Hum. Genet. 32, 13—16 (1976)

Origin of the Extra Chromosome No. 21 in Down's Syndrome

P. Wagenbichler[1], W. Killian[2], A. Rett[2], and W. Schnedl[3]

[1]I. Universitäts-Frauenklinik Wien
[2]Neurologisches Krankenhaus Rosenhügel, Abteilung für entwicklungsgestörte Kinder, Wien
[3]Histologisch-Embryologisches Institut, Wien

Received October 22, 1975

Summary. Eighteen of 38 examined families with children with Down's syndrome showed polymorphisms of chromosome 21 elucidating the origin of the extra chromosome 21. Maternal origin was found in 10 cases and paternal origin in 8 cases. In both sexes errors occurred both in the first and in the second meiotic division.

Introduction

By using the quinacrine fluorescence technique several human chromosomes could be shown to contain polymorphic regions which are inherited like Mendelian genes (Schnedl, 1971). These polymorphisms are extremely abundant in the acrocentric chromosomes permitting studies on the mechanisms which result in trisomy of acrocentric chromosomes. The most important syndrome in this group is trisomy 21, Down's syndrome.

In the first publication on the origin of the extra No. 21 in mongolism using polymorphisms of this chromosome (Licznerski and Lindsten, 1972), the extra 21 could definitely be traced to the mother. Further studies (Robinson, 1973; Mutton, 1973; Sasaki and Hara, 1973; Uchida, 1973) showed that the supernumerous chromosome 21 can be both of maternal and paternal origin. Moreover, both errors in first and second meiotic division may be involved.

Material and Methods

Chromosome preparations of 38 children with Down's syndrome and their parents were made from peripheral blood cultures. Mitotic cells were studies by quinacrine mustard fluorescence as described previously (Schnedl, 1973). The polymorphisms of chromosome No. 21 were studied both directly in the microscope and on microphotographs made on Kodak Plus X film. The polymorphisms were judged by subjective criteria, but this was no problem, since direct comparisons of the 3 chromosomes 21 in the patients and in the parents were performed. In 18 of 38 families the polymorphisms permitted conclusions on the origin of the extra 21 in the patient.

Results

As shown in Table 1, 8 of 18 children trisomic for chromosome 21 received 2 chromosomes 21 from the father and 10 patients received 2 chromosomes 21

Table 1. Origin of chromosome 21 in Down's syndrome

	Nondisjunction at meiotic division			
	I	II	uncertain	total
Father	4	3	1	8
Mother	7	2	1	10
Total	11	5	2	18

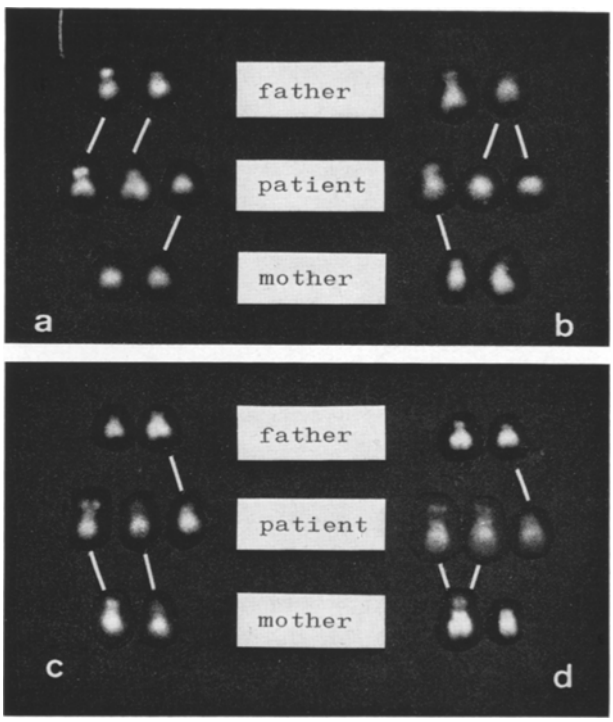

Fig. 1a—d. Chromosomes No. 21 from 4 children with Down's syndrome and their parents. (a) Trisomy 21 as a result of nondisjunction during I meiotic division in father. (b) Nondisjunction in the II meiotic division in father. (c) Nondisjunction in I meiotic division in mother. (d) Nondisjunction in the II meiotic division in mother

from the mother. In the 8 patients which resulted from nondisjunction in the father, 3 had two identical chromosomes 21, obviously the result of nondisjunction in the second meiotic division (Fig. 1b). In 4 cases the 3 chromosomes 21 were different: this means that they were caused by nondisjunction in the first meiotic division (Fig. 1a). In 1 case exact information concerning the location of the defect to first or second meiotic division could not be obtained.

In those patients who received 2 chromosomes from the mother, 7 showed the result of nondisjunctions in the first meiotic division, 2 were clearly caused

Table 2. Parental age

Origin of the extra chromosome 21				
	father		mother	
	age father	age mother	age father	*age mother*
	25	22	33	*25*
	26	19	30	*26*
	26	22	32	*32*
	28	32	35	*38*
	29	26	43	*39*
	41	31	38	*40*
	45	36	47	*41*
	51	42	42	*42*
			43	*43*
			45	*45*
Mean	33.9	28.8	38.8	37.1
S.E.	± 3.6	± 2.8	± 1.9	± 2.2

by nondisjunction in the second meiotic division, and 1 case remained uncertain. Examples of these situations are given in Figure 1 c and d.

The ages of the parents at the birth of the mongoloid children are listed in Table 2.

Discussion

When studying the correlation between birth frequencies of Down's syndrome and parental age (Penrose, 1933; Jenkins, 1933) some evidence for a major role of maternal age in the occurrence of Down's syndrome was found. The paternal age seemed to be of less importance. Since then, the origin of the extra chromosome 21 was mainly believed to be the result of a nondisjunction in the mother.

The recent methods, especially the quinacrine fluorescence techniques, make studies on the origin of the extra 21 in Down's syndrome possible. Mutations and cross over in the polymorphic regions of this chromosome are extremely rare (Craig-Holmes et al., 1975) permitting the use of these markers for tracing the origin of the extra chromosome. Several authors showed already that nondisjunction both in the mother and the father may be the cause for trisomy No. 21 (Licznerski and Lindsten, 1972; Robinson, 1973; Mutton, 1973; Sasaki and Hara, 1973; Uchida, 1973).

The present observations on a small number of cases show almost identical numbers for maternal and paternal origin of the extra 21 in Down's syndrome. In those cases, where the extra 21 was the result of a nondisjunction in the father, first and second meiotic divisions were affected to approximately equal numbers. However, in those children who received their extra 21 from the mother, nondisjunction at the first meiotic division contributed to the major part of the aberrations. This reflects the physiologic situations in both sexes: whereas in males both meiotic divisions occur subsequently, the first meiotic division in the female starts already during fetal life, is finished shortly before ovulation, and

the second division does not start until ovulation. Thus first and second meiotic divisions in the female may be influenced in entirely different ways. It does not come as a surprise, that nondisjunction does not occur at the same frequencies in female first and second meiotic division.

The distribution of the maternal and paternal ages indicates that errors in meiosis are age dependent in both sexes; possibly this tendency is more pronounced in mothers than in fathers. Since parental age plays a major role in evaluating the risk of occurrence in Down's syndrome, further studies on a large number of cases are needed to find out the correlation between the ages of both the mothers and the fathers of mongoloid children after having identified the parent, in which nondisjunction of No. 21 occurred.

References

Craig-Holmes, A. P., Moore, F. B., Shaw, M. W.: Polymorphism of human C-band heterochromatin. II. Family studies with suggestive evidence for somatic crossing over. Amer. J. hum. Genet. **27**, 178—189 (1975)

Jenkins, R. L.: Etiology of mongolism. Amer. J. Dis. Child. **45**, 506—519 (1933)

Licznerski, G., Lindsten, J.: Trisomy 21 in man due to maternal non-disjunction during the first meiotic division. Hereditas (Lund) **70**, 153—154 (1972)

Mutton, D. E.: Origin of the trisomic 21 chromosome. Lancet **1973 I**, 375

Penrose, L. S.: Relative effects of paternal and maternal age in mongolism. J. Genet. **27**, 219—227 (1933)

Robinson, J. A.: Origin of extra chromosome in trisomy 21. Lancet **1973 I**, 131—133

Sasaki, M., Hara, Y.: Paternal origin of the extra chromosome in Down's syndrome. Lancet **1973 II**, 1257—1258

Schnedl, W.: Unterschiedliche Fluoreszenz der beiden homologen Chromosomen Nr. 3 beim Menschen. Humangenetik **12**, 59—63 (1971)

Schnedl, W.: Analysis of the human karyotype by the recent banding techniques. Arch. Genet. **46**, 65—98 (1973)

Uchida, I. A.: Paternal origin of the extra chromosome in Down's syndrome. Lancet **1973 II**, 1258

Dr. W. Schnedl
Histologisch-Embryologisches Institut
Schwarzspanierstraße 17
A-1090 Wien, Austria