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Simpson-Golabi-Behmel Syndrome Type 1

Brian J Sajorda, BA,[1] Christina X Gonzalez-Gandolfi, BA,[1] Evan R Hathaway, MS, LCGC,[1] and Jennifer M Kalish, MD, PhD[2]

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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 palatal 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 anomalies. 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*, an intragenic or whole-gene deletion of *GPC3* that may include part or all of *GPC4*, or a large multiexon duplication of *GPC4* identified by molecular genetic testing. The diagnosis is usually established in a female proband who has suggestive findings and a heterozygous pathogenic variant in *GPC3*, an intragenic or whole-gene deletion of *GPC3* that may include part or all of *GPC4*, or a large multiexon duplication of *GPC4* 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, and seizures in a standard fashion by appropriate pediatric specialists. Speech therapy as

Author Affiliations: 1 Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. 2 Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; Email: kalishj@email.chop.edu.

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 from age four to seven years; no specific tumor screening protocol has been established for neuroblastoma, gonadoblastoma, or medulloblastoma. Annual (or as indicated) ophthalmologic and audiologic evaluations in childhood; sleep study if there are concerns about sleep disturbance or sleep apnea; routine monitoring of renal 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* or *GCP4* pathogenic variant in the family in order to identify as early as possible those who would benefit from preventive measures, such as tumor surveillance in males.

Genetic counseling

Simpson-Golabi-Behmel syndrome type 1 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 of their daughters and none of their sons. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible for families in which the pathogenic variant has been identified.

Diagnosis

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

Suggestive Findings

The diagnosis of SGBS1 **should be suspected** in males with the following findings:

- **Macrosomia** (weight or length ≥95th percentile)
- **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 facial features in older individuals
  - Macrocephaly with or without a prominent forehead
  - Macrostomia (abnormally large mouth)
  - Macroglossia (abnormally large tongue) 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
  - Small mandible (micrognathia) in neonates; macrognathia in older individuals
- **Multiple congenital anomalies** (see Clinical Description)
  - Congenital heart disease
  - Conduction defects (transient QT interval prolongation)

- Supernumerary nipples
- Diastasis recti / umbilical hernia
- Diaphragmatic hernia
- Renal dysplasia / nephromegaly
- Cryptorchidism/hypospadias in males
- Hand and feet anomalies (brachydactyly, cutaneous syndactyly, polydactyly)

Establishing the Diagnosis

Male proband. The diagnosis of SGBS1 **is established** in a male proband with suggestive findings and/or a hemizygous pathogenic variant in *GPC3*, an intragenic or whole-gene deletion of *GPC3* that may include part or all of *GPC4*, or a large multiexon duplication of *GPC4* identified by molecular genetic testing (see Table 1).

Female proband. The diagnosis of SGBS1 **is usually established** in a female proband with suggestive findings and a heterozygous pathogenic variant in *GPC3*, an intragenic or whole-gene deletion of *GPC3* that may include part or all of *GPC4*, or a large multiexon duplication of *GPC4* identified by molecular genetic testing (see Table 1).

Note: (1) Intragenic pathogenic *GPC4* variants have not been described in isolation and are usually an extension of a deletion that includes *GPC3* [Vuillaume et al 2018]; however, 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]. (2) There are currently no reports of a female proband with biallelic pathogenic variants in either *GPC3* or *GPC4*. (3) To date, *GPC3* remains the principal monogenic contributor to SGBS [Vuillaume et al 2018].

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, concurrent or serial single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, 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. Because the phenotype of SGBS1 is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of SGBS1 has not been considered are more likely to be diagnosed using genomic testing (see Option 2). Any molecular findings must be interpreted in the context of the affected individual's clinical presentation [Vuillaume et al 2018].

Option 1

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

Serial single-gene testing. Sequence analysis of *GPC3* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Note: Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.

- Sequence analysis of *GPC3* is performed first, followed by gene-targeted deletion/duplication analysis if no pathogenic variant is found.
- If no pathogenic variant is found, **chromosomal microarray analysis (CMA)**, which uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *GPC3* and *GPC4*) that cannot be detected by sequence analysis, may be considered next.

Note: (1) CMA cannot determine the location or orientation of a duplication. (2) If a deletion or duplication is of sufficient size, fluorescence in situ hybridization (FISH) can be used to test parental samples for inheritance of the deletion or duplication.

A multigene panel that includes *GPC3*, *GPC4*, and other genes of interest (see Differential Diagnosis) may also be considered. A multigene panel may identify the genetic cause of the condition at a reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (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.

Option 2

When the diagnosis of SGBS1 is not 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.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 (SGBS1)

Gene [1]	Proportion of SGBS1 Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Detectable by Method			
		Sequence analysis [3, 4]	Gene-targeted deletion/duplication analysis [5]	CMA [6]	Karyotype
GPC3	70% [7]	~55% [8]	~43% [8, 9]	Rare [10]	2 individuals [11]

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, 4]	Gene-targeted deletion/duplication analysis [5]	CMA [6]	Karyotype
GPC4	Rare	Unknown [12]	Unknown [12]	Rare [10, 13]	None reported

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Pathogenic variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Lack of amplification by PCR prior to sequence analysis can suggest a putative (multi)exon or whole-gene deletion on the X chromosome in affected males; confirmation requires additional testing by gene-targeted deletion/duplication analysis.
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. 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.
7. Spencer et al [2016]
8. Vuillaume et al [2018]
9. Gene-targeted methods will detect single-exon up to whole-gene deletions; however, breakpoints of large deletions and/or deletion of adjacent genes may not be determined. CMA testing is appropriate to define breakpoints of large deletions.
10. A contiguous deletion of *GPC3* and *GPC4* has been identified in one family with SGBS1 [Veugelers et al 1998].
11. Two females reported [Punnett 1994, Pilia et al 1996]
12. 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].
13. 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].

Clinical Characteristics

Clinical Description

Males

Simpson-Golabi-Behmel syndrome type 1 (SGBS1) is characterized by pre- and postnatal macrosomia, distinctive facies, and variable visceral, skeletal, and neurodevelopmental abnormalities.

Macrosomia. Virtually all persons with SGBS1 have pre- and postnatal overgrowth. As with other macrosomic syndromes, hypoglycemia may be present in the neonatal period.

Macrocephaly. See Suggestive Findings.

Characteristic facies. See Suggestive Findings.

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 [Golabi & Rosen 1984].

Oropharynx. Macroglossia is a characteristic feature. 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].

Neck. Cystic hygroma has been described [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.

Cardiothoracic. 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 frequently been described [Lin et al 1999]. Transient QT interval prolongation has also been reported [Gertsch et al 2010].

Lungs. Abnormal branching of the bronchi and an abnormal lower airway pit have been described in one affected individual [Glamuzina et al 2009].

Genitourinary. Nephromegaly, multicystic kidneys, hydronephrosis, hydroureter, and duplicated ureters are described. Other genitourinary anomalies include hypospadias, bifid scrotum, cryptorchidism, hydrocele, and inguinal hernia [Hughes-Benzie et al 1996].

Gastrointestinal. GI 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], duplication of the pancreatic duct, and polysplenia.

Skeletal. Skeletal anomalies can include vertebral fusion, scoliosis, pectus excavatum, rib anomalies (including cervical ribs), congenital hip dislocation [Terespolsky et al 1995], small sciatic notches, and flared iliac wings [Chen et al 1993]. Extra lumbar vertebrae, spina bifida occulta, coccygeal skin tag, 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 [Day & Fryer 2005]. Nail dysplasia, hypoplasia (particularly of the index finger), and hypoconvexity are common.

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

Central nervous system (CNS). Normal intelligence has been described, but mild to severe intellectual disability is common, with language delay being the most characteristic finding.

Neurologic manifestations are perhaps the most varied findings. Hypotonia and absent primitive reflexes, a high-pitched cry in neonates, seizures, and abnormal EEG have all been described. Hydrocephalus, epilepsy, and attention-deficit/hyperactivity disorder may also be present [Tenorio et al 2014].

CNS malformations include agenesis of the corpus callosum, Chiari malformation and hydrocephalus [Young et al 2006], and aplasia of the cerebellar vermis.

Neoplasia. An absolute incidence and relative risk for tumors has not been established; the embryonic tumor frequency in persons with SGBS1 is likely between 5% and 10%; however, these numbers are based on case reports [Lapunzina et al 1998, Lin et al 1999]. At least six tumor types have been described [Lapunzina et al 1998, Li et al 2001, Lapunzina 2005, Thomas et al 2012].

- Wilms tumor (in 4 individuals)

- Hepatoblastoma (2)
- Adrenal neuroblastoma (1)
- Gonadoblastoma (1)
- Hepatocellular carcinoma (1)
- Medulloblastoma (1)

See Wilms Tumor Overview.

Other

- Diaphragmatic hernia and associated lung hypoplasia [Chen et al 1993]. See Congenital Diaphragmatic Hernia Overview.
- Thymic hypoplasia and generalized lymphoid atrophy [Chen et al 1993]

Heterozygous Females

Due to skewed X-chromosome inactivation, carrier females can have manifestations of SBGS including macrosomia, macrocephaly, 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]. Tall stature, coarse facial features, and developmental delay have also been reported [Gertsch et al 2010].

To date, eight heterozygous females with clinical expression of SGBS1 have been reported [Schirwani et al 2019]. The molecular genetic causes in these eight females are as follows: heterozygous *GPC3* and *GPC4* duplication (3), *GPC3* deletion (2), balanced X-chromosome translocations (2), and a heterozygous *GPC3* duplication (1) [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]. Although the genotype-phenotype correlation remains unknown, postnatal overgrowth, coarse facial features, congenital heart defects, intellectual disability, and hernias appear to be common features [Schirwani et al 2019].

Two females with a heterozygous *GPC3* pathogenic variant were reported to have two different types of cancer: one had a sero-papilliferous cystoadenoma, a low-grade ovarian carcinoma; the other had breast cancer [Gurrieri et al 2011]. Information was not sufficient to exclude other possible genetic causes for breast/ovarian cancer in the family.

Genotype-Phenotype Correlations

In a study of genotype-phenotype correlations, Mariani et al [2003] determined that all deletions and single-nucleotide variants occurring in the eight *GPC3* exons result in loss of function with no phenotypic distinctions based on size or position of a deletion or single-nucleotide variant.

Penetrance

Penetrance in heterozygous females is unknown, but mildly affected females have been reported. All males reported with a *GPC3* pathogenic variant have had clinical findings of SGBS1.

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 SGBS:

- 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 pathogenic variants in *GPC3* and *GPC4*.

Differential Diagnosis

Table 2. Disorders to Consider in the Differential Diagnosis of SGBS1

Disorder	Gene(s)	MOI	Clinical Features of the Differential Dignosis Disorder	
			Overlapping w/SGBS1	Distinguishing from SGBS1
Simpson-Golabi-Behmel syndrome type 2 (infantile lethal variant) (OMIM 300209)	*OFD1*, *PIGA* [1]	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 individuals • Macrocephaly • Macrostomia • Macroglossia • Cleft lip &/or submucous cleft palate (w/bifid uvula); high & narrow palate • Small mandible (micrognathia) in neonates; macrognathia in older individuals • Multiple congenital anomalies	More lethal form usually associated w/hydrops fetalis [2]

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping w/SGBS1	Distinguishing from SGBS1
Beckwith-Wiedemann syndrome (BWS)	See footnote 3	See footnote 3	• 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 • Individuals w/BWS are less tall & less dysmorphic & have fewer visceral & skeletal malformations.
Sotos syndrome	*NSD1*	AD	• Hypertelorism • Broad forehead • Downslanting palpebral fissures • Hypoglycemia	Seizures are more common. [4]
Weaver syndrome (see *EZH2*-Related Overgrowth)	*EZH2*	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 [4]) • Psychomotor delay typically more prominent
Nevoid basal cell carcinoma syndrome (NBCCS, Gorlin syndrome)	*PTCH*	AD	• Macrocephaly • Coarse facial features • Bifid ribs	• Multiple jaw keratocysts frequently beginning in 2nd decade of life • Basal cell carcinomas usually from 3rd decade onwards

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping w/SGBS1	Distinguishing from SGBS1
Fryns syndrome	Unknown	AR	• Coarse facies • Diaphragmatic hernia w/ lung hypoplasia • Cleft lip/palate • Congenital heart defects • Ear anomalies • Macrostomia	• Hydrocephalus • Micro-/retrognathia

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

1. Fauth et al [2016]

2. Tenorio et al [2014]

3. BWS is associated with abnormal regulation of gene transcription through methylation at one or both imprinted domains on chromosome 11p15.5. Most alterations are postzygotic, but rare cases are due to deletions, duplications, or chromosome rearrangements affecting 11p15.5. Most individuals with BWS have no family history of BWS; approximately 5%-10% have a family history consistent with parent-of-origin autosomal dominant transmission.

4. Baujat et al [2005]

Other syndromes that may share overlapping features:

- **Perlman syndrome** (OMIM 267000), a rare autosomal recessive condition caused by biallelic pathogenic variants in *DIS3L2*, includes macrosomia and a high incidence of Wilms tumor; facial features are distinctive and neonatal mortality is high.
- **Nevo syndrome,** an autosomal recessive condition that shares vertebral anomalies, ear malformations, cryptorchidism, overgrowth, and intellectual disability with SGBS1. Nevo syndrome manifestations further include accelerated osseous maturation, large extremities, and hypotonia. This condition is caused by pathogenic variants in exon 9 of *PLOD1* [Giunta et al 2005]. (See Ehlers-Danlos Syndrome, Kyphoscoliotic Form.)
- **Marshall-Smith syndrome** (OMIM 602535), which shares advanced bone age and intellectual disability with SGBS1; differences include facial features and predisposition to fractures. This condition is caused by a heterozygous pathogenic variant in *NFIX* and frequently occurs *de novo*.
- **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.
- **Infant of a diabetic mother syndrome.** Infants born to diabetic mothers (IDM) 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.
- **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** (or Pallister-Killian syndrome), 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

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with Simpson-Golabi-Behmel syndrome type 1 (SGBS1), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Simpson-Golabi-Behmel Syndrome Type 1

System/Concern	Evaluation	Comment
Oropharynx	Assess for macroglossia & orofacial clefting.	Referral to craniofacial team, incl feeding specialists
Eyes	Ophthalmologic examination	
Ears/Hearing	Audiologic evaluation	
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; formal sleep study should be considered.	Particularly in those w/hypotonia & macroglossia
Renal	Examination for hypospadias & undescended testes in males	Referral to urologist, as needed
	Renal ultrasound to assess for renal anomalies	
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 alpha fetoprotein	As a baseline screen for hepatoblastoma
Musculoskeletal	Clinical evaluation for scoliosis	Particularly during times of rapid growth
Neurologic	Neurologic evaluation, head MRI, &/or EEG	If concerns for seizures
Endocrinologic	Assessment for hypoglycemia	In neonates
Miscellaneous/ Other	Developmental assessment	Incl speech & language assessment
	Consultation w/clinical geneticist &/or genetic counselor	

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Simpson-Golabi-Behmel Syndrome Type 1

Manifestation/Concern	Treatment	Considerations/Other
Macroglossia, micrognathia, &/or glossoptosis	Prompt standard treatment to maintain a secure airway; consider feeding/swallowing evaluation.	May require care of a craniofacial team
Cleft palate or bifid uvula	Assessment of feeding & management by a cleft/ craniofacial team	
Obstructive sleep apnea (OSA)	If due to macroglossia, consider management similar to Beckwith-Wiedemann syndrome.	Limited data are available on prevalence & treatment of OSA in individuals w/SGBS1.
	Sleep study & potential CPAP or hemiglossectomy, if indicated	
Feeding difficulties	Milder feeding issues may be managed w/special nipples or nasogastric feeding in consultation w/ specialist.	Limited data are available on treatment of feeding difficulties in individuals w/SGBS1.
	Gastrostomy tube may be considered in those w/ severe feeding issues.	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Eyes	Standard treatment for strabismus and cataracts	
Hearing	Standard treatment for hearing loss	
Congenital heart defects & conduction abnormalities	Standard treatment as per cardiologist	
Hypospadias/cryptorchidism in males	Standard treatment as per urologist	
Musculoskeletal findings (i.e., scoliosis)	Standard treatment as per orthopedist	
Seizure disorder	Standard treatment as per neurologist	
Hypoglycemia or suspected hyperinsulinism	Prompt treatment as per endocrinologist	Consider referral to tertiary care center for hyperinsulinism evaluation, if suspected.
Developmental delay	Early referral for developmental support/special education, which may incl physical therapy, occupational therapy, speech therapy, &/or cognitive therapy	Consider referral to a neurodevelopmental specialist &/or neuropsychiatric testing.
Cancer predisposition	For Wilms tumor, nephron sparing surgery should be considered, if possible.	See Surveillance for the recommended tumor-screening protocol.

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

Table 5. Recommended Surveillance for Males with Simpson-Golabi-Behmel Syndrome Type 1

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

1. Kalish et al [2017]

Little information on tumor risk in heterozygous females is available; there are currently only two 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 apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing of the *GPC3* or *GCP4* pathogenic variant in the family in order to identify as early as possible those who would benefit from preventive measures, such as tumor surveillance in males.

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

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —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 pathogenic variant; 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 [Romanelli et al 2007]. The frequency of germline mosaicism is currently unknown.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote or the affected male may have either a *de novo* hemizygous pathogenic variant in *GPC3*, a *de novo* intragenic or whole-gene deletion of *GPC3* that may include part or all of *GPC4*, or a *de novo* large multiexon duplication of *GPC4*, in which case the mother is not a heterozygote. The frequency of *de novo* pathogenic variants is about 20%-30% [Tenorio et al 2014].

Parents of a female proband

- A female proband may have inherited the pathogenic variant from either her mother (who may or may not have manifestations of SBGS1) or her father [Støve et al 2017], or the pathogenic variant may be *de novo*.
- Detailed evaluation of the parents and review of the extended family history may help distinguish probands with a *de novo* pathogenic variant from those with an inherited pathogenic variant. Molecular genetic testing of the mother (and possibly the father, or subsequently the father) may help determine whether the pathogenic variant 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 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 heterozygotes and may be affected, as heterozygous females with features of SGBS1 have been reported (see Clinical Description, Heterozygous Females).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the

general population (though still <1%) 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 a SGBS1-causing pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes and may be affected; heterozygous females with features of SGBS1 have been reported (see Clinical Description, Heterozygous Females).
- If the father of the proband has a pathogenic variant, he will transmit it to all of his daughters and none of his sons. To date, one case of transmission from an affected father to his affected daughter has been reported [Støve el al 2017].
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the pathogenic variant cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population (though still <1%) 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. 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].

Affected males transmit the pathogenic variant to:

- All of their daughters, who will be heterozygotes and may be affected; heterozygous females with features of SGBS1 have been reported (see Clinical Description, Heterozygous Females).
- None of their sons.

Offspring of a female proband. Women with a pathogenic variant have a 50% chance of transmitting the pathogenic variant to each child:

- Males who inherit the pathogenic variant will be affected.
- Females who inherit the pathogenic variant will be heterozygotes (carriers) and may be affected; heterozygous females with features of SGBS1 have been reported (see Clinical Description, Heterozygous Females).

Other family members. The proband's maternal aunts may be at risk of being heterozygotes for the *GPC3* and/or *GPC4* pathogenic variant, and the aunts' offspring may be at risk of being having the pathogenic variant and being affected.

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

Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the pathogenic variant has been identified in the proband.

Note: (1) 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). (2) Identification of female heterozygotes requires either (a) prior identification of the pathogenic variant in the family or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

If the pathogenic variant has not been identified in the family, physical examination of at-risk female relatives and X-chromosome inactivation studies to determine if skewing of X-chromosome inactivation is present may identify some possible heterozygotes [Author, personal observation].

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, clarification of carrier status of at-risk females, and discussion of the availability of prenatal 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 are heterozygotes, or are at risk of being heterozygotes.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the SGBS1-causing pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

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, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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.

- **National Library of Medicine Genetics Home Reference**
  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

Table A. continued from previous page.

GPC4	Xq26.2	Glypican-4	GPC4 @ LOVD	GPC4	GPC4

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
300168	GLYPICAN 4; GPC4
312870	SIMPSON-GOLABI-BEHMEL SYNDROME, TYPE 1; SGBS1

Introduction

GPC3 and *GPC4* both encode glycosylphosphatidylinositol-linked cell surface heparan sulfate proteoglycans, which belong 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, Hedgehog pathway, BMP signaling, and FGF signaling [Paine-Saunders et al 2000, Song et al 2005, Ng et al 2009].

GPC3

Gene structure. *GPC3* comprises eight exons that span more than 500 kb. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. All eight exons of *GPC3* have been found to harbor deletions, duplications, or single-nucleotide variants that lead to the Simpson-Golabi-Behmel syndrome type 1 (SGBS1) phenotype. The majority of SGBS1 cases are attributable to *GPC3*.

In a review of 120 persons with SGBS1 caused by 86 pathogenic variants in *GPC3*, large deletions were the most common (34.9%), then frameshifts (24.4%), nonsense variants (16.3%), missense variants (8.1%), large duplications (8.1%), splice site variants (4.7%), translocations (2.3%), and one in-frame indel (1.2%) [Vuillaume et al 2018].

Approximately 50% of *GPC3* deletions involve exon 8 [Veugelers et al 2000]. Single-nucleotide variants have been described in all exons; as expected, most occur in exon 3, the largest exon.

Normal gene product. Glypican-3 is a glycosylphosphatidylinositol-linked cell surface heparan sulfate proteoglycan [Pilia et al 1996].

Abnormal gene product. 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].

GPC4

Gene structure. *GPC4* is adjacent to the 3' end of *GPC3* and comprises nine exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Duplication of exons 1-9 of *GPC4* **without** a *GPC3* pathogenic variant also leads to the SGBS1 phenotype [Waterson et al 2010]. Note: Loss-of-function variants in *GPC4* are **not** associated with SGBS1 [Veugelers et al 2000].

Normal gene product. Glypican-4 is also a glycosylphosphatidylinositol-linked cell surface heparan sulfate proteoglycan [Veugelers et al 1998].

Abnormal gene product. The mechanism by which duplication of *GPC4* leads to the SGBS1 phenotype is unknown.

GPC3/GPC4 Complex Deletions and Duplications

Deletion. DiMaio et al [2017] reported a familial case of SGBS1 caused by deletion of *GPC3*, *TFDP3*, **and** *GPC4*. *TFDP3* (OMIM 300772) encodes a member of the DP family of transcription factors, but has no known disease association [DiMaio et al 2017].

Duplication. Males and female carriers with complex *GPC3* and *GPC4* duplications have been reported [Schirwani et al 2019]. Additional atypical SGBS1 features, such as brain malformations, have been noted in these patients with the dual duplication, suggesting that the new features may be associated with the *GPC4* duplication [Mujezinović et al 2016]. Mujezinović et al [2016] suggest that the *GPC4* duplication could cause a greater disruption of GPC3 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].

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Chapter Notes

Author Notes

Mr Hathaway is a licensed genetic counselor.

Dr Kalish is board certified in pediatrics and clinical genetics and is an Assistant Professor of Pediatrics and Genetics.

Author History

Kathy Culver, MS; California Pacific Medical Center (2006-2011)
Mahin Golabi, MD, MPH; California Pacific Medical Center (2006-2018)
Christina X Gonzalez-Gandolfi, BA (2018-present)
Evan R Hathaway, MS, LCGC (2018-present)
Aaron James; University of California San Francisco (2006-2011)
Jennifer M Kalish, MD, PhD (2018-present)
Alva Leung, BS; California Pacific Medical Center (2011-2018)
Christina Lopez, BS; California Pacific Medical Center (2011-2018)
Brian J Sajorda, BA (2018-present)

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