GENEReviews

Funded by the NIH · Developed at GeneTests (www.genetests.org), University of Washington, Seattle

SALL4-Related Disorders

Jürgen Kohlhase, MD
Institute of Human Genetics and Anthropology
University of Freiburg
Freiburg, Germany
jkohlhase@humangenetik-freiburg.de

Initial Posting: August 16, 2004.
Last Revision: March 12, 2008.

Summary

Disease characteristics. *SALL4*-related disorders include Duane-radial ray syndrome (DRRS, Okihiro syndrome) and acro-renal-ocular syndrome (AROS), two 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, vesico-ureteral reflux, bladder diverticula), ocular coloboma, and Duane anomaly. Rarely, *SALL4* mutations may cause clinically typical Holt-Oram syndrome (i.e., radial ray malformations and cardiac malformations without additional features). Additional clinical features include sensorineural and/or conductive deafness.

Diagnosis/testing. *SALL4* is the only gene known to be associated with *SALL4*-related disorders. Diagnosis is based on clinical findings and detection of a *SALL4* mutation. Direct sequencing of the complete *SALL4* coding region and testing to identify intragenic deletions are clinically available.

Management. *Treatment of manifestations:* surgery as needed for strabismus from Duane anomaly, malformations of the forearms, and congenital heart defects; hearing aids as needed; consideration of growth hormone therapy for treating growth-retarded children. *Surveillance:* routine monitoring of renal function in those with renal anomalies, even if renal function is normal initially. *Agents/circumstances to avoid:* drugs affecting the kidney if renal function is impaired, or the inner ear if hearing is impaired.

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

Diagnosis

Clinical Diagnosis

SALL4-related disorders include a spectrum of phenotypes previously thought to be distinct entities: Duane-radial ray syndrome (DRRS), or Okihiro syndrome; acro-renal-ocular syndrome (AROS) [Kohlhase et al 2003]; and rarely, Holt-Oram syndrome.

Duane-radial ray syndrome/Okihiro syndrome is established clinically in individuals with the following:

- **Duane anomaly,** characterized by 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.** Malformations 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 features** that are variably present (see Clinical Description)

Acro-renal-ocular syndrome is established clinically in individuals with the following:

- **Radial ray malformations**
- **Renal abnormalities** that can include mild malrotation, ectopia, horseshoe kidney, renal hypoplasia, vesico-ureteral reflux, bladder diverticula)
- **Ocular abnormalities** that can include ocular coloboma, Duane anomaly

Holt-Oram syndrome. Rarely, *SALL4* mutations may cause clinically typical Holt-Oram syndrome (i.e., radial ray malformations and cardiac malformations without additional features).

Molecular Genetic Testing

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

Gene. *SALL4* is the only gene associated with Duane-radial ray/Okihiro syndrome (DRRS) and acro-renal-ocular syndrome (AROS).

Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Clinical testing

- Direct sequencing of the complete *SALL4* coding region (exons 1-4) detects mutations in more than 80% of individuals with DRRS and AROS [Al-Baradie et al 2002; Kohlhase et al 2002; Kohlhase et al 2003; Borozdin, Wright et al 2004; Kohlhase et al 2005].
- Quantitative RealTime PCR using amplicons within the *SALL4* exons as well as within regions 5' and 3' of the transcription unit identified deletions of single exons (exons 1 and 4), of exons 1-3, or of the whole coding region in six independent families with DRRS and AROS [Borozdin, Boehm et al 2004]. In cases with whole-gene deletions, high resolution array CGH helped to determine the size of the deletions and other genes involved, which may help to predict the developmental outcome [Borozdin et al 2007].

- FISH analysis is also available to detect deletions; however, given the relatively small size of the gene, FISH analysis may have a low yield / limited utility.
- The combination of both techniques identifies a causative *SALL4* mutation or deletion in about 90%-95% of cases [Kohlhase et al 2005].

Table 1 summarizes molecular genetic testing for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
Sequence analysis	*SALL4* sequence variants	≤80%	Clinical Testing
Quantitative RealTime PCR	Deletions of *SALL4* exon(s) or whole-gene deletions	10%-15%	
FISH	Whole-gene deletions	Unknown	

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with *SALL4* mutations.

Clinical Description

Natural History

In addition to the clinical features described in the Diagnosis section, the clinical manifestations of *SALL4*-related disorders may include the following:

- **Eyes.** Microphthalmia (rare); iris, retinal, and choroidal colobomata; cataract; optic disc hypoplasia
- **Upper extremities.** Concomitant shortening of ulnae, syndactyly, radial clubhand, shortened humeri, hypoplasia of deltoid muscles
- **Kidneys.** Renal agenesis, crossed renal ectopia, position anomalies of kidneys
- **Ears/hearing.** Sensorineural and/or conductive deafness, abnormal pinnae, slit-like opening of auditory canals, small ears
- **Heart.** Atrial septal defect, ventricular septal defect, tetralogy of Fallot
- **Gastrointestinal.** Anal stenosis, imperforate anus
- **Face.** Epicanthal folds, ocular hypertelorism, flat nasal bridge, hemifacial microsomia
- **Lower extremities.** Talipes, clubfoot, tibial hemimelia, syndactyly of toes
- **Spine.** Fused vertebrae
- **Pituitary.** Growth hormone deficiency, postnatal growth retardation, pituitary hypoplasia

Of the 69 affected individuals from 23 families with *SALL4* mutations, 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. In 82.6% of families, at least one person has Duane anomaly and in 48%, at least one person has hearing loss. Radial ray malformations have been found in all families with

SALL4 mutations and in 91.3% of individuals with a mutation. Sixty-five percent of individuals with a mutation have Duane anomaly and 16% have hearing loss.

Genotype-Phenotype Correlations

Most mutations 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 point mutations, and these are expected to result in nonsense-mediated mRNA decay.

The only missense mutation identified so far (c.2663A>G) is associated with central midline defects (single upper incisor, pituitary hypoplasia, ocular hypotelorism) and is predicted to result in an increase of DNA binding capacity [Miertus et al 2006].

The only truncating mutation 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].

Persons with Okihiro syndrome and developmental delay are likely to have a larger deletion including *SALL4* and neighboring genes [Borozdin et al 2007]. Developmental delay/mental retardation associated with mutation within the *SALL4* gene has not been observed.

Penetrance

Penetrance is approximately 95%, but may be lower for certain mutations.

Two families are documented [Hayes et al 1985, Kohlhase et al 2002] in which either an individual who is known (on the basis of pedigree position) to have the *SALL4* mutation is not affected or an individual with a proven *SALL4* mutation does not show any signs of *SALL4*-related disorders. In the latter family, however, the phenotype was mild in all individuals with the mutation (i.e., presenting with only thenar hypoplasia and Duane anomaly).

Of 69 family members known in 2004 to have a mutation, only one (1.4%) was clinically unaffected [Kohlhase, personal observation].

Anticipation

Apparent increased severity in successive generations is attributed to ascertainment bias.

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 607323). Further families were reported by Temtamy et al (1975) and Okihiro et al (1977). Temtamy and 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].

Prevalence

The prevalence is unknown, partly because *SALL4*-related disorders have not been and are still not differentiated from Holt-Oram syndrome in many countries.

Differential Diagnosis

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

Holt-Oram syndrome. The main differential diagnosis is Holt-Oram syndrome, characterized by upper-limb malformations involving radial, thenar, or carpal bones; a personal and/or family history of congenital heart malformation, most commonly ostium secundum atrial septal defect (ASD) and ventricular septal defect (VSD), especially those occurring in the muscular trabeculated septum; and cardiac conduction defects. Holt-Oram syndrome is caused by mutations in the gene *TBX5*. Holt-Oram syndrome and *SALL4*-related disorders have the same type of radial ray malformations, although preaxial polydactyly only occurs with *SALL4* mutations and not *TBX5* mutations. The heart defects associated with *SALL4* mutations and *TBX5* mutations are similar [Borozdin, Boehm et al 2004] but ASD may be more common than VSD with *TBX5* mutations, whereas the opposite may apply for *SALL4*. Mutations of both genes may result in more severe heart defects like tetralogy of Fallot, but cardiac conduction defects have been observed less commonly with *SALL4* mutations as compared to *TBX5* mutations. Individuals with typical radial ray malformations and a renal or urogenital malformation (especially position anomalies of the kidneys), but without Duane anomaly, are more likely to have a *SALL4* mutation than a *TBX5* mutation.

Townes-Brocks syndrome. This syndrome is characterized by a triad of dysplastic ears, imperforate anus, and triphalangeal thumbs/preaxial polydactyly [Powell & Michaelis 1999]. Townes-Brocks syndrome is associated with mutations in *SALL1*. In a few individuals, complete overlap exists between Okihiro syndrome and Townes-Brocks syndrome [Kohlhase et al 2002; Borozdin, Boehm et al 2004]. In these individuals, *SALL4* molecular genetic testing should be considered if Duane anomaly is present and if *SALL1* molecular genetic testing did not reveal a mutation. Because radial aplasia has not been observed in individuals with a *SALL1* mutation [Kohlhase, unpublished data], its presence points towards a *SALL4* mutation even when all other features suggest Townes-Brocks syndrome.

Fanconi anemia. Individuals with radial ray malformations may also have Fanconi anemia. A range of additional features may be present, including other skeletal anomalies, heart defects, urogenital and renal anomalies, hypogonadism, ear anomalies, hearing loss, eye anomalies, imperforate anus, growth retardation, pigmentation anomalies, and developmental delay. Persons with Fanconi anemia often show anomalies of the blood cell count and develop progressive bone marrow failure with pancytopenia. There is a significant risk for leukemia and solid tumors. Developmental delay is not a feature of *SALL4*-related disorders apart from rare persons with multigene deletions that include the *SALL4* gene [Kohlhase, unpublished data], and Duane anomaly is not a feature of Fanconi anemia. Persons with radial ray anomalies and involvement of other organs who do not present with typical findings of Okihiro syndrome/AROS should be evaluated for Fanconi anemia by appropriate tests [i.e., chromosomal aberrations (breaks, radial figures) after cell cultivation in medium with DEB (diepoxybutane) and/or mitomycin C; see Fanconi Anemia for details].

Thrombocytopenia-absent radius (TAR) syndrome. Individuals with TAR syndrome have radial aplasia, but in contrast to *SALL4*-related disorders, the thumbs are never absent, although they may appear malformed. Thromobocytopenia does not typically occur in *SALL4*-related disorders; it may be only transiently detectable in TAR syndrome. Several other malformations may occur in TAR syndrome [Greenhalgh et al 2002]. TAR syndrome is caused by a 1q21.1 microdeletion in the presence of an as-yet unknown modifier [Klopocki et al 2007].

Arthrogryposis-ophthalmoplegia syndrome. In this syndrome, Duane anomaly is associated with deafness, muscle wasting, and contractures, but not typical radial limb malformations.

SALL4 mutations were not identified in one of the few families reported [McCann et al 2005].

Wildervanck syndrome. The Wildervanck syndrome consists of congenital perceptive deafness, Klippel-Feil anomaly and Duane anomaly. The disorder affects almost exclusively females. The cause of Wildervanck syndrome is unknown. *SALL4* mutations have not been detected in some persons who meet the diagnostic criteria for Wildervanck syndrome [Kohlhase, unpublished data].

Thalidomide embryopathy. From 1957 to 1962, malformed children were born to mothers who took the drug thalidomide for treatment of nausea and insomnia during pregnancy. Currently, thalidomide is 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 (including anotia, microtia, micropinna), 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. Mortality at or shortly after birth is approximately 40% [Miller & Strömland 1999]. 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 (i.e., Duane anomaly or kidney defects), a *SALL4* mutation is more likely to be found than a *TBX5* mutation [Kohlhase et al 2003].

Testing strategy for individuals with typical radial ray malformations

- Perform cardiac evaluation, ophthalmologic examination, and renal ultrasound examination in addition to a routine physical examination.
- If no features typical of *SALL4*-related disorders are found, *TBX5* molecular genetic testing is suggested as the first molecular test.
- If other features typical of *SALL4*-related disorders are found, *SALL4* molecular genetic testing is suggested as the first step.
- If clinical overlap exists with Townes-Brocks syndrome, *SALL1* molecular genetic testing should be the first test if the radial ray malformations do not include malformations of the radius itself; if malformation of the radius is present, *SALL4* molecular genetic testing is suggested as the first molecular test.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with a *SALL4*-related disorder, the following evaluations are recommended:

- **Eyes.** A complete eye examination by an ophthalmologist with special attention to extraocular movements and structural eye defects
- **Heart.** Baseline evaluation by a cardiologist including an echocardiogram
- **Kidneys.** Renal ultrasound examination and routine laboratory tests for renal function
- **Hearing.** See Hereditary Hearing Loss and Deafness Overview.

Treatment of Manifestations

Duane anomaly. Severe strabismus may require eye surgery.

Radial ray malformations. Severe malformations of the forearms may require surgery, e.g., surgery to correct aplasia of the thumb by constructing a functional thumb (pollicization).

Heart defects. Severe congenital heart defects may require surgery.

Hearing deficits. Hearing aids may be required.

Growth retardation. Growth hormone therapy should be considered for treating affected children.

Surveillance

Renal function should be regularly monitored in individuals with renal anomalies, even if no impairment of renal function is detected on initial examination.

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.

Testing of Relatives at Risk

Although reduced penetrance does not seem to be associated with most mutations, unaffected persons may consider molecular genetic testing prior to family planning. Children of affected persons who are themsleves not obviously affected may be tested for the mutation running in the family because individuals with the mutation 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 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.

Other

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

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

Risk to Family Members

Parents of a proband

- Most 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 new gene mutation. The proportion of cases caused by *de novo* mutations is approximately 40%-50% [Kohlhase, unpublished observation].
- Recommendations for the evaluation of parents of a proband with an apparent *de novoSALL4* mutation include 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, ultrasound examination of the kidneys, and molecular genetic testing if the *SALL4* mutation has been identified in the proband.

Note: Although most individuals diagnosed with a *SALL4*-related disorder have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected or has a *SALL4* mutation, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be about 1%-5% because of the possibility of germline mosaicism [Kohlhase, unpublished observation].
- If a *SALL4* disease-causing mutation cannot be detected in DNA extracted from the leukocytes of either parent, the two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported to date, it remains a possibility.

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

Other family members of a proband. The risk to other family members depends on the genetic status of the proband's parents. If a parent is found to be affected or to have a *SALL4* mutation, his or her family members are at risk.

Related Genetic Counseling Issues

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

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

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member should be identified before prenatal testing can be performed; however, prenatal testing may also be possible without prior testing of an affected member, for example if ultrasound indicates that the fetus is affected. Although such testing can determine whether or not the fetus has inherited the *SALL4* disease-causing mutation, 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.

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

Requests for prenatal testing for conditions such as *SALL4*-related disorders that do not affect intellect and have some treatment available are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, careful discussion of these issues is appropriate.

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

Molecular Genetics

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

Table A. Molecular Genetics of SALL4-Related Disorders

Gene Symbol	Chromosomal Locus	Protein Name
SALL4	20q13.13-q13.2	Sal-like protein 4

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

Table B. OMIM Entries for SALL4-Related Disorders

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

Table C. Genomic Databases for SALL4-Related Disorders

Gene Symbol	Entrez Gene	HGMD
SALL4	57167 (MIM No. 607343)	SALL4

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

Note: HGMD requires registration.

Normal allelic variants: The *SALL4* gene occupies about 18 kb (start codon to stop codon). It contains four exons (all coding) and three introns. The genomic sequence is available at www.ncbi.nlm.nih.gov (accession number NT_01132). Sixteen different non-pathogenic polymorphisms are currently known.

Pathologic allelic variants: Twenty-five of 27 reported and confirmed mutations predict premature protein truncation and are distributed over exons 2 and 3 of the gene [Al-Baradie et al 2002; Kohlhase et al 2002; Brassington et al 2003; Kohlhase et al 2003; Borozdin, Boehm et al 2004; Kohlhase et al 2005; Miertus et al 2006; Terhal et al 2006]. It is likely that all result in nonsense-mediated messenger decay and therefore haploinsufficiency of *SALL4*. All known mutations are private mutations with two exceptions (c.2593C>T and c.496dupC) [Al-Baradie et al 2002, Kohlhase et al 2003, Kohlhase et al 2005]. The mutation c.2593>T caused a mild phenotype in one family and a severe phenotype in another family. Six deletions were found in families with DRRS/Okihiro syndrome or acro-renal-ocular syndrome. Two families had heterozygous deletions of all four exons: two with deletions of exons 1-3, one with deletion of exon 1, and one with deletion of exon 4 [Borozdin, Boehm et al 2004]. These findings confirmed that haploinsufficiency for sal-like protein 4 is the pathogenic mechanism leading to the phenotype.

Normal gene product: *SALL4* encodes sal-like protein 4, a C2H2 (Krüppel-like) zinc finger transcription factor of the SAL type [Kohlhase et al 2002]. Sal-like protein 4 appears to be an essential developmental regulator. In the mouse, Sall4 is essential for the development of the epiblast and primitive endoderm from the inner embryonic cell mass [Elling et al 2006]. No embryonic or extra-embryonic endoderm stem cell lines can be established if *SALL4* is missing. Sal-like protein 4 interacts with Nanog and co-occupies Nanog genomic sites in embryonic stem cells [Wu et al 2006].

SALL4 cooperates with SALL1 in anorectal, heart, brain, and kidney development [Sakaki-Yumoto et al 2006]. Together with *TBX5*, *SALL4* is required for patterning and morphogenesis of the first digit of the upper limbs, with *SALL4* being regulated by Tbx5 in mouse [Koshiba-Takeuchi et al 2006] and zebrafish models [Harvey & Logan 2006] and acting together with Tbx5 on Fgf signaling, shown only in the mouse. In the heart, Sall4 and Tbx5 act synergistically on the *Gja5* promotor, but antagonistically on the *Nppa* gene [Koshiba-Takeuchi et al 2006]. Nothing is yet known about the function of *SALL4* in brain, especially brain stem development.

With respect to the upstream regulation of *SALL4*, it is known that *SALL4* is directly activated by TCF/LEF in the canonical Wnt signaling pathway [Bohm et al 2006].

Abnormal gene product: *SALL4* mutations likely lead to haploinsufficiency of sal-like protein 4, since all but two mutations are expected to undergo nonsense-mediated decay, and deletions of the whole gene seem to result in the same phenotype [Borozdin, Boehm et al 2004; Kohlhase et al 2005]. One mutation, p.Gln905X [Terhal et al 2006], is expected to escape nonsense-mediated mRNA decay and to result in a truncated protein with one nonfunctional zinc finger domain. Another mutation, p.H888R, 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.

Resources

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

National Library of Medicine Genetics Home Reference
Duane-radial ray syndrome

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

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

National Eye Institute
Low Vision

References

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

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Literature Cited

Al-Baradie R, Yamada K, St Hilaire C, Chan WM, Andrews C, McIntosh N, Nakano M, Martonyi EJ, Raymond WR, Okumura S, Okihiro MM, Engle EC. Duane radial ray syndrome (Okihiro syndrome) maps to 20q13 and results from mutations in SALL4, a new member of the SAL family. Am J Hum Genet. 2002;71:1195–9. [PubMed: 12395297]

Bohm J, Sustmann C, Wilhelm C, Kohlhase J. SALL4 is directly activated by TCF/LEF in the canonical Wnt signaling pathway. Biochem Biophys Res Commun. 2006;348:898–907. [PubMed: 16899215]

Borozdin W, Boehm D, Leipoldt M, Wilhem C, Reardon W, Clayton-Smith J, Becker K, Muhlendyck H, Winter R, Giray O, Silan F, Kohlhase J. SALL4 deletions are a common cause of Okihiro and acro-renal-ocular syndromes and confirm haploinsufficiency as the pathogenetic mechanism. J Med Genet. 2004;41:e113. [PubMed: 15342710]

Borozdin W, Graham JM Jr, Boehm D, Bamshad MJ, Spranger S, Burke L, Leipoldt M, Kohlhase J. Multigene deletions on chromosome 20q13.13-q13.2 including SALL4 result in an expanded phenotype of Okihiro syndrome plus developmental delay. Hum Mutat. 2007;28:830. [PubMed: 17623483]

Borozdin W, Wright MJ, Hennekam RC, Hannibal MC, Crow YJ, Neumann TE, Kohlhase J. Novel mutations in the gene SALL4 provide further evidence for acro-renal-ocular and Okihiro syndromes being allelic entities, and extend the phenotypic spectrum. J Med Genet. 2004;41:e102. [PubMed: 15286162]

Brassington AM, Sung SS, Toydemir RM, Le T, Roeder AD, Rutherford AE, Whitby FG, Jorde LB, Bamshad MJ. Expressivity of Holt-Oram syndrome is not predicted by TBX5 genotype. Am J Hum Genet. 2003;73:74–85. [PubMed: 12789647]

Elling U, Klasen C, Eisenberger T, Anlag K, Treier M. Murine inner cell mass-derived lineages depend on Sall4 function. Proc Natl Acad Sci U S A. 2006;103:16319–24. [PubMed: 17060609]

Ferrell RL, Jones B, Lucas RV Jr. Simultaneous occurrence of the Holt-Oram and the Duane syndromes. J Pediatr. 1966;69:630–4. [PubMed: 5921340]

Greenhalgh KL, Howell RT, Bottani A, Ancliff PJ, Brunner HG, Verschuuren-Bemelmans CC, Vernon E, Brown KW, Newbury-Ecob RA. Thrombocytopenia-absent radius syndrome: a clinical genetic study. J Med Genet. 2002;39:876–81. [PubMed: 12471199]

Halal F, Homsy M, Perreault G. Acro-renal-ocular syndrome: autosomal dominant thumb hypoplasia, renal ectopia, and eye defect. Am J Med Genet. 1984;17:753–62. [PubMed: 6426304]

Harvey SA, Logan MP. sall4 acts downstream of tbx5 and is required for pectoral fin outgrowth. Development. 2006;133:1165–73. [PubMed: 16501170]

Hayes A, Costa T, Polomeno RC. The Okihiro syndrome of Duane anomaly, radial ray abnormalities, and deafness. Am J Med Genet. 1985;22:273–80. [PubMed: 4050857]

Klopocki E, Schulze H, Strauss G, Ott CE, Hall J, Trotier F, Fleischhauer S, Greenhalgh L, Newbury-Ecob RA, Neumann LM, Habenicht R, Konig R, Seemanova E, Megarbane A, Ropers HH, Ullmann R, Horn D, Mundlos S. Complex inheritance pattern resembling autosomal recessive inheritance involving a microdeletion in thrombocytopenia-absent radius syndrome. Am J Hum Genet. 2007;80:232–40. [PubMed: 17236129]

Kohlhase J, Chitayat D, Kotzot D, Ceylaner S, Froster UG, Fuchs S, Montgomery T, Rosler B. SALL4 mutations in Okihiro syndrome (Duane-radial ray syndrome), acro-renal-ocular syndrome, and related disorders. Hum Mutat. 2005;26:176–83. [PubMed: 16086360]

Kohlhase J, Heinrich M, Schubert L, Liebers M, Kispert A, Laccone F, Turnpenny P, Winter RM, Reardon W. Okihiro syndrome is caused by SALL4 mutations. Hum Mol Genet. 2002;11:2979–87. [PubMed: 12393809]

Kohlhase J, Schubert L, Liebers M, Rauch A, Becker K, Mohammed SN, Newbury-Ecob R, Reardon W. Mutations at the SALL4 locus on chromosome 20 result in a range of clinically overlapping phenotypes, including Okihiro syndrome, Holt-Oram syndrome, acro-renal-ocular syndrome, and patients previously reported to represent thalidomide embryopathy. J Med Genet. 2003;40:473–8. [PubMed: 12843316]

Koshiba-Takeuchi K, Takeuchi JK, Arruda EP, Kathiriya IS, Mo R, Hui CC, Srivastava D, Bruneau BG. Cooperative and antagonistic interactions between Sall4 and Tbx5 pattern the mouse limb and heart. Nat Genet. 2006;38:175–83. [PubMed: 16380715]

McCann E, Fryer AE, Newman W, Appleton RE, Kohlhase J. A family with Duane anomaly and distal limb abnormalities: a further family with the arthrogryposis-ophthalmoplegia syndrome. Am J Med Genet A. 2005;139:123–6. [PubMed: 16278891]

Miertus J, Borozdin W, Frecer V, Tonini G, Bertok S, Amoroso A, Miertus S, Kohlhase J. A SALL4 zinc finger missense mutation predicted to result in increased DNA binding affinity is associated with cranial midline defects and mild features of Okihiro syndrome. Hum Genet. 2006;119:154–61. [PubMed: 16402211]

Miller MT, Stromland K. Teratogen update: thalidomide: a review, with a focus on ocular findings and new potential uses. Teratology. 1999;60:306–21. [PubMed: 10525208]

Okihiro MM, Tasaki T, Nakano KK, Bennett BK. Duane syndrome and congenital upper-limb anomalies. A familial occurrence. Arch Neurol. 1977;34:174–9. [PubMed: 843249]

Powell CM, Michaelis RC. Townes-Brocks syndrome. J Med Genet. 1999;36:89–93. [PubMed: 10051003]

Sakaki-Yumoto M, Kobayashi C, Sato A, Fujimura S, Matsumoto Y, Takasato M, Kodama T, Aburatani H, Asashima M, Yoshida N, Nishinakamura R. The murine homolog of SALL4, a causative gene in

Okihiro syndrome, is essential for embryonic stem cell proliferation, and cooperates with Sall1 in anorectal, heart, brain and kidney development. Development. 2006;133:3005–13. [PubMed: 16790473]

Temtamy SA, McKusick VA. The Genetics of Hand Malformations. Alan R Liss, New York, pp 133-5. 1978

Temtamy SA, Shoukry AS, Ghaly I, El-Meligy R, Boulos SY. The Duane radial dysplasia syndrome: an autosomal dominant disorder. Birth Defects Orig Art Ser XI:344-5. 1975

Terhal P, Rosler B, Kohlhase J. A family with features overlapping Okihiro syndrome, hemifacial microsomia and isolated Duane anomaly caused by a novel SALL4 mutation. Am J Med Genet A. 2006;140:222–6. [PubMed: 16411190]

Wu Q, Chen X, Zhang J, Loh YH, Low TY, Zhang W, Zhang W, Sze SK, Lim B, Ng HH. Sall4 interacts with Nanog and co-occupies Nanog genomic sites in embryonic stem cells. J Biol Chem. 2006;281:24090–4. [PubMed: 16840789]

Chapter Notes

Author Notes

Web site: www.humangenetik-freiburg.de

Acknowledgments

The author's research has received funding from the Wilhelm-Sander-Stiftung of Germany, a non-profit organization funding medical research, and from the Deutsche Forschungsgemeinschaft.

Revision History

- 12 March 2008 (cd) Revision: FISH analysis available on a clinical basis
- 19 January 2007 (me) Comprehensive update posted to live Web site
- 16 August 2004 (ca) Review posted to live Web site
- 1 March 2004 (jk) Original submission