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SOX2 Disorder

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Summary

Clinical characteristics

The phenotypic spectrum of *SOX2* disorder includes anophthalmia and/or microphthalmia, brain malformations, developmental delay / intellectual disability, esophageal atresia, hypogonadotropic hypogonadism (manifest as cryptorchidism and micropenis in males, gonadal dysgenesis infrequently in females, and delayed puberty in both sexes), pituitary hypoplasia, postnatal growth delay, hypotonia, seizures, and spastic or dystonic movements.

Diagnosis/testing

The diagnosis of *SOX2* disorder is established in a proband in whom molecular genetic testing identifies either a heterozygous intragenic *SOX2* pathogenic (or likely pathogenic) variant or a deletion of 3q26.33 involving *SOX2*.

Management

Treatment of manifestations: Treatment usually involves a multidisciplinary team including – as needed – an experienced pediatric ophthalmologist, ophthalmo-plastic surgeon (for children with anophthalmia and/or extreme microphthalmia), and early educational intervention through community vision services and/or school district; educational support for school-age children; pediatric endocrinologist; pediatric neurologist; and physical therapist and occupational therapist.

Surveillance: Routine follow up with specialists managing the vision, educational, endocrine, and neurologic manifestations.

Genetic counseling

SOX2 disorder, caused by an intragenic *SOX2* pathogenic variant or a deletion of 3q26.33 involving *SOX2*, is an autosomal dominant disorder. Approximately 60% of affected individuals have a *de novo* genetic alteration.

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Some affected individuals have inherited the genetic alteration from either an affected mother (transmission from an affected father to child has not been reported to date) or an unaffected parent with germline mosaicism. Once the causative genetic alteration has been identified in an affected family member (or in a parent who has a structural chromosome rearrangement involving the 3q26.33 region), prenatal testing for a pregnancy at increased risk is possible, and preimplantation genetic testing for *SOX2* disorder may be possible, depending on the specific familial genetic alteration.

GeneReview Scope

With the current widespread use of advanced molecular genetic testing, it is apparent that the clinical spectrum associated with *SOX2* pathogenic variants includes anophthalmia and/or microphthalmia as well as phenotypes with minimal or absent ocular findings. The term "*SOX2* disorder" is used in this *GeneReview* to refer to the complete phenotypic spectrum associated with heterozygous *SOX2* pathogenic variants. It encompasses all individuals with a *SOX2* pathogenic variant who should be evaluated for medically actionable manifestations across the entire phenotypic spectrum (regardless of clinical findings that prompted molecular genetic testing).

Diagnosis

Suggestive Findings

SOX2 disorder **should be considered** in individuals with the following clinical and brain MRI findings and family history.

Clinical findings

- Bilateral anophthalmia and/or microphthalmia
- Unilateral anophthalmia or microphthalmia
- Genital abnormalities. Frequently cryptorchidism and/or micropenis in males (commonly a manifestation of hypogonadotropic hypogonadism); infrequently uterus hypoplasia and ovary or vaginal agenesis in females
- Tracheoesophageal fistula and/or esophageal atresia
- Delayed motor development / learning disability
- Postnatal growth failure
- Seizures with gray matter heterotopia
- Spasticity, dystonia, or status dystonicus

Brain MRI. Malformation and/or gray matter heterotopia of the mesial temporal structures (hippocampal and parahippocampal), pituitary hypoplasia, and agenesis or dysgenesis of the corpus callosum are core features of *SOX2* disorder. Septum pellucidum defects, cerebellar hypoplasia, hypothalamic hamartoma, arachnoid cyst, and sellar or suprasellar tumors are also reported in multiple individuals [Ragge et al 2005, Sisodiya et al 2006, Gerth-Kahlert et al 2013, Blackburn et al 2018].

Family history is consistent with autosomal dominant inheritance, including simplex cases (i.e., a single occurrence in a family). Absence of a known family history does not preclude the diagnosis. See Genetic Counseling.

Establishing the Diagnosis

The diagnosis of *SOX2* disorder **is established** in a proband in whom molecular genetic testing identifies either a heterozygous intragenic *SOX2* pathogenic (or likely pathogenic) variant or a deletion that is intragenic or a deletion of 3q26.33 involving *SOX2* (see Table 1).

For details about heterozygous deletions of 3q26.33 involving *SOX2*, see Molecular Genetics.

Note: Note: Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel, and chromosomal microarray analysis [CMA]) and **comprehensive genomic testing** (CMA, 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 comprehensive genomic testing does not. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing that could include CMA (see Option 1), whereas those in whom the diagnosis of *SOX2* disorder has not been considered or previously made by CMA may be diagnosed using comprehensive genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of *SOX2* disorder, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *SOX2* is performed first. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis (which can include CMA).

  Note: Most deletions involving *SOX2* are large enough to be detected by CMA; those below the limit of detection by CMA can be detected by a gene-targeted deletion assay.

- **A developmental eye defects/oculome or intellectual disability multigene panel** that includes *SOX2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA 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*. Of note, given the rarity of *SOX2* disorder, some panels for intellectual disability may not include this gene. (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, which does not require the clinician to determine which gene is likely involved, is an option when *SOX2* disorder is not an easily achievable diagnosis. **CMA** is often used as a first step. If CMA does not detect a copy number variant, **genome sequencing** and/or **exome sequencing** may be used.

If exome sequencing is not diagnostic, **exome array** (when clinically available) can detect copy number variants, such as (multi)exon deletions or duplications that may not be identified by exome sequencing.

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 *SOX2* Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
S0X2	Sequence analysis [3]	~76% [4]
	Gene-targeted deletion/duplication analysis [5]	~24% (~21% that could also be resolved by CMA & ~3% that are below the limit of detection by CMA) [4, 5]
	CMA [6]	~21% [4, 5]

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, whole-exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Gerth-Kahlert et al [2013], Chassaing et al [2014], Suzuki et al [2014], Mauri et al [2015], Zanolli et al [2020]
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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to a whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes (e.g., those described by Suzuki et al [2014]) may not be detected by these methods [Chassaing et al 2014].
6. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *SOX2*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 3q26.33 region. CMA designs in current clinical use target the 3q26.33 region.

Clinical Characteristics

Clinical Description

SOX2 disorder comprises a phenotypic spectrum that can include anophthalmia and/or microphthalmia, brain malformations, developmental delay / intellectual disability, esophageal atresia, hypogonadotropic hypogonadism (manifest as cryptorchidism and micropenis in males, gonadal dysgenesis infrequently in females, and delayed puberty in both sexes), pituitary hypoplasia, postnatal growth delay, hypotonia, seizures, and spastic or dystonic movements.

To date, 174 individuals from 157 families have been identified with *SOX2* disorder [Williamson & FitzPatrick 2014, Gorman et al 2016, Dennert et al 2017, Blackburn et al 2018]. The following descriptions are based on these key reports, together with all other published cases and the authors' unpublished data.

Table 2. Select Features of *SOX2* Disorder: Frequency of Human Phenotype Ontology (HPO) Terms

Frequency of Phenotypic Feature in Case Reports (n=38)	HPO Term	HPO Term Frequency [1] in Case Reports (n=38)
Highly frequent	Anophthalmia	92
	Microphthalmia	37
	Micropenis	22
	Seizures	21
	Cryptorchidism	16
	Developmental delay	15
	Dystonia	12
Moderately frequent	Generalized hypotonia	8
	Hypoplasia of corpus callosum	8
	Motor delay	7
	Fever	7
	Coloboma	7
	Optic nerve hypoplasia	7
	Frontal bossing	7
	Spastic diplegia	7
	Feeding difficulties	6
	Wide nasal bridge	6
	Short stature	6
	Arachnoid cyst	6
	Growth delay	6
	Cataract	6
Less frequent	Hydrocephalus	5
	Delayed puberty	5
	Esophageal atresia	5
	Hypertelorism	5
	Short palpebral fissure	5
	Delayed speech & language development	5

Data were extracted from full text case reports exclusively describing *SOX2* disorder (n=38) using exact string matching. The Human Phenotype Ontology (HPO) enables use of precise, standardized, computationally accessible terms to describe phenotypic abnormalities. The ontology structure describes the relationship of terms to each other [Köhler et al 2019]. HPO terms that appear fewer than four times were excluded.

1. Frequency refers to the number of times the term was used in all included case reports.

Bilateral anophthalmia and/or microphthalmia. *SOX2* eye defects are usually bilateral, severe, and apparent at birth or on routine prenatal ultrasound examination. The degree of visual impairment is usually severe and consistent with the degree of structural abnormality in the eye. In general, retina tissue that is present has some functional activity. For example, even in extreme microphthalmia, functional retinal tissue can give some light/dark perception with or without color perception.

In the 174 individuals reported (114 individuals reviewed by Williamson & FitzPatrick [2014] plus 60 individuals reported subsequently), 76 (44%) had bilateral anophthalmia, 23 (13%) had anophthalmia with contralateral microphthalmia, and 20 (12%) had bilateral microphthalmia. The remaining individuals have a wide spectrum of eye malformations including the following:

- Unilateral anophthalmia or microphthalmia and a normal eye
- Unilateral anophthalmia with cataract in the contralateral eye
- Unilateral microphthalmia with coloboma or iris defect in the contralateral eye
- Bilateral or unilateral coloboma
- Optic nerve hypoplasia or aplasia
- Bilateral or unilateral congenital aphakia
- Cataract
- Retinal dysplasia
- Anterior segment dysgenesis (including sclerocornea or microcornea)
- Refractive error

Thirteen individuals with loss-of-function *SOX2* variants had bilateral structurally normal eyes. Seven had no ocular defects noted and six had mild ocular defects, including the following:

- A monozygotic twin with tracheoesophageal fistula and unilateral reduced palpebral fissure whose twin had unilateral anophthalmia as part of anophthalmia-esophageal atresia-genital abnormalities (AEG) syndrome [Zenteno et al 2006];
- A sibling fetus in a family with AEG syndrome, with brain anomalies and 11 rib pairs [Chassaing et al 2007];
- A woman with intellectual disability, corpus callosum agenesis, hypogonadotropic hypogonadism, vaginal agenesis, and spastic paraparesis [Errichiello et al 2018];
- A mother (with either heterozygosity or a high level of mosaicism of the *SOX2* pathogenic variant) with isolated hypogonadotropic hypogonadism who, following assisted conception, had two children with anophthalmia or microphthalmia and coloboma [Stark et al 2011];
- Two individuals identified in an intellectual disability cohort with mild microcornea, delayed speech and walking, esophageal stenosis, hearing deficits and mild facial hypoplasia in one; and strabismus, delayed speech, dystonic movements and spastic diplegia, hypogonadotropic hypogonadism, and corpus callosum and hippocampus malformation in the other individual [Dennert et al 2017];
- Three individuals with mild ocular defects (esotropia, macro excavated optic disc, or thin retinal layer) and a combination of developmental delay, seizures, hypotonia or dystonia, tracheoesophageal fistula, suprasellar teratoma, and gonadal dysgenesis [Shima et al 2017, Blackburn et al 2018, Pilz et al 2019];
- Four individuals, one of whom had a *de novo SOX2* frameshift variant and a phenotype of severe developmental delay, hypotonia, and facial dysmorphism with no ocular defects (see DECIPHER).

Anterior pituitary hypoplasia. The majority of affected individuals have some evidence of hypothalamic-pituitary axis dysfunction when detailed measurement of growth hormone and gonadotropins is undertaken [Tziaferi et al 2008]. Identification of significant dysregulation of the hypothalamic-pituitary-adrenal axis is particularly important to ensure that appropriate glucocorticoid supplementation is provided during periods of physiologic stress.

- **Postnatal growth failure.** Birth weight in most infants is normal for gestational age. However, most children have a reduced growth velocity in the first years of life resulting in symmetric growth failure.
- **Hypogonadotropic hypogonadism** was reported in 20 individuals, including two females with normal eyes [Stark et al 2011, Errichiello et al 2018] and two individuals with either unilateral retinal detachment or unilateral strabismus [Takagi et al 2014, Dennert et al 2017].

Genital abnormalities. In males, micropenis and cryptorchidism (often a manifestation of congenital hypogonadotropic hypogonadism) are common. Occasionally hypospadias is observed.

In females, malformations are less frequent and can include hypoplastic or hemi-uterus, ovary or vaginal agenesis, and vaginal adhesions [Errichiello et al 2018].

Dystonia and spasticity. Status dystonicus (a movement disorder emergency in which there is prolonged, generalized, intense, and painful muscle contraction) was originally reported in individuals with bilateral anophthalmia and a specific variant (see Genotype-Phenotype Correlations and Table 7) [Gorman et al 2016]; however, other variants, including the most common *SOX2* variant, were subsequently associated with this feature in two individuals with bilateral anophthalmia or bilateral optic disc abnormality [Martinez & Madsen 2019, Pilz et al 2019].

A minority of affected individuals develop early continual dystonic posturing that is similar to that seen in dystonic cerebral palsy but without evidence of basal ganglia injury on neuroimaging. These children should be considered at risk for status dystonicus, which can be triggered by any major physiologic stress and can lead to protracted periods of hospitalization and critical care.

Spasticity, including diplegia, paraparesis, or quadriparesis was reported in 13 individuals. One of these individuals, who also had a dystonic movement disorder and unilateral strabismus as the only eye defect, had a 1.6- to 2-megabase (Mb) deletion encompassing *SOX2* [Dennert et al 2017].

Delayed motor development was reported in the majority of affected children; the age of achieving independent walking ranged from 12 months to four years, although some individuals never achieve independent ambulation.

Intellectual ability is highly variable, ranging from normal to profound learning disability, with the majority having moderate learning disability. The degree of learning disability is not predictable by pathogenic variant type or presence or absence of eye involvement [Dennert et al 2017, Blackburn et al 2018, Errichiello et al 2018].

Seizures were observed in 22 individuals. Information on exact seizure type is limited, but most appeared to be grand mal tonic-clonic seizures that appeared in early childhood and responded well to standard anticonvulsant medication.

Sensorineural hearing loss. Seven children had apparently nonprogressive moderate sensorineural hearing loss requiring hearing aids.

Esophageal atresia with or without tracheoesophageal fistula. Esophageal atresia or stenosis was reported in nine and three individuals, respectively. Tracheoesophageal fistula was seen in the presence or absence of esophageal atresia. As these features can be present in children without severe structural eye defects [Zenteno et al 2006, Dennert et al 2017], they are not restricted to individuals with the full AEG syndrome [Williamson et al 2006].

Additionally, feeding difficulty or gastroesophageal reflux was observed in multiple individuals.

Genotype-Phenotype Correlations

Almost all *SOX2* pathogenic variants reported to date appear to represent heterozygous loss of function; thus, it is difficult to draw genotype-phenotype correlations.

Variable expressivity is observed with some recurrent pathogenic variants (Table 7).

- The most common variant, p.Asn24ArgfsTer65, which alters the SOX2 N-terminal region polyglycine repeat, is associated primarily with bilateral anophthalmia/microphthalmia; however, two individuals had

reduced palpebral fissure or optic disc abnormality [Zenteno et al 2005, Pilz et al 2019] and three individuals had normal eyes [Chassaing et al 2007, Blackburn et al 2018, Errichiello et al 2018].
- The p.Asp123Gly variant, which alters the SOX2 partner-binding region, displays phenotypes ranging from bilateral anophthalmia/microphthalmia (Families 1 and 2) to mild microcornea, retinal detachment, or refractive error with iris hypoplasia or retinal tuft (Family 1) [Mihelec et al 2009] or bilateral coloboma (Family 2) [Gerth-Kahlert et al 2013].
- The extraocular features of *SOX2* disorder, including AEG syndrome and dystonia, presented with the common p.Asn24ArgfsTer65 variant, but were absent from the two families with the p.Asp123Gly variant. Status dystonicus or severe dystonic cerebral palsy were predominantly observed in individuals with loss-of-function variants at Tyr160 or the surrounding amino acid residues [Gorman et al 2016].
- Large deletions encompassing *SOX2* and adjacent genes, ranging from 1.5 to ~9 Mb, do not cause any striking phenotypic differences when compared to smaller deletions (and intragenic variants) involving only *SOX2*. For details about heterozygous deletions of 3q26.33 involving *SOX2*, see Molecular Genetics.

Duplications encompassing *SOX2*, ranging from 40 kb to 104 Mb, do not appear to cause structural eye defects, but are associated with other features of *SOX2* disorder: developmental delay, intellectual disability, motor delay, hypotonia, and gastroesophageal reflux. Inheritance was observed as *de novo* constitutive or *de novo* mosaic events, or, less frequently, from parents with constitutional duplications (see DECIPHER).

Penetrance

Penetrance appears to be complete for nonmosaic loss-of-function pathogenic variants. Although normal eye development is possible in *SOX2* disorder, all such individuals had extraocular defects.

Nomenclature

Microphthalmia-anophthalmia-coloboma (MAC) was used as an umbrella term for the spectrum of severe eye malformations in early publications describing *SOX2* eye disorders. This may be an inappropriate acronym, as it implies that coloboma is an intrinsic part of all microphthalmia, which is not the case: coloboma has been reported but is not a common feature.

Each of the hypothetic explanations for the embryonic origin of the small or missing eyes associated with *SOX2* pathogenic variants predicts a different spectrum of clinical phenotypes.

- If the primary defect is in the mechanism of optic fissure closure, the predicted order of severity would be iris coloboma, choroidal/retinal coloboma, microphthalmia with coloboma or orbital cyst, and anophthalmia.
- If lens induction is impaired, the predicted clinical spectrum would be congenital cataract > microphthalmia > anophthalmia.
- If the main effects of *SOX2* are in retinal differentiation, the predicted clinical manifestations would be retinal dystrophy > microphthalmia.
- It is also possible that complete failure of optic vesicle formation results in anophthalmia without optic nerve formation.

It is not yet clear which of these spectra are associated with *SOX2* eye disorders, as most affected individuals have very small or absent eyes, which are thus morphologically unclassifiable. Optic fissure closure defects have been reported but are not a common feature.

Anophthalmia-esophageal atresia-genital abnormalities (AEG) syndrome was previously reported to be a distinct disorder, but is now known to be associated in some individuals with heterozygous pathogenic loss-of-function variants in *SOX2* [Williamson et al 2006, Zenteno et al 2006]; thus, it appears that esophageal atresia with or without tracheoesophageal fistula is a feature of *SOX2* disorder and not a separate condition. This is

consistent with the known expression of *SOX2* in the endoderm and genital ridge during development of chick and mouse embryos.

Prevalence

Prevalence is approximately 1:250,000 (UK estimate) [Author, personal data], extrapolated from Shah et al [2011], with no population differences noted.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with heterozygous pathogenic variants in *SOX2*.

Differential Diagnosis

Genes associated with ocular manifestations frequently observed in *SOX2* disorder (with or without nonocular comorbidities) are summarized in Table 3.

Table 3. Genes of Interest in the Differential Diagnosis of *SOX2* Disorder

Gene	Disorder	MOI	Ocular Phenotype	Other Clinical Features	Comment
ALDH1A3	Isolated microphthalmia 8 (OMIM 615113)	AR	Bilateral microphthalmia &/or anophthalmia	DD or autism in ~20% of affected persons	
BMP4	Syndromic microphthalmia 6 (OMIM 607932)	AD	Bilateral anophthalmia, optic disc aplasia/ hypoplasia	Small kidneys/renal cyst, small ears	Comorbidities present in 2 families [1]
GJA8	Cataract 1 (OMIM 116200)	AD	Bilateral microphthalmia, coloboma, cataract [2]	None	
NAA10	Lenz microphthalmia syndrome (OMIM 309800)	XL	Unilateral or bilateral microphthalmia &/or anophthalmia	• Malformations of the ears, teeth, fingers, skeleton, or genitourinary system • Mild-to-severe ID or DD in ~60% of affected males	Polyadenylation signal variants are assoc w/ familial anophthalmia. [3]
OTX2	*OTX2* anophthalmia syndrome (MCOPS5) (OMIM 610125)	AD	Ocular features almost identical to those frequently observed in *SOX2* disorder [4]	Brain features almost identical to those of *SOX2* disorder [4]	Esophageal atresia/ tracheo-esophageal fistula & dystonia are not assoc w/*OTX2* pathogenic variants.
PAX6	*PAX6* isolated aniridia (See *PAX6*-Related Aniridia.)	AD	Bilateral microphthalmia &/or coloboma, iris hypoplasia, cataract, lens subluxation [5]	None	
RAX	*RAX* microphthalmia (OMIM 611038)	AR	Bilateral microphthalmia &/or anophthalmia	~50% of affected individuals had DD or autism.	

Table 3. continued from previous page.

Gene	Disorder	MOI	Ocular Phenotype	Other Clinical Features	Comment
VSX2 (*CHX10*)	*VSX2* microphthalmia (OMIM 142993)	AR	Bilateral microphthalmia &/or anophthalmia	None	Affected families are of Middle Eastern ethnicity.

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; MCOPS5 = microphthalmia, syndromic 5; MOI = mode of inheritance; XL = X-linked

1. Reis et al [2011]; Author, unpublished data
2. Ma et al [2016], Ceroni et al [2019]
3. Johnston et al [2019]
4. Gerth-Kahlert et al [2013]
5. Deml et al [2016], Williamson et al [2020]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SOX2* disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *SOX2* Disorder

System/Concern	Evaluation	Comment
Constitutional	Measurement of weight, length/height, & head circumference	Assess for growth failure.
Eyes	Complete ophthalmologic exam by experienced pediatric ophthalmologist	• Incl best corrected visual acuity, assessment of refractive error, fundus exam • Consider referral to ophthalmo-plastic surgeon for children w/anophthalmia & extreme microphthalmia.
Brain malformation	High-resolution cranial MRI	• W/attention to brain/pituitary malformations, optic nerve/chiasm/tract • Mesial temporal heterotopia is highly assoc w/future epilepsy.
Anterior pituitary hypoplasia	Endocrine eval	Assess: • Growth hormone & thyroid function; • Gonadotropins (when age appropriate).
Genitourinary	Males: Assessment for micropenis &/or cryptorchidism	• Consider referral to urologist for cryptorchidism or other genital malformations. • For those w/micropenis, refer to endocrinologist for consideration of eval for hypogonadotropic hypogonadism.
	Females: Consider pelvic ultrasound exam &/or MRI, particularly in pubertal or postpubertal females.	Assess for uterine & ovarian anomalies.
DD/ID	Developmental assessment	• Incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education
Seizures	Neurologic exam	Incl EEG

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Spasticity	Neurologic exam	Referral to OT/PT to assess: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for ongoing PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Dystonia	Neurologic history & exam	Assess axial & peripheral tone to advise on likely efficacy of antispasmodic medications & procedures.
Hearing loss	Audiologic eval	Assess for sensorineural & conductive hearing loss.
Esophageal atresia ± tracheoesophageal fistula	Focused neonatal assessment	These major malformations constitute a surgical emergency.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *SOX2* disorder to facilitate medical & personal decision making
Family support/ resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support.	

ADL = activities of daily living; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; OT = occupational therapy/therapist; PT = physical therapy/therapist
1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with *SOX2* Disorder

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	Referral to physiotherapist if evidence of motor impairment
Anophthalmia/ Microphthalmia	Early referral to an experienced multidisciplinary team	• Prostheses: Consider optically clear expanders to stimulate growth of the orbit & periorbital tissues. • Community vision services through early intervention or school district
Anterior pituitary hypoplasia	Hormone replacement by pediatric endocrinologist	
Hypogonadotropic hypogonadism	Hormone replacement prior to expected onset of puberty by pediatric endocrinologist	
Seizures	Standardized treatment w/ASM by experienced neurologist	Education of parents/caregivers [1]
Spasticity	Orthopedist / physical medicine & rehab / PT/OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices & disability parking placard.

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Dystonia / Status dystonicus	PT, hydration, intensive care	Dystonia may worsen & can show acute change to status dystonicus, which should be considered a medical emergency.
Hearing loss	Hearing aids may be helpful per audiologist/otolaryngologist.	Community hearing services through early intervention or school district
Esophageal atresia ± tracheoesophageal fistula	Perinatal surgery	This constitutes a surgical emergency.

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on nonmedical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.

- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Communication Issues

Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 6. Recommended Surveillance for Individuals with *SOX2* Disorder

System/Concern	Evaluation	Frequency
Constitutional	Height, weight, & head circumference	Every 3-6 mos during childhood
Anophthalmia/ Microphthalmia	MRI, assessment of vision, ophthalmologic eval	Every 3-6 mos during childhood w/MRI only if change in clinical status, e.g., sudden change in light-dark or color perception
	Follow-up eval w/ophthalmo-plastic surgeon	
Brain malformation	Neurologic eval	Repeat MRI if change in neurologic status.
Anterior pituitary hypoplasia	Pituitary axis endocrine eval	Every 3-6 mos
Hypogonadotropic hypogonadism	Gonadotropin endocrine eval	Infancy, mid-childhood, then every 3-6 mos from age 8 yrs
Developmental delay / Intellectual disability	Neurodevelopmental assessment	Annually for 1st 5 yrs
	Monitor school progress.	Annually

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Seizures	EEG, brain MRI	If change in seizure frequency or type
Spasticity	By OT/PT	Every 3-6 mos during childhood or w/any progression of symptoms or signs, or deteriorating function
Dystonia / Status dystonicus	Neurologic eval	
Sensorineural hearing loss	Audiogram	Annually
Esophageal atresia ± tracheoesophageal fistula	Per treating pediatric surgeon	Per treating pediatric surgeon

OT = occupational therapist; PT = physical therapist

Evaluation of Relatives at Risk

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 access to 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

SOX2 disorder, caused by an intragenic *SOX2* pathogenic variant or a deletion of 3q26.33 involving *SOX2*, is an autosomal dominant disorder.

Risk to Family Members

Parents of a proband

- Approximately 60% of individuals diagnosed with *SOX2* disorder have an identified *de novo* genetic alteration (i.e., a genetic alteration that is not detectable in the biological parents of the proband) [Williamson & FitzPatrick 2014, Harding et al 2020].
- Some individuals diagnosed with *SOX2* disorder have an affected mother (transmission from an affected father to a proband has not been reported to date).
  - One individual with unilateral anophthalmia had a similarly affected mother [Gerth-Kahlert et al 2013].
  - Maternal transmission of an identical and recurrent pathogenic variant has been observed in two families: a four-generation family with eye defects ranging from microcornea or retinal tuft with refractive error to bilateral anophthalmia [Mihelec et al 2009]; and a mother with bilateral coloboma

and her child with bilateral anophthalmia/microphthalmia and coloboma [Gerth-Kahlert et al 2013].
    - A mother with a pathogenic variant (heterozygous or high-level mosaicism) who was minimally affected with isolated hypogonadotropic hypogonadism had two affected children: one with bilateral anophthalmia and subtle endocrine abnormalities and the other with unilateral microphthalmia with coloboma [Stark et al 2011].

- Some individuals diagnosed with *SOX2* disorder have a pathogenic variant inherited from an unaffected parent.
    - Maternal somatic/germline mosaicism was reported in four families with sib recurrence of *SOX2* disorder [Faivre et al 2006, Chassaing et al 2007, Schneider et al 2008, Zhou et al 2008].
    - Paternal transmission of a *SOX2* pathogenic variant is rare and has been reported in only two families to date. In both families, the fathers had somatic and germline mosaicism [Suzuki et al 2014] (see DECIPHER).

- Recommendations for the evaluation of the parents of a proband with an apparent *de novo* genetic alteration include detailed ophthalmologic examination and:
    - Molecular genetic testing (ideally of parental DNA extracted from more than one tissue source, e.g., leukocytes and buccal cells) if the proband has an intragenic *SOX2* pathogenic variant;
    - Routine karyotyping with additional FISH analysis if the proband has a deletion of 3q26.33 or other chromosome rearrangement involving 3q26.33, to determine if either parent has a balanced chromosome rearrangement involving the 3q26.33 region.

- If the genetic alteration identified in the proband is not identified in either parent, the following possibilities should be considered:

    - The proband has a *de novo* genetic alteration. Note: A pathogenic variant is reported as "*de novo*" if: (1) the pathogenic variant found in the proband is not detected in parental DNA; and (2) parental identity testing has confirmed biological maternity and paternity. If parental identity testing is not performed, the variant is reported as "assumed *de novo*" [Richards et al 2015].

    - The proband inherited a pathogenic variant from a parent with germline mosaicism. Note: Testing of parental DNA may not detect all instances of somatic and germline mosaicism.

      The incidence of parental germline mosaicism in *SOX2* disorder is approximately 4.5%. Recurrence of anophthalmia and/or microphthalmia has been reported in six families in which the phenotypically normal mother (4 families) or father (2 families) had confirmed somatic and germline mosaicism (see "Some individuals diagnosed with *SOX2* disorder…" above). An additional instance of probable but unconfirmed maternal germline mosaicism has been reported [Schneider et al 2009].

- The family history of some individuals diagnosed with *SOX2* disorder may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed without genetic testing of the parents of 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 is affected and/or has the genetic alteration identified in the proband, the risk to the sibs of inheriting the genetic alteration is 50%. Intrafamilial clinical variability is observed in *SOX2* disorder; a heterozygous sib may be more or less severely affected than the proband [Mihelec et al 2009].
- If the genetic alteration identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is greater than that of the general population because of the possibility of parental germline mosaicism. The incidence of parental germline mosaicism in *SOX2* disorder is

approximately 4.5% (see **Parents of a proband**). If a parent of the proband has germline mosaicism, the risk to the sibs of inheriting the *SOX2* pathogenic variant may be up to 50%.
- If a parent has a balanced structural chromosome rearrangement involving the 3q26.33 region, the risk to sibs is increased. The estimated risk depends on the specific chromosome rearrangement.

Offspring of a proband

- Each child of a female proband with a constitutional *SOX2* pathogenic variant has a 50% chance of inheriting the causative genetic alteration.
- Transmission of a constitutional loss-of-function pathogenic variant from a male proband to offspring has not been reported.

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the causative genetic alteration or a balanced structural chromosome rearrangement, the parent's family members may be at risk.

Related Genetic Counseling Issues

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.

Prenatal Testing and Preimplantation Genetic Testing

Once the causative genetic alteration has been identified in an affected family member (or a parent is known to have a structural chromosome rearrangement involving the 3q26.33 region), prenatal testing for a pregnancy at increased risk is possible and preimplantation genetic testing for *SOX2* disorder may be possible, depending on the specific familial variant.

Note: The severity of disease and specific clinical findings vary and cannot be accurately predicted by the family history or results of molecular genetic testing.

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.

- **International Children's Anophthalmia Network (ICAN)**
  Phone: 800-580-ican
  Email: info@anophthalmia.org
  www.anophthalmia.org

- **Microphthalmia, Anophthalmia and Coloboma Support**
  United Kingdom
  Phone: 0800 169 8088

Email: enquiries@macs.org.uk
www.macs.org.uk

- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision
- **National Federation of the Blind**
  Phone: 410-659-9314
  Email: nfb@nfb.org
  www.nfb.org

Molecular Genetics

Note on Table A, **Locus-Specific Databases**: See also the DECIPHER database.

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. SOX2 Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SOX2	3q26.33	Transcription factor SOX-2	SOX2 @ The Human Genetics Unit Edinburgh U.K.	SOX2	SOX2

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 SOX2 Disorder (View All in OMIM)

184429	SRY-BOX 2; SOX2
206900	MICROPHTHALMIA, SYNDROMIC 3; MCOPS3

Molecular Pathogenesis

SOX2 encodes the transcription factor SOX2 (317 amino acids) which has an HMG DNA-binding domain (amino acids 40-111), a partner-binding region, and a C-terminal transactivation region. The N-terminal region is of unknown function and contains short polyglycine and polyalanine repeats.

SOX2 is expressed in mouse embryonic stem cells and has been shown to act as part of a transcriptional activator complex for several important developmental genes including other genes known to be critical to eye development (e.g., *PAX6* and *MAF1*). It is an early marker of neurulation in chick embryos and shows site- and stage-specific expression in the developing nervous system, genital ridge, and foregut in all vertebrates studied. For a review article see Julian et al [2017].

Mechanism of disease causation. Heterozygous loss of function

***SOX2*-specific laboratory technical considerations.** As *SOX2* is a single-exon gene, there are no alternative splice transcripts and it is not subject to nonsense-mediated decay; however, loss-of-function variants have been observed throughout the exon.

Reported heterozygous deletions of 3q26.33 involving *SOX2* (~2%-3% of affected individuals, increasing to ~20% of affected individuals with bilateral anophthalmia/severe microphthalmia) [Williamson & FitzPatrick 2014; Author, unpublished data] include:

- A *de novo* deletion encompassing *SOX2* as the only gene [Suzuki et al 2014, Dennert et al 2017] or as part of a multigene deletion [Gerth-Kahlert et al 2013, Suzuki et al 2014, Dennert et al 2017];
- A cytogenetically visible deletion of 3q26.33 that either encompasses *SOX2* [Male et al 2002, Guichet et al 2004, Kelberman et al 2008] or involves an unbalanced translocation such as t(3;7)(q28;q21.1)-associated 6.7-Mb deletion [Male et al 2002];
- A *de novo* apparently balanced translocation involving 3q26.33, encompassing *SOX2*, such as t(3;11)(q26.3;p11.2)-associated 600-kb deletion and t(3;7)(q28;p21.3)-associated 2.7-Mb deletion [Fantes et al 2003, Williamson et al 2006].

Table 7. Notable *SOX2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_003106.4 NP_003097.1	c.70_89del20	p.Asn24ArgfsTer65	Most common pathogenic variant; accounts for ~20% of all pathogenic variants [Williamson & FitzPatrick 2014].
	c.368A>G	p.Asp123Gly	Recurrent familial variant assoc w/broad range of ocular phenotypes [Mihelec et al 2009, Gerth-Kahlert et al 2013]
	c.479dupA, c.480C>G, c.480C>A	p.Tyr160Ter	• Recurrent variant specifically assoc w/status dystonicus [Gorman et al 2016, Blackburn et al 2018] • Less frequent variants, esp those that alter residues adjacent to Tyr160, are also assoc w/severe phenotype.

Variants listed in the table have been provided by the authors. *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.

Chapter Notes

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- 30 July 2020 (bp) Comprehensive update posted live
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- 7 March 2008 (cd) Revision: FISH analysis available clinically
- 5 December 2007 (cd) Revision: deletion/duplication analysis available clinically
- 23 February 2006 (me) Review posted live
- 14 April 2005 (drf) Original submission

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