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SHORT Syndrome

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Summary

Clinical characteristics

SHORT syndrome is a mnemonic for *s*hort stature, *h*yperextensibility, *o*cular depression (deeply set eyes), *R*ieger anomaly, and *t*eething delay. It is now recognized that the features most consistently observed in SHORT syndrome are mild intrauterine growth restriction (IUGR); mild to moderate short stature; partial lipodystrophy (evident in the face, and later in the chest and upper extremities, often sparing the buttocks and legs); and a characteristic facial gestalt. Insulin resistance may be evident in mid-childhood or adolescence, although diabetes mellitus typically does not develop until early adulthood. Other frequent features include Axenfeld-Rieger anomaly or related ocular anterior chamber dysgenesis, delayed dentition and other dental issues, and sensorineural hearing loss.

Diagnosis/testing

The diagnosis of SHORT syndrome is established in a proband with compatible clinical features (with emphasis on the facial gestalt) and a heterozygous pathogenic variant in *PIK3R1* identified by molecular genetic testing.

Management

Treatment of manifestations: Glaucoma: reduce and stabilize intraocular pressure and to preserve vision. Sensorineural hearing loss: use of hearing aids. Dental anomalies: standard treatment; may include crowns and dental prostheses. Glucose intolerance and diabetes mellitus: to be followed by an endocrine specialist.

Surveillance: Regular monitoring of growth including height, weight, and body mass index. For all individuals with and without apparent anterior chamber anomaly: routine eye examinations to include measurement of intraocular pressure. Hearing assessment every two to three years. Screening for insulin resistance by oral glucose tolerance test every five years in the absence of diabetes. Annual screening lab tests for diabetes mellitus beginning after age ten years.

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Agents/circumstances to avoid: Administration of human growth hormone as it may exacerbate insulin resistance. One individual with SHORT syndrome had worsening insulin resistance when treated with metformin; additional study is needed to determine the effects of this drug.

Pregnancy management: If present, diabetes mellitus is managed as appropriate.

Genetic counseling

SHORT syndrome is inherited in an autosomal dominant manner. The proportion of individuals with SHORT syndrome caused by a *de novo* pathogenic variant is unknown but appears to be significant. Each child of an individual with SHORT syndrome has a 50% chance of inheriting the pathogenic variant. Prenatal testing for pregnancies at increased risk and preimplantation genetic testing are possible if the pathogenic variant has been identified in an affected family member.

Diagnosis

The designation SHORT syndrome was coined by Gorlin et al [1975] to reflect several of the most striking clinical features of the original reported cases: *s*hort stature, *h*yperextensibility, *o*cular depression (deeply set eyes), *R*ieger anomaly, and *t*eething delay. However, it is now recognized that these five features are neither required to make the diagnosis nor necessarily the most specific features of SHORT syndrome.

Suggestive Findings

SHORT syndrome **should be suspected** in individuals with some combination of the following findings:

- Intrauterine growth restriction
- Short stature
- Partial lipodystrophy
- Characteristic facial gestalt (see Figure 1). The face has a triangular appearance. The forehead is broad and the eyes are deep-set. The nose has a narrow tip and thin nasal alae. The columella is low-hanging. The middle and lower thirds of the face are relatively small. The corners of the mouth are downturned and the chin can be dimpled. The ears are often prominent but not low-set or posteriorly rotated.
- Axenfeld-Rieger anomaly or related anterior chamber ocular anomalies
- Delayed dentition
- Insulin resistance / diabetes mellitus

No formal diagnostic criteria have been published for SHORT syndrome; however, to date the presence of characteristic facial features is highly predictive for identifying a heterozygous *PIK3R1* pathogenic variant.

Establishing the Diagnosis

The diagnosis of SHORT syndrome **is established in a proband** with compatible clinical features (with emphasis on the facial gestalt) and a heterozygous pathogenic variant in *PIK3R1* identified by molecular genetic testing (see Table 1).

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (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. Individuals with the distinctive and recognizable facial features of SHORT syndrome described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a

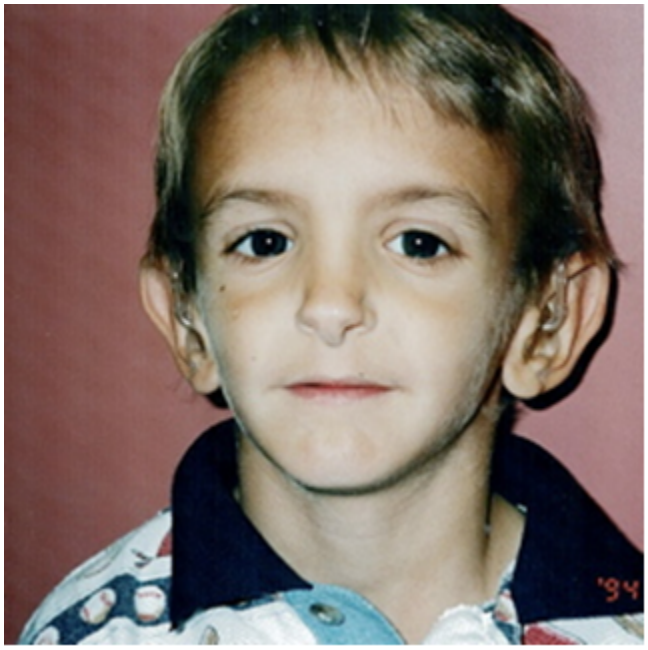

Figure 1. Facial features of SHORT syndrome. The face has a triangular appearance with a prominent forehead and deep-set eyes. The nose has characteristic thin nasal alae and a low-hanging columella. The corners of the mouth can be downturned and the chin can be dimpled. The ears are often pronounced, but not typically low-set.

Image kindly provided by Dr Cynthia Curry

less specific phenotype indistinguishable from many other inherited disorders with short stature and/or partial lipodystrophy are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *PIK3R1* is performed first to detect missense, frameshift, nonsense, and splice site variants. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications may be considered. However, to date such variants have not been identified as a cause of SHORT syndrome.
- **A multigene panel** that includes *PIK3R1* 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 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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by short stature or partial lipodystrophy, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **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. Note: To date such variants have not been identified as a cause of SHORT syndrome.

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 SHORT Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
PIK3R1	Sequence analysis [3]	31/31 probands [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]
Unknown [6]	NA	

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. 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. To date, a *PIK3R1* pathogenic variant has been identified in 40 individuals from 31 families with SHORT syndrome (reviewed in Avila et al [2016], Huang-Doran et al [2016], Klatka et al [2017], Hamaguchi et al [2018]). Of these, 22/31 families have the recurrent pathogenic variant c.1945C>T.
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. PIK3R1 is currently the only gene in which pathogenic variants are known to cause SHORT syndrome. Of note, an individual reported by Reardon & Temple [2008] had a clinical diagnosis of SHORT syndrome, but subsequent testing failed to identify a *PIK3R1* pathogenic variant, suggesting the possibility of genetic heterogeneity. However, in retrospect, the classic facial gestalt of SHORT syndrome was not present [Dyment et al 2013]. There has been a single report of an individual with a *de novo* variant in *PRKCE* and a SHORT-like presentation; however, this has not been replicated [Alcantara et al 2017]. A homozygous variant in *IGF1R* has also been reported to cause a SHORT-like syndrome; however, the child presented with developmental delay, multiple malformations, and a facies that differed from that seen in others with a diagnosis of *PIK3R1*-related SHORT syndrome [Prontera et al 2015].

Clinical Characteristics

Clinical Description

To date, a pathogenic variant in *PIK3R1* has been identified in 40 affected individuals from 31 families [Avila et al 2016, Huang-Doran et al 2016, Klatka et al 2017, Hamaguchi et al 2018]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of SHORT Syndrome

Feature	Proportion of Persons w/Feature
Intrauterine growth restriction	30/34

Table 2. continued from previous page.

Feature	Proportion of Persons w/Feature
Short stature	30/38 [1]
Partial lipodystrophy	31/35
Facial gestalt	40/40
Insulin resistance	18/23
Diabetes	11/18
Anterior chamber ocular defects	6/20
Delayed dentition	22/23

1. The remaining 8/40 individuals are described as short but with height between -2 SD and -1 SD.

Intrauterine growth restriction (IUGR). Infants with SHORT syndrome are usually born at or slightly before term and typically exhibit mild IUGR [Lipson et al 1989].

Short stature. Feeding difficulties and/or failure to thrive despite adequate caloric intake are commonly reported in young children.

- Mild-to-moderate short stature is usually present throughout childhood. Bone age may or may not be delayed. Other skeletal changes include gracile diaphyses and large and coned-shaped epiphyses [Haan & Morris 1998].
- Mild short stature has been seen in most adults reported to date. Adult height in males with a molecularly confirmed diagnosis of SHORT syndrome was between 155 and 163 cm and in females between 143 and 160 cm [Chudasama et al 2013, Dyment et al 2013, Thauvin-Robinet et al 2013].

Partial lipodystrophy. Partial lipodystrophy is very common in SHORT syndrome [Koenig et al 2003]. Lack of subcutaneous fat is evident in the face and later becomes more readily apparent in the chest and upper extremities. Although the buttocks and legs are often spared, localized regions of lipoatrophy at the elbows and buttocks have been reported [Aarskog et al 1983, Koenig et al 2003]. The hands also lack subcutaneous fat, and the skin has an aged, translucent appearance.

The body habitus is described as thin. All four adult males reported to date with a molecularly confirmed diagnosis had a body mass index (BMI) below 18.5 (range 13.5-17.9); four of eight adult females also had a BMI below 18.5 (range 15.1-22.5) [Chudasama et al 2013, Dyment et al 2013, Thauvin-Robinet et al 2013].

Characteristic facial gestalt. The characteristic facial features of SHORT syndrome – sometimes described as having an "aged" or "progeroid" appearance [Koenig et al 2003] – are present at birth and become increasingly apparent with age. Head shape is normal and occipital-frontal circumference is proportionate with other growth parameters. The vasculature of the scalp is prominent. The forehead is broad, palpebral fissures are deep-set, and alae nasi are thin with a low-hanging columella. The chin is small and can be dimpled. (See Figure 1.)

Insulin resistance / diabetes mellitus. Although insulin resistance may be evident in mid-childhood or adolescence, diabetes mellitus typically does not develop until early adulthood [Aarskog et al 1983, Schwingshandl et al 1993].

Axenfeld-Rieger anomaly or related anterior chamber ocular anomalies – also referred to as anterior chamber dysgenesis – have been reported in the majority of individuals with SHORT syndrome. Glaucoma, which has been reported in at least one individual at birth [Brodsky et al 1996], can also develop later [Bankier et al 1995]. Glaucoma is thought to be the result of poorly developed aqueous humor drainage structures of the anterior chamber of the eye.

The majority of individuals with a *PIK3R1* pathogenic variant have at least some ocular involvement including myopia, hyperopia, and/or astigmatism, and half have Rieger anomaly or related anterior chamber defects [Chudasama et al 2013, Dyment et al 2013, Thauvin-Robinet et al 2013, Schroeder et al 2014].

Delayed dentition. Delayed dentition is common in individuals with a molecularly confirmed diagnosis of SHORT syndrome. Other dental issues include hypodontia, enamel hypoplasia, and malocclusion. Multiple dental caries have also been reported [Koenig et al 2003].

Other

- Sensorineural hearing loss of 80-90 dB has been diagnosed within the first year of life. Among individuals with a molecularly confirmed diagnosis of SHORT syndrome, six have been reported with hearing loss [Avila et al 2016].
- While cognition is not affected in SHORT syndrome, some affected children have mild speech delay.
- Some, but not all, affected individuals exhibit hyperextensible joints and/or inguinal hernias.
- Although there does not appear to be an increased risk for life-threatening infections or evidence of clinical immunodeficiency, there have been reports of a nonspecific history of frequent infections [Koenig et al 2003].
- Nephrocalcinosis has been reported in a mother-son pair with a molecularly confirmed diagnosis [Reardon & Temple 2008]. Nephrocalcinosis was identified incidentally in the son at age two months (on an abdominal US examination performed for follow up of anorectal atresia); the nephrocalcinosis was stable when reassessed at age two years. The mother also developed nephrocalcinosis as an adult.
- Pulmonic stenosis and ectopic kidney have also been reported [Koenig et al 2003, Schroeder et al 2014, Bárcena et al 2014].
- Fertility is generally preserved in SHORT syndrome; ovarian cysts are commonly reported in affected females.

Genotype-Phenotype Correlations

To date no clear genotype-phenotype correlation is evident; however, pathogenic variants appear to cluster in the C-terminal SH2 domain of *PIK3R1*.

The recurrent missense pathogenic variant c.1945C>T has been identified in 22 of 31 families with SHORT syndrome. While individuals with this specific variant usually have typical SHORT syndrome, to date the numbers are too small to determine whether the phenotype observed with this pathogenic variant differs from that observed with other pathogenic variants.

Penetrance

The penetrance of SHORT syndrome appears complete in all individuals undergoing molecular genetic testing to date: all simplex cases (i.e., a single occurrence in a family) with parents available for testing have had a *de novo* *PIK3R1* pathogenic variant, and all familial cases have inherited the pathogenic variant from an affected parent.

Nomenclature

Since it was first described in the early 1970s, what appears to be SHORT syndrome has been described by different terms, including:

- Low-birthweight Rieger syndrome
- Autosomal partial lipodystrophy associated with Rieger anomaly, short stature, and insulinopenic diabetes *
- Absent iris stroma, narrow body build, and small facial bones *

* Individuals with the latter two disorders have subsequently been demonstrated to have a *PIK3R1* pathogenic variant and SHORT syndrome.

Prevalence

SHORT syndrome is very rare; fewer than 50 cases have been reported in the literature.

No ethnic predilection is known.

Genetically Related (Allelic) Disorders

To date, individuals with three different phenotypes have been reported with germline pathogenic variants in *PIK3R1*:

- One individual with an amino acid substitution in the N-terminal SH2 domain of *PIK3R1* had acanthosis nigricans and severe insulin resistance [Baynes et al 2000].
- One individual homozygous for a premature stop codon in exon 6 of *PIK3R1* resulting in absence of the p85α isoform (and not the other isoforms [p55α, p50α]) had agammaglobulinemia [Conley et al 2012].
- Immunodeficiency type 36, also known as activating PI3K-delta syndrome 2 (APDS2; OMIM 616005), is characterized by recurrent respiratory infections due to a primary immunodeficiency. It is caused by pathogenic splice site variation in *PIK3R1* that results in a skipping of exon 11. Of note, two reports have suggested that SHORT syndrome and APDS2 may coexist as a result of this splice variant. However, neither of the individuals were reported to have intrauterine growth restriction [Petrovski et al 2016, Bravo García-Morato et al 2017], and the images provided for one individual do not share the characteristic facial dysmorphology of SHORT syndrome [Bravo García-Morato et al 2017].

Sporadically occurring single tumors in the absence of any other findings of SHORT syndrome may harbor somatic variants in *PIK3R1*. For more details see Molecular Genetics, Cancer and Benign Tumors.

Differential Diagnosis

Table 3 provides a comparative analysis of disorders with some clinical similarities to SHORT syndrome.

Table 3. Genes of Interest in the Differential Diagnosis of SHORT Syndrome

Gene(s) / Genetic Mechanism	Differential Disorder	MOI	Features of Differential Disorder	
			Overlapping w/SHORT syndrome	Distinguishing from SHORT syndrome
11p15.5 hypomethylation mUPD7 *CDKN1C* *HMGA2* *IGF2* *PLAG1* [1]	Silver-Russell syndrome (SRS)	See footnote 2.	• IUGR & postnatal growth deficiency • Nonspecific facial features incl triangular-shaped face [3]	• More significant short stature in SRS than in SHORT syndrome • No eye anomalies or lipodystrophy in SRS

Table 3. continued from previous page.

Gene(s) / Genetic Mechanism	Differential Disorder	MOI	Features of Differential Disorder	
			Overlapping w/SHORT syndrome	Distinguishing from SHORT syndrome
AGPAT2 *BSCL2*	Berardinelli-Seip congenital lipodystrophy (BSCL)	AR	• BSCL is usually diagnosed at birth or shortly thereafter; severe BSCL may have prenatal-onset w/ IUGR. • All children w/ neonatal or infantile presentation demonstrate lipoatrophy in 1st yr of life. • Insulin resistance & subsequent diabetes mellitus become common in late adolescence & early adulthood.	Hepatomegaly, severe generalized lipodystrophy, & acromegaloid facial features in BSCL
FOXC1 *PITX2*	Nonsyndromic anterior chamber eye anomalies (OMIM 137600, 601631)	AD	Anterior chamber eye anomalies	Absence of other features assoc w/SHORT syndrome
IGF1R	Nonsyndromic IUGR [4]	AD	IUGR, short stature, glucose intolerance	• Absence of facial features of SHORT syndrome • ↑ IGF1
JAG1 *NOTCH2*	Alagille syndrome [5]	AD	Ocular & dental findings may be similar.	Liver disease in Alagille syndrome
LMNA	Hutchinson-Gilford progeria syndrome (HGPS)	AD	Micrognathia, short stature, absence of subcutaneous fat	• Clinical features of HGPS develop in childhood (vs typically evident at birth in SHORT syndrome). • Some features of accelerated aging w/ disease progression in HGPS are distinct from those in SHORT syndrome.
PTPN11	SHORT-like syndrome [6]	AD	IUGR, short stature, lipoatrophy, & metabolic abnormalities	Facial features not characteristic of SHORT syndrome

Table 3. continued from previous page.

Gene(s) / Genetic Mechanism	Differential Disorder	MOI	Features of Differential Disorder	
			Overlapping w/SHORT syndrome	Distinguishing from SHORT syndrome
UBR1	Johansson-Blizzard syndrome (OMIM 243800)	AR	IUGR, short stature, hypoplastic alae nasi, hypodontia, & hearing loss	Heart & genitourinary malformations, aplasia cutis congenital, pancreatic insufficiency

AD = autosomal dominant; AR = autosomal recessive; IGF1 = insulin-like growth factor 1; IUGR = intrauterine growth restriction; MOI = mode of inheritance; mUPD = maternal uniparental disomy

1. Silver-Russell syndrome (SRS) is genetically heterogeneous. Hypomethylation of the imprinted control region 1 (ICR1) at 11p15.5 causes SRS in 35%-50% of individuals, and mUPD7 causes SRS in 7%-10% of individuals. A small number of individuals with SRS have duplications, deletions, or translocations involving the imprinting centers at 11p15.5 or duplications, deletions, or translocations involving chromosome 7. Rarely, affected individuals with pathogenic variants in *CDKN1C*, *IGF2*, *PLAG1*, and *HMGA2* have been described.

2. Accurate assessment of SRS recurrence requires identification of the causative genetic mechanism in the proband.

3. Since it is possible that some individuals with a clinical diagnosis of SRS and normal molecular studies have a diagnosis of SHORT syndrome, careful consideration of the facial phenotype in these individuals is warranted.

4. Abuzzahab et al [2003], Kawashima et al [2005]

5. Alagille syndrome is a complex multisystem disorder involving the liver, heart, eyes, face, and skeleton.

6. Ranza et al [2020]

Hallerman-Streiff syndrome. The facial features of SHORT syndrome can also be similar to those seen in Hallerman-Streiff syndrome in early life. The molecular basis of Hallerman-Streiff syndrome is unknown (OMIM 234100).

Note: Copy number variations at several loci including *PITX2* (4q25) and *BMP4* (14q22.2) (which are frequently detected by chromosomal microarray analysis) can lead to syndromic anterior-chamber eye anomalies with phenotypes that to date have been clinically distinct from those of SHORT syndrome [Karadeniz et al 2004, Lines et al 2004, Reis et al 2011].

Management

Evaluations Following Initial Diagnosis

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

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with SHORT Syndrome

System/Concern	Evaluation	Comment
Short stature	Measure length & weight.	
Mild speech delay	Assess speech & language in those w/evidence of DD.	
Axenfeld-Rieger anomaly or related anterior chamber ocular anomalies	Exam by ophthalmologist experienced in mgmt of developmental eye disorders or glaucoma	
Hearing loss	Hearing assessment	
Delayed dentition	Dental exam	
Insulin resistance / diabetes mellitus	Assessment by endocrinologist & consideration of fasting glucose & oral glucose tolerance test	This is important in a person diagnosed w/SHORT syndrome as an older child (age >10 yrs) or later as an adult.

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Pulmonary stenosis	Echocardiogram	
Nephrocalcinosis	Abdominal US	
Genetic counseling	By genetics professionals [1]	To inform patients & families re nature, MOI, & implications of SHORT syndrome to facilitate medical & personal decision making

DD = developmental delay; MOI = mode of inheritance; US = ultrasound
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with SHORT Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Axenfeld-Rieger anomaly or related anterior chamber ocular anomalies	Treatment by ophthalmologist experienced in management of developmental eye disorders or glaucoma	Important to ↓ & stabilize ocular pressures & to preserve vision
Hearing loss	See Hereditary Hearing Loss and Deafness.	
Dental anomalies	Standard treatment & may incl crowns & dental prostheses.	
Insulin resistance / Diabetes mellitus	Standard treatment for glucose intolerance & diabetes mellitus w/diet, lifestyle, oral medication, & insulin under supervision of a specialist in diabetes care is recommended.	1 report found that treatment w/metformin → worsening of insulin resistance in 1 person w/ SHORT syndrome, suggesting need for caution in use of metformin & further study [Lewandowski et al 2019].

Surveillance

Table 6. Recommended Surveillance for Individuals with SHORT Syndrome

System/Concern	Evaluation	Frequency
Short stature	Monitor growth incl height, weight, & body mass index	Every 6-12 mos
Eye abnormality	Eye exams to incl measurement of intraocular pressure	Annually
Hearing loss	Hearing assessment	Every 2-3 yrs
Insulin resistance	Oral glucose tolerance test	Every 5 yrs in absence of diabetes
Diabetes	Fasting glucose, insulin, & HBA1c	Annually starting in later childhood (age >10 yrs)

Agents/Circumstances to Avoid

Given the increased risk for insulin resistance in individuals taking growth hormone, it has been suggested that growth hormone be contraindicated in individuals with SHORT syndrome [Thauvin-Robinet et al 2013].

One report observed a worsening of insulin resistance in a child with SHORT syndrome treated with metformin [Lewandowski et al 2019]. The report was limited to a single individual; as such, further study is needed to determine the effects of this drug.

Evaluation of Relatives at Risk

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

Pregnancy Management

Successful pregnancies have occurred in women with SHORT syndrome. If present, diabetes mellitus is managed as appropriate.

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

SHORT syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Some individuals diagnosed with SHORT syndrome have an affected parent.
- Twelve of the 40 individuals with SHORT syndrome diagnosed to date were found to have a *de novo* *PIK3R1* pathogenic variant; however, this is likely an underestimate as the parents of individuals representing simplex cases of SHORT syndrome have not been evaluated sufficiently to determine if the pathogenic variant occurred *de novo*.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the pathogenic variant found in the proband cannot be detected in leukocyte DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* pathogenic variant in the proband.* Although no instances of confirmed germline mosaicism have been reported, the occurrence of SHORT syndrome in a sib pair reported in Gorlin et al [1975] appears to have been due to germline mosaicism.

  * Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.
- The family history of some individuals diagnosed with SHORT syndrome may appear to be negative because of failure to recognize the disorder in family members because of a milder phenotypic presentation. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband. Note: To date, all parents found to be heterozygous for a *PIK3R1* pathogenic variant have had clinical manifestations of SHORT syndrome apparent on physical examination (primarily presence of short stature, lipodystrophy, and characteristic facial features).

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

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known *PIK3R1* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Gorlin et al 1975].
- If the parents have not been tested for the *PIK3R1* pathogenic variant identified in the proband but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for SHORT syndrome because of the possibility of parental germline mosaicism or the theoretic possibility of reduced penetrance in a heterozygous parent.

Offspring of a proband. Each child of an individual with SHORT syndrome has a 50% chance of inheriting the *PIK3R1* 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 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 young adults who are affected or at risk.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown).

Prenatal Testing and Preimplantation Genetic Testing

Once the *PIK3R1* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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

Resources

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

- **National Library of Medicine Genetics Home Reference**
  Short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly, and teething delay
- **Human Growth Foundation**
  www.hgfound.org

- **MAGIC Foundation**
  Phone: 800-362-4423
  Email: contactus@magicfoundation.org
  www.magicfoundation.org
- **National Eye Institute**
  Phone: 301-496-5248
  Email: 2020@nei.nih.gov
  Low Vision

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. SHORT Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PIK3R1	5q13.1	Phosphatidylinositol 3-kinase regulatory subunit alpha	PIK3R1base: Database for pathogenic mutations in the p85-alpha SH2 domain	PIK3R1	PIK3R1

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 SHORT Syndrome (View All in OMIM)

171833	PHOSPHATIDYLINOSITOL 3-KINASE, REGULATORY SUBUNIT 1; PIK3R1
269880	SHORT SYNDROME

Molecular Pathogenesis

PIK3R1 encodes the regulatory subunit (p85α) of the PI3K holoenzyme. The subunit p85α stabilizes the catalytic subunit (p110α) that regulates the AKT/mTOR pathway. This pathway is critical to proper cell proliferation and growth. When p85α binds to p110α, phosphatidylinositol (3,4) bisphosphate is converted to phosphoinositol (3,4,5) triphosphate, which thereby recruits AKT and initiates the downstream effectors of cellular growth.

Studies of fibroblasts and lymphoblasts of individuals with SHORT syndrome show a diminished capacity to activate the AKT pathway and downstream targets. Reduced p85α results in p110α not being available for downstream effects.

Mechanism of disease causation. Pathogenic variants are thought to cause SHORT syndrome via haploinsufficiency; however, few studies have investigated its underlying mechanism.

Table 7. Notable *PIK3R1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_181523.2 NP_852664.1	c.1945C>T	p.Arg649Trp	Recurrent variant [Chudasama et al 2013, Dyment et al 2013]

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

Cancer and Benign Tumors

Sporadic tumors (including glioblastomas, breast, endometrial, bladder, uroepithelial, ovarian, colorectal, and gastric) occurring as single tumors in the absence of any other findings of SHORT syndrome may harbor somatic *PIK3R1* variants that are **not** present in the germline; thus, predisposition to these tumors is not heritable.

Chapter Notes

Author Notes

Dr A Micheil Innes's research is focused on both the clinical delineation and the identification of the molecular basis of rare genetic conditions.

Dr David Dyment's research interests are the identification of the molecular causes of rare syndromic and neurogenetic diseases.

Both Dr Innes and Dr Dyment are investigators with Care for Rare – SOLVE, a pan Canadian collaboration to investigate the causes of rare genetic diseases and improve the clinical care for patients and families affected by them.

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- 4 June 2020 (ha) Comprehensive update posted live
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