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Clinical Case Reports

Moderate Down's Syndrome in Three Siblings Having Partial Trisomy 21q22.2→qter and Therefore no SOD-1 Excess

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Summary. Three mentally retarded siblings with moderate stigmata of Down's syndrome were found to have a partial trisomy 21q22.2→qter resulting from a maternal translocation t(4q+;21q−). By the exclusion of any excess of SOD-1 in them, we can confirm the nonessentiality of the sub-band 21q22.1 and of the SOD-1 excess for most of the Down's syndrome stigmata including the mental retardation. However, the sub-band 21q22.1 in triplicate might be required for the completion of the full syndrome, as for example is shown by the incomplete dermatoglyphic pattern on the palms in the patients.

Introduction

The responsibility of the band 21q22 for all the phenotypical features of classic trisomy 21 has been well documented by cases with partial trisomy 21q (Aula et al. 1973; Niebuhr 1974; Williams et al. 1975; Wahrman et al. 1976; Raoul et al. 1976; Hagemeijer and Smit 1977; Fryns et al. 1980). After the demonstration of the gene-dosage effect for superoxide dismutase (SOD-1) in trisomy 21 and its location on sub-band 21q22.1 (Sinet et al. 1976), cases with trisomic segments smaller than the whole band 21q22 are of interest. We found this condition in three siblings with trisomy 21q22.2→qter who showed the dissociation of the clinical expression of Down's syndrome from the SOD-1 excess as previously demonstrated by Mattei et al. (1981).

Case Reports

For genetic counselling of the only normal member of four siblings, we observed her three mentally retarded siblings: a female born in 1952, a male born in 1955, and a female born in 1957 (Fig. 1). Their parents born in 1926 and 1927 are non-consanguineous and healthy. The first pregnancy of the mother resulted in a spontaneous abortion at the third month in 1951. The mother is the fourth of six siblings, all of them are dead but her. The first one died of an unknown cause at the age of three weeks. The fifth one showed considerable physical and mental retardation and died of "apoplexy" at the age of 25 years. The mother's last sibling was still-born at term and the mother's parents are dead, they were normal and not consanguineous. In the father's family, there was no noteworthy medical history.

At the ages of 26, 23, and 21 years, the three siblings revealed a degree of mental retardation and behaviour to be expected in Down's syndrome. They have only been able to attend a sheltered workshop. The only difference in development among them was the eldest sister's better capacity to

Fig. 1. The siblings with moderate Down's syndrome stigmata: female 26 years old *(middle)*, male 23 years old *(left)*, female 21 years old *(right)*

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Table 1. Dermatoglyphic findings[a] from the family with t(4;21)

Digital patterns		Left					Right					TRFC	Walker index	General index
		5	4	3	2	1	1	2	3	4	5			
III.2	(F, retarded)	U	W^d	W^s	W^d	W^s	W^d	W^d	W^s	W^s	U	196	−3.37	−2.10
III.4	(M, retarded)	U	W^s	W^s	W^d	W^s	W^s	W^d	W^s	W^s	W^s	223	−3.29	−1.88
III.5	(F, retarded)	U	U	W^s	W^s	W^d	W^c	W^s	W^s	U	U	191	+0.75	+1.25
III.3	(F, normal)	U	U	U	R	U	U	R	U	U	U	135	−1.91	−3.99
II.4	(mother)	U	U	W^s	W^s	W^d	W^d	W^s	U	W^s	U	170	−5.63	−2.98
II.	(father)	U	U	U	W^s	W^s	W^s	R	U	U	U	181	−2.90	−3.71

Palmar patterns			Simian/Hypoth. creases		atd-angle (X°)	atd-angle (%)	a–b RC	Dysplasia
III.2	R:	9.7 .5′ .4 .−t′ .−A^c .0.V.0.L.	+	(+)	57	25	43	−
	L:	7.5″.5 .3 .−t′ .t^b .−L^r/A^c .0.V.0.L.	+	(+)	49	18	43	−
III.4	R:	9.7 .5″ .4 .−t′ .−A^c .0.V.0.L.	+	+	50	28	44	−
	L:	7.5″.5 .3 .−t′ .−A^c .0.V.0.L.	+	(+)	49	26	40	−
III.5	R:	9.7 .5 .1 .−t″.t^b .−L^c/A^r.0.V.0.L.	+	−	65	30	44	+
	L:	8.6 .5′ .1 .− t^b .−A^r .0.V.0.L.	+	−	—	—	44	+
III.3	R:	11.9 .7 .5′ .−t .−A^u .V.0.L.0.	−	−	37	8	34	−
	L:	9.7 .5″ .5′ .−t .−A^u .V.0.0.L.	−	−	36	8	36	−
II.4	R:	11.9 .7 .5′ .−t .−A^u .0.0.L.V.	+	−	41	10	30	−
	L:	11.7 .7 .5 .−t .t′ .−L^u .0.0.V.L.	+	−	56	30	38	−
II.Fa	R:	11.7 .7 .5′ .−t .t′ .t^b .−W^d .0.0.V.L.	−	−	49	32	33	−
	L:	9.0 .5″ .5′ .−t .−A^u .0.0.0.V.	−	−	37	7	40	−

Plantar patterns			Hallucal creases	Dysplasia	e	f	p	p′	p″	z	z′	z″
III.2	R:	I^d (20).0.L^d (3rd+4th IDA).L^t.0.	+	−	−	+	+	−	−	−	−	−
	L:	I^d (9).0.L^d (3rd+4th IDA).L^t.0.	(+)	−	−	+	−	+	−	−	−	−
III.4	R:	I^d (11).0.L^d (3rd+4th IDA).L^t.0.	(+)	−	−	+	+	−	−	−	−	−
	L:	I^d (11).0.L^d (3rd+4th IDA).L^t.0.	(+)	−	−	+	−	+	−	−	−	−
III.5	R:	I^d (16).0.L^d (3rd+4th IDA).L^t.0.	+	+	−	+	+	−	−	−	−	−
	L:	A^t .0.L^d (3rd+4th IDA).L^t.0.	+	+	−	+	+	−	−	−	−	−
III.3	R:	I^d (16).0.L^d.0 .0.0.	−	−	−	+	+	−	−	−	−	−
	L:	I^d (16).0.L^d.0 .0.0.	−	−	−	+	+	−	−	−	−	−
II.4	R:	W^s .L^p.L^d.0 .L^t.0.	−	−	+	+	+	−	−	+	−	−
	L:	W^s .V.L^d.0 .L^t.0.	−	−	+	+	+	−	−	+	−	−
II.Fa	R:	I^d (16).L^p.W^s.L^d .L^t.0.	−	−	−	+	+	+	−	+	+	−
	L:	I^d (15).V.I^d.0 .V.0.	−	−	−	+	+	−	−	+	−	−

[a] Nomenclature from Penrose, LS (1968). Memorandum on dermatoglyphic nomenclature. Birth Defects Orig. Artic. Ser. 6/3, Nat. Found.-March of Dimes, New York

IDA = Interdigital area

articulate. All the sibling had a short stature (160, 160, 150 cm), both sisters were corpulent, but the brother was rather slender. In addition, he has suffered from moderate extension defects of the major joints, on the legs more than on the arms. The facial stigmata of Down's syndrome were moderately expressed in all three siblings. In all of them, there were laterally upward slanting palpebral fissures, strabismus, myopia, dysplastic jughandle ears, double chin, lingua scrotalis, but they had relatively differentiated noses.

The dermatoglyphic analysis showed a significantly elevated incidence of stigmata typical of Down's syndrome, especially on their soles. Therefore the statistical calculations using the "Walker index" (Walker-Ford 1975) and the "General index" (Rodewald et al. 1976) showed ranges from normal to overlapping with the Down's syndrome population (Fig. 2). The most mentally retarded youngest sibling ranged closest in the direction of the full picture of Down's syndrome. The dermatoglyphic details of the family are summarized in Table 1.

Cytogenetic Studies

Chromosome preparations were made from short-term peripheral blood lymphocyte cultures from all members of the family, using Q-, G-, and R-banding. The karyotypes of them revealed the presence of 46 chromosomes. However, in the three mentally retarded siblings and in their mother, there was an elongation of the most distal band q35 of one chromosome 4. A translocation could definitively be confirmed by R-

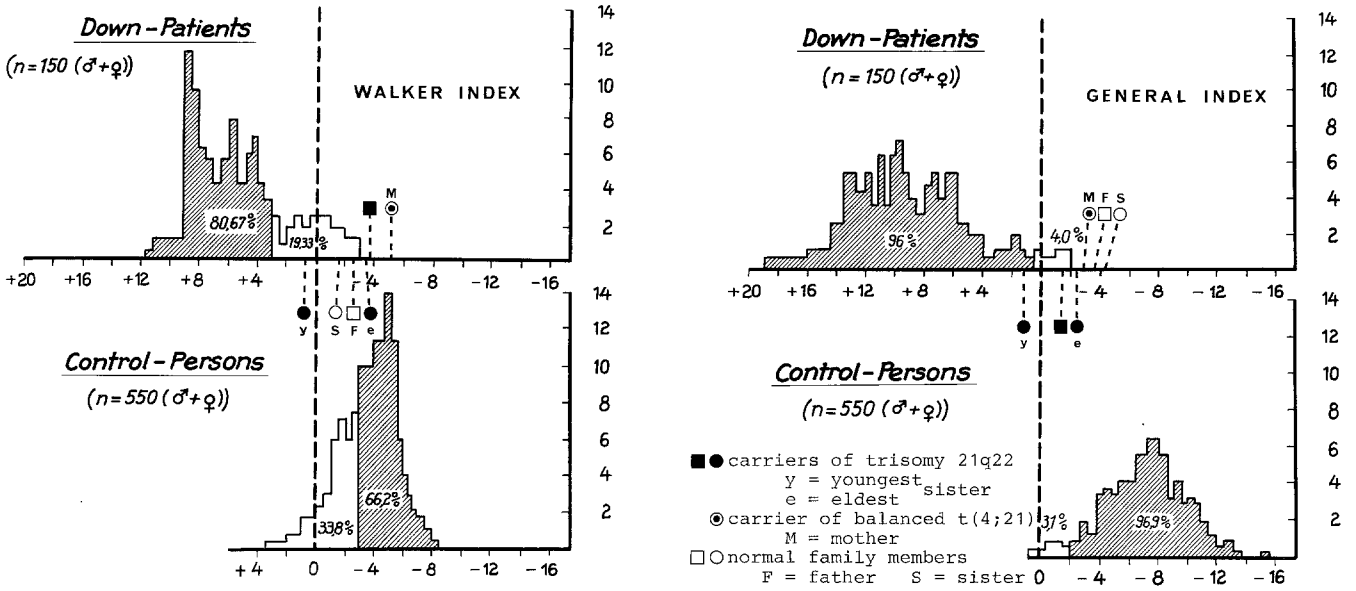

Fig. 2. Dermatoglyphic histograms of all family members compared with Down's syndrome patients and normal controls: Walker Index (Walker-Ford 1975) left and General Index (Rodewald et al. 1976) right

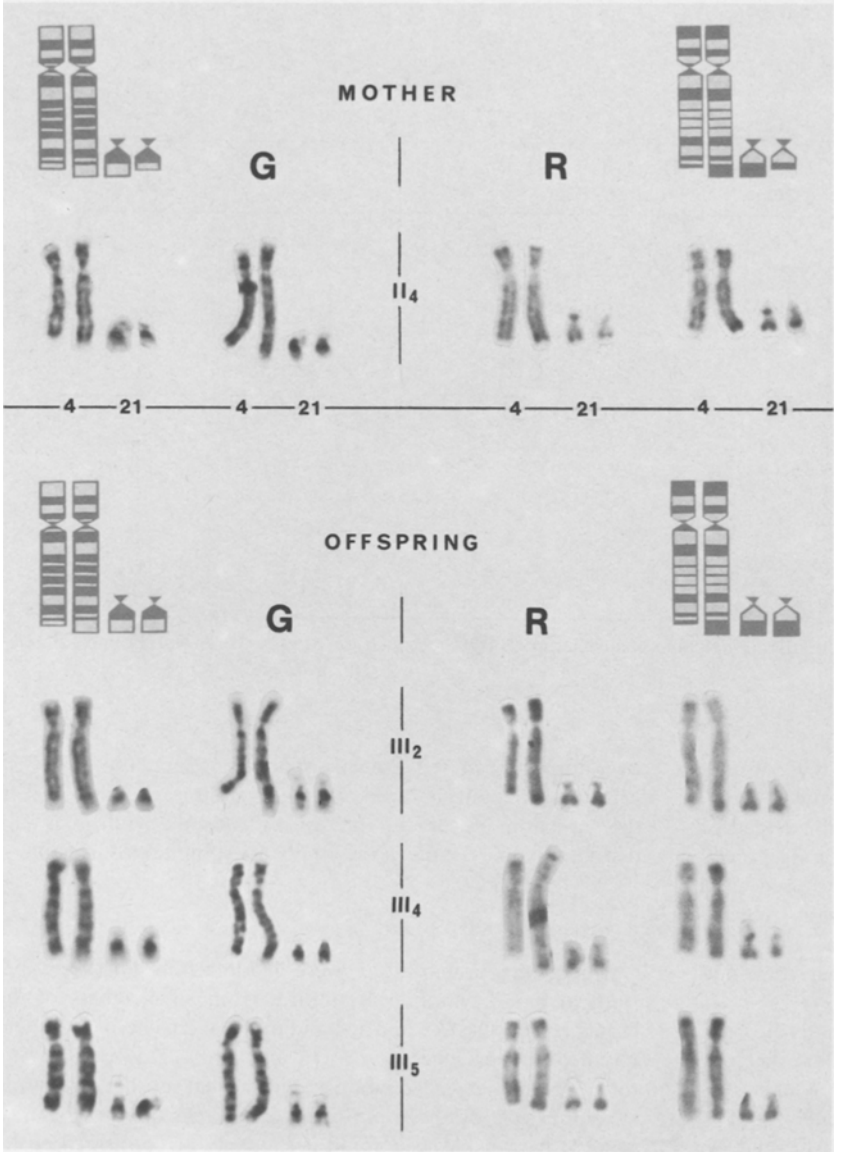

Fig. 3. Partial karyotypes of chromosomes 4 and 21 showing balanced translocation t(4q+;21q−) in the carrier mother, and partial trisomy for 21q22.2→21qter in the siblings (G and R banding)

banding which gave a particularly clear staining of this chromosome tip only weakly stained by Q- and G-banding (Fig. 3).

The origin of the translocated material was found in one of the mother's chromosome 21 which had lost more than the distal half of band q22. Because the deleted chromosome 21 is terminated by the break-point and the derivative chromosome der(4) is elongated by the translocated segment, there is no indication that the translocation was reciprocal. Therefore the karyotype of the mother is designated as: 46,XX,t(4;21)(4pter→4qter::21q22.2→21qter; 21pter→21q22.1). The retarded offspring then have a partial trisomy for 21q22.2→21qter in an unbalanced karyotype: 46,XX(resp.XY),−4,+der(4),t(4;21)(4pter→4qter::21q22.2→21qter)mat.

SOD-1 Studies

The enzymatic activity of superoxide dismutase 1 in erythrocytes was studied in all members of the family and compared to those of five normal control persons and three subjects with trisomy 21. The mean activity of the enzyme in the trisomy 21 controls (1140 µg SOD/g Hb) was significantly higher than that in the normal persons (722 µg SOD/g Hb; mean $\pm 3\sigma$: 595–850 µg SOD/g Hb). The ratio of the mean trisomic to normal activities is 1.58. Both parents and the normal sibling had activities within the mean normal values (father 758, mother 740, sibling 730 µg SOD/g Hb); the activities of the retarded siblings were 809, 845, and 927 µg SOD/g Hb, which are not significantly different from the mean activity in normal persons.

Discussion

Our results confirm the coordination of the SOD-1 locus with the sub-band 21q22.1 (Sinet et al. 1976) or with a region proximal to it (Leschot et al. 1981). In accordance with the observations of Mattei et al. (1981) we found neither the triplication of 21q22.1 nor the increased activity of SOD-1 to be "conditiones sine qua non" for most of the stigmata of Down's syndrome, including the mental retardation. Of course, the completion of the full syndrome obviously depends on these conditions. For example, the complete dermatoglyphic pattern on the palms typical of Down's syndrome, but lacking in our patients seems to be expressed in the presence of the sub-band 21q22.1 in triplicate.

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