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Townes-Brocks Syndrome

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Summary

Clinical characteristics

Townes-Brocks syndrome (TBS) is characterized by the triad of imperforate anus (84%), dysplastic ears (87%; overfolded superior helices and preauricular tags; frequently associated with sensorineural and/or conductive hearing impairment [65%]), and thumb malformations (89%; triphalangeal thumbs, duplication of the thumb [preaxial polydactyly], and rarely hypoplasia of the thumbs). Renal impairment (42%), including end-stage renal disease (ESRD), may occur with or without structural abnormalities (mild malrotation, ectopia, horseshoe kidney, renal hypoplasia, polycystic kidneys, vesicoutereral reflux). Congenital heart disease occurs in 25%. Foot malformations (52%; flat feet, overlapping toes) and genitourinary malformations (36%) are common. Intellectual disability occurs in approximately 10% of individuals. Rare features include iris coloboma, Duane anomaly, Arnold-Chiari malformation type 1, and growth retardation.

Diagnosis/testing

The diagnosis of TBS is based on clinical findings; identification of a heterozygous *SALL1* pathogenic variant on molecular genetic testing establishes the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Immediate surgical intervention for imperforate anus; early treatment of hearing loss; surgery for severe malformations of the hands; hemodialysis and possibly kidney transplantation for ESRD; surgery or medical treatment by a cardiologist for congenital heart defects.

Surveillance: Annual hearing evaluation; regular monitoring of renal function in individuals with and without renal anomalies, even if renal function is normal on initial examination.

Agents/circumstances to avoid: Medications that cause renal or otic toxicity.

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Genetic counseling

TBS is inherited in an autosomal dominant manner. The proportion of cases caused by *de novo* pathogenic variants is estimated at 50%. Each child of an individual with TBS caused by a *SALL1* pathogenic variant 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 the family.

Diagnosis

Suggestive Findings

Townes-Brocks syndrome (TBS) should be suspected in individuals with the following major and minor clinical features.

Major features

- Imperforate anus or anal stenosis in 84%
- Dysplastic ears in 87% (overfolded superior helices, microtia)
- Typical thumb malformations in 89% (preaxial polydactyly, triphalangeal thumbs, hypoplastic thumbs) without hypoplasia of the radius

Minor features

- Sensorineural and/or conductive hearing impairment
- Foot malformations
- Renal impairment with or without renal malformations
- Genitourinary malformations
- Congenital heart disease

Atypical (not suggestive of TBS)

- Radius hypoplasia on clinical examination or radiographs
- Cleft lip/palate

Establishing the Diagnosis

The diagnosis of TBS is established in a proband with three major features. If only two major features are present, the presence of minor features and the absence of atypical features further support the diagnosis. Identification of a heterozygous *SALL1* pathogenic variant on molecular genetic testing (see Table 1) establishes the diagnosis if clinical features are inconclusive.

Molecular testing approaches can include **single-gene testing**, use of a **multigene panel**, and **more comprehensive genomic testing**:

- **Single-gene testing.** Sequence analysis of *SALL1* is performed first followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- **A multigene panel** that includes *SALL1* and other genes of interest may also be considered. The genes included in multigene panels vary by laboratory and are likely to change over time. However, due to the existence of a highly homologous *SALL1* pseudogene (*SALL1P1*), capture-based gene panels may not be the optimal choice.

  Note: (1) A few individuals with clinical features of TBS have been found to have pathogenic variants in *SALL4* [Kohlhase et al 2002; Borozdin et al 2004; Kohlhase, personal communication]. Therefore, in

individuals with a diagnosis of TBS and negative *SALL1* testing, *SALL4* molecular genetic testing should be considered. (2) Molecular genetic testing of *SALL4* rather than *SALL1* is suggested as the first molecular test if the radius is involved and/or if Duane anomaly is present. See Differential Diagnosis, **Okihiro syndrome** and *SALL4*-Related Disorders.

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

- **More comprehensive genomic testing** (when available) including exome sequencing, genome sequencing, and mitochondrial sequencing may be considered if single-gene testing (and/or use of a multigene panel) fails to confirm a diagnosis in an individual with features of TBS.

  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 Townes-Brocks Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SALL1	Sequence analysis [3]	~70% [4]
	Gene-targeted deletion/duplication analysis [5]	~5% [6]
Unknown [7]	NA	

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Sequence analysis has detected pathogenic variants in more than 100 individuals with Townes-Brocks syndrome [Kohlhase et al 1998, Kohlhase et al 1999, Marlin et al 1999, Blanck et al 2000, Engels et al 2000, Kohlhase 2000, Salerno et al 2000, Surka et al 2001, Devriendt et al 2002, Kohlhase et al 2003, Botzenhart et al 2005, Walter et al 2006, Botzenhart et al 2007]. Sequence analysis in about 70% and deletion/duplication testing in about 5% identify a *SALL1* pathogenic variant or deletion in approximately 75% of persons with the classic triad of malformations as described by Kohlhase et al [1999].
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 gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Borozdin et al [2006] identified three and Bardakjian et al [2009] and Miller et al [2012] identified two further multiexon/whole-gene deletions.
7. A *SALL1* pathogenic variant has not been found in a number of individuals with the classic TBS phenotype; thus, locus heterogeneity appears likely.

Clinical Characteristics

In the two most recent studies [Botzenhart et al 2005, Botzenhart et al 2007] of 61 persons with novel *SALL1* pathogenic variants (not including the most common pathogenic variant, p.Arg276Ter), 84% had anal anomalies, 89% hand anomalies, and 87% ear anomalies; 67% had the characteristic triad.

Clinical Description

- **Gastrointestinal.** Imperforate anus, anal stenosis, chronic constipation, gastroesophageal reflux [Engels et al 2000]
- **Dysplastic ears** (overfolded superior helices, microtia), congenital sensorineural and/or conductive hearing loss ranging from mild to severe. Hearing loss that is mild may worsen with age (65% of individuals).

- **Thumb malformations.** Preaxial polydactyly, triphalangeal thumbs, and hypoplastic thumbs without hypoplasia of the radius
- **Lower extremities.** Clubfoot, overlapping toes (II and IV over III), syndactyly of toes, missing toes (III) (52% of individuals) [Surka et al 2001, Botzenhart et al 2005, Botzenhart et al 2007]
- **Kidneys.** Renal agenesis, renal hypoplasia, polycystic kidneys; functional impairment with or without structural abnormalities (42% of individuals) [Surka et al 2001, Botzenhart et al 2005, Botzenhart et al 2007]
- **Genitourinary.** Hypospadias, vaginal aplasia with bifid uterus, bifid scrotum, cryptorchidism (36% of individuals) [Surka et al 2001, Botzenhart et al 2005, Botzenhart et al 2007]
- **Heart.** Congenital heart disease in 50% of persons with the common p.Arg276Ter pathogenic variant [Kohlhase et al 2003] and 12%-25% of persons with other *SALL1* pathogenic variants [Surka et al 2001, Botzenhart et al 2005, Botzenhart et al 2007]. Defects include atrial septal defect, ventricular septal defect, tetralogy of Fallot, lethal truncus arteriosus, pulmonary valve atresia, and persistent ductus arteriosus [Surka et al 2001].
- **Central nervous system**
  - Intellectual disability (~10%)
  - Behavioral problems, observed in many children with TBS [Kohlhase, unpublished observations]
  - Arnold-Chiari malformation type I [Kohlhase, unpublished observations]
  - Cranial nerve palsy (nerves VI and VII)
  - 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), accounting for the aberrant ocular movements.
  - Hypoplasia of the dorsal part of corpus callosum
- **Growth.** Postnatal growth retardation. This poorly documented feature has been described in fewer than 6% to 29% of persons reported with TBS in the literature [Surka et al 2001]. The occurrence of postnatal growth retardation among individuals with a confirmed pathogenic variant is not known. Lawrence et al [2013] reported growth hormone deficiency in an individual with TBS, suggesting that this may also be the cause for growth retardation in other individuals with TBS.
- **Skeletal.** Rib anomalies (fused ribs, missing ribs, additional cervical ribs), mild vertebral anomalies (9%). Painful joints have been observed in several adults with TBS [Kohlhase, unpublished observations].
- **Eyes.** Microphthalmia (rare), iris coloboma, lamellar cataract, chorioretinal coloboma with loss of vision
- **Face.** Hemifacial microsomia [Kohlhase et al 1999, Keegan et al 2001]
- **Endocrine.** Congenital hypothyroidism (rare) [Lawrence et al 2013]

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been made for the majority of pathogenic variants, most of which are private.

The most common pathogenic variant and the only pathogenic variant found in more than two families is c.826C>T (p.Arg276Ter), detected in approximately half of simplex cases with TBS (i.e., a single occurrence in a family) and in one familial case to date [Kohlhase et al 2003]. This pathogenic variant is associated with greater frequency (50%) and severity of congenital heart defects than other pathogenic variants. Fifteen of 16 individuals with this pathogenic variant showed the characteristic triad of anal, thumb, and ear malformations (94%), indicating that this pathogenic variant is associated with a more severe phenotype.

In general, pathogenic variants within the hot spot region that is towards the 5' end in exon 2 appear to be associated with a more severe outcome than pathogenic variants towards the 3' in exon 2. In addition, the phenotype associated with deletions of *SALL1* appears to be milder than that associated with pathogenic

variants in the hot spot region, but only five families with larger deletions have been reported to date [Borozdin et al 2006, Bardakjian et al 2009, Miller et al 2012].

Penetrance

Penetrance appears to be complete, but expressivity is highly variable.

Anticipation

Apparent increased severity in successive generations is likely attributable to ascertainment bias.

Nomenclature

Feichtiger [1943] provided one of the earliest reports of Townes-Brocks syndrome.

Townes & Brocks [1972] were the first to report autosomal dominant transmission of the characteristic anomalies.

Kurnit et al [1978] used the term REAR syndrome (for *r*enal, *e*ar, *a*nal, and *r*adial malformations).

Monteiro de Pina-Neto [1984] was the first to use the term Townes-Brocks syndrome.

Prevalence

The prevalence is unknown, partly because the clinical diagnosis of Townes-Brocks syndrome is often complicated by overlap with VACTERL association, which may lead to an over-ascertainment of TBS prevalence. Martínez-Frías estimated the prevalence at 1:250,000 but did not use stringent diagnostic criteria for TBS [Martínez-Frías et al 1999].

Genetically Related (Allelic) Disorders

A *SALL1* nonsense variant, p.Arg1054Ter, was reported to cause a more severe TBS-like phenotype combined with severe neurologic defects. This variant does not cause a phenotype in a heterozygous state [Vodopiutz et al 2013].

Differential Diagnosis

The clinical presentation of Townes-Brocks syndrome (TBS) can overlap with Goldenhar syndrome (hemifacial microsomia) [Gabrielli et al 1993, Kohlhase et al 1999, Keegan et al 2001], Okihiro syndrome (but without malformations of the radius) [Borozdin et al 2004], and branchiootorenal syndrome [Engels et al 2000, Albrecht et al 2004]. TBS also overlaps with VACTERL association.

Goldenhar syndrome. The majority of individuals with oculo-auriculo-vertebral spectrum phenotypes do not have upper-limb or anal malformations. However, some persons with *SALL1* pathogenic variants have hemifacial microsomia. [Gabrielli et al 1993, Johnson et al 1996, Kohlhase et al 1999, Keegan et al 2001]. Therefore, while hemifacial microsomia alone is not suggestive of the presence of a *SALL1* pathogenic variant, it may occur in individuals with a *SALL1* pathogenic variant in addition to more typical TBS malformations.

Okihiro syndrome (Duane-radial ray syndrome) is characterized by Duane anomaly and radial ray defects, and less commonly by hearing loss and renal position anomalies (see *SALL4*-Related Disorders).

- In a few individuals with clinical TBS, causative *SALL4* variants were found instead of *SALL1* [Kohlhase et al 2002; Borozdin et al 2004; Kohlhase, personal communication]. In those individuals, both *SALL1* and *SALL4* molecular genetic testing should be considered.

- Duane anomaly can also occur with a *SALL1* pathogenic variant [Kohlhase et al 1999, Botzenhart et al 2005].
- Because radial aplasia or hypoplasia and thumb aplasia have not been observed in individuals with a *SALL1* pathogenic variant [Kohlhase, unpublished data], their presence points toward a *SALL4* pathogenic variant, even if all other features suggest TBS.

Branchiootorenal (BOR) syndrome. In two families eventually determined to have *SALL1* pathogenic variants, no affected individual had the typical triad of thumb, anal, and ear malformations. Instead, the presence of dysplastic ears and renal malformations or impaired renal function in family members initially led to the consideration of BOR syndrome [Engels et al 2000, Albrecht et al 2004].

VACTERL association (OMIM 192350) comprises *v*ertebral defects, *a*nal atresia, *c*ardiac defects, *t*racheo-*e*sophageal fistula, *r*enal malformations, and *l*imb defects. VACTERL is therefore an important differential diagnosis for simplex cases (i.e., a single affected individual in a family) with suspected TBS. To date, severe vertebral defects and tracheo-esophageal fistula have not been observed in persons with a *SALL1* pathogenic variant [Kohlhase, unpublished data]. Sib and offspring recurrence risks for VACTERL association are estimated at approximately 1%. A review summarizes current information on VACTERL association [Shaw-Smith 2006].

STAR syndrome (OMIM 300707) is characterized by toe syndactyly, telecanthus, anogenital malformations, and renal malformations similar to TBS. Facial features and toe syndactyly distinguish STAR syndrome from TBS. STAR syndrome is caused by mutation of *FAM58A* and inherited in an X-linked manner with likely lethality in males.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Townes-Brocks syndrome (TBS), the following evaluations are recommended:

- **Hearing.** Hearing evaluation as soon as the diagnosis of TBS is suspected (See Deafness and Hereditary Hearing Loss Overview.)
- **Kidneys.** Renal ultrasound examination and routine laboratory tests for renal function
- **Heart.** Baseline evaluation by a cardiologist including an echocardiogram
- **Eyes.** Ophthalmology examination to evaluate for ocular features of TBS and atypical finding of Duane anomaly.
- **Other.** Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

The following are indicated:

- **Imperforate anus.** Immediate surgical intervention is required.
- **Hearing loss.** Significant impairment requires early treatment, typically with hearing aids (see Deafness and Hereditary Hearing Loss Overview).
- **Thumb malformations.** Severe malformations of the hands may require surgery (e.g., removal of additional thumbs).
- **Renal.** Impaired renal function requires continuous monitoring, hemodialysis, and possibly kidney transplantation.
- **Heart defects.** Congenital heart defects may require surgery or medical treatment by a cardiologist.

Surveillance

Annual hearing evaluation is indicated.

Renal function should be regularly monitored in all individuals with and without renal anomalies, even if no impairment of renal function is detected on initial examination.

Agents/Circumstances to Avoid

Medications that cause renal or otic toxicity should be avoided.

Evaluation of Relatives at Risk

It is appropriate to evaluate relatives at risk in order to identify as early as possible those who would benefit from initiation of treatment and preventive measures.

- If the pathogenic variant in the family is known, molecular genetic testing can be used to clarify the genetic status of at-risk relatives.
- If the pathogenic variant in the family is not known, clinical evaluation for physical features, hearing problems, renal disease, and heart defects can be used to clarify the disease status of at-risk relatives.

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

Townes-Brocks syndrome (TBS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 50% of individuals diagnosed with TBS resulting from a *SALL1* pathogenic variant have an affected parent; about 50% have the disorder as the result of a *de novo* pathogenic variant [Kohlhase, unpublished observation].
- *De novo SALL1* pathogenic variants most commonly occur (~87.5%) on the paternally derived chromosome 16 without an obvious age effect [Böhm et al 2006].
- If the *SALL1* pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* pathogenic variant in the proband. Three individuals with mosaicism including the germline have been reported [Kohlhase et al 1999, Blanck et al 2000, Devriendt et al 2002].

- Recommendations for the evaluation of parents of a proband with an apparent *de novo SALL1* pathogenic variant include molecular genetic testing or physical examination, examination of the limbs (x-rays of the forearms, inspection of the feet) and ears, a hearing test, ultrasound examination of the kidneys and laboratory tests for renal function, and heart examination.
- The family history of some individuals diagnosed with TBS may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless appropriate evaluations (e.g., molecular genetic testing, physical examination) have been performed on the parents of the proband.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, s/he may have somatic mosaicism for the variant and may be mildly/minimally affected. Clinical signs in parents with somatic mosaicism for a pathogenic variant may be as mild as toes II and IV overlapping the third toe [Devriendt et al 2002].

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 has a *SALL1* pathogenic variant, the risk to the sibs of inheriting the pathogenic variant is 50%. With the exception of the p.Arg276Ter pathogenic variant, which has caused a severe phenotype in all known instances, results of molecular genetic testing cannot predict which manifestations will be present or their severity.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be about 1%-2% because of the possibility of germline mosaicism [Kohlhase, unpublished observation].

Offspring of a proband. Each child of an individual with Townes-Brocks syndrome has a 50% chance of inheriting the *SALL1* pathogenic variant.

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 affected, members of the parent's family are 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.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant, it is likely that the proband has a *de novo* variant. However, possible non-medical explanations including alternate paternity or maternity (e.g., with 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/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.

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

Prenatal Testing and Preimplantation Genetic Testing

Fetus with high a priori risk. If the *SALL1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk is possible.

Although this testing can determine whether or not the fetus has inherited the *SALL1* pathogenic variant, it cannot predict which manifestations will be present or their severity, with the exception of the p.Arg276Ter pathogenic variant, which has caused a severe phenotype in all known instances. High-resolution ultrasound examination is therefore recommended to evaluate the fetus for phenotypic manifestations. In a study of families with the pathogenic variant p.Arg276Ter, a fetus at risk was found to have a complex heart defect, preaxial polydactyly, foot malformations, and preauricular tags, suggesting TBS as the diagnosis [Kohlhase et al 2003].

Fetus with low a priori risk. If a fetus at no known increased risk for TBS has what appear to be features of classic TBS detected as early as the 16th week of pregnancy by a combination of high-resolution ultrasound and 3D ultrasound examinations, molecular genetic testing of *SALL1* can confirm the diagnosis.

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

Preimplantation genetic testing may be an option for families in which the *SALL1* pathogenic variant has been identified.

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**
  Townes-Brocks Syndrome
- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)
  Fax: 202-337-8314
  Email: info@agbell.org
  Listening and Spoken Language Knowledge Center
- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org
- **Medline Plus**
  Imperforate anus
- **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. Townes-Brocks Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SALL1	16q12.1	Sal-like protein 1	SALL1 database	SALL1	SALL1

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 Townes-Brocks Syndrome (View All in OMIM)

107480	TOWNES-BROCKS SYNDROME 1; TBS1
602218	SAL-LIKE 1; SALL1

Gene structure. *SALL1* occupies about 14.1 kb (start codon to stop codon). It contains four exons (all coding, two alternate first exons) and two introns. The genomic sequence is NC_000016.10.

Benign variants. More than 29 different non-pathogenic polymorphisms are currently known [Böhm et al 2006].

Pathogenic variants. All reported and confirmed pathogenic variants are truncating and located in exon 2 and intron 2 of the gene [Kohlhase et al 1998, Kohlhase et al 1999, Marlin et al 1999, Blanck et al 2000, Engels et al 2000, Kohlhase 2000, Salerno et al 2000, Surka et al 2001, Devriendt et al 2002, Kohlhase et al 2003, Walter et al 2006, Reardon et al 2007, van den Akker et al 2009, Choi et al 2010, Hwang et al 2014].

Forty-six out of the 56 known *SALL1* pathogenic variants (2013 data) were located between the coding regions for the glutamine-rich domain mediating SALL protein interactions and 65 bp 3' of the coding region for the first double zinc finger domain, narrowing the *SALL1* mutational hot spot region to a stretch of 802 bp within exon 2.

Based on studies in mouse and chicken [Kiefer et al 2003, Sweetman et al 2003], it appears likely that the pathogenic variants escape nonsense-mediated messenger decay and therefore do not result in haploinsufficiency of the protein encoded by *SALL1*. However, three families in whom larger deletions partially or completely removing *SALL1* clearly result in TBS have been described [Borozdin et al 2006]. One family had a heterozygous deletion of all exons, one had deletion of the entire *SALL1* gene and several neighboring genes, and one had deletion of intron 2 and partial deletion of exons 2 and 3. These findings confirm that SALL1 haploinsufficiency can cause the phenotype, but it appears that the phenotype associated with larger deletions is at least milder than that of c.826C>T (though not milder than the phenotype associated with several other single-nucleotide variants).

Table 2. *SALL1* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.826C>T	p.Arg276Ter	NM_002968.2
c.3160C>T	p.Arg1054Ter	

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.

Normal gene product. *SALL1* encodes a C2H2 zinc finger protein of the SAL type, similar to the SAL protein encoded by the *Drosophila* gene *spalt*. It contains four double zinc finger domains characteristically distributed over the protein. There are also two single zinc fingers, a C2HC domain at the N terminus and a C2H2 finger attached to the second double zinc finger. *SALL1* is found strictly in the cell nucleus; it binds to heterochromatic foci and contains repressor domains at the N-terminus and in the central region [Netzer et al 2001, Netzer et al 2006]. Expression of *csal1* (the chick ortholog of *SALL1*) in the limb is activated by ectopic SHH. However, this activation requires signals from the apical ectodermal ridge and involves FGF4/8 as well as Wnt3a and Wnt7a [Farrell & Munsterberg 2000], showing that *csal1* expression is under control of at least three different pathways. In zebrafish, the *SALL1* homolog *sall1a* is regulated by *tbx5* and required for *fgf10* and *fgfr2* expression in the posterior pectoral fin bud [Harvey & Logan 2006]. In the mouse, Sall1 was found to enhance the canonical Wnt signaling pathway by localizing to pericentromeric heterochromatin [Sato et al 2004].

Abnormal gene product. All *SALL1* pathogenic variants (except for the larger deletions) detected in persons with TBS to date result in premature stop codons. Since transcripts with a premature stop codon are in most instances rapidly degraded, these pathogenic variants are a priori likely to cause TBS via SALL1 haploinsufficiency [Hentze & Kulozik 1999, Maquat 2004]. Proof for SALL1 haploinsufficiency being involved in the pathogenesis of human TBS came from the recent detection of a heterozygous 75-kb deletion of the entire *SALL1* coding region in a family with TBS [Borozdin et al 2006].

However, the *Sall1* knock-out mouse showed that loss of Sall1 function does not result in defects that affect tissues other than kidney [Nishinakamura et al 2001]. Introducing a TBS pathogenic variant in mouse *Sall1* instead leads to a TBS-like phenotype, and the detection of truncated Sall1 proteins points to a role of those proteins in the pathogenesis of TBS [Kiefer et al 2003]. In the zebrafish, *sall1a* loss of function leads to defective limb development, which can be aggravated by concomitant knock-down of *sall4* [Harvey & Logan 2006].

Comparison of the phenotypes associated with a *SALL1* deletion or with the severe p.Arg276Ter pathogenic variant indicate that the malformations in the family with the 75-kb deletion were relatively mild [Borozdin et al 2006]. It could therefore be that *SALL1* deletions (i.e., SALL1 haploinsufficiency) cause milder phenotypes than truncating pathogenic variants. This would require that mutated *SALL1* transcripts with premature stop codons escape the NMD pathway and lead to truncated proteins similar to those detected in mice. However, truncated SALL1 proteins have not been found in lymphoblastoid and amniotic fluid cells of persons with TBS [Kohlhase & Rauchman, unpublished data], possibly because tissues most strongly expressing *SALL1* in the adult (brain and kidney) have not been accessible for investigation.

Csal (chicken) and Sall (mouse) proteins can interact with each other via mediation of an N-terminal glutamine-rich domain conserved in all known Sal proteins. Expression of truncated Sall1/ csal1 proteins is detected throughout the cell and not confined to the nucleus as full-length Sall1. Truncated Sall1 can interact with full-length Sall proteins and cause their displacement from the nucleus [Kiefer et al 2003, Sweetman et al 2003].

Alleles resulting from *SALL1* pathogenic variants in the 5' region of exon 2 encode for truncated proteins with strong repressor activity but without the central repression and heterochromatin localization domain [Netzer et al 2006]. Despite their potential to act as strong transcriptional repressors, these proteins will probably not

localize to the physiologic site of action, but bind other SAL proteins and move them from the nucleus to the cytoplasm. Pathogenic variants further 3' in *SALL1* likely result in milder phenotypes than the 5' pathogenic variants [Blanck et al 2000, Botzenhart et al 2005]. If some of those pathogenic variants lead to truncated proteins including both repression domains and the heterochromatin localization domain, these proteins could still localize to their place of action and have some residual function, which could explain the milder phenotype.

The critical point in pathogenesis appears to be the correct dosage of functional SALL1 protein at the heterochromatic foci. A deletion of one allele results in a 50% reduction of this dosage. A 5' truncating pathogenic variant possibly leads to a truncated protein, which does not reach its site of action and in addition probably even removes some full-length protein of the normal allele from the nucleus. Therefore, in most instances the more severe phenotype of the 5' truncating pathogenic variants may result from a greater than 50% reduction of the functional protein at the site of action.

The additive phenotype of the combined *sall4* and *sall1a* knock-down in zebrafish suggests that both genes may be able to compensate to some extent for each other. In view of the additive effects of *sall1a* and *sall4* knock-down on limb development it remains unclear if the TBS phenotype in humans is only caused by loss of SALL1 function or also by an effect of the hypothetic truncated SALL1 proteins on the function of other SALL proteins.

As the interaction between truncated SALL1 and functional SALL1 or other SALL proteins and the relocalization of the functional proteins requires the presence of the evolutionarily conserved glutamine-rich region in the amino-terminal part of the truncated protein, the effect of the *SALL1* pathogenic variants c.419delC and c.313delA, which would result in truncated proteins lacking the interaction domain, still needs to be explained, since the phenotypes associated with these pathogenic variants did not appear milder than the phenotypes resulting from other pathogenic variants [Kohlhase et al 1999, Botzenhart et al 2007].

Interestingly, 47 (82.5%) of 57 smaller pathogenic variants (2013 data) cluster within the 802-bp refined "hot spot region" between the coding sequence for the glutamine-rich domain and the coding sequence for the first double zinc finger, whereas only two pathogenic variants were found within the remaining 763 bp upstream in the coding region, and only six within the 2.4-kb coding region to the 3' end. Therefore, the existence of truncated proteins in cells of persons with TBS would not be surprising. If it holds true that *SALL1* single-nucleotide pathogenic variants lead to truncated SALL1 proteins with dominant-negative action, one could expect that all truncated proteins have at least slightly different characteristics. This could explain the considerable phenotypic variability observed in TBS.

Chapter Notes

Author Notes

Dr Kohlhase's website: www.humangenetik-freiburg.de

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