ELECTRONIC LETTER

A familial unbalanced subtelomeric translocation resulting in monosomy 6q27→qter

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Subtelomeric rearrangements have recently gained considerable interest through publications indicating that they may be a major cause for unexplained mental retardation and/or multiple congenital anomalies.^{1,2} As the subtelomeric regions have the highest gene density in the genome,³ subtelomeric aneusomies are in general thought to have a significant effect on the phenotype. Prenatal onset of growth retardation, a positive family history of mental retardation, and malformations have been discussed as being typically associated with subtelomeric defects.⁴

Here, we describe a family in which an unbalanced subtelomeric rearrangement segregated through at least two generations. The imbalance was caused by two rearranged chromosomes, a der(6)(6pter→6q27::16p13.12→16pter) and a del(16)(:p13.12→qter), which resulted in monosomy 6q27→qter. In these affected family members the monosomy caused very mild mental retardation without specific dysmorphic features. However, one family member with multiple congenital anomalies was a carrier of the der(6)(6pter→6q27::16p13.12→16pter) together with two normal copies of chromosome 16, which resulted in trisomy 16pter→p13.12 in addition to the partial monosomy 6q.

As the consequences of the 6q aneusomy on the phenotype were surprisingly mild, we decided to fine map the deleted region and to determine accurately the number of lost genes. The same was done for the 16p region. This case should contribute to a better phenotype-genotype correlation for the distal region of both the long arm of chromosome 6 and the short arm of chromosome 16.

CASE REPORT

The pedigree of the family is shown in fig 1.

A 30 year old woman (III.2) was referred by her gynaecologist to our genetic counselling service in the 15th gestational week of her first, uneventful pregnancy. She was mildly mentally retarded and had attended a school for persons with learning disabilities. No specific dysmorphic features were noted (fig 2).

Her mother (II.1) had the same learning disabilities and also no particular dysmorphic signs. Her father (II.2) was reported to be healthy.

The non-consanguineous partner (III.3) had two healthy children with another woman. His medical history was unremarkable.

The pregnant female had an older (III.1) and a younger sister (III.5) and a younger brother (III.4). The older sister (III.1) had also attended a school for persons with learning disabilities while the younger brother (III.4) had gone to secondary school leading to an intermediate qualification.

The younger sister (III.5) had attended secondary school leading to the lowest level of qualification in the German school system. She had two healthy children (IV.2 and IV.3), one spontaneous abortion (IV.4), and at the age of 26 years gave birth to a boy (IV.5) with multiple congenital anomalies.

The history of this child can be summarised as follows: Through ultrasound, hydrocephalus had been noted prena-

Key points

- We describe a family in which an unbalanced chromosome rearrangement is segregating. The imbalance was caused by two rearranged chromosomes, a der(6)(6pter→6q27::16p13.12→16pter) and a del(16)(:p13.12→qter), which resulted in monosomy 6q27→qter. The monosomy gave rise to a mild phenotype with mild mental retardation and no distinct dysmorphic features. One family member had in addition partial trisomy of 16p and a severe phenotype.
- Fine mapping of the translocation and deletion breakpoints of the two derivative chromosomes was performed using PACs and BACs selected from the Ensembl Genome Browser of the Sanger Institute.
- The deleted 6q region encompassed 2.6 Mb including 17 genes. The haploinsufficiency of the 17 genes did not result in major abnormalities.
- The detailed study of case reports as presented here should increase our knowledge of the mechanisms and genes contributing to abnormal phenotypes.

tally at 30 weeks of gestation. The child was delivered by caesarian section at 36 weeks of gestation with a birth weight of 2200 g. A surgical shunt was inserted to treat the hydrocephalus. The child was seen by our genetic counselling service at the age of 16 months. Dysmorphic signs noted on physical examination included dolichocephaly, low set and malformed ears, a short nose with anteverted nostrils and a broad nasal bridge, stenosis of the lacrimal ducts, prominent maxillae with flattened philtrum, hyperplasia of the gingiva, microretrognathia, a cleft palate, short webbed neck, narrow shoulders, tapering fingers with the second and fifth fingers overlapping the third and fourth fingers, hypoplastic thenar eminence, a crease along both tibiae, flat feet, hypoplastic toenails, partial syndactyly of the second and third toes, dimples at the shoulders, elbows, and metacarpophalangeal joints, and generalised hypoplastic musculature. Additional anomalies included a ventricular septal defect which had to be closed surgically, a patent left superior vena cava, corpus callosum agenesis, cerebellar dysplasia, hydrocephalus, seizures and episodes of apnoea, and kidney anomalies. The child died at the age of 26 months secondary to pneumonia (no consent was given to show pictures of this child).

Owing to the history of unexplained mild mental retardation in the family and the history of a child with multiple congenital anomalies, cytogenetic analyses were done on family members II.1, III.2, III.4, III.5, IV.5, and prenatally on IV.1.

METHODS

Banding analysis

Preparation of metaphase spreads and G banding analysis was done according to standard protocols.

Figure 1 Pedigree and hybridisation results obtained with subtelomere PACs for 6q (shown in red, clone name 57H24³) and 16p (shown in green, clone name 119L16⁶). Family members II.1, III.2, and III.5 show the same hybridisation pattern with monosomy 6q. IV.5 had three signals for 16p and one signal for 6q. III.4 and IV.1 had normal hybridisation patterns on chromosomes 6 and 16. Weak signals on 6pter are known cross hybridisations of clone 57H24.

Figure 2 Patient III.2, who has partial monosomy 6q27-qter as a result of two rearranged chromosomes, der(6)(6pter→6q27::16p13.12→16pter) and del(16)(p13.12→qter).

FISH with subtelomere probes

For the initial hybridisations we used a 6q (57H24³) and a 16p subtelomere PAC (119L16⁶). Using standard nick translation,

PAC 57H24 was labelled with biotin and PAC 119L16 with digoxigenin. Two hundred ng of each probe were ethanol precipitated together with unlabelled Cot-1 DNA (Roche Diagnostics) and salmon testis DNA (Sigma) and resuspended in 50% formamide and 15% dextran sulphate. This mixture was hybridised overnight at 37°C. Slides were washed with 4 × SSC/Tween (3 × 5 minutes at 37°C), 1 × SSC (3 × 5 minutes at 60°C), and blocked with 3% bovine serum albumin (30 minutes at 37°C). Avidin-Cy3.5 (Rockland) and anti-digoxigenin-FITC (Roche Diagnostics) were used for detection. Chromosomes were counterstained with 4',6-diamidino-2-phenylindole (DAPI).

To exclude that no other chromosome was involved in the aberrant chromosome 16 we used a commercially available subtelomere screen (ToTelVysion, Vysis).

FISH for high resolution 6q and 16p breakpoint mapping

The Ensembl Genome Browser of the Sanger Institute (<http://www.ensembl.org>)⁷ was used to select PAC and BAC clones for high resolution mapping of the 6q and the 16p breakpoint region. This constantly updated server (Cytoview, data presented here are based on release 7.29a.3) displays two groups of clone sets: first, a 1 Mb clone set selected to provide a set of evenly spaced clones at approximately 1 Mb intervals across the entire genome and, second, a tiling path of all the clones that were used to make the current human sequence assembly. In a first step, FISH mapped clones with a distance of 1 Mb were selected to narrow the breakpoints to a 1 Mb interval. In a second step, clones from the tile path that mapped inside the two flanking probes were hybridised. Altogether 11 6q probes and 11 16p probes were hybridised to obtain the mapping results presented here. The labelling and hybridisation procedures were essentially identical to the ones described above for the subtelomere PACs.

Determination of gene numbers

We used the Ensembl Genome Browser to determine the number of genes in the chromosomal regions involved. We counted the “Ensembl genes”, which include known, novel, and predicted genes.

Fluorescence microscopy and image analysis

Images were captured with a charge coupled device (CCD) camera (Sensys, Photometrics, Kodak KAF1400 chip) on a Leica DMRXA-RF8 epifluorescence microscope (Leica, Wetzlar, Germany). Automatic acquisition and overlaying of grey scale images were done with the Leica QFISH software (Leica Microsystems Imaging Solutions Ltd, Cambridge, UK) as described previously.⁸

RESULTS

Banding analysis in patient III.2 showed an apparent deletion of the short arm of chromosome 16. The banding pattern of the distal tip of one of the two 6q arms appeared to be abnormal (fig 3A). Assuming a translocation t(6;16), subtelomeric PAC probes 57H24 (6q) and 119L16 (16p) were hybridised. The 16p probe hybridised to the short arm of the normal chromosome 16 and to the distal tip of the long arm of the abnormal chromosome 6. However, only one signal for the 6q subtelomere probe was observed, which was on the normal chromosome 6 (fig 1, III.2). Therefore, the karyotype was provisionally defined as 46,XX,der(6)t(6;16),del(16)(p13).

This unexpected finding prompted a chromosome analysis of various family members. Chromosomes 6 and 16 of the index patient's mother showed the same morphology in G banding analysis (not shown) and again the PAC signal pattern with a missing 6q signal (fig 1, II.1). No other family members of generations I or II were available for chromosomal analysis.

Figure 3 G banded chromosomes 6 and 16 of family members III.2 (A) and IV.5 (B). For details see text.

In generation III, we were able to analyse the chromosomes of the index patient's younger sibs III.4 and III.5. As expected from the history of school performance, we found a balanced karyotype with two normal pairs of chromosomes 6 and 16 in the brother (fig 1, III.4) while the sister was also diagnosed with partial monosomy of chromosome band 6q27 (fig 1, III.5). The prenatal diagnosis done on IV.1 showed two normal copies of chromosomes 6 and 16.

In contrast, in patient IV.5, who had multiple congenital anomalies, G banding (fig 3B) and FISH (fig 1, IV.5) showed two normal copies of chromosomes 16 in addition to the der(6), resulting in a partial trisomy 16p in addition to the familial monosomy 6q27. Thus, the child inherited the der(6) together with the normal chromosome 16 copy from his mother.

We excluded that no other chromosome is involved in the aberrant chromosome 16 by using a commercially available subtelomere screen (ToTelVysion, Vysis; data not shown). Probes from the 1 Mb clone set and of the tiling path pinpointed the breakpoint on 6q27 between clones RP3-431P23 and RP11-164L23 (fig 4). The distance between these two clones is some 136 kb, defining the size of the lost fragment to a maximum of 2.67 Mb and to a minimum of 2.53 Mb. No further BAC clones were available between these two clones. According to the Ensembl database the lost 6q27 region harbours 17 genes. So far, no function is known for the majority of these deleted genes. Genes with known functions include the following. *KNSL3* (kinesin-like protein 3) has an ATP/GTP binding site and a kinesin motor region. *DLL1* (delta-like protein 1 precursor) may be involved in cell differentiation and communication. *PSMB1* (proteasome subunit beta type 1) has been associated in ubiquitin dependent protein degradation. *TBP* (transcription initiation factor TFIID) is involved in transcription regulation and initiation. *PDCD2* (programmed cell death protein 2) is a zinc finger gene (data according to: <http://www.ensembl.org>).

Clone RP11-457P5 spanned the breakpoint in chromosome band 16p13.12 (fig 4). Because of the size of this breakpoint spanning clone, the translocated 16p material encompassed a fragment between 18.61 and 18.75 Mb in size harbouring 335 genes.

Figure 4 Representative examples of fine mapping of the breakpoints of 6q and 16p on chromosomes of patient III.2. The breakpoint on the der(6) chromosome was mapped within band 6q27 between clones RP3-431P23 (red), which was the most distal 6q clone present on all der(6) chromosomes analysed, and RP11-164L23 (green), which was the most proximal clone lost on the der(6). The breakpoint on the del(16) chromosome was mapped within band 16p13.12 of the breakpoint spanning clone RP11-457P5 (red).

As result of our FISH analyses the two derivative chromosomes could be defined as der(6)(6pter→6q27::16p13.12→16pter) and del(16)(:p13.12→qter).

DISCUSSION

We describe a family with partial monosomy of chromosome band 6q27, occurring in several subjects in at least two generations. The monosomy was caused by two aberrant chromosomes, a der(6)(6pter→6q27::16p13.12→16pter) and a del(16)(:p13.12→qter). These two aberrant chromosomes may have originated from an "incomplete" translocation with failed fusion of the 6q fragment on 16p. An initially balanced translocation t(6;16)(q27;p13.12) with subsequent loss of the translocated material on the derivative chromosome 16 is another possibility.

The finding of familial monosomy 6q27→qter is extraordinary as its effects on the phenotype were very mild. This is in contrast to the common belief that aneusomies in subtelomeric regions have a severe effect on the phenotype.

The observed deletion of 6q is unlikely to represent a benign telomeric variant. Such polymorphisms without apparent consequences for the phenotype have been reported for the subtelomeric regions 2q, 9p, and Xp.^{9,10} In addition, a del(4)(q35.2) was described in an apparently normal female¹¹ and a duplication of 3q29, which was associated with only mild phenotypic effects.¹⁰

However, so far, terminal deletions of 6q have always been associated with consequences for the phenotype. Several terminal or interstitial 6q deletions have been described.¹² Breakpoints on 6q may be non-randomly distributed,¹³ but breakpoints in 6q27 are rare. The reported terminal deletions varied in respect to the exact breakpoint localisations and consequently the reported dysmorphic features varied considerably. In cases with terminal deletions with breakpoints in 6q24.3-q25 and intrauterine and postnatal growth retardation, a number of congenital anomalies and severe mental retardation were frequent findings.^{12–17} A terminal deletion with the breakpoint in 6q26 was reported to be associated with growth and mental retardation and multiple congenital anomalies including an ASD, abnormal retinal pigmentation, abnormal cervical vertebrae, and short upper extremities.¹⁸ A terminal deletion del(6)(q27→qter), occurring with a duplication dup(2)(pter→p25.3), was associated with mild dysmorphism, hypotonia, ataxia, mental retardation, and autistic features.¹⁹ A cryptic deletion of 6q27 in association with a paracentric inversion inv(6)(q22.1q27) was reported in a mildly retarded child with microcephaly, epicanthic folds, hypertelorism, wide nasal tip, short philtrum, everted upper lip, and low set ears.²⁰ The lack of these facial anomalies in our affected family members indicates that the deletion in our cases is probably smaller.

These difficulties in comparing phenotypes from different publications reflect the need for a standardised high resolution genotype-phenotype correlation for chromosomal abnormalities. The exact location of breakpoints can now be determined within kb range by using the BAC clone resources, which have emerged from the human genome project.²¹ This allows us to attribute the mild consequences of the partial monosomy 6q27 to both the small size of the lost region and its low gene density.

Of interest is the double segment imbalance in patient IV.5 consisting of monosomy 6q27→qter and trisomy 16pter→p13.12. In most cases of double segment imbalances, the deleted segment has a more severe effect on the phenotype than the duplicated region. This is not the case here, as the monosomy 6q27→qter alone is associated only with mild mental retardation.

In fact, many features of the child IV.5 have been repeatedly described in the context of a partial dup(16p) syndrome. These features include dolichocephaly, flat and broad nasal bridge and anteverted nares, microretrognathia, low set and malformed ears, cleft palate, webbed neck, flexed and tapering fingers, hypoplastic thenar eminence, contractures of different joints, kidney anomalies, seizures, mental retardation, and heart anomalies.^{22–30} Thus, the major characteristics of the phenotype in this patient may be caused by the partial trisomy 16p alone.

Furthermore, the partial monosomy 6q27 described here should be especially helpful in establishing a better phenotype-genotype correlation for this region. So far, little is known about the functions of most of the 17 lost genes. The now well defined cases presented here may help to shed some light on their functions. In addition, this monosomy highlights the difficulties in establishing something like a “subtelomere aneusomy phenotype”, which may define patients with subtelomeric defects based on characteristic phenotypic features.⁴ The family described here is a case in point that the effects on the phenotype depend critically on the size, on the gene density, and on the function of the genes within the deleted or duplicated chromosome fragment. Taking this into account, subtelomere defects could display a wide variety of different phenotypes and consequently it may be impossible to define a “subtelomere aneusomy phenotype”.

A number of sophisticated tools for efficient subtelomere screens based on multicolour FISH^{31–36} or on array CGH technologies^{37–38} have recently been published. The appropriate inception of these tools will considerably decrease the costs for

subtelomere screens and should also facilitate a standardised breakpoint localisation. Instead of a strong indication based on particular phenotypic features, the decreasing costs should allow an efficient telomere diagnosis in the majority of cases of idiopathic mental retardation and unexplained syndromes in the near future.

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