LETTER TO JMG

Genetic heterogeneity in Rubinstein–Taybi syndrome: delineation of the phenotype of the first patients carrying mutations in *EP300*

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Background: Rubinstein–Taybi syndrome (RSTS) is a congenital disorder characterised by growth retardation, facial dysmorphisms, skeletal abnormalities and mental retardation. Broad thumbs and halluces are the hallmarks of the syndrome. RSTS is associated with chromosomal rearrangements and mutations in the CREB-binding protein gene (*CREBBP*), also termed *CBP*, encoding the CREB-binding protein. Recently, it was shown that mutations in *EP300*, coding for the p300 protein, also cause RSTS. *CBP* and *EP300* are highly homologous genes, which play important roles as global transcriptional coactivators.

Objective: To report the phenotype of the presently known patients with RSTS (n=4) carrying germline mutations of *EP300*.

Results: The patients with *EP300* mutations displayed the typical facial gestalt and malformation pattern compatible with the diagnosis of RSTS. However, three patients exhibited much milder skeletal findings on the hands and feet than typically observed in patients with RSTS.

Conclusions: Part of the clinical variability in RSTS is explained by genetic heterogeneity. The diagnosis of RSTS must be expanded to include patients without broad thumbs or halluces.

Rubinstein–Taybi syndrome (RSTS, OMIM 180 849) is a rare congenital disorder characterised by growth retardation, typical facial dysmorphisms, skeletal abnormalities and mental retardation.^{1,2} Broad and angulated thumbs and halluces are considered to be the hallmark of the syndrome, which was termed the “broad thumb hallux syndrome” by Rubinstein and Taybi in their original publication in 1963.³ It has been shown that RSTS is associated with chromosomal rearrangements and mutations in the gene encoding the CREB-binding protein (*CREBBP* or *CBP*) located on the short arm of chromosome 16.⁴ However, the rate of *CBP* deletions/mutations in patients with classic RSTS is rather low, covering 40–60% only.^{5–7} It has been suggested, therefore, that the *CBP*-negative patients might carry mutations in other genes. This hypothesis was recently proven: we could demonstrate that mutations in *EP300*, coding for the p300 protein, also cause RSTS.⁵ *EP300* is located on the long arm of chromosome 22 (22q13.2) and spans approximately 90 kb. It consists of 31 exons encoding a protein of 2415 amino acids.⁸ *CBP* and *EP300* are highly homologous genes, which are considered to be key regulators of RNA polymerase II-mediated transcription, acting as transcriptional coactivators. In addition, these multidomain proteins have intrinsic histone acetyl transferase activity, thus playing a critical role in acetylation of histones and other proteins. Despite their high degree of homology, *CBP* and *p300* do not exhibit complete overlap in their respective functions and have

indeed been shown to exert some unique effects in vitro and in vivo.^{9,10}

Here, we describe four patients with RSTS carrying germline mutations in *EP300*, including the first three patients reported.⁵ We show that the phenotypes of the patients with *EP300* mutation differ from those harbouring *CBP* alterations (table 1). Mutations in either gene are associated with the classic facial features, mental retardation and other abnormalities typically associated with RSTS. Interestingly, however, none of the presently known patients with *EP300* mutations showed the classic malformations on both hands and feet, which originally have been considered mandatory for the diagnosis of RSTS. Although the number of patients with *EP300* mutations is still very small, our data point to phenotypic heterogeneity between patients with *EP300* and *CBP* mutations, thus confirming that these highly homologous proteins play discriminative roles in human development.

METHODS

Patients

The four patients carrying *EP300* mutations belong to a large cohort of about 100 individuals from different European countries with the suspected diagnosis of RSTS. DNA samples of the patients and their parents were sent to The Netherlands for molecular analysis. Parents provided written consent for the analysis. The molecular data and part of the clinical data of three of the four patients (patients 1, 3 and 4) have been reported previously.⁵

Molecular evaluation

Coding sequences of the *EP300* gene were screened on genomic DNA of the patients by denaturing gradient-gel electrophoresis and multiplex ligation-dependent probe amplification as described previously.^{5,11} The exact nature of the mutations was revealed by sequencing. Sequencing was performed on the ABI 3700 (Applied Biosystems, Foster City, California, USA) using the manufacturer's standard protocol and reagents. Sequencing was confirmed using a second reaction, performed on PCR fragments generated in an independent analysis.

RESULTS

Mutations in *EP300*

The mutations of patients 1 (254-1), 2 (276-1) and 3 (256-1) were detected using denaturing gradient-gel electrophoresis and were confirmed by sequencing.⁵ Patient 1 showed a transition from a C to a T at position 1942 (exon 10) of the *EP300* cDNA, causing a stop codon (p.R648X). This leads to a

Abbreviations: *CREBBP*, CREB-binding protein; OFC, occipitofrontal circumference; RSTS, Rubinstein–Taybi syndrome

Table 1 Comparison of the features of typical patients with Rubinstein–Taybi syndrome with those with *EP300* mutations

Gene/mutation	General RSTS phenotype ^{1 2 12 13}	Patient 1	Patient 2	Patient 3	Patient 4
	Positive or negative for <i>CBP</i> mutation	p.R648X (<i>EP300</i>)	p.Q1209fsX1226 (<i>EP300</i>)	p.S959fsX966 (<i>EP300</i>)	c.1200-?_94+?del (<i>EP300</i>)
Perinatal period					
Delivery	No consistent trend	Preterm	Preterm	NR	NR
Neonatal problems	Respiratory problems Feeding difficulties	No distress NR	Respiratory distress Reflux	NR Hypoglycaemia	NR NR
Growth					
Birth measurement	BW and BL usually above 10th centile	BW normal, BL normal	BW decreased, BL normal	BW normal, BL decreased	NR
Stature	Postnatal growth retardation leading to short stature	Normal stature	Short stature	Short stature	GH deficiency, short stature
Head and face					
Microcephaly	Pre- or postnatal onset	Prenatal	Postnatal	Prenatal	NR
Ocular region					
Palpebral fissures	Downslanting	Downslanting	Downslanting	Downslanting	Downslanting
Epicanthal folds	Frequent	Not present	Not present	Present	Not present
Eyebrows	Heavy, high arched	Heavy	Heavy	Heavy	Heavy
Eyelashes	Long	Normal	Long	Long	Long
Strabismus	Frequent	Present	Present	Discrete	Present
Nose					
Shape	Prominent, beaked	Prominent	Beaked	Prominent	Prominent
Columella	Long, deviated	Long	Long	Long	Long, deviated
Mouth					
Lips	Short upper lip, pouting lower lip	Pouting lower lip	Small lips	Pouting lower lip	Short upper lip
Mandible	Retrognathia, micrognathia	Retrognathia	Normal	Retrognathia	Normal
Dental findings	Crowded teeth, increased caries, talon cusps	Crowded	Crowded Marked caries	Crowded Talon cusps	NR
Ears	Abnormality in position, rotation, size	Posteriorly rotated	Posteriorly rotated	Posteriorly rotated	NR
Cardiac abnormalities	Frequent PDA, VSD, ASD	Normal	Asymmetric aortic valve	Normal	NR
Genitourinary system	Kidney anomalies, incomplete descent of testes	Cryptorchidism	Synechia of labia majora	Normal	NR
Mental development					
Cognitive abilities	IQ range 30–80	Nearly normal	Moderate MR	Slight MR	Slight MR
Language	Speech delay	Normal	Severely impaired	Speech delay	Normal
Behaviour	Distractability, resistance to change	Hyperactive	Hyperactive	Normal	NR
Personality	Usually friendly but aggressive outbursts	Very sociable	Very sociable	NR	NR

ASD, atrial septal defect; BL, birth length; BW, birth weight; CBP, CREB-binding protein; GH, growth hormone; PDA, patent ductus arteriosus; MR, mental retardation; NR, not reported; RSTS, Rubinstein–Taybi syndrome; VSD, ventricular septal defect.

predicted aberrant protein of 648 amino acids instead of 2415 amino acids of the full-length protein. The aberrant protein was missing various domains, such as the histone acetyl transferase domain. Analysis of the parents showed that the mutation had occurred de novo. Patient 2 was carrying a de novo deletion of a C at position 3625 in exon 20, inducing a frameshift (p.Q1209fsX1226). Analysis of patient 3 revealed a de novo deletion of eight base pairs at position c.2877–2884 in exon 15, inducing a frameshift (p.S959fsX966). The deletion in patient 4 (149-1) was identified by multiplex ligation-dependent probe amplification.^{5 11} Molecular analysis revealed a deletion of exon 1 in two independent screenings (c.1200-?_94+?del). Another screening was performed with additional probes annealing to the promoter region and to the first intron of the *EP300* gene. This screening confirmed the initial results and indicated that the deletion stretched from at least the promoter region to intron 1. Exon 2 was not deleted but the extent of the deletion at the 5' end was not determined.

Case reports

Patient 1 (254-1), 22-year-old man

Clinical history

Patient 1 is the only child of a healthy couple. Amniocentesis (advanced maternal age) revealed a normal male karyotype (46, XY). Delivery occurred by caesarian section 3 weeks before term. Weight at birth was 3010 g (P50), length was 46 cm (P10–50) and occipitofrontal circumference (OFC) 31 cm (<P10). Postnatal growth was normal, although OFC remained below the third centile. Motor milestones were reached in time (sitting without aid at 9 months and standing at 12 months), but cognitive development was delayed (first words at the age of 24 months). Neurological examination at the age of 12 months showed muscular hypertonia with discrete signs of spastic paraplegia. The boy had recurrent respiratory infections during the initial years of life. Bilateral cryptorchidism was surgically corrected at the age of 5 years. He was a hyperactive child with good expressive language skills and was described as

logorrhoeic, oversociable and always smiling. Developmental assessment at the age of 12 years revealed a dissociated profile with almost normal cognitive abilities but puerile behavioural traits. His IQ at that age was 86 (assessed by the Hamburg Wechsler intelligence III test, verbal subscore 87, performance subscore 89). He became overweight after puberty. Le Fort osteotomy was performed at the age of 18 years to correct a malocclusion of the teeth. His height was within normal ranges in both childhood and adulthood (178 cm at the age of 22 years; fig 1).

Somatic findings at the age of 4 years

He showed moderate microcephaly with a sloping forehead and a rather small maxilla. Additional findings were downslanting palpebral fissures, bushy eyebrows, a prominent nose with a long septum (extending below the alae), pouting lower lip and a narrow palate with irregularly positioned teeth (especially upper row). The ears were posteriorly rotated and the helix was slightly hypoplastic. He had one café-au-lait spot and one capillary hemangioma on the leg and multiple naevi on the face and thorax. The thumbs were normal in size and configuration.

Discrete clubbing of the distal phalanges and pronounced fetal finger pads were observed. The feet were flat with broad halluces without angulation. No sandal gaps, but slightly overlapping toes were observed.

Patient 2 (276-1), 8-year-old girl

Clinical history

Patient 2 is the first child of healthy non-consanguineous parents. Pregnancy was complicated by a urinary tract infection of the mother, and caesarian section was performed owing to pre-eclampsia in the 36th week of gestation. Weight at birth was 2070 g (<P10), length was 44 cm (on P10) and OFC was 31 cm (P10–50). The girl had neonatal respiratory difficulties and pronounced gastro-oesophageal reflux. Facial dysmorphism was noted but no classification was achieved. During the first few months, length and weight stabilised between third and tenth centiles but she developed moderate microcephaly. ECG revealed an asymmetric aortic valve. The girl had chronic constipation. Recurrent urogenital infections occurred, and synchia of the labia majora were diagnosed. Motor

Figure 1 (A–D) Patient 1 at the age of 10 years. (A, B) Note microcephaly, sloping forehead, downslanting palpebral fissures, bushy eyebrows, prominent nose with low columella and retroposition of lower jaw. (C, D) Note normal thumbs and prominent fetal finger pads. (E, F) The hands and feet of the patient at the age of 22 years. Note pes planus, broad halluces, short fifth digits and slightly overlapping toes on the left foot. Informed consent was obtained for publication of this figure.

milestones and cognitive development were delayed (sitting at 12 months, walking at 18 months and first words at 2 years). She was a hyperactive child who displayed very poor expressive language skills with echolalia. Her IQ was 55 (assessed at the age of 6 years by the Kaufman Assessment Battery for Children test, subscore values were not available). Her parents report episodes of hyperventilation and stereotypic hand movements (flapping). She was reported to be a cheerful girl with a very sociable personality (fig 2).

Somatic findings at the age of 8 years

Height was 115 cm, weight was 18 kg (both <P3) and she exhibited moderate microcephaly (OFC 48 cm, 8 mm <P3). She had a round face with hypoplastic maxilla, downslanting palpebral fissures, strabismus divergens, bushy eyebrows and long eyelashes. Additional findings included a sharp nose with a long columella and a featureless philtrum, short upper lips and irregularly positioned teeth. The ears were asymmetrical and posteriorly rotated. Hands and feet were normal, and thumbs and halluces were neither broad nor angulated. She showed generalised hypertrichosis.

Patient 3 (256-1), 7-year-old girl

Clinical history

No detailed information was available for patient 3 (fig 3).

Somatic findings at the age of 6.5 years

Height was 106.8 cm (<P3), weight 19.9 kg (P25) and OFC 46.2 cm (2 cm <P3). She had a round face with chubby cheeks, highly arched eyebrows and down slanting palpebral fissures. Additional findings were long eyelashes and high myopia (−15 D). The columella extended well below the alae. She had a pouting lower lip, highly arched palate and four talon cuspids on the upper incisors, which were also clearly visible on panoramic radiographs. The ears were posteriorly rotated and the helix was thickened. She displayed a discrete grimacing smile. Her hands had short distal phalanges and mild broadening of the thumbs was obvious. Radiographs revealed irregular ossification of the distal phalanges but normal configuration of the first metacarpal bones. Her feet showed proximally implanted and broad halluces, and splaying of the other toes. On radiographs, it became obvious that this was due to a very short and broad first metatarsal bone with an

Figure 2 Patient 2: (A, B) downslanting palpebral fissures, strabismus, long eyelashes, sharp nose with a long septum, featureless philtrum, hypoplastic maxilla and thin lips. (C–E) Normal hands and feet. Informed consent was obtained for publication of this figure.

Figure 3 Patient 3. (A) Note the short distal phalanges and mild broadening of the thumbs. (B) The hallux is proximally implanted and broad. (C) Note the short and broad first metatarsal bone, and partial duplication of the distal phalanx of the hallux. Informed consent was obtained for publication of this figure.

additional proximal epiphysis on the inside, giving rise to a delta shape. Also partial duplication of the distal phalanx of the hallux was found, and she had cone-shaped epiphyses of the proximal third and fourth phalanxes, as well as of the medial second and third phalanx. Furthermore, irregular ossification of the medial and distal phalanges was noted.

Patient 4 (149-1), 27-year-old man

Clinical history

Patient 4 is the child of healthy parents. Owing to the typical facial gestalt, the diagnosis of RSTS was already suspected in early childhood. The boy had complex febrile seizures and was treated with antiepileptic drugs for several years. He showed

postnatal growth retardation and was diagnosed as having growth hormone deficiency at the age of 9 years. He underwent hormonal replacement therapy until the age of 11 years. In the following years he was also diagnosed as having coeliac disease, and a gluten-free diet was established. At the age of 16 years he had an episode with severe oesophagitis causing chronic anaemia. Cognitive development was delayed from early on and the boy needed special education. He is now living in a sheltered environment (fig 4).

Somatic evaluation at the age of 27 years

The patient showed downslanting palpebral fissures, strabismus, heavy eyebrows and long eyelashes. The nose was prominent with deviation of the nasal septum that extended below the alae nasi. His upper lip was thin and he displayed a discrete grimacing smile. His hands were rather broad and the fingers were short. The configuration of the thumbs was normal. He had slightly broad halluces without angulation. No other irregularities were observed on the hands and feet.

DISCUSSION

RSTS is a dominantly inherited syndrome characterised by short stature, typical face, broad (and often angulated) thumbs and halluces, and mental retardation. About 50% of patients with classic RSTS carry deletions or mutations of *CBP*; in the remainder, the genetic basis remains undetermined. Recently, we could demonstrate mutations in the *EP300* gene in a small number of patients with RSTS, thus proving genetic heterogeneity.⁵ This raised the question of phenotypic differences between patients with RSTS harbouring *EP300* mutations as compared with those harbouring *CBP* mutations or the mutation-negative patients. We therefore performed a thorough analysis of the features and clinical course of the four patients with *EP300* mutations identified so far. The analysis showed that all four patients displayed most of the classic facial RSTS features, such as downward slanting palpebral fissures, a prominent nose with low-hanging nasal septum, a short upper lip and pouting lower lip. Also, they showed other manifestations typically associated with RSTS such as strabismus, hirsutism or genitourinary findings. The degree of mental retardation was variable, ranging from near-normal intellectual abilities (patient 1) to moderate mental retardation (patient 2). The combination of the facial gestalt with other features was compatible with the diagnosis of RSTS in all four patients. Interestingly, however, none of the patients with *EP300* mutations showed the classic combination of skeletal findings on both hands and feet (table 2). The two adult men (patients 1 and 4) showed moderately broad big toes, patient 3 showed an abnormally short first metatarsal bone of the hallux and duplication of the distal phalanx, and patient 2 showed normal feet. Strikingly, three of the four patients showed completely

Figure 4 Patient 4. (A) Note the bushy eyebrows, strabismus, long columella and deviation of the nasal septum. (B) Broad hand with mild brachyphalangy. (C) Mild broadening of the hallux. Informed consent was obtained for publication of this figure.

Table 2 Skeletal findings of patients carrying mutations of the *EP300* gene

<i>EP300</i> mutation identified	Patient 1 p.R648X	Patient 2 p.Q1209fsX1226	Patient 3 p.S959fsX966	Patient 4 c.1200-?_94+?del
Spine	Normal	Normal	NR	NR
Sternal or rib anomalies	None	None	None	NR
Hands				
Thumbs				
Broad thumbs	No	No	Yes	No
Short proximal phalanx	No	No	Yes	No
Radially deviated thumbs	No	No	No	No
Phalanges				
Broad/short terminal phalanges	No	No	Yes*	No
Clinodactyly of fifth fingers	No	No	No	No
Fetal finger pads	Yes	No	NR	NR
Feet				
Halluces				
Broad halluces	Discrete	No	Yes	Discrete
Radially deviated halluces	No	No	No	No
Duplicated phalanx	No	No	Yes†	No
Other findings	None	None	Yes‡	None
Toes				
Overlapping toes	Discrete	No	No	No
Splaying of toes	No	No	Yes	No
Pes planus	Yes	No	No	NR*

NR, not reported.

*Radiographs reveal irregular ossification of distal phalanges.

†Radiographs show partial duplication of the distal phalanx.

‡Very short and broad delta-shaped first metatarsal bone, leading to the proximal implantation of halluces.

normal thumbs without broadening or angulation. It is interesting to note that Rubinstein considered broad short thumbs and/or halluces as a prerequisite for the diagnosis.¹² In a large review on Dutch patients with RSTS, it was shown that broad thumbs are not seen in all patients with RSTS, but broad halluces are.¹³ In light of our observations on patients with *EP300* mutations, one might speculate that these differences are to a large extent due to genetic heterogeneity: patients with normal thumbs might rather carry mutations in *EP300* than in *CBP*.

Following this line, it is interesting to compare the phenotypes of transgenic mice, carrying either one inactive allele of the *CBP* or the *EP300* gene, with those of patients with RSTS. Mice lacking a single *CPB* allele or carrying a truncated form of the protein usually do not display skeletal abnormalities on their limbs, but show other skeletal manifestations present in patients with RSTS. These features include a large anterior fontanelle (due to delayed ossification of frontal bones), hypoplastic maxilla, abnormalities of the sternum and of the ribs.^{14, 15} By contrast, mice lacking one *EP300* allele do not show any skeletal malformations at all.¹⁶ These findings are in accordance with our observation on a milder skeletal phenotype in patients with *EP300* mutations compared with patients with classic RSTS.

Depending on the selection of the patients, the detection rate of *CBP* mutations in RSTS is 40–60%.^{5–7} We determined in our sample that *EP300* mutations are 10 times less frequent than *CBP* mutations.⁵ The unidentified mutations could reside in

parts of the two genes that were not screened—such as non-coding regulatory sequences—or in yet unidentified new RSTS genes. Although patients with *EP300* mutations might represent only a minority in RSTS, this diagnosis should not be missed: *CBP* and *EP300* are both implicated in cancerogenesis, and a germline mutation in either gene might increase the risk of developing a tumour.

In summary, we show that the skeletal phenotype of patients carrying germline mutations in *EP300* might differ from the classic picture observed in RSTS, and that this diagnosis must also be considered in patients without broad thumbs or halluces. Although the number of known patients is too small to draw firm conclusions, our findings suggest that at least part of the variability in RSTS is explained by the genetic heterogeneity and not by the variable expression of given mutations in one gene. More patients with *EP300* mutations have to be identified to confirm this hypothesis. Finally, our observations confirm that *CBP* and *EP300* play unique roles in vivo, despite their high degree of homology. However, the exact mechanism of how *CBP* or *EP300* deficiency leads to the specific RSTS phenotypes in humans still remains to be determined.

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Competing interests: None.

Informed consent from the patients (patients 1 and 4) or their parents (patients 2 and 3) was obtained for publication of the photographs.

Key points

- This is the first paper describing the phenotype of patients carrying germline mutations of *EP300*.
- Part of the clinical variability in Rubinstein-Taybi syndrome (RSTS) is explained by genetic heterogeneity.
- The diagnosis of RSTS must be extended to patients without broad thumbs or halluces.

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