

Townes-Brocks Syndrome

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Summary

Disease characteristics. Townes-Brocks syndrome (TBS) is characterized by the triad of imperforate anus (82%), dysplastic ears (88%) (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 (27%), including end-stage renal disease (ESRD) (42%), may occur with or without structural abnormalities (mild malrotation, ectopia, horseshoe kidney, renal hypoplasia, polycystic kidneys, vesicouteral reflux). [Congenital](#) heart disease occurs in 25%. Foot malformations (52%) (flat feet, overlapping toes) and genitourinary malformations (36%) are common. Mental retardation occurs in approximately 10% of cases. Rare features include iris coloboma, Duane anomaly, Arnold-Chiari malformation type 1, and growth retardation.

Diagnosis/testing. *SALL1* is the only [gene](#) known to be associated with TBS. The diagnosis of TBS is based on clinical findings; detection of a *SALL1* [mutation](#) confirms the diagnosis. Direct [sequencing](#) of the complete *SALL1* [coding region](#) and quantitative Real Time [PCR](#) analysis to identify intragenic and larger [deletions](#) are clinically available.

Management. *Treatment of manifestations:* immediate surgical intervention for imperforate anus; surgery for severe malformations of the hands; routine management of [congenital](#) heart defects; hemodialysis and possibly kidney transplantation for ESRD; early treatment of hearing loss. *Surveillance:* regular monitoring of renal function in individuals with and without renal anomalies, even if renal function is normal on initial examination.

Genetic counseling. TBS is inherited in an [autosomal dominant](#) manner. The proportion of cases caused by *de novo* [mutations](#) is estimated to be approximately

50%. Each child of an individual with TBS caused by a *SALL1* mutation has a 50% chance of inheriting the mutation. Prenatal diagnosis for pregnancies at increased risk is available on a clinical basis.

Diagnosis

Clinical Diagnosis

Townes-Brocks syndrome (TBS) is diagnosed clinically based on the presence of the following:

- Imperforate anus
- Dysplastic ears (overfolded superior helices, microtia)
- Typical thumb malformations (preaxial polydactyly, triphalangeal thumbs, hypoplastic thumbs) without shortening of the radius

In the two most recent studies [Botzenhart et al 2005 , Botzenhart et al 2007] of 61 persons with novel *SALL1* mutations [not including the most common mutation p.R276X (c.826C>T)], 84% had anal anomalies, 89% hand anomalies, and 87% ear anomalies. 67% had the characteristic triad.

In persons who show only two typical malformations, presence of additional anomalies commonly seen in TBS (for example renal malformations, hearing loss or heart defects) (see Clinical Description) can lead to the diagnosis.

Testing

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by at least one US CLIA-certified laboratory or a clinical laboratory outside the US. GeneTests does not independently verify information provided by laboratories and does not warrant any aspect of a laboratory's work. Listing in GeneTests does not imply that laboratories are in compliance with accreditation, licensure, or patent laws. Clinicians must communicate directly with the laboratories to verify information. —ED.

Gene. *SALL1* is the only gene associated with Townes-Brocks syndrome.

Clinical uses

- Confirmatory diagnostic testing
- Prenatal diagnosis

Clinical testing

- **Sequence analysis.** Direct sequencing of the complete *SALL1* coding region (exons 1 through 3) detected mutations in more than 100 of 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].

- **Deletion/duplication testing.** Quantitative RealTime PCR using amplicons within the *SALL1* introns and/or exons as well as within regions 5' and 3' of the transcription unit identified three different deletions in three patients: deletion of part of exon 2, intron 2 and exon 3; deletion of the entire *SALL1* coding region; and a larger deletion including several neighboring genes [Borozdin et al 2006].

Both techniques together identify a causative *SALL1* mutation or deletion in about 70% of persons with the classic triad of malformations as described by Kohlhase et al (1999).

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Townes-Brocks Syndrome

Test Methods	Mutations Detected	Mutation Detection Rate	Test Availability
Sequence analysis	<i>SALL1</i> sequence variants	≤70%	Clinical Testing
Deletion/duplication testing	Deletions of <i>SALL1</i> exons 1-3 or whole-gene deletions	<5%	

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click [here](#).

Genetically Related (Allelic) Disorders

No other distinct phenotypes are associated with *SALL1* mutations.

Clinical Description

Natural History

In addition to the clinical features described in the Diagnosis section, the clinical manifestations of Townes-Brocks Syndrome may include the following:

- **Eyes.** Microphthalmia (rare), iris coloboma, lamellar cataract, chorioretinal coloboma with loss of vision
- **Kidneys.** Renal agenesis, renal hypoplasia, polycystic kidneys; functional impairment with or without structural abnormalities (42% of cases) [Surka et al 2001 , Botzenhart et al 2005 , Botzenhart et al 2007]
- **Hearing.** Congenital sensorineural and/or conductive hearing loss ranging from mild to severe. Hearing loss that is mild may worsen with age (65% of cases).
- **Heart.** Congenital heart disease occurs in 50% of persons with the common p.R276X mutation [Kohlhase et al 2003] and 12%-25% of persons with other

SALL1 mutations [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].

- **Gastrointestinal.** Anal stenosis, chronic constipation, gastroesophageal reflux [Engels et al 2000]
- **Face.** Hemifacial microsomia [Kohlhase et al 1999 , Keegan et al 2001]
- **Lower extremities.** Club foot, overlapping toes (II and IV over III), syndactyly of toes, missing toes (III) (52% of cases) [Surka et al 2001 , Botzenhart et al 2005 , Botzenhart et al 2007]
- **Genitourinary.** Hypospadias, vaginal aplasia with bifid uterus, bifid scrotum, cryptorchidism (36% of cases) [Surka et al 2001 , Botzenhart et al 2005 , Botzenhart et al 2007]
- **Central nervous system**
 - Mental retardation (about 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
- **Skeletal.** Rib anomalies (fused ribs, missing ribs, additional cervical ribs), mild vertebral anomalies (9% of cases). Painful joints have been observed in several adults with TBS [Kohlhase, unpublished observations].
- **Endocrine.** Congenital hypothyroidism (rare)
- **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 mutation-positive individuals is not known.

Genotype-Phenotype Correlations

No [genotype-phenotype correlations](#) have been made for the majority of [mutations](#), most of which are private.

The most common [mutation](#) and the only [mutation](#) found in more than two families is c.826C>T (p.276X) detected in about half of [simplex cases](#) with TBS (i.e., a single occurrence in a family) and only one [familial](#) case to date [Kohlhase et al 2003]. This [mutation](#) is associated with a higher rate (50%) and higher severity of [congenital](#) heart defects than other [mutations](#). Fifteen of 16 [heterozygotes](#) for the [mutation](#) showed the characteristic triad of anal, thumb, and ear malformations (94%), indicating that the [mutation](#) is associated with a more severe [phenotype](#).

In general, [mutations](#) within the [hotspot](#) region that is more 5' in [exon 2](#) seem to be associated with a more severe outcome than [mutations](#) further 3' in [exon 2](#). In addition, the [phenotype](#) associated with [deletions](#) of *SALL1* seems to be milder than that associated with [mutations](#) in the [hotspot](#) region, but only three families with [deletions](#) have been reported to date [[Borozdin et al 2006](#)].

Penetrance

[Penetrance](#) seems 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 and Brocks \(1972\)](#) were 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 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. Martinez-Frias estimated the prevalence as 1:250,000 but did not use stringent diagnostic criteria for TBS [[Martinez-Frias et al 1999](#)].

Differential Diagnosis

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

No other distinct [phenotypes](#) are associated with *SALL1* [mutations](#), but the clinical presentation of Townes-Brocks syndrome (TBS) can overlap with Goldenhar syndrome (hemifacial microsomia) [[Gabrielli et al 1993](#) , [Keegan et al 2001](#) , [Kohlhase et al 1999](#)], Okihiro syndrome (but without malformations of the radius) [[Borozdin et al 2004](#)], and branchiootorenal syndrome [[Engels et al 2000](#) , [Albrecht et al 2004](#)]. Furthermore, TBS overlaps with VACTERL association.

Goldenhar syndrome. The majority of individuals with oculo-auriculo-vertebral spectrum [phenotypes](#) do not have upper limb or anal malformations. On the other hand, some persons with *SALL1* [mutations](#) 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* [mutation](#), it may occur in individuals with a *SALL1* [mutation](#) in addition to more typical TBS malformations.

Okhiro syndrome (Duane-radial ray syndrome). This 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, complete overlap exists between Okhiro syndrome and TBS [[Kohlhase et al 2002](#) , [Borozdin et al 2004](#)]. In those individuals, [SALL1](#) and [SALL4 molecular genetic testing](#) should be considered. Duane anomaly can also occur with a [SALL1 mutation](#) [[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 mutation](#) [Kohlhase, unpublished data], their presence points toward a [SALL4 mutation](#), even if all other features suggest TBS.

[Branchiootorenal \(BOR\) syndrome](#) . In two families eventually determined to have [SALL1 mutations](#), 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. The VACTERL association 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 [SALL1 mutations](#) [Kohlhase, unpublished data]. Sib and offspring [recurrence risks](#) for VACTERL association are estimated to be approximately 1%. A recent review summarizes current information on VACTERL association [[Shaw-Smith 2006](#)].

Testing strategy for individuals with typical thumb, anal, and ear malformations

- Perform cardiac evaluation, ophthalmologic examination, and renal ultrasound examination in addition to a routine physical examination.
- Check for renal impairment by routine laboratory tests even if the kidneys appear normal on ultrasound.
- Perform hand/ forearm X-ray investigations to evaluate for involvement of the radius.
- If at least two out of three classic major TBS features (anal, ear, and typical thumb malformations) are found, [SALL1 molecular genetic testing](#) is suggested as the first step. Presence of additional minor features (i.e., those commonly observed in TBS) increases the likelihood of finding a [SALL1 mutation](#). Atypical features (i.e., not yet reported to occur with [SALL1](#) mutations) may decrease the [SALL1 mutation](#) detection rate, but currently it does not seem possible to tell which atypical features are true negative predictors of a [SALL1 mutation](#) except for concomitant involvement of the radius.
- [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.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Townes-Brocks syndrome (TBS):

- **Heart.** Baseline evaluation by a cardiologist including an echocardiogram
- **Kidneys.** Renal ultrasound examination and routine laboratory tests for renal function
- **Hearing.** Hearing evaluation as soon as the diagnosis of TBS is suspected (See [Deafness and Hereditary Hearing Loss Overview](#))

Treatment of Manifestations

- **Imperforate anus.** Immediate surgical intervention is required.
- **Thumb malformations.** Severe malformations of the hands may require surgery, e.g., removal of additional thumbs.
- **Heart defects.** Severe [congenital](#) heart defects may require surgery if functionally relevant.
- **Renal.** Function impairment requires continuous monitoring, hemodialysis, and possibly kidney transplantation.
- **Hearing loss.** Significant impairment requires early treatment, mostly with hearing aids (See [Deafness and Hereditary Hearing Loss Overview](#)).

Surveillance

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.

Testing of Relatives at Risk

See [Genetic Counseling](#) for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search [ClinicalTrials.gov](#) 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, 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](#). —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 Townes-Brocks syndrome resulting from a [SALL1 mutation](#) have an [affected](#) parent and about 50% of individuals with Townes-Brocks syndrome have the disorder as the result of a *de novo* [mutation](#) [Kohlhase, unpublished observation].
- *De novo mutations* in [SALL1](#) mostly occur in about 87.5% on the paternally derived [chromosome 16](#) without an obvious age effect [Bohm et al 2006].
- If a [SALL1 disease-causing mutation](#) cannot be detected in the [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](#). Three cases of [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 mutation](#) include 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. Clinical signs in parents with [somatic mosaicism](#) for a [mutation](#) may be as mild as toes II and IV overlapping the third toe [Devriendt et al 2002].

Note: Although about 50% of individuals diagnosed with Townes-Brocks syndrome 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 upon the genetic status of the proband's parents.
- If a parent of the [proband](#) is [affected](#), 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%-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 [mutation](#).

Other family members of a [proband](#). The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be [affected](#), 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](#) or maternity (i.e., 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 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 DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Fetus with high a priori risk. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation if the disease-causing mutation has been identified in an affected family member.

Although this testing can determine whether or not the fetus has inherited the SALL1 disease-causing mutation, it cannot predict which manifestations will be present or their severity, with the exception of the p.R276X (c.826C>T) mutation, 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 mutation p.R276X, 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].

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

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 be performed to confirm the diagnosis.

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 may differ from that in the text; tables may contain more recent information. —ED.

Molecular Genetics of Townes-Brocks Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
SALL1	16q12.1	Sal-like protein 1

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.

OMIM Entries for Townes-Brocks Syndrome

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

Genomic Databases for Townes-Brocks Syndrome

Gene Symbol	Entrez Gene	HGMD	GeneCards	GDB	GenAtlas
<i>SALL1</i>	602218	SALL1	<i>SALL1</i>	4216161	<i>SALL1</i>

For a description of the genomic databases listed, click [here](#).

Normal allelic variants: The *SALL1* gene occupies about 14.1 kb (start codon to stop codon). It contains three exons (all coding) and two introns. The genomic sequence is available at www.ncbi.nlm.nih.gov (accession number NC_000016.8); 29 different non-pathogenic polymorphisms are currently known [Bohm et al 2006].

Pathologic allelic variants: All reported and confirmed mutations are truncating and positioned 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]. Forty-six out of the 56 known *SALL1* mutations are 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 hotspot region to a stretch of 802 bp within exon 2.

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

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, 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 orthologue 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* homologue *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* mutations (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 mutations 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 gene 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 affecting tissues other than the kidneys [Nishinakamura et al 2001]. Introducing a TBS mutation in the mouse *Sall1* gene 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 [McLeskey 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.R276X mutation indicate that the malformations in the family with the 75-kb deletion seemed rather mild [Borozdin et al 2006]. It could therefore be that *SALL1* deletions (i.e., *SALL1* haploinsufficiency) cause milder phenotypes than truncating mutations. 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 the mice with a TBS mutation. However, truncated *SALL1* proteins have not been found in lymphoblastoid and amniotic fluid cells of persons with TBS [Kohlhase and 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 [McLeskey Kiefer et al 2003, Sweetman et al 2003].

Alleles resulting from *SALL1* mutations 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. Mutations further 3' in the *SALL1* gene likely result in milder phenotypes than the 5' mutations [Blanck et al 2000, Botzenhart et al 2005]. If some of those mutations 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 might explain the milder phenotype.

The critical point in the pathogenesis seems 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 [mutation](#) 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 [mutations](#) might result from a reduction of the functional [protein](#) at the site of action by more than 50%.

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 hypothetical 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 evolutionary conserved glutamine-rich region in the aminoterminal part of the truncated [protein](#), the effect of the TBS-causing *SALL1* [mutations](#) 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 [mutations](#) did not appear milder than the [phenotypes](#) resulting from other [mutations](#) [Kohlhase et al 1999 , Botzenhart et al 2007].

Interestingly, 47 out of 57 (82.5%) smaller [mutations](#) cluster within the 802 bp-large refined "hot spot region" between the coding sequence for the glutamine-rich [domain](#) and around the coding sequence for the first double zinc finger, whereas only two [mutations](#) 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* [point mutations](#) lead to truncated SALL1 [proteins](#) with dominant-negative action, one could expect that all truncated [proteins](#) have at least slightly different characteristics. This might explain the considerable [phenotypic](#) variability observed in TBS.

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. -ED.

- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
3417 Volta Place NW
Washington DC 20007
Phone: 866-337-5220; 202-337-5220; 202-337-5221 (TTY)
Fax: 202-337-8314
Email: info@agbell.org
www.agbell.org
- **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

- **Congenital Heart Information Network**

600 North 3rd Street First Floor
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- **Medline Plus**

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- **National Association of the Deaf**

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Phone: 301-587-1788 (voice); 301-587-1789 (TTY)

Fax: 301-587-1791

Email: NADinfo@nad.org

www.nad.org

- **National Eye Institute**

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References

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Published Statements and Policies Regarding Genetic Testing

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

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