U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Stevens CA. Rubinstein-Taybi Syndrome. 2002 Aug 30 [Updated 2019 Aug 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Rubinstein-Taybi Syndrome

Synonym: Broad Thumb-Hallux Syndrome

Cathy A Stevens, MD[1]

Created: August 30, 2002; Updated: August 22, 2019.

Summary

Clinical characteristics

Rubinstein-Taybi syndrome (RSTS) is characterized by distinctive facial features, broad and often angulated thumbs and halluces, short stature, and moderate-to-severe intellectual disability. The characteristic craniofacial features are downslanted palpebral fissures, low-hanging columella, high palate, grimacing smile, and talon cusps. Prenatal growth is often normal, then height, weight, and head circumference percentiles rapidly drop in the first few months of life. Short stature is typical in adulthood. Obesity may develop in childhood or adolescence. Average IQ ranges between 35 and 50; however, developmental outcome varies considerably. Some individuals with *EP300*-RSTS have normal intellect. Additional features include ocular abnormalities, hearing loss, respiratory difficulties, congenital heart defects, renal abnormalities, cryptorchidism, feeding problems, recurrent infections, and severe constipation.

Diagnosis/testing

The diagnosis of RSTS is established in a proband with characteristic clinical features. Identification of a heterozygous pathogenic variant in *CREBBP* or *EP300* confirms the diagnosis if clinical features are inconclusive.

Management

Treatment of manifestations: Early intervention programs, special education, vocational training to address developmental disabilities, referral to behavioral specialists / psychologists, and support groups / resources for family members; standard treatment for eye abnormalities, hearing loss, sleep apnea, cardiac anomalies, renal anomalies, cryptorchidism, and dental anomalies; aggressive management of gastroesophageal reflux and constipation; surgical repair of significantly angulated thumbs or duplicated halluces.

Surveillance: Monitoring of growth and feeding, especially in the first year of life; annual eye and hearing evaluations; routine monitoring for cardiac, renal, and dental anomalies.

Author Affiliation: 1 Director, Medical Genetics, Professor, Pediatrics, University of Tennessee College of Medicine, Chattanooga, Tennessee; Email: cathy.stevens@erlanger.org.

Copyright © 1993-2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved.

Genetic counseling

RSTS is inherited in an autosomal dominant manner. RSTS typically occurs as the result of a *de novo* pathogenic variant in the family; most individuals represent simplex cases (i.e., the only affected member in a family). In most instances, the parents of an individual with RSTS are not affected. When the parents are clinically unaffected, sibs are still presumed to be at increased risk for RSTS because of the possibility of a mild phenotype in a heterozygous parent or parental somatic and/or germline mosaicism. The empiric recurrence risk for sibs is less than 1%. Individuals with RSTS rarely reproduce. The risk to offspring is 50%. Once the pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Diagnosis

Suggestive Findings

Rubinstein-Taybi syndrome (RSTS) **should be suspected** in individuals with the following characteristic clinical findings:

- Craniofacial appearance (see Figure 1)
- Downslanted palpebral fissures
- Convex nasal ridge with low-hanging columella
- High palate
- Grimacing smile
- Talon cusps (an accessory cusp-like structure on the lingual side of the tooth), usually occurring on the maxillary incisors of the permanent dentition

Other features (see Figure 2 and Figure 3)

- The thumbs and halluces are almost always broad and often angulated.
- The distal phalanges of the fingers may appear broad.
- The proximal phalanges may be abnormally shaped. Radiographs of the hands and feet in individuals with RSTS are unusual but not necessarily diagnostic.
- Almost all males have undescended testes.
- Structural abnormalities of the urinary tract are common.
- Congenital heart defects of various types occur in approximately one third of individuals.

Growth

- While prenatal growth is often normal, height, weight, and head circumference percentiles rapidly drop in the first few months of life. Short stature is typical in adulthood.
- Obesity may develop, particularly in adolescence or adulthood.

Intellectual disability. The average IQ ranges between 35 and 50; however, developmental outcome varies considerably. Some individuals with *EP300*-RSTS have normal intellect [Fergelot et al 2016].

Establishing the Diagnosis

The diagnosis of RSTS **is established** in a proband with the above Suggestive Findings. Identification of a heterozygous pathogenic variant in *CREBBP* or *EP300* by molecular genetic testing can confirm the diagnosis if clinical features are inconclusive (see Table 1).

Figure 1. Typical facial appearance in individuals with RSTS. Note arched brows, downslanted palpebral fissures, low-hanging columella, and grimacing smile.

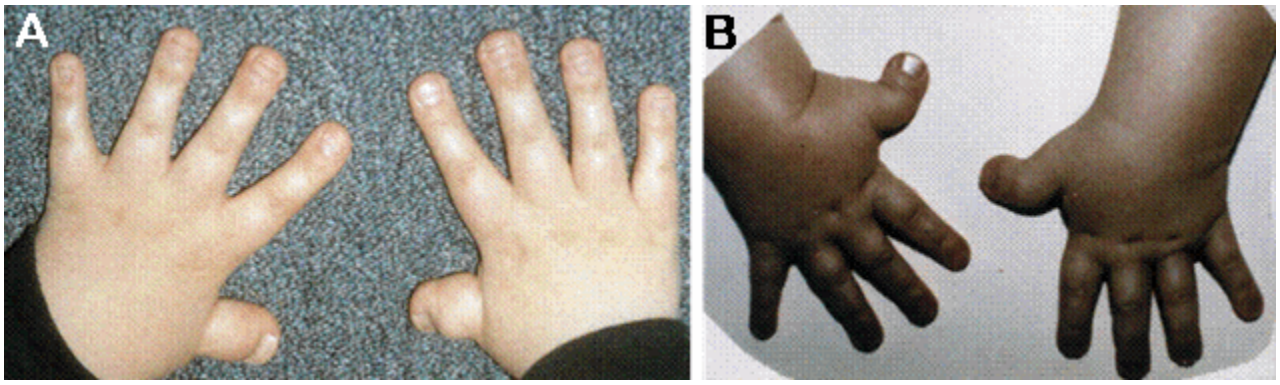

Figure 2. Broad terminal phalanges (A) and broad, radially deviated thumbs (B)

Figure 3. Broad, partially duplicated halluces

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of RSTS 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 with a phenotype indistinguishable from many other inherited disorders with short stature and/or intellectual disability are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of RSTS, molecular genetic testing approaches can include **single gene testing** or use of a **multigene panel**. **Chromosomal microarray analysis** can be useful in some situations:

- **Serial single-gene testing.** Sequence analysis detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis of *CREBBP* first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis of *CREBBP* to detect intragenic deletions or duplications. If no pathogenic variant is found, perform sequence analysis of *EP300*. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis of *EP300*.
- **A multigene panel** that includes *CREBBP*, *EP300*, and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost 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 this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.
- **Chromosomal microarray analysis (CMA)** uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *CREBBP* and *EP300*) that cannot be detected by sequence analysis.

  Note: (1) Since a significant proportion of *CREBBP* pathogenic variants are large deletions, RSTS may be diagnosed by CMA performed without prior consideration of a diagnosis of RSTS. (2) Allelic disorders associated with contiguous gene deletions involving *CREBBP* and limited phenotypic overlap with RSTS have been reported (see Genetically Related Disorders). For individuals with features of RSTS as well as these related disorders, chromosomal microarray analysis (CMA) should be performed first.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by short stature and/or intellectual disability, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is another option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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 Rubinstein-Taybi Syndrome

Gene [1, 2]	Proportion of Rubinstein-Taybi Syndrome Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/duplication analysis [5]
CREBBP	50%-60% [6]	~80%	~20% [7]
EP300	8%-10% [8]	>99%	<1% [9]
Unknown [10]	~30%	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 allelic variants detected in these genes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. 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 quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected by these methods (see Genetically Related Disorders).
6. Coupry et al [2002], Bartsch et al [2005], Bentivegna et al [2006], Schorry et al [2008]
7. Stef et al [2007], Spena et al [2015]
8. Negri et al [2015], Fergelot et al [2016]
9. Fergelot et al [2016]
10. RSTS may be caused by pathogenic variants in another gene(s) in up to 30% of individuals [Bartsch et al 2005].

Clinical Characteristics

Clinical Description

Rubinstein-Taybi syndrome (RSTS) is frequently recognized at birth or in infancy because of the striking facial features and characteristic hand and foot findings. Problems in early life include respiratory difficulties, feeding problems, poor weight gain, recurrent infections, and severe constipation. Moderate intellectual disability is typical.

Growth. Although prenatal growth is usually normal, growth deficiency begins in the first year of life. There is typically an absence of a growth spurt in adolescence. While BMI is normal for males at age 21, it is increased for females at this age. Many adults develop obesity [Stevens et al 2011]. Average height for adult males is 162.6 cm and for adult females is 151.0 cm [Beets et al 2014]. Beets et al [2014] published growth charts for RSTS.

Eye findings include strabismus, refractory errors, ptosis, nasolacrimal duct obstruction, cataracts, coloboma, nystagmus, glaucoma, and corneal abnormalities.

Hearing loss. Recurrent or refractory middle ear disease can result in conductive hearing loss. Sensorineural hearing loss may also be seen.

Respiratory. Obstructive sleep apnea is often a considerable problem and may be caused by the combination of a narrow palate, micrognathia, hypotonia, obesity, and easy collapsibility of the laryngeal walls. There are reported incidences of intubation and anesthesia complications. Aspiration, asthma, and recurrent upper respiratory infections may also occur.

Cardiac. Approximately one third of affected individuals have a variety of congenital heart defects (e.g., atrial septal defect, ventricular septal defect, patent ductus arteriosus, coarctation of the aorta, pulmonary stenosis, bicuspid aortic valve, pseudotruncus arteriosus, aortic stenosis, vascular ring, conduction abnormalities).

Genitourinary. Renal abnormalities, including hydronephrosis and duplications, are very common. Other genitourinary complications include hypospadias, vesicoureteral reflux, nephrolithiasis, and urinary tract infections. Almost all boys have undescended testes.

Gastrointestinal. Feeding problems, gastroesophageal reflux, and constipation are common. Malrotation should be suspected if there is bilious vomiting, recurrent abdominal pain, failure to pass stool, or bloody stools [Stevens 2015].

Orthopedic. In addition to angulated thumbs and duplicated halluces, orthopedic issues include dislocated patellae, lax joints, spine curvatures, Legg-Perthes disease, slipped capital femoral epiphysis, and cervical vertebral abnormalities.

Neurologic. Occasional craniospinal and posterior fossa abnormalities including Chiari malformation, syringomyelia, os odontoideum, and cervical cord compression have been reported [Marzuillo et al 2013]. There may also be spinal cord tethering or lipoma. Seizures or abnormal EEG findings can occur.

Dental. Dental problems include crowding of teeth, malocclusion, multiple caries, hypodontia, hyperdontia, natal teeth, and talon cusps on the upper incisors of the secondary dentition.

Skin. Keloids may occur with only minimal trauma to the skin. Pilomatrixomas have been reported [Boot et al 2018].

Recurrent infection is reported in some individuals and includes otitis media, pneumonia, and other respiratory infections. There are reports of individuals with humoral or cellular immunodeficiency.

Tumors. Various benign and malignant tumors have been reported in individuals with RSTS including neuroblastoma, rhabdomyosarcoma, medulloblastoma, and hematologic malignancies. A recent study of Dutch individuals with RSTS did not confirm an increased risk for malignancies. However, the incidence of meningiomas and pilomatrixomas was significantly elevated [Boot et al 2018]. There are currently no standard screening protocols for tumors.

Puberty. Puberty and sexual development are normal.

Development and intellect. Delayed development is typical in children with RSTS. In one study, the average age of walking was 30 months, first words 25 months, and toilet training 62 months. Speech delay occurs in 90% of children and some remain largely nonverbal. Waite et al [2016] noted deficits in verbal and visuospatial working memory.

The average IQ in one study was 51 and in another study was 36. IQ scores range from 25 to 79. Performance IQ is usually higher than verbal IQ. Some individuals with *EP300*-RSTS have normal intellect [Fergelot et al 2016].

In one study of adults with RSTS, families reported a decline in abilities over time in 32%, including decreased social interaction, more limited speech, and worsening stamina and mobility [Stevens et al 2011].

Behavior. Impulsivity, distractibility, instability of mood, and stereotypies are frequently observed [Verhoeven et al 2010]. Other abnormal behaviors include attention problems, hyperactivity, self-injurious behaviors, and aggressive behaviors. Approximately 62% of adults with RSTS were reported to have autistic-like behaviors and one third had unreasonable fears or anxiety [Stevens et al 2011]. There may be an insistence on sameness and repetitive questioning [Waite et al 2015]. Crawford et al [2017] noted higher levels of panic attack, agoraphobia, and obsessive-compulsive disorder.

Phenotype Correlations by Gene

EP300 pathogenic variants cause a phenotype that resembles *CREBBP*-RSTS. However, with the exception of the low-hanging columella, the facial features in *EP300*-RSTS are less marked. Although the thumbs and halluces are broad, angulation is very uncommon. Intellectual disability is variable but is usually less severe and occasionally normal [Fergelot et al 2016].

Genotype-Phenotype Correlations

CREBBP. Stef et al [2007] did not observe a difference in phenotype based on *CREBBP* deletion size. Rusconi et al [2015] described 14 individuals with *CREBBP* deletions ranging from single exons to the whole gene and flanking regions. They noted that individuals with deletions extending beyond *CREBBP* did not always have a more severe phenotype than individuals with *CREBBP* missense variants. Spena et al [2015] noted that pathogenic variants outside the histone acetyltransferase domain may be associated with a mild phenotype. Somatic mosaicism may result in a milder phenotype [Gervasini et al 2007, Chiang et al 2009].

See Genetically Related Disorders for a discussion of contiguous gene deletions involving *CREBBP*.

Mosaic microdeletions have been noted by Gervasini et al [2007] and Schorry et al [2008]; these individuals tended to have a less severe phenotype than those with non-mosaic deletions.

Prevalence

Hennekam et al [1990b] reported a birth prevalence of 1:100,000 to 1:125,000 for RSTS in the Netherlands. RSTS appears to be pan ethnic.

Genetically Related (Allelic) Disorders

Microduplication of *CREBBP*. This disorder has limited phenotypic overlap with Rubinstein-Taybi syndrome (RSTS) and is associated with mild-to-moderate intellectual disability, normal growth, facial dysmorphism (not similar to facial dysmorphism in RSTS), minor extremity abnormalities, and variable other features [Marangi et al 2008, Thienpont et al 2010, Mattina et al 2012, Demeer et al 2013].

Intragenic *CREBBP* and *EP300* pathogenic variants. Germline pathogenic variants in *CREBBP* and *EP300* are also known to be associated with Menke-Hennekam syndrome (OMIM 618332 and 618333). This condition is caused by missense variants in the last part of exon 30 or the beginning part of exon 31 of *CREBBP* or the homologous regions of *EP300*. No individuals with Menke-Hennekam syndrome share the typical facial characteristics of RSTS or broad/angulated thumbs or halluces. Facial characteristics include ptosis, telecanthus, short and upslanted palpebral fissures, depressed nasal ridge, short nose, anteverted nares, short columella, and long philtrum. Other features include short stature, intellectual disability, microcephaly, feeding difficulties, seizures, autistic behavior, and other variable findings [Menke et al 2016, Menke et al 2018, Banka et al 2019].

Differential Diagnosis

For individuals with the distinctive facial features and hand and foot abnormalities, the diagnosis of Rubinstein-Taybi syndrome (RSTS) is usually straightforward.

Broad/angulated thumbs and halluces may be seen in the *FGFR*-related craniosynostosis syndromes (e.g., Pfeiffer syndrome, Apert syndrome), in Saethre-Chotzen syndrome, and in Greig cephalopolysyndactyly syndrome. The presence of craniosynostosis and the difference in facial features should differentiate these disorders (see Table 2).

Table 2. Other Genes of Interest in the Differential Diagnosis of Rubinstein-Taybi Syndrome (RSTS)

Gene(s)	Disorder	MOI	Clinical Features of Differential Diagnosis Disorder	
			Overlapping w/RSTS	Distinguishing from RSTS
FGFR1 *FGFR2*	Pfeiffer syndrome & Apert syndrome (see *FGFR*-related craniosynostosis syndromes)	AD	Broad/angulated thumbs & halluces	• Bicoronal craniosynostosis or cloverleaf skull • Distinctive facial features
TWIST1	Classic Saethre-Chotzen syndrome	AD	Broad/angulated thumbs & halluces	• Coronal synostosis (unilateral or bilateral), facial asymmetry, ptosis, & characteristic appearance of the ear (small pinna w/prominent crus) • Syndactyly of digits 2 & 3 of the hand variably present • Mild-to-moderate DD & ID reported; normal intelligence is more common.
GLI3	Typical Greig cephalopolysyndactyly syndrome (GCPS)	AD	Broad/angulated thumbs & halluces	• Preaxial polydactyly or mixed pre- & postaxial polydactyly, widely spaced eyes, & macrocephaly • Individuals w/mild GCPS may have subtle craniofacial findings. • Individuals w/severe GCPS may have seizures, hydrocephalus, & ID.
HOXD13	Brachydactyly type D (OMIM 113200)	AD	Unilateral or bilateral shortening of the distal phalanx of the thumb	Absence of other features (broad thumbs seen as an isolated finding)
SRCAP [1]	Floating-Harbor syndrome	AD	• Facial features (e.g., low-hanging columella) • Short thumbs & broad fingertips • Short stature	• Normal OFC • Absence of downslanting palpebral fissures • Thumbs not usually deviated & halluces not broad

AD = autosomal dominant; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; OFC = occipital frontal circumference

1. Floating-Harbor syndrome is caused by a pathogenic variant in *SRCAP*, which encodes an SNF2-related chromatin-remodeling factor that serves as a coactivator for CREB-binding protein. This likely accounts for the phenotypic overlap with RSTS.

Keipert syndrome is characterized by broad thumbs and halluces but is distinguished by hearing loss and characteristic facial features. The genetic basis of Keipert syndrome is unknown (OMIM 255980).

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Rubinstein-Taybi syndrome (RSTS), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended [Wiley et al 2003].

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Rubinstein-Taybi Syndrome

System/Concern	Evaluation	Comment
Neurologic	Ultrasound of spinal canal in neonatal period to screen for tethered cord	MRI of spinal canal should be performed in older children if symptomatic.
Constitutional	Measurement of growth	Plot parameters on RSTS growth charts.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Neurodevelopmental	Multidisciplinary developmental &/or neuropsychological evaluation	Assess: gross & fine motor, speech/language, cognitive, & vocational skills; behavior.
Ophthalmologic	Ophthalmologic examination	Evaluate for strabismus, refractory errors, ptosis, nasolacrimal duct obstruction, cataracts, coloboma, nystagmus, glaucoma, & corneal abnormalities.
Audiologic	Hearing evaluation	Recommended: auditory brain stem evoked response testing (see Hereditary Hearing Loss and Deafness Overview for details of evaluation)
Pulmonary	Evaluation for obstructive sleep apnea by polysomnography	If indicated by snoring, particular sleeping posture, night wakefulness, & excessive daytime sleepiness
Cardiac	Echocardiogram	Evaluation by cardiologist for structural heart defects
Genitourinary	• Renal ultrasound examination • Consider VCUG. • Assess for presence of cryptorchidism in males.	Refer to urologist for undescended testes by age 6-12 mos.
Gastrointestinal	• Assess for gastroesophageal reflux as warranted. • Assess for constipation.	Upper GI study if symptoms of malrotation
Orthopedic	Assess thumbs & halluces, joints, & spine.	
Dental/Orthodontic	Dental & orthodontic evaluations	
Other	Consultation w/clinical geneticist &/or genetic counselor	

VCUG = voiding cystourethrogram

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Rubinstein-Taybi Syndrome

Manifestation/Concern	Treatment	Considerations/ Other
Developmental & behavioral concerns	• Early intervention programs, special education, & vocational training to address developmental disabilities • Behavior management strategies incl referral to behavioral specialist / psychologist & consideration of medication if needed	Refer family to support groups & other resources.
Ocular manifestations	Standard treatment as per ophthalmologist	
Hearing loss	Standard treatment as per audiologist	
Obstructive sleep apnea	Treatment as per pulmonologist	
Cardiac anomalies	Standard treatment as per cardiologist	
Renal anomalies	Standard treatment as per nephrologist &/or urologist	
Cryptorchidism	Standard treatment as per urologist	
Gastroesophageal reflux &/or constipation	• Standard medical management of gastroesophageal reflux & constipation • Consider tube feeding as needed for failure to thrive.	
Significantly angulated thumbs or duplicated halluces	Surgical repair as per orthopedist	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/ Other
Dental anomalies	Standard treatment as per dentist &/or orthodontist	

Prevention of Secondary Complications

Individuals with RSTS can be difficult to intubate because of the easy collapsibility of the laryngeal wall. An anesthesiologist comfortable with managing complex pediatric airway problems should therefore administer general anesthesia when needed. Individuals with RSTS may require earlier intubation and later extubation than other individuals undergoing similar procedures.

Surveillance

Table 5. Recommended Surveillance for Individuals with Rubinstein-Taybi Syndrome

System/Concern	Evaluation	Frequency
Growth	Monitor weight & linear growth w/ RSTS growth charts.	Frequently during 1st yr of life & at regular checkups
Ocular manifestations	Ophthalmologic evaluation	Annually or as necessary
Hearing loss	Audiologic evaluation	• Annually • More frequent if patient has history of recurrent otitis media
Dental anomalies	Dental & orthodontic evaluation	Beginning at age 1 yr; continue every 6 mos or as per dentist/ orthodontist

Evaluation of Relatives at Risk

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

Pregnancy Management

Preeclampsia was reported in 12/52 mothers whose fetus had *EP300*-RSTS and 2/59 of those with *CREBBP*-RSTS [Fergelot et al 2016].

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, 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. —ED.

Mode of Inheritance

Rubinstein-Taybi syndrome (RSTS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Most individuals diagnosed with RSTS have the disorder as the result of a *de novo* pathogenic variant and are the only affected member of their families.
- Rarely, an individual diagnosed with RSTS has the disorder as the result of an inherited *CREBBP* or *EP300* pathogenic variant. Because of variable clinical expression, there is a small chance that a parent with normal intelligence is heterozygous for a *CREBBP* or *EP300* pathogenic variant [Bartsch et al 2010, López et al 2016]. There should be a higher clinical suspicion of parental heterozygosity for an *EP300* pathogenic variant (i.e., vs a *CREBBP* pathogenic variant) in an apparently asymptomatic parent because *EP300* is associated with a milder RSTS phenotype [López et al 2016].
- Recommendations for the evaluation of parents of a proband include clinical examination for physical findings associated with RSTS and, if a *CREBBP* or *EP300* pathogenic variant has been identified in the proband, molecular genetic testing.
- If a pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the proband most likely has a *de novo* pathogenic variant; another possible explanation is somatic and/or germline mosaicism in a parent. Parental somatic and germline mosaicism has been reported [Chiang et al 2009, Bartsch et al 2010, Tajir et al 2013].
- The family history of some individuals diagnosed with RSTS may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless appropriate molecular genetic testing has been performed on the parents of the proband.
- Note: If the parent is the individual in whom the pathogenic variant first occurred, s/he may have somatic mosaicism for the variant and may be mildly/minimally affected [Chiang et al 2009, Bartsch et al 2010].

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

- If a parent of the proband is affected and/or is known to have the *CREBBP* or *EP300* pathogenic variant identified in the proband, the risk to the sibs is 50%.
- If the proband has a known *CREBBP* or *EP300* pathogenic variant that cannot be identified in the leukocyte DNA of either parent, the most likely explanation is that the proband has a *de novo* pathogenic variant. However, the recurrence risk to sibs is still greater than that of the general population because of the possibility of parental somatic and/or germline mosaicism. Somatic and germline mosaicism have been reported in the parents of individuals with RSTS [Chiang et al 2009, Bartsch et al 2010, Tajir et al 2013].
- If the parents have not been tested for a causative pathogenic variant but are apparently asymptomatic, sibs are still presumed to be at increased risk for RSTS because of the possibility of a mild phenotype in a heterozygous parent or parental somatic and/or germline mosaicism. The empiric recurrence risk for sibs is less than 1%.

Offspring of a proband. Each child of an individual with RSTS has a 50% chance of inheriting the RSTS-related pathogenic variant [Cotsirilos et al 1987, Hennekam et al 1989, Marion et al 1993, Petrij et al 2000, Bartsch et al 2010].

Other family members. The risk to other family members of a proband depends on the genetic status of the proband's parents: if a parent has the pathogenic variant, his or her family members may be at risk.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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 have had a child with RSTS.

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, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

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

A priori low-risk pregnancies. RSTS is not usually diagnosed by prenatal ultrasound. However, routine prenatal ultrasound examination may identify findings such as growth restriction, polyhydramnios, broad thumbs, and brain abnormalities that raise the possibility of RSTS in a fetus not known to be at increased risk [Van-Gils et al 2019].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Resources

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

- **National Library of Medicine Genetics Home Reference**
  Rubinstein-Taybi syndrome
- **Understanding Rubinstein-Taybi syndrome: A Guide for Families and Professionals**
  www.ucucedd.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. Rubinstein-Taybi Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CREBBP	16p13.3	CREB-binding protein	CREB Binding Protein (CREBBP) @ LOVD	CREBBP	CREBBP
EP300	22q13.2	Histone acetyltransferase p300	E1A binding protein p300 (EP300) @ LOVD	EP300	EP300

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 Rubinstein-Taybi Syndrome (View All in OMIM)

180849	RUBINSTEIN-TAYBI SYNDROME 1; RSTS1
600140	CREB-BINDING PROTEIN; CREBBP
602700	E1A-BINDING PROTEIN, 300-KD; EP300
613684	RUBINSTEIN-TAYBI SYNDROME 2; RSTS2

The CREBB-binding protein (CREBBP) is ubiquitously expressed and is involved in transcriptional coactivation of many different transcription factors. It has intrinsic histone acetyltransferase (HAT) activity and acts as a scaffold to stabilize additional protein interactions with the transcription complex via chromatin remodeling. CREBBP regulates the expression of many genes affecting cellular pathways such as cell growth control, cellular differentiation, apoptosis, and tumor suppression [Negri et al 2016]. Germline pathogenic variants in *CREBBP* may lead to a truncated CREB-binding protein or one with an amino acid substitution. Pathogenic variants in the HAT domain interfere with the acetylation of histones, which is an important step in transcription activation. CREBBP also acetylates p53, a tumor suppressor pathway known to be deregulated in many human cancers.

EP300 encodes the p300 transcriptional coactivator protein, which shares 63% homology with *CREBBP* at the amino acid level. It functions as HAT, regulating transcription via chromatin remodeling and playing an important role in cell proliferation and differentiation. Pathogenic variants result in truncated p300 protein or absence of allele expression, which may lead to loss of HAT activity.

Mechanism of disease causation. The mechanism of disease causation is largely unknown. However, two models considered are haploinsufficiency and dominant-negative inhibition [Park et al 2014].

References

Literature Cited

Banka S, Sayer R, Breen C, Barton S, Pavaine J, Sheppard SE, Bedoukian E, Skraban C, Cuddapah VA, Clayton-Smith J. Genotype-phenotype specificity in Menke-Hennekam syndrome caused by missense variants in exon 30 or 31 of CREBBP. Am J Med Genet A. 2019;179:1058–62. PubMed PMID: 30892814.

Bartsch O, Kress W, Kempf O, Lechno S, Haaf T, Zechner U. Inheritance and variable expression in Rubinstein-Taybi syndrome. Am J Med Genet A. 2010;152A:2254–61. PubMed PMID: 20684013.

Bartsch O, Schmidt S, Richter M, Morlot S, Seemanova E, Wiebe G, Rasi S. DNA sequencing of CREBBP demonstrates mutations in 56% of patients with Rubinstein-Taybi syndrome (RSTS) and in another patient with incomplete RSTS. Hum Genet. 2005;117:485–93. PubMed PMID: 16021471.

Beets L, Rodriguez-Fonseca C, Hennekam RC. Growth charts for individuals with Rubinstein-Taybi syndrome. Am J Med Genet A. 2014;164A:2300–9. PubMed PMID: 24989455.

Bentivegna A, Milani D, Gervasini C, Castronovo P, Mottadelli F, Manzini S, Colapietro P, Giordano L, Atzeri F, Divizia MT, Uzielli ML, Neri G, Bedeschi MF, Faravelli F, Selicorni A, Larizza L. Rubinstein-Taybi syndrome: spectrum of CREBBP mutations in Italian patients. BMC Med Genet. 2006;7:77. PubMed PMID: 17052327.

Boot MV, van Belzen MJ, Overbeek LI, Hijmering N, Mendeville M, Waisfisz Q, Wesseling P, Hennekam RC, de Jong D. Benign and malignant tumors in Rubinstein-Taybi syndrome. Am J Med Genet A. 2018;176:597–608. PubMed PMID: 29359884.

Chiang PW, Lee NC, Chien N, Hwu WL, Spector E, Tsai ACH. Somatic and germ-line mosaicism in Rubinstein-Taybi syndrome. Am J Med Genet. 2009;149A:1463–7. PubMed PMID: 19533794.

Cotsirilos P, Taylor JC, Matalon R. Dominant inheritance of a syndrome similar to Rubinstein-Taybi. Am J Med Genet. 1987;26:85–93. PubMed PMID: 3812583.

Coupry I, Roudaut C, Stef M, Delrue MA, Marche M, Burgelin I, Taine L, Cruaud C, Lacombe D, Arveiler B. Molecular analysis of the CBP gene in 60 patients with Rubinstein-Taybi syndrome. J Med Genet. 2002;39:415–21. PubMed PMID: 12070251.

Crawford H, Waite J, Oliver C. Diverse profiles of anxiety related disorders in fragile X, Cornelia de Lange and Rubinstein-Taybi syndromes. J Autism Dev Disord. 2017;47:3728–40. PubMed PMID: 28144878.

Demeer B, Andrieux J, Receveur A, Morin G, Petit F, Julia S, Plessis G, Martin-Coignard D, Delobel B, Firth HV, Thuresson AC, Lanco Dosen S, Sjors K, Le Caignec C, Devriendt K, Mathieu-Dramard M. Duplication of 16p13.3 and the CREBBP gene: confirmation of the phenotype. Eur J Med Genet. 2013;56:26–31. PubMed PMID: 23063576.

Fergelot P, van Belzen M, van Gils J, Afenjar A, Armour CM, Arveiler B, Beets L, Burglen L, Busa T, Collet M, Deforges J, de Vries BBA, Dominguez Garrido E, Dorison N, Dupont J, Francannet C, Garcia-Minaur S, Gabau Vila E, Gebre-Medhin S, Gener Querol B, Genevieve D, Gerard M, Gervanisi CG, Goldenberg A, Josifova D, Lachlan K, Mas S, Maranda B, Moilanen JS, Nordgren A, Parent P, Rankin J, Reardon W, Rio M, Roume J, Shaw A, Smigiel R, Sojo A, Solomon B, Stembalska A, Stumpel C, Suarez F, Terhal P, Thomas S, Touraine R, Verloes A, Vincent-Delorme C, Wincent J, Peters DJM, Bartsch O, Larizza L, Lacombe D, Hennekam RC. Phenotype and genotype in 52 patients with Rubinstein-Taybi syndrome caused by EP300 mutations. Am J Med Genet A. 2016;170:3069–82. PubMed PMID: 27648933.

Gervasini C, Castronovo P, Bentivegna A, Mottadelli F, Faravelli F, Giovannucci-Uzielli ML, Pessagno A, Lucci-Cordisco E, Pinto AM, Salviati L, Selicorni A, Tenconi R, Neri G, Larizza L. High frequency of mosaic CREBBP deletions in Rubinstein-Taybi syndrome patients and mapping of somatic and germ-line breaks. Genomics. 2007;90:567–73. PubMed PMID: 17855048.

Hennekam RC, Lommen EJ, Strengers JL, Van Spijker HG, Jansen-Kokx TM. Rubinstein-Taybi syndrome in a mother and son. Eur J Pediatr. 1989;148:439–41. PubMed PMID: 2920750.

Hennekam RC, Van Den Boogaard MJ, Sibbles BJ, Van Spijker HG. Rubinstein-Taybi syndrome in The Netherlands. Am J Med Genet Suppl. 1990b;6:17–29. PubMed PMID: 2118773.

López M, Seidel V, Santibáñez P, Cervera-Acedo C, Castro-de Castro P, Domínguez-Garrido E. First case of inherited Rubinstein-Taybi syndrome associated with a novel EP300 variant. BMC Med Genet. 2016;17:97–101. PubMed PMID: 27964710.

Marangi G, Leuzzi V, Orteschi D, Grimaldi ME, Lecce R, Neri G, Zollino M. Duplication of the Rubinstein-Taybi region on 16p13.3 is associated with a distinctive phenotype. Am J Med Genet A. 2008;146A:2313–7. PubMed PMID: 18688873.

Marion RW, Garcia DM, Karasik JB. Apparent dominant transmission of the Rubinstein-Taybi syndrome. Am J Med Genet. 1993;46:284–7. PubMed PMID: 8488872.

Marzuillo P, Grandone A, Coppola R, Cozzolino D, Festa A, Messa F, Luongo C, Del Giudice EM, Perrone L. Novel cAMP binding protein-BP (CREBBP) mutation in a girl with Rubinstein-Taybi syndrome, GH deficiency, Arnold Chiari malformation and pituitary hypoplasia. BMC Med Genet. 2013;14:28. PubMed PMID: 23432975.

Mattina T, Palumbo O, Stallone R, Pulvirenti RM, Dio LD, Pavone P, Carella M, Pavone L. Interstitial 16p13.3 microduplication: case report and review of genotype-phenotype correlation. Eur J Med Genet. 2012;55:747–52. PubMed PMID: 23032921.

Menke LA, Gardeitchik T, Hammond P, Heimdal KR, Houge G, Hufnagel SB, Ji J, Johansson S, Kant SG, Kinning E, Leon EL, Newbury-Ecob R, Paolacci S, Pfundt R, Ragge NK, Rinne T, Ruivenkamp C, Saitta SC, Sun Y, Tartaglia M, Terhal PA, van Essen AJ, Vigeland MD, Xiao B, Hennekam RC, et al. Further delineation

of an entity caused by CREBBP and EP300 mutations but not resembling Rubinstein-Taybi syndrome. Am J Med Genet A. 2018;176:862–76. PubMed PMID: 29460469.

Menke LA, van Belzen MJ, Alders M, Cristofoli F, Ehmke N, Fergelot P, Foster A, Gerkes EH, Hoffer MJV, Horn D, Kant SG, Lacombe D, Leon E, Maas SM, Melis D, Muto V, Park SM, Peeters H, Peters DJM, Pfundt R, van Ravenswaaij-Arts CMA, Tartaglia M, Hennekam RCM, et al. CREBBP mutations in individuals without Rubinstein-Taybi phenotype. Am J Med Genet A. 2016;170:2681–93. PubMed PMID: 27311832.

Negri G, Magini P, Milani D, Colapietro P, Rusconi D, Scarano E, Bonati MT, Priolo M, Crippa M, Mazzanti L, Wischmeijer A, Tamburrino F, Pippuci T, Finelli P, Larizza L, Gervanisi C. From whole gene deletion to point mutations of EP300-positive Rubinstein-Taybi patients: new insights into the mutational spectrum and peculiar clinical hallmarks. Hum Mutat. 2016;37:175–83. PubMed PMID: 26486927.

Negri G, Milani D, Colapietro P, Forzano F, Della Monica M, Rusconi D, Consonni L, Caffi LG, Finelli P, Scarano G, Magnani C, Selicorni A, Spena S, Larizza L, Gervasini C. Clinical and molecular characterization of Rubinstein-Taybi syndrome patients carrying distinct novel mutations of the EP300 gene. Clin Genet. 2015;87:148–54. PubMed PMID: 24476420.

Park E, Kim Y, Ryu H, Kowall NW, Lee J, Ryu H. Epigenetic mechanisms of Rubinstein-Taybi syndrome. Neuromolecular Med. 2014;16:16–24. PubMed PMID: 24381114.

Petrij F, Dauwerse HG, Blough RI, Giles RH, van der Smagt JJ, Wallerstein R, Maaswinkel-Mooy PD, van Karnebeek CD, van Ommen GJ, van Haeringen A, Rubinstein JH, Saal HM, Hennekam RC, Peters DJ, Breuning MH. Diagnostic analysis of the Rubinstein-Taybi syndrome: five cosmids should be used for microdeletion detection and low number of protein truncating mutations. J Med Genet. 2000;37:168–76. PubMed PMID: 10699051.

Rusconi D, Negri G, Colapietro P, Picinelli C, Milani D, Spena S, Magnani C, Silengo MC, Sorasio L, Curtisova V, Cavaliere ML, Prontera P, Stangoni G, Ferrero GB, Biamino E, Fischetto R, Piccione M, Gasparini P, Salviati L, Selicorni A, Finelli P, Larizza L, Gervasini C. Characterization of 14 novel deletions underlying Rubinstein-Taybi syndrome: an update of the CREBBP deletion repertoire. Hum Genet. 2015;134:613–26. PubMed PMID: 25805166.

Schorry EK, Keddache M, Lanphear N, Rubinstein JH, Srodulski S, Fletcher D, Blough-Pfau RI, Grabowski GA. Genotype-phenotype correlations in Rubinstein-Taybi syndrome. Am J Med Genet A. 2008;146A:2512–9. PubMed PMID: 18792986.

Spena S, Milani D, Rusconi D, Negri G, Colapietro P, Elcioglu N, Bedeschi F, Pilotta A, Spaccini L, Ficcadenti A, Magnani C, Scarano G, Selicorni A, Larizza L, Gervanisi C. Insights into genotype-phenotype correlations from CREBBP point mutation screening in a cohort of 46 Rubinstein-Taybi syndrome patients. Clin Genet. 2015;88:431–40. PubMed PMID: 25388907.

Stef M, Simon D, Mardirossian B, Delrue MA, Burgelin I, Hubert C, Marche M, Bonnet F, Gorry P, Longy M, Lacombe D, Coupry I, Arveiler B. Spectrum of CREBBP gene dosage anomalies in Rubinstein-Taybi syndrome patients. Eur J Hum Genet. 2007;15:843–7. PubMed PMID: 17473832.

Stevens CA. Intestinal malrotation in Rubinstein-Taybi syndrome. Am J Med Genet A. 2015;167A:2399–2401. PubMed PMID: 26097216.

Stevens CA, Pouncey J, Knowles D. Adults with Rubinstein-Taybi syndrome. Am J Med Genet. 2011;155A:1680–4. PubMed PMID: 21671385.

Tajir M, Fergelot P, Lancelot G, Elalaoui SC, Arveiler B, Lacombe D, Sefiani A. Germline mosaicism in Rubinstein-Taybi syndrome. Gene. 2013;518:476–8. PubMed PMID: 23352794.

Thienpont B, Bena F, Breckpot J, Philip N, Menten B, Van Esch H, Scalais E, Salamone JM, Fong CT, Kussmann JL, Grange DK, Gorski JL, Zahir F, Yong SL, Morris MM, Gimelli S, Fryns JP, Mortier G, Friedman JM, Villard L, Bottani A, Vermeesch JR, Cheung SW, Devriendt K. Duplications of the critical Rubinstein-Taybi

deletion region on chromosome 16p13.3 cause a novel recognizable syndrome. J Med Genet. 2010;47:155–61. PubMed PMID: 19833603.

Van-Gils J, Naudion S, Toutain J, Lancelot G, Attie-Bitach T, Blesson S, Demeer B, Doray B, Gonzales M, Martinovic J, Whalen S, Taine L, Arveiler B, Lacombe D, Fergelot P. Fetal phenotype of Rubinstein-Taybi syndrome caused by CREBBP mutations. Clin Genet. 2019;95:420–6. PubMed PMID: 30633342.

Verhoeven WMA, Tuinier S, Kuijpers HJH, Egger JIM. Psychiatric profile in Rubinstein-Taybi syndrome. Psychopathology. 2010;43:63–8. PubMed PMID: 19940543.

Waite J, Beck SR, Heald M, Powis L, Oliver C. Dissociation of cross-sectional trajectories for verbal and visuo-spatial working memory development in Rubinstein-Taybi syndrome. J Autism Dev Disord. 2016;46:2064–71. PubMed PMID: 27011324.

Waite J, Moss J, Beck SR, Richards C, Nelson L, Arron K, Burbidge C, Berg K, Oliver C. Repetitive behavior in Rubinstein-Taybi syndrome: parallels with autism spectrum phenomenology. J Autism Dev Disord. 2015; 2015;45:1238–53. PubMed PMID: 25491025.

Wiley S, Swayne S, Rubinstein JH, Lanphear NE, Stevens CA. Rubinstein-Taybi syndrome medical guidelines. Am J Med Genet A. 2003;119A:101–10. PubMed PMID: 12749047.

Chapter Notes

Author Notes

The Rubinstein-Taybi Syndrome Program at Cincinnati Children's is one of the country's leading programs for the care of children with RSTS and provides expert confirmation of diagnosis as well as the latest treatments and support.

Revision History

- 22 August 2019 (sw) Comprehensive update posted live
- 7 August 2014 (me) Comprehensive update posted live
- 20 August 2009 (cd) Revision: sequence analysis, deletion/duplication analysis, and prenatal diagnosis available clinically for *EP300* mutations
- 16 April 2009 (me) Comprehensive update posted live
- 26 June 2007 (cd) Revision: sequence analysis and mutation scanning available clinically
- 2 October 2006 (me) Comprehensive update posted live
- 20 December 2005 (cs) Revision: *EP300* mutations found to cause some cases of RSTS
- 13 September 2004 (cd) Revision: testing
- 22 July 2004 (me) Comprehensive update posted live
- 30 August 2002 (tk,me) Review posted live
- 5 April 2002 (cs) Original submission

License

GeneReviews® chapters are owned by the University of Washington. Permission is hereby granted to reproduce, distribute, and translate copies of content materials for noncommercial research purposes only, provided that (i) credit for source (http://www.genereviews.org/) and copyright (© 1993-2020 University of Washington) are included with each copy; (ii) a link to the original material is provided whenever the material is published elsewhere on the Web; and (iii) reproducers, distributors, and/or translators comply with the GeneReviews® Copyright Notice and Usage Disclaimer. No further modifications are allowed. For clarity, excerpts of GeneReviews chapters for use in lab reports and clinic notes are a permitted use.

For more information, see the GeneReviews® Copyright Notice and Usage Disclaimer.

For questions regarding permissions or whether a specified use is allowed, contact: admasst@uw.edu.