

## Letter to the Editor

# Inverted Duplication/Deletion of Chromosome 8p: Mild Clinical Phenotype

### To the Editor:

Abnormalities of chromosome 8p are well documented with a delineated clinical picture consisting of developmental disabilities and birth defects [Barber et al., 1994; Guo et al., 1995; Minelli et al., 1993; Mitchell et al., 1994; Priest, 1995; Wu et al., 1996]. About 40 cases of inv dup 8p and more than 30 cases of del 8p have been described [Devriendt et al., 1998; Guo et al., 1995; Priest, 1995; Wu et al., 1996]. In many cases of inv dup 8p, a simultaneous deletion of the telomeric region 8p23.3-pter has been demonstrated [Barber et al., 1994; Guo et al., 1995; Henderson et al., 1992; Jensen et al., 1982; Minelli et al., 1993; Mitchell et al., 1994]. The clinical phenotype of these cases of inv dup del 8p consistently involves agenesis of the corpus callosum (ACC), hypotonia, mental retardation, and dysmorphic features. Less consistent findings include congenital heart defects, eye abnormalities such as coloboma of the iris and strabismus, and development of contractures and scoliosis in severely retarded adults [de Die-Smulders et al., 1995].

We report on an 18-month-old female who was evaluated for mild motor delays and significant speech and language delays. Facial dysmorphic features included frontal bossing; bilateral epicanthal folds; depressed nasal bridge; flared alae nasi; hypoplastic columella; wide mouth with thin upper lip; prominent premaxilla; and a narrow high palate (Fig. 1). Ears were large and posteriorly rotated. Distal phalanges of the first toes were hypoplastic. There was mild generalized hypotonia. She had a friendly and sociable personality. A brain magnetic resonance imaging scan showed hypoplasia of the posterior body of the corpus callosum with asymmetric enlargement of the posterior left ventricle suggestive of partial agenesis of the corpus callosum. She had no congenital heart defects, eye, or skeletal abnormalities. High resolution chromosome analysis was obtained from stimulated peripheral blood cultures of both the patient and her parents. Twenty G-banded metaphases were analyzed for both the proband and her parents and 15 metaphases were exam-

ined for each fluorescence in situ hybridization (FISH) study. Chromosome analysis revealed inv dup (8)(p23.1p12) (Figs. 2A, 2B). FISH with chromosome 8 painting probe (Oncor) showed fluorescence staining through the entire length of both chromosome 8 homologues (Fig. 3A). The chromosome 8p telomere probe (Oncor) detects locus D8S596 at 8p23-ter. The 8p telomere probe, when used in combination with the chromosome 8  $\alpha$ -satellite probe (Oncor) showed signals in the telomeric region only on the normal chromosome 8p in the patient; it was absent in the abnormal 8p (Fig. 3B). Parental chromosomes were normal. Therefore, the karyotype of the patient is designated as 46,XX,inv dup del(8)(qter→p23.1::p23.1→p12:) de novo. The distal breakpoint involved in the rearrangement is 8p23.1, and sequences distal to p23.1 are presumed to be deleted based on FISH analysis using the 8p telomere probe. This patient has several of the reported features of inv dup 8p including partial agenesis of the corpus callosum and mild facial dysmorphisms; however, her developmental delay is milder than the severe mental retardation reported in patients with comparably sized duplications [Guo et al., 1995]. Her speech delay is significant.

The contribution of the deletion to the clinical phenotype of the rearrangement remains unclear. Deletion of the 8p23.1-pter region in many patients is associated with congenital heart defects, mental retardation, and speech delay but not ACC, which is a feature of dup 8p and trisomy 8p [Digilio et al., 1994; Wu et al., 1996;



Fig. 1. Patient at age 18 months. Note the bilateral epicanthal folds, depressed nasal bridge, and flared alae nasi.

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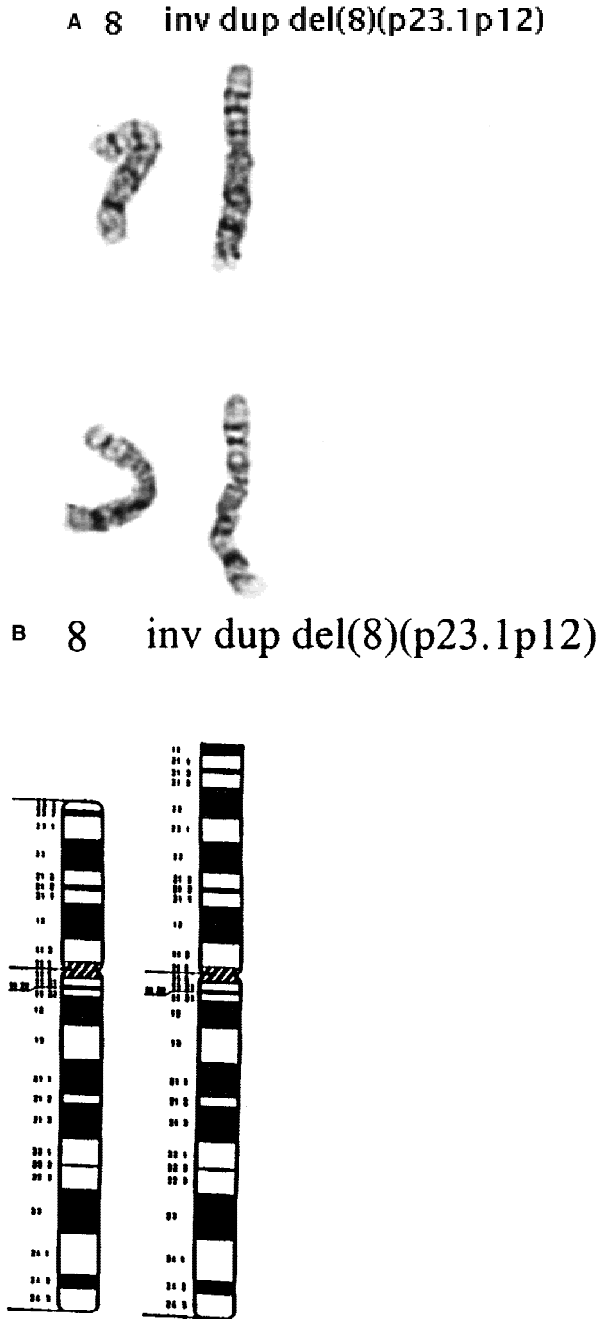


Fig. 2. **A:** Pairs of chromosomes 8 from two cells with GTG banding. The inv dup del 8 chromosome is the right member of each pair. **B:** Ideogram of the normal and inv dup del 8.

Zuffardi et al., 1994]. ACC may be partial or complete and is known to be of heterogeneous etiology. Because of the association with dup 8p and trisomy 8p, it has been suggested that a presumptive malformation-causing gene may lie in the 8p21-pter region [Digilio et al., 1994]. Other studies have narrowed this region to 30 cm, between D8S137 and D8S35 [Zuffardi et al., 1994]. Further research is required to establish the nature of this putative gene and its role in brain development through a dosage effect.

Clinical data and cytogenetics of five children and

two adults with inv dup 8p were reported by de Die-Smulders et al. [1995]. They also compared the clinical manifestations of their patients to previously reported cases and suggested that the clinical picture in young children is characterized by facial anomalies, hypotonia, and severe developmental delay, whereas in older patients the facial traits are less characteristic and spastic paraplegia may develop. Although orthopedic problems like contractures, joint deformation, and scoliosis have not been reported in children, they have been reported in adults with this chromosome abnormality, presumably as a result of neurological abnormality.

Dhooge et al. [1994] reported direct transmission of a tandem duplication of 8p in a woman to two of her children who were mildly retarded. In three members of a family with mild mental retardation reported by Brooks et al. [1998] the region 8p22→8pter was tandemly duplicated because of a paternal Y;8 translocation. Engelen et al. [1995] reviewed direct and inverted duplications and reported that patients with inverted duplications 8p21.1→8p21.3 have profound mental retardation, while those with 8p22→8p23.1 tandem duplication had borderline-to-mild mental retardation. This patient seems to belie the suggestion that the distal deletion contributes to severity of mental retardation. Other factors such as a delay in diagnosis and lack

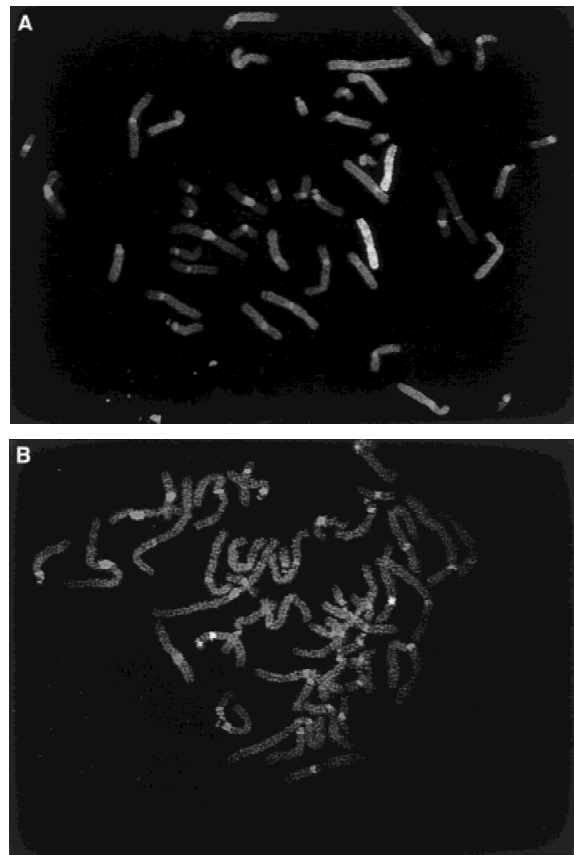


Fig. 3. **A:** Chromosome 8 painting probe hybridized to the normal and inv dup del 8. **B:** Fluorescent signals at the centromere and telomere of chromosomes 8. Note the absence of telomere signal on inv dup del (8) chromosome.

of early intervention may have contributed to severity of delays in earlier reported cases. ACC may be a clinical clue to abnormalities of chromosome 8p. Patients with this rearrangement should also be studied for the distal deletion so its role in the pathogenesis of the rearrangement and its phenotype may be better understood.

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