SickKids | Genome Diagnostics

Russell-Silver syndrome

The main feature of Russell-Silver syndrome (RSS) is low birth weight followed by continued growth delays after birth. Individuals with RSS typically have proportionately short stature and normal head circumference. Certain characteristic facial features may also be present (triangular face, down-turned angles of the mouth, prominent forehead, prominent nasal bridge and a small jaw). Other variable features may be seen in children with RSS (see For More Information). Some individuals with RSS will have many of the possible characteristics associated with RSS while others will have very few.

Genetics

RSS is a complex multigenic disorder caused by abnormalities in different genetic regions:

- **In ~35% of RSS patients the cause is alterations in an imprinted growth regulatory gene, H19, on chromosome 11p15.5.**
- Imprinting: Most autosomal genes are expressed (turned on) in both the paternally and maternally inherited gene copies. Imprinted genes are different in that they are expressed (turned on) in a parent of origin specific manner.
- H19 works to suppress or hold back growth. Usually, the maternal copy of H19 is expressed (on) and the paternal copy of H19 is methylated (off). Individuals with RSS due to H19 abnormalities have both the maternal AND paternal copies of H19 expressed (both on).
- **In ~10% of RSS patients the cause is uniparental disomy (UPD) of chromosome 7.** Patients with RSS due to UPD have two copies of chromosome 7 from their mother and no chromosome 7 from their father.
- **In a small number of RSS patients other gene changes on chromosome 7 or the chromosome 11p15.5 region are found.** Some of these are changes in gene copy numbers (duplications) or larger chromosomal rearrangements.

Test Methods

Methylation status: Methylation-specific Multiplex-Ligation-dependent Probe Amplification (MS-MLPA) is used to determine the methylation status of H19.

Gene Dosage Analysis: MLPA is used to determine the relative copy numbers of several genes in the 11p15.5 region.

Microsatellite analysis for UPD: A PCR-based microsatellite assay is used to compare the genetic material contributed from each parent on chromosome 7. Parental samples are required.

Who Should be Tested?

- Individuals suspected of having RSS.
- Fetuses at risk of having RSS (e.g. intrauterine growth retardation (IUGR), positive family history of RSS).

Test sensitivity

There are several molecular alterations associated with RSS. Testing with MLPA of 11p15.5 and UPD7 will detect about 49% of RSS patients. See the chart below for details.

Etiologic heterogeneity in RSS

MLPA Testing of 11p15.5:	Copy number (11p15.5 region)	Methylation Status of H19	KCNQ10T1	Freq.
Hypomethylation H19	Normal	Hypo	Normal	35%
Maternal duplication 11p15.5	Abnormal	Hypo*	Hyper*	~4%

UPD Chromosome 7 Testing:	Frequency
Maternal UPD 7**	~10%

*Depends on the extent of the duplication. **MLPA analysis of 11p15.5 will be normal if maternal UPD7 is detected.

For More Information

The MAGIC foundation—http://www.magicfoundation.org/www/docs/112/russel-silver-syndrome

GeneTests online clinical information resource - http://www.genetests.org/profiles/rss

To locate a genetics center near you, please visit the Canadian Association of Genetic Counsellors website at www.cagc-accg.ca or the National Society of Genetic Counselors website at www.nsgc.org

SickKids

1. Some cases of RSS may warrant a cytogenetic analysis to detect chromosome translocations .

2. Parental samples are required for UPD7 testing.

3. A negative molecular test result does not rule out the diagnosis of RSS.

4. These tests were developed and its performance characteristics validated by the Genome Diagnostics Laboratory at the Hospital for Sick Children. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.