

Down's Syndrome with an Unusual Karyotype

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The association between trisomy of a chromosome in the G group and Down's syndrome was reported by Lejeune, Gautier, and Turpin (1959). Though some doubt prevails, the extra chromosome is generally accepted as being a No. 21 of the Denver system. The extra material may become translocated onto another chromosome, usually another acrocentric chromosome.

The purpose of the present communication is to report a patient with Down's syndrome whose chromosome complement contains a presumptive t(GqGq) translocation, or G-isochromosome for the long arm (Gqi). There is also present a minute stable metacentric fragment which may be a short arm isochromosome (Gpi) or result from fusion of the short arms of the two missing G chromosomes (t(GpGp)).

Case Report

Clinical Findings. The patient is a 14-year-old mentally defective, cyanotic, Negro male with stigmata of Down's syndrome.

At the time of his birth the mother was 17 years of age and the father was 19. The maternal grandmother was 22 years old when the mother was born. There are two half-sibs, ages 11 years and 8 years, both of whom are clinically normal. A brother of the father is reported to be mentally retarded and is thought to have Down's syndrome. This cannot be confirmed because the father is unavailable for further history.

The propositus weighed 2625 g. at birth. When first seen at 2 years of age he was noted to be severely retarded—unable to sit or talk. He had the typical facies of Down's syndrome characterized by brachiocephaly, upward outward slanting of the eyes, epicanthal folds, flattened nasal bridge, small, low-set ears, and open mouth with a protruding tongue. There were no Brushfield spots. Other features included a short neck with loose skin at the nape, short broad hands and feet with stubby fingers and toes, the first toe being large and having a wide space and cleft between the first and second

toes of each foot. He was hypotonic and there was hyperextensibility of the extremities.

The patient's development during his 14 years of life was very slow, both mentally and physically. He sat alone at 3½ years and walked at 9 years. His course was characterized by repeated periods in hospital because of congestive heart failure. At 14 years of age (Fig. 1) his height was 119 cm.; weight 28.75 kg.; head circumference 51.25 cm.; and chest 63.75 cm. In addition to the features mentioned above, his eyebrows showed exaggerated proliferation and almost met in the midline. The tongue had a scrotal appearance and his lips were thickened. He had many dental abnormalities—malocclusion, missing teeth, abnormal alignment, peg-shaped and rather severe periodontal disease. Examination of the heart revealed moderate enlargement, with a prominent xyphoid impulse, a single second sound which was greatly accentuated, and a ventricular gallop at the left sternal border. A grade 1 short systolic murmur and a loud ejection sound were heard in the pulmonary area. There were no simian lines. His fingers and toes were clubbed. He still manifests his hypotonia and hyperextensibility though to a lesser extent. The testes could not be palpated.

Dermatoglyphic Studies. These revealed 9 ulnar loops on the digits, with a double loop on the right index finger. The left palmar axial triradius was in the t' (20%) with an *atd* angle of 42°; on the right the triradius was in the t' position (43%), the *atd* angle being 52°. There were loops in the third palmar interdigital areas and small distal loops bilaterally in the hallucal areas of the soles. The total dermatoglyphic index, as devised by Walker (1958), was Log. +2.1.

Chromosome Studies. Using the technique of Moorhead *et al.* (1960), chromosome studies were done on the peripheral blood of the patient four times: November 1963, January 1964, September 1965, and May 1967. All the cultures revealed a modal chromosome count of 47 (Table). Representative karyotypes from all cultures showed the same cytological peculiarities. There were 4 small acrocentric chromosomes. In addition there was one metacentric chromosome slightly larger than those in the 19–20 group and a small chromosome which also appeared to be metacentric (Fig. 2). On analysis of 50 cells this small chromosome was

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FIG. 1. Facies of propositus at 14 years of age, showing mongoloid features.

TABLE
CHROMOSOME COUNTS

Date	No. of Chromosomes						Total Cells Counted
	< 44	44	45	46	47	48	
Nov. 1963	0	0	0	0	29	1	30
Jan. 1964	0	0	0	1	48	1	50
Sept. 1965	0	0	0	0	20	0	20
May 1967	1	1	0	2	46	0	50

associated with an acrocentric chromosome in 28 spreads (56%), and on occasion was associated with one or more acrocentrics on each end (Fig. 3).

Chromosome analysis on the mother revealed a normal female complement of 46 chromosomes. The father was not available for studies.

Discussion

There have been several published reports of Down's syndrome with a translocation of the t(GqGq) type. The metacentric chromosome GqGq which resembles those in the F group has been explained in one of three ways: a translocation between the long arms of both homologues of pair 21, a translocation between the long arms of one chromosome 21 and one chromosome 22, and an isochromosome for the long arm of a chromosome

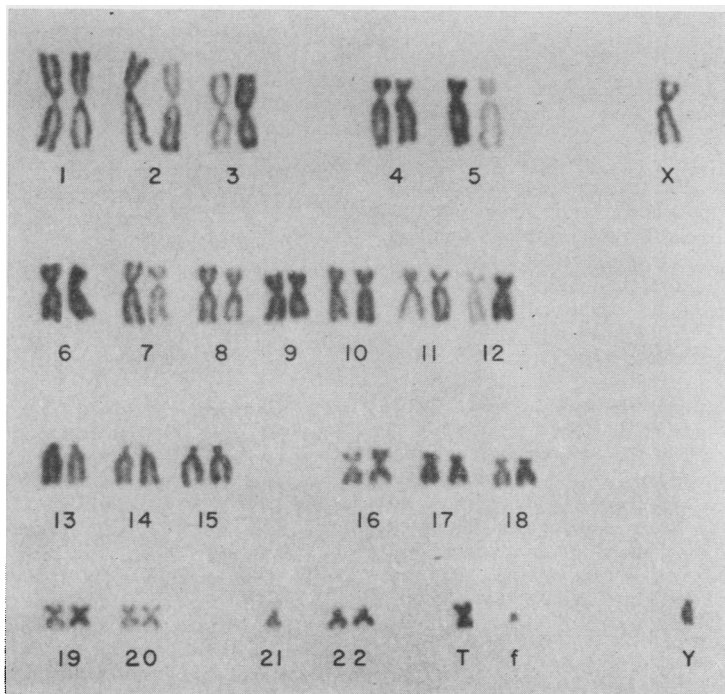


FIG. 2. Karyotype of propositus. T assumed to be a t(GqGq) translocation or G-isochromosome for the long arm (Gqi), and f a short arm isochromosome (Gpi) or fusion of short arms of the two missing G chromosomes (t(GpGp)).

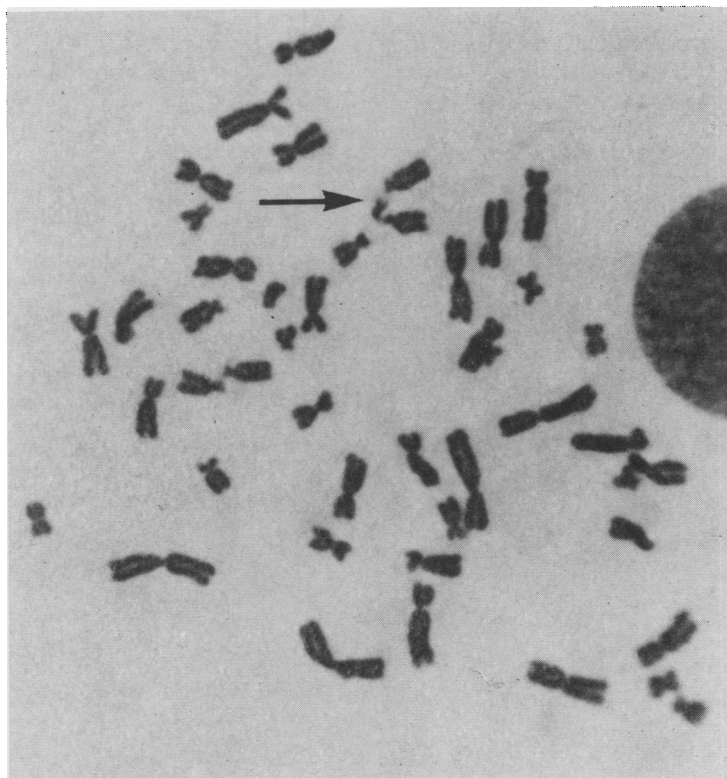


FIG. 3. Representative metaphase of propositus, showing association between fragment and acrocentric chromosomes.

21 (Hamerton *et al.*, 1961). If fragments were present, they were lost in subsequent mitoses probably because they were acentric and did not move to the spindle or because they were too small. Penrose, Ellis, and Delhanty (1960) reported a patient with Down's syndrome whose karyotype from a skin culture on one occasion was deficient in two small acrocentric chromosomes and had a small extra metacentric chromosome. In the culture from a second skin biopsy taken a year later the same cytological abnormality was again found, but there was noted an additional centric particle which was thought to have been of relatively recent origin. Another patient with Down's syndrome described by Gray, Mutton, and Ashby (1962) revealed that about 25% of the cells analysed contained an extra fragment with both arms resembling the satellite-bearing arms of the acrocentrics. The present case had a karyotype similar to those reported by Penrose and Gray, but the small metacentric fragment was found in all spreads and was known to have been present for at least 4 years, indicating that in this child the small metacentric fragment was stable.

As suggested by Marsden *et al.* (1966), it may be possible to interpret the additional chromosome resembling the F group in Down's syndrome as a G-isochromosome for the long arm (Gqi). The findings in the present case could, therefore, also be interpreted as evidence of isochromosomes for both arms of one of the G group chromosomes, the large metacentric chromosome being the G-isochromosome for the long arm (Gqi) and the small metacentric chromosome being the isochromosome for the short arm (Gpi). Another explanation for the finding would be that a centric fusion, as described by Turpin and Lejeune (1965), had occurred. In their material, and apparently in that reported by others, the centric fragment had been lost. In the present case the centric fragment was present and appeared to be stable.

Summary

A 14-year-old mentally retarded Negro male is reported, with many features of Down's syndrome, including an atrioventricular canal with Eisenmenger's physiology, and an unusual karyotype. On repeated peripheral blood cultures only 4 small

acrocentric chromosomes were found. In addition, there was a metacentric chromosome somewhat larger than those in the F group and a small metacentric fragment, consistently present, which was associated with one or more acrocentric chromosomes in 28 of 50 spreads. These chromosomal peculiarities are compared with two other reported patients.

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