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NLM Citation: Graziano C, Olivucci G. *SALL1*-Related Townes-Brocks Syndrome. 2007 Jan 24 [Updated 2024 Aug 8]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

SALL1-Related Townes-Brocks Syndrome

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Created: January 24, 2007; Updated: August 8, 2024.

Summary

Clinical characteristics

SALL1-related Townes-Brocks syndrome (*SALL1*-TBS) is characterized by the triad of imperforate anus or anal stenosis, dysplastic ears (overfolded superior helices and preauricular tags; frequently associated with sensorineural and/or conductive hearing impairment), and thumb malformations (duplication of the thumb [preaxial polydactyly], triphalangeal thumbs, and, rarely, hypoplasia of the thumbs) without hypoplasia of the radius. Impaired kidney function, including end-stage kidney disease (ESKD), may occur with or without structural abnormalities (mild malrotation, ectopia, horseshoe kidney, renal hypoplasia, polycystic kidneys, vesicoureteral reflux). Foot malformations (flat feet, overlapping toes) and genitourinary malformations are common. Congenital heart disease occurs in 15% of affected individuals. Developmental delay and/or learning difficulties occur in approximately 15% of affected individuals. Rare features include growth deficiency, Duane anomaly, iris coloboma, and Chiari I malformation.

Diagnosis/testing

The diagnosis of *SALL1*-TBS is established in a proband with characteristic clinical findings and a heterozygous pathogenic variant in *SALL1* identified by molecular genetic testing.

Management

Treatment of manifestations: Immediate surgical intervention for imperforate anus; stool softeners, prokinetics, osmotic agents, or laxatives as needed for constipation; standard treatment of gastroesophageal reflux; early treatment of hearing loss; surgery for severe malformations of the hands; hemodialysis and possibly kidney transplantation for ESKD; management of genitourinary anomalies per urologist or gynecologist; surgery or medical treatment by cardiologist for congenital heart defects; developmental and educational support as needed; neuropsychiatric management as needed for behavioral issues; growth hormone therapy for those with growth hormone deficiency; management of ocular issues per ophthalmologist.

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Surveillance: Assess for constipation and assess growth and thyroid function at each visit; annual audiology evaluation; monitor kidney function annually in individuals with and without kidney anomalies, even if kidney function is normal on initial examination; monitor developmental progress, educational needs, and behavioral assessment annually; ophthalmology examination per ophthalmologist.

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

Evaluation of relatives at risk: Clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an individual with *SALL1*-TBS in order to identify as early as possible those who would benefit from clinical evaluation and prompt initiation of treatment for kidney disease and other features of *SALL1*-TBS.

Pregnancy management: Consider prenatal cardiac and nephrology evaluations in pregnant women with *SALL1*-TBS.

Genetic counseling

SALL1-TBS is inherited in an autosomal dominant manner. About 50% of individuals diagnosed with *SALL1*-TBS have the disorder as the result of a *de novo* pathogenic variant. Each child of an individual with *SALL1*-TBS has a 50% chance of inheriting the pathogenic variant. Once the *SALL1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

SALL1-related Townes-Brocks syndrome (*SALL1*-TBS) **should be suspected** in individuals with the following major and minor clinical features and family history.

Major features

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

Minor features

- Sensorineural and/or conductive hearing impairment
- Foot malformations
- Impaired kidney function with or without kidney malformations
- Genitourinary malformations
- Congenital heart disease

Family history is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *SALL1*-TBS is **established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *SALL1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview*

is understood to include likely pathogenic variants. (2) Identification of a heterozygous *SALL1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of *SALL1*-TBS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *SALL1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.
- **A multigene panel** that includes *SALL1*, *SALL4*, and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) Individuals with clinical features of TBS have been found to have pathogenic variants in *SALL4* [Kohlhase et al 2002, Borozdin et al 2004]. 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, **Duane-radial ray syndrome** and *SALL4*-Related Disorders). (2) Due to the existence of a highly homologous *SALL1* pseudogene (*SALL1P1*), capture-based gene panels may not be able to distinguish between *SALL1* pathogenic variants and variants within the pseudogene. (3) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (4) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (5) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (6) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

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

Option 2

When the diagnosis of *SALL1*-TBS has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. Note: A highly homologous *SALL1* pseudogene (*SALL1P1*) may complicate interpretation of exome sequencing results.

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 *SALL1*-Related Townes-Brocks Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
SALL1	Sequence analysis [3]	>90% [4]
	Gene-targeted deletion/duplication analysis [5]	<10% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

SALL1-related Townes-Brocks syndrome (*SALL1*-TBS) is characterized by the triad of imperforate anus or anal stenosis, dysplastic ears (frequently associated with hearing impairment), and thumb malformations without hypoplasia of the radius. Impairment of kidney function may occur with or without structural abnormalities. Foot malformations, genitourinary malformations, and congenital heart disease are common. Of 165 affected individuals from 101 families with a *SALL1* pathogenic variant, approximately 80% had the three major features or two major plus minor features, whereas 20% had a partial clinical expression [Kohlhase et al 1998, Kohlhase et al 1999, Marlin et al 1999, Kohlhase et al 2003, Borozdin et al 2006, Botzenhart et al 2007, and 30 additional reports]. The following description of the phenotypic features associated with this condition is based on these reports. Some features may be underestimated due to later onset (e.g., impaired kidney function) or incomplete physical examination.

Table 2. *SALL1*-Related Townes-Brocks Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Imperforate anus or anal stenosis	70%	
Dysplastic ears	87%	
Thumb malformations	76%	Without hypoplasia of the radius
Sensorineural &/or conductive hearing impairment	62%	
Foot malformations	43%	
Kidney anomalies &/or impaired kidney function	40%	
Genitourinary malformations	22%	
Congenital heart disease	15%	
Developmental delay / learning difficulties	15%	

Based on 165 affected individuals from 101 families with a confirmed *SALL1* pathogenic variant

Gastrointestinal manifestations include imperforate anus, anal stenosis, anteriorly placed anus, chronic constipation, and gastroesophageal reflux [Engels et al 2000].

Ear anomalies and hearing loss. Dysplastic ears are common, including overfolded superior helices, preauricular tags, and microtia. Congenital sensorineural and/or conductive hearing loss ranges from mild to severe. Hearing loss that is mild can worsen with age [Yan et al 2024].

Thumb malformations include preaxial polydactyly, triphalangeal thumbs, and, rarely, hypoplastic thumbs without hypoplasia of the radius.

Lower extremity findings include flat feet, clubfoot, overlapping toes (second and fourth toes overlapping third toe), syndactyly of the toes, and missing toes (typically third toe) [Surka et al 2001].

Kidney manifestations include mild malrotation, ectopia, or horseshoe kidney, renal agenesis, renal hypoplasia, polycystic kidneys, and vesicoureteral reflux. Functional impairment with or without structural abnormalities is also frequent [Botzenhart et al 2007, Stein et al 2024].

Genitourinary manifestations include hypospadias, vaginal aplasia with bifid uterus, bifid scrotum, and cryptorchidism [Botzenhart et al 2005, Botzenhart et al 2007].

Congenital heart disease is reported in 50% of persons with the common p.Arg276Ter pathogenic variant [Kohlhase et al 2003] and approximately 15% of all persons with *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.

Developmental delay and learning difficulties are reported in approximately 15% of individuals, but adults do not usually have intellectual disability. If they do, it is mild.

Behavioral problems are observed in some children with *SALL1*-TBS, especially attention-deficit/hyperactivity disorder.

Postnatal growth deficiency. 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 deficiency among individuals with a confirmed *SALL1* pathogenic variant is not known. Growth hormone deficiency was reported in one individual with TBS [Lawrence et al 2013], suggesting this may be the cause for growth deficiency in other individuals with TBS. Growth deficiency may be secondary to chronic kidney insufficiency in some children with *SALL1*-TBS.

Other skeletal manifestations include rib anomalies (fused ribs, missing ribs, additional cervical ribs) and mild vertebral anomalies reported in 9% of individuals. Painful joints have been observed in several adults with *SALL1*-TBS [J Kohlhase, unpublished observations].

Ocular manifestations include Duane anomaly, iris coloboma, lamellar cataract, chorioretinal coloboma with loss of vision, and, rarely, microphthalmia [Valikodath et al 2020].

Central nervous system manifestations in individuals with *SALL1*-TBS include Chiari I malformation [J Kohlhase, unpublished observations], cranial nerve palsy (cranial nerves VI and VII), and hypoplasia of the dorsal part of the corpus callosum.

Hemifacial microsomia has been reported [Kohlhase et al 1999, Keegan et al 2001].

Congenital hypothyroidism is a rare feature of *SALL1*-TBS [Lawrence et al 2013, Yan et al 2024]. Note: Almost 5% of individuals with a rare disorder have been reported to have more than one molecular diagnosis [Posey et al 2017]. It is possible that rare features associated with *SALL1*-TBS may have an independent molecular cause.

Genotype-Phenotype Correlations

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

The most common pathogenic variant, c.826C>T (p.Arg276Ter), is associated with greater frequency (50%) and severity of congenital heart defects than other *SALL1* 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 toward the 5' end in exon 2 appear to be associated with a more severe outcome than pathogenic variants towards the 3' end 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, based on a limited number of individuals (nine individuals from five distinct families) with large deletions involving only *SALL1* [Borozdin et al 2006, Miller et al 2012, Stevens & May 2016, Innoceta et al 2023].

Penetrance

Penetrance is likely 100%, if individuals at the mild end of the phenotypic spectrum are included. Note: One *SALL1* variant, p.Arg1054Ter, was associated with a severe phenotype when present in homozygosity. Eleven individuals heterozygous for p.Arg1054Ter had no features of *SALL1*-TBS, but this variant was found to preserve some degree of SALL1 function.

Nomenclature

Townes-Brocks syndrome was previously referred to as REAR syndrome (for *r*enal, *e*ar, *a*nal, and *r*adial malformations) [Kurnit et al 1978].

Prevalence

Approximately 200 individuals with *SALL1*-TBS are reported in the medical literature. The population prevalence is not known. The prevalence of pathogenic *SALL1* variants was 1:1,592 among a large cohort of individuals with monogenic kidney disease [Stein et al 2024], and 1:2,952 among individuals with hearing loss [Yan et al 2024].

Genetically Related (Allelic) Disorders

An individual with homozygous p.Arg1054Ter *SALL1* nonsense variants was reported to have 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

Table 3. Genes of Interest in the Differential Diagnosis of *SALL1*-Related Townes-Brocks Syndrome

Gene(s)	Disorder	MOI	Features of Disorder	Comment / Distinguishing Features
CCNQ	STAR syndrome (OMIM 300707)	XL	• Toe syndactyly, telecanthus, anogenital & renal malformations similar to TBS • Likely lethal in males	Facial features & toe syndactyly distinguish STAR syndrome from *SALL1*-TBS.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	Comment / Distinguishing Features
DACT1	Townes-Brocks syndrome 2 (TBS2) (OMIM 617466)	AD	*DACT1* pathogenic variants have been identified in families w/incompletely penetrant AD CAKUT. [1] In 1 family w/ loss-of-function *DACT1* pathogenic variant, affected persons had CAKUT, anal, &/or external ear anomalies, leading to the designation TBS2. [2]	Thumb anomalies have not been reported.
EYA1 *SIX1* *SIX5*	Branchiootorenal (BOR) syndrome (See Branchiootorenal Spectrum Disorder.)	AD	Ear malformations assoc w/hearing impairment, branchial fistulae & cysts, & renal malformations	• In 2 families later determined to have *SALL1*-TBS, the presence of dysplastic ears & renal malformations / impaired kidney function initially led to consideration of BOR syndrome. • Note: No affected family members had the typical *SALL1*-TBS triad of thumb, anal, & ear malformations. [3]
SALL4	Duane-radial ray syndrome (DRRS, Okihiro syndrome) (See *SALL4*-Related Disorders.)	AD	• Duane anomaly & radial ray defects • Less commonly, hearing loss & renal position anomalies	• In persons w/features suggestive of *SALL1*-TBS, both *SALL1* & *SALL4* molecular genetic testing should be considered. *SALL4* pathogenic variants have been identified in a few persons w/ clinical features suggestive of *SALL1*-TBS. [4] • Molecular genetic testing of *SALL4* rather than *SALL1* is suggested as the first molecular test if the radius is involved &/or if Duane anomaly is present (Duane anomaly is an atypical finding in *SALL1*-TBS; radial hypoplasia/aplasia & thumb aplasia have not been observed in *SALL1*-TBS).
SF3B2	*SF3B2*-related hemifacial microsomia (Goldenhar syndrome, oculo-auriculo-vertebral spectrum) (OMIM 164210)	AD	*SF3B2* pathogenic variants are identified in ~3% of persons representing simplex cases (i.e., the only person w/hemifacial microsomia in a family) & ~25% of individuals w/ positive family history. [5]	The majority of persons w/hemifacial microsomia do not have upper-limb or anal malformations. However, some persons w/ *SALL1* pathogenic variants have hemifacial microsomia. Therefore, while isolated hemifacial microsomia is not suggestive of *SALL1*-TBS, hemifacial microsomia may be present w/other typical findings of *SALL1*-TBS.
FREM1	Bifid nose w/ or w/o anorectal & renal anomalies (BNAR) (See *FREM1* Autosomal Recessive Disorders.)	AR	Bifid or wide nasal tip, anorectal anomalies, & renal malformations	Facial features & absence of thumb anomalies distinguish BNAR from *SALL1*-TBS.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	Comment / Distinguishing Features
TBX5	Holt-Oram syndrome (HOS)	AD	• Upper-limb defects involving carpal bone(s) &, variably, radial &/or thenar bones • Congenital heart malformation • Thumb anomalies can resemble those in *SALL1*-TBS.	External ear & anal anomalies are not typical in HOS.

AD = autosomal dominant; CAKUT = congenital anomalies of kidney and urinary tract; MOI = mode of inheritance; TBS = Townes-Brocks Syndrome; XL = X-linked

1. Christians et al [2023]
2. Webb et al [2017]
3. Engels et al [2000], Albrecht et al [2004]
4. J Kohlhase, personal observations
5. Unger et al [2023]

VACTERL association (OMIM 192350) – a disorder of unknown genetic cause – comprises *v*ertebral defects, *a*nal atresia, *c*ardiac defects, *t*racheo*e*sophageal fistula, *r*enal malformations, and *l*imb defects. VACTERL association is therefore an important differential diagnosis for simplex cases (i.e., a single affected individual in a family) with suspected Townes-Brocks syndrome. To date, severe vertebral defects and tracheoesophageal fistula have not been observed in persons with a *SALL1* pathogenic variant. Sib and offspring recurrence risks for VACTERL association are estimated at approximately 1%.

Management

No clinical practice guidelines for *SALL1*-related Townes-Brocks syndrome (*SALL1*-TBS) have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *SALL1*-TBS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *SALL1*-Related Townes-Brocks Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Gastrointestinal	• Referral to surgeon for anal anomalies if present • Assessment for constipation &/or gastroesophageal reflux	
Hearing	Hearing eval (See Genetic Hearing Loss Overview.)	
Musculoskeletal	• Clinical assessment for upper- & lower-extremity anomalies • Radiographs as recommended by orthopedist	Referral to orthopedist as needed
Kidney	• Renal ultrasound • Assessment of kidney function w/serum electrolyte concentrations, BUN, & creatinine	
Genitourinary anomalies	Referral to urologist/gynecologist as needed	
Cardiac	Eval by cardiologist w/echocardiogram	

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Neurodevelopment	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns
Endocrine	Assessment for growth deficiency	Referral to endocrinologist as needed
Eyes	Complete eye exam by ophthalmologist to evaluate for ocular features of *SALL1*-TBS & atypical finding of Duane anomaly	
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *SALL1*-TBS to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

BUN = blood urea nitrogen; MOI = mode of inheritance; *SALL1*-TBS = *SALL1*-related Townes-Brocks syndrome
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. *SALL1*-Related Townes-Brocks Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Imperforate anus	Immediate surgical intervention is required.	
Constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	
Gastroesophageal reflux	Treatment per gastroenterologist	
Hearing loss	Significant impairment requires early treatment, typically w/hearing aids (see Genetic Hearing Loss Overview).	
Thumb malformations / Other musculoskeletal manifestations	• Mgmt per orthopedist • Severe malformations of hands may require surgery (e.g., removal of additional thumbs).	
Kidney	Mgmt per nephrologist &/or urologist	Impaired kidney function requires continuous monitoring, hemodialysis, & possibly kidney transplantation.
Genitourinary anomalies	Mgmt per urologist/gynecologist	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Heart defects	Congenital heart defects may require surgery or medical treatment by cardiologist.	
Neurodevelopment/ Neuropsychiatric	• Developmental & education support as needed • Neuropsychiatric referral & mgmt as needed for behavioral issues	
Endocrine	Growth hormone therapy for those w/growth hormone deficiency	
Eyes	Mgmt per ophthalmologist	

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *SALL1*-Related Townes-Brocks Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Gastrointestinal	Assessment for constipation	At each visit
Hearing	Audiology eval	Annually
Kidney	Assessment of kidney function w/serum electrolyte concentrations, BUN, & creatinine	Monitor annually in all persons w/ & w/o kidney anomalies, even if no impairment of kidney function is detected on initial exam.
Neurodevelopment	• Monitor developmental progress & educational needs. • Behavioral assessment	Annually
Endocrine	Assessment of growth & thyroid function	At each visit
Eyes	Ophthalmology exam	Per ophthalmologist

BUN = blood urea nitrogen

Agents/Circumstances to Avoid

Medications that cause renal or otic toxicity should be avoided.

Evaluation of Relatives at Risk

Molecular genetic testing for the *SALL1* pathogenic variant identified in the proband is appropriate for apparently asymptomatic older and younger at-risk relatives of an individual with *SALL1*-TBS in order to identify as early as possible those who would benefit from clinical evaluation and prompt initiation of treatment for kidney disease and other features of *SALL1*-TBS.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Consider prenatal cardiac evaluation in pregnant women with *SALL1*-TBS. Impairment of kidney function can progress significantly during pregnancy and warrants a nephrology evaluation.

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

SALL1-related Townes-Brocks syndrome (*SALL1*-TBS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- About 50% of individuals diagnosed with *SALL1*-TBS have an affected family member(s) [C Graziano & G Olivucci, unpublished observations].
- About 50% of individuals diagnosed with *SALL1*-TBS have the disorder as the result of a *de novo* pathogenic variant. *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 proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism.* Four individuals with somatic and gonadal mosaicism have been reported [Kohlhase et al 1999, Blanck et al 2000, Devriendt et al 2002, van den Akker et al 2009]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present only in the germ (gonadal) cells only.

      * A parent with somatic and gonadal mosaicism may be mildly/minimally affected. Clinical signs in parents with somatic mosaicism for a *SALL1* pathogenic variant may be as mild as second and fourth toes overlapping the third toe [Devriendt et al 2002]. In a family with two affected sibs, a mother with presumed somatic and gonadal mosaicism (the *SALL1* pathogenic variant identified in the affected sibs was not identified in maternal leukocyte DNA) was reported to have isolated anteriorly placed anus [Blanck et al 2000].
- The family history of some individuals diagnosed with *SALL1*-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 molecular genetic testing has demonstrated that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Although the penetrance of *SALL1*-TBS appears to be complete in heterozygous individuals, clinical expressivity can be highly variable. 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 in a heterozygous sib or the severity of manifestations.
- If the parents have not been tested for the *SALL1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for *SALL1*-TBS because of the possibility of parental gonadal mosaicism.

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

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected and/or is known to have the *SALL1* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

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

Family planning

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

Prenatal Testing and Preimplantation Genetic Testing

Once the *SALL1* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. Although this testing can determine if the fetus has inherited a familial *SALL1* pathogenic variant, it cannot predict which manifestations will be present or the severity of manifestations, with the exception of the p.Arg276Ter pathogenic variant, which has caused a severe phenotype in all known instances. In a fetus found to have a *SALL1* pathogenic variant, high-resolution ultrasound examination can be used to evaluate phenotypic manifestations (e.g., complex heart defects, preaxial polydactyly, foot malformations, and preauricular tags) [Kohlhase et al 2003].

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

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  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. SALL1-Related 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 SALL1-Related Townes-Brocks Syndrome (View All in OMIM)

107480	TOWNES-BROCKS SYNDROME 1; TBS1

Table B. continued from previous page.

602218	SAL-LIKE 1; SALL1

Molecular Pathogenesis

SALL1 encodes Sal-like protein 1 (SALL1), a C2H2 zinc finger protein of the SAL type. 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].

Most *SALL1* pathogenic variants are truncating and located in exon 2 or intron 2. However, a few families in whom larger deletions partially or completely removing *SALL1* clearly result in Townes-Brocks syndrome (TBS) have been described [Borozdin et al 2006, Miller et al 2012, Innoceta et al 2023]. It remains unclear if TBS is only caused by loss of SALL1 function or also by a dominant-negative effect of truncated SALL1 proteins on the function of other SAL proteins. The recurrent p.Arg276Ter pathogenic variant was reported to escape nonsense-mediated decay and causes a severe phenotype, suggesting a dominant-negative mechanism that may be common to other *SALL1* variants [Kiefer et al 2003].

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 localize to the physiologic site of action but binds other SAL proteins and moves them from the nucleus to the cytoplasm. 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. Furthermore, truncated SALL1 might impede the function of primary cilia, since primary fibroblasts derived from *SALL1*-TBS exhibit a higher rate of ciliogenesis, abnormally elongated cilia, and aberrant cilia disassembly [Bozal-Basterra et al 2018].

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.

Mechanism of disease causation. Loss of function and possible dominant-negative effect of some truncating variants

***SALL1*-specific laboratory technical considerations.** Due to the existence of a highly homologous *SALL1* pseudogene (*SALL1P1*), capture-based gene panels may not be able to distinguish between *SALL1* pathogenic variants and variants within the pseudogene.

Table 7. Notable *SALL1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_002968.3 NP_002959.2	c.826C>T	p.Arg276Ter	See Genotype-Phenotype Correlations.
	c.3160C>T	p.Arg1054Ter	See Genetically Related Disorders.

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

Chapter Notes

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Revision History

- 8 August 2024 (sw) Comprehensive update posted live
- 14 January 2016 (me) Comprehensive update posted live
- 3 May 2012 (me) Comprehensive update posted live
- 24 January 2007 (me) Review posted live
- 17 November 2006 (jk) Original submission

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