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# BALANCED CHROMOSOME REARRANGEMENTS AND ABNORMAL PHENOTYPE

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Analysis of the results of 3411 routine cytogenetic examinations initiated by abnormal phenotype or family history revealed that out of 44 cases with balanced structural aberration 12 patients had an abnormal phenotype. Of the 12 cases, there were four reciprocal translocations, three Robertsonian translocations, and five pericentric inversions. Eight rearrangements were inherited, one had occurred de novo, and three were of unknown origin. Each carrier parent was apparently healthy. In all of the four cases with reciprocal translocation the rearrangements were of paternal origin. None of the clinical abnormalities could be assigned specifically to the breakpoints. Explaining the association of balanced chromosomal rearrangement and clinical abnormalities, possibilities of causal relationship and by chance coincidence are discussed.

## INTRODUCTION

Balanced chromosomal rearrangements usually do not cause abnormal phenotype. However, they have been reported repeatedly in association with mental retardation and/or congenital anomalies over the past years /1,2,3,4,5,8/. To explain the relationship between the abnormal phenotype and the apparently balanced karyotype, several hypotheses have been suggested, viz. 1/ submicroscopical aneuploidy, 2/ a gene mutation at the breakpoint, 3/ position effect /6/, but this association deserves further clarification. We therefore decided to analyse our cases with balanced chromosomal rearrangement found in routine diagnostic cytogenetic activity and tried to find out whether the clinical symptomatology could be related to the hypotheses mentioned.

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## MATERIAL

The study group comprises 3411 patients referred for chromosome analysis to the Pediatric Department of University Medical School, Pécs between 1974 and 1989, and to the Pediatric Department of County Hospital, Győr between 1980 and 1989. Chromosome analyses were indicated according to the generally accepted clinical practice, viz. by abnormal phenotype, by reproductive failure, or by having a first degree relative with structural chromosome aberration. Chromosome analyses performed in any screening program were excluded.

## RESULTS

A total of 615 cases with abnormal karyotype were found among 3411 patients whose cytogenetic examination was initiated by phenotype or history suggesting chromosome aberration. Out of the 615 constitutional chromosome abnormalities, 499 (81.1%) were numerical and 116 (18.9%) were structural aberrations. The structural aberration was "balanced" in 44 cases, i.e. in 7.2% of the total (Table I).

TABLE I

Type of aberration in 3411 patients referred for chromosome analysis because of suspected chromosome anomaly

| Aberration | No. | % |
|---|---|---|
| Numerical | 499 | 81.1 |
| Structural | 116 | 18.9 |
| unbalanced | 72 | 11.7 |
| balanced | 44 | 7.2 |

Table II shows that the majority of balanced structural aberrations were discovered in the course of family studies initiated by unbalanced aberration in a member of the family, i.e. in the index patient. Surprisingly, there were only a few

cases discovered on the base of repeated spontaneous abortions. The low ratio may result from referral bias (both laboratories are functioning in pediatric clinics). Twelve cases, i.e. 1.9% of all aberrations were diagnosed in patients who were referred for examination because of abnormal phenotype (Table II).

TABLE II

Reason of referral for chromosome analysis in 44 cases with balanced structural aberration

| Indication | No. |
|---|---|
| Family study | 23 |
| Spontaneous abortions | 9 |
| Abnormal phenotype | 12 |

Table III summarizes the cytogenetic findings and the main clinical features of patients whose cytogenetic examination was initiated by abnormalities in the phenotype. Neither the mental retardation, nor the major/minor malformations of these patients could be explained by any other clinical and laboratory tests or by pre-, peri-, or postnatal history. It is interesting that in all of the 4 cases with balanced reciprocal translocation the aberrations were of paternal origin, but the number of cases does not allow to draw any conclusion. In the majority of cases the balanced aberration was familial (in 3 cases the parents, or any of them, were not accessible for chromosome analysis). Neither of the transmitting parents showed phenotypic abnormalities.

TABLE III

Balanced chromosome aberration with abnormal phenotype

| Case No. | Chromosome aberration | Clinical abnormalities |
|---|---|---|
| Case 1. | t(5/14) pat | some features of Turner syndrome |
| Case 2. | t(6/12) pat | some features of Turner syndrome |
| Case 3. | t(3/19) pat | fetal hydrops |
| Case 4. | t(11/13) pat | esophageal atresia |
| Case 5. | t(D/D) ? | mental retardation, syndactyly on feet, facial dysmorphism |
| Case 6. | t(13/15) mat | mental retardation, microcephaly |
| Case 7. | t(14/21) pat | mental retardation, facial dysmorphism |
| Case 8. | inv(2) mat | mental retardation, facial dysmorphism |
| Case 9. | inv(5) de novo | hypogonadism, micropenis |
| Case 10. | inv(9) ? | some features of Turner syndrome |
| Case 11. | inv(9) pat | ano-uro-genital malformation |
| Case 12. | inv(9) ? | hypogonadism, obesity |

## DISCUSSION

One quarter of our patients with "balanced" structural aberration had phenotype abnormalities. This could be the result of submicroscopic aneuploidy caused by a tiny deletion or duplication prior to chromosomal rearrangement. However, none of the clinical abnormalities could be assigned specifically to the breakpoints. In addition, in 8 cases the probands' rearrangement was also found in one of the parents who had no clinical abnormalities. Although meticulous examination of "healthy" subjects - which was not done in every carrier parent in this retrospective study - may reveal latent features of microdeletions or trisomies /7/, the parent/offspring difference in the clinical manifestation of an

apparently same rearrangement might be explained by secondary duplications or deletions arising at meiosis leading to phenotype abnormalities in the child, but also this possibility can be excluded by the lack of specific karyotypic/phenotypic correlation.

Clinical abnormalities in the offspring and normal phenotype in the parent with the same rearrangement could be explained by gene mutation at the breakpoint, if we suppose heterozygosity at the locus in the other parent, and hence, homozygosity in the offspring. However, the clinical manifestation did not suggest a known autosomal recessive disorder in any of the index patients.

The most plausible explanation seems to be a by chance coincidence of a chromosomal rearrangement and clinical abnormalities of unknown reason without any causal relationship. Since most chromosome analyses are done because of phenotypic abnormalities, an ascertainment bias favoring the discovery of a rearrangement in a subject with an abnormal phenotype certainly contributes to an unduly high rate of mental retardation and/or malformation among carriers of apparently balanced rearrangements. However, if we want to rely on this explanation in genetic counseling for estimating the reproductive risk of a person with a "balanced" chromosomal rearrangement, further studies on larger population are needed.

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