Two cases of partial trisomy 8p and partial monosomy 21q in a family with a reciprocal translocation (8;21)(p21.1;q22.3)

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Abstract

We report on two mentally retarded adults with an unbalanced karyotype resulting from a familial balanced translocation between chromosomes 8 and 21, t(8;21)(p21.1;q22.3). This translocation has not been reported before. Both patients had partial trisomy 8p and partial monosomy 21q. Fluorescence in situ hybridisation (FISH) was used to determine the chromosomal breakpoints more precisely. The first patient showed mild mental retardation and facial dysmorphism, slightly resembling the earlier described trisomy 8p phenotype. He did not resemble his affected niece, who was more severely retarded, had serious epilepsy, but lacked the facial dysmorphism. Comparing the data of both patients with published reports of trisomy 8p, marked differences were found between patients with an inversion duplication (inv dup) 8p, patients with partial trisomy 8p caused by an unbalanced translocation, and our patients. Inv dup(8p) causes a recognisable phenotype, whereas the phenotype of trisomy 8p resulting from a translocation is much more variable, probably because of the accompanying monosomies. However, even the same abnormal karyotype can cause different phenotypes, as our patients show.

Counselling carriers of the balanced translocation in this family, a 20-25% recurrence risk for unbalanced offspring and a 25% risk for miscarriages seem appropriate.

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Keywords: chromosome aberration; monosomy 21q; translocation (8p;21q); trisomy 8p

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Partial trisomy 8p is a relatively frequent anomaly, especially as a result of an inversion duplication.^{1,2} The phenotype of inversion duplication (inv dup) 8p is well delineated, comprising profound psychomotor retardation, quite specific facial dysmorphism, and neurological and orthopaedic anomalies.^{1,3-5} Most reports on partial monosomy 21q concern ring chromosome 21. The phenotype is variable, owing to different breakpoints in 21q. A deletion 21q with the breakpoint near the telomere does not have major phenotypic effects.⁶⁻¹⁰

In this paper two patients from one family are presented with partial trisomy 8p and a

small partial monosomy 21q resulting from a familial translocation. Their phenotypes differ significantly, although they have the same karyotype. We compare both patients with published reports on partial trisomy 8p and discuss the differences and possible explanations for these. Finally, the implications for genetic counselling of carriers of the balanced translocation are discussed.

Case reports

Patient 1 (II.2 in fig 1) was a male aged 51 years. The pregnancy, delivery, and neonatal period were uneventful. He had no congenital anomalies. In the second year of life developmental retardation became apparent. As a toddler he had tantrums, but later on he was quiet and friendly. He was physically healthy, except for an unexplained attack of unconsciousness at the age of 20 years, for which he was treated with antiepileptic drugs for several years. Speech was well developed. He had had education for the mildly mentally retarded. He was able to read and write a little. He lived in a home for the mildly mentally handicapped and worked in sheltered employment. On examination he was a healthy, slender man, who was shy and friendly. Height was 166.5 cm (below the 3rd centile), weight 52 kg (25th centile), and head circumference 56.5 cm (50th centile). Facial features included arched eyebrows, hypertelorism (inner canthal distance (ICD) 4 cm), large, dysplastic, anteverted ears, a large mouth with a full lower lip, and a pronounced mandible (figs 2 and 3). The legs showed many varicose veins.

Patient 2 (III.3 in fig 1) was the 23 year old niece of case 1. Pregnancy and delivery were uneventful. Developmental retardation became evident at the age of 6 months. She started walking at the age of 2½ years and at the age of 4 years she spoke only single words. In the first years of life she had several atonic attacks. Since the age of 4 years she has had grand mal and petit mal attacks, for which she was hospitalised in a centre for epileptic patients for 1½ years. She had a mild pyramidal disorder resulting in a mild spastic gait and motor impairment of the hands. She was hyperactive, demanded much attention, and spoke short sentences. IQ was 54 (WISC). On examination she was a moderately to mildly retarded female with a normal habitus. Height was 175.5 cm, weight 60 kg, and head circumference 55.5 cm (all within normal limits). She had mild flattening of the occiput, but no apparent facial dysmorphism (fig 4). There were many naevi on the skin.

Figure 1 Pedigree of the family.

Family history

An older brother of patient 1 (II.1 in fig 1) died on the fifth day of life. He had a congenital heart defect. More exact data were not available. Another brother and two sisters were healthy. An older sister of patient 2 (III.1 in fig 1) died at the age of 6 months with a congenital heart anomaly. No other abnormalities had been noticed by the parents. Medical data were not available. Two brothers were healthy and one of them is a carrier of the balanced translo-

Figure 2 Front view of patient 1: arched eyebrows, hypertelorism, large, malformed, anteverted ears, and large mouth with full lower lip. (All photographs reproduced with permission.)

Figure 3 Side view of patient 1: pronounced mandible.

cation. The mother had one spontaneous abortion.

Materials and methods

CYTOGENETICS

Chromosomes were prepared from peripheral blood lymphocyte cultures using a modification of the synchronisation method of Dutrillaux and Viegas-Pequignot¹¹ by treatment overnight with thymidine, followed by incubation with 5-BrdU for six hours and ethidium bromide for 1.5 hours before harvest. Chromosome banding was performed by treatment with trypsin followed by staining with Giemsa to obtain a GTG banded pattern.

FLUORESCENCE IN SITU HYBRIDISATION (FISH)

In this analysis the following chromosome band specific probes were used: centromere 8, pJM 128¹²; 8p23.1-23.3, 59C1¹³; 8p23.1, 196B11 (Y Nakamura, personal communication); 8p21.3, cCI8-448 (Y Nakamura, personal communication); 8p21.1, cCI8-560 (Y Nakamura, personal communication). The centromere specific and band specific probes were labelled by nick translation with biotin-11-dUTP. For FISH with these probes, the protocol of Lichter *et al*¹⁴ was followed. The slides were examined with a Zeiss Axiophot microscope and photographed using Scotch chrome 640 ASA colour slide film.

Results

Cytogenetic examination of GTG banded metaphases showed an unbalanced karyotype in both patients, with extra chromosome material at the long arm of chromosome 21. Subsequent analysis of the chromosomes of the parents of patient 2 showed a balanced reciprocal translocation in the mother, her karyotype being: 46,XX,t(8;21)(p21.1;q22.3) (fig 5). FISH with the probes 59C1, 196B11, and cCI8-448 specific for chromosome bands 8p23.1-23.3, 8p23.1, and 8p21.3 on metaphases of both patients showed that the probes hybridised at the p arm of chromosome 8 and

Figure 4 Patient 2: no major dysmorphism.

Figure 5 Partial karyotype showing normal GTG banded chromosomes 8 and 21 and the derivative chromosomes (top) and their idiogram (bottom).

at the q arm of the derivative chromosome 21 (fig 6C, D, E). Probe cCI8-560 specific for chromosome band 8p21.1 hybridised more proximally in the p arm of the chromosomes 8, but no signal was detected in the derivative chromosome 21 (fig 6F). We concluded that the breakpoint in the p arm of chromosome 8 is situated in chromosome band 8p21.1 and the breakpoint in chromosome 21 is situated in band 21q22.3. The karyotype of patient 1 is 46,XY,der(21)t(8;21)(p21.1;q22.3) and of patient 2 is 46,XX,der(21)t(8;21)(p21.1;q22.3)mat.

Discussion

We report on two patients from one family with trisomy 8p21.1→8pter and monosomy 21q22.3→21qter resulting from a familial

translocation t(8;21)(p21.1;q22.3). Cases of partial trisomy 8p have frequently been published, either resulting from an inv dup(8p)^{1 3 5} or an unbalanced translocation.¹⁵⁻³⁰ The main clinical features of partial trisomy 8p and of our patients are summarised in table 1. There are marked differences between the features in patients with inv dup(8p) and in patients with partial trisomy 8p resulting from a translocation, although they are often trisomic for the same chromosome region. Hypotonia, agenesis of the corpus callosum, characteristic facial dysmorphism, and severe psychomotor retardation are found in inv dup(8p), whereas postnatal growth delay, high or cleft palate, hypertelorism, and cardiac defects are frequent in the second group. Possible explanations for these differences are a position effect in inversion duplications and monosomy for another chromosome region in most translocation cases, which makes this group less homogeneous than the inv dup group.

Although patient 1 shares the eversion of the lower lip, the large mouth, and large ears with the inv dup group, patient 2 had none of the facial features of either group. She had epilepsy and spasticity. Epilepsy has only been reported in a few inv dup patients,^{2 24 31 32} whereas spasticity is more common (table 1). A possible explanation for the differences between our patients and the published cases could be the contribution of the partial monosomy 21q to the phenotype in our patients, which is, however, hard to define. Estabrooks *et al*³³ reported on a patient with a terminal deletion 21(q22.3) and holoprosencephaly. Ring chromosomes 21 with the breakpoint in band 21q22.3 have been reported in phenotypically normal persons.^{7 8 10 34}

Marked differences were found between patient 1 and patient 2. Patient 1 showed facial dysmorphism, short stature, and mild mental retardation, whereas patient 2 had no facial dysmorphism and normal height, but more severe mental retardation and neurological

Figure 6 (A) Metaphase chromosomes of patient 2 after FISH with a chromosome 8 specific paint. Large arrows point to the chromosomes 8, the small arrow points to der(21). (B) Metaphase chromosomes of patient 2 after FISH with a chromosome 21 specific paint. Arrows point to chromosome 21 and the der(21). (C) Metaphase chromosomes of patient 2 after FISH with the centromere 8 specific probe pJM 128 and probe 59C1 specific for chromosome band 8p23.1-p23.3. Large arrows point to the centromere of chromosomes 8, small arrows point to the signal on the p arm of chromosome 8 and the der(21). (D) Same as (C) with probe 196B11 specific for 8p23.1. (E) Same as (C) with probe cCI8-448 specific for 8p21.3. (F) Same as (C) with probe cCI8-560 specific for 8p21.1 but without a signal on the der(21).

Table 1 Main clinical features of reported patients with inversion duplications 8p, with partial trisomy 8p resulting from translocations, and of our patients

Clinical data	Inv dup* (n=33) pos/inf	Transl (n=17) pos/inf	Patient 1	Patient 2
Postnatal growth delay	5/19	8/8	+	-
Mental retardation	33/33	10/10	+	+
Hypotonia	24/25	4/6	-	-
Spastic paraplegia	8/20	1/3	-	+
(Partial) corpus callosum agenesis	10/13	4/9	?	?
Prominent forehead	25/31	1/3	-	-
Sagging cheeks	12/19	2/11	-	-
Eversion of lower lip	21/30	4/10	+	-
Large mouth	22/31	3/13	+	-
High/cleft palate	18/30	11/11	-	-
Large ears	28/30	0/5	+	-
Hypertelorism	2/26	5/8	+	-
Cardiac defect	6/31	11/14	-	-

Inv dup=inversion duplication, transl=translocation, pos=positive, inf=informative, +=present, -=absent, ?=unknown.

*Adapted from de Die-Smulders *et al.*⁵

anomalies. A possible explanation for this observation is a different methylation pattern depending on the transmitting parent (genomic imprinting). However, there is no convincing evidence of imprinted genes on chromosomes 8 and 21.

Both patient 1 and patient 2 had a sib who died in the first year of life with a congenital heart malformation. It is possible that they also had an unbalanced translocation, either the same as the present patients, or the opposite (partial monosomy 8p and partial trisomy 21q). Heart malformations have been reported in partial trisomy 8p (table 1), as well as in partial monosomy 8p³⁵ and in terminal deletion 21q.^{10 36}

Risk of unbalanced offspring in carriers of a balanced reciprocal translocation depends on the length and genetic constitution of the exchanged segments. In our family both possible unbalanced karyotypes are probably viable, as a deletion 8p21→8pter has been reported in several patients³⁵ and it is unlikely that partial trisomy of the small terminal part of 21q predisposes significantly to early fetal loss, as even complete trisomy 21 is viable. Risk figures come from empirical data.³⁷ A 20-25% recurrence risk for unbalanced offspring and a 25% risk for miscarriages seem appropriate for carriers of the balanced translocation in this family.

In conclusion, whereas inv dup(8p) causes a well defined phenotype, partial trisomy 8p resulting from a translocation is very variable. Dysmorphic signs, growth and mental retardation, and other anomalies can vary considerably even between family members with exactly the same karyotype, as the reported family shows.

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