



Widening the clinical spectrum of Pitt-Rogers-Danks/Wolf-Hirschhorn syndromes

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Abstract

Chromosomal rearrangements involving partial deletion of the short arm of chromosome 4 and partial duplication of the short arm of chromosome 8 have been described both in Pitt-Rogers-Danks syndrome (PRDS) and Wolf-Hirschhorn syndrome (WHS), the former being considered a milder phenotype of the latter. We describe a patient with partial deletion of chromosome 4 and partial duplication of chromosome 8 documented by array-comparative genomic hybridization (Array-CGH). In addition to the typical features of PRDS, the patient exhibited some clinical signs (genital hypoplasia, radioulnar synostosis and mesomelic limb shortness) infrequently, or never previously, reported in PRDS. These findings broaden the spectrum of anomalies generally associated with these syndromes.

Key words: Pitt-Rogers-Danks syndrome, Robinow syndrome, translocation t(4;8), Wolf-Hirschhorn syndrome.

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Chromosome rearrangements involving partial deletion of the short arm of chromosome 4 and partial duplication of the short arm of chromosome 8 have been described in patients with Pitt-Rogers-Danks syndrome (PRDS; MIM 262350; Clemens *et al.*, 1996), which has been considered to be part of the phenotypic variability of Wolf-Hirschhorn syndrome (WHS; MIM 194190; Zollino *et al.*, 1996). The affected individuals present with intrauterine growth retardation, severe mental delay, short stature, microcephaly, large forehead, prominent eyes, hypertelorism/telecanthus, beaked nose, large mouth, maxillary hypoplasia and joint hyperextensibility (Clemens *et al.*, 1996; Linderman-Kusse *et al.*, 1996; Pitt *et al.*, 1984).

We describe a patient carrying the chromosomal imbalance typically found in PRDS but also presenting with unusual clinical manifestations. This observation widens the clinical spectrum classically associated with PRDS.

The patient (Figure 1a) was referred because of psychomotor retardation. She was born at term by C-section delivery. Birth weight was 1700 g (< 3rd centile), length

41 cm (< 3rd centile) and head circumference (OFC) 31 cm (< 2nd centile). Prenatal ultrasonography had shown intrauterine growth retardation. She presented feeding difficulties, and developmental milestones were delayed. Clinical evaluation at 3 years of age showed short stature (76 cm, < 3rd centile), low weight (7610 g, < 3rd centile), microcephaly (OFC 42 cm, < 2nd centile), frontal bossing and balding, midface hypoplasia, long eyelashes, epicanthal folds, prominent eyes, impression of hypertelorism, long palpebral fissures, depressed nasal bridge, short philtrum, triangular mouth, thin upper lip, highly arched palate, dental malocclusion, short neck and pectus excavatum. Labia majora and minora were hypoplastic. Upper limbs had mesomelic shortness with radioulnar synostosis (Figure 1b), and limited elbow supination. Hands were short with brachydactyly and 5th finger clinodactyly. Interatrial communication and gastroesophageal reflux were surgically repaired. Radiographs showed delayed bone age (chronological age: 1 year; bone age: 2 months). She had frequent seizures. Karyotype had been reported to be normal.

Array-comparative genomic hybridization (array-CGH) analysis was performed using DNA from peripheral blood lymphocytes (Rosenberg *et al.*, 2006). The slides containing triplicates of ~3,500 large insert clones spaced at ~1.0 Mb density over the full genome were produced at

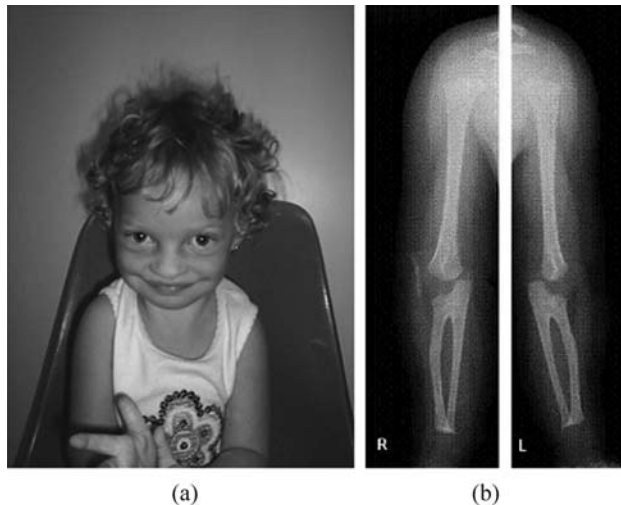


Figure 1 - Deletion 4p and duplication 8p revealed by array-CGH (A and C), and confirmed by FISH (B and D): The deleted (A) and duplicated (B) clones are shown in the array profiles and corresponding chromosome ideograms. After FISH a derivative chromosome 4 was identified, showing deletion of clone GS-36-21 (B), and addition of clone GS-580-L5 (D). Arrows point to der(4).

the Leiden University Medical Center. Information regarding the full set of clones is available at the Wellcome Trust Sanger Institute mapping database site, Ensembl. Copy number alterations detected by array-CGH were validated by fluorescence *in situ* hybridization (FISH) (Rosenberg *et al.*, 1994). The parents were tested for the presence of alterations confirmed in the patient.

In order to determine the parental origin of the chromosome rearrangement, we genotyped markers D4S412 and D4S2935 mapped to chromosome 4p and D8S264 and D8S277 mapped to chromosome 8p (ABI PRISM Linkage Mapping Set v.2.5-MD10 kit, Applied Biosystems). For DNA amplification we used a final volume of 10 μ L containing 50-100 ng of genomic DNA, 0.5 μ L of primers marked with fluorochromes (5 μ M) and 6 μ L of True Allele Premix. The amplified products and the size standard (MegaBace TM "ET550-R Size Standard") were run on a MegaBace TM1000 sequencer (Amersham Biosciences) and analyzed using the Genetic Profiler v.1.5 software.

This study was approved by the National Research Ethics Committee (CONEP), and informed consent was obtained from the legal guardian of the patient.

Array-CGH analysis (Figure 2A and C) demonstrated a terminal deletion of a segment (\sim 8 Mb to 10 Mb) distal to clone RP11-117J13 (4p16.1), and a terminal duplication encompassing a segment (\sim 6.5-Mb to 8 Mb) of the short arm of chromosome 8 distal to clone CTD-2629116 (8p23.1). These alterations were confirmed by FISH of subtelomeric probes of chromosomes 4 (GS-36-21) and 8 (GS-580-L5) to metaphase chromosomes (Figure 2B and D), FISH of the same probes hybridized to the chromo-

somes of the parents did not reveal any alteration of these segments.

Microsatellite analyses showed a single allele of paternal origin at the loci mapped to chromosome 4 (D4S412 and D4S2935) and a more amplified maternal allele at loci mapped to chromosome 8 (D8S264 and D8S277), thus pointing to the maternal origin of the chromosomal imbalance (data not shown). Indeed, whenever investigated, unbalanced t(4;8) translocations have been proven to be of maternal origin (Zollino *et al.*, 2004).

The rearranged derivative chromosome 4 [der(4)] in our patient resulted from a *de novo* translocation between chromosomes 4 and 8. These translocations are relatively frequent, and appear to be mediated by clusters of olfactory receptor genes with high sequence identity on the short arms of chromosomes 4 and 8 (Giglio *et al.*, 2001; Giglio *et al.*, 2002). In our patient, a \sim 6.5-8 Mb segment from chromosome 8 was translocated to chromosome 4. The breakpoint on chromosome 4 mapped close to the distal gene cluster, and the der(4) had a deletion encompassing \sim 8-10 Mb of the short arm. This is considered a large deletion including the Wolf-Hirschhorn critical region (Zollino *et al.*, 2004).

The der(4) in our patient has been previously associated with PRDS (Clemens *et al.*, 1996). Our patient presented the clinical findings most frequently associated with this syndrome, but some of her clinical signs, namely genital hypoplasia, radioulnar synostosis and mesomelic limb shortness, were rarely or never reported in this condition. The only PRDS patient described previously with radioulnar synostosis had an atypical phenotype without intrauterine growth retardation, short stature, microcephaly or seizures, important signs for the diagnosis of the syndrome. This patient did not carry the deletion of the WHS critical region (Zollino *et al.*, 1996). Genital hypoplasia was described in a single patient by Donnai *et al.* (1986), but the mesomelic shortness observed in our patient has not been previously reported in PRDS syndrome. Indeed, short stature, mesomelic limb shortness and genital hypoplasia are clinical signs found in more than 70% of Robinow syndrome patients (Butler and Wadlington, 1987; Mazzeu *et al.*, 2007). However, the combination of symptoms in our patient is not typical of Robinow syndrome patients, particularly regarding craniofacial features. The observation of the characteristic chromosomal imbalance allowed us to confirm diagnosis of PRDS.

Pitt-Rogers-Danks syndrome is considered to be part of the clinical spectrum of Wolf-Hirschhorn syndrome since the deleted segment in chromosome 4 is similar in both syndromes (Bergmann *et al.*, 2005; Wright *et al.*, 1998; Wiczorek *et al.*, 2000; Zollino *et al.*, 1996). However, unbalanced translocations involving chromosomes 4 and 8 like the one described here are less frequent in WHS than in PRDS patients, the latter presenting a less severe phenotype, which sometimes does not include midline de-

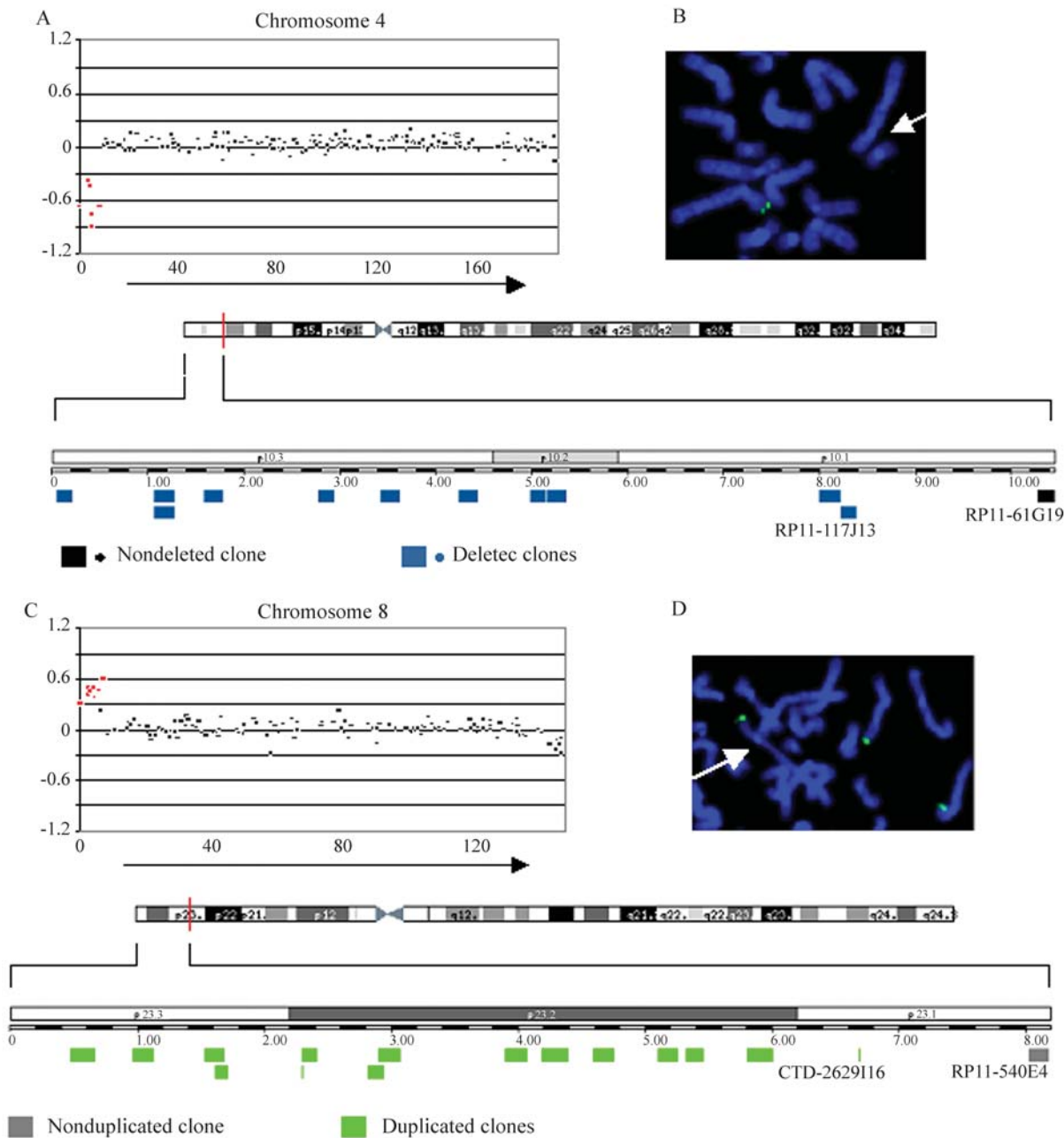


Figure 2 - (A) Patient at age 5 years; (B) Patient's arm X-rays showing mesomelic shortness and radioulnar synostosis (R, Right; L, Left).

fects. The extension of the deletion of chromosome 4 in carriers of the derivative chromosome 4 could be an explanation for the differences in the severity of phenotypes, as reported in WHS deletions (Zollino *et al.*, 2004). The manifestation of recessive genes uncovered by the deletion would add to the phenotypic variability. The patient described here has a large deletion on chromosome 4 extending ~8-10 Mb, but a milder clinical phenotype than WHS patients. The possibility remains that the duplication of chromosome 8 could partially compensate for the absence of segments on chromosome 4, thus resulting in a less severe clinical phenotype in some carriers of large deletions

on chromosome 4 associated with chromosome 8 duplication, as in the case of our patient.

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Internet Resources

Ensembl (<http://www.ensembl.org/>).

Online Medelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/omim>.

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