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Heritable Heteromorphism of the N. 16 Chromosome Pair in Man*

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1. Introduction

During cytogenetic researches in collaboration between the Institute of Genetics and the Institute of Clinical Oculistics, we have found a patient affected by myopia, with a caryotype characterized by heteromorphism of pair 16. This anomaly, first observed by Jennings and Turner (1961), is uncommon and differently considered.

This paper presents the data obtained by cytogenetic investigation of the patient and her family (for the pedigree of the proposita cf Fig. 1).

2. Methods

Chromosome studies were made on cells cultured from the peripheral blood, using a modification of the technique of Hungerford (1965). Fifty mitoses from each member of the family were counted and analyzed; and twenty photographed using a Zeiss microscope (Planapocr. obj. 100 x).

3. Results

The abnormal caryotype has been observed first in the proposita (II 4). It appears that the two homologous chromosomes of the pair N. 16 are clearly different in length and arm ratio (Fig. 2).

According to our observations one member shows the normal length and arm ratio; on the contrary, the other chromosome differs from an increased length of the long arm. The same variation between the two 16s has been observed in eight of the 21 members of the family group investigated. Fig. 3 shows chromosomes N. 13 to 18 from each of the 8 affected members. The arm ratio of the heteromorphous pair, resulting from the examination of 15 mitoses regarding each individual is re-

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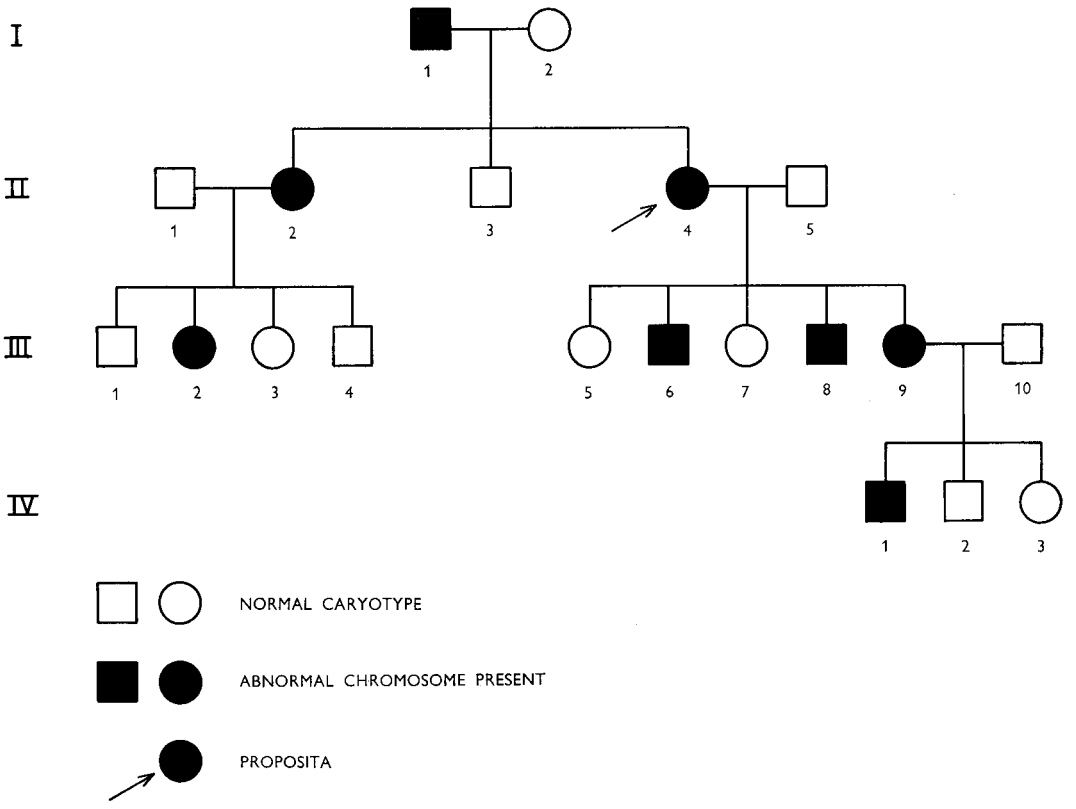

Fig. 1. Pedigree of the family.

ported in Tab. I. All family members were physically and mentally normal and in good health. Seven out of 8 anomaly carriers showed different degree of myopia and the last one appeared quite normal (cf Tab. II).

4. Discussion

Autosomal variants similar to that just described have previously been reported. The first caryotype which probably shows the heteromorphous 16s has been observed by Jennings and Turner (1961). The anomaly carrier was a girl presenting mental defect, deafness, webbing of the neck, genital infantilism and other minor congenital anomalies. These authors explain the case as a monosomy for chromosome 16 with occurrence of an additional chromosome in Groups 6 to 12. The suggested mechanisms, by which this caryotype might have arisen, were: " A double and reciprocal non-disjunction having occurred during meiosis, resulting in monosomy for chromo-

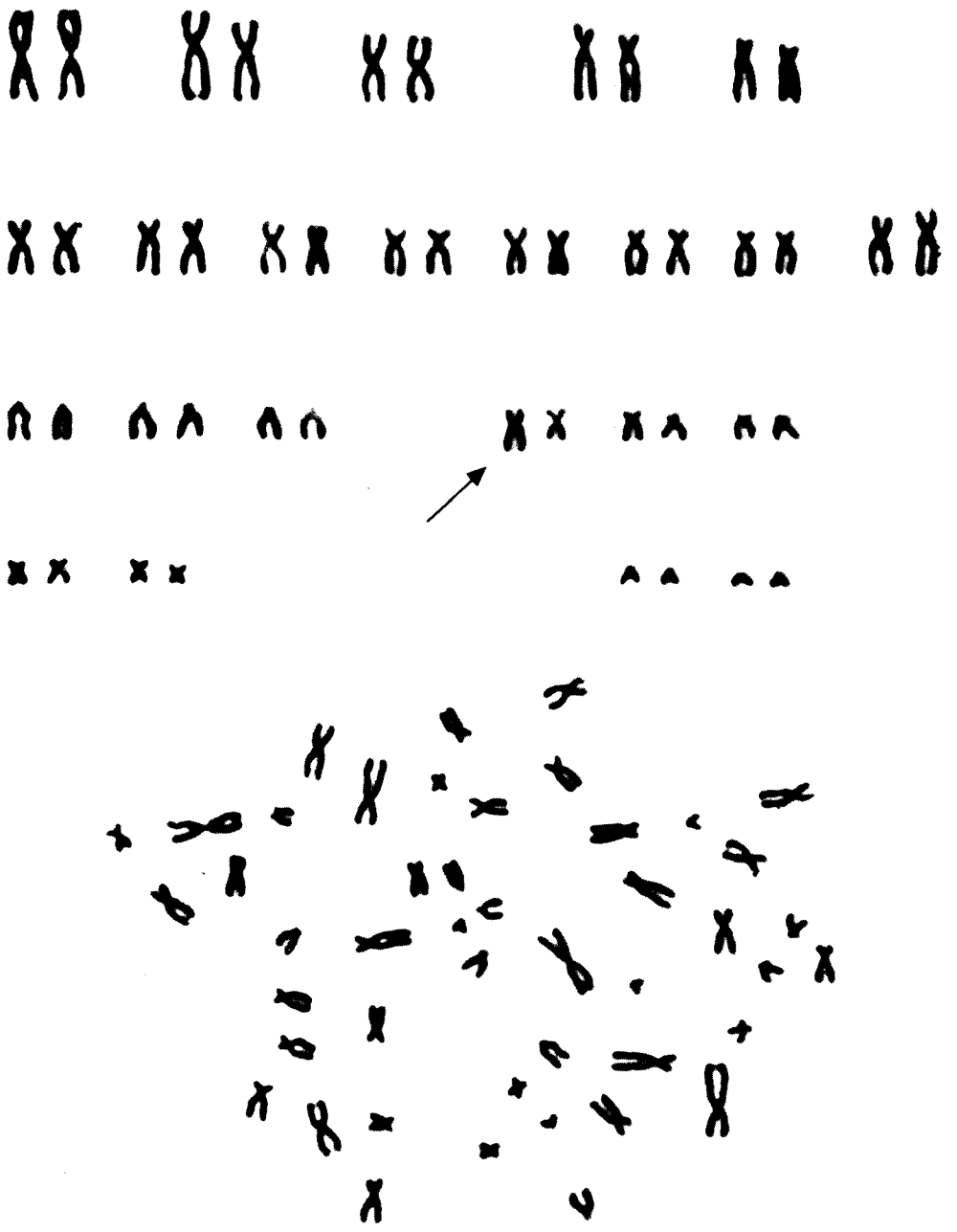

Fig. 2. Caryotype of proposita (II-4), × 2400; × 1700.

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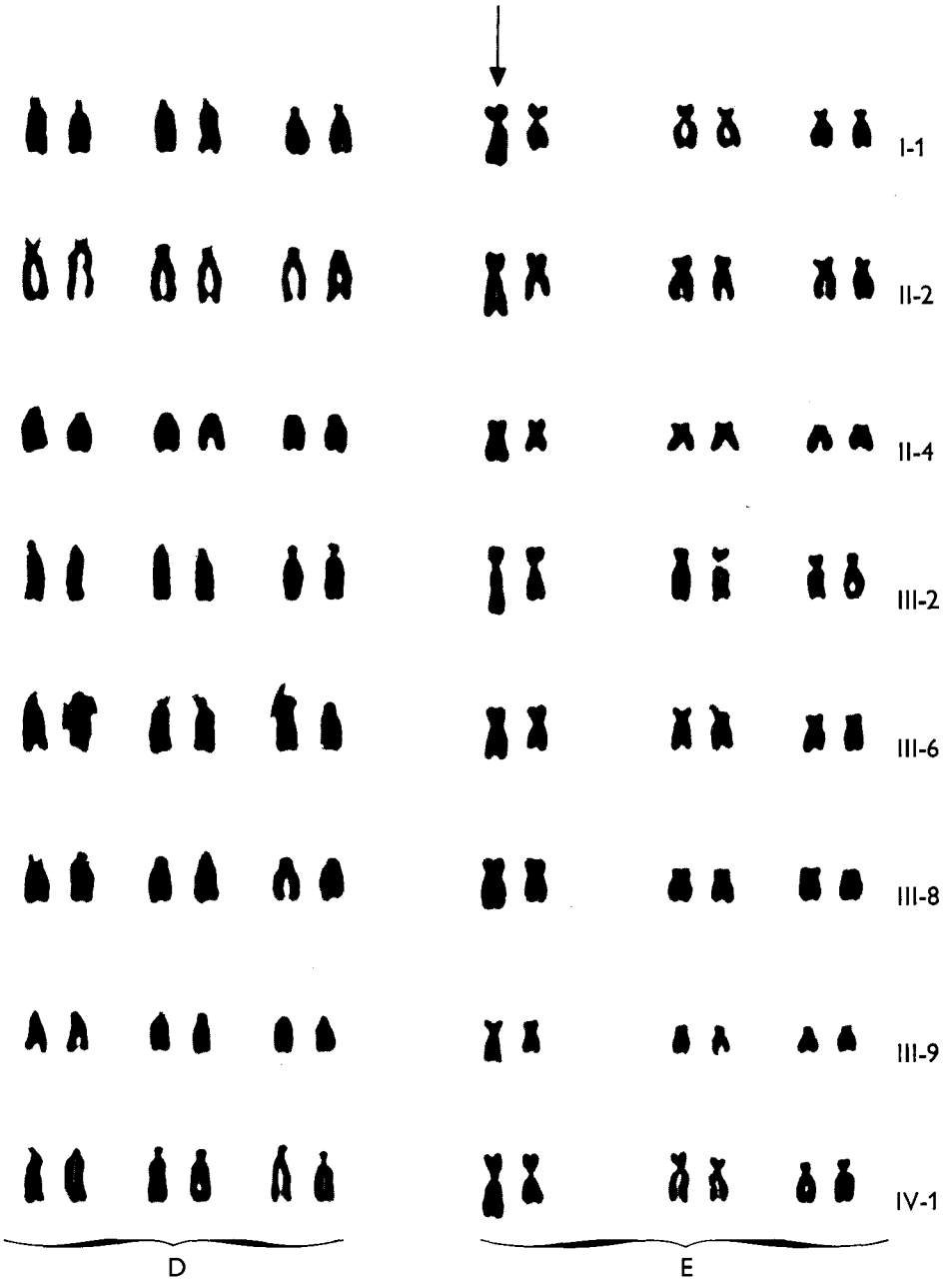

Fig. 3. Chromosomes N. 13 to 18 from the affected family members; × 2400.

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Tab. I. Arm ratios of the two N. 16 chromosomes

Subject	N.	I-1	II-2	II-4	III-2	III-6	III-8	III-9	IV-1
Normal	16	1.60	1.33	1.22	1.47	1.26	1.35	1.43	1.44
Abnormal	16	2.72	2.55	2.33	2.22	2.73	2.88	2.55	2.47

Tab. II. Ocular findings

Patient	Age	Visual acuity	Sph
I-1	83	OD 6/10	—3.5 (cicatricial stage of trachoma)
		OS 5/10	—5
II-2	47	OD 9/10	—6 (cicatricial stage of trachoma)
		OS 10/10	—6.5
II-4	62	OD: cataract removed	(cicatricial stage of trachoma)
		OS	—7
III-2	19	OD 10/10	—2.50 ax, —1.5 cyl ax 180°
		OS 10/10	—2.75 ax, —1.5 cyl ax 180°
III-6	28	OD 10/10	—1.5
		OS 10/10	—1
III-8	32	OD 10/10 emmetrope	
		OS 10/10	
III-9	33	OD 10/10	—4
		OS 10/10	—5
IV-1	4	OD 10/10	—1
		OS 10/10	—1.5

some 16 and trisomy for one of the 6 to 12 Group chromosomes... A translocation on the one chromosome 16 of chromatin material from another chromosome..." (Jennings and Turner, 1961, p. 832). Two years later a similar case was described clinically and somatically by Carr (1963), who interpreted the abnormal caryotype as due to " considerable discrepancy in size between the normal chromosome 16 and the only other which could be paired with it" (Carr, 1963, p. 459-460). Further studies of the family of this patient showed that her father and two brothers had the same abnormal caryotype though they were physically normal. Thus the relation between the abnormal caryotype and the phenotype remains uncertain.

In the same year two more cases of an abnormal N. 16 chromosome pair were reported by de Morsiers and Gauthier (1963) and Bray and Mukherjee (1963). The first case was characterized by the additional occurrence of an olfacto-genital dysplasia and a long Y.

In the second case, observed in an infant with a degenerative disease of the central nervous system, " a presumed translocation involving 2 chromosomes of Group 16-18" (Bray and Mukherjee, 1963, p. 234) produced two heteromorphic pairs

(N. 16 and 17). Soon later Tips et al (1964) reported an unusual chromosome mosaicism in a family of a patient with gonadal dysgenesis: " three abnormal leucocyte cell lines associated with a 16' chromosome [1] were found in siblings, the mother and her co-twin, and the maternal grandfather, all of whom had anomalies of the face, palate and digits. Mosaic leucocyte karyotypes in each affected person represented cell lines (16, 16-16'), (16-16') and (16)." (Tips et al, 1964, p. 330). Several instances of two unequal N. 16 chromosomes have been reported by Makino and his school (Makino, 1963, 1964; Sasaki et al, 1963). Twenty three patients with heart defects, including three mongoloids, were studied, and 9 out of these cases showed the heteromorphous 16s.

It is necessary to report what Makino considers as abnormal chromosome: the shorter metacentric homologous of N. 16 pair which we think to be the normal one. He writes: " the abnormal manifestation of N. 16 is probably related to the particular structure of this chromosome, and may be the result of a partial deletion of a small segment of the long arm, or, less likely, by irregular condensation of the chromosomes" (Makino, 1963, p. 74). Inversely, the other chromosome partner is normal for Makino and abnormal (i.e. longer, with atypical arm ratio) according to our interpretation.

Between the nine cases reported as abnormal by Makino, one is also affected by Down's disease. The coincidence of two unequal 16s with one or more different etiologies seems merely casual, thus Starkmann and Shaw (1967) [2] report a negro mongoloid with G trisomy and the " enlarged " chromosome 16, and German et al (1966) three cases in a family with heart disease. Two members of this family were normal and the other one had a heart disease. Both Starkmann and Shaw (1967) and German et al (1966) seem to favour the interpretation of the abnormal length of one 16 as due to structural change, instead of variation in coiling.[3]

Moores et al (1966), during a survey of 250 cases of congenital heart disease, found some instances of two unequal 16s in two family groups. The marker chromosome was observed in more generations and was present in clinically normal relatives. Moores et al considered this marker chromosome as a variation due to inherited alteration of secondary constriction in the long arm and unrelated to congenital heart disease.

Starting from the Makino's report, Kelly and Almy (1966, 1967) investigated several mongoloids with congenital heart diseases and confirmed the observations of Makino on the chromosome morphology of 16s and its clinical implications.

[1] «... the 16' had unusually large long arms» (cf p. 331).

[2] Starkmann and Shaw (1967), p. 169: «Thus, we do not feel that our findings are due to despiralization or abnormal coiling producing a generalized prominence of heterochromatin».

[3] German (1966), p. 520: «In the present study of chromosomal morphological variation in relation to human cardiac malformations, there is the suggestion that certain embryonic developmental anomalies are sometimes correlated with the inheritance of small morphological, very possibly structural, chromosomal variations which are known to exist in normally developed individuals in the general population».

In the same year three more cases of this chromosome heteromorphism were published by Grimaud et al (1967), Crawford et al (1967), Frederic et al (1967). The first paper deals with a chromosome study on deafmutes. Thirty-two out of 34 patients had regular caryotype. The other two subjects presented the chromosome anomaly. Further studies of the families of these two patients were performed. The father of the first subject was found to have normal caryotype, but the mother's chromosomes showed the heteromorphous pair. A second family group, physically normal, was quite unusual in that the chromosome anomaly occurred to the mother, four brothers and one sister. The father and another brother had the regular caryotype. Grimaud suggests that a balanced translocation might be present in the healthy members of the family. The umbalanced condition would be responsible for the observed deafmutism.

The second case mentioned before, is not quite certain, judging from the chromosome morphology (cf Crawford et al, 1967, p. 1075; Fig. 1). The difference between the two N. 16 chromosomes seems to be very strong and these authors explain the shorter member " as having a deletion (either interstitial or terminal) distal to the secondary constriction of the long arm of the normal chromosome 16 " (Crawford et al, p. 1076). This patient, a 26 months old child, mental retarded Caucasian female, has been examined, with the family from the blood group systems. The Duffy blood group gave an unespected result. The cells of the mother and father reacted strongly with the serum but those of the child were not reactive. Crawford et al (1967, p. 1076) conclude " that either the propositus has a previously underscribed *Fy* allele or that the absence of the expected Fy^b allele in the child is the result of loss of chromosomal material which includes the locus of Duffy gene ".

The third paper by Frederic et al (1967) describes a patient affected with Stein-Leventhal syndrome. " The chromosomal examination..., did not reveal an anomaly of the heterochromosomes, but an asymmetry of the 16th pair " (Frederic et al, 1967, p. 36-37). The chromosome anomaly is esteemed as due to an unknown translocation, and its meaning is discussed with regard to Stein-Leventhal syndrome.

In other instances the occurrence of this chromosome heteromorphism has been observed only for subjects with any demonstrable anomaly. Such reports have been published by Jacobs et al (1964), Hall (1964), Court Brown et al (1965), Nuzzo et al (1966), Lejeune (1966) and Therkelsen et al (1967).

The longer N. 16 chromosome is usually estimated as due to genetically determined alterations in coiling; however, the possibility of structural rearrangement is not refused. The first hypothesis stands on the presence of a secondary constriction on the long arm of the 16s as described by Saksela (1962) and Sasaki (1963). The heteromorphous caryotype which we have already described represents a case similar to those mentioned above. The abnormal chromosome N. 16 seems to segregate regularly and to be inherited by both sons and daugthers of carriers. The variation of arm ratio seems likely due to a structural rearrangement, instead of a change in coiling.

The review of the literature clearly shows the absence of stable phenotypical

manifestations related to this chromosome heteromorphism. At present neither the biological meaning of these autosomal variants nor their relation to the etiology of different diseases can be established.

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Summary

A family is described with heteromorphism of N. 16 chromosome pair. The abnormal submetacentric chromosome was found in a total of 8 family members. Seven out of these carriers show a variable degree of myopia.

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RIASSUNTO

Si descrive in un gruppo familiare l'eteromorfismo ereditario della coppia cromosomica 16. Il tipo anomalo, submetacentrico, fu osservato in 8 membri di tale famiglia. Sette di essi presentavano miopia di vario grado.

RÉSUMÉ

Un hétéromorphisme héréditaire du couple chromosomique N. 16 est décrit chez un groupe familial, huit membres duquel présentaient le type anomale sub-métacentrique; sept d'entre eux présentaient aussi miopie de différent degré.

ZUSAMMENFASSUNG

Beschreibung von erblichem Heteromorphismus des Chromosomenpaars 16 in einer Sippe, bei welcher der anomale, submetazentrische Typ in 8 Fällen beobachtet wurde, von denen sieben Kurzsichtigkeit verschiedenen Grades aufwiesen.

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