U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Porter JM, Pena LDM, Spillmann RC, et al. Shashi-Pena Syndrome. 2024 Nov 7. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Shashi-Pena Syndrome

Synonym: SHAPNS

Julie M Porter, MD, PhD,[1] Loren DM Pena, MD, PhD,[2] Rebecca C Spillmann, MS, CGC,[3] Amanda Johnson,[4] and Vandana Shashi, MD[3]

Created: November 7, 2024.

Summary

Clinical characteristics

Shashi-Pena syndrome is characterized by distinctive facial features accompanied by variable further clinical findings. Facial features may include glabellar nevus simplex, widely spaced and prominent/proptotic eyes with epicanthal folds and ptosis, arched eyebrows, broad nasal tip, and low-set/posteriorly rotated ears. Dental anomalies may include early eruption and loss of teeth as well as small and fragile teeth. Most affected individuals have infantile hypotonia that frequently resolves over time. Macrosomia and macrocephaly are also common. Affected individuals can have variable developmental delay / intellectual disability, ranging from low-average intellectual abilities to severe intellectual disability. They often demonstrate difficulties with attention and aggressive behavior. Affected individuals may have feeding difficulties that require supportive nasogastric or gastrostomy tube feeding, skin findings (capillary malformations, deep palmar creases, hypertrichosis), skeletal anomalies (scoliosis/kyphosis, hypermobility, frequent fractures), congenital heart defects, seizures, hypoglycemia (most typically in infancy, may be due to hyperinsulinism), vision abnormalities (strabismus, amblyopia), conductive hearing loss, sleep apnea, temperature dysregulation, and global volume loss on brain MRI.

Diagnosis/testing

The diagnosis of Shashi-Pena syndrome is established in a proband with suggestive clinical findings and a heterozygous pathogenic variant in *ASXL2* identified by molecular genetic testing.

Management

Treatment of manifestations: Feeding therapy for those with feeding difficulties; consideration of nasogastric or gastrostomy tube placement for those with persistent feeding issues. Review of healthy eating habits; surveillance for euglycemia, hyperlipidemia, hypertension, and consideration of referral to nutrition for those who develop

Author Affiliations: 1 Cincinnati Children's Hospital and Medical Center, Cincinnati, Ohio; Email: julie.lander@hsc.utah.edu. 2 Cincinnati Children's Hospital and Medical Center; University of Cincinnati, Cincinnati, Ohio; Email: loren.pena@alumni.duke.edu. 3 Duke University, Durham, North Carolina; Email: rebecca.crimian@duke.edu; Email: vandana.shashi@duke.edu. 4 ARRE Foundation, Portland, Maine; Email: amanda@arrefoundation.org.

obesity. For infants with hypoglycemia, standard treatment with dextrose and avoidance of fasting is reasonable; octreotide has been used in those with hyperinsulinism. Rapid assessment and management of recurrent otitis media. Pressure-equalizing tubes may be indicated for those with conductive hearing loss. Standard treatment for developmental delay / intellectual disability / neurobehavioral issues, dental anomalies, epilepsy, scoliosis/kyphosis, hip dysplasia, congenital heart defects, ptosis, strabismus, refractive error, and sleep apnea.

Surveillance: At each visit, measure growth parameters; evaluate nutritional status and safety of oral intake; monitor for the following: developmental progress and educational needs; difficulties with attention, anger outbursts, and aggression; signs of ADHD, autism, and anxiety; new manifestations, such as seizures and changes in tone; signs/symptoms of temperature dysregulation; signs/symptoms of sleep apnea; signs of feeding difficulties; development of scoliosis/kyphosis; and signs/symptoms of hypoglycemia. As clinically indicated, consider spine radiographs and DXA scan in those with scoliosis/kyphosis and bony fractures, respectively; dental and/or orthodontic evaluation for those with more significant dental issues; ophthalmology evaluation; blood glucose monitoring if there are concerns about hypoglycemia; and audiology evaluation.

Agents/circumstances to avoid: Prolonged fasting should be avoided in those with hypoglycemia.

Genetic counseling

Shashi-Pena syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. Therefore, the risk to other family members is presumed to be low. Once the *ASXL2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Shashi-Pena syndrome have been published.

Suggestive Findings

Shashi-Pena syndrome **should be considered** in individuals with the following clinical findings and family history.

Clinical findings

- Distinctive facial features (most recognizable in infancy and becoming less discernible in older individuals) (see Figure 1):
  - Nevus simplex in the glabellar region of the forehead
  - Widely spaced and prominent/proptotic eyes with epicanthal folds
  - Ptosis
  - Arched eyebrows
  - Broad nasal tip
  - Low-set/posteriorly rotated ears
- Macrosomia, defined as weight and length/height >2 standard deviations (SD) above the mean for age and sex.
- Macrocephaly, defined as a head circumference that is >2 SD above the mean for age and sex
- Generalized hypotonia of infancy
- Mild-to-severe developmental delay or intellectual disability
- Seizures, which may be febrile and/or non-febrile; among the non-febrile seizures, focal, generalized tonic-clonic, and absence have been described.
- Dental findings, including early tooth eruption, premature loss of primary dentition, and small teeth
- Congenital heart defects
- Hypoglycemia that typically starts in the neonatal period and can be persistent into older ages

- Deep palmar/plantar creases
- Skeletal manifestations, including scoliosis/kyphosis or frequent fractures

Family history. Because Shashi-Pena syndrome is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Potentially, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations), although all known affected individuals to date have had a *de novo* genetic change.

Establishing the Diagnosis

The diagnosis of Shashi-Pena syndrome **is established** in a proband with suggestive clinical findings and a heterozygous pathogenic (or likely pathogenic) variant in *ASXL2* identified by molecular genetic testing (see Table 1 and Molecular Genetics).

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 both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of a heterozygous *ASXL2* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing) 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 Shashi-Pena syndrome 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 Shashi-Pena syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *ASXL2* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: (1) To date, all pathogenic variants associated with the classic findings of Shashi-Pena syndrome have been *de novo* frameshift, nonsense, or damaging splice variants in the last two exons of *ASXL2* resulting in premature protein truncation (see Molecular Genetics). (2) A few individuals with pathogenic *ASXL2* missense variants or genetic rearrangements involving *ASXL2* have been reported with some overlapping neurodevelopmental features of Shashi-Pena syndrome, but they typically lack many other characteristic features of Shashi-Pena syndrome. For a more complete discussion, see Genetically Related Disorders.
- **A multigene panel (intellectual disability panel, overgrowth panel, macrocephaly panel, or hypoglycemia panel)** that includes *ASXL2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) 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

Figure 1. Photographs of six affected individuals at different ages. Distinctive facial features include epicanthal folds, widely spaced eyes, a wide nasal bridge, broad nasal tip, and a glabellar nevus simplex.

Reproduced with permission from Shashi et al [2016]

custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician.

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

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 Shashi-Pena Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
ASXL2	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4, 6]

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. Shashi et al [2016]; Alqaisi & Hassona [2022]; Murphy et al [2022]; Ho et al [2023]; Yuan et al [2023]; Zheng et al [2023]; JM Porter, LDM Pena, RC Spillmann, A Johnson, & V Shashi, unpublished data
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. To date, no large intragenic deletions/duplications have been reported in individuals with Shashi-Pena syndrome.

Clinical Characteristics

Clinical Description

Shashi-Pena syndrome is characterized by distinctive facial features accompanied by variable further clinical findings, which may include macrocephaly, dental anomalies, congenital heart defects, seizures, hypoglycemia, hypotonia, developmental delays / intellectual disabilities, skeletal abnormalities, and global volume loss on brain MRI.

To date, at least 23 individuals have been identified with pathogenic truncating variants in *ASXL2*, including published and non-published individuals [Shashi et al 2016; Alqaisi & Hassona 2022; Murphy et al 2022; Ho et al 2023; Yuan et al 2023; Zheng et al 2023; JM Porter, LDM Pena, RC Spillmann, A Johnson, & V Shashi, unpublished data]. The following description of the phenotypic features associated with this condition is based on these individuals.

Table 2. Shashi-Pena Syndrome: Frequency of Select Features [1, 2]

Feature	Number of Persons w/Feature	Comment
Glabellar nevus simplex	23/23 (100%)	
Distinctive facial features	22/22 (100%)	See Suggestive Findings.
Dental abnormalities	14/14 (100%)	Early eruption & loss; small, fragile teeth
Developmental delay / intellectual disability	20/21 (95%)	Variable, ranging from low-average intellectual abilities to severe intellectual disabilities
Hypotonia	19/20 (95%)	Gradual improvement w/age; likely to be central
Other skin findings	17/20 (85%)	Capillary malformations (11/20), deep palmar creases (6/20), hypertrichosis (4/20)
Feeding difficulties (newborn)	17/20 (85%)	May require nasogastric/gastrostomy tube feeding, but usually resolve over time
Feeding difficulties (childhood)	5/18 (28%)	
Skeletal anomalies	14/17 (82%)	May incl scoliosis/kyphosis, hypermobility, &/or frequent fractures

Table 2. continued from previous page.

Feature	Number of Persons w/Feature	Comment
Congenital heart defects	17/21 (81%)	ASD, PFO, PDA
Macrocephaly	15/20 (75%)	Congenital & acquired both reported
Vision abnormalities	11/15 (73%)	Strabismus, amblyopia; ptosis is part of the distinctive facial features
Behavior problems	10/14 (71%)	Aggression, anger outbursts
Seizures	12/18 (67%)	Febrile &/or non-febrile
Hypoglycemia	13/20 (65%)	Most often in neonates & may be due to hyperinsulinism; frequently resolves over time
Macrosomia	10/18 (55%)	
Hearing loss	7/15 (47%)	Typically conductive
Sleep apnea	7/15 (47%)	May be obstructive or mixed central/obstructive
Temperature dysregulation	6/14 (43%)	

ASD = atrial septal defect; PFO = patent foramen ovale; PDA = patent ductus arteriosus
1. Data is derived from 12 published individuals and 11 unpublished individuals [Shashi et al 2016; Alqaisi & Hassona 2022; Murphy et al 2022; Ho et al 2023; Yuan et al 2023; Zheng et al 2023; JM Porter, LDM Pena, RC Spillmann, A Johnson, & V Shashi, unpublished data].
2. Data points were missing for some individuals, so the denominator for each feature is indicated in the table.

Skin. Glabellar nevus simplex has been seen in all individuals diagnosed with Shashi-Pena syndrome but may fade with age. Other dermatologic findings include deep palmar creases, hypertrichosis, and capillary malformations.

Craniofacial features. Individuals with Shashi-Pena syndrome demonstrate a distinct facial gestalt summarized in Suggestive Findings (see Figure 1). Notably, these features tend to be more evident at younger ages and may not be as readily recognizable in older individuals.

Dental. Teeth often erupt early and are small with weak enamel [Alqaisi & Hassona 2022]. Likewise, primary teeth are often lost early with early eruption of secondary (permanent) teeth. Additional dental features include:

- Gingival overgrowth
- Microdontia
- Sialorrhea
- Increased alveolar bone density

Developmental delay (DD) and/or intellectual disability (ID). To date, almost all identified individuals with Shashi-Pena syndrome have demonstrated some degree of developmental delay and/or intellectual disability ranging from mild to severe.

- Gross motor delays have manifested as delayed walking (range: age 18 months to after age 4 years).
- Verbal communication may be achieved as early as age two years, although some affected individuals continued to be nonverbal at age four years.
- The range of intellectual abilities extends from low-average IQ (reported in one such person) to severe ID.

Other neurologic features

- **Hypotonia** is observed in almost all infants with Shashi-Pena syndrome and tends to improve as affected individuals enter childhood to adolescence.

- **Temperature dysregulation.** Several affected individuals reported overheating easily and higher basal body temperatures.
- **Seizures** have been reported in about two thirds of individuals with Shashi-Pena syndrome.
    - Of these, about one third have febrile seizures only, one third have non-febrile seizures only, and one third have both febrile and non-febrile seizures.
    - Among non-febrile seizures, generalized tonic-clonic, focal, and absence seizures have been described.
    - There is no specific pattern of EEG changes noted in people with Shashi-Pena syndrome, but EEG findings tend to be consistent with the reported seizure type.
    - Seizures are typically well controlled with standard anti-seizure medications when needed (see Management).

Neurobehavioral/psychiatric manifestations. Anger outbursts and aggression are common and can be difficult to manage. No specific treatment has been found to be superior for behavioral challenges. Anxiety, attention-deficit/hyperactivity disorder, and autism spectrum disorder, either as single diagnoses or in combination, have been observed in a few affected individuals, but there is not enough data to determine if these are consistent findings in individuals with Shashi-Pena syndrome.

Growth. At least two thirds of individuals with Shashi-Pena syndrome have macrosomia, which may be associated with advanced bone age. Macrocephaly is present in about three quarters of affected individuals. Macrocephaly and macrosomia may be present at birth or develop over time.

Gastrointestinal problems. The majority of affected individuals demonstrate feeding difficulties from infancy, most likely due to low tone. Typically this is transient and may be accompanied by poor uncoordinated suck/latch, which can translate into oral apraxia in childhood. Dysphagia and aspiration are not common findings in this condition, and affected individuals are typically able to eat by mouth as children and into adulthood. However, some affected individuals experience sensory issues / food texture aversions.

Musculoskeletal features. Skeletal abnormalities are common in Shashi-Pena syndrome.

- About two thirds of affected individuals have scoliosis/kyphosis (11/16; 69%) and/or joint hypermobility (9/14; 64%), although without frank joint dislocations.
- Scoliosis/kyphosis may require significant surgical intervention.
- A predisposition to fractures (5/17; 29%) and hip dysplasia have been noted in fewer than one third of affected individuals.

Cardiac abnormalities. Cardiac anomalies have been identified in about 80% of people with Shashi-Pena syndrome. The most common reported findings are atrial septal defects or patent ductus arteriosus. Other rare findings may include the following:

- Ventricular septal defects
- Coarctation of the aorta
- Pulmonary artery valve thickening
- Pulmonary artery stenosis

Ophthalmologic involvement. About three quarters of people with Shashi-Pena syndrome have ophthalmologic findings, most commonly strabismus and amblyopia. Ptosis is one of the distinctive facial features seen in affected individuals but does not typically impact vision.

Endocrinologic. More than half of affected individuals have hypoglycemia at some point in life.

- The exact presentation is variable. Some affected individuals experienced hypoglycemia only in the neonatal period, others had episodic hypoglycemia, and one affected individual had severe hypoglycemia requiring continuous feeds.
- Hyperinsulinism has been documented in at least two affected individuals, and one was successfully treated with octreotide [Yuan et al 2023] (see Management).

Hearing loss has been identified in approximately half of reported individuals. This is typically conductive hearing loss and may normalize after intervention such as pressure-equalizing (PE) tubes. Multiple sets of PE tubes may be needed. One affected individual had sensorineural hearing loss and received cochlear implants.

Respiratory issues. Nearly half of reported individuals have sleep apnea. While this has not been well characterized in people with Shashi-Pena syndrome, obstructive and mixed obstructive/central sleep apnea has been described. Some affected individuals require positive pressure ventilation during sleep.

Other reported findings

- **Neuroimaging.** Brain MRI findings are common (15/17; 88%) but are nonspecific. Affected individuals have been noted to have white matter volume loss and increased extra-axial cerebral space.
- **Hematologic.** Granulocytopenia and thrombocytopenia were reported together in one affected individual [Jiao et al 2022] but have not otherwise been identified as a recurring feature of Shashi-Pena syndrome.

Genotype-Phenotype Correlations

Although no genotype-phenotype correlations have been identified, thus far all pathogenic variants associated with the classic findings of Shashi-Pena syndrome have been *de novo* pathogenic frameshift, nonsense, or damaging splice variants in the last two exons of the gene resulting in premature protein truncation (see Molecular Genetics).

Prevalence

The exact prevalence of Shashi-Pena syndrome is unknown; it likely is an ultra-rare condition [Richter et al 2018].

Genetically Related (Allelic) Disorders

No phenotypes other than that discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ASXL2*.

A few individuals with missense variants or genetic rearrangements involving *ASXL2* have been reported with some overlapping neurodevelopmental features of Shashi-Pena syndrome, but reported individuals lack many other characteristic features of Shashi-Pena syndrome.

- **Missense variants** in *ASXL2* have been reported as pathogenic and as variants of uncertain clinical significance [Cuddapah et al 2021; JM Porter, LDM Pena, RC Spillmann, A Johnson, & V Shashi, unpublished data] in individuals with features including developmental delay or intellectual disability. However, the individuals do not demonstrate the classic features of Shashi-Pena syndrome and the variants are often identified in an unaffected parent. Thus, there is insufficient information at this time to determine if the missense variants are associated with a neurodevelopmental phenotype without other classic features of Shashi-Pena syndrome.
- **Chromosome abnormalities.** There have been no reported *ASXL2* exonic deletions in individuals with the phenotype of Shashi-Pena syndrome, and there is no evidence thus far that haploinsufficiency of the

protein encoded by *ASXL2* (putative Polycomb group protein ASXL2) contributes to this phenotype. The DECIPHER database lists seven individuals with cytogenetic deletions encompassing *ASXL2* and other adjacent genes (ranging from 35 to 141 genes) and phenotypes including developmental delays or intellectual disabilities, among other manifestations [Firth et al 2009]. Because of the nature of the contiguous gene deletion, the specific contribution of the *ASXL2* deletion to these phenotypes cannot be determined.

One family with a balanced t(2;11)(p23;q23) translocation that disrupted normal expression of *ASXL2* has been reported [Wang et al 2021]. The proband demonstrated developmental delay but was lacking many key features of Shashi-Pena syndrome, including the facial gestalt and macrocephaly. The translocation was found in two additional family members (the proband's father and paternal grandmother) who had overall normal development and no significant features of Shashi-Pena syndrome. This report demonstrated a decrease in *ASXL2* mRNA levels in affected individuals, which is inconsistent with the proposed dominant-negative mechanism of disease causation (see Molecular Genetics).

Sporadic tumors (including liver cancer, myeloid malignancies, and pancreatic cancer) occurring as single tumors in the absence of any other findings of Shashi-Pena syndrome frequently contain a somatic pathogenic variant in *ASXL2* that is not present in the germline. In these circumstances predisposition to these tumors is not heritable.

Differential Diagnosis

Table 3. Genes of Interest in the Differential Diagnosis of Shashi-Pena Syndrome

Gene / Genetic Mechanism	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/Shashi-Pena syndrome	Distinguishing from Shashi-Pena syndrome
ASXL1	Bohring-Opitz syndrome	AD	• Glabellar nevus simplex • Hypertelorism, prominent eyes • Hypertrichosis • Seizures	• Poor postnatal weight gain & linear growth • Microcephaly • More severe feeding difficulties incl cyclic vomiting • High myopia • BOS posture [1] • Severe-to profound-ID
ASXL3	*ASXL3*-related disorder (Bainbridge-Ropers syndrome)	AD	• DD • Hypotonia • Feeding difficulties • Epilepsy	• Marfanoid habitus • Pectus excavatum • Joint flexion w/contractures
Abnormal methylation at 11p15.5; *CDKN1C* [2]	Beckwith-Wiedemann syndrome	See footnote 2.	• Macrosomia • Glabellar nevus simplex	• Distinctive facial appearance (in some persons) • Asymmetric growth
GPC3	Simpson-Golabi-Behmel syndrome type 1	XL	• Macrosomia • Widely spaced eyes	• Coarse facial features • Macroglossia • Bifid uvula
NSD1	Sotos syndrome	AD	• Overgrowth (height &/or head circumference ≥2 SD above mean) • ID • Congenital heart defects • Advanced bone age	• Overall facial gestalt • Prognathism

Table 3. continued from previous page.

Gene / Genetic Mechanism	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/Shashi-Pena syndrome	Distinguishing from Shashi-Pena syndrome
PTEN	*PTEN* hamartoma tumor syndrome	AD	• Macrocephaly • DD	• Hamartomatous polyps • Cancer
RRAS2 [3]	*RRAS2*-related Noonan syndrome	AD	• Glabellar nevus simplex • Macrocephaly • Hypertelorism	Facial appearance is characteristic.

AD = autosomal dominant; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked
1. The Bohring-Opitz syndrome (BOS) posture, which is most striking in early childhood and often becomes less apparent with age, is characterized by flexion at the elbows with ulnar deviation and flexion of the wrists and metacarpophalangeal joints.
2. Beckwith-Wiedemann syndrome (BWS) is associated with either an epigenetic or genomic alteration leading to abnormal methylation at 11p15.5 or a heterozygous BWS-causing pathogenic variant in *CDKN1*. The risk to the sibs of a child with BWS depends on the genetic basis of BWS in the proband.

Management

No clinical practice guidelines for Shashi-Pena syndrome have been published.

Evaluations Following Initial Diagnosis

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

Table 4. Shashi-Pena Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters, incl head circumference	To assess for macrocephaly & overgrowth
Dental	Dental eval	Typically for those age >3 yrs at time of diagnosis
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neurobehavioral screening assessment	For persons age >12 mos: screening for concerns incl difficulties w/ attention, anger outbursts, & aggression. Screening may follow the AAP guidelines to include M-CHAT-R/F™ and other instruments to assess for autistic features.
Neurologic	Neurologic eval	• Consider brain MRI for rapidly ↑ head circumference or focal seizures. • Consider EEG if seizures are a concern. • Incl assessment for temperature dysregulation.
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in those w/ feeding difficulties.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) • Clinical assessment for scoliosis/kyphosis & history of fractures
Cardiovascular	Echocardiogram	To evaluate for congenital heart defects
Eyes	Ophthalmologic eval	To assess for ptosis, strabismus, & vision abnormalities
Endocrine	• In neonates, obtain serum blood glucose level • In older infants & children, assess for signs/symptoms of hypoglycemia; consider obtaining a serum glucose level in those w/ suspicious symptoms.	If hypoglycemia is present in neonatal period, eval for evidence of hyperinsulinism.
Hearing	Audiologic eval	Assess for hearing loss.
Respiratory	Consider sleep study.	For those who have signs/symptoms concerning for sleep apnea
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of Shashi-Pena syndrome to facilitate medical & personal decision making
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support

AAP = American Academy of Pediatrics; ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; M-CHAT-R/F^{TM} = Modified Checklist for Autism in Toddlers, Revised, with Follow-Up; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for Shashi-Pena syndrome. 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. Shashi-Pena Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Dental anomalies	Standard treatment per dentist/orthodontist	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Feeding difficulties	• Feeding therapy • Nasogastric or gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval
Obesity	• Review of healthy eating habits • Surveillance for euglycemia, hyperlipidemia, hypertension	Consider referral to nutritionist.
Scoliosis, kyphosis, hip dysplasia	Standard treatment per orthopedist	May require significant surgical intervention
Congenital heart defects	Standard treatment per cardiologist	Several persons w/ASDs have required surgical closure.
Ptosis, strabismus, refractive error	Standard treatment per ophthalmologist	
Hypoglycemia	Standard treatment: dextrose, avoiding fasting, continuous feeds, octreotide, if appropriate	Consider referral to endocrinologist.
Hearing	• Rapid assessment & mgmt of recurrent otitis media; PE tubes may be indicated. • Hearing aids may be helpful per otolaryngologist.	• Community hearing services through early intervention or school district • 1 affected person received cochlear implants.
Sleep apnea	Standard treatment per otolaryngologist &/or sleep medicine specialist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASD = atrial septal defect; ASM = anti-seizure medication; OT = occupational therapy; PE = pressure-equalizing; PT = physical therapy

1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

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 as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

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 for those who qualify based on established motor, language, social, or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

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

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US 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 and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).

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 should be assessed at each visit, and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

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. Shashi-Pena Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Constitutional	• Measure growth parameters. • Evaluate nutritional status & safety of oral intake.	At each visit
Development	Monitor developmental progress & educational needs.	
Neurobehavioral/Psychiatric [1]	• Monitor for difficulties w/attention, anger outbursts, & aggression. • Monitor for signs of ADHD, autism spectrum disorder, & anxiety.	
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures & changes in tone. • Monitor for signs/symptoms of temperature dysregulation.	
Respiratory	Monitor for signs/symptoms of sleep apnea.	
Gastrointestinal	Monitor for signs of feeding difficulty.	
Musculoskeletal	• Physical medicine, OT/PT assessment of mobility, self-help skills • Clinical exam for scoliosis/kyphosis	
	Spine radiographs	As clinically indicated
	DXA scan	
Dental	Dental &/or orthodontic eval	As clinically indicated for those w/more significant dental issues
Eyes	Ophthalmology eval	Annually or as clinically indicated
Endocrine	• Assess for signs/symptoms of hypoglycemia. • Monitor & educate caregivers re symptoms of hypoglycemia or hyperglycemia.	At each visit
	Blood glucose monitoring	As clinically indicated
Hearing	Audiology eval	

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

ADHD = attention-deficit/hyperactivity disorder; DXA = dual-energy x-ray absorptiometry; OT = occupational therapy; PT = physical therapy

1. Referral to a developmental pediatrician or mental health provider with experience working with children with complex needs may be indicated.

Agents/Circumstances to Avoid

Prolonged fasting should be avoided in those with hypoglycemia.

Evaluation of Relatives at Risk

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

Pregnancy Management

In general, women with epilepsy or a seizure disorder of any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of anti-seizure medication (ASM) during pregnancy reduces this risk. However, exposure to ASMs may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from ASM exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of ASMs to treat a maternal seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given ASM during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

See MotherToBaby for further information on medication use during pregnancy.

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

Shashi-Pena syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- To date, all known individuals with Shashi-Pena syndrome have the disorder as the result of a *de novo* *ASXL2* pathogenic variant.
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
    - The proband has a *de novo* pathogenic variant.
    - The proband inherited a pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism. * Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

      * A parent with somatic and gonadal mosaicism for an *ASXL2* pathogenic variant may be mildly/minimally affected.

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

- If a parent of the proband is heterozygous for the *ASXL2* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- If the *ASXL2* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the possibility of parental gonadal mosaicism [Rahbari et al 2016].

Offspring of a proband. Each child of an individual with Shashi-Pena syndrome has a 50% chance of inheriting the *ASXL2* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *ASXL2* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *ASXL2* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

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

- **ASXL Rare Research Endowment (ARRE) Foundation**
  Email: info@arrefoundation.org
  arrefoundation.org/shashi-pena
- **ASXL-Related Disorders and Chromatinopathies Registry**
  Natural History Study
  Email: asxl-chromatin-registry@mednet.ucla.edu

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. Shashi-Pena Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ASXL2	2p23.3	Putative Polycomb group protein ASXL2	ASXL2	ASXL2

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 Shashi-Pena Syndrome (View All in OMIM)

612991	ASXL TRANSCRIPTIONAL REGULATOR 2; ASXL2
617190	SHASHI-PENA SYNDROME; SHAPNS

Molecular Pathogenesis

ASXL2 is one of three Polycomb group protein genes that act as histone methyltransferases and are implicated in embryogenesis, encoding the putative Polycomb group protein ASXL2. In mice, *Asxl2* has been reported to regulate skeletal, lipid, and glucose homeostasis and cardiac development [Khan et al 2014, Izawa et al 2015]. The three *ASXL* genes (*ASXL1*, *ASXL2*, and *ASXL3*) are involved in body patterning and encode proteins that participate in epigenetic regulation. Each one of the *ASXL* genes is involved in a developmental disorder: in addition to *ASXL2* pathogenic variants, loss-of-function pathogenic variants in *ASXL1* lead to Bohring-Opitz syndrome, and *ASXL3* loss-of-function pathogenic variants lead to Bainbridge-Ropers syndrome (see Differential Diagnosis). Although the three conditions share overlapping features, individuals with Shashi-Pena syndrome are distinguished by findings of overgrowth and a greater variation in intellectual abilities. Another distinction is that the mechanism of disease causation for Shashi-Pena syndrome appears to be through a dominant-negative effect. This is supported by biallelic expression in blood for both wild type and mutated *ASXL2* alleles. All variants identified to date map to the final two exons of *ASXL2*, and the lack of reduction in transcript expression supports escape from nonsense-mediated decay for transcripts from the variant alleles. Additional molecular studies are needed to confirm and elucidate the dominant-negative mechanism.

Mechanism of disease causation. Current evidence indicates that the mechanism of disease is dominant-negative.

***ASXL2*-specific laboratory technical considerations.** In the original clinical publication by Shashi et al [2016], *ASXL2* was described to have 12 exons. Since then, the transcript has been updated to include 13 exons. This update does not change the original observation of all pathogenic variants being located in the final two exons.

Chapter Notes

Acknowledgments

We gratefully acknowledge the families with Shashi-Pena syndrome and the ARRE Foundation for their support in data gathering as we expand our understanding of the disorder.

We would like to acknowledge Wenying Zhang, MD, PhD, MBA, and Yaning Wu, MD, PhD, from Cincinnati Children's Hospital for assistance in interpretation of genomic data.

The authors also wish to acknowledge funding support from the Undiagnosed Diseases Network, which made the 2016 publication of the initial cohort of affected individuals possible.

Revision History

- 7 November 2024 (ma) Review posted live
- 8 March 2024 (lp) Original submission

References

Literature Cited

Alqaisi D, Hassona Y. Oral findings and healthcare management in Shashi-Pena syndrome. Spec Care Dentist. 2022;42:432-6. PubMed PMID: 34902171.

Cuddapah VA, Dubbs HA, Adang L, Kugler SL, McCormick EM, Zolkipli-Cunningham Z, Ortiz-González XR, McCormack S, Zackai E, Licht DJ, Falk MJ, Marsh ED. Understanding the phenotypic spectrum of ASXL-related disease: ten cases and a review of the literature. Am J Med Genet A. 2021;185:1700-11. PubMed PMID: 33751773.

Firth HV, Richards SM, Bevan AP, Clayton S, Corpas M, Rajan D, Van Vooren S, Moreau Y, Pettett RM, Carter NP. DECIPHER: database of chromosomal imbalance and phenotype in humans using Ensembl resources. Am J Hum Genet. 2009;84:524-33. PubMed PMID: 19344873.

Ho SKL, Cheng SSW, Cheng THT, Leung LT, Lam EKY, Mok MTS, Lo IFM, Luk HM. Extending the phenotype of Shashi-Pena syndrome: a case report and review of literature. Clin Dysmorphol. 2023;32:139-46. PubMed PMID: 37195319.

Izawa T, Rohatgi N, Fukunaga T, Wang QT, Silva MJ, Gardner MJ, McDaniel ML, Abumrad NA, Semenkovich CF, Teitelbaum SL, Zou W. ASXL2 regulates glucose, lipid, and skeletal homeostasis. Cell Rep. 2015;11:1625-37. PubMed PMID: 26051940.

Jiao Z, Zhao X, Wang Y, Wei E, Mei S, Liu N, Kong X, Shi H. A de novo and novel nonsense variants in ASXL2 gene is associated with Shashi-Pena syndrome. Eur J Med Genet. 2022;65:104454. PubMed PMID: 35182806.

Khan FF, Li Y, Balyan A, Wang QT. WTIP interacts with ASXL2 and blocks ASXL2-mediated activation of retinoic acid signaling. Biochem Biophys Res Commun. 2014;451:101-6. PubMed PMID: 25065743.

Murphy SA, O'Rourke NE, O'Grady MJ. Prepubertal onset of type 2 diabetes in Shashi-Pena syndrome due to ASXL2 mutation. Am J Med Genet A. 2022;188:2803-7. PubMed PMID: 35716351.

Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. Nat Genet. 2016;48:126-33. PubMed PMID: 26656846.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Richter T, Janoudi G, Amegatse W, Nester-Parr S. Characteristics of drugs for ultra-rare diseases versus drugs for other rare diseases in HTA submissions made to the CADTH CDR. Orphanet J Rare Dis. 2018;13:15. PubMed PMID: 29386040.

Sarma AK, Khandker N, Kurczewski L, Brophy GM. Medical management of epileptic seizures: challenges and solutions. Neuropsychiatr Dis Treat. 2016;12:467-85. PubMed PMID: 26966367.

Shashi V, Pena LD, Kim K, Burton B, Hempel M, Schoch K, Walkiewicz M, McLaughlin HM, Cho M, Stong N, Hickey SE, Shuss CM; Undiagnosed Diseases Network; Freemark MS, Bellet JS, Keels MA, Bonner MJ, El-Dairi M, Butler M, Kranz PG, Stumpel CT, Klinkenberg S, Oberndorff K, Alawi M, Santer R, Petrovski S, Kuismin O, Korpi-Heikkilä S, Pietilainen O, Aarno P, Kurki MI, Hoischen A, Need AC, Goldstein DB, Kortüm F. De novo truncating variants in ASXL2 are associated with a unique and recognizable clinical phenotype. Am J Hum Genet. 2016;99:991-9. PubMed PMID: 27693232.

Wang Y, Tan J, Wang Y, Liu A, Qiao F, Huang M, Zhang C, Zhou J, Hu P, Xu Z. Diagnosis of Shashi-Pena syndrome caused by chromosomal rearrangement using nanopore sequencing. Neurol Genet. 2021;7:e635. PubMed PMID: 34841066.

Yuan M, Shan Y, Xu F, Yang L, Sun C, Cheng R, Wu B, Zhang Z, Cao Y, Zhang R, Zhou W, Cheng G, Hu L. A newborn with a pathogenic variant in ASXL2 expanding the phenotype of SHAPNS: a case report and literature review. Transl Pediatr. 2023;12:86-96. PubMed PMID: 36798937.

Zheng Y, Yang L, Niu M, Zhao S, Liang L, Wu Y, Li T, Yang F, Yang Z, Wang Y, Wang D. Identification of a de novo variant in the ASXL2 gene related to Shashi-Pena syndrome. Mol Genet Genomic Med. 2023;11:e2251. PubMed PMID: 37493007.

License