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Three cases with rare interstitial rearrangements of chromosome 1 characterized by multicolor banding

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Abstract. In this report, we describe three unrelated patients with similar symptoms such as mental retardation, growth delay and multiple phenotypic abnormalities. GTG-banding analysis revealed karyotypes with add(1p) in two cases and an add(1q) in the third. Fluorescence in situ hybridization (FISH) analysis using high resolution multicolor banding (MCB) characterized the aberrations of the abnormal chromosomes 1 as a (sub)terminal duplication and inverted duplications, respectively. Although three different chromosomal regions i.e. 1p36.1, 1p36.2→1p31.3 and 1q41→1q44 were involved, all three patients had similar patterns of dysmorphic findings. These cases demonstrate the power of MCB in the characterization of small interstitial chromosomal aberrations and resulted in the characterization of three previously unreported congenital chromosome 1 rearrangements.

Various cytogenetically detectable congenital aberrations of chromosome 1 are described throughout the literature. As recently outlined by Ballif et al. (2004) deletion of the most distal, telomeric band of chromosome 1p is one of the most commonly observed structural abnormalities detected by routine cytogenetic analysis: loss of 1p36 occurs in ~1 in 5,000 live births. In contrast, other rearrangements of the region 1p36→p32 (excluding translocations) have been described only rarely, i.e. three cases with duplications (Elejalde et al., 1984; Garcia-Heras et al., 1999; Warden et al., 2001) and one with an inversion (Cogulu et al., 2003). For the distal long arm of chromosome 1 (bands q32→q44), excluding interchromosomal translocations, only duplications have been described to date (for review see Bartsch et al., 2001 and Nowaczyk et al., 2003).

Here, we report two cases of (partly overlapping) duplication and inverted duplication within a chromosomal region of 1p and one case with an inverted duplication within 1q32→q44. Each of the cases presented have "unique" breakpoints, which have not been described to date. The three cases are compared with each other and with available cases from the literature.

Methods and results

The clinical data of the three patients are summarized in Table 1, and their faces are shown in Fig. 1. Banding cytogenetics revealed evidence of altered chromosomes 1p in patients M-1 and M-2 and a karyotype of 46,XX,add(1q) for patient B (Fig. 1). Fluorescence in situ hybridization (FISH) using a multicolor banding (MCB) probe set for chromosome 1 (Liehr et al., 2002) was applied for further characterization of the derivative chromosomes in the three cases (Fig. 1). MCB revealed the following aberrations M-1: 46,XX,dup(1)(p36.1p36.1), M-2: 46,XY,dup(1)(p36.2p31.3), B: 46,XX,inv dup(1)(q41q44). Additionally, subtelomeric probes for 1p (PAC 14e10) and/or 1q (PAC 160H23) were applied which confirmed the MCB results (not shown).

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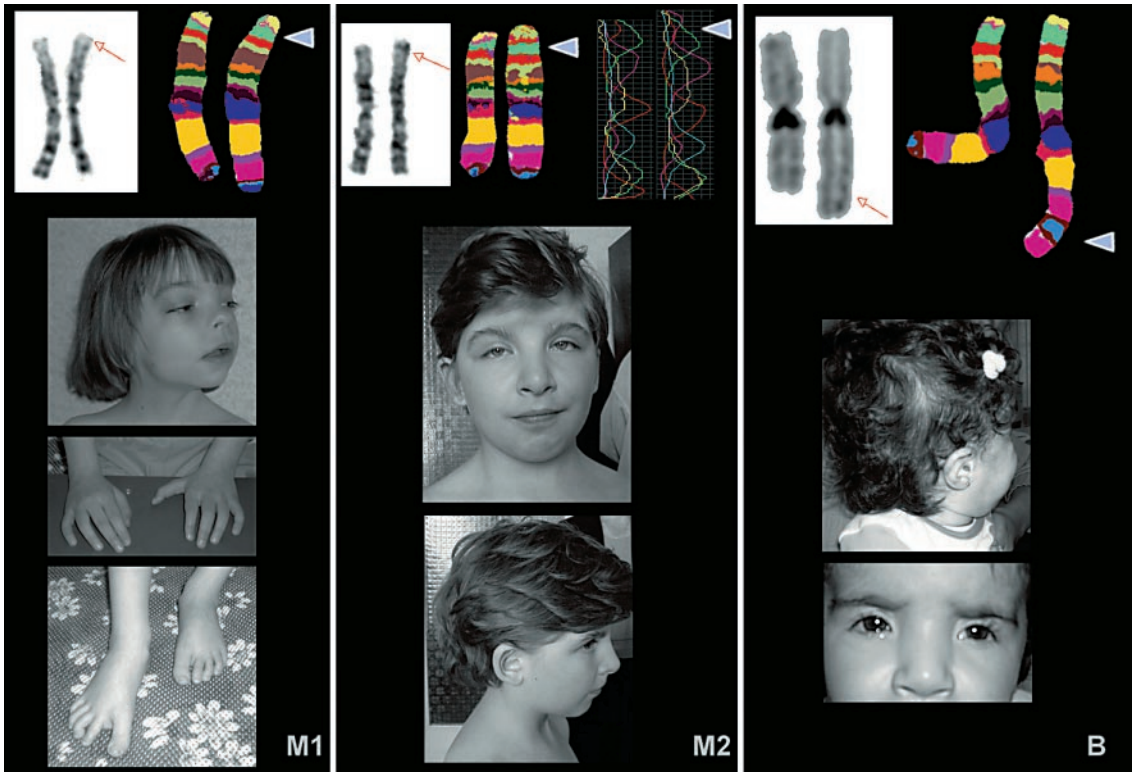

Fig. 1. Normal and derivative chromosomes 1 plus the facial appearance of all three studied patients M-1, M-2 and B: Each pair of chromosomes no. 1 of all three patients is shown after inverted DAPI-banding and multicolor banding (MCB) using a chromosome 1 specific probe set. MCB results are presented in pseudocolor depiction and the corresponding aberrations are highlighted by red arrows and blue arrowheads in inverted DAPI-banding and MCB figures, respectively. The evaluation of the MCB-results is carried out as described in Liehr et al. (2002), not on pseudocolors but on the fluorochrome-profiles as exemplified for case M-2. In addition to the facial appearance, for patient M-1 the mild brachydactyly and clinodactyly of V fingers plus the sandal gap are also shown.

Discussion

While partial duplications of chromosome 1q32→q44 are described more frequently in the literature (e.g. Bartsch et al., 2001; Nowaczyk et al., 2003), duplications within the region 1p36.2→1p31 are very rarely described (Elejalde et al., 1984; Garcia-Heras et al., 1999; Warden et al., 2001; Cogulu et al., 2003).

Patient M-1 was identified to be carrier of a dup(1)(p36.1 p36.1), patient M-2 had a dup(1)(p36.2p31.3). The only cytogenetically similar cases are those described by Elejalde et al. (1984), Garcia-Heras et al. (1999), Warden et al. (2001) and Cogulu et al. (2003) with a dir dup(1)(p35p31), an inv dup(1)(p34.1p31), an inv dup(1)(q34.3p32.2) and an inv(1)(p36.2 p13.2), respectively. However, the chromosomal regions of these previously reported cases do not directly overlap those described in the present case M-1. Nonetheless it is interesting to note that previously published cases show comparable heart defects like those present in patient M-1.

Patient B showed an inv dup(1)(q41q44). This patient has a karyotype similar to that previously described by De Brasi et al. (2001) in a case with a classical phenotype of trisomy 1q42→qter. According to Bartsch et al. (2001) such rearrangements can be classified to the group IV of partial trisomy 1q carriers. Even though the clinical description revealed some common features between our case B, the five cases summarized in Bartsch et al. (2001), and an additional case (Mewar et al., 1994), the case described by De Brasi et al. (2001) is almost identical to our case B. On the other hand, three of the six patients (Mewar et al., 1994; Bartsch et al., 2001) carry other, additional chromosomal imbalances in addition to a duplication in 1q, making the specific influence of this chromosomal region for assessment of the clinical phenotype more difficult. Accordingly, cases described by Mewar et al. (1994) and De Brasi et al. (2001) show subterminal deletions – while case B described here does not.

In summary, we present three further cases of the rare group of patients with rearrangements involving material exclusively of chromosome 1 origin. Although three regions of chromosome 1 are involved, all three patients exhibit striking phenotypic similarities, such as mental and growth retardation (3/3), hypertelorism (3/3), low set and dysmorphic ears (3/3), strabismus (3/3), muscular hypotonia (3/3), short neck (3/3), *pes planus* (3/3), high palate (2/3), high arched eyebrows (2/3), long

Table 1. Clinical details of the three patients M-1, M-2 and B

Clinical signs	Patient M-1	Patient M-2	Patient B
Karyotype	46,XX,dup(1)(p36.1p36.1)	46,XY,dup(1)(p36.2p31.3)	46,XX,inv dup(1)(q41q44)
Pregnancy details	G1; P1; birth at term complicated: mother had pyelonephritis, >risk for early spontaneous abortion	G1;P1; birth at term	mother had hypertension during pregnancy, and gained 22 kg
Birth details	normal	normal	born by Cesarean section
Apgar	not available	not available	6-8
weight	3250 g	2900 g	3260 g
length	48 cm	50 cm	49.5 cm
OFC	36 cm	not available	37 cm
Age when studied	at birth; at 1 year and at 5 years	at 6 years and at 9 years 4 months	at 1 year 8 months
Craniofacial findings			
hypertelorism	+	+	+
low-set ears	+ and dysmorphic	+ and dysmorphic	+ and dysmorphic
microcephaly	not available	+	moderate hydrocephaly in CAT scan
high palate	+	not available	+
arched eyebrows	+	+	–
additional findings	mild face hypoplasia (left side) retromicrognathia narrow palpebral fissures broad short nose, long philtrum short teeth	low forehead mild synophrys mild antimongoloid position of eyeaxes narrow palpebral fissures mild hypoplasia of alae nasi mild prognatia	irregular alveolar bridge long philtrum
Eyes		normal ocular fundi	
ptosis	+	+ (mild)	–
strabismus	+	+	+
nystagmus	+	–	–
Heart	heart defect	no heart defect	
ventricular septal defect	+ (pers. foramen ovale, incl. add. chorda in left ventricle, tachycardia and systolic murmur)	–	+ (incl. interatrial SD)
Body			
umbilical hernia	+ (small)	–	+
muscular hypotonia	+	+ (mild)	+ (mild)
short neck	+	+	+
additional findings	torticollis left, narrow torax with mild deformation, polytelia paratrophia (mild obesity) two sacral dimples	mild funnel chest deformation wing scapulas	–
Growth	delay; at 5 years: growth retardation – short stature	moderate growth delay	growth delay
Weight	at 1 year: 7 kg	at 6 years: 17 kg	8 kg (<3rd centile)
Height	at 1 year: 71.5 cm	at 6 years: 108 cm	72 cm
OFC	at 1 year: 44 cm (<3rd centile)	at 6 years: 47 cm	not available
Feet and hands	plano-valgus feet	normal appearance	
pes planus	+ (severe)	+	+
additional findings	brachydactyly (mild) clinodactyly of V fingers overlapping toes sandal gap hip dislocation	–	–
Metabolism	not available	no metabolic abnormalities	no metabolic abnormalities
Development	mentally delayed	delayed	delayed: i.e. sitting but not walking
Speech	delayed dysarthria	delayed	delayed
Behavior	behavior difficulties	behavior difficulties and moderate hyperactivity	not available
Seizures	since 3 6/12 years old	+ febrile (in history)	–
Additional problems	not available	not available	4 episodes of diarrhea and fever failure to thrive

philtrum (2/3) and ventricular septal defect (2/3). However, from a clinical point of view, those are mainly unspecific symptoms or dysmorphic signs. The ascertainment of further cases with similar breakpoints is of high importance for a more detailed genotype-phenotype correlation and formation of specific subgroups in the future.

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