CREBBP and EP300 mutational spectrum and clinical presentations in a cohort of Swedish patients with Rubinstein–Taybi syndrome

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Abstract
Rubinstein–Taybi syndrome (RTS) is a rare autosomal dominant congenital disorder characterized by distinctive facial features, broad thumbs and halluces, growth retardation, and a variable degree of cognitive impairment. CREBBP is the major causative gene and mutations in EP300 are the cause of RTS in a minority of patients. In this study, 17 patients with a clinical diagnosis of RTS were investigated with direct sequencing, MLPA, and array-CGH in search for mutations in these two genes. Eleven patients (64.7%) had disease-causing point mutations or a deletion in CREBBP and in one patient (5.9%) a causal de novo frameshift mutation in EP300 was identified. This patient had broad thumbs, mild intellectual disability, and autism. In addition, an inherited missense mutation of uncertain clinical significance was identified in EP300 in one patient and his healthy father, and three patients had intronic nucleotide changes of uncertain clinical significance in CREBBP. Snoring and sleep apnea were common in both groups and four of the patients’ mothers had preeclampsia during pregnancy. Importantly, difficulties associated with anesthesia were frequently reported and included delayed or complicated emergency in 53.3% of patients.

Introduction
Rubinstein–Taybi syndrome (RTS [OMIM 180849]) is an autosomal dominant congenital disorder with an estimated incidence of 1:100,000–125,000. RTS is characterized by distinctive facial features (downward slanting palpebral fissures, arched eyebrows, beaked nose, columella below alae nasi and micrognathia), skeletal...
abnormalities (typically broad thumbs and halluces), growth retardation, microcephaly, and a variable degree of cognitive impairment and behavioral problems (Roelfsema and Peters 2007; Schorry et al. 2008). A few familial cases demonstrating germline and somatic mosaicism have been reported (Chiang et al. 2009; Bartsch et al. 2010a).

Around 10% of the patients with RTS have microdeletions of chromosome 16p13.3 involving CREBBP, and in approximately 50% of the patients point mutations in CREBBP are found (Schorry et al. 2008). There is no clear genotype–phenotype correlation (Schorry et al. 2008). Mutations in EP300 are the cause of RTS in a minority of patients, and to the best of our knowledge only 16 patients have been described to date (Roelfsema et al. 2005; Bartholdi et al. 2007; Zimmermann et al. 2007; Foley et al. 2009; Bartsch et al. 2010b; Tsai et al. 2011; Woods et al. 2014; Negri et al. 2015; Solomon et al. 2015). Eleven additional mutations are listed in the database LOVD (http://chromium.liacs.nl/LOVD2/variants.php?action=search_all). CREBBP and EP300 are ubiquitously expressed and are highly homologous genes. CREBBP, a 150 kb gene with 31 exons, encodes the 2442 amino acid CREB-binding protein. EP300 is located on chromosome 22q13.2 and its 31 exons encode the E1A-1-binding protein p30, consisting of 2415 amino acids. The two proteins act as transcriptional coactivators by forming scaffolds between the RNA polymerase II complex and DNA-binding transcription factors. They also affect gene expression by serving as histone acetyltransferases (HATs). There are, however, subtle differences between these two proteins and their expression pattern

### Table 1. Clinical data.

| Patient | 1 | 2 | 3 | 4 | 5 | 6 |
|---------|---|---|---|---|---|---|
| Mutation | Del\(^1\) | Ns\(^1\) | Ns\(^1\) | Ss\(^1\) | Fs\(^1\) | Ns\(^1\) |
| Sex | F | M | F | M | M | M |
| Age (diagnosis/examined) | 1 m/32 y | 17 y/21 y | 13 y/13 y | n.i./16 y | 2 y/2 y | 1 y/17 y |
| Mat. preeclampsia | – | + | – | – | – | – |
| Gestation week | 40 | 35 | 41 | 40 | 41 | n.i. |
| Birth weight (g) | 3200 | 2100 | 3175 | 2760 | 3570 | n.i. |
| Birth length (cm) | 48 | 45 | 47 | 46 | n.i. | n.i. |
| Postnatal length | –4 SD | –7 SD | –2 SD | n.i. | –1.5 SD | –5 SD |
| Microcephaly | + (–3.5 SD) | + | + | + | + (–4 SD) | (–2 SD) |
| Seizure | + | ++ | ++ | + | n.i. | + |
| Hypotonia | + | + | – | + | – | + |
| Hirutism | + | – | + | n.i. | n.i. | + |
| Beaked nose/columella below alae nasi | +/+ | +/+ | +/+ | +/+ | n.i./n.i. | +/+ |
| Down-sllanting palpebral fissures | + | + | + | + | + | + |
| Long eye lashes/Arched eyebrows | +/+ | +/+ | +/+ | +/+ | n.i./n.i. | +/+ |
| Micrognathia | – | – | + | + | n.i. | + |
| Highly arched palate | + | + | + | + | + | + |
| Broad thumbs/halluces | +/+ | +/+ | +/+ | +/+ | +/+ | +/+ |
| Radially deviated thumbs | + | – | – | – | n.i. | + |
| Heart/Urogenital malformation | n.i. | –/– | –/– | –/+ | –/+ | –/+ |
| Keloids/Tumors | –/– | –/– | –/+ | –/+ | –/+ | –/+ |
| Impaired hearing/vision | –/+ | –/– | –/+ | –/+ | –/+ | –/+ |
| Kyphosis/Scoliosis | +/+ | +/+ | +/+ | +/+ | –/+ | –/+ |
| Epilepsy | – | – | – | – | – | – |
| Speech delay | + | + | + | + | + | + |
| Intellectual disability | Mild | Severe | Severe | Moderate | Mild | Moderate |
| Behavior | Sociable/Autism | –/– | +/+ | n.i./n.i. | +/– | n.i./n.i. | +/n.i. |
| Anxiety/Agression | –/– | –/– | +/+ | n.i./n.i. | –/– | –/– |
| Short attention span | – | – | n.i. | – | n.i. | – |
| Recurrent infections | + | + | + | – | n.i. | + |
| Constipation | + | + | – | – | n.i. | – |
| Apnea/snoring | –/+ | –/– | +/+ | –/+ | +/+ | +/+ |
| Complicated emergence after anesthesia | + | + | n.i. | – | + | – |

Del, Deletion; Ns, Nonsense; Ss, Splice site; Ms, Missense; n.i., no information available; m, month; y, year.

\(^1\)CREBBP

\(^2\)EP300
During embryogenesis is not completely overlapping (Roelfsema and Peters 2007).

In this study, we report the mutation spectrum in CREBBP and EP300 among 17 patients with a clinical diagnosis of RTS, including a novel pathogenic EP300 mutation and intronic CREBBP alterations of uncertain clinical significance, together with detailed clinical phenotypes.

**Materials and Methods**

**Patients**

Seventeen patients with a clinical diagnosis of RTS were included after obtaining informed consent and the study was performed with approval of the regional ethics committee at the Karolinska Institutet, Stockholm. All the patients were examined by clinical geneticists at the clinical genetics department at the Karolinska University Hospital. The Genomic DNA from the patients and their parents, when available, was isolated from peripheral blood according to the standard procedures. Clinical data is summarized in Table 1.

**Clinical information of patients 2 (foot malformation), 12 and 13 (EP300 mutations)**

Patient 2 was the third child to healthy nonconsanguineous parents. There was no family history of malformations or intellectual disability. The boy was born at gestation week 35 due to premature rupture of membranes. The birth weight was 2100 g (−2 SD) and birth length 45 cm (−1 SD). In the neonatal period, muscular hypotonia, bilateral

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| n.s. | n.s. | F | M | n.i. | 11/12 | 14 | 15 | 16 | 17 |
|------|------|---|---|-----|-------|-----|-----|-----|-----|
| n.i/4 y | 2 m/12 y | 2 y/10 y | 2 y/17 y | 2 y/5 y | 1.5 y/5 y | 11 m/13 y | 12 y/18 y | 1 y/1 y | 9 y/14 y |
| n.i. | + | − | + | − | + | − | − | − | n.i. | − |
| n.i. | 42 | 38 | 40 | n.i. | 38 | 39 | 42 | 37 | 37 | 41 |
| n.i. | 4150 | 2635 | 2340 | n.i. | 2780 | 3625 | 3145 | 2800 | n.i. | 2980 |
| n.i. | 52 | 47 | 47 | n.i. | 47 | 51 | 49 | 48 | n.i. | 50 |
| −1 SD | −2 SD | −3.5 SD | −2 SD | −2 SD | −3 SD | −1.5 SD | −3.5 SD | −6 SD | −3.5 SD | −1 SD |
| − | − | − | −2 SD | + | − | 1.5 SD | + | − | − | −1 SD |
| n.i. | + | ++ | + | + | − | + | + | + | + | + |
| n.i. | + | − | − | − | − | + | + | + | + | + |
| n.i. | + | n.i. | + | + | + | + | + | + | + | + |
| n.i. | n.i. | + | + | + | + | + | + | + | + | + |
| n.i. | + | + | + | + | + | + | + | + | + | + |
| n.i. | + | − | n.i. | −1 SD | + | + | − | + | + | + |
| n.i. | − | + | − | − | n.i. | −1 SD | + | + | + | + |
| n.i. | − | + | + | + | + | + | + | + | + | + |
| n.i. | + | + | Mild | + | − | − | − | − | − | − |
| n.i. | n.i. | +/n.i. | −/− | n.i. | −/+ | −/+ | −/+ | −/+ | −/+ | −/+ |
| n.i. | + | + | + | + | + | + | + | + | + | + |
| n.i. | + | + | + | + | + | + | + | + | + | + |
| n.i. | + | + | + | + | + | + | + | + | + | + |
| n.i. | + | + | + | + | + | + | + | + | + | + |
| n.i. | + | + | + | + | + | + | + | + | + | + |
| n.i. | + | + | + | + | + | + | + | + | + | + |
cryptorchidism, breathing difficulties, broad thumbs and
halluces, syndactyly IV and V, and a hemangioma in the
forehead was noted. He started walking at an age of
3.5 years but even at an older age he needed a wheelchair
for longer transportations. The boy had no spoken lan-
guage but communicated with approximately 25 signs. He
had severe ID, short stature, microcephaly, and facial
appearance characteristic for RTS. In addition he had a
delayed maturation of the skeleton, severe scoliosis, and an
unusual foot malformation (Fig. 1).

Patient 12 was the first child born to healthy noncon-
sanguineous parents. The mother, however, had broad
thumbs. The parents have had five miscarriages. The
mother had high blood pressure during the pregnancy
and labor was induced due to preeclampsia. The boy was
born at gestation week 38 + 3. The birth weight was 2780 g
(−1.5 SD), birth length 47 cm (−1.6 SD), and
head circumference (HC) 33 cm (−1.5 SD). At an age of
2 years the HC had decreased to −5 SD and at age
5 years the height and weight had decreased to −3 SD
and −2.5 SD, respectively. In addition to microcephaly,
he had arched eyebrows, long eyelashes, columella below
alae nasi, downward slanting palpebral fissures, epicanthal
folds and a highly arched palate. He had broad thumbs,
clinodactyly of digit V, and broad halluces. He had a
ventricular septal defect and cryptorchidism. He walked
independently at an age of 20 months and had a mild
developmental delay. There was a speech delay with the
first spoken words at an age of 24 months, with a better
understanding then expressive language. Furthermore he
developed behavioral problems including self-mutilation
and daily temper tantrums. Other observed anomalies
included a short plica aryepiglottica and frequent
pneumonias.

Patient 13 was the second child to healthy consan-
guineous parents. A paternal uncle had intellectual
disability. The boy was born at gestation week 39 + 3
after a normal pregnancy. The birth weight was 3625 g
(M), birth height 51 cm (M) and HC 35 cm (M). At an
age of 6 years there was no growth retardation or
microcephaly (although HC had decreased to −1.5 SD).
He had muscular hypotonia, walked independently at an
age of 2 years, spoke his first words at an age of 2 years
and had a cognitive developmental delay. He had
dysmorphic facial features including arched eyebrows,
long eyelashes, low hairline, columella below alae nasi,
downward slanting palpebral fissures, and low set ears.
He had broad thumbs with radial angulation, broad
halluces and pectus excavatum. He had frequent otitis
and underwent tonsillectomy.

Array-CGH

Array comparative genomic hybridization was performed
in all the patients except patient 3, 4, 6, and 10 (lack of
DNA) to search for microdeletions and microduplica-
tions. 244K/180K oligonucleotide arrays with complete
gene coverage produced by Agilent Technologies (Palo
Alto, CA) or Oxford Gene Technology (Oxford, UK) were
used. Experiments were performed according to the
manufacturers’ protocol. After hybridization and washing,
the slides were scanned on an Agilent Microarray Scanner
and captured images were analyzed with Feature Extrac-
tion Software v.9.113 (Agilent Technologies) and DNA
analytics v. 4.0 or Cytosure Interpret Software v.3.3.2
(Oxford Gene Technologies). A threshold of at least three
consecutive aberrant probes was applied, resulting in an
average resolution of approximately 30 kb. Genomic posi-
tions are according to the NCBI36/hg18 build in UCSC.

Sequencing and MLPA

Polymerase chain reaction (PCR) amplification, followed
by direct sequencing of the coding sequence and the corre-
sponding exon–intron boundaries of CREBBP (GRCh38:
CM000678.2) and EP300 (GRCh38:CM000684.2) was
performed according to the standard procedures. Primers
used for PCR amplification of CREBBP were previously
reported by Coupry et al. (2002), except primers for ampli-
fication of exon 1, 2, 18, 27, 30, and 31 for which additional
primers were designed in order to improve the readability
of the sequences (primer sequences available upon request).
Sequencing of the coding regions was performed using Big Dye Terminator cycle sequencing kit 3.1 (Applied Biosystems, Foster City, CA) according to the manufacturer’s standard protocol and sequenced on an ABI genetic analyzer. ABI SEQSCAPE software version 2.5 (Applied Biosystems) was used to perform sequence analysis. A search for intragenic deletions and duplications was performed by MLPA. The commercial kits P313 and P333 were used (MRC Holland, Amsterdam, the Netherlands). The MLPA reaction was performed according to the manufacturer’s standard protocol and reagents. Data analysis was performed using Microsoft Excel. Analysis of EP300 was performed in the patients without pathogenic CREBBP mutations, but was unfortunately not possible in patients 16 and 17 due to lack of DNA. Parental samples were analyzed for the variants identified in the child (not done for patients 3 and 7).

Results

The clinical phenotypes of the patients are summarized in Table 1. The patients displayed a classic RTS-phenotype with characteristic facial features, broad thumbs, and halluces and a variable degree of intellectual disability. Five patients had autism and eight patients had behavioral problems comprising anxiety and/or aggression. Fifty percent had a pronounced short stature (less than –2.5 SD). Patient 2 had a very rare morphology of his right foot (Fig. 1). Ten patients had trouble with snoring and/or sleep apnea (often improved after surgery). Difficulties associated with anesthesia comprising delayed or complicated (apnea, agitation, postoperative breathing difficulties) emergence was reported in 8/15 patients (53.3%) for which information were available. Maternal preeclampsia was reported for three patients with CREBBP mutations and one patient with EP300 mutation.

The CREBBP and EP300 mutations identified in our cohort of 17 Swedish patients with a clinical diagnosis of RTS are summarized in Table 2. Ten patients (58.8%) had causal point mutations in CREBBP, comprising six nonsense mutations, two frameshift mutations, one missense mutation and one splice-site mutation. Eight of the mutations were found to be de novo after testing of both parents, but for two of the patients (3 and 7) DNA samples for both parents were not available and the inheritance pattern was thus unknown (although the mother was excluded as a carrier in patient 3). One patient (5.9%) had a 240 kb deletion of chromosome 16p13.3 including the first two exons of CREBBP. In EP300, one (5.9%) likely causal de novo frameshift mutation was identified in patient 12 and an inherited missense mutation of uncertain clinical significance was identified in patient 13.

Three patients had intronic nucleotide changes in CREBBP that are not reported as normal variants previously (to the best of our knowledge). Two of the variants were de novo and for one patient parental DNA was not available. None of them were found in 175 healthy controls. No intragenic deletions or duplications of CREBBP or EP300 were detected by MLPA (not performed in patient 1).

Table 2. CREBBP and EP300 mutation spectrum.

| Patient | Exon | Nucleotide change | Amino acid change | Inheritance | Controls |
|---------|------|------------------|-------------------|-------------|----------|
| CREBBP |      |                  |                   |             |          |
| 1       | 1–2  | Del(chr16:3818420–4057031), 240 kb |                   | n.i.        |          |
| 2       | 2    | c.778C>T         | p.Gln260X         | de novo     |          |
| 3       | 4    | c.1069C>T        | p.Gln357X         | Mother excluded |          |
| 4       | 9    | c.1941+1G>A      | p.?              | de novo     |          |
| 5       | 14   | c.3014_3015insC  | p.Ser938fs        | de novo     |          |
| 6       | 18   | c.3452G>A        | p.Trp1151X        | de novo     |          |
| 7       | 18   | c.3517C>T        | p.Arg1173X        | n.i.        |          |
| 8       | 24   | c.4078C>T        | p.Arg1360X        | de novo     |          |
| 9       | 27   | c.4400_4401insATGT | p.Thr1468fs   | de novo     |          |
| 10      | 28   | c.4613C>G        | p.Pro1538Arg      | de novo     | 190 negative |
| 11      | 31   | c.5635C>T        | p.Gln1879X        | de novo     |          |
| EP300   |      |                  |                   |             |          |
| 12      | 30   | c.4783_4784delTT | p.Phe1595fs       | de novo     |          |
| 13      | 31   | c.5824A>T        | p.Met1942Leu      | Inherited, healthy father | 189 negative |
| CREBBP |      |                  |                   |             |          |
| 13      | 25   | c.4134-6T>C      | p.?              | de novo     | 175 negative |
| 14      | 15   | c.2881-13G>A     | p.?              | de novo     | 190 negative |
| 15      | 21   | c.3836+5G>C      | p.?              | n.i.        | 175 negative |

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**Discussion**

Patients 1–12 were found to have pathogenic mutations (de novo, truncating, and/or previously described as pathogenic). Due to lack of parental DNA, it was not possible to determine if the mutations were de novo or not in patients 1, 3, and 7. However, these mutations are likely to be pathogenic because they either remove the 5′ end of the gene or lead to premature stop codons, and in addition, the mutation found in case 7 had been reported previously (Bentivegna et al. 2006; Roelfsema and Peters 2007). The previously unreported missense mutation (p.P1538R) found in patient 10 was considered pathogenic as it was de novo, located in the HAT domain, was not detected in 190 control subjects and was predicted to be probably damaging using the bioinformatics tool PolyPhen (http://genetics.bwh.harvard.edu/pph2/).

Three patients had intronic mutations in CREBBP of uncertain clinical significance. The T>C transition (six nucleotides before exon 25) identified in patient 14 was not predicted to introduce a new splice site using the in silico tool Alamut (Alamut v 2.0; Interactive Biosoftware). However, in patient 15, the G>A transition (13 nucleotides before exon 15) was predicted to disrupt the splice site and introduce a new splice site. This change was not detected in parental DNA or in healthy controls making it a good candidate for being the cause of the syndrome in this patient. Also, the G>C transition (5 nucleotides after exon 21) was predicted to disrupt the splice site by Alamut, but in this patient the inheritance is not known. Unfortunately, RNA from these three individuals was not available and further experiments are needed to evaluate the pathogenicity. The relatively low diagnostic yield in RTS might, to a certain degree, be due to the intronic mutations not immediately adjacent to the intron–exon boundaries.

Of the detected EP300 mutations, the de novo frameshift mutation in patient 12 is considered pathogenic while the inherited missense mutation (p.M1942L) found in patient 13 is of uncertain clinical significance. Although the missense mutation was not identified in the healthy control subjects, it was predicted to be benign by polyphen and the patient’s father was healthy in contradiction for it being pathogenic. However, a paternal uncle had an unexplained ID (DNA unfortunately not available) and reduced penetrance is another possibility. In addition, one missense mutation (p.N1511T), inherited from a healthy mother and considered not causative, has been previously reported (Negri et al. 2015). Clinical manifestations in 16 previously described patients with EP300 mutations have frequently comprised a characteristic facial appearance, microcephaly, short stature, broad thumbs, varying degrees of developmental delay, neuropsychiatric traits, and only occasionally multiple congenital anomalies (Negri et al. 2015; Solomon et al. 2015). While comparing patient 12 with these patients, we can add to the evolving picture of a phenotype comprising broad thumbs but absence of radial deviation of thumbs and halluces, mild DD, and presence of neuropsychiatric traits.

There may be an association with preeclampsia in mothers of patients with RTS. Including our patient, nine (52.9%) of the 17 hitherto reported EP300 mutation-positive patients included a maternal history of preeclampsia (Negri et al. 2015; Solomon et al. 2015). However, in our cohort of CREBBP mutation-positive patients, three out of eight mothers had preeclampsia. Our cohort is relatively small and the information was only available for eight of the mothers, but it gives rise to the question if it is rather the general RTS characteristics of the fetus that may be associated with the preeclampsia than specifically the EP300 mutations.

Rubinstein–Taybi syndrome is a rare syndrome but many children with the diagnosis undergo several operations. Delayed recovery from anesthesia in RTS have been reported previously (Dunkley and Dearlove 1996), although to a lesser extent than in our patient cohort. Therefore, we urge anesthesiologists to be aware of the possibility of delayed recovery and to use sedative agents with caution.

**Conclusions**

We here report the CREBBP and EP300 mutation spectrum in a cohort of 17 Swedish patients with a clinical diagnosis of RTS. Our results confirm that mutations in CREBBP are the major cause of RTS and we report a novel causative EP300 mutation. Three patients had intronic findings of uncertain clinical significance in CREBBP, of which at least one is a good candidate for being the causative mutation. Preeclampsia was reported in mothers of RTS patients with both CREBBP and EP300 mutations. In addition, anesthesiologists should be aware that there may be a delayed emergence after anesthesia.

**Acknowledgments**

We are grateful to the patients and their families for their participation in this study. We would like to express our gratitude to Eva Ekblom for the valuable administrative assistance and to Peter Gustavsson and Giedre Grigelioniene for providing the clinical data. This work was supported by funds from the Swedish Research Council, Stockholm County Council, Karolinska Institutet, Linne och Josef Carlsson Foundation, Kronprinsessan Lovisa Foundation, Frimurare Barnhuset i Stockholm, The Swed-
ish Brain Foundation (Hjärnfonden), The Swedish Childhood Cancer Foundation, Sällskapet Barnavårds and the Karolinska Institutet Research funds.

**Conflict of Interest**
The authors declare no conflict of interest.

**References**
Bartholdi, D., J. H. Roelfsema, F. Papadia, M. H. Breuning, D. Niedrist, R. C. Hennekam, et al. 2007. Genetic heterogeneity in Rubinstein-Taybi syndrome: delineation of the phenotype of the first patients carrying mutations in EP300. J. Med. Genet. 44:327–333.

Bartsch, O., W. Kress, O. Kempf, S. Lechno, T. Haaf, and U. Zechner. 2010a. Inheritance and variable expression in Rubinstein-Taybi syndrome. Am. J. Med. Genet. A 152A:2254–2261.

Bartsch, O., J. Labonte, B. Albrecht, D. Wieczorek, S. Lechno, U. Zechner, et al. 2010b. Two patients with EP300 mutations and facial dysmorphism different from the classic Rubinstein-Taybi syndrome. Am. J. Med. Genet. A 152A:181–184.

Bentivegna, A., D. Milani, C. Gervasini, P. Castronovo, F. Mottadelli, S. Manzini, et al. 2006. Rubinstein-Taybi Syndrome: spectrum of CREBBP mutations in Italian patients. BMC Med. Genet. 7:77.

Chiang, P. W., N. C. Lee, N. Chien, W. L. Hwu, E. Spector, and A. C. Tsai. 2009. Somatic and germ-line mosaicism in Rubinstein-Taybi syndrome. Am. J. Med. Genet. A 149A:1463–1467.

Coupry, I., C. Roudaut, M. Stef, M. A. Delrue, M. Marche, I. Burgelin, et al. 2002. Molecular analysis of the CBP gene in 60 patients with Rubinstein-Taybi syndrome. J. Med. Genet. 39:415–421.

Dunkley, C. J., and O. R. Dearlove. 1996. Delayed recovery from anaesthesia in Rubinstein-Taybi syndrome. Paediatr. Anaesth. 6:245–246.

Foley, P., D. Bunyan, J. Stratton, M. Dillon, and S. A. Lynch. 2009. Further case of Rubinstein-Taybi syndrome due to a deletion in EP300. Am. J. Med. Genet. A 149A:997–1000.

Negri, G., D. Milani, P. Colapietro, F. Forzano, M. Della Monica, D. Rusconi, et al. 2015. Clinical and molecular characterization of Rubinstein-Taybi syndrome patients carrying distinct novel mutations of the EP300 gene. Clin. Genet. 87:148–154.

Roelfsema, J. H., and D. J. Peters. 2007. Rubinstein-Taybi syndrome: clinical and molecular overview. Expert Rev. Mol. Med. 9:1–16.

Roelfsema, J. H., S. J. White, Y. Ariyurek, D. Bartholdi, D. Niedrist, F. Papadia, et al. 2005. Genetic heterogeneity in Rubinstein-Taybi syndrome: mutations in both the CBP and EP300 genes cause disease. Am. J. Hum. Genet. 76:572–580.

Schorry, E. K., M. Keddahe, N. Lanphear, J. H. Rubinstein, S. Srodulski, D. Fletcher, et al. 2008. Genotype-phenotype correlations in Rubinstein-Taybi syndrome. Am. J. Genet. A 146A:2512–2519.

Solomon, B. D., D. L. Bodian, A. Khromykh, G. G. Mora, B. C. Lanpher, R. K. Iyer, et al. 2015. Expanding the phenotypic spectrum in EP300-related Rubinstein-Taybi syndrome. Am. J. Med. Genet. A 167A(5):1111–1116.

Tsai, A. C., C. J. Dossett, C. S. Walton, A. E. Cramer, P. A. Eng, B. A. Nowakowska, et al. 2011. Exon deletions of the EP300 and CREBBP genes in two children with Rubinstein-Taybi syndrome detected by aCGH. Eur. J. Hum. Genet. 19:43–49.

Woods, S. A., H. B. Robinson, L. J. Kohler, D. Agamanolis, G. Sterbenz, and M. Khalifa. 2014. Exome sequencing identifies a novel EP300 frame shift mutation in a patient with features that overlap Cornelia de Lange syndrome. Am. J. Med. Genet. A 164A:251–258.

Zimmermann, N., A. M. Acosta, J. Kohlhase, and O. Bartsch. 2007. Confirmation of EP300 gene mutations as a rare cause of Rubinstein-Taybi syndrome. Eur. J. Hum. Genet. 15:837–842.