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SALL4-Related Disorders

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Summary

Clinical characteristics

SALL4-related disorders include Duane-radial ray syndrome (DRRS, Okihiro syndrome), acro-renal-ocular syndrome (AROS), and *SALL4*-related Holt-Oram syndrome (HOS) – three phenotypes previously thought to be distinct entities.

- DRRS is characterized by uni- or bilateral Duane anomaly and radial ray malformation that can include thenar hypoplasia and/or hypoplasia or aplasia of the thumbs, hypoplasia or aplasia of the radii, shortening and radial deviation of the forearms, triphalangeal thumbs, and duplication of the thumb (preaxial polydactyly).
- AROS is characterized by radial ray malformations, renal abnormalities (mild malrotation, ectopia, horseshoe kidney, renal hypoplasia, vesicoureteral reflux, bladder diverticula), ocular coloboma, and Duane anomaly.
- Rarely, pathogenic variants in *SALL4* may cause clinically typical HOS (i.e., radial ray malformations and cardiac malformations without additional features).

Diagnosis/testing

The diagnosis of a *SALL4*-related disorder is established in a proband with suggestive findings and a heterozygous pathogenic variant in *SALL4* identified by molecular genetic testing.

Management

Treatment of manifestations: Surgery as needed for strabismus from Duane anomaly, malformations of the forearms, and congenital heart defects; management of renal anomalies per nephrologist and/or urologist; antiarrhythmic medications or pacemaker for those with conduction defects or heart block; cardiologist can assist in determining the need for anticoagulants and antibiotic prophylaxis for bacterial endocarditis; hearing aids as needed; consideration of growth hormone therapy for children with growth deficiency; treatment of pituitary hypoplasia per endocrinologist.

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Surveillance: Ophthalmologic exam with frequency as recommended by ophthalmologist; monitor renal function in those with renal anomalies, even if renal function is normal initially; periodic renal ultrasound evaluation if renal position anomalies could cause obstruction; periodic echocardiographic surveillance may be recommended for individuals with certain congenital heart defects; in those at risk for conduction defects, EKG at least annually with consideration of annual Holter monitor in those with known conduction defects; at least annual blood counts in those with a history of thrombocytopenia and leukocytosis; audiologic evaluation as needed; assessment of growth and for signs and symptoms of pituitary hypoplasia at each visit.

Agents/circumstances to avoid: Drugs affecting the kidney if renal function is impaired, or the inner ear if hearing is impaired; certain medications may be contraindicated in those with arrhythmias.

Genetic counseling

SALL4-related disorders are inherited in an autosomal dominant manner. The proportion of cases caused by a *de novo* pathogenic variant is approximately 40%-50%. Each child of an individual with a *SALL4*-related disorder has a 50% chance of inheriting the pathogenic variant. Prenatal testing for a pregnancy at increased risk is possible if the pathogenic variant has been identified in an affected family member.

GeneReview Scope

SALL4-Related Disorders: Included Phenotypes
• Duane-radial ray syndrome (DRRS) / Okihiro syndrome • Acro-renal-ocular syndrome (AROS) • *SALL4*-related Holt-Oram syndrome (HOS)

For synonyms and outdated names see Nomenclature.

Diagnosis

Suggestive Findings

SALL4-related disorders include a spectrum of phenotypes: Duane-radial ray syndrome (DRRS), or Okihiro syndrome; acro-renal-ocular syndrome (AROS); and *SALL4*-related Holt-Oram syndrome (HOS). A *SALL4*-related disorder **should be suspected** in individuals with clinical features of DRRS, AROS, or HOS.

DRRS clinical features

- **Duane anomaly.** Uni- or bilateral limitation of abduction of the eye associated with retraction of the globe and narrowing of the palpebral fissure on adduction. The abducens nucleus and nerve (cranial nerve VI) are absent and the lateral rectus muscle is innervated by a branch of the oculomotor nerve (cranial nerve III), which explains the aberrant ocular movements (see Duane Syndrome).
- **Radial ray malformation.** Thenar hypoplasia and/or hypoplasia or aplasia of the thumbs; hypoplasia or aplasia of the radii; shortening and radial deviation of the forearms; triphalangeal thumbs; and duplication of the thumb (preaxial polydactyly)
- **Other features** are variably present; see Clinical Characteristics.

AROS clinical features

- Radial ray malformations
- Renal abnormalities: mild malrotation, ectopia, horseshoe kidney, renal hypoplasia, vesicoureteral reflux, and bladder diverticula
- Ocular abnormalities: ocular coloboma and Duane anomaly

SALL4-related HOS clinical features

- Upper-extremity malformations: radial, thenar, and/or carpal bones, including preaxial polydactyly
- Congenital heart malformations: ventricular septal defects, atrial septal defects, and tetralogy of Fallot
- Cardiac conduction defects (less common than in *TBX5*-related HOS)

  Note: HOS is a heterogeneous phenotype in which 70% of affected individuals have pathogenic variants in *TBX5*; see Differential Diagnosis and Holt-Oram Syndrome for further clinical information on this condition.

Establishing the Diagnosis

The diagnosis of a *SALL4*-related disorder **is established** in a proband with suggestive findings and a heterozygous pathogenic variant in *SALL4* identified by molecular genetic testing (see Table 1).

Note: Identification of a heterozygous *SALL4* variant of uncertain significance does not establish or rule out the diagnosis of this disorder.

Molecular genetic testing approaches can include single-gene testing (see Option 1) or use of a multigene panel (see Option 2) depending on the phenotype.

Option 1

When the phenotypic findings suggest the diagnosis of a *SALL4*-related disorder, consider **single-gene testing**:

- Sequence analysis of *SALL4* is performed first to detect small intragenic deletions/insertions and missense, nonsense, and splice site variants. 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.

Option 2

When the phenotype falls outside of the typical spectrum of *SALL4*-related disorders, consider a **multigene panel** that includes *SALL4* and other genes of interest (see Differential Diagnosis) 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 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.

Table 1. Molecular Genetic Testing Used in *SALL4*-Related Disorders

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2, 3] Detectable by Method
SALL4	Sequence analysis [4]	85%-90% [5]
	Deletion/duplication analysis [6]	10%-15% [7]

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.
5. Al-Baradie et al [2002], Kohlhase et al [2002], Kohlhase et al [2003], Borozdin et al [2004b], Kohlhase et al [2005]
6. 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.
7. Borozdin et al [2004a], Borozdin et al [2007]

Clinical Characteristics

Clinical Description

SALL4-related disorders include Duane-radial ray syndrome (DRRS, Okihiro syndrome), acro-renal-ocular syndrome (AROS), and *SALL4*-related Holt-Oram syndrome (HOS) – three phenotypes previously thought to be distinct entities [Al-Baradie et al 2002, Kohlhase et al 2002, Kohlhase et al 2003, Borozdin et al 2004a, Borozdin et al 2004b, Kohlhase et al 2005, Borozdin et al 2007].

- DRRS is characterized by uni- or bilateral Duane anomaly and radial ray malformation that can include thenar hypoplasia and/or hypoplasia or aplasia of the thumbs, hypoplasia or aplasia of the radii, shortening and radial deviation of the forearms, triphalangeal thumbs, and duplication of the thumb (preaxial polydactyly).
- AROS is characterized by radial ray malformations, renal abnormalities (mild malrotation, ectopia, horseshoe kidney, renal hypoplasia, vesicoureteral reflux, bladder diverticula), ocular coloboma, and Duane anomaly.
- Rarely, pathogenic variants in *SALL4* may cause clinically typical HOS (i.e., radial ray malformations and cardiac malformations without additional features).

Of 69 affected individuals from 23 families with a *SALL4* pathogenic variant, 13% show the triad of Duane anomaly, radial ray malformation, and sensorineural hearing loss originally described for Okihiro syndrome; 45% have Duane anomaly and radial defects; and 21% have radial defects only. To date, more than 100 individuals with a pathogenic variant in *SALL4* have been identified [Al-Baradie et al 2002, Kohlhase et al 2002, Kohlhase et al 2003, Borozdin et al 2004a, Borozdin et al 2004b, Kohlhase et al 2005, Borozdin et al 2007, Vanlerberghe et al 2019, van de Putte et al 2020, and others]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *SALL4*-Related Disorders: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Duane anomaly	65%	Other ocular anomalies rarely reported
Radial ray anomaly	>90%	
Renal abnormality	38%	
Congenital heart anomaly	15%	

Table 2. continued from previous page.

Feature	% of Persons w/Feature	Comment
Cardiac conduction defect	Rare	
Hearing loss	16%	
Choanal atresia	5%	
Short stature	7%	

J Kohlhase, unpublished data

Ocular. Duane anomaly is the most common ocular finding. Other ocular anomalies include iris, retinal, and choroidal colobomata, cataract, optic disc hypoplasia, and microphthalmia (structural eye anomalies are rare).

Musculoskeletal. Radial ray anomalies can include thenar hypoplasia and/or hypoplasia or aplasia of the thumbs; hypoplasia or aplasia of the radii; shortening and radial deviation of the forearms; triphalangeal thumbs; and duplication of the thumb (preaxial polydactyly). Other reported upper-extremity anomalies include concomitant shortening of ulnae, syndactyly, radial clubhand, carpal bone anomalies, shortened humeri, and hypoplasia of deltoid muscles. Lower-extremity anomalies include talipes, clubfoot, tibial hemimelia, and syndactyly of toes. Fused vertebrae have also been reported.

Renal anomalies include mild malrotation, ectopia, crossed renal ectopia, horseshoe kidney, renal hypoplasia, renal agenesis, vesicoureteral reflux, and bladder diverticula.

Cardiac. Congenital heart malformations include ventricular septal defect, atrial septal defect, and tetralogy of Fallot. Cardiac conduction defects are also reported but are less common than in *TBX5*-related HOS.

Ears/hearing. Sensorineural and/or conductive deafness can occur. Ear anomalies include abnormal pinnae, slit-like opening of auditory canals, and small ears.

Gastrointestinal features can include anal stenosis and imperforate anus.

Characteristic facial features reported in some individuals include epicanthal folds, widely spaced eyes, depressed nasal bridge, and hemifacial microsomia.

Pituitary. Growth hormone deficiency, postnatal growth deficiency, pituitary hypoplasia

Development and cognition are normal.

Other

- **Central nervous system.** Neural tube defects (rare); meningomyelocele has been observed in two affected individuals [J Kohlhase, unpublished data].
- **Mild thrombocytopenia and leukocytosis** were reported in some affected individuals with one *SALL4* pathogenic frameshift variant from one family. See IVIC syndrome (OMIM 147750).
- **Isolated ventricular septal defects (VSD).** Two *SALL4* missense variants have been reported to be associated with isolated VSD [Wang et al 2010]. However, since neither of these missense variants affects amino acids with known functional domains, it is unclear if this phenotype is clearly associated with pathogenic variants in *SALL4*.

Genotype-Phenotype Correlations

Most *SALL4* loss-of-function variants are private or have been observed in no more than three independent families. The phenotype of larger deletions (not extending into other genes) is not significantly different from that caused by almost all truncating single-nucleotide variants, and these are expected to result in nonsense-mediated mRNA decay.

The only clearly pathogenic missense variant identified to date in an individual with malformations (c.2663A>G, p.His888Arg) affects an essential coordinating amino acid and is associated with central midline defects (single upper incisor, pituitary hypoplasia, widely spaced eyes). It is predicted to result in an increase of DNA binding capacity [Miertus et al 2006].

The only truncating pathogenic variant predicted to escape nonsense-mediated mRNA decay is associated with extensive clinical variability and severe hemifacial microsomia in one affected member of the reported family [Terhal et al 2006].

Some pathogenic missense variants have been reported to result in a gain of function, and those variants have been reported to cause premature ovarian failure alone, without developmental disorder (see Genetically Related Disorders) [Wang et al 2019].

Penetrance

Penetrance is approximately 95% but may be lower for certain pathogenic variants.

In two reported families. An individual known (on the basis of pedigree position) to have the *SALL4* pathogenic variant is unaffected; an individual with a proven *SALL4* pathogenic variant shows no signs of a *SALL4*-related disorder [Hayes et al 1985, Kohlhase et al 2002]. In the latter family, however, the phenotype was mild in all individuals with the pathogenic variant (i.e., presenting with only thenar hypoplasia and Duane anomaly).

Of 69 family members known in 2004 to have a *SALL4* pathogenic variant, only one (1.4%) was clinically unaffected [J Kohlhase, personal observation]. No further case of non-penetrance is known to the author.

Nomenclature

One of the earliest reports of Duane anomaly occurring together with radial ray defects is that of Ferrell et al [1966] (earlier reports are cited in OMIM). Further families were reported by Temtamy et al [1975] and Okihiro et al [1977]. Temtamy & McKusick [1978] named the syndrome Duane/radial dysplasia syndrome (DR syndrome, later modified to Duane-radial ray syndrome [DRRS]). The term "Okihiro syndrome" was first used by Hayes et al [1985].

The term "acro-renal-ocular syndrome" was used in 1984 to describe a family with autosomal dominant inheritance of thumb abnormalities, renal malformations, and ocular coloboma, ptosis, and Duane anomaly [Halal et al 1984].

Holt-Oram syndrome has also been referred to as heart-hand syndrome, a nonspecific designation that could apply to any number of conditions with involvement of these structures.

Prevalence

The prevalence is unknown, partly because in many countries *SALL4*-related disorders have not been and are still not differentiated from HOS caused by pathogenic variants in *TBX5*, or from other heart-hand syndromes.

Genetically Related (Allelic) Disorders

Premature ovarian failure. Three *SALL4* missense variants have been reported to be associated with premature ovarian failure (POI) (see Table 7) [Wang et al 2019]. All three variants result in increased SALL4 protein expression and increased activation of the downstream gene *POU5F1*, suggesting that these variants act as gain-of-function variants. None of these variants were detected in individuals with *SALL4*-related disorders, and individuals with *SALL4* loss-of-function variants have not been reported to have decreased fertility or POI.

Therefore, while *SALL4* loss-of-function variants lead to Duane-radial ray syndrome (DRRS, Okihiro syndrome), acro-renal-ocular syndrome, and *SALL4*-related Holt-Oram syndrome, *SALL4* gain-of-function variants are not associated with those phenotypes but interfere with ovarian function.

Persons with DRRS and developmental delay are likely to have a larger deletion including *SALL4* and neighboring genes [Borozdin et al 2007].

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of *SALL4*-Related Disorders

Gene(s) [1]	Disorder	MOI	Overlapping Clinical Features	Comment / Distinguishing Features
TBX5	*TBX5*-related Holt-Oram syndrome (*TBX5*-HOS)	AD	Upper-limb malformations (radial, thenar, or carpal bones); CHD (ostium secundum ASD, VSD, esp those occurring in muscular trabeculated septum, & cardiac conduction defects)	Preaxial polydactyly is almost exclusively assoc w/*SALL4*-RD. In *TBX5*-HOS ASD may be more common than VSD, whereas the opposite may apply for *SALL4*-RD. Cardiac conduction defects are observed less commonly in *SALL4-RD* than in *TBX5*-HOS. Persons w/typical radial ray malformations & renal or urogenital malformation (esp position anomalies of kidneys) but w/o Duane anomaly are more likely to have *SALL4*-RD than *TBX5*-HOS.
SALL1	Townes-Brocks syndrome (TBS)	AD	Dysplastic ears, imperforate anus, & triphalangeal thumbs / preaxial polydactyly	Radial aplasia has not been observed in TBS.
RBM8A	Thrombocytopenia absent radius (TAR) syndrome	AR	Bilateral absence of radii; other skeletal, cardiac, & GI anomalies	In TAR syndrome: thumbs are never absent but may appear malformed; thrombocytopenia is generally transient.
BRCA1 *BRCA2* *BRIP1* *ERCC4* *FAAP100* *FANCA* *FANCB* *FANCC* *FANCD2* *FANCE* *FANCF* *FANCG* *FANCI* *FANCL* *FANCM* *MAD2L2* *PALB2* *RAD51* *RAD51C* *RFWD3* *SLX4*	Fanconi anemia (FA)	AR AD XL [2]	Radial ray malformations; other skeletal, cardiac, & GI anomalies	In FA: progressive bone marrow failure, cancer susceptibility, DD/ID In *SALL4*-RD: Duane anomaly

Table 3. continued from previous page.

Gene(s) [1]	Disorder	MOI	Overlapping Clinical Features	Comment / Distinguishing Features
UBE2T *XRCC2*				

AD = autosomal dominant; AR = autosomal recessive; ASD = atrial septal defect; CHD = congenital heart defect; DD = developmental delay; ID = intellectual delay; MOI = mode of inheritance; *SALL4*-RD = *SALL4*-related disorders; VSD = ventricular septal defect; XL = X-linked

1. Genes are ordered by relevance to the differential diagnosis of *SALL4*-related disorders.

2. Fanconi anemia (FA) can be inherited in an autosomal recessive manner, an autosomal dominant manner (*RAD51*-related FA), or an X-linked manner (*FANCB*-related FA).

Disorders of unknown cause associated with Duane anomaly

- **Arthrogryposis-ophthalmoplegia syndrome.** In this syndrome, Duane anomaly is associated with deafness, muscle wasting, and contractures, but not typical radial limb malformations. A *SALL4* pathogenic variant was not identified in one of the few families reported [McCann et al 2005].
- **Wildervanck syndrome** (OMIM 314600) consists of congenital perceptive deafness, Klippel-Feil anomaly, and Duane anomaly. The disorder affects females almost exclusively. *SALL4* pathogenic variants have not been detected in some persons who meet the diagnostic criteria for Wildervanck syndrome [J Kohlhase, unpublished data].

Thalidomide embryopathy. Thalidomide is currently prescribed to treat conditions such as multiple myeloma, HIV, and leprosy. Fetal abnormalities related to thalidomide administration during pregnancy include amelia, phocomelia, radial hypoplasia, external ear abnormalities, facial palsy, eye abnormalities (anophthalmos, microphthalmos, Duane anomaly, cranial nerve misrouting resulting in "crocodile tears"), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations also occur. If an individual with a diagnosis of thalidomide embryopathy has a child with radial ray malformations similar to those seen in Holt-Oram syndrome and *SALL4*-related disorders and additional malformations (e.g., Duane anomaly, kidney defects), a *SALL4* pathogenic variant is more likely to be found than a *TBX5* pathogenic variant [Kohlhase et al 2003].

Management

No clinical practice guidelines for *SALL4*-related disorders have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a *SALL4*-related disorder, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with *SALL4*-Related Disorders

System/Concern	Evaluation	Comment
Eyes	Complete eye exam by ophthalmologist w/special attn to extraocular movements & structural eye defects	
Musculoskeletal	• Clinical assessment for upper- & lower-extremity anomalies • X-rays if needed by orthopedist	Referral to orthopedist as needed
Renal	• Renal ultrasound exam • Assess renal function w/serum electrolyte concentrations, BUN, & creatinine.	

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Cardiac	• Eval by cardiologist • Echocardiogram • EKG	If cardiac conduction defect is suspected, a more extensive eval may be needed esp when structural heart defects are present.
Hearing	See Hereditary Hearing Loss and Deafness Overview.	
Anal stenosis / Imperforate anus	Referral to surgeon for anal anomalies if present	
Endocrine	• Assess for growth deficiency &/or growth hormone deficiency. • Assess for signs/symptoms of pituitary hypoplasia.	Referral to endocrinologist as needed
Cytopenias	CBC to evaluate for thrombocytopenia &/or leukocytosis	Referral to hematologist if needed
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *SALL4*-related disorders to facilitate medical & personal decision making

BUN = blood urea nitrogen; CBC = complete blood count; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with *SALL4*-Related Disorders

Manifestation/Concern	Treatment	Considerations/Other
Duane anomaly	Severe strabismus may require eye surgery.	
Radial ray malformations	Severe malformations of forearms may require surgery, e.g., surgery to correct aplasia of thumb by constructing functional thumb (pollicization)	
Renal anomalies	Mgmt per nephrologist &/or urologist	
Cardiac anomalies &/or conduction defects	• Cardiac surgery, if required for congenital heart defect, is standard. • Cardiologist can assist in determining need for antiarrhythmic medications & surgery. • Persons w/severe heart block may require pacemaker implantation.	Cardiologist can assist in determining need for anticoagulants & antibiotic prophylaxis for bacterial endocarditis.
Hearing deficits	Hearing aids may be required.	
Growth hormone deficiency	Growth hormone therapy should be considered.	
Pituitary hypoplasia	Treatment per endocrinologist	

Surveillance

Table 6. Recommended Surveillance for Individuals with *SALL4*-Related Disorders

System/Concern	Evaluation	Frequency
Ocular anomalies	Ophthalmologic exam	Per ophthalmologist

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Renal anomalies	Monitor renal function (e.g., serum creatinine), even if no impairment of renal function is detected on initial exam.	• Every 6-12 mos in 1st yrs of life • If renal function remains normal, screening intervals may be extended.
	Renal ultrasound	• Repeat if renal position anomalies could cause obstruction. • Frequency depends on clinical situation.
Cardiac anomalies	Echocardiogram	Every 1-5 yrs depending on nature & significance of cardiac malformation, as recommended by cardiologist
Cardiac conduction defects (incl those at risk for conduction defects)	• EKG • Consider Holter monitor.	Annually or more often, as recommended by cardiologist
Thrombocytopenia &/or leukocytosis	CBC	At least annually [1]
Hearing	Audiologic eval	Per audiologist &/or ENT
Endocrine	Assess growth & for signs/symptoms of pituitary hypoplasia.	At each visit

CBC = complete blood count

1. Data are sparse on the natural history of thrombocytopenia in individuals with *SALL4* pathogenic variants; thus, it is unknown at present if more severe complications may occur.

Agents/Circumstances to Avoid

Drugs affecting renal clearance or the inner ear should be avoided in individuals with impaired renal function and/or hearing impairment.

Certain medications may be contraindicated in individuals with arrhythmias.

Evaluation of Relatives at Risk

Children of affected persons who are themselves not obviously affected should be tested for the pathogenic variant present in the family because individuals with a *SALL4* pathogenic variant should undergo clinical evaluation for hearing problems, renal disease, eye disease, and heart defects.

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

SALL4-related disorders are inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Many individuals diagnosed with a *SALL4*-related disorder have an affected parent.
- A proband with a *SALL4*-related disorder may have the disorder as the result of a *de novo* pathogenic variant. The proportion of individuals with a *SALL4*-related disorder caused by a *de novo* pathogenic variant is approximately 40%-50% [J Kohlhase, unpublished data].
- Recommendations for the evaluation of parents of a proband who appears to be the only affected family member (i.e., a simplex case) include molecular genetic testing for the *SALL4* pathogenic variant identified in the proband and/or physical examination, ophthalmologic examination for structural malformations of the eyes as well as eye movement disorders, examination of the limbs (x-rays of the forearms), examination of the heart, and ultrasound examination of the kidneys.
- 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.
- The family history of some individuals diagnosed with a *SALL4*-related disorder may appear to be negative because of reduced penetrance or failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated 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 has a *SALL4* pathogenic variant, the risk to the sibs is inheriting the pathogenic variant is 50%. The penetrance of *SALL4*-related disorders is approximately 95% in heterozygous individuals but may be lower for certain pathogenic variants (see Penetrance).
- If the *SALL4* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *SALL4* pathogenic variant but are clinically unaffected, sibs are still presumed to be at increased risk for a *SALL4*-related disorder because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with a *SALL4*-related disorder has a 50% chance of inheriting the pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has a *SALL4* pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

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

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

For a pregnancy known to be at increased risk for a *SALL4*-related disorder. Once the *SALL4* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. Although such testing can determine whether or not the fetus has inherited the *SALL4* pathogenic variant, it cannot predict which manifestations will be present or the severity of the manifestations. High-resolution ultrasound examination is therefore recommended to evaluate the fetus for phenotypic manifestations.

For a pregnancy not known to be at increased risk for a *SALL4*-related disorder. A *SALL4* pathogenic variant may be detected for the first time in a family if radial malformations are detected on ultrasound examination as an incidental prenatal finding and prenatal genetic analysis reveals a *SALL4* pathogenic variant. If a larger deletion is found, chromosomal microarray analysis may be used to determine if neighboring genes, in additional to *SALL4*, are included in the deletion (see Genetically Related Disorders).

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.

- **MedlinePlus**
  Duane-radial ray syndrome
- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org
- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision

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. SALL4-Related Disorders: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SALL4	20q13.2	Sal-like protein 4	SALL4 database	SALL4	SALL4

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 SALL4-Related Disorders (View All in OMIM)

607323	DUANE-RADIAL RAY SYNDROME; DRRS
607343	SAL-LIKE 4; SALL4

Molecular Pathogenesis

SALL4 encodes sal-like protein 4 (SALL4), a C2H2 (Krüppel-like) zinc finger transcription factor of the SAL type [Kohlhase et al 2002]. SALL4 appears to be an essential developmental regulator. No embryonic or extra-embryonic endoderm stem cell lines can be established if Sall4 is missing. Sall4 interacts with Nanog and co-occupies Nanog genomic sites in embryonic stem cells [Wu et al 2006].

Apart from its role in embryonic and stem cell development, Sall4 is involved in malignant transformation. More than 1,000 putative *Sall4* target genes were identified, including many known to have roles in stem cell self-renewal and blood differentiation [Yang et al 2008, Gao et al 2013]. Since human *SALL4* is upregulated in some tumor types, especially hepatocellular carcinoma [Yong et al 2013], cancer-related targets are being sought. One direct target is *ABCA3*, encoding an ATP-binding cassette drug transport protein, which contributes to chemotherapeutic drug resistance [Jeong et al 2011].

Mechanism of disease causation. *SALL4* pathogenic variants related to developmental disorders likely lead to haploinsufficiency or some degree of loss of SALL4 function, since all but two pathogenic variants responsible for malformation syndromes are expected to undergo nonsense-mediated decay, and deletions of the whole gene appear to result in the same phenotype [Borozdin et al 2004a, Kohlhase et al 2005].

One pathogenic variant, p.Arg905Ter, is expected to escape nonsense-mediated mRNA decay and to result in a truncated protein with one nonfunctional zinc finger domain [Terhal et al 2006].

Another pathogenic variant, p.His888Arg, exchanges one of the essential amino acids for zinc coordination in a zinc finger and is predicted to result in increased DNA binding of the respective zinc finger [Miertus et al 2006].

Missense variants reported to be causative for premature ovarian insufficiency have been reported to result in a gain of function [Wang et al 2019]. Carriers of such variants do not show any of the malformations that are characteristic for *SALL4*-related malformation syndromes, whereas female subjects affected by such syndromes have not been reported to suffer from ovarian dysfunction.

Table 7. Notable *SALL4* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_020436.5 NP_065169.1	c.2663A>G	p.His888Arg	See Molecular Pathogenesis, **Mechanism of disease causation**.
	c.2713C>T	p.Arg905Ter	
	c.541G>A	p.Val181Met	Gain-of-function variants in premature ovarian dysfunction
	c.1790A>G	p.Lys597Arg	
	c.2279C>T	p.Thr760Ile	

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

Chapter Notes

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Author Notes

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- 1 March 2004 (jk) Original submission

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