FAMILIAL 21/22 TRANSLOCATION

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A family is described with 21/22 translocation, where chromosome segregation appeared to follow theoretical expectations, rather than empirical risk figures, in male and female carriers alike.

The usefulness of prenatal genetic studies in genetic counseling is also demonstrated.

INTRODUCTION

The incidence of the GqGq translocation among the patients with Down's syndrome is 2-4% (Mikkelsen 1967); according to some statistics it is even lower (Hongell et al. 1972).

Nowadays, reliable data are available on the recurrence risk of both regular trisomy G and translocation trisomies (Hamerton 1968, Mikkelsen and Stene 1970). In translocation cases, the risk depends on the rearrangement type and the sex of the carrier. In DqGq translocation, the risk in female carriers is approximately 10%. An almost identical risk was observed in the limited number of 21/22 translocation cases studied. In the case of male carriers of 21/22 translocation, the risk cannot be estimated, but appears to be lower.

According to Hamerton (1971) only 5.6% of the GqGq translocations are hereditary, while 94.4% arise *de novo*.

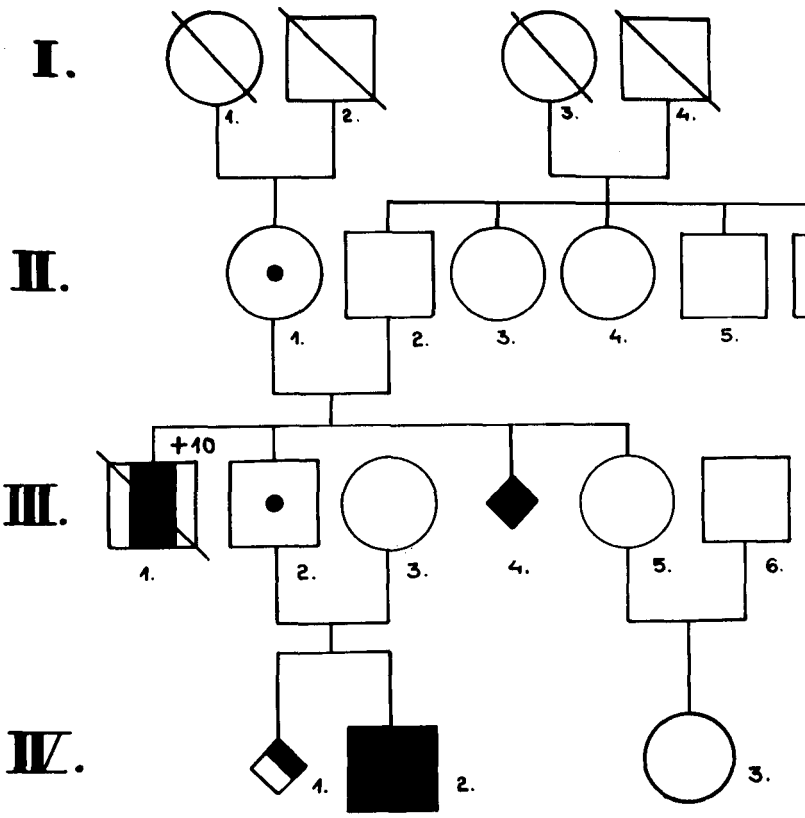
The limited number of reports on familial cases of 21/22 translocation prompted us to report a family where chromosomal segregation followed theoretical expectations rather than empirical risk figures.

CASE HISTORY

B.A., a 24-year-old woman, has been married 4 years (III.3 on the pedigree shown in Fig. 1). She had one previous pregnancy, terminated by induced abortion (IV.1). She was admitted to our department in the 38th week of her second pregnancy on account of dry labour.

A few hours after admission a normal delivery took place with skull presentation. The newborn began crying at once. Its weight was 2500 g, its weight percentile less than 10, its length 48 cm, the weight of the placenta 320 g. Soon after delivery it was noticed that the umbilical cord was shorter than the average (30 cm), there was a large protruding tongue, oblique palpebral fissures, epicanthus fold, a flat profile and nose bridge, muscle hypotension and a lack of Moro reflex. Fourteen hours after delivery, blood was taken from one of the scalp veins of the newborn for chromosome analysis. The lymphocyte culture was not successful because of a technical fault. The parents refused to permit a second sampling of blood.

Only four years later was light thrown on the familial antecedents when a member of the family (the sister of the child's father: III.5) was admitted to our department. When she was questioned in



II.1. 45, XX, G–, G–, t/GqGq/+
II.2. 46, XY
III.1. Clinically Down's syndrome
III.2. 45, XY, G–, G–, t/GqGq/+
III.4. Spontaneous abortion
III.5. 46, XX
IV.1. Artificial interruption
IV.2. 46, XY, G–, t/GqGq/+
IV.3. 46, XX

Fig. 1

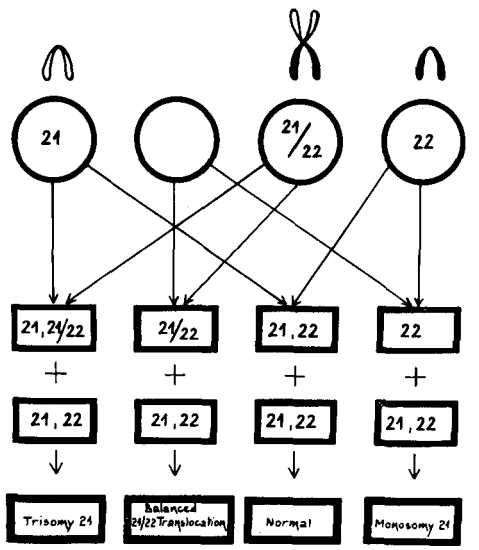


Fig. 2

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detail about the family anamnesis, it was found that a brother (III.1) of the father (III.2) died at the age of 10, and though no cytogenetic investigation occurred, he was unequivocally considered to have had Down's syndrome on the basis of the characteristic symptoms detected in the course of the hospital investigations. The sister (III.5) of the child's father was admitted to our department in the 38th week of her first pregnancy. Though there was no question of giving her preventive treatment on account of the advanced state of her pregnancy, even in case of Down's syndrome, a chromosome investigation was carried out with the peripheral blood of her mother. We were able to persuade her brother (III.2) to subject himself to an investigation, so blood was taken also from the four-year-old boy (IV.2).

The karyotype of the child (IV.2) was 46,XY,G-,t/GqGq/+; that of the father (III.2), 45,XY, G-,G-,t/GqGq/+. Satellite association could often be observed among the D and G chromosomes. The sister (III.5) of the father and the child's grandfather (II.2) showed a normal karyotype, whereas the karyotype of the grandmother (II.1) was 45,XX,G-,G-,t/GqGq/+. The great-grandparents are not living: we were not able to examine any other relatives of the family. Further family studies revealed that the grandmother (II.1) had had an additional pregnancy which was interrupted spontaneously (III.4).

On the basis of the results of the above investigations, the sister (III.5) of the child's father was assured that the chance of her bearing a Down's syndrome child was not greater than that of the general population. The delivery took place two weeks later and the newborn girl proved to be healthy on the basis of the external signs (IV.3). The result of the chromosome analysis performed from the cord blood was 46,XX.

A more exact chromosome analysis is being planned, employing a special staining and fluorescence method, but, for the present, the members of the family could not be persuaded to subject themselves to further investigations. The 21/22 translocation seems to be verified without any special staining since the segregation argues in favour of it (there also are healthy offsprings). The balanced translocation-carriers (II.1 and III.2) are average persons, both somatically and mentally; no characteristic signs of Down's syndrome, nor any other similar signs, could be observed.

DISCUSSION

Phenotypically normal 21/22 translocation carriers (45,XX or XY, 21-,22-,t/21q22q/+) can theoretically have four kinds of offsprings (Fig. 2): translocational Down's syndrome (46,XX or XY, 22-,t/21q22q/+); healthy, but carriers like themselves; karyotype normal, and 21 monosomies.

Since G 21 monosomy usually results in miscarriage, such cases might be excluded from our calculation of livebirths.

The balanced 21/22 translocation carriers can be recognized by the fact that they have diseased and healthy offsprings alike, some of the healthy ones also being balanced carriers. In contrast to this, every offspring of the 21/21 translocation carriers will be afflicted with Down's syndrome. Only in a mosaic case, can the birth of a healthy descendant be imagined (Waxman and Arakaki 1966).

Soudek et al. (1966, 1968) have an interesting observation concerning a family, where, in one of the balanced translocation carriers, the rearranged chromosome proved to be acrocentric and not metacentric in consequence of the pericentric inversion of the translocation chromosome.

In Hungary, Méhes (1969) was the first to find GqGq translocation trisomy. Intrauterine chromosome analysis was carried out in the same family by us, the GqGq translocational Down's syndrome was diagnosed prenatally and the pregnancy was interrupted (Papp et al. 1971, 1972).

Stene (1970) performed the statistical analysis of seven families on the basis of literary reports (Pfeiffer 1963, Yunis et al. 1965, Jackson and Ashford 1967, Scheibenreiter et al. 1968, Yang and Rosenberg 1969).

Of the descendants of the female 21/22 translocation carriers, 8.9% were found to be afflicted with Down's syndrome, as opposed to the theoretical chance of 33%. The chance of a phenotypically normal child becoming a balanced carrier was found to be about 53%.

In contrast to the above-given empirical data, in our case the inheritance of 21/22 translocation followed theoretical expectations.

The great-grandparents are dead: therefore it was impossible to carry out investigations on them, so that we do not know whether the translocation came about *de novo* in the grandmother (II.1), or was inherited. In the four pregnancies of the balanced carrier grandmother (II.1) all of the four theoretical variations can be found. Her first child was afflicted with Down's syndrome (III.1), and, though no cytogenetic investigation was carried out in this case, it had in all probability a translocation trisomy. The phenotypically normal male (III.2) was in all probability a balanced translocation carrier. The spontaneous abortion (III.4) was probably caused by chromosome deficiency of the G 21 monosomy type. The sister (III.5) proved to have a normal karyotype, so that she did not endanger her descendants from such a viewpoint — as the karyotype of her first child (IV.3) verifies.

The limited data in our family suggest that the 21/22 translocation was inherited according to theoretical expectations in both male and female carriers. The determination of the karyotype in each member of the family proved to be a valuable help at genetic counseling. In the case of a further pregnancy of III.3 it would certainly be advisable to resort to amniocentesis and intrauterine chromosome analysis. There is no need of this in the further pregnancies of III.5, because the risk is not greater than in the general population.

In this way pedigree analyses, supplemented by cytogenetic investigations, become indispensable tools of both genetic counseling and prenatal diagnostics.

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RIASSUNTO

Traslocazione Familiare 21/22

Viene descritta una famiglia con ricorrenza di traslocazione 21/22 con segregazione corrispondente ai rapporti teorici in portatori di sesso sia maschile che femminile. I risultati sono di rilievo sia ai fini della consulenza genetica che della diagnosi prenatale.

RÉSUMÉ

Translocation Familiale 21/22

Une famille est décrite, atteinte de translocation 21/22 avec ségrégation correspondante aux rapports théoriques chez des conducteurs de sexe soit masculin soit féminin. Les résultats intéressent la consultation génétique ainsi que le diagnostic prénatal.

ZUSAMMENFASSUNG

Familie mit rekurrenter 21/22 Translokation

Beschreibung einer Familie mit rekurrenter 21/22-Translokation, wo die Segregation bei männl. sowohl als weibl. Trägern dem theoretischen Verhältnis entspricht. Die Ergebnisse sind sowohl für die Erbberatung als für die pränatale Diagnose von Bedeutung.

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