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# Apparent Dominant Transmission of the Rubinstein-Taybi Syndrome

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**The cause of the Rubinstein-Taybi syndrome (RTS), a multiple congenital anomalies/mental retardation (MCA/MR) syndrome first described in 1963, remains obscure. Recently, a deletion of chromosomal material at 16p13.3 has been found in some patients with the disorder, but no such deletion can be identified in the majority of affected individuals. Although the disorder has been well documented to be concordant in at least 7 monozygotic twin pairs and in one non-twin sib pair, only one clear-cut case of parent-to-child transmission has been reported previously. We present here a mother and daughter, both of whom appear to be affected with RTS, strongly suggesting either autosomal or X-linked dominant transmission. The paucity of previous cases of parent-to-child transmission may be related to either decreased fertility or decreased fitness in affected individuals.**



KEY WORDS: autosomal dominant inheritance x-linked dominant inheritance, multiple malformation syndrome, broad thumb-hallux syndrome, mental retardation

## INTRODUCTION

First described in 1963, the Rubinstein-Taybi syndrome (RTS) is an MCA/MR syndrome that combines distinctive craniofacial changes ("beaked" nose with a broad bridge and septum that extends below the alae, ocular hypertelorism, with heavy or highly arched eyebrows and downward obliquity of the palpebral fissures, minimal abnormalities of the ears, and mild microstomia with micrognathia and highly arched palate), skeletal abnormalities (broad terminal phalanges of hallux and thumb with angulation deformity, and abnormal shape of the proximal phalanges with broad terminal phalanges of other fingers, as well as anomalies of the pelvis), and growth and developmental delay [Rubinstein, 1990]. Although relatively uncommon, more than 570 affected individuals have been reported.

At the present time, the cause of RTS is not clearly known. Although most cases occur sporadically, some data suggest heterogeneity. Concordance for the disorder with phenotypic variability, as well as discordance, has been reported in MZ twins. Affected non-twin sibs with normal-appearing parents have been observed, and consanguinity has been reported in the parents of some affected individuals. Prenatal teratogenic exposure has been reported, although no consistent pattern of exposure has been documented [Hennekam et al., 1990].

Recently, 3 unrelated patients with manifestations of RTS and de novo apparently balanced chromosomal rearrangements involving breakpoints at the p13.3 subband on chromosome 16 have been reported [Imaizumi et al., 1991; Tommerup et al., 1991; Lacombe et al., 1992]. Using fluorescent in situ hybridization (FISH), Hennekam and his colleagues have found a microdeletion in several RTS patients at 16p13.3. Although these data appear to establish a locus for the RTS gene in this region, molecular studies have failed to detect deletions in the majority of patients studied [Hennekam, 1992]. This finding appears to strengthen the argument in favor of heterogeneity.

A clear example of dominant inheritance of RTS has previously been observed in only one family, in which a mother and her son appeared to be affected [Hennekam et al., 1989]. We report here a second case of transmission of RTS from a mother to her daughter. Molecular analysis using FISH failed to establish the presence of a deletion at 16p13.3 in either of our patients.

## CLINICAL REPORTS

### Patient 1

The proposita was evaluated at 5 months because of minor anomalies. She had been the 2,900 g product of a full term gestation born by normal spontaneous vaginal delivery to a 24-year-old primigravid woman and a 37-year-old man. The pregnancy was complicated by gesta-

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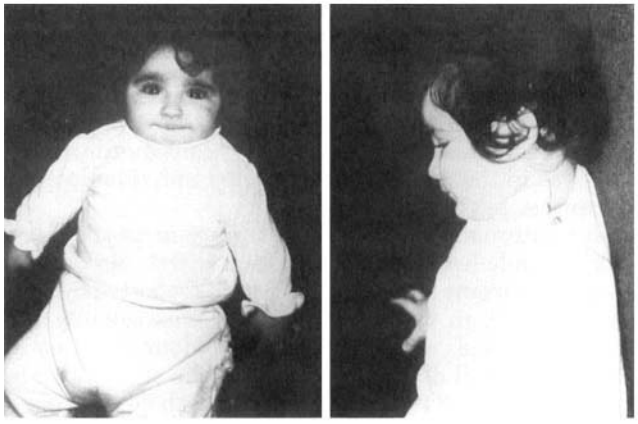

Fig. 1: Frontal and lateral facial view of the proposita (patient 1). Note facial anomalies, including mild asymmetry, ocular hypertelorism, downward obliquity of the palpebral fissures, retrognathia, and raised nasal bridge with septum extending below alae nasae.

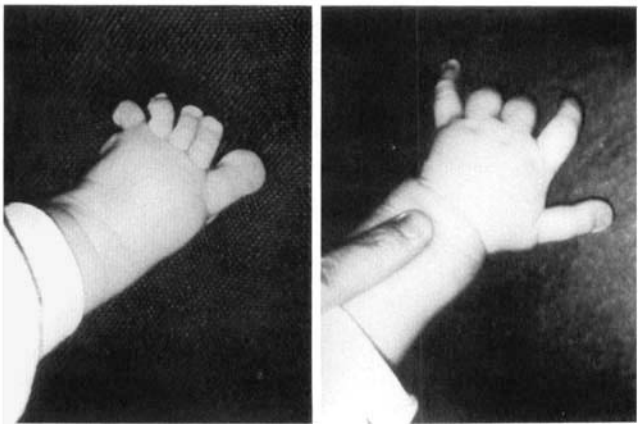

Fig. 2: The proposita's hand and foot, showing broadness of the thumb and other fingers, as well as the proximal insertion of the thumb, and broad halluces.

tional diabetes, for which the mother was treated with insulin during the third trimester. The mother denied the use of alcohol or any other drugs.

When first seen, the infant was a well-nourished infant with an unusual facial appearance (Fig. 1). Her length of 62 cm and weight of 6.8 kg were both at the 25th centile. She had a flat occiput and prominence of the forehead with an open anterior fontanelle; the head circumference (OFC) was 40 cm (40th centile). There was mild facial asymmetry, ocular hypertelorism, with inner canthal distance (31 mm) and interpupillary distance (50 mm) greater than the 95th centile, downward obliquity of the palpebral fissures, bilateral epicanthal folds, mildly abnormal ears with flat helices bilaterally, a raised nasal bridge with the nasal septum extending below the nasal alae, a highly arched palate, and mild retrognathia. Anomalies of the trunk included slight shortness of the sternum and bilateral supernumerary nipples. There was distal shortness of the upper limbs; the fingers were broad and foreshortened, and the thumbs, which were especially broad, were proximally inserted (Fig. 2); the palmar crease pattern was normal bilaterally. The toes were also short, and the great toes were both broad. Other findings and neurodevelopmental status were normal.

Chromosomes were apparently normal (46,XX). On the basis of the physical findings exhibited by the proposita, a diagnosis of RTS was made.

### Patient 2

The mother of the proposita was 25 years old at the time of her daughter's first visit. She had been born to a 22-year-old woman, but knew neither her birth weight nor her father's age at the time of her birth. Her early history had been complicated by "a swallowing problem" during the first years of her life, which had caused her to gain weight slowly but had resolved spontaneously by age 5 years. Having been labelled "learning disabled" in elementary school, she had attended special education classes and had dropped out of school in 11th grade. More recent medical problems have included migraine headaches and chronic low back pain, the latter thought to be related to the woman's underlying scoliosis.

The mother had a height of 150 cm (<3rd centile on standard growth curve, but 50th centile on RTS growth curve [Stevens et al., 1990]) and weight of 50 kg (10th centile on standard growth curve; nearly 50th centile on RTS growth curve [Stevens et al., 1990]) and she was microcephalic (OFC 51 cm). Her face was round and the nose was beaked and deviated from the midline (Fig. 3). She was hyperteloric, had minor anomalies of her ears, and a highly arched palate. Her hands were short, with brachydactyly of all digits; her thumbs were broad and slightly proximally placed (Fig. 4). There was no broadening of the great toes. Her chromosomes were also apparently normal (46,XX).

The family history was otherwise unremarkable. The mother's family was from Puerto Rico. The mother was unaware of the origin of her daughter's father's family, but consanguinity was denied.

During childhood, because of her failure to gain weight, learning disabilities, and minor anomalies, she

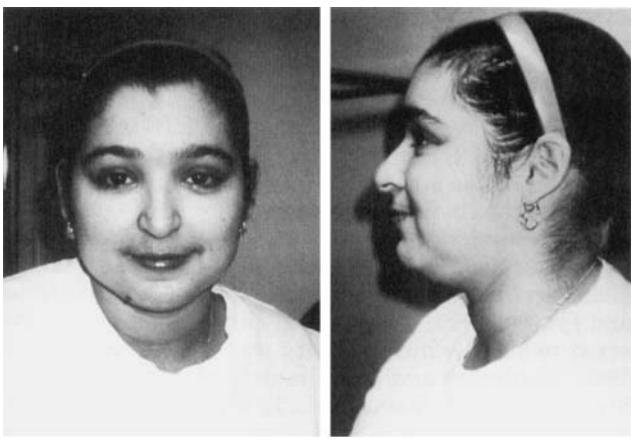

Fig. 3: Frontal and lateral view of the mother of the proposita (patient 2). Note round face; ocular hypertelorism; beaked, deviated nose; and other minor anomalies.

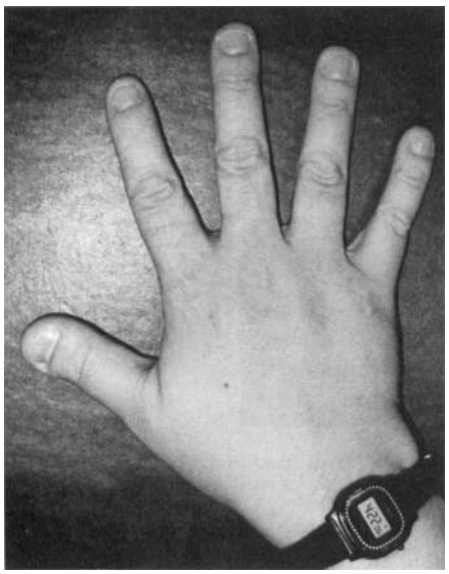

Fig. 4: Hand of the mother of the proposita (patient 2), showing brachydactyly with broad thumbs.

had been evaluated by a clinical geneticist. A presumptive diagnosis of RTS had been made at that time. Our findings supported that diagnosis.

### FISH Studies:

Fluorescent in situ hybridization using a probe corresponding to the 16p13.3 region was carried out in the laboratory of Dr. Raoul C.M. Hennekam (Clinical Genetics Center, Utrecht, the Netherlands) on metaphase preparations of lymphocytes obtained from patients 1 and 2. Dosage analysis failed to confirm the presence of a deletion in this region in either patient.

## DISCUSSION

The RTS most commonly occurs sporadically. In a few instances the RTS has been known to occur in more than one member of a family. Evidence supporting cytogenetic and teratogenic causes, as well as autosomal recessive and either X-linked or autosomal dominant inheritance exists [Hennekam et al., 1990]. The mother and daughter pair reported here supports the latter of these patterns.

Autosomal recessive inheritance of RTS is suggested on the basis of: concordance in MZ twins; the presence of the syndrome in sibs born to apparently unaffected parents; and the finding of consanguinity in the parents of affected individuals. Concordance for the disorder in MZ twins has been well documented in 7 cases [Pfeiffer, 1968; Gorlin et al., 1990; Schinzel et al., 1979; Baraitser and Preece, 1983; Widd, 1983] and in 5 cases of same-sexed twins in which zygosity was not certain [Kroth, 1966; Holthusen and Panteliadis, 1971; Buchinger and Stroder, 1973; Schinzel et al., 1979]. The syndrome has occurred in at least one sib pair in whom enough descriptive information was available to confidently confirm the diagnosis: in 1966, Johnson described an affected brother and sister. Other familial recurrences, specifically those reported by Takeuchi [1966], Gillies and Roussonis [1985], Hayem et al. [1970], and Levy-Leblond et al. [1969], and Shah and Patel [1984], were judged by Hennekam et al. [1990] to lack significant evidence for confirmation of the diagnosis in one or both members of the sib pairs. Finally, consanguinity has occurred in the parents of 10 affected individuals [Hennekam, et al. 1990].

But autosomal recessive inheritance in most cases of RTS is made less tenable by 2 facts. First, discordance for the syndrome has occurred in twins reported by Kajii et al. [1981], in which monzygosity was reliably confirmed. Second, as pointed out by Hennekam et al. [1990], the well documented recurrence of the disorder in only one of 708 reported sib-pairs, with no evidence of increased fetal wastage, makes this pattern of inheritance highly unlikely.

In 1989, Hennekam et al. described a mother and son with RTS syndrome. However, although her clinical course was typical of RTS, the authors had reservations about the diagnosis in the mother because her great toes were only moderately wide and her thumbs were normal. However, these findings are explanable on the basis of variability of expression.

Other multigenerational examples of presumed RTS suggestive of autosomal dominant inheritance with incomplete penetrance and/or variable expressivity have been reported, but in each family, the diagnosis has been difficult to confirm. Presumed examples of affected uncles and nephews have been reported twice—in 1984 by Kirstenmacher and Punnett, and in 1985 by Gillies and Roussounis. In the former, insufficient data were available to make the diagnosis with confidence; in the latter family, the facial appearance of neither individual was typical of RTS, and no photographs of the limbs were presented. Finally, a mother and 2 of her children with RTS-like features were reported by Cotsirilos et al. [1987], but these authors concluded that their patients had a different entity.

Therefore, the mother and daughter presented here represent only the second well-documented case of parent-to-child transmission of RTS. These patients offer strong support that, at least in some cases, RTS can be transmitted in a dominant manner. Because male-to-male transmission has not been documented, X-linked dominant inheritance cannot be excluded. However, as the disorder is equally distributed among males and females, and there is no evidence of increased pregnancy wastage, autosomal dominant inheritance seems more likely.

The lack of other pedigrees showing dominant inheritance of this disorder may be due simply to the fact that very few individuals with RTS have reproduced. In fact, the mother of the proband presented here represents only the third affected woman known to have delivered a baby. In addition to the family reported by Hennekam et al. [1989], a woman with RTS reported by Rohmer et al. [1970] delivered a premature but otherwise healthy and unaffected infant. Lack of reproductive fitness or decreased fertility, could cause the effects of dominant inheritance to remain hidden.

Reports of 3 unrelated patients with RTS who have

each had apparently de novo balanced chromosomal rearrangements involving breakpoints at 16p13.3 have raised the question of whether a gene for RTS is present in this region. In 1991, Imaizumi and Kuroki described a girl with RTS who had a reciprocal translocation involving chromosomes 2p13.3 and 16p13.3 [karyotype 46,XX,t(2;16)(p13.3;p13.3)]. Later, Tommerup et al. [1991] reported the case of a child with RTS who also had a reciprocal translocation, this one involving breakpoints at 7q34 and 16p13.3. Most recently, Lacombe et al. [1992] described a girl with features of RTS who had a pericentric inversion of the sixteenth chromosome [46,XX,inv(16) (p13.3;q13)]. With this information, Hennekam and his colleagues, using FISH, documented microdeletions at the 16p13.3 region in approximately 25% of the patients with RTS studied. This evidence unequivocally confirms assignment of a locus for an RTS gene to the 16p13.3 subband region.

But the presence of patients with features of RTS in whom no deletion in this region can be document strongly suggests that the entity is heterogeneous. Other explanations include the presence of uniparental disomy in non-deleted cases, with expression occurring either through imprinting or homozygosity for the abnormal gene, or the presence of a submicroscopic deletion, too small to be detected by presently available molecular technology. Further studies of this and other multigenerational families is necessary before a final conclusion can be reached.

In summary, we present a mother and daughter, both of whom are affected with RTS, but neither of whom demonstrate a deletion of 16p13.3 This family strongly suggests that, at least in some cases, RTS is inherited in either an X-linked, or, more likely, an autosomal dominant fashion, possibly through the transmission of a still undetected chromosomal deletion. This must be considered when offering counseling to affected individuals and their families.

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