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ORIGINAL INVESTIGATION

Evidence for a new contiguous gene syndrome, the chromosome 16p13.3 deletion syndrome alias severe Rubinstein–Taybi syndrome

Oliver Bartsch · Sasan Rasi · Alicia Delicado · Sarah Dyack · Luitgard M. Neumann · Eva Seemanová · Marianne Volleth · Thomas Haaf · Vera M. Kalscheuer

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Abstract Rubinstein–Taybi syndrome (RSTS) is a well-known autosomal dominant mental retardation syndrome with typical facial and skeletal abnormalities. Previously, we have reported two patients presenting with RSTS and additional clinical features including failure to thrive, seizures, and intractable infections (Bartsch et al. in Eur J Hum Genet 7:748–756, 1999). Recently we identified a third patient with this condition, termed here severe RSTS, or chromosome 16p13.3 deletion syndrome. The three patients died in infancy, and all displayed a specific mutation, a chromosomal microdeletion including the 3′-end of the *CREBBP* gene. Using fluorescence in situ hybridization and closely spaced DNA probes, we characterized the deletion intervals in these patients and in three individuals with a deletion of *CREBBP* and typical RSTS. The deleted DNA segments were found to greatly vary in size, spanning from ~40 kb to >3 Mb. Four individuals, including the patients with severe RSTS, exhibited deletions containing gene/s in addition to *CREBBP*. The patients with severe RSTS all had deletions comprising telomeric neighbor genes of *CREBBP*, including *DNASE1*, a dominant gene encoding a nuclease that has been associated with systemic lupus erythematodes. Our findings suggest that severe RSTS is distinct from RSTS and represents a novel true contiguous gene syndrome (chromosome 16p13.3 deletion syndrome). Because of the risk of critical infections and high mortality rate, we recommend that the size of the deletion interval should be determined in *CREBBP* deletion-positive patients with RSTS, especially in young children. Further studies are needed to delineate the clinical spectrum of the new disorder and to clarify the role of DNASE1.

O. Bartsch (✉) · S. Rasi · T. Haaf
Institute for Human Genetics, Mainz University School of Medicine, 55101 Mainz, Germany
e-mail: bartsch@humgen.klinik.uni-mainz.de

A. Delicado
Genética Médica, Hospital Universitario "La Paz", 28046 Madrid, Spain

S. Dyack
IWK Health Centre, Dalhousie University, Halifax, NS, Canada B3K 6R8

L. M. Neumann
Institute of Human Genetics, Charité Campus Virchow-Klinikum, 13353 Berlin, Germany

E. Seemanová
Institute of Medical Biology and Genetics, 2nd Medical School, Charles University, 15006 Prague 5, Czech Republic

M. Volleth
Institute for Human Genetics, Otto von Guericke University, 39120 Magdeburg, Germany

V. M. Kalscheuer
Max-Planck Institute for Molecular Genetics, 14195 Berlin, Germany

Introduction

Rubinstein–Taybi syndrome (RSTS, MIM 180849) is a well known autosomal dominant disorder with an estimated prevalence of 1/125,000 live births (Hennekam et al. 1990; Wiley et al. 2003). Along with the ATRX spectrum of disorders and the ICF, Rett, and Coffin–Lowry syndromes, the RSTS belongs to the group of "chromatin disorders", that are caused by alterations

of proteins modifying the chromatin structure (Hendrich and Bickmore 2001). Frequent clinical features include postnatal short stature, microcephaly, typical face with low hairline, dense hair, beaked ("Cyranotype") or straight nose, hypoplastic alae nasi, broad thumbs and great toes with radial angulation, and mild to moderate mental retardation (Rubinstein 1990; Wiley et al. 2003). Other features include coloboma, cardiac anomalies, keloid formation in scars, and increased risk of tumor formation.

Following the observation of patients with RSTS and cytogenetic rearrangements at chromosome 16p13.3 or submicroscopic deletions within 16p13 (Imaizumi and Kuroki 1991; Breuning et al. 1993), RSTS was found to be caused, in most cases, by heterozygous molecular mutations in the *CREBBP* gene (MIM 600140) (Petrij et al. 1995; Coupry et al. 2002; Bartsch et al. 2005). A smaller subset of patients, around 8–12%, demonstrated *CREBBP* gene deletions (Breuning et al. 1993; Bartsch et al. 1999) or exon deletions (Coupry et al. 2004) and recently, *EP300* gene mutations were identified as another, rare cause of RSTS in ~3% of patients (Roelfsema et al. 2005).

There has been some controversy whether RSTS represents a single phenotype with only minor variation between patients (Rubinstein 1990; Wiley et al. 2003), or a clinical spectrum of milder and more severe phenotypes. Towards the mild end of the spectrum, we have recently proven the "incomplete RSTS" by identifying milder (missense) *CREBBP* mutations among these patients (Bartsch et al. 2002, 2005). Phenotypes were similar to RSTS but with either normal intelligence, normal stature, less typical facial appearance, and/or atypical skeletal changes (Cotsirilos et al. 1987; Bartsch et al. 2002, 2005). At the severe end of the spectrum, there have been reports of children with RSTS and serious complications resulting in death within the first 2 years of life (Kimura et al. 1993; Bartsch et al. 1999). Previously, we have reported *CREBBP* gene deletions in two of these patients (Bartsch et al. 1999). Here we identify another case of RSTS and death in infancy associated with a *CREBBP* gene deletion.

We report here the first study of 16p13.3 deletion intervals in patients with severe RSTS. We determined the deletion intervals of three patients with severe RSTS and three individuals with typical RSTS. Patients with severe RSTS had contiguous gene deletions involving up to 3 Mb, all of which included *CREBBP* and *DNASE1* (gene for deoxyribonuclease I, MIM 125505), a dominant distal neighbor gene of *CREBBP* implicated in systemic lupus erythematodes (SLE, MIM 152700). Deletions restricted to *CREBBP* were associated with typical RSTS, which is not surprising.

Materials and methods

Patients

The research was approved by the responsible Ethics Committee. Nine individuals with *CREBBP* gene deletions (including six previously reported patients: Bartsch et al. 1999, 2002: patients A–D, 9, and 10) were identified in the course of diagnostic fluorescence in situ hybridization (FISH) analyses in a total of 190 unrelated patients with either a definitive or a tentative diagnosis of RSTS and normal GTG-banded karyotypes. Of these, six had typical RSTS and three presented with RSTS and additional clinical signs ("severe RSTS"; life-threatening malformations, failure to thrive, and/or critical infections). The latter three patients all died in their first year of life. Materials for this study were available from the three patients with severe RSTS (Bartsch et al. 1999, 2002: patients A, B, and 9) and from three novel deletion-positive patients with typical RSTS.

FISH analysis

FISH was performed using standard metaphase spreads from peripheral blood lymphocytes or from EBV-transformed lymphoblastoid cells. DNA probes (Table 2) included four cosmids for the *CREBBP* gene, RT100, RT191, RT203, and RT166, (Bartsch et al. 2002) and 19 BACs covering a 4.2 Mb region around the *CREBBP* gene. BACs were obtained from the Children's Hospital Oakland Research Institute (http://www.chori.org/) and the Resource Center of the German Human Genome Project. Amplification of cosmid/BAC DNA and labeling of probes was performed using standard degenerate oligonucleotide primed polymerase chain reaction (DOP PCR) or using DOP shuttle PCR as previously described (Bartsch et al. 1999; Zhu et al. 2004).

Results

Clinical reports

Clinical features are summarized in Table 1. All parents were healthy and non-consangineous and all family histories were unremarkable. Probands 1 and 2 with severe RSTS were previously reported (Bartsch et al.

Table 1 Clinical features of RSTS patients in this study

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patients with RSTS (Rubinstein 1990)
Gender	F	M	M	M	F	F	46% F, 54% M
Rare or uncommon features							
Death in infancy	Yes, died at 5 weeks of age	Yes, died at 7 months of age	Yes, died at 9 months of age	No, alive and well at the age of 14 years	No, alive and well at the age of 16 months	No, alive and well at the age of 13 months	–
Failure to thrive	+	+	+	–	–	–	–
Life-threatening infections	+	+	+	–	–	–	–
Severe neonatal convulsions, multifocal hypsarrhythmia	–	+	–	–	–	–	–
Hypoplastic left heart	+	–	–	–	–	–	–
Polysplenia, disturbance of laterality	+	–	–	–	–	–	–
Anteriorly placed anus	–	–	–	–	–	+	–
Typical features							
Microcephaly (<2nd percentile)	+	+	+	–	–	–	94%
Facial hypertrichosis, dense hair	+	+	+	+	+	+	100%
Down slanting palpebral fissures	+	+	+	–	+	+	90%
Prominent beaked or straight nose	+	+	+	+	+	NK	93%
Columella below the alae nasi	+	+	+	+	+	+	78%
Highly arched palate	+	+	NK	+	+	+	93%
Receding chin	+	+	+	+	+	+	75%
Broad thumbs or halluces	+	+	+	+	+	+	100%
Congenital heart defect	+	+	–	–	–	+	34%
Kidney a bnormality	+	–	+	–	–	+	52%
Feeding difficulties in infancy	+	+	+	–	–	+	77%
Hypotonia, lax ligaments	+	+	+	+	+	+	70%

NK Not known

1999: patients A and B). Proband 3 was previously reported with RSTS at the age of 6 weeks (Bartsch et al. 2002: patient 9). Following failure to thrive and numerous severe respiratory infections, he died of pneumonia at the age of 9 months. Further information was not available.

Proband 4 was born at 41 weeks of gestation. Length was 47 cm (25th percentile), weight 2,550 g (10th

prcentile), and OFC 32.5 cm (25th percentile). He had a long philtrum, thin upper lip, narrow highly arched palate, micrognathia, large malformed ears, short fingers, and broad thumbs. He also had undescended testes, hypertrichosis, a hypoglycemic episode on day three of life, and pedal edema resolving in his first week of life. Cerebral ultrasound was normal, and renal ultrasound indicated mild pyelectasis on the left. He first walked at the age of 3 years. When seen again at 14 years, height was 150 cm (10th percentile), weight 44 kg (body mass index 19.5 kg/m^2), and OFC 52.4 cm (3rd to 10th percentile). He showed full eyebrows, long palpebral fissures, epicanthal folds, prominent beaked nose, dental malocclusion, broad thumbs and halluces, and had moderate mental retardation.

Proband 5 was diagnosed with RSTS at the age of 4 weeks. At the age of 10 weeks, length was 57 cm (75th percentile), weight 4,930 g (75th percentile), and OFC 36 cm (3rd to 10th percentile). She had dense scalp hair with low anterior and posterior hairlines, a capillary hemangioma on the forehead, downslanting palpebral fissures, highly arched palate, straight nose, micrognathia, bilateral incomplete simian creases, widely spaced nipples, broad thumbs with radial angulation, broad great toes, and a cavernous hemangioma on the right labia majora. She also had mild hypotonia, but no feeding difficulties. Cerebral and abdominal ultrasounds and hearing tests were normal. At the age of 12 months, her family doctor noted good health, normal length and weight (3rd to 10th percentile), microcephaly (OFC 41 cm, −3.5 SD) and a motor development corresponding to an age of 6 months. When recently seen at the age of 16 months, she was in good physical condition.

Proband 6 was born at 38 weeks of gestation. Length was 47 cm (25th percentile), weight 2,880 g (25th to 50th percentile), and OFC 33.5 cm (50th percentile). At 4 days of age she was transferred to a tertiary care center because of respiratory distress. She was hirsuite and had a low posterior hairline, generous fontanelles, downslanting palpebral fissures, hypoplastic alae nasi, columella below her nares, micrognathia, a highly arched palate, and overfolded superior pinnae. She also had broad thumbs with mild medial deviation, broad first toes, hypoplastic toenails, and an anteriorly placed anus. At 5 weeks of age she had a urinary tract infection and was treated with trimethoprim-sulfamethoxazole. At 13 weeks of age, cerebral and abdominal ultrasounds revealed a partially absent corpus callosum, moderate to severe hydronephrosis on the right, and a bilateral duplication of the collecting system. Skeletal X-rays showed broad terminal first phalanges of thumbs and great toes and a bifid sacrococcygeal segment. She had a patent ductus arteriosus requiring surgical closure, bilateral retinal colobomas, and hearing loss in her left ear. At the age of 13 months she had muscular hypotonia and chronic constipation, but was thriving, alert and attentive. Length was 66 cm (<3rd percentile), weight 7,900 g (<3rd percentile), and OFC 43.5 cm (3rd percentile).

FISH mapping of deletions

Cosmid and BAC probes from the critical 16p13.3 region were hybridized to metaphases (Fig. 1) of the six probands in order to delineate the deletion regions. The results are summarized in Table 2. All deletions were heterozygous. The smallest deletion was ~40 kb in size (proband 5) and the largest spanned >3,000 kb (proband 3) (Fig. 2). The 16p telomere was always present on the deleted chromosomes. The most telomeric breakpoint was found ~1,000 kb distal to *CREBBP* (proband 2) and the most centromeric breakpoint was >2,700 kb proximal to *CREBBP* on chromosome 16p13.2 (proband 3). In probands 4 and 5 with typical RSTS the deletions were restricted to the *CREBBP* gene. In contrast, probands 1–3 with severe RSTS and proband 6 had deletions including *CREBBP* and at least three other genes (Table 2, Fig. 2). The region of overlap that is deleted in patients 1–3 with severe RSTS, but present in probands 4–6 with typical RSTS, contains the genes *DNASE1* and *TRAP1* (gene for tumor necrosis factor type 1 receptor associated protein, MIM 606219).

Discussion

Here, nine out of 190 patients with a tentative diagnosis of RSTS or definitely RSTS displayed 16p13.3 deletions and of these, three patients had critical infections and died in their first year of life ("severe RSTS"). Early death is unusual in RSTS; prior to the 1970s many patients with RSTS died of cardiac defects and respiratory infections (Hennekam et al. 1990; Rubinstein 1990; Wiley et al. 2003), but apart from our three patients, we are aware of only two other cases from recent years, a 20-month old boy with absent thymus who died of intractable respiratory infections (Kimura et al. 1993) and a newborn with hypoplastic left heart who died on his fifth day of life during palliative surgery (Hanauer et al. 2002). The former patient was not evaluated for *CREBBP* deletions or molecular mutations, and the latter (Hanauer et al. 2002) had a normal FISH test with the cosmid probe RT1.

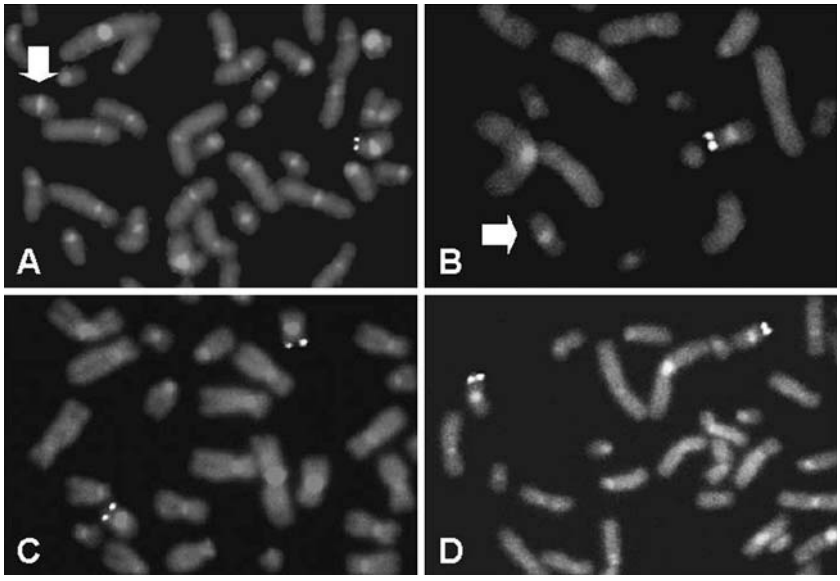

Fig. 1 **a-d** Partial metaphase spreads hybridized with different BAC probes, chromosomes are counterstained with DAPI. **a**, **b** Patients 2 and 6 hybridized with BACs 951C12 and 295D4, respectively. FISH signals are present on only one of the two homologous chromosomes 16. *Arrows* indicate the homologues 16 with a deletion. **c**, **d** Patients 2 and 6 hybridized with BACs 489J2 and 19H6, respectively. FISH signals are seen on both chromosomes 16

Our observations indicate a higher mortality rate among individuals with RSTS and *CREBBP* deletion (3 of 9) than among the other patients in this series (0 of 181). The difference in mortality is also significant when the *CREBBP* deletion RSTS patients (3 in 9) are compared to the patients with RSTS and proven molecular mutation (0 in 19) (Bartsch et al. 2005) (Fisher's exact test; $P < 0.05$). These differences strongly suggest that large (contiguous gene) deletions involving neighbor gene/s of *CREBBP* lead to a higher mortality rate than those mutations that are restricted to *CREBBP*. Here we refer to this novel contiguous gene syndrome as "16p13.3 deletion syndrome" or "severe RSTS".

Previous studies of patients with RSTS indicated 16p13.3 deletions sized up to 560–650 kb and including the 5′- and 3′-flanking regions of *CREBBP* (Petrij et al. 1995, 2000; Coupry et al. 2002, 2004). This study demonstrates differences between the various 16p13.3 deletions in patients with either RSTS or severe RSTS. The sizes of the deletions ranged from 40 kb (patient 5) to 800 kb (patient 6) in typical RSTS, and from 400 kb (patient 1) to >3,000 kb (patient 3) in severe RSTS. Deletions of patients with severe RSTS all included distal (3′-flanking) neighbor genes to *CREBBP* (*TRAP1*, *DNASE1*), and the >3,000 kb deletion and the 2,700 kb deletion (patient 2) in these patients represent the largest 16p13.3 deletions reported so far. Breakpoints were located from ~1,000 kb distal to to ~2,700 kb proximal to the *CREBBP* gene; each patient had different, private breakpoints.

All four contiguous gene deletion-positive patients in this study presented clinical features uncommon to RSTS (Rubinstein 1990; Wiley et al. 2003), including hypoplastic left heart, polysplenia and other laterality defects, and necrotizing enterocolitis (patient 1), neonatal epilepsy (patient 2), serious infections (patients 2 and 3), failure to thrive (patient 3), and anteriorly placed anus (patient 6). Patients 1–3 (severe RSTS) shared a deletion overlap at *CREBBP*, *TRAP1*, and *DNASE1* (Fig. 2, Table 2), and patients 4–6 (clinically diagnosed with typical RSTS) showed no deletion at *TRAP1* and *DNASE1*. Human TRAP1 is a mitochondrial ATP-binding protein that may possibly function in a chaperone pathway involved in mitochondrial import or apoptosis (Felts et al. 2000) and to our knowledge, TRAP1 has not been associated with human disease. *DNASE1* mutations have been associated with SLE, a disorder of the autoimmune system leading to an increased rate of infections (Yasutomo et al. 2001). Moreover, experimental evidence suggests that in SLE, increased CREM (cAMP-responsive element modulator) may sequester the transcription coactivators CREBBP and p300, thereby making them unavailable for CREB and other transcription factors (Solomou et al. 2001). Hence, *DNASE1* is a strong potential candidate for some of the additional features in the patients with 16p13.3 contiguous gene deletions. DNASE1 deficiency and reduced clearance of nuclear DNA–protein complexes after cell death may propagate general vasculitis, a mechanism potentially explaining the failure to thrive, serious infections, and epilepsy in patients 2 and 3. In patient 1 (hypoplastic left heart and necrotizing enterocolitis), the contribution of gene/s apart from *CREBBP* to her serious clinical course and death remains equivocal. Cardiac anomalies are frequent in RSTS (32.6% of patients, Stevens and Bhakta 1995), and hypoplastic left heart

Table 2 DNA probes and results of FISH

Clone	Distance from 16pter (Mb)[a]	Chromosome band or marker[a]	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
BAC RP11-20I23	2.425–2.583	AC093525, *CGI-14*, *PDPK1*, *ATP6V0C*	+	+				
BAC RP11-67B18	2.476–2.655	AC146517		+				
BAC RP11-951C12	2.609–2.815	AQ724027 to AQ723946		–				
BAC RP11-473M20	2.978–3.158	AC108134, *MMPL1*, *TNFRSF12A*, *MMP25*, *CLDN6*, *CLDN9*, *NK4*		–				
BAC RP11-74N16	3.139–3.292	AQ268787 to AQ268784	+	–				
BAC RP11-433P17	3.292–3.471	AC025283, *ZNF597*, *OR2C1*, *ZNF434*, *ZNF75A*, *ZNF174*, *FLJ14154*	+	–	+	+	+	
BAC RP11-6C20	3.515–3.680	B49362 to B49363, *BTBD12*, *DNASE1*, *TRAP1*	–			+		
BAC RP11-103P19	3.532–3.727	AQ314485 to AQ314487, *NOD3*, *DNASE1*, *TRAP1*, *CREBBP* exons 31-27	–		dim	+		+
Cosmid LANL-RT100	3.714–3.755	*CREBBP* exons 31-17	–	–	–	–	+	–
Cosmid LANL-RT191	3.761–3.801	AC004509, *CREBBP* exons 13-3	–	–	–	–	+	–
Cosmid LANL-RT203	3.800–3.836	*CREBBP* intron 2-3, exon 3	–	–	–	–	+	–
Cosmid LANL-RT166	3.841–3.879	CREBBP exons 2-1	–	–	–	–	–	–
BAC RP11-95J11	3.800–3.965	AC007151, *CREBBP* exons 3-1, *ADCY9* exons 11-10	dim	–		dim	dim	–
BAC RP11-95P2	4.114–4.289	AC009171, *SRL*, *TFAP4*	+	–	–	+	+	–
BAC RP11-295D4	4.289–4.461	AC012676, *MAGM*, *DNAJA3*	+	–		+	+	–
BAC RP11-35P16[b]	4.441–4.599	AC007606, *HMOX3*, D16S2980	+	–	–	+	+	–
BAC RP11-554K21[b]	4.526–4.691	AC013282, *MGRN1*						dim or +
BAC RP11-605C23[b]	4.647–4.852	AQ358284 to AQ358202						+
BAC RP11-61L4[b]	4.797–4.966	AC027687, *UBN1*, D16S2903, *PPL*	+	–		+	+	+
BAC RP11-382N13	5.146–5.365	AC074051, D16S3134, D16S2770	+	–	–			
BAC RP11-691J20	5.170–5.391	AQ614422 to AQ438535, D16S3327, D16S2770		–				
BAC RP11-489J2[b]	5.373–5.534	no data, D16S2839, D16S2988		+				
BAC RP11-19H6	5.726–5.907	AC012175, D16S784, D16S2822		+	–			+
BAC RP11-578P21	6.010–6.171	Chromosome 16p13.3, AC023829			–			
BAC RP11-468I15	6.457–6.616	Chromosome 16p13.2, AC007223, D16S506			–			

+ Not deleted, signal present at the deleted homologue of chromosome 16; – deleted, signal absent from the deleted homologue of chromosome 16; *dim* partially deleted, diminished signal intensity

[a] Data compiled December 2005 using the UCSC and the Ensembl Human Genome Browsers

[b] Human genome high-resolution BAC re-arrayed clone set (the "32 k cloneset"), http://www.bacpac.chori.org/pHumanMinSet.htm

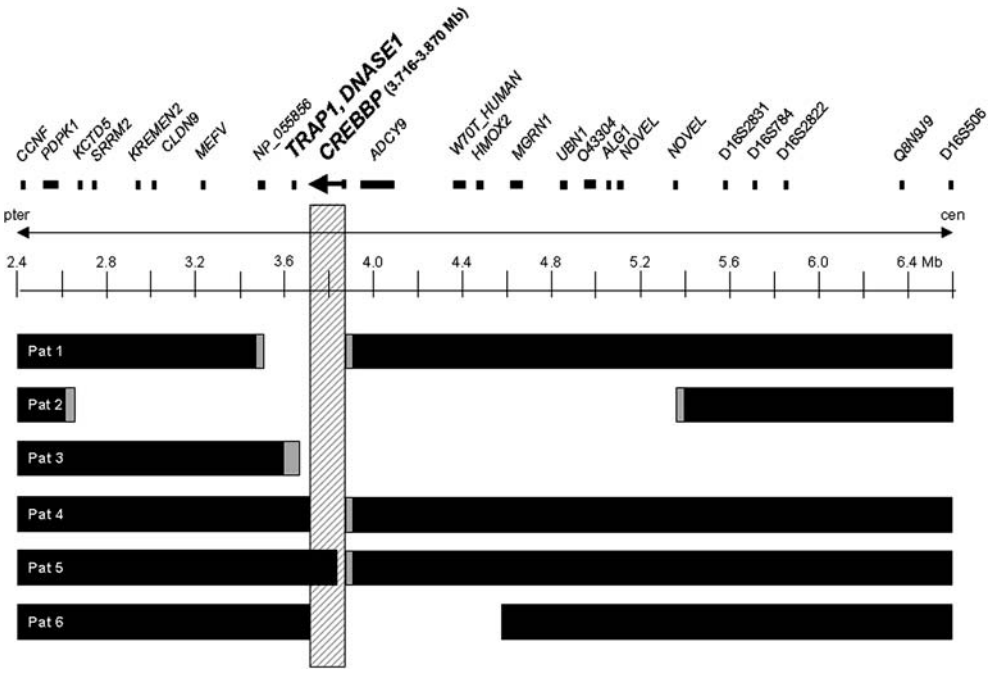

Fig. 2 Graphic representation of chromosome 16p13.3 deletions in patients 1–3 with severe RSTS and in patients 4–6 with classical RSTS. The *upper part* shows the position of genes and markers located in the critical region from 2.4 to 6.6 Mb on chromosome 16; the *vertical shaded bar* indicates the position of *CREBBP*. *Black bars* represent DNA segments present in patients. *Gray bars* represent partially deleted regions indicated by FISH signals with diminished intensity. *White areas* indicate deletions in patients

was reported in a boy with RSTS who died 5 days old with two normal hybridization signals using cosmid probe RT1 (Hanauer et al. 2002). However, the mutation in the boy remained unknown and his normal FISH test using probe RT1 does not rule out a partial deletion of *CREBBP* including neighbor genes.

In summary, we have outlined here a new contiguous gene syndrome, the 16p13.3 deletion syndrome or severe RSTS, characterized by the combination of RSTS, serious infections and other additional features, that results from large (contiguous gene) deletions involving *CREBBP* and, most likely, *DNASE1*. Further studies are needed to elucidate the potential role of DNASE1 in severe RSTS.

Electronic database information

Accession numbers and URLs for data presented herein are as follows: for genetic map, genomic sequences, cosmids, BACs, and genes: Ensembl Genome Browser, http://www.ensembl.org/ and UCSC Human Genome Browser, http://www.genome.ucsc.edu/cgi-bin/hgGateway; for the human genome high-resolution BAC re-arrayed clone set (the "32 k clone-set"): http://www.bacpac.chori.org/pHumanMinSet.htm; and for RSTS [MIM 180849], SLE [MIM 152700], *CREBBP* [MIM 600140], *DNASE1* [MIM 125505], and *TRAP1* [MIM 606219]: Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

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