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Deletion at Chromosome 16p13.3 as a Cause of Rubinstein-Taybi Syndrome: Clinical Aspects

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Summary

In the accompanying paper, a chromosomal localization of the Rubinstein-Taybi syndrome by cytogenetic investigations with fluorescence in situ hybridization techniques at chromosome 16p13.3 is described. We investigated 19 of these patients and their parents (*a*) to ascertain the parental origin of the chromosome with the deletion in families where such a deletion was detected, (*b*) to disclose whether uniparental disomy plays a role in etiology, and (*c*) to compare clinical features in patients with a deletion to those in individuals in whom deletions were not detectable. Molecular studies showed a copy of chromosome 16 from each parent in all 19 patients. Uniparental disomy was also excluded for five other chromosome arms known to be imprinted in mice. None of the probes used for determining the origin of the deleted chromosome proved to be informative. The clinical features were essentially the same in patients with and without visible deletion, with a possible exception for the incidence of microcephaly, angulation of thumbs and halluces, and partial duplication of the halluces. A small deletion at 16p13.3 may be found in some patients with Rubinstein-Taybi syndrome. Cytogenetically undetectable deletions, point mutations, mosaicism, heterogeneity, or phenocopy by a nongenetic cause are the most probable explanations for the absence of cytogenetic or molecular abnormalities in other patients with Rubinstein-Taybi syndrome.

Introduction

The Rubinstein-Taybi syndrome (RTS) is a well-known cause of mental handicap. It was first delineated in 1963 by J. Rubinstein and H. Taybi (Rubinstein and Taybi 1963). At present, more than 600 affected persons have been reported in the literature (Hennekam et al. 1990*a;* Rubinstein 1990). The prevalence at birth has been estimated to be 1/125,000 living newborns (Hennekam et al. 1990*a*). A teratogenic cause has been postulated to be the cause of the disorder, but an autosomal recessive pattern of inheritance, an autosomal dominant inheritance with variable expression, or multifactorial inheritance has also been stated to be possible (for review, see Hennekam et al. 1990*a*). Recently, it was concluded that an autosomal dominant mutation, either as a (sub)microscopic deletion or duplication or as a point mutation, is the most probable explanation for its cause (Hennekam et al. 1990*a*). As part of a broad survey of RTS patients in The Netherlands (Hennekam et al. 1990*a*, 1990*b*, 1990*c*, 1990*d*, 1991, 1992; Stevens et al. 1990), we investigated cytogenetically 24 patients, and, in 6 of them, a submicroscopic deletion at 16p13.3 was detected by fluorescence in situ hybridization (FISH) (see the accompanying paper [Breuning et al. 1993]). Here we report the results of molecular studies (*a*) to ascertain the parental origin of the deletion, (*b*) to investigate whether uniparental disomy plays a role in the etiology of RTS, and (*c*) to disclose

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whether there are clinical differences between patients with and without a detectable deletion.

Subjects, Material, and Methods

In 1985, one of us (R.C.M.H.) started a study of RTS patients living in The Netherlands. Criteria for inclusion were based on the combination of mental retardation and characteristics of the face, hands, and feet (Rubinstein 1990). A more detailed description of the criteria for inclusion and ascertainment is given elsewhere (Hennekam et al. 1990*a*). At present, 58 persons with RTS are located. Twenty-four of them were selected merely on the basis of accessibility and convenience of the patients. All patients were examined by the same clinical geneticist (R.C.M.H.) using a standardized protocol (Hennekam et al. 1990*c*). Nineteen of the patients have been reported before (Hennekam et al. 1990*c*). The major clinical characteristics of the patients are summarized in table 1. Blood sampling was also performed on the parents of 19 patients.

Genomic DNA was isolated from venous blood of patients and their parents, according to the method of Miller et al. (1988). To ascertain the parental origin of the chromosome 16 copies in each patient, the following highly polymorphic regions on chromosome 16 were analyzed: anonymous CA-repeat markers D16S261, D16S265, and D16S186 (table 2) and the polymorphic region adjacent to the downstream alpha-globin genes (Reeders et al. 1985). The analysis of CA-repeat markers was performed in a consecutive manner. First, all families were tested with marker D16S261. Next, those who were not informative for this marker were tested with D16S265. Finally, the remaining non-informative families were examined for D16S186. The actual analysis of these markers was performed according to the procedure of Weber and May (1989). In short, a polymorphic region was amplified by PCR in the presence of ^{32}P-dCTP (Amersham). The PCR products were then separated on a 6.6% denaturing polyacrylamide gel. Electrophoresis was for 3 h at 35 V/cm. After fixation by a 15-min incubation in a solution of methanol and acetic acid (10% each [v/v]), the gel was dried, and the individual bands were visualized on Kodak X-ray film by overnight autoradiography. The alpha-globin genes' polymorphic region was analyzed using the 3'HVR probe for Southern blot analysis (Reeders et al. 1985). With these methods we were able to deduce the parental origin of the chromosome 16 copies of affected persons by comparing the genotype of a patient with those of the parents. To investigate the possible contribution of uniparental disomy of other chromosomes to the etiology of RTS, in particular of those chromosomes that seem to be subjected to parental imprinting (Hall 1990), polymorphic repeat loci were selected for chromosomes 4, 6, 11, 15, 16, and 19 (table 2). Similar to the analysis of chromosome 16 markers, the analysis was performed in a consecutive manner, under the conditions described by Weber and May (1989). Other autosomes known to be imprinted in the homologous genomic regions of the mouse (Hall 1990) are still subject to further studies.

Results

Parental Origin of Deletions and Uniparental Disomy

Of the five patients with a detectable deletion examined with RFLPs, none is informative for parental origin (data not shown). To investigate the possible involvement of uniparental disomy for chromosome 16 in the etiology of RTS, 19 families were analyzed with highly polymorphic CA-repeat markers. With these markers one can easily discriminate between the normal biparental origin and iso- or heterodisomy of the chromosome 16 copies of a patient. Two examples of the analysis with marker D16S265 are shown in figure 1. In both families the affected child appears to be heterozygous, excluding possible uniparental isodisomy for this chromosome. Further, both the father and the mother have contributed an allele to the genotype of the child, thereby also excluding the possibility of uniparental heterodisomy. Altogether, three polymorphic markers—D16S261, D16S265, and D16S186 (table 2)—used in a consecutive manner were sufficient to obtain information on all families. Table 3 indicates, in detail, with which of these markers decisive information about possible uniparental disomy was obtained in each family. In all 19 cases studied here, a normal segregation of the chromosomes 16 was observed, excluding both maternal and paternal iso- and heterodisomy for chromosome 16 from the etiology of RTS in these patients. Since RTS may be heterogeneous (see Discussion), uniparental disomy has also been investigated for other autosomes known to be imprinted in mice (Hall 1990). When the marker loci listed in table 2 have been used in the same consecutive way as that employed for the chromosome 16 markers, no clue for abnormal segregation of paternal or maternal chromosomes has been found for chromosomes 4, 6, 11, 15, 16, and 19.

Relation between Deletion and Phenotype

The clinical features of the patients are outlined in table 1, and the six patients with a detectable deletion

Table 1

Comparison of Clinical Data of Six Patients with RTS and a Deletion at 16p13.3 versus Patients without Detectable Deletion and versus General Findings in Dutch Patients with RTS and in RTS Patients in the Literature

	Patient(s)								
	1	2	3	4	5	6	7–24 (%)	Dutch (n = 45) (%)	Literature (n = 571) (%)
General characteristics:									
Maternal age (years)	35.5	30.3	29.4	29.7	28.5	29.2	28.7	29.0	Unknown
Paternal age (years)	39.2	34.2	28.4	30.7	27.9	34.6	32.5	31.2	Unknown
Gender	F	F	M	F	F	M	7 F/11 M	26 F/19 M	46% F/54% M
Age (years)	3	13	19	20	36	37	Mean 24	Mean 18.1	Mean 4.5
Cognitive functioning[a]	45–50	25–30	<25	45–50	<25	<25	Mean 33	Mean 35.6	74% IQ<50
Length	<P3	P5	<P3	<P3	<P3	<P3	78%<P3	75%<P3	78%<P2
Head:									
Skull circumference	<P3	P25	<P3	P5	<P3	<P3	32%<P3	35%<P3	95%<P2
Prominent forehead	+	−	−	−	−	−	33	33	60
Heavy or highly arched eyebrows	−	+	+	+	−	+	84	74	68
Long eyelashes	+	+	+	−	+	+	83	87	51
Downward-slanted palpebral fissures	+	+	+	+	+	+	78	88	90
Prominent or beaked nose	−	+	+	+	+	+	79	94	93
Nasal septum below alae	+	+	+	+	+	+	84	93	78
Small-appearing mouth	+	+	−	−	+	−	89	84	56
Highly arched palate	+	+	+	+	+	+	94	89	93
Talon cusps	−	+	+	+	+	...[b]	63	27[c]/92[d]	No data
Retro/micrognathia	−	+	+	+	+	−	68	72	75
Ear abnormalities[e]	+	+	+	−	+	+	83	82	81
Hands:									
Broad thumbs	+	+	+	+	+	+	94	87	100
Radially deviated thumbs	+	−	+	−	−	+	53	33	48
Broad terminal phalanx of fingers	+	+	+	+	+	+	79	87	73
Clinodactyly	+	−	+	+	−	+	75	62	49
Feet:									
Broad halluces	+	+	+	+	+	+	100	100	100
Varus/valgus angulation of halluces	−	−	+	+	+	−	26	24	23
Duplicated halluces	−	−	+	−	+	+	5	11	16
Internal organs:									
Congenital heart defect	+[f]	−	−	−	−	−	37	24	34
Kidney abnormality	−	+[g]	−	−	−	−	21	17	52
Cryptorchidism	NA	NA	+	NA	NA	+	83	78	82
Other:									
Hirsutism	+	+	+	+	−	+	76	75	75
Stiff gait	−	+	+	−	+	+	60	85	87
Lax ligaments	+	+	+	+	+	−	82	82	70
Cervical hyperkyphosis	−	+	+	−	+	−	57	62	63
Clinical history:									
Feeding problems	+	+	+	+	+	+	75	71	77
Obstipation	−	+	+	−	+	−	43	58	54
Recurrent conjunctivitis	−	−	+	−	+	+	56	49	37
Recurrent respiratory infections	−	−	+	+	−	+	63	69	78
Electroencephalogram abnormalities	−	−	−	?	+	−	36	52	66

NOTE.—NA = Not applicable; P = percentile.

[a] Expressed as IQ.

[b] Edentulous at time of diagnosis. Patient is said to have had a "double row of teeth."

[c] Deciduous teeth.

[d] Permanent teeth.

[e] Mild abnormalities in position, rotation, size, or shape of the ears.

[f] Pulmonary valve stenosis and persistent ductus Botalli.

[g] Duplicated ureters; her urethra has an abnormal opening in the upper vaginal wall (female hypospadias).

Table 2

Simple Sequence Repeat Markers Used to Determine the Parental Origin of Specific Chromosomes in Patients with RTS

Locus	Map Position	Heterozygosity
D4S179	4p16.3	.23
D4S192	4q26-q34	.77
F13A1	6p25-p24	.78
D6S89	6p24-p23	.92
D6S105	6p	.79
IGF2R	6p25-q27	.58
D6S87	6q	.60
INT2	11q13	.85
D11S527	11q13.5	.88
D11S35	11q22	.88
CD3D	11q23	.74
D11S420	11q23.3-q24	.70
D15S10	15q11-q13	.50
CYP19	15q21.1	.91
D16S186	16q21	.57
D16S261	16q	.71
D16S265	16q	.77
D19S75	19q12-q13.1	.64
D19S47	19q13.1	.74
D19S180	19q	.75

NOTE.—Symbols and data are according to Williamson et al. (1991).

are illustrated in figure 2. None has any family history of relevance, and none of the parents are known to be consanguineous. All 24 patients are unrelated.

In addition to the data shown in table 1, patients 2 and 4 are known to have ankylosis of the distal interphalangeal joints of the thumbs and halluces. Patient 2 has, in addition, a menometrorrhagia. Patient 3 is suffering from severe sleep apnea caused by collapse of the laryngeal wall. Patient 4 has recurrent patella luxations. Patient 5 had surgical interventions because of bilateral buphthalmos and currently has severe myopia (−17) and cataract. Patient 6 is known to have a hypogonadotrophic hypogonadism and is still growing at age 37 years. Furthermore, he has a progressive, soft, and asymptomatic swelling of his lips and cheeks, which is more pronounced on the left and which resembles Melkersson-Rosenthal syndrome (Graff-Radford 1981).

The presence or absence of each cardinal manifestation has been analyzed in relation to the deletion at 16p13.3. For better comparison, the data from an earlier study of Dutch patients with RTS (Hennekam et al. 1990*c*) and from a recent survey of the literature (Rubinstein 1990) are added to table 1. There are only a few differences in clinical characteristics between patients with and without a detectable deletion. Four of the six with a deletion have a true microcephaly (skull circumference smaller than 2 SDs below the mean). This is found in only one-third of the other patients. This difference is even more expressed if one takes into account the age at measurement, as microcephaly is more frequent in infancy and childhood compared with adulthood (Stevens et al. 1990). This may also be the explanation for the difference in incidence of microcephaly between Dutch patients and the study of the literature (Rubinstein 1990). Other anthropometric measurements, including length, give equal results for both groups (data not shown).

Cephalometry has been possible in patient 4 and patient 5 (patient 11 and patient 16 in Hennekam et al. 1991). They both show the main cephalometric characteristics of RTS. The mean correlations with 16 other patients with RTS are .69 (patient 4) and .71 (patient 5).

Comparison of the findings for the extremities shows

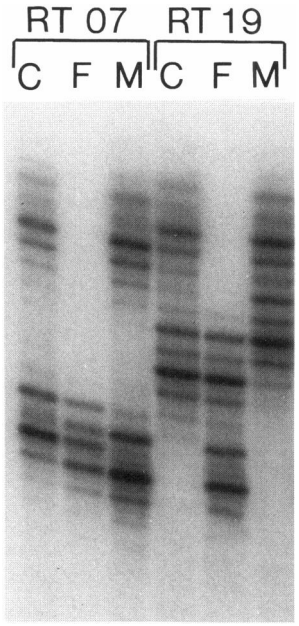

Figure 1 Determination of the parental origin of the chromosome 16 copies in RTS patients in two families, RT07 and RT19, using the polymorphic CA-repeat marker D16S265. DNA was isolated from the affected child and from the parents and was analyzed by PCR amplification, electrophoretic separation, and subsequent autoradiography of the amplification products, as described in Subjects, Material, and Methods. The parental origin of each of the child's alleles, i.e., of each chromosome 16 copy, was determined by comparing the band pattern of this person with that of the parents. C = Affected child; F = father; and M = mother.

Table 3

Polymorphic Markers Providing Information about Specific Patterns of Segregation of Chromosome 16 in Individual Families

Family	Maternal Isodisomy	Maternal Heterodisomy	Paternal Isodisomy	Paternal Heterodisomy
RT01	D16S261	D16S265	D16S261	D16S261
RT02	D16S186	D16S261	D16S186	D16S261
RT03	D16S265	D16S261	D16S265	D16S261
RT04	D16S186	D16S261	D16S186	D16S261
RT05	D16S261	D16S261	D16S261	D16S261
RT06	D16S261	D16S261	D16S261	D16S261
RT07	D16S265	D16S265	D16S265	D16S265
RT08	D16S261	D16S265	D16S261	D16S265
RT09	D16S261	D16S261	D16S261	D16S261
RT10	D16S261	D16S265	D16S261	D16S265
RT11	D16S186	D16S261	D16S186	D16S261
RT12	D16S261	D16S261	D16S261	D16S261
RT13	D16S261	D16S261	D16S261	D16S261
RT14	D16S261	D16S261	D16S261	D16S261
RT15	D16S265	D16S261	D16S265	D16S261
RT16	D16S261	D16S261	D16S261	D16S186
RT17	D16S265	D16S265	D16S265	D16S261
RT18	D16S261	D16S261	D16S261	D16S265
RT19	D16S265	D16S265	D16S265	D16S265

a tendency to more frequent angulation of the first rays of hands and feet, as well as partial duplication of the halluces in patients with a deletion. Other findings are about equally frequent. Metacarpophalangeal pattern profile analysis shows high correlations with the appropriate type, when age and presence or absence of radial angulation are taken into consideration (Hennekam et al. 1990*d*). Correlation coefficients are as follows: patient 1, .77; patient 2, .90; patient 3, .85; patient 4, .79; patient 5, .67; and patient 6, .94. In most, these values are higher than the mean correlation coefficient (.78) of hand profiles in RTS.

The cognitive functioning shows a wide variation both in patients with a detectable deletion and in patients without a detectable deletion. There are no essential differences between the two groups, in attainment of motor milestones or in behavior, temperament, or social competency (Hennekam et al. 1992).

Discussion

A syndrome is defined as a pattern of multiple anomalies known or thought to be pathogenetically related and not known to represent a single sequence or a polytopic field defect (Benirschke et al. 1979; Spranger et al. 1982). This implicates generally a single cause for a syndrome but does not exclude the possibility that syndromes may be causally heterogeneous. Despite some 300 publications on more than 600 patients worldwide, RTS was still at the general, nonspecific level of syndrome definition until recently. Our finding, at FISH, of a de novo submicroscopic deletion at 16p13.3 in six patients with RTS (see accompanying paper [Breuning et al. 1993]) allows the establishment of a cytogenetic anomaly as its cause in at least some of the patients.

It remains uncertain why a deletion was not found in all patients. Imprinting of that part of chromosome 16 may be one possible explanation (Hall 1990), as it has been in Prader-Willi syndrome and Angelman syndrome. The present study shows normal biparental disomy in all 16 patients. However, this does not exclude imprinting of chromosome 16 as a cause for RTS, since mutations altering the initiation, maintenance, or erasure of the imprint may cause human disease in the absence of uniparental disomy (Wagstaff et al. 1992).

Furthermore, several other options remain open to explain our findings: the most probable one is, in our opinion, the presence of molecular deletions so small that they could not be detected by the presently used probes and methods. Alternatively, a point mutation, either in heterozygous or homozygous state, may give rise to RTS, too. Third, the deletion may not be present in the peripheral blood lymphocytes that were studied

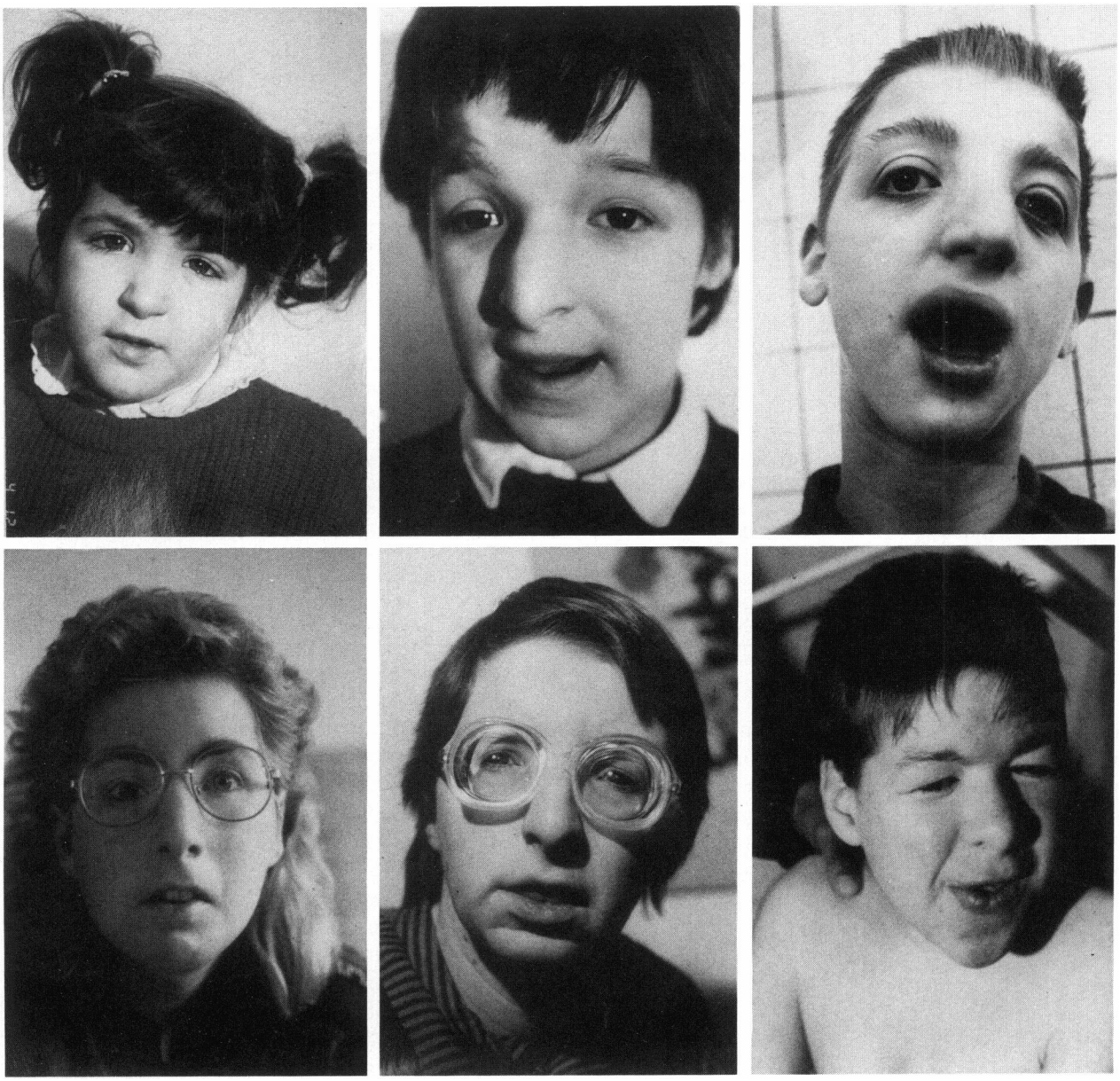

Figure 2 Facial appearance of the six patients with RTS and a deletion at 16p13.3. *Top row, left to right,* Patient 1, age 3.1 years; patient 2, age 11.5 years; and patient 3, age 15.8 years. *Bottom row, left to right,* Patient 4, age 16.9 years; patient 5, age 31.3 years; and patient 6, age 31.5 years.

but may be present only in other as yet unstudied tissues. In this respect, it should be mentioned that there are 12 RTS patients reported to have a cytogenetic anomaly, and 3 of them had a mosaicism (Davison et al. 1967; Bazacliu et al. 1973; Hennekam et al. 1989); in none was chromosome 16 involved. We will initiate studies in fibroblasts to investigate this further.

A phenocopy by a nongenetic cause may be another explanation. However, a recent review of reported teratogenic data in RTS patients failed to show any consistent chemical or environmental exposure (Hennekam et al. 1990*a*). Furthermore, a clustering of patients in time or place has never been reported.

The last possibility may be heterogeneity. We have investigated this in part by high-resolution banding of 24 patients, without finding any abnormality (see the

accompanying paper [Breuning et al. 1993]), and by initiating a search for uniparental disomy of all autosomes known to be imprinted in the homologous regions of the mouse (chromosomes 2, 4–7, 9, 11, 15, 16, and 19–22) (Searle et al. 1989; Hall 1990). No clues for abnormal segregation of these parental chromosomes has been found thus far by studying chromosome 4, 6, 11, 15, and 19. A submicroscopic deletion is, of course, not excluded in this way. It should be mentioned in this respect that there are two female adults with RTS who show, in addition, two unusual features—namely, early aging and intracranial meningioma (Bilir et al. 1990; Hennekam et al. 1990*c*, fig. 8). One of them (Hennekam et al. 1990*c*) is known to have mosaicism: 46,XX/47,XX, +der(20)qter-13.3-p11.2. Chromosomal investigations of the other patient have not been possible yet (G. Wilson, personal communication). Careful prometaphase banding investigations of this patient and other patients with similar additional findings may provide a clue to another chromosomal localization of RTS. On the other hand, the mosaicism in the first patient may be coincidence, and the presence of premature aging and a meningioma may be caused by an unusual deletion at 16p13.3 involving genes that are usually not deleted in RTS. Also, uniparental disomy may be an explanation for this combination of abnormalities.

Clinically, the differences between patients with and without visible deletion are minimal. The sole exceptions may be the incidence of microcephaly, angulation of the thumbs and halluces, and duplication of the halluces. The number of patients is too small, however, to allow firm conclusions in this respect. It is important, in future patients, to analyze the correlation of the phenotype in relation to the detected deletion. RTS may well be a contiguous gene syndrome (Schmickel 1986; Ballabio 1991), i.e., a disorder resulting from the involvement of adjacent genes on a chromosome. The phenotypic variation among patients may thus reflect different ranges of molecular rearrangements. Careful analysis of the different components of the phenotype may allow mapping and cloning of the disease genes in the region of 16p13.3.

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References

Ballabio A (1991) Contiguous deletion syndromes. Curr Opin Genet Dev 1:25–29

Bazacliu E, Tonceanu S, Carp G, Ghisoiu V, Rosca GH, Rosca S (1973) Rubinstein-Taybi syndrome with karyotype changes and recurring pneumopathy (translated from the Rumanian). Fiziologia 22:645–650

Benirschke K, Lowry RB, Opitz JM, Schwarzacher HG, Spranger JW (1979) Developmental terms: some proposals: first report of an international working group. Am J Med Genet 3:297–302

Bilir BM, Bilir N, Wilson GN (1990) Intracranial angioblastic meningioma and an aged appearance in a woman with Rubinstein-Taybi syndrome. Am J Med Genet Suppl 6:69–72

Breuning MH, Dauwerse HG, Fugazza G, Saris JJ, Spruit L, Wijnen H, Tommerup N, et al (1993) Rubinstein-Taybi syndrome caused by submicroscopic deletions within 16p13.3. Am J Hum Genet 52:249–254

Davison BCC, Ellis HL, Kuzemko JA, Roberts DF (1967) Mental retardation with facial abnormalities, broad thumbs and toes and unusual dermatoglyphics. Dev Med Child Neurol 9:588–593

Graff-Radford SB (1981) Melkersson-Rosenthal syndrome: a review of the literature and a case report. S Afr Med J 60:71–74

Hall JG (1990) Genomic imprinting: review and relevance to human diseases. Am J Hum Genet 46:857–873

Hennekam RCM, Baselier JCA, Beyaert E, Bos A, Blok JB, Jansma JBM, Thirbecke-Nilsen VV, et al (1992) Psychological and speech studies in Rubinstein-Taybi syndrome. Am J Ment Retard 96:645–660

Hennekam RCM, Lommen EJP, Strengers JCM, Van Spijker KG, Jansen-Kokx TMG (1989) Rubinstein-Taybi syndrome in a mother and son. Eur J Pediatr 148:439–441

Hennekam RCM, Stevens CA, Van de Kamp JJP (1990*a*) Etiology and recurrence risk in Rubinstein-Taybi syndrome. Am J Med Genet Suppl 6:56–64

Hennekam RCM, Van den Boogaard MJ, Dijkstra PF, Van de Kamp JJP (1990*b*) Metacarpophalangeal pattern profile analysis in Rubinstein-Taybi syndrome. Am J Med Genet Suppl 6:48–50

Hennekam RCM, Van den Boogaard MJ, Sibbles BJ, Van Spijker HG (1990*c*) Rubinstein-Taybi syndrome in the Netherlands. Am J Med Genet Suppl 6:17–29

Hennekam RCM, Van den Boogaard MJ, Van Doorne JM (1991) A cephalometric study in Rubinstein-Taybi syndrome. J Craniofac Genet Dev Biol 11:33–40

Hennekam RCM, Van Doorne JM (1990*d*) Oral aspects of Rubinstein-Taybi syndrome. Am J Med Genet Suppl 6:42–47

Miller SA, Dykes DD, Polesky HF (1988) A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic Acids Res 16:1215

Reeders ST, Breuning MH, Davies KE, Nicholls RD, Jarman AP, Higgs DR, Pearson PL, et al (1985) A highly polymorphic marker linked to adult polycystic kidney disease on chromosome 16. Nature 317:542–544

Rubinstein JH (1990) Broad thumb-hallux (Rubinstein-Taybi) syndrome 1957–1988. Am J Med Genet Suppl 6:3–16

Rubinstein JH, Taybi H (1963) Broad thumbs and toes and facial abnormalities. Am J Dis Child 105:588–608

Schmickel RD (1986) Contiguous gene syndromes: a component of recognizable syndromes. J Pediatr 109:231–241

Searle G, Peters J, Lyon MF (1989) Chromosome maps of man and mouse. IV. Ann Hum Genet 53:89–140

Spranger J, Benirschke K, Hall JG, Lenz W, Lowry RB, Opitz JM, Pinsky L, et al (1982) Errors of morphogenesis: concepts and terms. J Pediatr 100:160–165

Stevens CA, Hennekam RCM, Blackburn BL (1990) Growth in Rubinstein-Taybi syndrome. Am J Med Genet Suppl 6:51–55

Wagstaff J, Knoll JHM, Glatt KA, Shugart YY, Sommer A, Lalande M (1992) Maternal but not paternal transmission of 15q11-13 linked nondeletion Angelman syndrome leads to phenotypic expression. Nature Genet 1:291–294

Weber JL, May PE (1989) Abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. Am J Hum Genet 44:388–396

Williamson R, Bowcock A, Kidd K, Pearson P, Schmidtke J, Ceverha P, Chipperfield M, et al (1991) Human genome mapping 11: report of the DNA committee and catalogues of cloned and mapped genes, markers formatted for PCR and DNA polymorphisms. Cytogenet Cell Genet 58:1663–1696