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# Ritscher-Schinzel Syndrome

Synonyms: 3C Syndrome, Cranio-Cerebello-Cardiac Dysplasia

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## Summary

### Clinical characteristics

Ritscher-Schinzel syndrome (RSS) is a clinically recognizable condition that includes the cardinal findings of craniofacial features, cerebellar defects, and cardiovascular malformations resulting in the alternate diagnostic name of 3C syndrome. Dysmorphic facial features may include brachycephaly, hypotonic face with protruding tongue, flat appearance of the face on profile view, short midface, widely spaced eyes, downslanted palpebral fissures, low-set ears with overfolding of the upper helix, smooth or short philtrum, and high or cleft palate. Affected individuals also typically have a characteristic metacarpal phalangeal profile showing a consistent wavy pattern on hand radiographs. RSS is associated with variable degrees of developmental delay and intellectual disability. Eye anomalies and hypercholesterolemia may be variably present.

### Diagnosis/testing

The diagnosis of Ritscher-Schinzel syndrome is established in a proband with suggestive clinical findings, including characteristic dysmorphic facial features, and/or by the identification of biallelic pathogenic variants in *WASHC5* in a male or female or a hemizygous pathogenic variant in *CCDC22* in a male by molecular genetic testing.

### Management

*Treatment of manifestations:* Standard treatment for obesity, obstructive sleep apnea, cleft palate, congenital heart defects, hypercholesterolemia, renal anomalies, immunodeficiency, and developmental delay / intellectual disability.

*Surveillance*: Measurement of growth parameters (particularly weight); assessment of developmental progress, mobility, self-help skills, and educational needs; and monitoring for symptoms of obstructive sleep apnea at each visit; ophthalmology evaluation annually or as clinically indicated; measurement of lipid profile periodically starting in childhood.

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## Genetic counseling

*WASHC5*-related RSS is inherited in an autosomal recessive manner; *CCDC22*-related RSS is inherited in an X-linked manner.

- **Autosomal recessive inheritance.** At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- **X-linked inheritance.** If the mother of the proband has a *CCDC22* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes (carriers) and will usually not be affected.

Once the causative pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

# Diagnosis

Consensus clinical diagnostic criteria for Ritscher-Schinzel syndrome (RSS) have not been established. Leonardi et al [2001] suggested minimal clinical diagnostic criteria based on 28 affected individuals reported in the literature. They proposed that the following three criteria all be met:

- Congenital heart malformation(s) other than patent ductus arteriosus alone
- Dandy-Walker malformation, cerebellar vermis hypoplasia, or enlarged cisterna magna
- Cleft palate OR ocular coloboma OR four of the following:
  - Prominent occiput
  - Prominent forehead
  - Downslanted palpebral fissures
  - Widely-spaced eyes
  - Depressed nasal bridge
  - Micrognathia

However, these clinical criteria would exclude affected individuals who may not exhibit cerebellar or cardiac malformations in whom Ritscher-Schinzel syndrome has been molecularly confirmed.

## Suggestive Findings

Ritscher-Schinzel syndrome (RSS) **should be suspected** in an individual with intellectual disability, characteristic facial features, cardiac malformations, malformations of the posterior fossa, and characteristic hand radiographs.

**Clinical findings**

- Mild-to-severe intellectual disability
- Characteristic dysmorphic facial features
  - Macrocephaly
  - Brachycephaly
  - Flat occiput (prominent occiput in some)
  - Hypotonic face with a tendency to a protruding tongue
  - Short midface
  - Flat appearance of the face on profile view
  - Highly arched and thick eyebrows
  - Downslanted palpebral fissures

- Widely spaced eyes
- Depressed nasal bridge
- Low-set ears; overfolding of the upper helix
- Smooth or short philtrum
- High palate or cleft palate
- Short broad neck with a low posterior hair line and webbing

**Imaging findings**

- Cardiac malformations (See Clinical Description, **Cardiac malformations**.)
- Brain MRI
  - Dandy-Walker malformation
  - Hypoplasia or dysplasia of the cerebellar vermis
  - Hydrocephalus
- Hand radiographs
  - Brachydactyly, especially of the second ray
  - Shortening of the first metacarpal and the fifth distal phalanx
  - Characteristic metacarpal phalangeal pattern profile (See Clinical Description, **Limb abnormalities**.)

## Establishing the Diagnosis

The diagnosis of Ritscher-Schinzel syndrome **is established** in a proband with suggestive clinical findings including **characteristic dysmorphic facial features**, and/or by the identification of biallelic pathogenic (or likely pathogenic) variants in *WASHC5* in a male or female OR a hemizygous pathogenic (or likely pathogenic) variant in *CCDC22* in a male by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) The identification of variant(s) of uncertain significance cannot be used to confirm or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (concurrent or serial single-gene testing, multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Ritscher-Schinzel syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of Ritscher-Schinzel syndrome has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

### Option 1

When the phenotypic and radiographic findings suggest the diagnosis of Ritscher-Schinzel syndrome molecular genetic testing approaches can include concurrent or serial single-gene testing, or use of a **multigene panel**.

**Single-gene testing.** Sequence analysis of *WASHC5* and *CCDC22* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected, although inability to amplify an exon may suggest a whole-exon or larger deletion in a male with an X-linked condition.

- If the individual is of First Nations (FN) heritage (indigenous people of Canada who are not Metis or Inuit) or is female, sequence analysis of *WASHC5* is recommended first.

  If only one or no pathogenic variant is found, gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications may be considered.

- In a male proband who is not of FN heritage, sequence analysis of *CCDC22* may be considered first.

**A multigene panel** that includes *WASHC5*, *CCDC22*, 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 diagnosis of Ritscher-Schinzel syndrome is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Chromosomal microarray analysis (CMA)** and **exome sequencing** are most commonly used; **genome sequencing** is also possible.

**Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications that cannot be detected by sequence analysis.

Individuals with a chromosome 6p25 deletion have features that can overlap with RSS (see Differential Diagnosis) [Descipio et al 2005, Micheil Innes 2005].

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 Ritscher-Schinzel Syndrome (RSS)

| Gene [1, 2] | Proportion of RSS Attributed to Pathogenic Variants in Gene | Proportion of Pathogenic Variants [3] Detectable by Method | |
|---|---|---|---|
| | | Sequence analysis [4] | Gene-targeted deletion/ duplication analysis [5] |
| *CCDC22* | <2% [6] | Unknown | Unknown [7] |
| *WASHC5* | >98% [8] | ~99% [9] | Unknown [7] |

*Table 1. continued from previous page.*

| Gene [1, 2] | Proportion of RSS Attributed to Pathogenic Variants in Gene | Proportion of Pathogenic Variants [3] Detectable by Method | |
|---|---|---|---|
| | | Sequence analysis [4] | Gene-targeted deletion/ duplication analysis [5] |
| Unknown [10] | Unknown | NA | |

*1.* Genes are listed in alphabetic order.
*2.* See Table A. Genes and Databases for chromosome locus and protein.
*3.* See Molecular Genetics for information on variants detected in this gene.
*4.* 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.
*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.* A variant in this gene was reported in two male sibs of Austrian origin [Kolanczyk et al 2015]. Another variant was reported in a family from a large X-linked kindred with limited clinical information [Voineagu et al 2012].
*7.* No data on detection rate of gene-targeted deletion/duplication analysis are available.
*8.* This refers to the proportion of affected individuals of First Nations heritage; the proportion of affected individuals of other ethnicities who have biallelic pathogenic variants in *WASHC5* is unknown.
*9.* All affected individuals of First Nations heritage from Northern Ontario and Manitoba who were tested for a sequence variant in this gene were found to be homozygous for the c.3335+2T>A variant [Elliott et al 2013]. Most other *WASHC5* reported variants are associated with spastic paraplegia 8 (see Genetically Related Disorders).
*10.* Individuals from a large Colombian kindred identified as having RSS were not identified to have any pathogenic variants in *WASHC5* or *CCDC22*, indicating genetic heterogeneity [Pira-Paredes et al 2017].

# Clinical Characteristics

## Clinical Description

Ritscher-Schinzel syndrome (RSS) is relatively rare but is a clinically recognizable condition that includes characteristic dysmorphic facial and skeletal features. This disorder is associated with variable degrees of developmental delay and intellectual disability. Malformations have involved many organs and systems including the eye, central nervous system (CNS), and cardiovascular and skeletal systems. Cardinal features include craniofacial features, cerebellar defects, and cardiovascular malformations resulting in the alternate diagnostic name of 3C syndrome.

The following clinical information is based on numerous published reports [Ritscher et al 1987, Lauener et al 1989, Verloes et al 1989, Marles et al 1995, Leonardi et al 2001, Elliott et al 2013, Friesen et al 2013, Kolanczyk et al 2015, Bartuzi et al 2016].

For a concise summary of the timeline from the original description of RSS to the ultimate identification of the underlying molecular mechanisms, click here (pdf).

**Growth.** Most affected individuals have a normal birth weight. They tend to have mild short stature and many develop obesity in later childhood that progresses in adulthood [Marles et al 1995, Leonardi et al 2001].

Individuals with a short neck who are obese are at increased risk of developing obstructive sleep apnea.

**Craniofacial features.** The classic dysmorphic craniofacial features are summarized in Suggestive Findings.

- While the palate may be highly arched, fewer than 5% of affected individuals have a cleft palate.
- About 20% of affected individuals have micrognathia.

**Eye anomalies.** Coloboma of the iris and optic nerve is present in about 20% of affected individuals.

**Cardiac malformations.** A variety of cardiac malformations have been described affecting more than half of individuals with RSS. These include:

- Atrioventricular canal defect
- Mitral valve anomalies, including cleft mitral valve
- Atrial septal defect
- Ventricular septal defect
- Double-outlet right ventricle
- Aortic stenosis
- Pulmonary stenosis
- Tetralogy of Fallot

**Limb abnormalities.** Upper-limb abnormalities are present in the majority of affected individuals, including:

- Brachydactyly, with the second ray being the most severely affected [Friesen et al 2013]
- Camptodactyly
- Proximally placed thumbs
- Abnormalities of the palmar creases

A study by Friesen et al [2013] involving eight individuals with RSS from Manitoba and Northwestern Ontario also found significant shortening of the first metacarpal and the fifth distal phalanx. The metacarpal phalangeal pattern profile generated showed a consistent wavy pattern. Also noted were consistent radiographic changes including: overtubulation of the bones (especially metacarpals 2-4), prominent tufts of the distal phalanges and a hypoplastic fifth distal phalanx.

**Neurodevelopmental findings.** Most individuals with RSS are significantly intellectually impaired. Hypotonia at birth is common. Motor coordination and speech are delayed.

Most affected individuals achieve ambulation and are able to ultimately feed themselves. Most develop limited but meaningful speech.

**Brain malformations.** The most common CNS malformations are Dandy-Walker malformation or variant, cerebellar vermis hypoplasia, posterior fossa cysts, and (less frequently) hydrocephalus.

**Disorders of cholesterol metabolism.** Some affected individuals have been found to have hypercholesterolemia, with elevated LDL cholesterol levels that can lead to atherosclerotic plaque deposition. Hypercholesterolemia has been demonstrated to be present in childhood, although xanthomas have not been reported in affected individuals. Hypercholesterolemia is hypothesized to be due to mislocalization of the low-density lipoprotein receptor, accompanied by decreased LDL uptake [Bartuzi et al 2016] (see Phenotype Correlations by Gene).

**Other abnormalities.** The following have been reported in fewer than 10% of affected individuals; it is unknown whether these are rare features of RSS or if they represent coincidental findings:

- Absent ribs
- Adrenal hypoplasia
- Anal atresia
- Congenital glaucoma
- Clubbed foot [Konya et al 2015]
- Cutis aplasia
- Hemangioma
- Hemivertebrae
- Hypospadias
- Inguinal hernia

- Malrotation of the gut
- Nail hypoplasia
- Nipple hypoplasia
- "Penis hypoplasia"
- Polydactyly, without further description of the location or type
- Renal malformations

In one affected individual, humoral immune deficiency was described [Lauener et al 1989]; it was subsequently found to result from secondary loss of IgG via the gastrointestinal system [Zankl et al 2003].

## Phenotype Correlations by Gene

***CCDC22.*** Males with a hemizygous pathogenic variant in *CCDC22* are more likely to have:

- Upslanted palpebral fissures, an uncommon finding in those who are of First Nations heritage [Kolanczyk et al 2015];
- A more strikingly large, protruding tongue than seen in individuals with variants in *WASHC5*;
- Additional ectodermal findings (nail hypoplasia, abnormal dentition and aplasia cutis congenital).

***WASHC5.*** Some individuals with biallelic pathogenic variants in *WASHC5* also develop hypercholesterolemia.

## Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified; all individuals identified to date with RSS who are of First Nations heritage have the homozygous variant in *WASHC5*.

## Nomenclature

*WASHC5* was previously termed *KIAA0196*.

Kolanczyk et al [2015] suggested that the group of disorders including the X-linked and autosomal recessive forms of RSS be termed WASHopathies (see Molecular Genetics).

## Prevalence

RSS is rare and, although individuals have been reported with "3-C syndrome/RSS," not all reports include those who have the characteristic craniofacial features.

For the First Nations cohort (Northern Manitoba and Northwestern Ontario), the carrier frequency is estimated at 1:9 individuals [Elliott et al 2013].

# Genetically Related (Allelic) Disorders

Pathogenic variants in *WASHC5* are also known to be associated with spastic paraplegia 8.

Individuals with X-linked intellectual disability (ID) have been reported to have variants in *CCDC22* [Starokadomskyy et al 2013]. Because the clinical data presented in this article are limited, it is unclear if these reported individuals have mild features of RSS or if they truly have nonsyndromic X-linked ID.

# Differential Diagnosis

**6p25 deletion** (OMIM 612582). Individuals with a chromosome 6p25 deletion have features that can overlap with Ritscher-Schinzel Syndrome (RSS) [Descipio et al 2005, Micheil Innes 2005]. 6p25 deletion syndrome shares the following features with RSS: intellectual disability, Dandy-Walker malformation, hydrocephalus,

congenital heart defects, anomalies of the anterior chamber of the eye, and craniofacial findings (prominent forehead, midface hypoplasia, downslanting palpebral fissures, hypertelorism, epicanthal folds, ptosis, proptosis, external ear anomalies, flat nasal bridge, short or smooth philtrum, and a high arched palate).

6p25 deletion can be distinguished from RSS by the presence of the 6p25 deletion on chromosomal microarray analysis and an overall craniofacial gestalt distinct from RSS.

**Other chromosome anomalies** may be also be associated with intellectual disability, congenital heart defects, and craniofacial dysmorphisms and can be distinguished by the presence of a chromosome abnormality.

**Table 2.** Disorders to Consider in the Differential Diagnosis of Ritscher-Schinzel Syndrome

| DiffDx Disorder | Gene(s) | MOI | Clinical Features of DiffDx Disorder | |
|---|---|---|---|---|
| | | | Overlapping w/RSS | Distinguishing from RSS |
| Joubert Syndrome | >30 genes [1] | AR<br>(XL, digenic) [2] | • ID<br>• Hypoplasia of the cerebral vermis<br>• Ocular colobomas | • Polydactyly<br>• Retinal dystrophy<br>• Cystic kidneys<br>• Presence of "molar tooth sign" neuroradiologic finding |
| Ellis-van Creveld syndrome | *EVC*<br>*EVC2* | AR | • CHD<br>• Dandy-Walker malformation<br>• Limb & palate anomalies | • Polydactyly<br>• Short ribs<br>• Absence of characteristic RSS facial features |
| Cornelia de Lange syndrome | *HDAC8*<br>*NIPBL*<br>*RAD21*<br>*SMC1A*<br>*SMC3* | AD [3]<br>XL | • ID<br>• CHD<br>• Craniofacial dysmorphisms<br>• Distal limb anomalies | • Absence of cerebellar hypoplasia<br>• Characteristic facial features |
| CHARGE syndrome | *CHD7* | AD [3] | • ID<br>• Dysmorphic facial features<br>• Coloboma<br>• Palate anomalies<br>• CHD | • Choanal atresia<br>• Inner-ear dysgenesis<br>• Facial nerve palsies<br>• Pituitary dysfunction<br>• Absence of characteristic RSS facial features |
| Kabuki syndrome | *KDM6A*<br>*KMT2D* | AD<br>XL [4] | • ID<br>• Coloboma<br>• Palate anomalies<br>• Dysmorphic craniofacial features | • Characteristic facial features<br>• Persistence of fetal fingertip pads |
| Frontonasal dysplasia (OMIM PS136760) | *ALX1*<br>*ALX3*<br>*ALX4* | AR | • ID<br>• Dysmorphic craniofacial features<br>• Hypertelorism<br>• Palate anomalies<br>• Distal limb anomalies | • Encephalocele<br>• Nasal clefting<br>• Distinctive craniofacial features |
| RSS-like syndrome [5] | *VPS35L* | AR | • ID<br>• Dysmorphic craniofacial features<br>• CHD<br>• Coloboma<br>• Cerebellar vermis hypoplasia | • Severe growth restriction<br>• Microphthalmia<br>• Periventricular nodular heterotopia<br>• Chondrodysplasia punctata<br>• Mesomelia of upper extremities |

*Table 2. continued from previous page.*

| DiffDx Disorder | Gene(s) | MOI | Clinical Features of DiffDx Disorder | |
|---|---|---|---|---|
| | | | Overlapping w/RSS | Distinguishing from RSS |
| Loucks-Innes syndrome [6] | *DPH1* | AR | • ID<br>• Short stature<br>• Dandy-Walker malformation, cerebellar vermis hypoplasia, & posterior fossa cyst<br>• CHD<br>• Renal anomalies | • Distinctive craniofacial features<br>• Ectodermal findings |

AD = autosomal dominant; AR = autosomal recessive; CHD = congenital heart defect; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; RSS = Ritscher-Schinzel syndrome; XL = X-linked

*1.* See Joubert Syndrome.

*2.* Joubert syndrome is predominantly inherited in an autosomal recessive manner. Joubert syndrome caused by pathogenic variants in *OFD1* is inherited in an X-linked manner. Digenic inheritance has been reported.

*3.* Typically caused by a *de novo* pathogenic variant

*4.* The proportion of Kabuki syndrome caused by *de novo* variants is unknown, but is likely high based on clinical experience.

*5.* Kato et al [2020]

*6.* Loucks et al [2015]

# Management

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Ritscher-Schinzel syndrome (RSS), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 3.** Recommended Evaluations Following Initial Diagnosis in Individuals with Ritscher-Schinzel Syndrome

| System | Evaluation | Comment |
|---|---|---|
| **Constitutional** | Measure growth parameters. | To assess for short stature &/or obesity |
| **Respiratory** | Consider polysomnogram. | In those w/obesity & symptoms of sleep apnea |
| **Craniofacial** | Clinical assessment for cleft palate &/or micrognathia | Consider referral to craniofacial clinic. |
| **Eyes** | Ophthalmology eval | To evaluate for eye anomalies & visual acuity |
| **Cardiovascular** | Echocardiogram to screen for congenital heart defects | Consider referral to cardiologist. |
| | Lipid profile [1] | To screen for hypercholesterolemia in older children, adolescents, & adults |
| **Renal** | Renal ultrasound | To evaluate for structural renal anomalies |
| **Neurologic** | Neurologic eval | |
| | Brain MRI, if not performed as part of initial investigations | Structural brain abnormalities are commonly seen in addition to hydrocephalus. |
| **Development** | Developmental assessment | • To incl motor, adaptive, cognitive, & speech/ language eval<br>• Eval for early intervention / special education |
| **Psychiatric/ Behavioral** | Neuropsychiatric eval | • For persons age >12 mo<br>• Particularly useful at school entry to help formulate an appropriate education plan |

*Table 3. continued from previous page.*

| System | Evaluation | Comment |
|---|---|---|
| **Immunologic** | Immunologic screening [2] | • In those w/repeated bacterial infections<br>• Consider referral to immunologist. |
| **Miscellaneous/ Other** | Consultation w/clinical geneticist &/or genetic counselor | To incl genetic counseling |
| | Family support/resources | Assess need for:<br>• Community or online resources such as Parent to Parent;<br>• Social work involvement for parental support;<br>• Home nursing referral. |

*1.* Including measurement of total cholesterol, HDL, and LDL cholesterol concentrations. Fasting is not required [Mora 2016].
*2.* Including serum immunoglobulin levels and assessment of previous immune responses (e.g., measurement of titers from previous immunizations)

## Treatment of Manifestations

**Table 4.** Treatment of Manifestations in Individuals with Ritscher-Schinzel Syndrome

| Manifestation/Concern | Treatment | Considerations/Other |
|---|---|---|
| **Obesity** | Standard treatment | Incl referral to nutritional specialists to monitor food intake & weight |
| **Obstructive sleep apnea** | Standard treatment | May incl weight control, removal of tonsils/ adenoids, &/or CPAP |
| **Cleft palate** | Standard surgical treatment, ideally by a specialized craniofacial team | |
| **Congenital heart defects** | Standard treatment | |
| **Hypercholesterolemia** | Standard treatment incl consideration of oral HMG-CoA reductase inhibitors (statins) [1] | Other considerations incl optimizing weight, ↑ physical activity, & optimizing dietary fiber intake |
| **Renal anomalies** | Standard treatment per urologist &/or nephrologist | |
| **Immunodeficiency** | Standard treatment per immunologist | |
| **Family/Community** | • Ensure appropriate social work involvement to connect families w/local resources, respite, & support.<br>• Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies. | • Ongoing assessment of need for palliative care involvement &/or home nursing<br>• Consider involvement in adaptive sports or Special Olympics. |

*1.* Particularly if other cardiovascular risk factors (smoking, diabetes mellitus, hypertension) are identified

## Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States; standard recommendations may vary from country to country.

**Ages 0-3 years.** Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

**Ages 3-5 years.** In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies and an individualized

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

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

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

## Motor Dysfunction

**Gross motor dysfunction.** Physical therapy is recommended to maximize mobility.

**Fine motor dysfunction.** Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

**Oral motor dysfunction.** Assuming that the individual is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended for affected individuals who have difficulty feeding due to poor oral motor control.

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

## Surveillance

**Table 5.** Recommended Surveillance for Individuals with Ritscher-Schinzel Syndrome

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Eyes** | Ophthalmology eval | Annually or as clinically indicated |
| **Cardiovascular** | Lipid profile [1] | Periodically [2] |
| **Constitutional** | Measurement of growth parameters, esp weight | At each visit |
| **Respiratory** | Monitor for symptoms of obstructive sleep apnea. | |
| **Musculoskeletal** | Physical medicine, OT/PT assessment of mobility, self-help skills | |
| **Development** | Monitor developmental progress & educational needs. | |
| **Miscellaneous/ Other** | Assess family need for social work support (e.g., respite care, home nursing, other local resources) & care coordination. | |

OT = occupational therapy; PT = physical therapy
*1.* Including measurement of total cholesterol, HDL, and LDL cholesterol concentrations
*2.* Specific frequency may depend on initial cholesterol levels; in those without elevated cholesterol levels, screening every few years may be appropriate.

## Evaluation of Relatives at Risk

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

## 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

Ritscher-Schinzel syndrome (RSS) caused by pathogenic variants in *WASHC5* is inherited in an autosomal recessive manner.

RSS caused by pathogenic variant in *CCDC22* is inherited in an X-linked manner.

## Autosomal Recessive Inheritance – Risk to Family Members

**Parents of a proband**

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *WASHC5* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Sibs of a proband**

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

**Offspring of a proband.** To date, individuals with RSS are not known to reproduce.

**Other family members.** Each sib of the proband's parents is at a 50% risk of being a carrier of a *WASHC5* pathogenic variant.

**Carrier detection.** Carrier testing for at-risk relatives requires prior identification of the *WASHC5* pathogenic variants in the family.

## X-Linked Inheritance – Risk to Family Members

**Parents of a male proband**

- The father of an affected male will not have the disorder nor will he be hemizygous for the *CCDC22* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives and if the *CCDC22* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.
- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or the affected male may have a *de novo CCDC22* pathogenic variant, in which case the mother is not a carrier. The frequency of males with a *de novo* pathogenic variant is unknown.

**Sibs of a male proband.** The risk to sibs depends on the genetic status of the mother:

- If the mother of the proband has a *CCDC22* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the pathogenic variant will be heterozygotes (carriers) and will usually not be affected.
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *CCDC22* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to sibs is slightly greater than that of the general population because of the possibility of maternal germline mosaicism.

**Offspring of proband.** Affected males are not known to reproduce.

**Other family members.** The proband's maternal aunts may be at risk of being carriers for the pathogenic variant and the aunts' offspring, depending on their sex, may be at risk of being carriers of being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose, information that could help determine genetic risk status of the extended family.

**Heterozygote detection.** Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the *CCDC22* pathogenic variant has been identified in the proband.

- Females who are heterozygous (carriers) for this X-linked disorder will usually not be affected
- Identification of female heterozygotes requires either (a) prior identification of the *CCDC22* pathogenic variant in the family or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

## Related Genetic Counseling Issues

**Family planning**

- The optimal time for determination of genetic risk, clarification of carrier status, 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 carriers or are at risk of being carriers.

**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). For more information, see Huang et al [2022].

## Prenatal Testing and Preimplantation Genetic Testing

**Molecular genetic testing.** Once the RSS-causing pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

**Ultrasound findings.** RSS caused by pathogenic variants in *WASHC5* is associated with increased nuchal translucency thickness [Rusnak et al 2008]. First-trimester prenatal ultrasound is recommended in at-risk pregnancies to evaluate for cardiac anomalies and increased nuchal translucency. It has not been established whether RSS caused by pathogenic variants in *CCDC22* demonstrates increased nuchal translucency.

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.*

- **MyGene2**

  *Families with rare genetic conditions may use MyGene2 to search for and contact other families who have the same condition or mutations in the same gene in order to share information and offer support. Note: Other families with Ritscher-Schinzel syndrome may not be registered with this resource.*

  mygene2.org/MyGene2/families

- **Canadian Organization for Rare Disorders (CORD)**

  Canada

  www.raredisorders.ca

- **National Organization for Rare Disorders (NORD)**

  www.rarediseases.org

# 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.** Ritscher-Schinzel Syndrome: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|

*Table A. continued from previous page.*

| | | | | | |
|---|---|---|---|---|---|
| *CCDC22* | Xp11.23 | Coiled-coil domain-containing protein 22 | CCDC22 @ LOVD | CCDC22 | CCDC22 |
| *WASHC5* | 8q24.13 | WASH complex subunit 5 | KIAA0196 database | WASHC5 | WASHC5 |

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 Ritscher-Schinzel Syndrome (View All in OMIM)

| | |
|---|---|
| 220210 | RITSCHER-SCHINZEL SYNDROME 1; RTSC1 |
| 300859 | COILED-COIL DOMAIN-CONTAINING PROTEIN 22; CCDC22 |
| 300963 | RITSCHER-SCHINZEL SYNDROME 2; RTSC2 |
| 610657 | WASH COMPLEX, SUBUNIT 5; WASHC5 |

## Molecular Pathogenesis

The genes involved in both autosomal (*WASH5C*) and X-linked (*CCDC22*) forms of RSS encode proteins belonging to a family known as "WASHopathies" [Kolanczyk et al 2015]. Both proteins encoded by these genes play a role in the function of the WASH and are involved in actin polymerization and multiple endosomal transport processes.

*CCDC22* encodes amino acid coiled-coil domain-containing protein 22 that interacts with the functional WASH complex. It is expressed in many human tissues (with highest expression in a number of blood cell lineages) and plays a role in NFκB signaling. CCDC22 contains:

- An N-terminal conserved domain;
- A C-terminal coiled coil domain that is similar to structural maintenance of chromosomes (SMC) proteins.

*WASHC5* encodes strumpellin (WASH complex subunit 5), a highly conserved WASH complex protein that is ubiquitously expressed. It is predicted to have several functional domains [Elliott et al 2013]:

- Multiple transmembrane domains, with the N-terminal region (amino acids 1-240) comprising six α helices and two β strand segments
- A central region (amino acids 241-971) comprising spectrin-repeat domains
- A C-terminal region (residues 792-1159) demonstrating structural similarity to exportin-5 and importin β-1

The *W*iskott-*A*ldrich syndrome protein and *S*CAR *h*omolog (WASH) complex is required by certain transmembrane proteins in the endosomal compartment to reach their appropriate cellular destinations. The pentameric protein complex, that also consists of WASH1, FAM21, strumpellin, KIAA1033 (aka SWIP) and CCDC53 is recruited to endosomes by the retromer complex. The COMMD/CCDC22/CCDC93 (aka CCC) complex interacts and colocalizes with retromer and the WASH complex (reviewed in Bartuzi et al [2016]). The CCC complex regulates the level of circulating low-density lipoprotein (LDL) cholesterol by mediating the endosomal trafficking of the LDL receptor (LDLR). LDLR is an endosomal cargo of the CCC-associated WASH complex, and inactivation of the complex also results in LDLR mislocalization and impaired LDL uptake, ultimately resulting in hypercholesterolemia in individuals with RSS. See *WAS*-Related Disorders.

**Mechanism of disease causation.** RSS occurs through a loss-of-function mechanism.

Western blot analysis revealed that the p.Tyr557Cys variant resulted in a 50% decreased expression of CCDC22 in affected versus control individuals.

The p.Thr17Ala variant resulted in a fivefold decrease in mRNA levels in addition to increased levels of abnormally spliced transcripts retaining intron 1.

The *WASHC5* c.3335+2T>A pathogenic variant, common in the First Nations cohort, is predicted to cause exon 27 skipping, resulting in a frameshift and a premature stop after amino acid 1128. The abnormal stumpellin is predicted to lose 99 C-terminal amino acids normally encoded by exons 27-29; these were replaced by 68 novel C-terminal residues. There was a mean 7.8-fold reduction in the relative amount of transcript produced, indicating that the transcript may be targeted for nonsense-medicated decay. The abnormal protein was reduced by 60% as compared to control.

**Table 6.** Notable Ritscher-Schinzel Syndrome Pathogenic Variants by Gene

| Gene [1] | Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|---|
| *CCDC22* | NM_014008.4<br>NP_054727.1 | c.1670A>G | p.Tyr557Cys | Functional evidence demonstrates a loss-of-function mechanism [Voineagu et al 2012]. |
| | | c.49A>G | p.Thr17Ala | |
| *WASHC5* | NM_014846.3<br>NP_055661.3 | c.3335+2T>A | NA | Common variant in the FN population [Elliott et al 2013] |

FN = First Nations; NA = not applicable
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.
*1.* Genes from Table 1 in alphabetic order.

# Chapter Notes

## Author Notes

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