A de novo complex chromosomal rearrangement involving chromosomes 2, 8 and 13 in a dysmorphic case with polysyndactyly

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We report herein a case with dysmorphic features, polysyndactyly and psychomotor mental retardation, who had an apparently balanced de novo translocation between chromosomes 8 and 13 as well as a de novo insertion within chromosome 2 itself.

This case is worth mentioning in the sense that it bears two de novo rearrangements with five breakpoints. The correlation between the possible disrupted genes within the given breakpoints and the phenotype of the case will be discussed.

Key words: polysyndactyly, dysmorphism/psychomotor retardation, complex chromosomal rearrangements, fluorescence in situ hybridization.

Simple reciprocal translocations are formed when a reciprocal exchange of material takes place between two chromosomes[1]. Approximately 1 in 500 newborns is a carrier for a reciprocal translocation[2], while interchromosomal insertion is a much rarer entity, with an estimated prevalence of 1 in 80,000[3]. The rearrangements between two or more chromosomes with more than three breakpoints and exchange of genetic material are called complex chromosomal rearrangements (CCRs)[4]. Typically, CCRs are three-way translocations with one breakpoint in each chromosome; however, CCRs with up to 15 breakpoints have been reported[5,6]. In CCRs, different rearrangements may coexist on the same chromosome, such as a translocation and an inversion or an insertion. CCRs occur mostly de novo and present with clinical symptoms even when the rearrangements are apparently balanced at the cytogenetic level. In such cases, the phenotypic abnormalities are thought to result from disruption of gene(s) at chromosome breakpoint(s), additional cryptic rearrangements, or position effect[7-12].

Conventional cytogenetics is of limited use in determining whether a CCR is balanced or unbalanced. In such cases, fluorescence in situ hybridization (FISH) techniques can be applied to the analysis of such rearrangements, together with standard cytogenetic techniques.

Herein, we report a further case with an apparently balanced de novo translocation between chromosomes 8 and 13 as well as a de novo insertion of chromosome 2, in which FISH revealed the involvement of three chromosomes and five breakpoints (8q24.13, 13q21.2, 2p16.2, 2q33.2, 2q22.2).

Case Report

The index case, a two-year and three-month-old boy, was the first child born to a non-consanguineous marriage. The family and the pregnancy history were both unremarkable. He was born by cesarean section due to breech presentation. His birth weight and height were within normal percentiles. His birth head circumference was not noted. Hand anomalies (syndactyly of the third and fourth fingers of the

left hand with a mesoaxial polydactyly; duplicated third finger of the right hand, with a partial cutaneous syndactyly) were noted at birth.

Physical examination revealed microcephaly (46 cm, mean for 12 months), brachycephaly, bilateral epicanthic folds, blue sclera, downslanting palpebral fissures, prominent eyelashes, and smooth philtrum (Fig. 1a). Operation scars due to reconstructive surgery were evident on both hands. Flexion creases of the third and fourth fingers of the left hand were faint with a camptodactyly of the second and third fingers (Fig. 1b). Duplicated third finger of the right hand had no visible flexion creases (Fig. 1c). Bilateral hockey creases, bilateral plantar grooves of the feet and positional anomaly of the fourth left toe were noted.

Head control was attained at six months and sitting without support at 18 months. He was non-ambulatory and could speak only with one-word sentences. There was no eye contact.

Cytogenetic and Molecular Cytogenetic Studies

Cytogenetic analyses were done on blood lymphocytes by high-resolution banding technique using thymidine. GTG banding procedure was used for routine analysis.

Fluorescence in situ hybridization (FISH) with whole chromosome painting libraries, arm-specific and telomeric probes were essential for the characterization of the rearrangement. The hybridization and application were performed according to manufacturer's protocols. Chromosomes were counterstained by DAPI (4', 6-diamidino-2-phenyl-indole). FISH results were evaluated with microscopes equipped for epifluorescence (Nikon) and image capture software (Scientific Systems PSI).

High-resolution GTG banding showed a 46,X Y,t(8,13)(q24.13;q21.2), ins(2)(?) karyotype with an apparently balanced translocation between chromosomes 8 and 13 as well as a suspected insertion within chromosome 2 (Figs. 1d, 1e). Parental karyotypes were normal (46,XX and 46,XY). FISH study confirmed a balanced translocation between chromosomes 8 and 13. Chromosome 2 was fully painted and telomeres were intact, thereby proving that the rearrangement was within chromosome 2 with no other chromosome involved. Further FISH study using arm-specific probes for chromosome 2 and subtelomeric probes confirmed the previous findings. However, the breakpoints for the insertion could not be determined precisely. Karyotype of the index case with suspected breakpoints was interpreted as 46,XY,t(8;13)(q24.13;q21.2),in s(2) (p16.2q33.2q22.2?) (Figs. 1f, 1g).

Discussion

De novo translocations have been helpful in identifying new genes throughout the history of genetics. Patients with specific phenotypes who had apparently balanced translocations have led to candidate gene approaches. Genes that lie between the region involving the breakpoints of the patient, shown to result in a similar trait in an animal model beforehand, have been selected as the disease-causing gene, yielding valuable information about the human genome.

The finding showed that 23% of the CCRs, although apparently balanced, have been ascertained among individuals with multiple congenital abnormalities and/or mental retardation[13]. The present case provides evidence that de novo apparently balanced CCRs may be associated with imbalance in the breakpoints of rearrangements and cause clinical findings.

There are more than 100 genes listed in the OMIM gene map within the regions of the five breakpoints revealed by karyotype in our case, with some attributed to specific disorders and others having no known cellular function.

It could be suggested that a few of the genes from this list might be related to the phenotype observed in our patient. Of these possible candidates, PTK2 and ENPP2, both located in the 8q24 region, are highly expressed in the brain and have been found to regulate focal adhesion, cell growth and interactions in the central nervous system. Furthermore, ENPP2's transcript in the central nervous system was found to be identical to a tumor cell motility-stimulating factor, which could affect neuronal migration in the developing brain. POU4F1, a gene located in 13q21.1, encodes a transcription factor that was found to be highly expressed in the developing sensory nervous system and retina. The disruption of these genes and many yet to be cloned that are within the region of the five breakpoints could have contributed to the psychomotor mental retardation of our case.

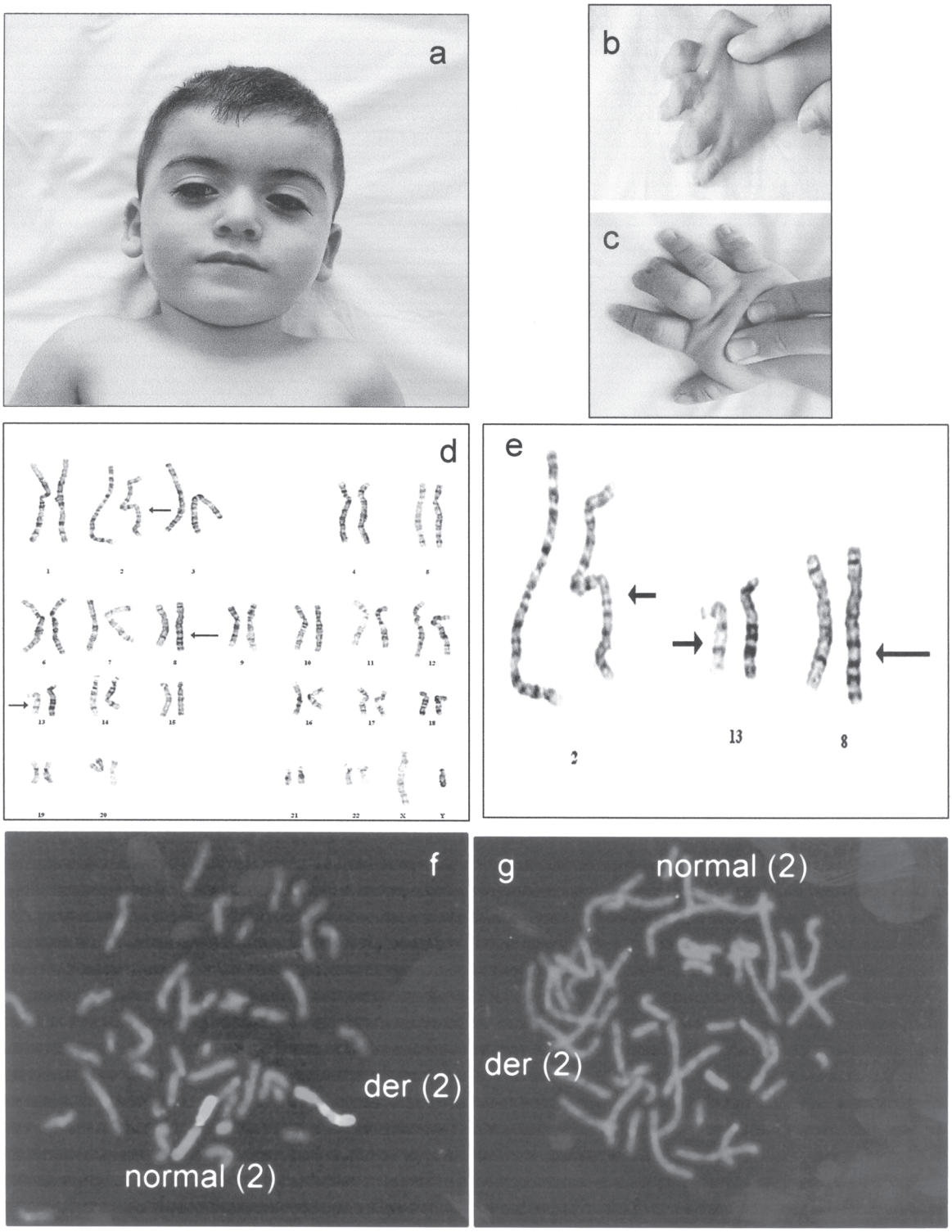

Fig. 1. (a) Facial appearance of the patient; (b) Post-operative appearance of the left hand; (c) Right hand of the patient showing duplicated distal third finger with partial cutaneous syndactyly; (d) Chromosome GTG-banded karyotype showed a non-specific band pattern of chromosome 2 and apparently balanced reciprocal translocation between chromosomes 8 and 13; (e) Partial karyotype of the patient; (f) FISH using arm-specific probe chromosome 2 demonstrated that the non-specific band pattern originated from an interstitial translocation between p and q arm of chromosome 2; (g) FISH using chromosome 2-specific p and q subtelomere probes showed that signals were normal in localization.

Polysyndactyly, apart from being an isolated feature, is also seen as an additional feature in many syndromes. One of the non-syndromic polysyndactyly phenotypes, synpolydactyly 1 (SPD 1), causative gene, HOXD13, has been mapped to the 2q32 region, which is in the vicinity of one of our suspected breakpoints. In SPD 1, there is usually syndactyly of the third and fourth fingers associated with polydactyly of all components or of part of the fourth finger in the web. Associated findings are fifth finger clinocamptodactyly and metacarpal anomalies, fourth and fifth toe syndactyly, pre-postaxial polydactyly, second-fifth toe middle phalangeal hypoplasia, triangular distal phalanges, six metatarsals, and normal tarsals. Our case had similar findings of bilateral syndactyly of the third and fourth fingers with mesoaxial polydactyly and bilateral clinodactyly of the fifth finger. These observations led us to think that HOXD13 may be one of the genes, which when disrupted, could have contributed to the phenotype of our patient, and the suspected breakpoint was more likely to pass through 2q32 instead of 2q33.2.

As more genes within the aforementioned regions are cloned and the cellular functions of these genes are delineated, the factors that contribute to the phenotype can be better understood. It would thus be reasonable to keep in mind that the genotype-phenotype correlations discussed here are limited to the list of cloned genes within the region. Any one of the clinical features may be due to the disruption of a gene or tandemly located consecutive genes that have yet to be cloned.

Generally, the more chromosomes involved and the more breakpoints present, the more difficult it is to characterize the derivative chromosomes generated by the rearrangement. Precise definitions of CCRs and their real complexity can only be provided by means of molecular cytogenetics. The introduction of FISH techniques has greatly enhanced the resolution power of conventional cytogenetic analysis[14]. In the present case, FISH techniques using specific probes were also employed to permit accurate characterization of the derivative chromosomes.

In conclusion, our case showed the necessity of FISH investigations as an adjunct to conventional cytogenetic analysis in the characterization of CCRs. The increased resolution made possible by FISH in detecting additional complexity and cryptic insertions, in the present and previously reported CCR cases, is essential if accurate reproductive risk assessments and genetic counseling are to be offered. We believe that further studies to delineate the breakpoints of our case could be helpful in identifying the causative genes for the phenotype.

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