	Annually or as needed
	Monitor for signs of low self-esteem & other psychologic issues.	At each visit in older children as they enter adolescence

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from surveillance and treatment of hearing, vision, renal, and other manifestations. Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known;

- A careful physical examination to look for subtle physical findings of BOFS 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.

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

Branchiooculofacial syndrome (BOFS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 40%-50% of individuals diagnosed with BOFS have an affected parent [Milunsky et al 2011].
- Approximately 50%-60% of individuals diagnosed with BOFS have the disorder as the result of a *de novo* *TFAP2A* pathogenic variant [Milunsky et al 2011].
- If a molecular diagnosis has been established in the proband and the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to confirm their genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

      * A parent with somatic and germline mosaicism for a *TFAP2A* pathogenic variant may be mildly/minimally affected [Milunsky et al 2011].
- The family history of some individuals diagnosed with BOFS may appear to be negative because of failure to recognize the disorder in family members or a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed without molecular genetic testing to establish that neither parent is heterozygous for the pathogenic variant identified in the proband.

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

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%. BOFS is associated with almost complete penetrance; however, significant intrafamilial variability has been observed [Milunsky et al 2011].
- If the proband has a known *TFAP2A* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental mosaicism [Milunsky et al 2011].
- If the parents appear to be clinically unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of a milder phenotypic presentation in a heterozygous parent and the possibility of parental mosaicism.

Offspring of a proband. Each child of an individual with BOFS has a 50% chance of inheriting the *TFAP2A* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *TFAP2A* pathogenic variant, the parent's 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.

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.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *TFAP2A* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. 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 Cleft Palate-Craniofacial Association**
  Phone: 919-933-9044
  acpa-cpf.org
- **Face Equality International**

United Kingdom
faceequalityinternational.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. Branchiooculofacial Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
TFAP2A	6p24.3	Transcription factor AP-2-alpha	TFAP2A database	TFAP2A	TFAP2A

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 Branchiooculofacial Syndrome (View All in OMIM)

107580	TRANSCRIPTION FACTOR AP2-ALPHA; TFAP2A
113620	BRANCHIOOCULOFACIAL SYNDROME; BOFS

Molecular Pathogenesis

TFAP2A is a retinoic acid-responsive member of the AP-2 family of transcription factors that regulate gene expression during embryogenesis of the eye, ear, face, body wall, limbs, and neural tube [Schorle et al 1996, Zhang et al 1996, Ahituv et al 2004, Nelson & Williams 2004]. TFAP2A is also involved in tumorigenesis, with protein expression levels affecting cell transformation, tumor growth, metastasis, and survival [Jean et al 1998, Heimberger et al 2005, Orso et al 2007]. Numerous gene interactions likely underlie the variability in phenotype resulting from molecular defects involving TFAP2A. TFAP2A is known to be expressed in premigratory and migratory neural crest cells [Hilger-Eversheim et al 2000, Li & Cornell 2007] and is required for early morphogenesis of the lens [Gestri et al 2009].

Although the pathogenic variants occur throughout the gene, a hot spot region in exons 6 and 7 that contains missense variants in about 90% of probands/families with BOFS has been identified [Milunsky et al 2011].

Li et al [2013] demonstrated that several pathogenic variants in the DNA-binding domain can have dominant-negative activity on wild type AP-2α protein. Hence, differences in activity due to null, hypomorphic, or antimorphic alleles may lead to the phenotypic variability characteristic of BOFS.

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

As of January 2018, there is no disease advocacy organization ("support group") for BOFS. Through Dr Lin, several parents of children with BOFS have reached out to the families of newly diagnosed individuals.

Acknowledgments

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Revision History

- 28 September 2023 (sw) Comprehensive update posted live
- 29 March 2018 (ha) Comprehensive update posted live
- 31 May 2011 (me) Review posted live
- 11 January 2011 (al) Original submission

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