R.C.P.U. NEWSLETTER

R.C. Philips Research and Education Unit

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A statewide commitment to the problems of mental retardation December 2020

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Russell Silver syndrome

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Introduction

Russell-Silver syndrome (RSS), also known as Silver-Russell syndrome, is a rare genetic disorder that is mainly known to cause poor growth before and after birth, as well as body asymmetry in affected individuals. RSS primarily presents in early infancy and childhood and affects girls and boys equally. It is estimated that 1 in 15,000 births are affected with this condition, but this figure is likely to be an underestimate. Life expectancy of individuals with RSS is not thought to be affected.

Aside from the hallmark features of poor growth and body asymmetry, RSS can be accompanied by other clinical features and symptoms. The main clinical features and symptoms of RSS are listed below. However, not all individuals with Russell-Silver syndrome will experience all of these symptoms, and some will experience other symptoms not listed.

Clinical Symptoms

- Slow growth before and after birth
- Failure to thrive
- Poor appetite and feeding difficulties
- Hypoglycemia
- Short stature
- Prominent forehead/frontal bossing
- Small chin
- Triangular face
- Limb-length discrepancy
- Body asymmetry
- Clinodactyly
- Delayed development
- Speech and language problems
- Learning disabilities

Figure 1.
Small chin, prominent forehead

Image from:
https://en.wikipedia.org/wiki/Silver%E2%80%93Russell_syndrome

Figure 2.
Fifth finger clinodactyly

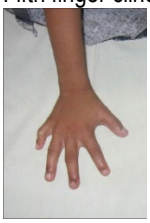

Image from:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3475919/figure/F2/

Figure 3.
Triangular face, short stature, body asymmetry

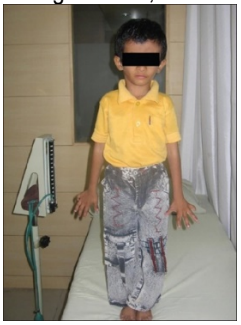

Image from:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3475919/figure/F1/

Beyond Mendelian Inheritance

Russell-Silver syndrome strays from simple Mendelian inheritance patterns. Not only does it often occur in a non-traditional way; it can also occur in more than one way (genetically heterogenous). This can make the confirmation of a clinical diagnosis via genetic testing, challenging. In fact, only about 60% of individuals with a clinical diagnosis of Russell-Silver syndrome are found to have a genetic cause.

Parent of Origin Matters

Imprinting

It is relatively well known that for the most part, genes come in pairs. Individuals inherit a copy of one gene from their mother and one copy of the same gene from their father. However, when it comes to a pair of genes, we do not always express both copies. In fact, there are situations where only one copy out of the two will be expressed, depending on which parent it was inherited from. The remaining copy (allele) must be silenced for normal development. If the allele that needs to be expressed undergoes genetic modifications known as epigenetic changes (i.e. methylation or hypomethylation) it can create a situation where there is reduced protein expression; and in certain cases, result in a genetic disorder. RSS has been found to occur in cases where there is hypomethylation in a region of chromosome 11.

Figure 4.

Normal vs. Hypomethylated region of chromosome 11 that causes RSS

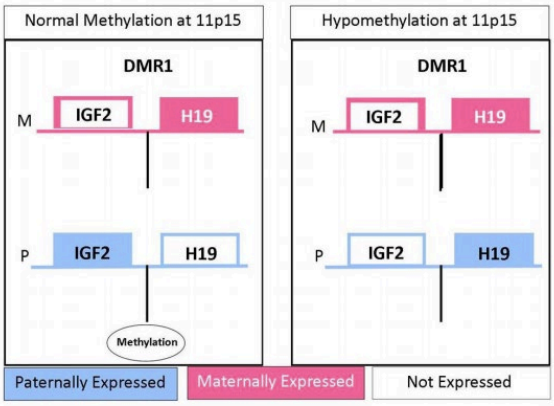

Image from:

Emory Genetics Laboratory. Emory University School of Medicine. https://www.egl-eurofins.com/documents/BWRS.pdf

Uniparental Disomy

Uniparental disomy (UPD) occurs when an individual inherits a pair of chromosomes (i.e. chromosome 7) from the same parent, and none from the other parent. This is different than when an individual inherits a pair of chromosomes from one parent, and a third single copy of the same chromosome from the other parent as is the case in a trisomy. Like in a trisomy event, uniparental disomy is believed to occur due to non-disjunction (a lack of chromosome separation) in the reproductive cell of the parent whose pair gets inherited, as well as a trisomy rescue event shortly after fertilization. Essentially, it is thought that in some cases where trisomy has occurred, UPD will occur as an autocorrection mechanism. UPD is also thought to occur by the union of a sperm or egg cell with two copies of a specific chromosome with a sperm/egg containing no copies of that chromosome. RSS has also been found to occur when an individual has maternal UPD of chromosome 7- in other words, two chromosome 7s that both came from the mother.

Figure 5.

Uniparental Disomy

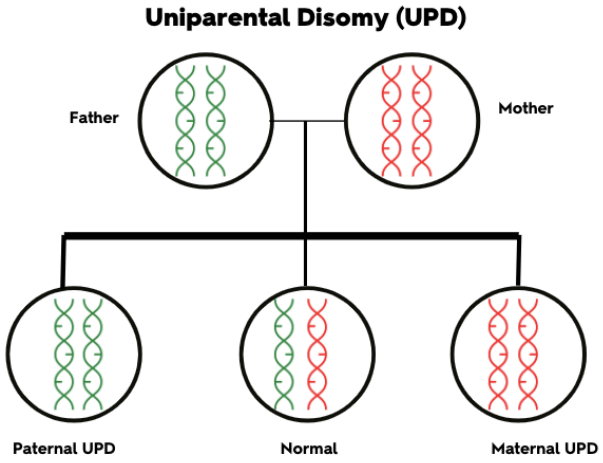

Image created by Stefania Alastre, using canva.com

Single Gene Variants

In rare cases, RSS has been found to occur due to mutations in any of the following genes: IGF2, HMGA2, PLAG1, and CDKN1C.

Diagnosis

RSS is a condition that is clinically diagnosed. However, testing for the known genetic causes of the condition can confirm the clinical diagnosis in about 60% of cases. This information is useful to guide treatments, as well as provide recurrence risk information for the family. Due to the multiple mechanisms for RSS, genetic testing is sometimes a multi-step process.

Figure 6. Flow chart for investigation and diagnosis of RSS.

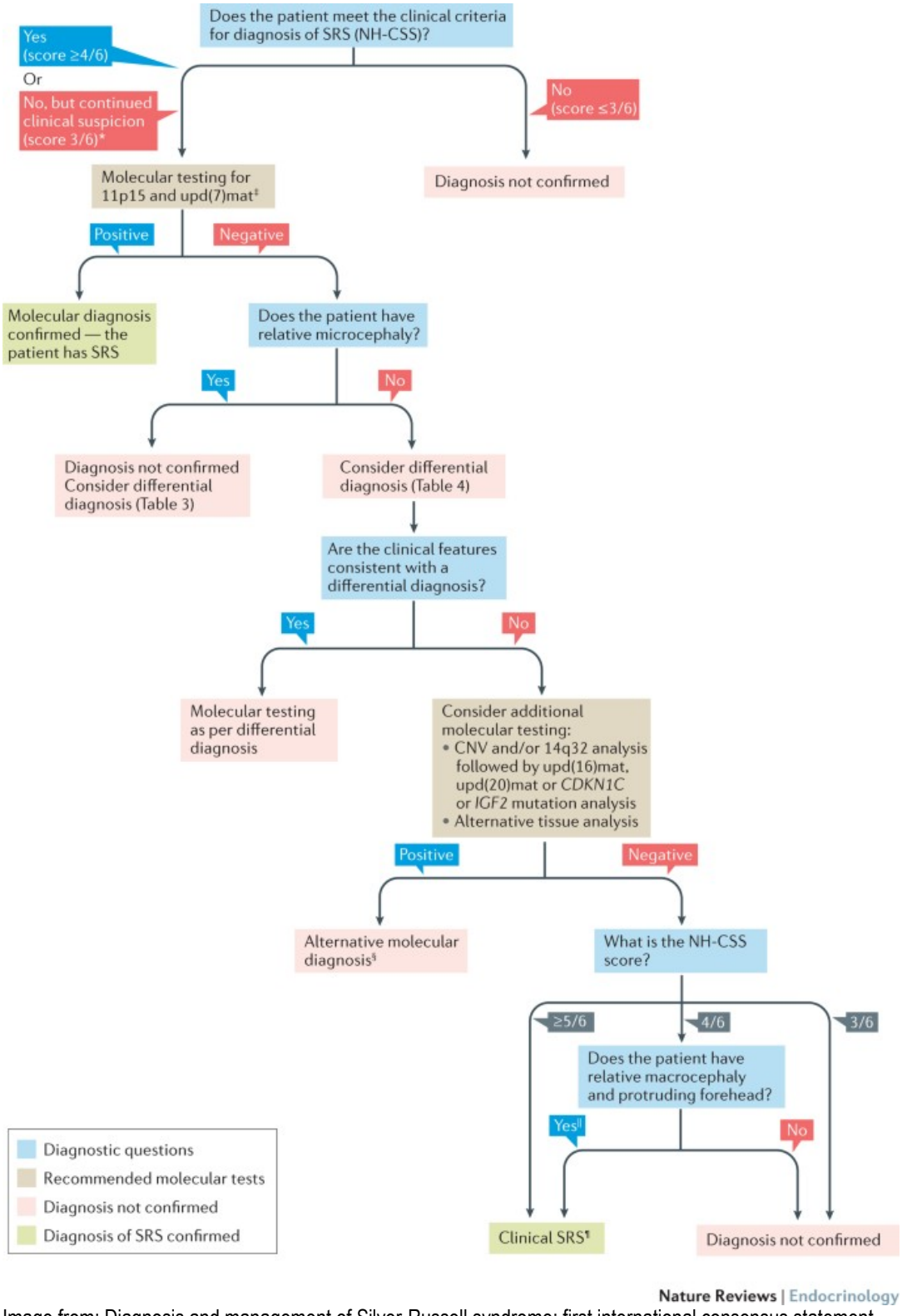

Image from: Diagnosis and management of Silver-Russell syndrome: first international consensus statement

Management
Given the different symptoms that can present in individuals with RSS, a multidisciplinary approach is needed for appropriate treatment. Children with RSS will often have to establish care with a pediatric geneticist, endocrinologist, and other specialists as needed. Additionally, early involvement with speech therapy, physical therapy, and occupational therapy will allow for individuals with RSS to reach their full potential.

For a comprehensive guideline for supervision of patients with RSS, please refer to: Wakeling, E., Brioude, F., Lokulo-Sodipe, O. *et al.* Diagnosis and management of Silver–Russell syndrome: first international consensus statement. *Nat Rev Endocrinol* 13, 105–124 (2017).

Genetic Counseling
Genetic counseling is recommended for all individuals with a suspected or a clinical diagnosis of RSS. Due to the complexity of the different etiologies that can cause RSS, parents of an affected individual may benefit from a personalized discussion about their specific risk for a future baby to also have RSS. Additionally, affected individuals may wish to learn what their risks are to have a baby with the same condition.

Resources

- Child Growth Foundation
  - Website: http://www.childgrowthfoundation.org
- Genetic and Rare Diseases (GARD)
  - Website: http://rarediseases.info.nih.gov/GARD/
- Human Growth Foundation
  - Website: http://www.hgfound.org/
- MAGIC Foundation
  - Website: http://www.magicfoundation.org
- Little People of America, Inc.
  - Website: http://www.lpaonline.org/
- The Arc
  - Website: http://www.thearc.org

About the RCPU

The Raymond C. Philips Research and Education Unit began in 1978 when the legislature established section 393.20, F.S., of what is now known as the "prevention" legislation. It is named after Raymond C. Philips, who was the Superintendent of Gainesville's Tacachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tacachale campus and is funded through a contract with the Department of Children and Families and the Department of Health.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects.
Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

The R.C. Philips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health.

Acknowledgments:

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