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Original Investigations

Duplication of the Short Arm of Chromosome 9. Analysis of Five Cases

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Summary. Five females with duplication of the short arm of one chromosome 9 are reported, one tetrasomic and four trisomic for 9p. The tetrasomy is due to an isochromosome 9p while the trisomies are due in one case to an intrachromosomal duplication present in lymphocytes but not in fibroblasts, two are secondary to translocations with chromosomes 22 and 13 respectively, and one is a mosaic with a cell line with an additional deleted chromosome 9 present in lymphocytes and fibroblasts. This analysis indicates that duplications 9p may result in impairment of ovarian function. The phenotypic differences between trisomy and tetrasomy 9p are discussed.

Introduction

Duplications of the short arm of chromosome 9 are reported frequently and their cytogenetic aspects and phenotypic correlations have been repeatedly reviewed by Rethoré (1977), Schinzel (1979), Baccichetti et al. (1979), and Rodewald et al. (1979). In fact, trisomy 9p is a relatively common chromosome abnormality while tetrasomy for the short arm of chromosome 9 is a rare condition (Abe et al. 1977; Ghymers et al. 1973; Rutten et al. 1974; Orye et al. 1975; Wisniewski et al. 1978; Moedjono et al. 1980). We report one case of tetrasomy 9p and four cases of trisomy 9p, one due to an intrachromosomal duplication, two secondary to translocations with chromosomes 22 and 13, respectively, and one with a cell line with an additional deleted chromosome 9.

Case Reports

Sex, date of birth, parental ages, birth weight; and age, height, and weight at examination of the five patients are given in Table 1 and their appearances in Fig. 1.

Case 1. (C.E.) The mother had had three previous pregnancies resulting in two normal, healthy boys and an abortion at the second month. As a newborn the patient had a short period of severe cyanosis and showed developmental and psychomotor deficiency from the first month of life. At physical examination in February 1979 the head circumference was 43 cm (3rd percentile). The anterior fontanelle was 5×6 cm wide and the metopic suture was not completely closed. Internal hydrocephalus was suspected. The facies was peculiar with a flat appearance, bulbous nose with a prominent bridge and round extremity, and relative jaw hypoplasia with temporo-mandibular joint limitation. The superior lip frenulum was hypertrophic and crossed the gingival arch. The mouth was small. There was also a slightly mongoloid slant of the eyes and a tendency to convergent strabismus. The nails were long and dysplastic. Joint hyperlaxity was present. Skeletal age showed a five months delay. Clinical investigation was negative for heart and lung conditions, but echocardiographic findings indicated the possibility of a transposition of the great vessels. The electroencephalogram showed undifferentiated immaturity. The fundus examination showed pallor of the large papillae and dystrophy of chorioretinic pigmentation. Routine laboratory examinations gave normal results, except for a high IgM level.

Table 1. Sex, date of birth, parental ages, birth weight; and age, height, and weight at examination

Case No.	Sex	Date of birth	Age of parents at birth (years)		Birth weight (g)	Height (cm), weight (kg), and age (years) at examination		
			M	F				
1	F	22.2.1978	32	34	2500	72	8.2	1
2	F	15.9.1963	26	35	2050	136.5	28.7	15
3	F	23.11.1978	32	33	2530	—	—	—
4	F	1967	33	37	2400	121	23.5	12
5	F	12.9.1955	30	42	4000	163	52	23

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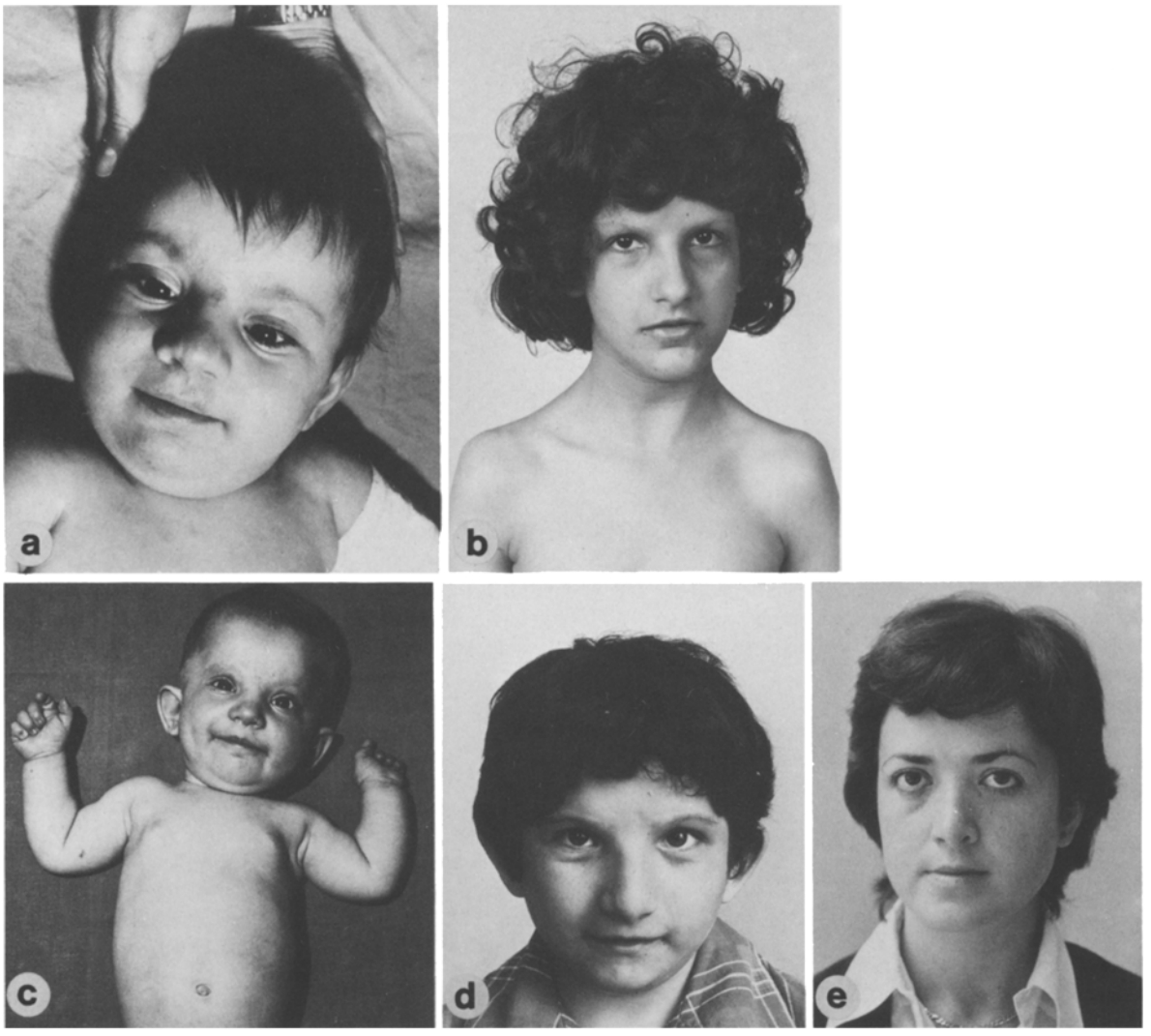

Fig. 1. The five patients. **a** Case 1 aged 1 year, **b** Case 2 aged 15 years, **c** Case 3 aged 6 months, **d** Case 4 aged 12 years, **e** Case 5 aged 26 years

Case 2. (C.A.) The patient was delivered at the eighth month. She has a healthy brother born in 1961. She had sucking difficulties and since the first months of life growth and psychomotor retardations were noticed. She said her first two-syllable words at 24 months and walked at four years of age. Her I.Q. evaluation (Stanford-Binet) performed in 1970 was 44. She was found to be a β-thalassemia heterozygote. She was observed by us at the age of 15 years because of short stature and puberty delay. There were no signs of pubertal development. The face was characterized by asymmetrical and malformed protruding ears, hypertelorism, deeply set eyes with convergent strabismus, antimongoloid slant of eyes, everted lower lip, and dental malocclusion. The hands showed bilateral hypoplasia of the fourth metacarpal bone, clinodactyly of the fifth finger and hypoplastic nails. A moderate valgismus was detected at the elbows and knees. Her skeletal age was 11 years. Several mental deficiency was present with an I.Q. of 37.

Case 3. (F.A.) The patient was born at the 37th week of pregnancy by cesarian section due to suspected fetal impairment. The mother had a myomatosis uteri. At birth the patient's length was 49 cm (50th percentile) and the head circumference 33 cm (50th percentile). Diffuse subcyanosis was present. There was muscular hypotonia of the four limbs and it was not possible to excite deep reflexes. The face showed a prominent forehead, narrow palpebral fissures, prominent nose bridge and grossly shaped nose, small mouth with microretrognathia, short philtrum, and poorly formed ears. Simian creases were present on both hands, and the fingers were short.

Case 4. (M.G.) The patient was born at term before a normal twin brother. She had four healthy brothers and a younger brother who died shortly after birth but no information about him is available. At the age of 12 years she was observed by us because of psychomotor and mental retardation. She had marked hyposomic dwarfism and microbrachycephaly. The skull measurements (antero-posterior 14 cm; latero-lateral 12.5 cm; circumference 47 cm) were below the third percentile. The fontanelles were sealed. Other signs were sunken eyes; convergent strabismus; antimongoloid slant of the palpebral fissures; interpupillar distance of 6 cm; low set ears; scarcely edged, hypoplastic vertical branch of anthelix; large nose; the mouth was kept half open with a typical fish-like posture; craniofacial dysmorphism, with amimic expression of the face, and low set hair; cylindro-conical thorax, otherwise an apparently normal

Table 2. The karyotype(s) of the five cases and the techniques used to define them

Case No.	Type and number of cells examined		Karyotype(s)	Bands
1	Lymphocytes	66	47,XX,+i(9p)	QFQ, GTG, C
	Fibroblasts	43	46,XX	
2	Lymphocytes	20	46,XX,dup(9p)(pter→p12::p24→qter)	QFQ, RBA, C
	Fibroblasts	20	46,XX,dup(9p)(pter→p12::p24→qter)	
3	Lymphocytes	20	46,XX,−22,+der(22),t(9;22)(9pter→9q11::22p11→22qter)	QFQ, GTG, C
4	Lymphocytes	20	46,XX,−13,+der(13),t(9;13)(9pter→9p11::13p11→13qter)	GTG
5	Lymphocytes	65	46,XX	QFQ, GTG, DaDAPI, C
		35	47,XX,+del(9)(q13)	
	Fibroblasts	77	46,XX	
		8	47,XX,+del(9)(q13)	

trunk with no umbilical hernia; muscular hypotony with no backbone deviations; flat feet; hands with extended palm length; relatively short fingers, bilateral clinodactyly of the second and fifth fingers, and less pronounced clinodactyly of other fingers. The patient had mental and psychomotor retardation. Verbal communication was limited to a very few words and syllables, and her language was poor, scarcely articulated, and nearly unintelligible. At 14 years of age menarche had not yet occurred.

Case 5. (S.E.) The parents are distantly related but it was not possible to define the degree of consanguinity. She had a healthy brother, born in 1953. No major developmental problem or disease was noticed. Menarche occurred at 13 years of age and she had regular menstruations until the age of 20 years. Afterwards no menstruations took place without hormonal therapy and she was observed because of secondary amenorrhea. At physical examination the only peculiarities were bilateral cubitus valgus; multiple pigmented nevi, mostly on her arms; short upper lip and philtrum, rounded chin; long palms of hands in relation to fingers; monolateral clinodactyly of the fifth finger, and hypotrophy of the labia minora. Her intellectual development is perfectly normal and she works as a teacher in a primary school. A biopsy of the ovary performed in December 1978 showed a decreased number of primary follicles, while the analysis of an endometrium biopsy showed a deficient secretive phase due to progesterone deficiency. After the biopsy was performed she had regular menstruations without any need for therapy and this situation has remained unchanged till March 1982.

Dermatoglyphics

Case 1 (Courtesy of Dr. A. Rodewald). There were ten small ulnar loops on the fingertips, low total finger ridge count (TFRC = 96; mean value for Italian females = 127) tranverse direction on the dermal ridges (Turpin-Index: right = 30; left = 31), absence of b and c triradii on the right hand and of c triradius on the left hand, dislocation of the d triradius to radial, t′ triradius on the right hand, both hands also show simian creases, hypothenar creases, and a reduced distal crease.

Case 4. There were bilateral simian transverse crease and bilateral axial triradius in t′. *Right hand: atd* angle, 54°; digital pattern: ulnar loop on first, third, fourth, and fifth finger; total fingertip ridge count: 19; line bridge count: 43; subdigital triradii present in $a \rightarrow 5$, *b* and *c* fused 7, $d \rightarrow 11$, $t' \rightarrow 13$. *Left hand:* atd angle, 53°8′; digital pattern: ulnar loop on second and fourth finger; arch on second, third, and fifth finger; total fingertip ridge count: 4; line b ridge count: 44; subdigital triradii present in $a \rightarrow 4$, *b* and *c* fused $\rightarrow 7$, $d \rightarrow 11$, $t' \rightarrow 13$. Both dermatoglyphic pattern combinations are consistent with the characteristics for trisomy 9p syndrome (Rodewald et al. 1979).

Cytogenetic Studies

The type of culture examined, cytogenetic diagnosis, and the banding methods used for each of the five cases are summarized in Table 2. The parents of Cases 1, 2, 3, and 4 had normal karyotypes. The father of Case 5 was dead but the mother and brother had normal karyotypes. The relevant chromosome cut outs for the five cases are reproduced in Fig. 2. Further cytogenetic information for each of the cases is described below.

Case 1. Lymphocytes showed consistently 47 chromosomes while all the fibroblasts had a normal karyotype. The extra chromosome, similar in size and appearance to chromosome 16, was interpreted as an isochromosome for the short arm of chromosome 9. C-banding revealed a very narrow centromeric region with no evidence of the p12 heterochromatic region and this was confirmed by QFQ banding.

Case 2. The patient had an abnormal chromosome 9 interpreted as a tandem duplication of the entire short arm p12pter attached to the band p24 in lymphocytes and fibroblasts.

Case 3. There was an abnormal chromosome 22 to whose centromeric region was attached the short arm of a chromosome 9. In QFQ banding no pale region was present at the centromere of the derivative chromosome indicating the absence of portions of the p12 heterochromatic region of chromosome 9. However, with C-banding the centromeric portion of the abnormal chromosome was larger than that of the centromere of chromosome 22. It is possible that the centromeric portion of the abnormal chromosome is composed of the closely associated centromeres of chromosome 22 and chromosome 9.

Case 4. The abnormal chromosome was composed of the long arm of a chromosome 13 and of the short arm of a chromosome 9.

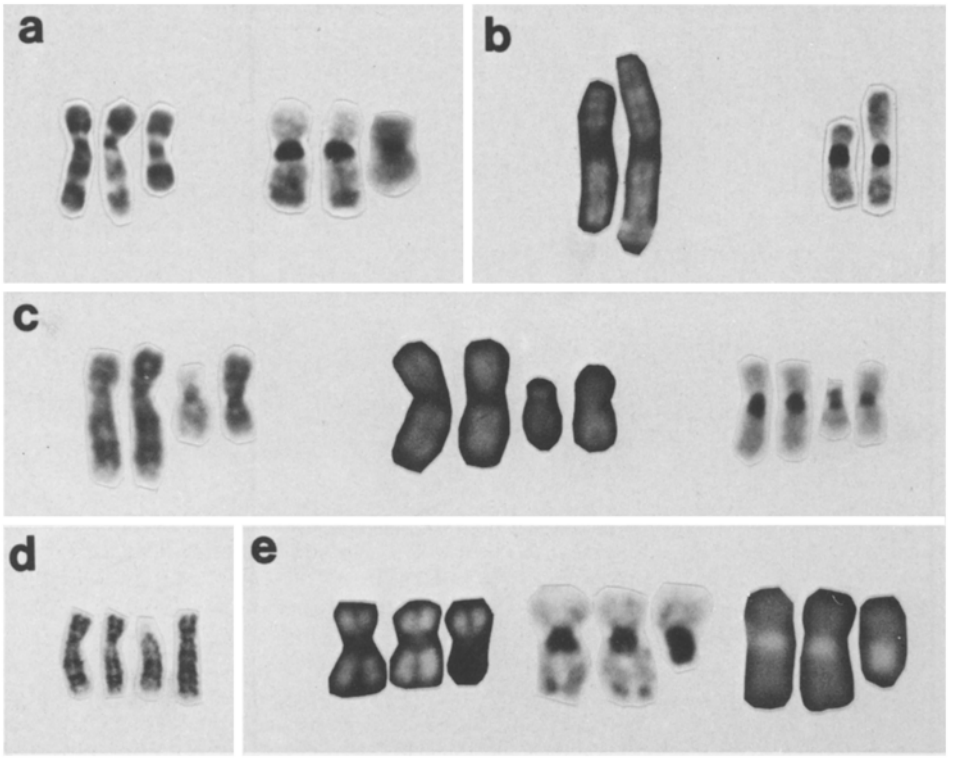

Fig. 2. a *Case 1.* The two chromosomes 9 and the i(9p) in GTG- *(left)* and in C-banding *(right).* **b** *Case 2.* The chromosome 9 and the dup(9) in RBA *(left)* and in C-banding *(right).* **c** *Case 3.* The two chromosomes 9, the 22, and the translocated 22/9 in GTG- *(left),* QFQ- *(middle),* and in C-banding *(right).* **d** *Case 4.* The two chromosomes 9, the 13, and the translocated 13/9 in GTG-banding. **e** *Case 5.* The two chromosomes 9 and the del(9) in QFQ- *(left),* C- *(middle),* and Da-DAPI-banding *(right)*

Case 5. Mosaicism was present in lymphocytes and in fibroblasts, the abnormal cells being more numerous in lymphocytes (Table 2). The extra chromosome was interpreted as consisting of the short arm, the centromere, and the p12 heterochromatic region of a chromosome 9. The constriction was usually very extended with a despiralized appearance. Neither the mother nor the brother showed in their karyotypes a chromosome 9 with a p12 region comparable to that of the patient's extra chromosome, but the father of the patient was dead.

Discussion

1. The Phenotype

Moedjono et al. (1980) reviewing the clinical findings of 9p tetrasomy found in addition to several features common to the trisomy 9p syndrome, some more severe malformations such as congenital heart defect and hydrocephalus, which were present also in our case. The dermatoglyphic studies in our case and in the case of Rutten et al. (1974), showed a pattern comparable to that found in trisomy 9p, while in the case described by Orye et al. (1975) no peculiar features were noted about the dermal ridge system of the patient. The presence of hydrocephalus in our case and in that of Rutten et al. (1974), both tetrasomic only for the short arm of chromosome 9, is not in agreement with the hypothesis of Baccichetti et al. (1979) who claimed that hydrocephalus is due, in addition to trisomy of the short arm, to the presence of trisomy of portions of the long arm that include at least 9q21.

The clinical features of our Cases 2, 3, and 4 are comparable to those considered characteristic of the trisomy 9p syndrome. The three patients have the typical facies with deep eyes, strabismus, large nose, and also short stature and mental retardation.

Patient 5, in whom the trisomy is in the mosaic form, has some features of trisomy 9p such as rounded facies, antimongoloid slant of the eyes, bulbous nose tip, short upper lip, but all these signs are so slight that she looks a completely normal woman. In fact these signs were only noticed on close inspection and with the previous knowledge of the signs of trisomy 9p. She had secondary anenorrhea for two years before examination and this indicates impairment of ovarian function which could be due to the chromosome abnormality. In fact, late menarche is not infrequent in 9p trisomy (Rethoré 1977). Our case 2 at the age of 15 years had not yet had menarche but hormonal levels indicated a prepubertal stage and our Case 4 also had not had menarche at the age of 14 years. The case described by Gripenberg et al. (1977) of free trisomy 9p in an elderly woman, who had some irregular menstruation, indicates that impairment of ovarian function is relatively common in trisomy 9p.

2. Origin of the Chromosomal Abnormalities

Case 1. Among six cases of partial tetrasomy 9p three (Rutten et al. 1974; Orye et al. 1975; Moedjono et al. 1980) had the same abnormal chromosome as that found in our case, while in the other three various portions of the p12 heterochromatic region (Ghymers et al. 1973) and of the long arm (Abe et al. 1977; Wisniewski et al. 1978) were involved. Three of the cases reported in the literature were mosaics. In the case of Ghymers et al. (1973) and in our case, the abnormal chromosome was consistently present in blood cultures while the fibroblasts showed a normal karyotype. In this respect, the cases of Abe et al. (1977), Wisniewski et al. (1978), and Moedjono et al. (1980) are not informative because only blood cultures were examined. Various mechanisms could be postulated to explain the origin of this abnormal chromosome. Rutten et al. (1974) postulated one of two possibilities. In the first one a disturbance of meiosis I in which two of the four chromatids of a bivalent 9 are rearranged

to form an apparent isochromosome which would then not disjoin from a normal No. 9. The second hypothesis of Rutten et al. (1974) assumes a selective endoreduplication of the entire centric short arm of chromosome No. 9 during meiosis I or during a postzygotic mitosis. We can postulate additional mechanisms of origin. A non-disjunction followed by a deletion or a centric fusion with formation of the isochromosome by reunion of the broken extremities in a normal zygote would explain concurrently the abnormal chromosome and the mosaicism. In two cases reported by Smith et al. (1978) and Sandig et al. (1979) a trisomy 9 originated from a 2:2 segregation of two de novo translocations involving 9q in which one of the products contained a 9p that became an isochromosome. A similar event followed by a 3:1 segregation (with the normal 9, the isochromosome, and the other normal chromosome implied in the translocation going in the same gamete) could result in tetrasomy 9p.

Case 2. De novo duplications of the chromosome 9 short arm similar to this case have been described by Rethoré and Lafourcade (1974), Chiyo et al. (1976), Baccichetti et al. (1979), Zadeh et al. (1981), and Fryns et al. (1979). In at least four of these cases the duplicated segment was interpreted as inverted while in our case it seems to be in tandem. A translocation between the homologous or the sister chromatids 9 at the points p12 and p24, respectively, can originate such an abnormal chromosome in a parental germinal cell. An insertion of the segment 9p12p24 within the short arm of the other chromosome 9 with a break at band p24 would also result into a chromosome like that found in our case.

Cases 3 and 4. The abnormal chromosomes in these cases originate by an adjacent I segregation of a translocation during parental gametogenesis. According to the pachytene diagram of these two translocations the type of resulting unbalance is in agreement with the preferential criteria of segregation as listed by Jalbert et al. (1980). The preferential tendency of chromosome 9 to rearrange with a short arm and the juxtacentromeric region of acrocentric and preferentially with chromosomes 15 and 22 has already been indicated by Lurie et al. (1976).

Case 5. There are on record several cases of free trisomy 9p similar to that found in our case but none of them is a mosaic. Their origin could be traced to a parental gametic non-disjunction followed by a deletion or vice versa. The case reported by Surana et al. (1976) indicated that a missegregation of a centric fission of one parental chromosome 9 can be an alternative origin for this type of abnormality. One of these two events could also be the origin of the abnormality in our case which, however, requires a further assumption to explain the mosaicism. This could have originated either by the post-zygotic loss of the extra chromosome or alternatively by the post-zygotic origin of the abnormality itself.

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