GENEReviews

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Russell-Silver Syndrome

[*Silver-Russell Syndrome*]

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Summary

Disease characteristics. Russell-Silver syndrome (RSS) is characterized by intrauterine growth retardation accompanied by postnatal growth deficiency. The birth weight of affected individuals is typically two or more SD below the mean, and postnatal growth two or more SD below the mean for length or height. Affected individuals typically have proportionately short stature, normal head circumference, fifth-finger clinodactyly, typical facial features, and limb-length asymmetry that may result from hemihypotrophy with diminished growth of the affected side. Growth velocity is normal in children with RSS. The average adult height of males is 151.2 cm and that of females is 139.9 cm. Evidence exists that children with RSS are at significant risk for developmental delay (both motor and cognitive) and learning disabilities.

Diagnosis/testing. RSS is a genetically heterogeneous condition and for most affected individuals represents a phenotype rather than a specific disorder. The diagnosis is therefore primarily based upon identification of consistent clinical features, especially prenatal and postnatal growth retardation with normal head circumference. About 10% of individuals with RSS will have maternal uniparental disomy for chromosome 7, confirmatory testing for which is available clinically. Epigenetic mutations of the imprinted region of chromosome 11p15.5 appear also to be implicated in some individuals with RSS; testing for these changes is clinically available.

Management. Treatment may include growth hormone therapy, physical, occupational, speech, and language therapy, and an individualized education plan. Treatment of gastroesophageal reflux initially with positioning and thickened feeds is recommended along with use of acid-blocking medications; surgical management with fundoplication may be necessary. Lower-limb length discrepancy exceeding 3 cm requires intervention; in older children, distraction osteogenesis or epiphysiodesis can be considered. Severe micrognathia or cleft palate is managed by a multidisciplinary craniofacial team. Males with cryptorchidism should be referred to a urologist; orchiopexy may be required. Males with micropenis should be referred to an endocrinologist; androgenic hormone therapy may be indicated. Surveillance includes monitoring of: growth velocity; blood glucose concentration for hypoglycemia in infants and as needed in older children; limb length at each well-child visit in early childhood for evidence of asymmetric growth; and speech/language development.

Genetic counseling. RSS has multiple etiologies including: maternal uniparental disomy for chromosome 7, possible mutations or epigenetic changes that modify expression of genes in the imprinted region of chromosome 11p15.5, and autosomal dominant or autosomal recessive

inheritance. When a proband has RSS as the result of maternal uniparental disomy for chromosome 7, both parents are predicted to be unaffected, the risk to the sibs is not increased over that of the general population, and the risk to offspring is probably low. Prenatal diagnosis for RSS is usually not possible: because most occurrences are in a single individual in a family, most pregnancies are not identified to be at increased risk for recurrence.

Diagnosis

Clinical Diagnosis

Russell-Silver syndrome (RSS) is a genetically heterogeneous condition and represents a phenotype rather than a specific disorder in most individuals. This is supported by observations that RSS:

- Has multiple causes including uniparental (maternal) disomy of chromosome 7, autosomal dominant inheritance, and autosomal recessive inheritance;
- Demonstrates variable response to growth hormone and variable late catch-up growth;
- Is associated with varying developmental outcomes.

The clinical diagnosis of RSS is dependent upon the presence of intrauterine growth retardation accompanied by postnatal growth deficiency [Silver et al 1953, Russell 1954, Price et al 1999]. No signs or features are pathognomonic for RSS.

The most critical diagnostic clinical features [Price et al 1999]:

- Intrauterine growth retardation (IUGR): birth weight 2 SD or more below the mean
- Postnatal growth retardation: length or height 2 SD or more below the mean
- Normal head circumference, often with the appearance of "pseudohydrocephalus"
- Fifth-finger clinodactyly
- Limb-length asymmetry

Additional features that can aid in the diagnosis:

- Short stature with normal upper- to lower-segment ratio, normal skeletal survey, and frequently delayed bone age
- Typical facial phenotype of broad prominent forehead with small triangular face, small narrow chin, and down-turned corners of the mouth
- Hypoglycemia
- Brachydactyly, camptodactyly
- Café au lait spots
- Arm span less than height

Testing

RSS is genetically heterogeneous. Approximately 10% of affected individuals have maternal uniparental disomy for chromosome 7 [Moore et al 1999, Hannula et al 2001].

Cytogenetic studies. Chromosome anomalies in individuals with RSS are rare. However, a few individuals with cytogenetic anomalies have been reported, some consistent with or suggesting possible gene location.

Very rarely, individuals with RSS have rearrangements of 17q25 [Ramirez-Duenas et al 1992, Midro et al 1993].

Chromosome 7 anomalies include the following:

- Mosaic trisomy 7 in two children who had maternal uniparental heterodisomy for chromosome 7 [Flori et al 2005, Font-Montgomery 2005], one of whom was identified prenatally [Font-Montgomery 2005]
- Interstitial deletion of the long arm of chromosome 7 [del(7)(q21.1q21.3)] in one child [Courtens et al 2005]
- Submicroscopic duplication of 7p11.2-p12 (including *GRB10*, an imprinted gene), identifiable only with fluorescence in situ hybridization (FISH) [Joyce et al 1999, Monk et al 2000]

Molecular Genetic Testing

Molecular Genetic Testing —Genes. Because of the accepted genetic heterogeneity of RSS, several genes have been implicated.

Maternal uniparental disomy (UDP) of chromosome 7 has been implicated in 7%-10% of RSS [Moore et al 1999, Hannula et al 2001, Kim et al 2005]. One study demonstrated maternal uniparental disomy at two imprinted genes on chromosome 7, *GRB10*, which maps to 7p11.2-p12 and *MEST* (also known as *PEG1*), which maps to 7q32. *GRB10* is paternally imprinted and *MEST* is maternally imprinted [Kim et al 2005]. Maternal overexpression of *GRB10* can result from gene duplication or maternal uniparental disomy of chromosome 7 [Joyce et al 1999, Monk et al 2000]. Kim et al (2005) demonstrated abnormal methylation of *GRB10*, but this finding has not been reported by any other investigators to date.

Genetic or epigenetic mutations in the imprinted region on chromosome 11p15.5 may cause RSS [Gicquel et al 2005]. The importance of imprinted genes at chromosome 11p15.5 for fetal growth has been documented [DiChiara et al 1990, Fitzpatrick et al 2002]. The overgrowth syndrome Beckwith-Wiedemann syndrome results from epigenetic alterations in the 11p15 imprinted region [Gaston et al 2001]. Genes in this cluster include *IGF2* and *KCNQ1OT1*, which are paternally expressed and maternally imprinted, and *CDKNIC* and *H19*, which are maternally expressed and paternally imprinted. One study showed partial loss of paternal methylation at three loci in the 11p15 telomeric imprinted region [imprinting center region 1 (ICR1)], *H19* promoter, and *IGF2* differentially methylated region (DMR2) [Gicquel et al 2005]. However, in another study of 40 individuals with RSS, no pathogenic mutation in the 11p15 imprinted region was identified in either *IGF2* or *CDKN1C* [Obermann et al 2004]. More recently, in 51 individuals with RSS who were studied for epimutations in ICR1 (imprinting center region 1) and *KCNQ1OT1*, 31% were found to have demethylation in ICR1 and no methylation changes were noted in *KCNQ1OT1* [Eggermann et al 2006]. The authors therefore estimate that 35% of individuals with RSS will have 11p15 imprinting defects as a result of epimutation of ICR1 or maternal duplication of 11p15 [Eggermann et al 2006]. Therefore, it appears that loss of paternal methylation at the H19-IGF2 (ICR1) imprinting site may be the underlying cause in a sizable number of RSS cases. More recently, a maternally inherited duplication of the centromeric ICR2 has been identified in one individual with RSS [Schonherr et al 2007]. The implications of this finding and its contribution to the number of cases with RSS are unclear, pending further study.

Clinical use

- **Confirmatory diagnosis.** Uniparental disomy (UPD) studies are useful in establishing the diagnosis of UPD7 for individuals with suspected RSS; however, the

great majority of affected individuals diagnosed to date have no identifiable cause for their diagnosis.

Clinical testing

- **Uniparental disomy studies.** Both maternal isodisomy and heterodisomy have been reported [Bernard et al 1999, Price et al 1999].
- Methylation analysis of *H19*

Research testing. Molecular genetic testing for *GRB10*, *PEG1/MEST*, *ICR1*, *H19*, and *IGF2* is performed on a research basis only.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Russell-Silver Syndrome

Test Method	Genetic Mechanism	% of Affected Individuals	Test Availability
Analysis of polymorphic markers on chromosome 7 of affected individual and parents	Maternal UPD7	~7%-10%	Clinical Testing
Methylation analysis	*H19* methylation analysis	35%	
Molecular analysis of chromosome rearrangement	Gene localization from chromosome rearrangement	<1%	Research only
Sequence analysis, methylation analysis	Gene mutation *GRB10*	<1%	
	MEST	<1%	
	ICR1 sequence variant (chromosome 11p15)	Unknown	
	IGF2 sequence variant	Unknown	
Sequence analysis	*H19* sequence variant	Unknown	

Testing Strategy for a Proband

Clinically available testing for RSS is limited to the following:

- **Cytogenetic analysis,** which should include high-resolution chromosome studies with emphasis on duplication of 11p15.5, duplication of chromosome 7p11-p12, and possible mosaicism for chromosome 7
- **Maternal uniparental disomy 7 studies**
- ***H19* methylation analysis**

Note: Methylation analysis for *H19* is available for diagnosis of RSS. Investigational studies have analyzed both *H19* and *IGF2*. Although it likely will identify most, if not all epimutations, further studies will be needed to determine if testing solely for *H19* is sufficient for diagnosis or if testing for *IGF2* needs to be performed as well.

Genetically Related (Allelic) Disorders

Isolated hemihypertrophy may result from mutations related to epigenetic alterations in the 11p15 imprinted region [Gicquel et al 2005].

Clinical Description

Natural History

Growth. The early problems for children with Russell-Silver syndrome (RSS) are generally related to growth and feeding. Children with RSS have intrauterine growth retardation with

postnatal growth deficiency. Growth parameters with growth charts for European children have been published [Wollmann et al 1995]. Growth charts for North American children with RSS are available from the MAGIC Foundation.

Growth velocity is normal. In individuals not treated with growth hormone, the average adult height of males is 151.2 cm (-7.8 SD) and that of females is 139.9 cm (-9 SD) [Wollmann et al 1995].

Growth is expected to be proportionate, although most individuals with RSS have a short arm span compared to height with a normal upper- to lower-segment ratio [Silver et al 1953, Saal et al 1985].

Most children said to have RSS who have demonstrated catch-up growth in later childhood [Saal et al 1985] probably had conditions other than classic RSS.

Growth hormone deficiency. The incidence of growth hormone deficiency in individuals with RSS remains controversial. Although several studies have demonstrated normal serum concentration of growth hormone in children with RSS, some children with RSS and growth hormone deficiency have been reported [Cassidy et al 1986]. In one study of children with RSS who did not have chromosome 7 maternal uniparental disomy, 45% of those with symptoms of hypoglycemia or biochemically documented hypoglycemia had growth hormone deficiency [Azcona & Stanhope 2005].

The use of human growth hormone in children with intrauterine growth retardation has significantly improved growth and final height [Albanese & Stanhope 1997, Azcona et al 1998, Czernichow & Fjellestad-Paulsen 1998, Saenger 2002]. Specifically, children with RSS have benefited from growth hormone supplementation [Albanese & Stanhope 1997], including significant growth acceleration and improved final height [Azcona et al 1998] and continued normal growth rate after the discontinuation of growth horome therapy [Azcona & Stanhope 1999]. One study demonstrated significant increase in height in children with RSS treated with growth hormone, but without a change in body or limb asymmetry [Rizzo et al 2001]. Nonetheless, it is difficult to interpret the results of studies of children with RSS who have received growth hormone, given the known genetic heterogeneity of the disorder. It is accepted that many children with RSS do not achieve normal stature even with administration of human growth hormone (see Management).

Neurodevelopment. Besides the growth issues, neurodevelopment is probably of greatest concern to parents. Despite reassurances about "normal intelligence" in individuals with RSS in earlier reports, evidence is increasing that children with this condition are at significant risk for developmental delay (both motor and cognitive) and learning disabilities. In one study of 20 children with RSS between the ages of six and 12 years, the average IQ was 86. In addition, 36% of these children required special education and 48% required speech therapy [Lai et al 1994]. The specific etiology of the RSS was not identified for any of the children studied. In another study, the average IQ in 36 children with RSS was 95.7 compared to 104.20 in sibling controls. Of note, the two children with maternal uniparental disomy for chromosome 7 had IQs of 81 and 84, respectively [Noeker & Wolloman 2004].

Hypoglycemia. Children with RSS have little subcutaneous fat, are quite thin, and often have poor appetites; they are at risk for hypoglycemia with any prolonged fast, including surgery [Tomiyama et al 1999]. In a study of children with RSS, contributing factors for hypoglycemia included reduced caloric intake, often secondary to poor appetite and feeding; reduced body mass; and, in several children, growth hormone deficiency [Azcona & Stanhope 2005]. Although most children had clinical symptoms of hypoglycemia, especially excessive sweating, several were asymptomatic.

Diaphoresis in early childhood may be associated with hypoglycemia, although diaphoresis may occur in the absence of hypoglycemia [Stanhope et al 1998].

Gastrointestinal disorders are common [Anderson et al 2002]. Problems include gastroesophageal reflux disease, esophagitis, food aversion, and failure to thrive. Some of these issues may be iatrogenic (i.e., related to treatments for poor growth). Reflux esophagitis should be suspected in children with either food aversion or aspiration.

Skeletal abnormalities in individuals with RSS are generally limited to limb-length asymmetry that, at least some individuals, may be hemihypotrophy with diminished growth of the affected side.

Because it is used as a diagnostic criterion, fifth-finger clinodactyly is among the most frequently described skeletal anomalies in individuals with RSS.

In a systematic study of orthopedic manifestations in 25 individuals with RSS, 19 had metacarpal and phalangeal abnormalities, nine had scoliosis, five had toe syndactyly, and three had developmental dysplasia of the hips [Abraham et al 2004].

Severe craniofacial anomalies are uncommon. Some individuals with RSS have Pierre Robin sequence and cleft palate. Dental and oral abnormalities are rare. Microdontia, high-arched palate, and dental crowding secondary to the relative micrognathia and small mouth have been reported [Cullen & Wesley 1987, Kulkarni et al 1995, Orbak et al 2005]. Poor oral hygiene in the presence of dental crowding can lead to increased risk for dental caries.

Genitourinary problems have been observed but are uncommon. The most common anomalies are hypospadias and cryptorchidism. Renal anomalies, including hydronephrosis, renal tubular acidosis, posterior urethral valves, and horseshoe kidney have been reported [Arai et al 1988, Ortiz et al 1991].

Neoplasia. Individuals with RSS do not appear to have a significantly increased incidence of neoplasia despite occasional reports of rare malignancies, including Wilms tumor, hepatocellular carcinoma, and craniopharyngioma [Draznin et al 1980, Chitayat et al 1988, Bruckheimer & Abrahamov 1993].

Genotype-Phenotype Correlations

No known genotype-phenotype correlations exist.

Despite the recognized genetic heterogeneity of RSS, it appears that children with maternal UPD7 have clinical features indistinguishable from those seen in individuals with other etiologies for this condition [Bernard et al 1999].

Further studies are needed to determine if limb and body asymmetry are more likely to be associated with epigenetic mutations of the imprinted region of 11p15.

The low risk of malignancy is significant, given that at least some individuals with RSS have mutations in the imprinted region of chromosome 11p15 that have been associated with Wilms tumor, hepatoblastoma, and other abdominal tumors in individuals with Beckwith-Wiedemann syndrome. The tumor risk, therefore, appears to be increased with mutations related to overgrowth, as opposed to growth retardation.

Prevalence

The prevalence is estimated to be one in 100,000 [Christoforidis et al 2005].

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Intrauterine growth retardation and short stature. The differential diagnosis of Russell-Silver syndrome (RSS) includes any condition that can cause intrauterine growth retardation and short stature.

Many chromosome conditions can be misdiagnosed as RSS, including deletion 15q26.1, which results in a deletion of the gene encoding the insulin-like growth factor 1 receptor *(IGF1R*). However, individuals with this deletion have microcephaly, mental retardation, and other features, including brachydactyly, that distinguish them from individuals with RSS. In a series of 33 individuals with RSS, none was found to have *IGF1R* gene mutations [Abu-Amero et al 1997].

Other chromosome disorders that may present with features suggestive of RSS include Yq deletions [Leppig et al 1991], diploid/triploid mixoploidy (because of the limb asymmetry) [Graham et al 1981], and mosaic Turner syndrome [Li et al 2004]. Individuals with features characteristic of RSS who have mosaic trisomy 18 and deletions of 18p have been reported [Chauvel et al 1975, Christensen & Nielsen 1978]. For this reason, chromosome studies, preferably high-resolution analysis, should be performed to evaluate for chromosome abnormalities in children with phenotypic similarities.

Disorders of DNA repair, including Fanconi anemia syndrome, Nijmegen breakage syndrome, and Bloom syndrome, are frequently associated with intrauterine growth retardation and short stature. In these conditions, additional clinical features, including microcephaly, skin sensitivity to sunlight, and limb anomalies, are usually evident.

One condition that has been confused with RSS is an X-linked disorder of short stature with skin hyperpigmentation. Partington (1986) described the first cases and referred to this as X-linked RSS. This condition may be difficult to distinguish from classic RSS in the absence of a positive family history.

The 3-M syndrome is characterized by pre- and postnatal growth retardation, distinctive facial features (relatively large head, frontal bossing, pointed and prominent chin, fleshy and upturned nose, full lips and eyebrows, and a hypoplastic midface), and radiologic abnormalities. Intelligence is normal. Final height is 5 to 6 SD below the mean. Characteristic radiologic findings are slender long bones, thin ribs, tall vertebral bodies that become foreshortened over time, spina bifida occulta, small pelvis, small iliac wings, and retarded bone age. Mutations in *CUL7* are causative. Inheritance is autosomal recessive.

Children with fetal alcohol syndrome (FAS) usually have intrauterine growth retardation, microcephaly, failure to thrive, and often triangular facies. For most children with fetal alcohol syndrome in utero exposure to ethanol can be documented and facial findings (short palpebral fissures, flat philtrum, and thin upper lip) are often distinctive.

The IMAGe syndrome is a recently described entity characterized by **i**ntrauterine growth restriction, **m**etaphyseal dysplasia, **a**drenal hypoplasia congenita, and **ge**nital abnormalities including cryptorchidism and micropenis. Head circumference is normal [Vilain et al 1999, Pedreira et al 2004]. Inheritance is thought to be X-linked recessive.

A skeletal survey should be performed to exclude a skeletal dysplasia that may mimic RSS.

Note: Bone age may be delayed in children with RSS; however, delayed bone age is a nonspecific finding frequently seen in children with intrauterine growth retardation from many etiologies.

Microcephaly. Individuals with RSS have a normal head circumference. When the head circumference is more than 3 SD below the mean, another etiology for growth retardation should be sought.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Russell-Silver syndrome (RSS):

- Assessment and plotting of growth curves. For European children, see Wollmann et al (1995); for North American children, see the MAGIC Foundation.
- Physical examination for evaluation of possible limb-size asymmetry and oral and craniofacial abnormalities
- For most children with RSS, evaluation for growth hormone deficiency by standard methods
- For children with diaphoresis, evaluation for hypoglycemia
- For children suspected of having gastroesophageal reflux disease (GERD), evaluation for esophagitis including barium swallow studies, pH probe, and endoscopy
- Screening assessment of neuro-cognitive development, language, and muscle tone

Treatment of Manifestations

Growth. Most children with intrauterine growth retardation, including those with RSS, appear to benefit from human growth hormone therapy even in the absence of growth hormone deficiency. Such treatment is best undertaken in a center with experience in managing growth disorders.

Children with any condition associated with body differences and/or short stature are often sensitive about body image. These factors can play a significant role in self-image, peer relationships, and socialization. Thus, psychological counseling is frequently helpful for children with RSS.

Growth hormone deficiency. Treatment with human growth hormone is necessary in the presence of documented growth hormone deficiency.

Neurodevelopment

- For infants with hypotonia, referral to an early-intervention program and physical therapist
- For children with evidence of delay, referral for early intervention and speech and language therapy
- Working with the school system to address learning disabilities through appropriate neuropsychological testing and an individualized educational plan

Hypoglycemia should be treated in a standard manner with dietary supplementation, frequent feedings, and use of complex carbohydrates.

Gastrointestinal disorders should be aggressively managed.

Treatment of gastroesophageal reflux initially with positioning and thickened feeds is recommended along with use of acid blocking medications (preferably proton pump inhibitors such as omeprazole or patoprazole) as needed. Surgical management with fundoplication may be necessary in more severe cases or in instances in which conservative measures are unsuccessful.

Feeding aversion can be addressed with therapy by a speech pathologist and/or occupational therapist.

Skeletal abnormalities. Lower-limb length discrepancy exceeding 3 cm can lead to compensatory scoliosis and thus requires intervention. Initial treatment is use of a shoe lift. In older children, distraction osteogenesis or epiphysiodesis can be considered.

Craniofacial anomalies can be appropriately managed by pediatric dentists in childhood and orthodontists in adolescence. Orthognathic surgery is rarely required. For those children with severe micrognathia or cleft palate, management by a multidisciplinary craniofacial team is recommended.

Genitourinary abnormalities

- Referral of males with cryptorchidism to a urologist; surgery as required
- Referral of males with micropenis to an endocrinologist; androgenic hormone therapy as indicated

Surveillance

The following are appropriate:

- Monitoring of growth with special attention to growth velocity
- In infancy and in older children with diaphoresis or poor appetite, monitoring of blood glucose concentration for hypoglycemia
- At each well-child visit in early childhood, examination and measurement of limb-length discrepancy
- Close monitoring of speech and language development

Therapies Under Investigation

Search ClinicalTrials.gov 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.

Other

It will be important to look at the long-term effects of growth hormone therapy on children with RSS, especially with respect to influence on final adult height and any possible changes in orthopedic management for those individuals with limb-length asymmetry.

The risk for malignancies in individuals with RSS is low. Although body asymmetry may be present, it appears not to be hemihypertrophy, as seen in Beckwith-Wiedemann syndrome; therefore, routine serial abdominal and renal sonograms are not indicated for children with RSS.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as

information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Russell-Silver syndrome (RSS) has multiple etiologies including: maternal uniparental disomy for chromosome 7 (discussed here) and autosomal dominant or autosomal recessive inheritance. Most commonly, it occurs in a single individual in a family.

Risk to Family Members — Maternal Uniparental Disomy 7

Parents of a proband. When a proband has RSS as the result of maternal uniparental disomy for chromosome 7, both parents are predicted to be unaffected.

Sibs of a proband. When a proband has RSS as the result of maternal uniparental disomy for chromosome 7, the risk to the sibs is not increased over that of the general population.

Offspring of a proband. The risk to offspring is probably low. No data to determine recurrence risks for probands with maternal UPD7 are available.

Other family members of a proband. When a proband has RSS as the result of maternal uniparental disomy for chromosome 7, the risk to other family members is not increased over that of the general population.

Related Genetic Counseling Issues

Empiric risk. Ten percent of individuals with RSS have maternal UPD7; all 10% represent simplex cases (i.e., a single occurrence within a family). In the remaining 90% of affected individuals, RSS is attributable to a multitude of different causes. Autosomal dominant and autosomal recessive inheritance [Ounap et al 2004] are rare. Therefore, most individuals with RSS represent simplex cases. Family history should include heights and birth weights of parents and sibs. In the absence of other affected individuals in the family, genetic counseling should be directed toward sporadic recurrence risk.

DNA banking. 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, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. See DNA banking for a list of laboratories offering this service.

Prenatal Testing

Prenatal diagnosis for RSS is usually not possible: because most occurrences of RSS are in a single family member only, most pregnancies are not identified to be at increased risk for the disorder.

Low-risk pregnancies. For pregnancies in which intrauterine growth retardation is identified by fetal ultrasonography, prenatal testing can be made available for maternal UPD7, utilizing PCR molecular testing of the parents and fetal cells obtained by amniocentesis. Because intrauterine growth retardation often cannot be satisfactorily identified until the third trimester, the options for prenatal diagnosis are limited.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Russell-Silver Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
H19	11p15.5	H19, imprinted maternally expressed untranslated mRNA
IGF2	11p15.5	Insulin-like growth factor II
Unknown	Chromosome 7	Unknown

Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Russell-Silver Syndrome

103280	H19 GENE; H19
147470	INSULIN-LIKE GROWTH FACTOR II; IGF2
180860	SILVER-RUSSELL SYNDROME; SRS

Table C. Genomic Databases for Russell-Silver Syndrome

Gene Symbol	Entrez Gene	HGMD
H19	283120 (MIM No. 103280)	H19
IGF2	3481 (MIM No. 147470)	IGF2

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Molecular Genetic Pathogenesis

See Molecular Genetic Testing.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select*  *for the most up-to-date Resources information.*—ED.

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Russell Silver syndrome

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References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

American College of Medical Genetics (2001) Statement on diagnostic testing for uniparental disomy (pdf)

Literature Cited

Abraham E, Altiok H, Lubicky JP. Musculoskeletal manifestations of Russell-Silver syndrome. J Pediatr Orthop. 2004;24:552–64. [PubMed: 15308907]

Abu-Amero S, Price S, Wakeling E, Stanier P, Trembath R, Preece MA, Moore GE. Lack of hemizygosity for the insulin-like growth factor I receptor gene in a quantitative study of 33 Silver Russell syndrome probands and their families. Eur J Hum Genet. 1997;5:235–41. [PubMed: 9359045]

Albanese A, Stanhope R. GH treatment induces sustained catch-up growth in children with intrauterine growth retardation: 7-year results. Horm Res. 1997;48:173–7. [PubMed: 9378463]

Anderson J, Viskochil D, O'Gorman M, Gonzales C. Gastrointestinal complications of Russell-Silver syndrome: a pilot study. Am J Med Genet. 2002;113:15–9. [PubMed: 12400060]

Arai Y, Wakabayashi Y, Pak K, Tomoyoshi T. Horseshoe kidney in Russell-Silver syndrome. Urology. 1988;31:321–3. [PubMed: 2895527]

Azcona C, Stanhope R. Absence of catch-down growth in Russell-Silver syndrome after short-term growth hormone treatment. Horm Res. 1999;51:47–9. [PubMed: 10095170]

Azcona C, Stanhope R. Hypoglycaemia and Russell-Silver syndrome. J Pediatr Endocrinol Metab. 2005;18:663–70. [PubMed: 16128243]

Azcona C, Albanese A, Bareille P, Stanhope R. Growth hormone treatment in growth hormone-sufficient and -insufficient children with intrauterine growth retardation/Russell-Silver syndrome. Horm Res. 1998;50:22–7. [PubMed: 9691209]

Bernard LE, Penaherrera MS, Van Allen MI, Wang MS, Yong SL, Gareis F, Langlois S, Robinson WP. Clinical and molecular findings in two patients with Russell-Silver syndrome and UPD7: comparison with non-UPD7 cases. Am J Med Genet. 1999;87:230–6. [PubMed: 10564876]

Bruckheimer E, Abrahamov A. Russell-Silver syndrome and Wilms tumor. J Pediatr. 1993;122:165–6. [PubMed: 8380450]

Cassidy SB, Blonder O, Courtney VW, Ratzan SK, Carey DE. Russell-Silver syndrome and hypopituitarism. Patient report and literature review. Am J Dis Child. 1986;140:155–9. [PubMed: 3946325]

Chauvel PJ, Moore CM, Haslam RH. Trisomy-18 mosaicism with features of Russel-Silver syndrome. Dev Med Child Neurol. 1975;17:220–4. [PubMed: 1132609]

Chitayat D, Friedman JM, Anderson L, Dimmick JE. Hepatocellular carcinoma in a child with familial Russell-Silver syndrome. Am J Med Genet. 1988;31:909–14. [PubMed: 2853572]

Christensen MF, Nielsen J. Deletion short arm 18 and Silver-Russell syndrome. Acta Paediatr Scand. 1978;67:101–3. [PubMed: 626060]

Christoforidis A, Maniadaki I, Stanhope R. Managing children with Russell-Silver syndrome: more than just growth hormone treatment? J Pediatr Endocrinol Metab. 2005;18:651–2. [PubMed: 16128241]

Courtens W, Vermeulen S, Wuyts W, Messiaen L, Wauters J, Nuytinck L, Peeters N, Storm K, Speleman F, Nothen MM. An interstitial deletion of chromosome 7 at band q21: a case report and review. Am J Med Genet A. 2005;134:12–23. [PubMed: 15732063]

Cullen CL, Wesley RK. Russell-Silver syndrome: microdontia and other pertinent oral findings. ASDC J Dent Child. 1987;54:201–4. [PubMed: 3473100]

Czernichow P, Fjellestad-Paulsen A. Growth hormone in the treatment of short stature in young children with intrauterine growth retardation. Horm Res 49 Suppl. 1998;2:23–7. [PubMed: 9716823]

DeChiara TM, Efstratiadis A, Robertson EJ. A growth-deficiency phenotype in heterozygous mice carrying an insulin-like growth factor II gene disrupted by targeting. Nature. 1990;345:78–80. [PubMed: 2330056]

Draznin MB, Stelling MW, Johanson AJ. Silver-Russell syndrome and craniopharyngioma. J Pediatr. 1980;96:887–9. [PubMed: 7189211]

Eggermann T, Schönherr N, Meyer E, Obermann C, Mavany M, Eggermann K, DRanke MB, Wollmann HA. Epigenetic mutations of 11p15 in Silver-Russell syndrome are restricted to the telomeric imprinting domain. J Med Genet. 2006;43:615–6.

Fitzpatrick GV, Soloway PD, Higgins MJ. Regional loss of imprinting and growth deficiency in mice with a targeted deletion of KvDMR1. Nat Genet. 2002;32:426–31. [PubMed: 12410230]

Flori E, Girodon E, Samama B, Becmeur F, Viville B, Girard-Lemaire F, Doray B, Schluth C, Marcellin L, Boehm N, Goossens M, Pingault V. Trisomy 7 mosaicism, maternal uniparental heterodisomy 7 and Hirschsprung's disease in a child with Silver-Russell syndrome. Eur J Hum Genet. 2005;13:1013–8. [PubMed: 15915162]

Font-Montgomery E, Stone KM, Weaver DD, Vance GH, Das S, Thurston VC. Clinical outcome and follow-up of the first reported case of Russell-Silver syndrome with the unique combination of maternal uniparental heterodisomy 7 and mosaic trisomy 7. Birth Defects Res A Clin Mol Teratol. 2005;73:577–82. [PubMed: 16007591]

Gaston V, Le Bouc Y, Soupre V, Burglen L, Donadieu J, Oro H, Audry G, Vazquez MP, Gicquel C. Analysis of the methylation status of the KCNQ1OT and H19 genes in leukocyte DNA for the diagnosis and prognosis of Beckwith-Wiedemann syndrome. Eur J Hum Genet. 2001;9:409–18. [PubMed: 11436121]

Gicquel C, Rossignol S, Cabrol S, Houang M, Steunou V, Barbu V, Danton F, Thibaud N, Le Merrer M, Burglen L, Bertrand AM, Netchine I, Le Bouc Y. Epimutation of the telomeric imprinting center

region on chromosome 11p15 in Silver-Russell syndrome. Nat Genet. 2005;37:1003–7. [PubMed: 16086014]

Graham JM, Hoehn H, Lin MS, Smith DW. Diploid-triploid mixoploidy: clinical and cytogenetic aspects. Pediatrics. 1981;68:23–8. [PubMed: 6264378]

Hannula K, Lipsanen-Nyman M, Kontiokari T, Kere J. A narrow segment of maternal uniparental disomy of chromosome 7q31-qter in Silver-Russell syndrome delimits a candidate gene region. Am J Hum Genet. 2001;68:247–53. [PubMed: 11112662]

Joyce CA, Sharp A, Walker JM, Bullman H, Temple IK. Duplication of 7p12.1-p13, including GRB10 and IGFBP1, in a mother and daughter with features of Silver-Russell syndrome. Hum Genet. 1999;105:273–80. [PubMed: 10987657]

Kim Y, Kim SS, Kim G, Park S, Park IS, Yoo HW. Detection of maternal uniparental disomy at the two imprinted genes on chromosome 7, GRB10 and PEG1/MEST, in a Silver-Russell syndrome patient using methylation-specific PCR assays. Clin Genet. 2005;67:267–9. [PubMed: 15691366]

Kulkarni ML, Venkataramana V, Sureshkumar C, Shabeer HM. Russell-Silver syndrome: a study of 3 cases. Ann Dent. 1995;54:56–60. [PubMed: 8572550]

Lai KY, Skuse D, Stanhope R, Hindmarsh P. Cognitive abilities associated with the Silver-Russell syndrome. Arch Dis Child. 1994;71:490–6. [PubMed: 7726606]

Leppig KA, Saal HM, et al. Distal deletion of Yq in a patient with phenotype of Russell-Silver syndrome. Am J Hum Genet. 1991;49:301.

Li CC, Chodirker BN, Dawson AJ, Chudley AE. Severe hemihypotrophy in a female infant with mosaic Turner syndrome: a variant of Russell-Silver syndrome? Clin Dysmorphol. 2004;13:95–8. [PubMed: 15057125]

Midro AT, Debek K, Sawicka A, Marcinkiewicz D, Rogowska M. Second observation of Silver-Russell syndrome in a carrier of a reciprocal translocation with one breakpoint at site 17q25. Clin Genet. 1993;44:53–5. [PubMed: 8403458]

Monk D, Wakeling EL, Proud V, Hitchins M, Abu-Amero SN, Stanier P, Preece MA, Moore GE. Duplication of 7p11.2-p13, including GRB10, in Silver-Russell syndrome. Am J Hum Genet. 2000;66:36–46. [PubMed: 10631135]

Moore GE, Abu-Amero S, Wakeling E, Hitchins M, Monk D, Stanier P, Preece M. The search for the gene for Silver-Russell syndrome. Acta Paediatr Suppl. 1999;88:42–8. [PubMed: 10626544]

Noeker M, Wollmann HA. Cognitive development in Silver-Russell syndrome: a sibling-controlled study. Dev Med Child Neurol. 2004;46:340–6. [PubMed: 15132265]

Obermann C, Meyer E, Prager S, Tomiuk J, Wollmann HA, Eggermann T. Searching for genomic variants in IGF2 and CDKN1C in Silver-Russell syndrome patients. Mol Genet Metab. 2004;82:246–50. [PubMed: 15234339]

Orbak Z, Orbak R, Kara C, Kavrut F. Differences in dental and bone maturation in regions with or without hemihypertrophy in two patients with Russell-Silver syndrome. J Pediatr Endocrinol Metab. 2005;18:701–10. [PubMed: 16128247]

Ortiz C, Cleveland RH, Jaramillo D, Blickman JG, Crawford J. Urethral valves in Russell-Silver syndrome. J Pediatr. 1991;119:776–8. [PubMed: 1658284]

Ounap K, Reimand T, Magi ML, Bartsch O. Two sisters with Silver-Russell phenotype. Am J Med Genet A. 2004;131:301–6. [PubMed: 15523618]

Partington MW. X-linked short stature with skin pigmentation: evidence for heterogeneity of the Russell-Silver syndrome. Clin Genet. 1986;29:151–6. [PubMed: 3955866]

Pedreira CC, Savarirayan R, Zacharin MR. IMAGe syndrome: a complex disorder affecting growth, adrenal and gonadal function, and skeletal development. J Pediatr. 2004;144:274–7. [PubMed: 14760276]

Price SM, Stanhope R, Garrett C, Preece MA, Trembath RC. The spectrum of Silver-Russell syndrome: a clinical and molecular genetic study and new diagnostic criteria. J Med Genet. 1999;36:837–42. [PubMed: 10544228]

Ramirez-Duenas ML, Medina C, Ocampo-Campos R, Rivera H. Severe Silver-Russell syndrome and translocation (17;20) (q25;q13). Clin Genet. 1992;41:51–3. [PubMed: 1633648]

Rizzo V, Traggiai C, Stanhope R. Growth hormone treatment does not alter lower limb asymmetry in children with Russell-Silver syndrome. Horm Res. 2001;56:114–6. [PubMed: 11847473]

Russell A. A syndrome of intra-uterine dwarfism recognizable at birth with cranio-facial dysostosis, disproportionately short arms, and other anomalies (5 examples). Proc R Soc Med. 1954;47:1040–4. [PubMed: 13237189]

Saal HM, Pagon RA, Pepin MG. Reevaluation of Russell-Silver syndrome. J Pediatr. 1985;107:733–7. [PubMed: 2414426]

Saenger P. US experience in evaluation and diagnosis of GH therapy of intrauterine growth retardation/small-for-gestational-age children. Horm Res 58 Suppl. 2002;3:27–9. [PubMed: 12435893]

Schönherr N, Meyer E, Roos A, Schmidt A, Wollmann HA, Eggermann T. The centromeric 11p15 impritning centre is also involved in Silver-Russell syndrome. J Med Genet. 2007;44:59–63.

Silver HK, Kiyasu W, George J, Deamer WC. Syndrome of congenital hemihypertrophy, shortness of stature, and elevated urinary gonadotropins. Pediatrics. 1953;12:368–76. [PubMed: 13099907]

Stanhope R, Albanese A, Azcona C. Growth hormone treatment of Russell-Silver syndrome. Horm Res 49 Suppl. 1998;2:37–40. [PubMed: 9730671]

Tomiyama H, Ibuki T, Nakajima Y, Tanaka Y. Late intraoperative hypoglycemia in a patient with Russell-Silver syndrome. J Clin Anesth. 1999;11:80–2. [PubMed: 10396727]

Vilain E, Le Merrer M, Lecointre C, Desangles F, Kay MA, Maroteaux P, McCabe ER. IMAGe, a new clinical association of intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies. J Clin Endocrinol Metab. 1999;84:4335–40. [PubMed: 10599684]

Wollmann HA, Kirchner T, Enders H, Preece MA, Ranke MB. Growth and symptoms in Silver-Russell syndrome: review on the basis of 386 patients. Eur J Pediatr. 1995;154:958–68. [PubMed: 8801103]

Chapter Notes

Revision History

- 9 March 2007 (hs) Revision: methylation analysis for *H19* clinically available
- 7 September 2006 (me) Comprehensive update posted to live Web site
- 5 March 2004 (me) Comprehensive update posted to live Web site
- 2 November 2001 (me) Review posted to live Web site
- February 2001 (hs) Original submission