

RUBINSTEIN-TAYBI SYNDROME (RSTS RTS)

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October 12, 2025

RECOMMENDED CITATION

mohammad looti (2025). *RUBINSTEIN-TAYBI SYNDROME (RSTS RTS)*.
PSYCHOLOGICAL SCALES. Retrieved from <https://scales.arabpsychology.com/?p=42225>

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Primary Disciplinary Field(s): Medical Genetics, Pediatrics, Developmental Biology

1. Core Definition

Rubinstein-Taybi Syndrome, often abbreviated as **RSTS** or **RTS**, is a rare, complex, multisystem congenital disorder characterized primarily by short stature, intellectual disability ranging from moderate to severe, distinctive facial features, and specific skeletal anomalies, most notably broad thumbs and great toes. Classified as a neurodevelopmental condition, RSTS affects multiple organ systems and requires intensive multidisciplinary medical management throughout the individual's lifespan. Due to the high variability in its presentation, the severity of symptoms differs significantly among affected individuals, although the characteristic constellation of physical traits usually facilitates clinical diagnosis. The estimated prevalence of RSTS is approximately 1 in 100,000 to 125,000 live births globally, underscoring its classification as a truly rare disease.

Genetically, RSTS is defined by pathogenic variants or deletions involving either the **CREBBP** gene or, less commonly, the **EP300** gene. Both of these genes encode for crucial histone acetyltransferases (HATs) that play a fundamental role in regulating gene expression and chromatin remodeling, particularly during embryonic development and neurogenesis. The disruption of these epigenetic regulatory mechanisms leads to the widespread developmental abnormalities observed in RSTS. The inheritance pattern is typically **autosomal dominant**, meaning only one copy of the altered gene in each cell is sufficient to cause the disorder; however, the vast majority of cases (estimated at 90% to 95%) arise from *de novo* mutations in individuals with no prior family history of the syndrome.

The syndrome represents a significant challenge in pediatric care due to its broad spectrum of associated medical complications. Beyond the defining physical traits, individuals with RSTS have an increased susceptibility to various health issues, including congenital heart defects, renal anomalies, vision and hearing deficits, dental abnormalities, and significant feeding difficulties during infancy. Crucially, as noted in initial descriptions of the disease, there is a statistically greater predisposition for developing both benign and malignant neoplasms, including specific types of leukemia and lymphomas, necessitating rigorous oncological surveillance throughout life.

2. Etymology and Historical Development

The recognition of Rubinstein-Taybi Syndrome as a distinct clinical entity occurred in the mid-twentieth century, arising from the confluence of clinical observations made by two independent American physicians. The syndrome is eponymously named after pediatrician **Jack H. Rubinstein** (born 1925) and radiologist **Hooshang Taybi** (1919-2006). Although similar cases had been

sporadically reported earlier in medical literature, it was their detailed documentation that formalized the diagnostic criteria.

Dr. Rubinstein, working at the Children's Hospital in Cincinnati, Ohio, published his seminal findings in 1963, providing a detailed account of seven unrelated patients who shared the unique triad of intellectual disability, broad thumbs/toes, and characteristic facial features. Almost concurrently, Dr. Taybi, based in San Francisco, provided significant radiological descriptions of the skeletal abnormalities associated with the condition, particularly focusing on the unique malformations of the distal phalanges. Their combined observations led to the disorder being formally recognized and established in the medical lexicon, initially as the Rubinstein-Taybi-Syndrome in 1963 and 1964. The foundational work established the clinical phenotype, setting the stage for future genetic investigation into its etiology.

The understanding of RSTS transitioned significantly from phenotypical observation to molecular definition in the 1990s. In 1991, researchers localized the genetic defect responsible for RSTS to chromosome 16. This breakthrough was followed by the identification of the causative gene in 1998: the **CREBBP** (CREB binding protein) gene, located at 16p13.3. This discovery revolutionized diagnosis, allowing for molecular confirmation and providing critical insight into the pathophysiology, linking the syndrome to defects in chromatin regulation. Later, around 2005, a second, less common causative gene, **EP300** (E1A binding protein p300), located on chromosome 22, was identified, accounting for a smaller percentage of RSTS cases, further solidifying RSTS as a disorder of transcriptional control.

3. Genetics and Etiology

The etiology of RSTS is rooted in the molecular mechanisms governing gene regulation, making it a classic example of a **chromatin remodeling disorder**. As established, RSTS results from heterozygous pathogenic mutations or deletions in either the *CREBBP* or *EP300* genes. The *CREBBP* gene is the primary locus, accounting for approximately 50% to 60% of diagnosed clinical cases, while *EP300* mutations account for about 5% to 8% of cases. In a significant minority of individuals clinically diagnosed with RSTS, no pathogenic variant is identifiable in either gene, suggesting the existence of other, yet-to-be-discovered genetic loci or regulatory defects.

Both *CREBBP* and *EP300* encode proteins that function as histone acetyltransferases (HATs). HATs are critical enzymes that add acetyl groups to lysine residues on histone proteins, a process known as histone acetylation. This modification generally loosens the chromatin structure, making the DNA more accessible to transcription factors and thereby promoting gene expression. The *CREBBP* protein (and the highly homologous *EP300* protein) acts as a critical transcriptional coactivator, interacting with numerous transcription factors to control the expression of hundreds of genes involved in cell differentiation, proliferation, apoptosis, and central nervous system

development.

When a mutation occurs in *CREBBP* or *EP300*, it often results in a **haploinsufficiency** state--meaning that the cell produces only half the normal amount of functional protein, or the resulting truncated protein is non-functional. This reduction in HAT activity impairs the necessary acetylation required for the proper expression of developmental genes. This failure in precise transcriptional control during critical windows of development is believed to underlie the multiple congenital anomalies and intellectual disability characteristic of the syndrome. Research suggests that *EP300* mutations tend to be associated with slightly less severe intellectual impairment compared to *CREBBP* mutations, although phenotypic overlap is substantial.

4. Key Clinical Manifestations

The clinical phenotype of RSTS is highly distinctive, combining recognizable craniofacial and skeletal features with neurodevelopmental delay. The diagnosis often relies on the recognition of this specific constellation of signs, which fall into several major categories.

The **craniofacial characteristics** are often the most defining feature. These typically include microcephaly (small head size), highly arched eyebrows, long eyelashes, prominent nose (often with a beaked or "columella extending below the alae" appearance), and a relatively small mouth. Ocular anomalies, such as tear duct obstructions, ptosis (droopy eyelids), and refractive errors, are also frequent. Dental anomalies, including hypodontia and small teeth, contribute to the distinctive oral phenotype.

The **skeletal abnormalities** are pathognomonic for RSTS. The most commonly cited feature is the presence of **broad and angulated thumbs and first toes**. These digits may be radially deviated and are often the first feature noted by clinicians. Other skeletal issues include short stature (present in nearly all individuals), scoliosis or kyphosis, and sternal abnormalities. Individuals with RSTS also exhibit joint hypermobility, which can contribute to orthopedic issues later in life.

Neurodevelopmental and Behavioral characteristics are central to the diagnosis. All individuals with RSTS experience some degree of global developmental delay and intellectual disability, which typically ranges from moderate to severe. Communication skills are often significantly affected, with expressive language lagging behind receptive language. Behavioral profiles frequently include cheerful and friendly dispositions, but may also involve attention deficit hyperactivity disorder (ADHD), anxiety, or, less commonly, features of Autism Spectrum Disorder (ASD). Sleep disturbances are also a commonly reported problem.

5. Associated Medical Complications and Surveillance

Beyond the primary diagnostic features, RSTS is associated with several serious systemic

complications that necessitate specialized medical monitoring and intervention. These complications arise due to the widespread impact of defective gene regulation across various organ systems.

One of the most concerning aspects of RSTS is the documented increased risk of developing neoplasms. This predisposition is thought to be linked to the regulatory roles of **CREBBP** and **EP300** in cell cycle control and tumor suppression. Individuals with RSTS possess a greater lifetime chance of developing certain noncancerous and cancerous growths. Specific malignancies noted include **leukemia** (particularly acute lymphoblastic leukemia or ALL), **neuroblastomas**, and **lymphomas**. Due to this heightened risk, surveillance protocols, often involving regular blood counts and physical examinations, are crucial components of RSTS management.

Furthermore, a significant percentage of patients present with **congenital heart defects** (e.g., patent ductus arteriosus, atrial septal defects), which may require surgical correction in infancy. Gastrointestinal issues, including chronic constipation and gastroesophageal reflux (GERD), are highly prevalent and often complicate feeding. Renal anomalies, such as duplicated collecting systems or hydronephrosis, also occur and require routine renal screening. Finally, recurrent infections, particularly ear infections (otitis media) and respiratory tract infections, are common, possibly reflecting subtle immune dysfunction associated with the syndrome.

6. Diagnosis and Management

Diagnosis of RSTS is initially based on clinical findings, utilizing established scoring systems that evaluate the presence and severity of the key features (broad thumbs/toes, facial dysmorphism, and intellectual disability). However, definitive diagnosis relies on molecular genetic testing. This testing typically involves sequencing the *CREBBP* and *EP300* genes to identify a pathogenic mutation or performing chromosomal microarray analysis to detect a deletion encompassing the gene locus.

Management of RSTS is inherently multidisciplinary and highly individualized, focusing on addressing the specific medical and developmental needs of the patient.

Developmental Therapy: Early intervention programs are essential, including physical therapy (to address muscle hypotonia and mobility), occupational therapy (to improve fine motor skills and feeding), and speech-language therapy (to facilitate communication development).

Surgical Intervention: Orthopedic surgery may be required to correct severe angulation of the thumbs or toes, or to address scoliosis. Ophthalmic and otolaryngological interventions are common for structural abnormalities or chronic ear issues.

Medical Monitoring: Regular cardiac screening, renal ultrasounds, and detailed developmental assessments are mandatory. Given the tumor risk, ongoing oncological surveillance, guided by specific clinical recommendations, is a critical component of care.

Educational Support: Due to intellectual disability, individuals with RSTS require specialized educational settings and individualized education plans (IEPs) tailored to their unique learning styles and cognitive challenges.

7. Significance and Impact

Rubinstein-Taybi Syndrome holds substantial significance not only for the affected individuals and their families but also for the broader field of medical genetics. Clinically, the diagnosis provides clarity and allows families to access targeted resources, specialized medical care, and genetic counseling regarding recurrence risk. Support organizations, such as the **Rubinstein-Taybi Syndrome Support Group**, play a vital role in connecting families and funding targeted research efforts.

From a scientific perspective, RSTS serves as a crucial model for understanding **chromatin biology** and the role of histone modification in human development and disease. Studying the precise mechanisms by which *CREBBP* and *EP300* haploinsufficiency disrupts developmental pathways provides insights into the molecular basis of other congenital disorders and illuminates the fundamental processes of neurogenesis and transcriptional regulation. Furthermore, the link between RSTS and an increased cancer risk has positioned the syndrome as an important focus for cancer research, helping scientists understand how defects in chromatin remodeling contribute to oncogenesis. The syndrome thus impacts multiple domains, bridging developmental medicine, oncology, and epigenetic research.

Further Reading

[Rubinstein-Taybi Syndrome - Genetics Home Reference \(GHR\)](#)

[Rubinstein-Taybi Syndrome - Wikipedia](#)

[Rubinstein-Taybi Syndrome - National Organization for Rare Disorders \(NORD\)](#)

[Rubinstein-Taybi Syndrome - GeneReviews \(NCBI\)](#)