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Rubinstein-Taybi Syndrome

Synonym: Broad Thumb-Hallux Syndrome

Cathy A Stevens, MD[1]

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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. Characteristic craniofacial features include 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*-related 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. A heterozygous pathogenic variant in *CREBBP* or *EP300* identified by molecular genetic testing 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.

Pregnancy management: Preeclampsia or placental abnormalities have been reported in some pregnancies with RSTS.

Genetic counseling

RSTS is inherited in an autosomal dominant manner. 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 a *CREBBP* or *EP300* pathogenic variant inherited from a heterozygous or mosaic parent. Each child of an individual with RSTS has a 50% chance of inheriting the RSTS-related pathogenic variant. Once the RSTS-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing for RSTS are possible.

Diagnosis

Suggestive Findings

Rubinstein-Taybi syndrome (RSTS) **should be suspected** in individuals with the following characteristic clinical and neuroimaging findings and family history.

Major features

- 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.
- Most 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. Absence of the pubertal growth spurt adds to the reduced final height for males and females.
- Microcephaly is present within the first few months of life and typically persists into 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*-related RSTS have normal intellect.

Neuroimaging findings. The most common feature on brain imaging is a dysmorphic or dysplastic corpus callosum (73.6%).

Family history. Because Rubinstein-Taybi syndrome is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family). Rarely, the family history may be consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations).

Establishing the Diagnosis

The diagnosis of RSTS **is established** in a proband with the aforementioned suggestive findings. Identification of one of the following on molecular genetic testing can confirm the diagnosis especially if clinical features are inconclusive (see Table 1):

- A heterozygous pathogenic (or likely pathogenic) variant in *CREBBP* or *EP300* (65%-70% of affected individuals) [Fergelot et al 2016, Pérez-Grijalba et al 2019]
- A heterozygous deletion of chromosome 16p13.3 (*CREBBP*) or 22q13.2 (*EP300*) (10% of affected individuals) [Negri et al 2015, Pérez-Grijalba et al 2019]

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) Identification of a heterozygous variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include **gene-targeted 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 other inherited disorders with similar features 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 a **multigene panel**. **Chromosomal microarray analysis** can be useful in some situations.

- **A multigene panel** that includes *CREBBP*, *EPP300*, 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.

- **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.

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

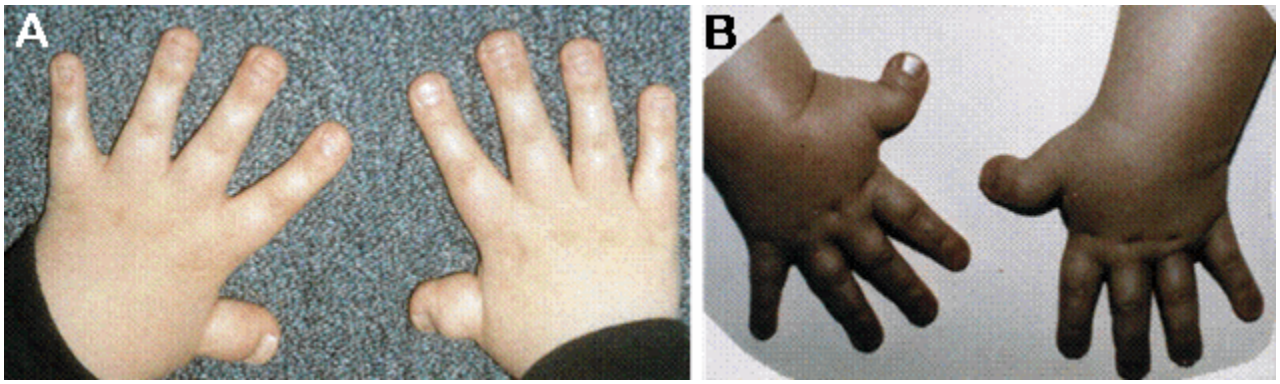

Figure 2. Broad terminal phalanges (A) and broad, radially deviated thumbs (B)

Figure 3. Broad, partially duplicated halluces

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) Clinical features associated with contiguous gene deletions involving *CREBBP* that have limited phenotypic overlap with RSTS have been reported (see Genetically Related Disorders).

For an introduction to CMA click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of

reported *CREBBP* and *EP300* pathogenic variants to date are within the coding region and are likely to be identified on exome sequencing.

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 RSTS Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [3] Identified by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
CREBBP	55%-60% [6]	~88% [7]	~12% [7]
EP300	8%-10% [8]	~93% [9]	~7% [9]
Unknown [10]	~30%		

RSTS = Rubinstein-Taybi syndrome
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 these genes.
4. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; 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. 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). Exome and genome sequencing may be able to detect deletions/ duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
6. Pérez-Grijalba et al [2019]; data also derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
7. Spena et al [2015], Cross et al [2020]
8. Negri et al [2015], Fergelot et al [2016]
9. Fergelot et al [2016], Cohen et al [2020]
10. RSTS may be caused by pathogenic variants in other genes in up to 30% of individuals [Fergelot et al 2016].

Clinical Characteristics

Clinical Description

Rubinstein-Taybi syndrome (RSTS) is a multisystem disorder characterized by short stature, variable structural abnormalities, characteristic facial appearance, broad thumbs and halluces, and variable degrees of intellectual disability. The most consistent craniofacial features are microcephaly, highly arched eyebrows, downslanted palpebral fissures, convex nasal ridge, low-hanging columella, and grimacing smile. The thumbs and halluces are broad and often angulated [Hennekam et al 1990, Stevens et al 1990].

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 issues, poor weight gain, recurrent infections, and severe constipation.

To date, at least 600 individuals have been identified with a pathogenic variant in *CREBBP* or *EP300* [Fergelot et al 2016, Pérez-Grijalba et al 2019, Cross et al 2020, Douzgou et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of Rubinstein-Taybi Syndrome

Feature	% of Persons w/Feature	Comment
Growth deficiency	73%	
Eye findings	80%	
Hearing loss	30%	Mostly conductive, but can also be sensorineural
Respiratory features	Common	Infections, aspiration
Cardiac features	33%	
Genitourinary anomalies	27%	Cryptorchidism most common (~78%-100% of affected males)
Gastrointestinal features	88%	Feeding difficulties, constipation
Skeletal abnormalities	Common	20% scoliosis, 92% thumb/hallux anomalies
Neurologic issues	21%	
Dental anomalies	73%	Talon cusps, enamel hypoplasia
Skin findings	24%	Keloids, pilomatrixomas
Recurrent infections	17%	Primarily respiratory
Tumors	30%	Benign and malignant
Developmental delays	98%	
Behavioral issues	41% autism/autistic features, 27%-64% anxiety	
Brain MRI abnormalities	74%	Various findings

Wiley et al [2003], Schorry et al [2008], Stevens et al [2011], Milani et al [2015], Fergelot et al [2016], Boot et al [2018], Douzgou et al [2022]

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. A higher incidence of microcephaly and growth restriction has been noted in infants with *EP300* pathogenic variants, possibly related to the increased incidence of preeclampsia.

While body mass index is normal for males at age 21, it is increased for females at this age. Many adults develop obesity of unclear etiology [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, congenital glaucoma, and corneal and retinal 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 commonly occurs 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 problems due to facial anatomy and laryngo-, tracheo-, and bronchomalacia and anesthesia complications. These include arrhythmias and obstructive symptoms occurring post extubation. Aspiration, asthma, and recurrent upper respiratory infections may also occur. Interstitial lung disease has also been reported in several individuals [Bradford et al 2022].

Cardiac. Approximately one third of affected individuals have 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 of the renal system, are very common. Other genitourinary complications include hypospadias, vesicoureteral reflux, nephrolithiasis, and urinary tract infections. Most boys have undescended testes.

Gastrointestinal. Feeding problems, gastroesophageal reflux, and constipation are very common. Intestinal malrotation should be suspected if there is bilious vomiting, recurrent abdominal pain, failure to pass stool, or bloody stools [Stevens 2015]. Anorectal malformations have also been reported [Belanger Deloge et al 2023].

Orthopedic. In addition to angulated thumbs and duplicated halluces, orthopedic issues include dislocated patellae, lax joints, spine curvatures, Legg-Perthes disease, increased fracture risk, and cervical vertebral abnormalities.

Neurologic. The most common intracranial malformation involves abnormal structure of the corpus callosum. Occasional craniospinal and posterior fossa abnormalities including Chiari malformation, Dandy-Walker 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 (most commonly on the upper incisors of the secondary dentition).

Skin. Keloids may occur with only minimal trauma to the skin. Pilomatrixomas (sometimes multiple) are relatively common [Boot et al 2018]. Ingrown nails are common, especially in the partially duplicated thumbs and halluces.

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

Tumors. There are early reports of various benign and malignant tumors in individuals with RSTS including neuroblastoma, rhabdomyosarcoma, medulloblastoma, and hematologic malignancies. A 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 recommendations for additional surveillance for malignancy before the age of 40 years.

Endocrine. Persistent hyperinsulinemic hypoglycemia has been reported in a few children with RSTS, primarily in those with *EP300* pathogenic variants [Welters et al 2019].

Puberty. Puberty and sexual development are typically 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 [Stevens et al 1990]. 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 of affected individuals in one study was 51 and in another study 36 [Stevens et al 1990, Hennekam et al 1992]. IQ scores range from 25 to 79. Performance IQ is usually higher than verbal IQ [Stevens et al 1990, Hennekam et al 1992]. Some individuals with *EP300*-related RSTS have normal intellect [Fergelot et al 2016].

In one study of adults with RSTS, families reported a decline in developmental 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, overfriendliness, increased pain threshold, 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.

Brain MRI findings. The most common feature on brain imaging is a dysmorphic or dysplastic corpus callosum (73.6%) with or without minor dysplasia of the cerebellar vermis, periventricular posterior white matter hyperintensity, and other less common anomalies. Other infrequent findings include Chiari malformation, Dandy-Walker malformation, and underdeveloped pituitary gland.

Prognosis. More than 90% of individuals with RSTS survive into adulthood [Milani et al 2015].

It is unknown whether life span in RSTS is abnormal. One reported individual is alive at age 67 years [Stevens et al 2011], demonstrating that survival into adulthood is possible. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Phenotype Correlations by Gene

EP300 pathogenic variants cause a phenotype that resembles *CREBBP*-related RSTS. However, except for the low-hanging columella, the facial features in *EP300*-related RSTS are less marked. Keloids are also less frequent. Maternal preeclampsia, intrauterine growth restriction, and microcephaly are more common in individuals with *EP300* pathogenic variants. 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

The type and location of pathogenic variants in *CREBBP* and *EP300* do not correlate with specific physical features, malformations, cognition, or behavior. An exception is missense variants between the end of exon 30 and the beginning of exon 31 in both *CREBBP* and *EP300*. This phenotype is distinct from RSTS and is known as Menke-Hennekam syndrome (see Genetically Related Disorders).

EP300. In one study examining many variants, no correlation was found between overall phenotype severity and the type of pathogenic variant or location of the pathogenic variant relative to the HAT domain or exon 31. Similar observations were made between genotype and severity of intellectual disability and presence of major organ difference [Cohen et al 2020].

CREBBP. Deletions of variable sizes involving *CREBBP* have been reported in many individuals with RSTS to date. Stef et al [2007] and Pérez-Grijalba et al [2019] 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* pathogenic missense variants.

Spena et al [2015] noted that pathogenic variants outside the histone acetyltransferase domain may be associated with a mild phenotype. Pérez-Grijalba et al [2019] did not find a correlation of pathogenic variant type, location,

or involvement of the HAT domain with disease severity. Somatic mosaicism may result in a milder phenotype [Gervasini et al 2007, Chiang et al 2009].

Mosaic microdeletions of *CREBBP* have been reported by Gervasini et al [2007] and Schorry et al [2008]; these individuals tended to have a less severe phenotype than those with nonmosaic deletions.

See Genetically Related Disorders for a discussion of other copy number abnormalities involving *CREBBP*.

Prevalence

The birth prevalence RSTS in the Netherlands has been estimated to be between 1:100,000 and 1:125,000 [Hennekam et al 1990].

Genetically Related (Allelic) Disorders

Intragenic *CREBBP* and *EP300* pathogenic variants. Germline pathogenic variants in *CREBBP* and *EP300* are also known to be associated with Menke-Hennekam syndrome (OMIM PS618332). 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 Rubinstein-Taybi syndrome (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].

Contiguous gene deletions/duplications. The 16p13.3 microduplication [Demeer et al 2013], which encompasses the *CREBBP* gene, is characterized by dysmorphic facial features (not similar to RSTS), cardiac and renal defects, cleft palate, and dysgenesis of the corpus callosum [Kang et al 2023]. The 16p13.3 deletion (also known as severe RSTS) includes the *CREBBP* gene as well as variable other contiguous genes. Clinical features include poor growth, developmental brain abnormalities, seizures, and intractable infections [Bartsch et al 2005].

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 3).

Table 3. Genes of Interest in the Differential Diagnosis of Rubinstein-Taybi Syndrome

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/RSTS	Distinguishing from RSTS
FGFR1 *FGFR2* *FGFR3*	Pfeiffer syndrome & Apert syndrome (See *FGFR*-Related Craniosynostosis Syndromes Overview.)	AD	Broad/angulated thumbs & halluces	• Bicoronal craniosynostosis or cloverleaf skull • Distinctive facial features

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Features of Disorder	
			Overlapping w/RSTS	Distinguishing from RSTS
GLI3 [1]	Typical Greig cephalopolysyndactyly syndrome (GCPS)	AD	Broad/angulated thumbs & halluces	• Preaxial polydactyly or mixed pre- & postaxial polydactyly, widely spaced eyes, & macrocephaly • Persons w/mild GCPS may have subtle craniofacial findings. • Persons w/severe GCPS may have seizures, hydrocephalus, & ID.
GPC4	Keipert syndrome (OMIM 301026)	XL	Broad thumbs & halluces	• Hearing loss • Characteristic facial features
HOXD13	Brachydactyly type D (OMIM 113200)	AD	Unilateral or bilateral shortening of distal phalanx of thumb	Absence of other features suggestive of RSTS (i.e., broad thumbs seen as an isolated finding)
SRCAP [2]	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
TWIST1	Classic Saethre-Chotzen syndrome	AD	Broad/angulated thumbs & halluces	• Coronal synostosis (unilateral or bilateral), facial asymmetry, ptosis, & characteristic appearance of ear (small pinna w/prominent crus) • Syndactyly of digits 2 & 3 of hand variably present • Mild-to-moderate DD & ID reported; normal intelligence is more common.
NIPBL *SMC1A* *SMC3* *RAD21* *HDAC8* *BRD4*	Cornelia de Lange syndrome	AD XL	Short stature, facial dysmorphism, ID	Limb reduction defects
KMT2A	Wiedemann-Steiner syndrome	AD	Short stature, facial dysmorphism, ID	Hypertrichosis cubiti, absence of typical hand/foot findings

AD = autosomal dominant; DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance; OFC = occipital frontal circumference; RSTS = Rubinstein-Taybi syndrome

1. Greig cephalopolysyndactyly syndrome is associated with either a heterozygous pathogenic variant of *GLI3* or a deletion of chromosome 7p14.1 involving *GLI3*.

2. 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.

Management

Clinical practice guidelines for Rubinstein-Taybi Syndrome (RSTS) have been published by Wiley et al [2003].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with RSTS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 4. Rubinstein-Taybi Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth	Plot parameters on RSTS growth charts.
Neurologic	• Neurologic eval • Ultrasound of spinal canal in neonatal period should be considered to screen for tethered cord.	• MRI of spinal canal should be performed in older children if symptomatic. • Consider EEG if seizures are a concern.
Development	Multidisciplinary developmental &/or neuropsychological eval	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for concerns incl sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Thumbs & halluces, joints, & spine • Gross motor & fine motor skills • Contractures, clubfoot, & kyphoscoliosis • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Assess for gastroesophageal reflux as warranted. • Consider eval for gastrostomy tube placement in persons w/ dysphagia &/or aspiration risk. • Assess for constipation. • Upper GI study if symptoms of malrotation
Eyes	Ophthalmologic eval	To assess for strabismus, refractive errors, ptosis, nasolacrimal duct obstruction, cataracts, coloboma, nystagmus, glaucoma, & corneal abnormalities that may require referral for subspecialty care &/or low vision services
Hearing	Audiologic eval	• Assess for hearing loss. • Auditory brain stem response testing is recommended (see Genetic Hearing Loss Overview for details).
Cardiovascular	Cardiac eval	• Eval by cardiologist for structural heart defects • Echocardiogram
Respiratory	Pulmonary eval	Eval for obstructive sleep apnea by polysomnography if indicated by snoring, particular sleeping posture, night wakefulness, & excessive daytime sleepiness
Genitourinary	Nephrology & urology evals	• Renal ultrasound exam • Consider VCUG. • Assess for presence of cryptorchidism in males. • Refer to urologist for undescended testes by age 6-12 mos.
Dental/Orthodontic	Dental & orthodontic evals	Assess palate, tooth number & position, talon cusps, caries, & periodontal disease.
Endocrine	Endocrinology eval	Eval for hyperinsulinemia if there are symptoms of hypoglycemia such as jitteriness, muscle weakness, or seizures
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of RSTS to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent • Social work involvement for parental support • Home nursing referral

Based on Wiley et al [2003]
ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; GI = gastrointestinal; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; RSTS = Rubinstein-Taybi syndrome; VCUG = voiding cystourethrogram
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for RSTS.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. Rubinstein-Taybi Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	• Consider need for positioning & mobility devices, disability parking placard. • For significantly angulated thumbs or duplicated halluces, surgical repair per orthopedist. Recurrence of deviation may occur after surgery. Decision reg surgery may need to be postponed until function of hands can be accurately evaluated (typically age 3-4 yrs).
Gastrointestinal	Standard treatment by gastroenterologist/ dietician	• Standard mgmt of gastroesophageal reflux & constipation • Consider tube feeding as needed for failure to thrive. • Stool softeners, prokinetics, osmotic agents, dietary changes, or laxatives as needed
Eyes	Ophthalmologist	Refractive errors, strabismus
	Ophthalmic subspecialist	More complex findings (e.g., cataract, retinal dystrophy, glaucoma)
	Low vision services	• Children: through early intervention programs and/or school district • Adults: low vision clinic &/or community vision services/occupational therapy/mobility services

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Hearing	Hearing aids may be helpful per otolaryngologist.	Community hearing services through early intervention or school district
Cardiac	Standard treatment per cardiologist	• Monitoring by echocardiogram; surgery if necessary • The frequency of hypertension is not ↑ in adults. • Treatment as in general population
ENT	Standard treatment of obstructive sleep apnea / recurrent otitis	Consider polysomnogram, CPAP, removal of tonsils/adenoids, tympanostomy tubes as clinically indicated.
Genitourinary	Standard treatment per nephrologist &/or urologist	• Standard treatment of cryptorchidism • Provide developmentally appropriate sex education/ contraception as needed.
Dental	Standard treatment per dentist &/or orthodontist	Treatment for talon cusps if interfering w/occlusion, mouth closure, or causing caries
Skin	Monitor for keloids/pilomatrixomas.	• No treatment protocols for keloids but options incl steroid injection, laser, radiation, cryotherapy, & surgery. • Pilomatrixomas can be surgically removed if symptomatic.
Family/Community	• Ensure appropriate social work involvement to connect families w/ local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for home nursing support • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; CPAP = continuous positive airway pressure; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

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 and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

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 should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

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.

Neurobehavioral/Psychiatric Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. Rubinstein-Taybi Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Growth	Monitor weight & linear growth w/RSTS growth charts.	• Frequently during 1st yr of life & at regular checkups. • If growth differs from expected, assess for growth hormone deficiency.
Neurologic	Monitor those w/seizures as clinically indicated.	At each visit
	Assess for new manifestations such as seizures, changes in tone, & movement disorders.	
Development	Monitor developmental progress & educational needs.	
Neurobehavioral/ Psychiatric	Assessment for anxiety, ADHD, ASD, aggression, & self-injury	
Musculoskeletal	• Physical medicine, OT/PT assessment of mobility, self-help skills • Eval of gait • Bone density study if recurrent fractures	
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	
Gastrointestinal	Monitor for constipation.	
Respiratory	Monitor for evidence of aspiration, respiratory insufficiency, & sleep apnea.	
Ophthalmologic involvement	Ophthalmologic eval	Annually or as necessary
	Low vision services	Per treating clinicians
Hearing loss	Audiologic eval	Annually (more frequently if person has history of recurrent otitis media)
Cardiovascular	Cardiac eval	At diagnosis & then per cardiologist

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Genitourinary	Renal & urologic eval	At diagnosis & then monitor for symptoms at each visit
Dental anomalies	Dental & orthodontic eval	Beginning at age 1 yr; continue every 6 mos or per dentist/orthodontist
Endocrine	Eval for hypoglycemia	At each visit
Immunologic	• Vaccinations per general population • If recurrent infections, baseline immune workup	At each visit
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy; RSTS = Rubinstein-Taybi syndrome

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*-related RSTS and 2/59 of those with *CREBBP*-related RSTS [Fergelot et al 2016]. In another study, 4/12 individuals with *EP300*-related RSTS had pregnancies complicated by preeclampsia or placental abnormalities including one report of uteroplacental malperfusion. Polyhydramnios was noted in two pregnancies [Cohen et al 2020].

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

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 a *CREBBP* or *EP300* pathogenic variant inherited from a heterozygous or mosaic parent.
  - 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].
  - Parental somatic and germline mosaicism has been reported [Chiang et al 2009, Bartsch et al 2010, Tajir et al 2013, Lin et al 2021].
- Recommendations for the evaluation of parents of a proband include clinical examination for physical findings associated with RSTS and, if a molecular diagnosis has been established in the proband, testing for the *CREBBP* or *EP300* pathogenic variant identified in the proband.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism [Chiang et al 2009, Bartsch et al 2010, Tajir et al 2013, Lin et al 2021].* Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

    * If the parent is the individual in whom the pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected [Chiang et al 2009, Bartsch et al 2010].
- The family history of some individuals diagnosed with RSTS may appear to be negative because of failure to recognize the disorder in affected family members. Therefore, an apparently negative family history cannot be confirmed unless a molecular diagnosis has been established in the proband and molecular genetic testing of the parents has established that neither parent is heterozygous for the pathogenic variant identified in the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/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 [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, the parent's 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/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 have had a child with RSTS.

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

Once the RSTS-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing 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 and preimplantation genetic testing. While most health care centers would consider use of prenatal and preimplantation genetic 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.

- **MedlinePlus**
  Rubinstein-Taybi syndrome
- **National Organization for Rare Disorders (NORD)**
  Rubinstein-Taybi Syndrome

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

Table A. continued from previous page.

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

CREBBP and *EP300* encode histone acetyltransferases (HAT) that act as transcriptional coactivators. The CREB-binding protein (CREBBP) is ubiquitously expressed and is involved in transcriptional coactivation of many different transcription factors. It has intrinsic 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 CREBBP 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 a 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. Loss of function (haploinsufficiency)

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 Rubinstein-Taybi syndrome (RSTS) and provides expert confirmation of diagnosis as well as the latest treatments and support.

Brittany Simpson, MD (brittany.simpson2@stjude.org), is actively involved in clinical research regarding individuals with RSTS. **Dr Jane Waite** (j.waite@aston.ac.uk) in the United Kingdom is collecting data on the behavioral phenotype in RSTS. They would be happy to communicate with persons who have any questions regarding diagnosis of RSTS or other considerations.

Dr Simpson is also interested in hearing from clinicians treating families affected by RSTS in whom no causative pathogenic variant has been identified through molecular genetic testing of the genes known to be involved in RSTS.

Contact Dr Simpson to inquire about review of *CREBBP* and *EP300* variants of uncertain significance.

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- 9 November 2023 (gm) Comprehensive update posted live
- 22 August 2019 (sw) Comprehensive update posted live
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