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Simpson-Golabi-Behmel Syndrome Type 1

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Summary

Clinical characteristics

Simpson-Golabi-Behmel syndrome type 1 (SGBS1) is characterized by pre- and postnatal macrosomia; distinctive craniofacial features (including macrocephaly, coarse facial features, macrostomia, macroglossia, and palate abnormalities); and, commonly, mild-to-severe intellectual disability with or without structural brain anomalies. Other variable findings include supernumerary nipples, diastasis recti / umbilical hernia, congenital heart defects, diaphragmatic hernia, genitourinary defects, and gastrointestinal issues. Skeletal anomalies can include vertebral fusion, scoliosis, rib anomalies, and congenital hip dislocation. Hand anomalies can include large hands and postaxial polydactyly. Affected individuals are at increased risk for embryonal tumors including Wilms tumor, hepatoblastoma, adrenal neuroblastoma, gonadoblastoma, hepatocellular carcinoma, and medulloblastoma.

Diagnosis/testing

The diagnosis of SGBS1 is established in a male proband with suggestive findings and/or a hemizygous pathogenic variant in *GPC3* or an intragenic or whole-gene deletion of *GPC3* identified by molecular genetic testing. The diagnosis is usually established in a female proband with suggestive findings and a heterozygous pathogenic variant in *GPC3* or an intragenic or whole-gene deletion of *GPC3* identified by molecular genetic testing.

Management

Treatment of manifestations: Prompt treatment of neonatal hypoglycemia and airway obstruction resulting from micrognathia and glossoptosis. Treatment of cleft lip and/or cleft palate or macroglossia and related feeding difficulties, obstructive sleep apnea, ophthalmologic issues, hearing loss, heart defects, urogenital abnormalities, skeletal abnormalities, seizures, Wilms tumor, and other types of tumors per standard recommendations by

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appropriate pediatric specialists. Speech therapy as needed. Neurodevelopmental assessment to determine the need for special education, occupational therapy, and/or physical therapy.

Surveillance: Screening for Wilms tumor and hepatoblastoma with abdominal ultrasound and serum AFP level every three months from time of diagnosis until age four years; renal ultrasound every three months until age seven years; no specific tumor screening protocol has been established for neuroblastoma, gonadoblastoma, or medulloblastoma, but follow up with a cancer predisposition specialist every six months is recommended. Annual (or as indicated) ophthalmologic and audiologic evaluations in childhood; sleep study if there are concerns about sleep dysregulation including sleep apnea; routine monitoring of kidney function if renal anomalies are present; evaluation for scoliosis at least annually or during periods of rapid growth; monitoring of serum glucose level in the neonatal period; monitoring of developmental progress at each visit through adolescence.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing of the *GPC3* pathogenic variant in the family in order to identify as early as possible those who would benefit from preventive measures such as tumor surveillance.

Pregnancy management: Gestational hypertension, diabetes, preeclampsia, fetal distress, and preterm labor have all been reported in mothers of individuals with SGBS1. Fetal macrocephaly and overgrowth may necessitate cesarean delivery or early induction of labor.

Genetic counseling

SGBS1 is inherited in an X-linked manner. If the mother of the proband has a pathogenic variant, the chance of transmitting the pathogenic variant in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected. Females who inherit the pathogenic variant will be carriers, although due to X-chromosome inactivation, carrier females may have manifestations of SGBS1. Males with SGBS1 will pass the pathogenic variant to all their daughters and none of their sons. Carrier testing for at-risk relatives and prenatal testing for a pregnancy at increased risk are possible for families in which the pathogenic variant has been identified.

Diagnosis

For the purposes of this *GeneReview*, the terms "male" and "female" are narrowly defined as the individual's biological sex at birth as it determines clinical care [Caughey et al 2021].

Consensus clinical diagnostic criteria for Simpson-Golabi-Behmel syndrome type 1 (SGBS1) have not been established.

Suggestive Findings

SGBS1 **should be suspected** in probands with the following clinical findings and family history.

Clinical findings

- **Linear somatic overgrowth**
- **Macrocephaly**
- **Characteristic facial features**
  - Widely spaced eyes, epicanthal folds, and downslanted palpebral fissures
  - Redundant, furrowed skin over the glabella
  - Wide nasal bridge and anteverted nares in infants; broad nose and coarsening of the facial features in older individuals
  - Prominent forehead

- Macrostomia
- Macroglossia with or without a midline groove in the lower lip and/or deep furrow in the middle of the tongue
- Cleft lip and/or submucous cleft palate (with a bifid uvula); high and narrow palate
- Micrognathia in neonates; macrognathia in older individuals

- **Cardiac manifestations.** Congenital heart disease (e.g., pulmonary stenosis, cardiomyopathy, ventricular septal defect, patent ductus arteriosus, patent foramen ovale, arrythmias), conduction defects (transient QT interval prolongation)
- **Genitourinary manifestations.** Renal dysplasia, nephromegaly, duplicated renal system, cryptorchidism or hypospadias in males
- Other features
  - Supernumerary nipples
  - Diastasis recti / umbilical hernia
  - Diaphragmatic hernia
  - Hand and foot anomalies (brachydactyly, cutaneous syndactyly, polydactyly, shortened distal phalanges, fingernail dysplasia)

Family history is consistent with X-linked inheritance (e.g., no male-to-male transmission). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

Male proband. The diagnosis of SGBS1 **is established** in a male proband with suggestive findings and a hemizygous pathogenic (or likely pathogenic) variant in *GPC3* or an intragenic or whole-gene deletion of *GPC3* identified by molecular genetic testing (see Table 1).

Female proband. The molecular diagnosis of SGBS1 **is usually established** in a female proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *GPC3* or an intragenic or whole-gene deletion of *GPC3* 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 hemizygous or heterozygous variant of uncertain significance in *GPC3* 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, chromosomal microarray analysis) and **comprehensive genomic testing** (exome sequencing, genome sequencing) depending on the phenotype. Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not.

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of SGBS1, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel.**

- **Single-gene testing.** Sequence analysis of *GPC3* is performed first to detect missense, nonsense, 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 *GPC3* and other genes of interest (see Differential Diagnosis) may also be considered. A multigene panel may 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. Notes: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

- **Chromosomal microarray (CMA)** which uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications including *GPC3* that cannot be detected by sequence analysis may be considered next if no pathogenic variant is found. Note: CMA cannot determine the orientation of copy number abnormalities.

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

Option 2

When the diagnosis of SGBS1 has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible. To date, the majority of *GPC3* pathogenic variants reported are within the coding or canonical splice site region and are likely to be identified on exome sequencing.

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 Simpson-Golabi-Behmel Syndrome Type 1

Gene [1]	Proportion of SGBS1 Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method		
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]	CMA [5]
GPC3	~90% [6]	~57% [7]	~43% [7]	Rare [8]

Table 1. continued from previous page.

Gene [1]	Proportion of SGBS1 Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method		
		Sequence analysis [3]	Gene-targeted deletion/ duplication analysis [4]	CMA [5]
Unknown	~10%			

SGBS1 = Simpson-Golabi-Behmel syndrome type 1

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. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. 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.

5. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *GPC3* and *GPC4*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the Xq26.2 regions.

6. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020] and Klein et al, unpublished data. Of note, most reported individuals are males. Molecular causes reported in females to date include heterozygous *GPC3* and *GPC4* duplication (3 individuals), *GPC3* deletion (2 individuals), balanced X-chromosome translocations (2 individuals), and a heterozygous *GPC3* duplication (1 individual).

7. Vuillaume et al [2018]

8. Contiguous deletions of *GPC3* and *GPC4* have been identified in multiple families with SGBS1 [Veugelers et al 1998, Schirwani et al 2019, Peng et al 2023]. There are case reports of multigene deletions that extend into *GPC4*, and a single case of SGBS1 with a pathogenic variant in *GPC4*; however, the role of *GPC4* in SGBS1 pathogenesis remains unknown [Waterson et al 2010]. Intragenic pathogenic *GPC4* variants have not been described in isolation and are usually an extension of a deletion that includes *GPC3* [Spencer et al 2016]. Duplication of exons 1-9 in *GPC4* without deletion or mutation of *GPC3* was found in the original family described by Golabi & Rosen [1984] in which no *GPC3* pathogenic variant had been identified [Waterson et al 2010]. DiMaio et al [2017] reported a familial case of SGBS1 caused by deletion of *GPC3*, *TFDP3*, and *GPC4.* Schirwani et al [2019] identified one family that had a pathogenic deletion extending into both *GPC3* and *GPC4*. Sha et al [2022] described another unique multigene deletion encompassing *GPC3*, *GPC4*, and other genes in a fetus with features of SGBS1.

Clinical Characteristics

Clinical Description

Males and females can present similarly with Simpson-Golabi-Behmel syndrome type 1 (SGBS1). However, there is skewing of males to females in a 9:1 ratio. Individuals of both sexes present with overgrowth, characteristic facial features, skeletal abnormalities, and genitourinary dysfunction. Males often present with cryptorchidism. Females are less likely to present with severe manifestations of SGBS1, potentially due to skewed X-chromosome inactivation. There have not been extensive studies of sex differences in SGBS1 due to the small number of females reported to date and mildly affected or unaffected female carriers who do not present until they have an affected son.

Affected Males

SGBS1 is characterized by pre- and postnatal overgrowth, distinctive facies, and variable visceral, skeletal, and neurodevelopmental abnormalities. To date, 159 individuals have been identified with a pathogenic variant in *GPC3* [Klein et al, unpublished data]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Simpson-Golabi-Behmel Syndrome Type 1: Frequency of Select Features

System	Feature	% of Persons w/Feature
Overgrowth	Overgrowth (linear growth ≥2 SD above mean for age & sex)	85%
	Macrocephaly (OFC ≥2 SD above mean for age & sex)	34%
Facial features	Characteristic facial features	87%
	Macroglossia	88%
	Macrostomia	85%
	Ear deformities	80%
	Frontal bossing	85%
	High-arched or cleft palate	75%
	Hypertelorism	85%
	Thick lips	63%
Cardiac	Congenital heart disease	55%
	Conduction cardiac defects	36%
Genitourinary	Renal dysplasia, nephromegaly, duplicated renal system	72%
	Cryptorchidism, hypospadias in males	61%
Musculoskeletal	Hand & foot anomalies (brachydactyly, cutaneous syndactyly, polydactyly)	49%
Neurodevelopmental	Intellectual disability	60%
Neoplasia	Hepatoblastoma & Wilms tumor (most common)	11%
Other features	Supernumerary nipples	64%
	Diastasis recti, umbilical hernia	35%
	Diaphragmatic hernia	29%
	Organomegaly	59%

Klein et al, unpublished data
OFC = occipital frontal circumference; SD = standard deviation

Overgrowth

- **Somatic overgrowth.** Virtually all individuals with SGBS1 have either pre- or postnatal overgrowth. 68% of individuals present with postnatal overgrowth and 61% of individuals present with prenatal overgrowth [Klein et al, unpublished data]. At this time, no reference ranges or SGBS1-specific growth curves have been developed. There are currently no reports of hemihypertrophy or lateralized overgrowth.

  As with other overgrowth syndromes, hypoglycemia may be present in the neonatal period; however, hypoglycemia is rare in SGBS1 and is not considered to be a cardinal feature.

- **Macrocephaly.** Macrocephaly is reported in just over one third of individuals with SGBS1. Most present with macrocephaly in the prenatal period and continue to be macrocephalic throughout their life [Klein et al, unpublished data]. The most common complication of congenital macrocephaly in individuals with SGBS1 is difficulties with vaginal delivery, leading to increased risk of cesarean section deliveries [Klein et al, unpublished data]. Additionally, ventriculomegaly and ventricular hemorrhage, which are seen in some affected individuals, may confound the early identification of macrocephaly [Garganta & Bodurtha 1992, Li & McDonald 2009].

Characteristic facies include the following:

- Widely spaced eyes, epicanthal folds, and downslanted palpebral fissures
- Redundant, furrowed skin over the glabella
- Wide nasal bridge and anteverted nares in infants; broad nose and coarsening of the facial features in older individuals
- Prominent forehead
- Macrostomia
- Macroglossia with or without a midline groove in the lower lip and/or deep furrow in the middle of the tongue
- Cleft lip and/or submucous cleft palate (with a bifid uvula); high and narrow palate
- Micrognathia in neonates; large mandible (macrognathia) in older individuals

Cardiac. A range of cardiac features are seen:

- Congenital heart defects are variable; septal defects are common. Pulmonic stenosis, aortic coarctation, transposition of the great vessels, and patent ductus arteriosus or patent foramen ovale have been reported.
- Conduction defects and arrhythmias have also been described [Lin et al 1999]. Transient QT interval prolongation has also been reported [Gertsch et al 2010], as has AV or right bundle branch block [König et al 1991, Neri et al 2013, Xiang et al 2020].

Genitourinary. Nephromegaly, nephroblastomatosis, multicystic kidneys, hydronephrosis, hydroureter, supernumerary kidneys, and duplicated ureters have been described [Schmidt et al 2017, Reischer et al 2021].

Other genitourinary anomalies include hypospadias, penile hypoplasia, ambiguous genitalia, anal atresia, bifid scrotum, cryptorchidism, hydrocele, and inguinal hernia [Hughes-Benzie et al 1996, Romanelli et al 2007, Villarreal et al 2013, Halayem et al 2016, Magini et al 2016, Fu et al 2019].

Musculoskeletal. Skeletal anomalies can include vertebral fusion, scoliosis, pectus excavatum, rib anomalies (including cervical ribs), congenital hip dislocation [Terespolsky et al 1995, Garavelli et al 2012], small sciatic notches, and flared iliac wings [Chen et al 1993, Garavelli et al 2012]. Extra lumbar vertebrae, spina bifida (open and occulta) [Hughes-Benzie et al 1992, Van Borsel et al 2008], coccygeal skin tag, metaphyseal dysplasia of the femur [Yamashita et al 1995], and bony appendage have also been documented [Golabi & Rosen 1984].

Hand anomalies such as large hands, broad thumbs, and brachydactyly are common. Other findings include syndactyly, clinodactyly, and postaxial polydactyly. Striking index finger hypoplasia with congenital abnormalities of the proximal phalanx have been reported [Verloes et al 1995, Day & Fryer 2005]. Nail dysplasia, hypoplasia (particularly of the index finger), and hypoconvexity are common [Garavelli et al 2012, Cottereau et al 2013, Bu et al 2022].

Advanced bone age, including presence of ossified carpal bones in a newborn, has been described [Chen et al 1993, Watanabe et al 2022].

Neurologic and neurodevelopmental. Neurologic manifestations are perhaps the most variable findings. Hypotonia and absent primitive reflexes, a high-pitched cry in neonates, seizures, and abnormal EEG have all been described.

Normal intelligence has been described, but mild-to-severe intellectual disability is common, with language delay being the most characteristic finding.

Hydrocephalus, epilepsy, and attention-deficit/hyperactivity disorder may also be present [Van Borsel et al 2008, Tenorio et al 2014, Halayem et al 2016].

Brain abnormalities have been reported, including agenesis of the corpus callosum, Chiari malformation, hydrocephalus, and hypoplasia of the cerebellar vermis [Young et al 2006].

Neoplasia. The tumor risk in SGBS1 is estimated to be 11.3%, with the most common types being hepatoblastoma and Wilms tumor [Shimojima et al 2016, Spencer et al 2016]. The median age of neoplastic onset is 17.5 months with a 7:1 male-to-female ratio. With this risk and based on the guidelines for screening in cancer predisposition syndromes that lead to hepatoblastoma and Wilms tumor, individuals with SGBS1 should undergo tumor screening (see Surveillance).

Additionally, several tumors have been reported in single individuals, but it is unknown if they are related to the pathogenesis of SGBS1 or reflect the underlying population-level neoplastic risk. Each of the following has been reported in single individuals:

- Acute lymphoblastic leukemia [Sakazume et al 2007]
- Ameloblastoma [Kaya et al 2019]
- Diffuse neonatal hemangiomatosis [Poetke et al 2002]
- Hepatocellular carcinoma [Lapunzina et al 1998]
- Medulloblastoma [Thomas et al 2012]
- Pancreatic carcinoma [Rodríguez-Criado et al 2005]
- Renal neuroblastoma [Hughes-Benzie et al 1992]

Other manifestations

- **Oropharynx.** Macroglossia is a characteristic feature. In some cases, the tongue may enlarge such that it interferes with breathing and/or sleeping [Paludetti et al 2003], but the need for surgical intervention has not been determined to date. Other anomalies include various degrees of palatal clefting (including submucous cleft and bifid uvula), laryngeal cleft, and laryngeal web. Obstructive sleep apnea may be present. Silent aspiration leading to chronic respiratory infections and bronchiectasis has also been described [Glamuzina et al 2009, Tenorio et al 2014].
- **Eyes.** Esotropia, cataracts, and coloboma of the optic disc [Golabi & Rosen 1984] have been noted. Ocular nerve palsies and strabismus can occur.
- **Ears.** Minor ear abnormalities are frequent, most often preauricular tags, fistulas, ear lobule creases, and helical dimples. Conductive hearing loss has been described, but the incidence is not known. Overall, 37% of individuals have some form of ear deformity or conductive hearing loss [Golabi & Rosen 1984; Garganta & Bodurtha 1992; Griffith et al 2009; Magini et al 2016; Chong et al 2018; Klein et al, unpublished data].
- **Neck.** Cystic hygroma, thymic hypoplasia, and generalized lymphoid atrophy have been described but are rare [Chen et al 1993].
- **Thoracoabdominal wall.** Supernumerary nipples are common, either one or multiple, unilateral or bilateral. Diastasis recti and umbilical hernias are observed frequently; however, true omphalocele is rare [Terespolsky et al 1995, Li & McDonald 2009, Schmidt et al 2017].
- **Lungs.** Abnormal branching of the bronchi and an abnormal lower airway pit have been described in one affected individual [Glamuzina et al 2009]. Diaphragmatic hernia and associated lung hypoplasia have been reported [Chen et al 1993, Shimojima et al 2016, Chong et al 2018, Reischer et al 2021]. See Congenital Diaphragmatic Hernia Overview.
- **Gastrointestinal.** Gastrointestinal anomalies include pyloric ring, Meckel's diverticulum, intestinal malrotation [Golabi & Rosen 1984], hepatosplenomegaly, pancreatic hyperplasia of islets of Langerhans, choledochal cysts [Kim et al 1999, Shimojima et al 2016], duplication of the pancreatic duct, polysplenia, liver cysts, biliary atresia [Jedraszak et al 2014], inguinal hernia, and supernumerary kidney [Schmidt et al 2017, Chong et al 2018].

Heterozygous Females

Due to skewed X-chromosome inactivation, heterozygous females can have variable manifestations of SBGS1 ranging from completely unaffected to fully recapitulating the severe phenotype, including overgrowth, widely spaced eyes, broad and upturned nasal tip with prominent columella, macrostomia, prominent chin, hypoplastic fingernails, coccygeal skin tag and bony appendage, extra lumbar and thoracic vertebrae, and accessory nipples [Golabi & Rosen 1984, Fernandes et al 2021]. Tall stature, coarse facial features, and developmental delay have also been reported [Gertsch et al 2010].

To date, nine heterozygous females with clinical expression of SGBS1 have been reported [Punnett 1994, Pilia et al 1996, Yano et al 2011, Mujezinović et al 2016, Shimojima et al 2016, Vaisfeld et al 2017, Schirwani et al 2019]. These cases encompass the full spectrum of SGBS1. Further, cancer has been reported in some of these affected females, including two females with a heterozygous *GPC3* pathogenic variant with two different types of cancer: one had a seropapilliferous cystoadenoma, a low-grade ovarian carcinoma; the other had breast cancer [Gurrieri et al 2011]. Information was insufficient to exclude other possible genetic causes for breast/ovarian cancer in the family. An affected female with a Wilms tumor has also been reported [Fernandes et al 2021], as well as a female with a hepatoblastoma [Shimojima et al 2016].

Genotype-Phenotype Correlations

There are no known genotype-phenotype correlations for SGBS1 to date.

Penetrance

All males reported with a *GPC3* pathogenic variant have clinical findings of SGBS1. Penetrance in heterozygous females is unknown, but unaffected or mildly affected females have been reported [Shimojima et al 2016, Fernandes et al 2021].

Nomenclature

SGBS1 was initially described by Simpson et al [1975], with later accounts by Golabi & Rosen [1984] and Behmel et al [1984].

Terms no longer in use for SGBS1:

- Gigantism-dysplasia syndrome
- Encephalo-tropho-schisis syndrome
- Golabi-Rosen syndrome
- Simpson dysmorphia syndrome

Prevalence

The prevalence of SGBS1 is unknown; however, it is believed to be underdiagnosed due to the wide spectrum of clinical severity.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with germline pathogenic variants in *GPC3*.

Germline pathogenic variants in *GPC4* are associated with Keipert syndrome (OMIM 301026). Keipert syndrome is a monogenetic syndrome caused by pathogenic variants in *GPC4* and characterized by facial and skeletal abnormalities. Common phenotypes are macrocephaly, frontal bossing, hypertelorism, broad nose, and digital abnormalities. Skeletal malformations have also been noted, and some affected individuals exhibit

learning delays. In contrast to SGBS1, there is no pattern of visceromegaly, neoplasms, genitourinary dysfunction, or congenital heart defects [Amor et al 2019]. Some but not all the features common to SGBS1 are influenced by *GPC4*. However, these features also appear in individuals with exclusive pathogenic variants in *GPC3*.

Sporadic tumors (including Wilms tumor) occurring as single tumors in the absence of any other findings of SGBS1 frequently contain a somatic pathogenic variant in *GPC3* that is **not** present in the germline. In these circumstances, predisposition to these tumors is not heritable.

Differential Diagnosis

Table 3. Disorders to Consider in the Differential Diagnosis of Simpson-Golabi-Behmel Syndrome Type 1

Gene(s)	Disorder	MOI	Clinical Features of This Disorder	
			Overlapping w/SGBS1	Distinguishing from SGBS1
See footnote 1.	Beckwith-Wiedemann syndrome (BWS)	See footnote 1.	• Macrosomia • Macroglossia • Ear anomalies • Diastasis recti • Hypoglycemia • Genitourinary malformations • ↑ incidence of tumors	• Appreciably different facial features (midface flattening in BWS; broader forehead in SGBS1) • Absence of relative macrocephaly • Absence of skeletal abnormalities • Omphalocele • Phenotype often less pronounced w/age (In SGBS1, characteristic features may not be present in infancy.) • Hemihypertrophy/lateralized overgrowth more common • Persons w/BWS are less tall & less dysmorphic, w/fewer visceral & skeletal malformations.
DIS3L2	Perlman syndrome (OMIM 267000)	AR	• Macrosomia • High incidence of Wilms tumor	• Distinctive facial features • Neonatal mortality is high.
DNMT3A	Tatton-Brown-Rahman syndrome (*DNMT3A* overgrowth syndrome)	AD	• Overgrowth • macrocephaly • Intellectual disability • Cryptorchidism	• Behavioral/psychiatric issues • Seizures • Distinctive facial features • Acute myeloid leukemia predisposition • Joint hypermobility • Hypotonia
EZH2	*EZH2*-related Weaver syndrome (See *EZH2*-Related Overgrowth.)	AD	• Overgrowth • Umbilical hernia • Ear anomalies • Hypotonia • Advanced bone age • Vertebral defects • Hypertelorism	• Flat occiput • Deep horizontal chin crease, large ears • Absence of downslanting palpebral fissures, dental malocclusion, & central groove of lower lip (all characteristic of SGBS1 [2]) • Psychomotor delay typically more prominent

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features of This Disorder	
			Overlapping w/SGBS1	Distinguishing from SGBS1
NFIX	*NFIX*-related Malan syndrome (OMIM 614753)	AD	• Postnatal overgrowth • Advanced bone age • Macrocephaly • Downslanting palpebral fissures	• Marfanoid habitus w/long & slender body, low body mass, long & narrow face, arachnodactyly, long tapered fingers • Aggressive, self-injurious behavior • Normal birth weight
NFIX	Marshall-Smith syndrome (OMIM 602535)	AD	• Advanced bone age • Intellectual disability	• Distinctive facial features • Predisposition to fractures
NSD1	Sotos syndrome	AD	• Hypertelorism • Broad forehead • Downslanting palpebral fissures • Hypoglycemia	Seizures are more common. [2]
OFD1 *PIGA* [3]	Simpson-Golabi-Behmel syndrome type 2 (infantile-lethal form) (OMIM 300209)	XL	• Macrosomia • Widely spaced eyes, epicanthal folds, downslanted palpebral fissures • Redundant, furrowed skin over the glabella • Wide nasal bridge & anteverted nares in infants; broad nose & coarse facial appearance in older persons • Macrocephaly • Macrostomia • Macroglossia • Cleft lip &/or submucous cleft palate (w/bifid uvula); high & narrow palate • Small mandible (micrognathia) in neonates; macrognathia in older persons • Multiple congenital anomalies	More lethal form usually assoc w/ hydrops fetalis [4]
PIGN	Fryns syndrome	AR	• Coarse facies • Diaphragmatic hernia w/ lung hypoplasia • Cleft lip/palate • Congenital heart defects • Ear anomalies • Macrostomia	• Hydrocephalus • Micro- & retrognathia

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features of This Disorder	
			Overlapping w/SGBS1	Distinguishing from SGBS1
PLOD1	Nevo syndrome [5] (See *PLOD1*-Related Kyphoscoliotic Ehlers-Danlos Syndrome.)	AR	• Overgrowth • Vertebral anomalies • Ear malformations • Cryptorchidism • Intellectual disability	• Accelerated osseous maturation • Large extremities • Hypotonia
PTCH	Nevoid basal cell carcinoma syndrome (Gorlin syndrome)	AD	• Macrocephaly • Coarse facial features • Bifid ribs	• Multiple jaw keratocysts frequently beginning in 2nd decade of life • Basal cell carcinomas usually from 3rd decade onward
SETD2	*SETD2*-related neurodevelopmental disorder w/macrocephaly/ overgrowth (also referred to as Luscan-Lumish syndrome or Sotos-like syndrome) (See *SETD2* Neurodevelopmental Disorders.)	AD	• Intellectual Disability • Macrocephaly • Overgrowth • Advanced bone age • Frontal bossing • Low-set ears	• Behavioral findings • Eye findings • Hypotonia • Hyponatremia • Respiratory issues • Epilepsy • Arched eyebrows • Micrognathia w/mandibular hypoplasia
SUZ12	*SUZ12*-related overgrowth syndrome (Imagawa-Matsumoto syndrome) (OMIM 618786)	AD	• Pre- and postnatal overgrowth • Macrocephaly • Frontal bossing • Hypertelorism • Downslanting palpebral fissures • Low & broad nasal bridge • Musculoskeletal abnormalities • Genitourinary abnormalities (umbilical hernia, cryptorchidism) • Structural brain abnormalities	• Respiratory issues, scoliosis • Widened distal ulnas • Widened distal femurs • Coxa valga • Flat feet • Pronation of feet • ↓ muscle bulk • Phimosis • Recurrent respiratory infections • Aspiration of thin liquids

AD = autosomal dominant; AR = autosomal recessive; MOI = mode of inheritance; XL = X-linked

1. BWS is associated with abnormal regulation of gene transcription in two imprinted domains on chromosome 11p15.5 (also known as the BWS critical region). Regulation may be disrupted by any one of numerous mechanisms. Approximately 85% of individuals with BWS have no family history of BWS; approximately 15% have a family history consistent with parent-of-origin autosomal dominant transmission.

2. Baujat et al [2005]

3. Fauth et al [2016]

4. Tenorio et al [2014]

5. Giunta et al [2005] convincingly demonstrated that Nevo syndrome is part of the spectrum of kEDS; thus, the term "Nevo syndrome" does not refer to a distinct disorder but is now incorporated into kEDS.

Other genetic disorders that may share overlapping features with SGBS1 include:

- **Elejalde syndrome** (acrocephalopolydactylous dysplasia) (OMIM 256710). Infrequently described, Elejalde syndrome includes findings of macrosomia, abnormal facies, craniosynostosis with acrocephaly, omphalocele, organomegaly, cystic renal dysplasia, and polydactyly.

- **Mosaic trisomy 8.** Phenotype is variable, with characteristic findings of advanced growth, long slender trunk with multiple skeletal abnormalities (spinal deformities, contractures of fingers and toes), absence of the corpus callosum, and moderate intellectual disability. Typical facial features include high, prominent forehead, hypertelorism, full lips, and micrognathia.
- **Mosaic tetrasomy 12p** (Pallister-Killian syndrome; OMIM 601803) is characterized by variegated skin pigmentation; facial anomalies including prominent forehead with sparse anterior scalp hair, ocular hypertelorism, short nose with anteverted nares, and flat nasal bridge; and developmental delay.

Diabetic embryopathy (or infant of a diabetic mother syndrome). Infants born to diabetic mothers have a higher rate of congenital malformations. Sacral agenesis or hypogenesis and/or caudal dysgenesis are classic findings [Williamson 1970], but other frequently observed anomalies include congenital heart defects, renal anomalies, vertebral anomalies, limb defects, and structural brain abnormalities.

Management

No clinical practice guidelines for Simpson-Golabi-Behmel syndrome type 1 (SGBS1) 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 SGBS1, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. Simpson-Golabi-Behmel Syndrome Type 1: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Oropharynx	Assess for macroglossia & orofacial clefting.	Referral to craniofacial team incl feeding specialists
Eyes	Ophthalmologic exam	
Ears/Hearing	Audiologic eval	
Cardiac	Consider chest radiograph, EKG, & echocardiogram.	To evaluate for structural heart defects & conduction abnormalities
Respiratory	Assess for upper-airway sufficiency & signs/symptoms of sleep apnea; consider formal sleep study.	Particularly in those w/hypotonia & macroglossia
Renal	Exam for hypospadias & undescended testes in males; renal ultrasound to assess for renal anomalies	Referral to urologist as needed
Abdomen/Pelvis	Abdominal/pelvic ultrasound to initiate tumor screening	Further studies (e.g., MRI) may be indicated if findings are suspicious for a tumor.
	Measurement of serum AFP	As a baseline screen for hepatoblastoma
Musculoskeletal	Clinical eval for scoliosis	Particularly during times of rapid growth
Neurologic	Neurologic eval, head MRI, &/or EEG	If concerns for seizures
Endocrinologic	Assessment for hypoglycemia	In neonates
Development	Developmental assessment	Incl speech-language assessment
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of SGBS1 to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
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

AFP = alpha-fetoprotein; MOI = mode of inheritance; SGBS1 = Simpson-Golabi-Behmel syndrome type 1
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for SGBS1.

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. Simpson-Golabi-Behmel Syndrome Type 1: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Macroglossia, micrognathia, &/or glossoptosis	Prompt standard treatment to maintain secure airway; consider feeding/swallowing eval.	May require care of craniofacial team
Cleft palate or bifid uvula	Assessment of feeding & mgmt by cleft/craniofacial team	
Obstructive sleep apnea	• If due to macroglossia, consider mgmt similar to Beckwith-Wiedemann syndrome. • Sleep study & potential CPAP or hemiglossectomy if indicated	Limited data are available on prevalence & treatment of OSA in persons w/ SGBS1.
Feeding difficulties	• Milder feeding issues may be managed w/special nipples or nasogastric feeding in consultation w/ specialist. • Consider gastrostomy tube in those w/severe feeding issues.	Limited data are available on treatment of feeding difficulties in persons w/ SGBS1.
Eyes	Standard treatment for strabismus & cataracts	
Hearing	Standard treatment for hearing loss	
Congenital heart defects & conduction abnormalities	Standard treatment per cardiologist	
Hypospadias/cryptorchidism in males	Standard treatment per urologist	
Musculoskeletal findings (i.e., scoliosis)	Standard treatment per orthopedist	
Seizure disorder	Standard treatment per neurologist	
Hypoglycemia or suspected hyperinsulinism	Prompt treatment per endocrinologist	Consider referral to tertiary care center for hyperinsulinism eval if suspected.
Developmental delay	Early referral for developmental support / special education, which may incl PT, OT, speech therapy, &/or cognitive therapy	Consider referral to neurodevelopmental specialist &/or neuropsychiatric testing.

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Cancer predisposition	For Wilms tumor, nephron sparing surgery should be considered if possible.	See Surveillance for recommended tumor-screening protocol.

CPAP = continuous positive airway pressure; OT = occupational therapy; OSA = obstructive sleep apnea; PT = physical therapy; SGBS1 = Simpson-Golabi-Behmel syndrome type 1

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized education plan (IEP) is developed.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. Affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

In the US:

- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction. Physical therapy is recommended to maximize mobility.

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding due to poor oral motor control.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties.

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. Simpson-Golabi-Behmel Syndrome Type 1: Recommended Surveillance for Males

System/Manifestation	Evaluation	Frequency/Comment
Eyes	Ophthalmologic eval	Annually in childhood or as indicated
Hearing	Audiologic eval	
Respiratory	Sleep study	If history of sleep disturbance
Renal	Routine monitoring of kidney function	If renal anomalies present
Musculoskeletal	Eval for scoliosis	At least annually or during periods of rapid growth
Endocrine	Monitor serum glucose levels for hypoglycemia secondary to ↑ risk for hyperinsulinemia.	In neonatal period
Neurodevelopment	Monitor for developmental progress.	At each clinic visit
Cancer predisposition	Tumor screening for Wilms tumor & hepatoblastoma	• Abdominal ultrasound & serum AFP level every 3 mos from time of diagnosis until age 4 yrs • Renal ultrasound every 3 mos until age 7 yrs
	Tumor screening for neuroblastoma & gonadoblastoma	Insufficient data to determine utility of screening in persons w/SGBS1
	Follow up w/cancer predisposition specialist & physical exam	Every 6 mos [1]

AFP = alpha-fetoprotein; SGBS1 = Simpson-Golabi-Behmel syndrome type 1
1. Kalish et al [2017]

Little information on tumor risk in heterozygous females is available; there are currently only a few reports of tumors in females with SGBS1 (see Clinical Description, Heterozygous Females). However, screening can be considered in affected females.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of older and younger at-risk male and female relatives of an affected individual by molecular genetic testing for the familial SGBS1-related genetic alteration in order to identify as early as possible those who would benefit from preventive measures such as tumor surveillance in males. Specific recommendations depend on the sex of the paternal source of the pathogenic variant and are family specific.

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

Pregnancy Management

A number of gestational complications have been reported in the mothers of individuals with SGBS1, including gestational hypertension, diabetes, preeclampsia, fetal distress, and preterm labor. Fetal macrocephaly and overgrowth may necessitate cesarean delivery or early induction of labor [Terespolsky et al 1995, Shimojima et al 2016, Schmidt et al 2017, Ridnõi et al 2018, Fu et al 2019, Toczewski et al 2020].

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

Simpson-Golabi-Behmel syndrome type 1 (SGBS1) is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder, nor will he be hemizygous for the SBGS1-causing genetic alteration; therefore, he does not require further testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote and may demonstrate some features of the condition. Note: If a woman has more than one affected child and no other affected relatives, and if the pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case):
  - The mother may be a heterozygote.
  - The affected male may have a *de novo* SBGS1-causing genetic alteration (in which case the mother is not a heterozygote). The frequency of *de novo* SBGS1-causing genetic alterations is about 20%-30% [Tenorio et al 2014].
  - The mother may have somatic/germline mosaicism [Romanelli et al 2007, Yano et al 2011]. The frequency of germline mosaicism is currently unknown.
- Molecular genetic testing capable of detecting the SBGS1-causing genetic alteration identified in the proband is recommended for the mother to confirm her genetic status and to allow reliable recurrence risk assessment.

Parents of a female proband

- A female proband may have inherited the SBGS1-causing genetic alteration from either her mother (who may or may not have manifestations of SBGS1) or her father or the genetic alteration may be *de novo*.
- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* SBGS1-causing genetic alteration from those with an inherited genetic alteration. Molecular genetic testing of the mother (and possibly the father, or subsequently the father) may help determine whether the genetic alteration was inherited.

Sibs of a male proband. The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has an SBGS1-causing genetic alteration, the chance of transmitting the genetic alteration in each pregnancy is 50%.
  - Males who inherit the genetic alteration will be affected.
  - Females who inherit the genetic alteration will be heterozygotes. Due to skewed X-chromosome inactivation, heterozygous females may have manifestations of SBGS1 (see Clinical Description, Heterozygous Females).
- If the proband represents a simplex case and if the SBGS1-causing genetic alteration cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population

because of the possibility of maternal germline mosaicism. Maternal germline mosaicism has been reported [Romanelli et al 2007].

Sibs of a female proband. The risk to sibs depends on the genetic status of the parents:

- If the mother of the proband has an SGBS1-causing genetic alteration, the chance of transmitting it in each pregnancy is 50%.
  - Males who inherit the genetic alteration will be affected.
  - Females who inherit the genetic alteration will be heterozygotes. Due to skewed X-chromosome inactivation, heterozygous females may have manifestations of SBGS1 (see Clinical Description, Heterozygous Females).
- If the father of the proband has an SGBS1-causing genetic alteration, he will transmit it to all of his daughters and none of his sons. Transmission from an affected father to his affected daughter has been reported in one family to date [Støve el al 2017].
- If the proband represents a simplex case and if the SGBS1-causing genetic alteration cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism (both maternal and paternal germline mosaicism have been reported in SGBS1 [Romanelli et al 2007, Agatep et al 2014]).

Offspring of a male proband

- Affected males transmit the SGBS1-causing genetic alteration to all of their daughters and none of their sons.
- To date, only one affected male has been reported to reproduce; the affected male was only diagnosed after the fetal demise of the affected child [Støve et al 2017].

Offspring of a female proband. Women with an SGBS1-causing genetic alteration have a 50% chance of transmitting the genetic alteration to each child.

Other family members. The proband's maternal aunts may be at risk of being heterozygous for the SGBS1-causing genetic alteration, and the aunts' offspring may be at risk of having the genetic alteration and being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* SGBS1-causing genetic alteration arose, information that could help determine genetic risk status of the extended family.

Heterozygote Detection

Identification of apparently asymptomatic female heterozygotes requires prior identification of the SGBS1-causing genetic alteration in the family.

Note: Females who are heterozygous for this X-linked disorder may be affected; heterozygous females with features of SGBS1 have been reported (see Clinical Description, Heterozygous Females).

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk male 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 who are at risk of having an SGBS1-causing genetic alteration.

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancies. Once the SGBS1-causing genetic alteration has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Low-risk pregnancies. In pregnancies in which SGBS1 is suspected because of fetal overgrowth or congenital anomalies, the use of genomic testing (including chromosomal microarray and exome sequencing) can aid in diagnosis [Kehrer et al 2016].

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

Resources

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

- **MedlinePlus**
  Simpson-Golabi-Behmel syndrome

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. Simpson-Golabi-Behmel Syndrome Type 1: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
GPC3	Xq26.2	Glypican-3	GPC3 database	GPC3	GPC3

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 Simpson-Golabi-Behmel Syndrome Type 1 (View All in OMIM)

300037	GLYPICAN 3; GPC3
312870	SIMPSON-GOLABI-BEHMEL SYNDROME, TYPE 1; SGBS1

Molecular Pathogenesis

GPC3 encodes a glycosylphosphatidylinositol-linked cell surface heparan sulfate proteoglycan, which belongs to the glypican family. Heparan sulfate proteoglycans bind and regulate the activities of a variety of extracellular ligands essential to cellular functions. Glypicans have a role in cell growth and cell division. Abnormal glypican function may affect pathways such as Wnt signaling, the hedgehog pathway, BMP signaling, and FGF signaling [Paine-Saunders et al 2000, Song et al 2005, Ng et al 2009]. Glypican-3 is a glycosylphosphatidylinositol-linked cell surface heparan sulfate proteoglycan [Pilia et al 1996].

Most individuals with Simpson-Golabi-Behmel syndrome type 1 (SGBS1) have pathogenic variants in *GPC3*. The mechanism by which a pathogenic loss-of-function *GPC3* variant leads to the SGBS1 phenotype is unknown. Yano et al [2011] reported that at least 43% loss of functional *GPC3* protein is required to develop the SGBS1 phenotype in heterozygous females (total detection rate is unknown) [Yano et al 2011].

***GPC3*/*GPC4* complex copy number abnormalities.** Glypican-4, encoded by *GPC4*, is also a glycosylphosphatidylinositol-linked cell surface heparan sulfate proteoglycan [Veugelers et al 1998]. *GPC4* is adjacent to the 3' end of *GPC3* and comprises nine exons. Males and female carriers with complex *GPC3* and *GPC4* copy number abnormalities have been reported [Schirwani et al 2019]. Additional atypical SGBS1 features, such as brain malformations, have been noted in individuals with dual duplications, suggesting that atypical or new features may be associated with duplications of *GPC4* [Mujezinović et al 2016]. Mujezinović et al [2016] suggested that the *GPC4* duplication could cause a greater disruption of glypican-3 expression, altering the phenotypic expression [Mujezinović et al 2016]. The mechanism by which duplication of *GPC3* and *GPC4* leads to the SGBS1 phenotype is unknown. Schirwani et al [2019] reported two heterozygous females with 45%-56% of the active X-chromosome-containing complex *GPC3*/*GPC4* duplications. These females manifested mild SGBS1 features including intellectual disability and developmental delay [Schirwani et al 2019]. Duplication of *GPC4* without a *GPC3* pathogenic variant has been very rarely reported in association with an SGBS1 phenotype [Waterson et al 2010]. However, the mechanism by which duplication of *GPC4* leads to the SGBS1 phenotype is unknown. Of note, loss-of-function variants in *GPC4* are not associated with SGBS1 [Veugelers et al 2000].

Mechanism of disease causation. Loss of function

Chapter Notes

Author Notes

Mr Hathaway is a licensed genetic counselor.

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Dr Kalish (kalishj@chop.edu) and Dr Klein (kleinsd@chop.edu) are actively involved in research regarding individuals with Simpson-Golabi-Behmel syndrome type 1 (SGBS1) and related overgrowth syndromes. They would be happy to communicate with persons who have any questions regarding diagnosis of SGBS1 or other overgrowth syndromes with or without a causative variant identified through molecular genetic testing of known overgrowth genetic or epigenetic causes.

Contact Drs Kalish and Klein to inquire about review of *GPC3*/*GPC4* variants of uncertain significance.

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