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D8S7 is consistently deleted in inverted duplications of the short arm of chromosome 8 (inv dup 8p)

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Abstract. Ten patients with inverted duplication of 8p (inv dup 8p) were studied with cytogenetic, biochemical and molecular techniques. The duplication for the region 8p12–p22 was always associated with a deletion of the locus D8S7 (mapped in 8p23.1) as demonstrated with the probe pSW50 by both in situ hybridization and Southern blot. Restriction fragment length polymorphisms detected by probes pSW50 (1 case) and by pG2LPL35 (locus LPL) (two cases) were informative as to a maternal origin of the anomaly. The activity of glutathione reductase, whose gene maps in the duplicated region at 8p21.1, was increased in all patients. The recognizable phenotype of inv dup 8p includes neonatal hypotonia, prominent forehead, large mouth with everted lower lip, abnormally shaped large ears, brain malformations and severe mental retardation. Our findings indicate that the chromosome rearrangement is homogeneous at least for the presence of the deletion and support the hypothesis of a common mechanism of origin.

Introduction

Fewer than 30 cases of inverted duplication of the short arm of chromosome 8 (inv dup 8p) have been reported. Proximal breakpoints have been indicated as being at 8p11 (eight cases: Weleber et al. 1976; Rethoré et al. 1977; Mattei et al. 1980; Feldman et al. 1990), 8p12 (four cases: Taylor et al. 1977; Dill et al. 1987; Feldman et al. 1990; Nevin et al. 1990) or 8p21 (twelve cases: Taylor et al. 1977; Hongell et al. 1978; Jensen et al. 1982; Fryns et al. 1985; Kleczkowska et al. 1987; Feldman et al 1990; Gorinati et al. 1991; Mitchell et al. 1991), whereas distal breakpoints are at 8p22 (seven cases: Rethoré et al. 1977; Fryns et al. 1985; Dill et al. 1987; Kleczkowska et al. 1987; Gorinati et al. 1991) or 8p23 (seventeen cases: Weleber et al. 1976; Taylor et al. 1977; Hongell et al. 1978; Mattei et al. 1980; Jensen et al. 1982; Feldman et al. 1990; Nevin et al. 1990). In the majority of cases, the duplicated region includes the locus for the glutathione reductase (GSR) gene, located at 8p21.1. Indeed, a gene dosage effect for this enzyme was reported by several authors (Taylor et al. 1977; Mattei et al. 1980; Jensen et al. 1982; Nevin et al. 1990; Gorinati et al. 1991). In addition to the duplication, a deletion within the distal part of 8p, 8p23, was suggested by cytogenetic techniques in eight cases (Weleber et al. 1976; Rethoré et al. 1977; Mattei et al. 1980; Jensen et al. 1982; Gorinati et al. 1991) and demonstrated by Dill et al. (1987) who reported the deletion of the locus D8S7 (which maps to 8p23) in a patient with inv dup 8p. Mitchell et al. (1991) reported in a second case the deletion of the DEF1 locus which also maps at 8p23. Thus, the inv dup 8p seems to be a complex rearrangement resulting not only in a duplication for a major portion of 8p, but also in a minimal deletion for the distal portion of it. To clarify whether a deletion is indeed always associated with the duplication in this anomaly, we studied ten new patients with cytogenetic, biochemical and molecular techniques. The finding that the locus D8S7 was consistently deleted in all of them strongly indicates that the rearrangement is homogeneous and supports the hypothesis of a common mechanism of origin.

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Table 1. Karyotype, results of GSR assay and main symptoms of the ten patients with inv dup 8p

Case number	Karyotype[a]		GSR[b]	Main symptoms
	Duplication	Deletion		
1	p12–p22	p23.1	1.97	Hypotonia, brain anomalies, dysmorphic face, MR
2	p12–p22	p23.1	2.14	Hypotonia, heart malformation, deceased
3	p21.1–p22.1	p23.1	1.87	Hypotonia, brain anomalies, dysmorphic face
4	p12 p22	p23.1	1.55	Hypotonia, brain anomalies, dysmorphic face, MR
5	p12–p22	p23.1–pter	1.56	Hypotonia, brain anomalies, dysmorphic face, MR
6	p12–p22	p23.1	1.62	Low birth weight, short stature, dysmorphic face, MR
7	p12–p22	p23.1	1.58	Hypotonia, dysmorphic face, MR
8	p12–p22	p23.1	2.43	Hypotonia, brain anomalies, dysmorphic face, short stature, MR
9	p12–p22	p23.1	1.49	Low birth weight, brain anomalies, dysmorphic face, MR
10	p12–p22	p23.1	1.62	Hypotonia, brain anomalies, dysmorphic face, MR

[a] Only the extension of the duplicated and of the deleted region is indicated
[b] The results of GSR assay are expressed as ratios between the patient's activity and the mean of their parents' activities. Control data are reported under "Analysis of GSR"
MR, Mental retardation

Table 2. Clinical symptoms observed in our patients and in cases from the literature

	Literature	Present cases	Total
Sex (M/F)	10/13	6/4	16/17
Parental age (years)			
Father (*n*)	34.08 ± 10.31 (12)	35.12 ± 4.32 (8)	34.57 ± 8.31 (20)
Mother (*n*)	30.50 ± 6.10 (12)	33.25 ± 2.91 (8)	31.65 ± 5.11 (20)
Birth weight (at or below 10 cent.)	9/14	2/7	11/21
Birth length (at or below 10 cent.)	1/ 7	0/3	1/10
Hypotonia at birth	16	6/7	22/23
Prominent forehead	12	5	17
Large/abnormally shaped ear	9	5	14
Broad nasal bridge	10	5	15
Large mouth	11	6	17
Everted lower lip	11	7	18
High arched palate	12	6	18
Micrognatia	11	4	15
Short neck	6	3	9
Scoliosis, kyphosis	8/12	2/4	10/16
Slender extremities	6	3	9
Brain abnormalities[a]	10	6	16
Psychomotor retardation[b]	21	8	29
Expressive language absent or severely delayed	9/10	3	12/13

[a] Demonstrated by neonatal echography or CT scan, include agenesis of corpus callosum, ventricle enlargement, agenesis of cerebellar vermis, cerebral hypoplasia
[b] In four patients, no follow up information after birth is available

Materials and methods

Patients

The main symptoms of the patients, their cytogenetic data and results of GSR assays are summarized in Table 1. Case 3 was extensively described by Gorinati et al. (1991). Detailed clinical features of our patients, compared with those in the literature, are reported in Table 2. In this table, single figures refer to the number of patients for whom the symptom is quoted; when two figures are entered (i.e. 5/7, five out seven), it implies that the symptom was clearly absent in some patients.

Cytogenetic studies

Chromosome analyses were performed by conventional G-banding and Q-banding on lymphocytes from the patients and their parents. Prometaphase chromosomes were analysed in all cases with the exception of case 1. In this case, cultured skin fibroblasts were also studied.

In situ hybridization

In situ hybridization was performed with pSW50 (Wood et al. 1986a) in cases 2, 6 and 9, and with pBS8.9 (Wood et al. 1986b) in case 6. Their loci, respectively D8S7 and D8S11, map at 8p23 (Wood et al . 1986a, b). The plasmids were labelled with biotin-16-dUPT by nick translation according to the Boehringer Mannheim protocol. Hybridizations were performed in 50% formamide/2 × SSC (1 × SSC = 150 m*M* NaCl/15 m*M* sodium citrate, pH 7.0), using 200 ng probe per slide at 37°C for 12–16 h. Post hybridization washing was carried out in 50% formamide/2 × SSC (three washes, 3 min each) at 42°C, and then in 2 × SSC at room temperature (five washes 2 min each). In all cases, detection was performed according to the ONCOR detection kit with two amplification steps. Chromosomes were counterstained with propidium iodide (1 μg/ml) and banded with 4,6 diamino-2-phenyl-indole (DAPI; 0.5 μg/ml).

GSR assay

GSR activity was measured on red blood cells according to George and Franke (1976). The results are expressed as the ratio between patient's activity and the mean of the parental activities. Malate dehydrogenase or peptidase A were tested as control enzymes in each of the families.

Molecular analysis

DNA extraction, restriction enzyme digestion, electrophoresis, blotting and hybridization were carried out with routine methods using Hybond N (Amersham) membranes. The probes pSW50 (D8S7) and G80 (D7S373) (Raimondi et al. 1987), the latter used as a control probe, were labelled by random priming. We studied concurrently the patient and his (her) parents. Densitometric scanning of autoradiographs was performed with Profil UNO-Sebia equipment. The intensity of hybridization was measured transversely for each family and for both probes. The ratios between D8S7 and G80 were then calculated and the results are listed in Table 4. In families, where one of the parents was heterozygous, scanning was performed on the more frequent 3.1-kb allele. Cases 7, 8 and 9 were also studied with probe pG2LPL35 (the lipoprotein lipase locus; LPL) (Heinzman et al. 1987), which maps at 8p22 (Sparkes et al. 1987).

Paternity testing

DNAs from the ten families were studied according to the methods reported by Gill et al. (1991), with the probes pYNH24 (D2S44) (Nakamura et al. 1987a), pJCZ3.1 (D19S20) (Nakamura et al. 1987b) and 3'HVR (D16S85) (Higgs et al. 1986).

Results

Cytogenetic analysis

The karyotypes of the patients are reported in Table 1. The interpretation of the abnormalities was reached by the combination of cytogenetic and molecular results. The chromosomal rearrangement was considered to be identical in cases 1, 2, 4, and 6–10, which we analysed in the same laboratory. In cases 3 (Gorinati et al. 1991) and 5, analysed in two other laboratories, two distinct interpretations were given (Table 1). Figure 1 shows partial karyotypes from representative cases 6, 9 and 10. All parents had a normal karyotype.

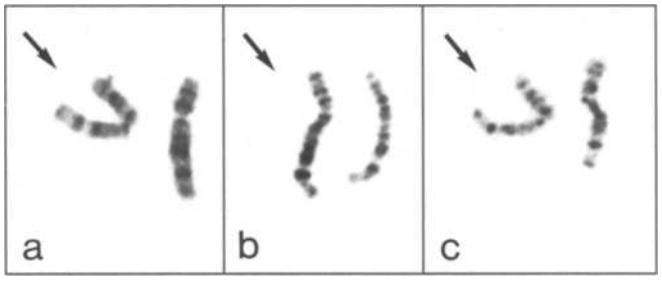

Fig. 1. Partial karyotypes of the normal and rearranged *(arrows)* chromosomes 8, from cases 10 **a**, 6 **b** and 9 **c**; G-banding

In situ hybridization

The results of in situ hybridization are reported in Table 3 and in Fig. 2. In the three cases analysed with pSW50 and in the one case analysed with pBS8.9, hybridization signals were present at p23 in the normal chromosome 8, whereas the inv dup 8p showed only a few signals scattered along the whole chromosome.

Analysis of GSR

Table 1 gives the ratios between GSR activity and the mean of the parents' activities for each patient. The ratio was 1.09 ± 0.15 (n = 20) in the control group and 1.78 ± 0.31 (n = 10) in the group of inv dup 8p. The difference between the means is statistically significant (t = 64.276, $P < 0.001$).

Molecular analysis

All paternities were confirmed with a probability >99.9%, calculated by the Essen-Moller equation. The probe pSW50 recognizes at D8S7 a *Hin*dIII restriction fragment length polymorphism (RFLP) with two alleles of 3.1 and 2.4 kb with frequencies of 0.84 and 0.16, respectively (Alkan et al. 1989). We found 5 heterozygotes (Table 4) among the 20 parents (expected 5.3). The results of DNA hybridization with D8S7 and G80 (control probe) for cases 1, 2, 3, 7 and 10 are illustrated in Fig. 3.

In case 10 (Fig. 3), the father shows both the 3.1-kb and 2.4-kb alleles, the mother is homozygous for the 3.1-kb allele, whereas only the 2.4-kb paternal allele is present in child. Thus the rearrangement causing the loss of the 3.1-kb allele originated in the maternal chromosome.

Other cases were not informative as to the origin of the anomaly and were analyzed by densitometric scanning to assess whether one or two alleles were present in the propositi. In cases 1–5, the parents are homozygous for

Table 3. Results of in situ hybridization

Case	pSW50			pBS8.9		
	Mitoses with at least one spot on chromosome 8/ mitoses examined	No. spots on		Mitoses with at least one spot on chromosome 8/ mitoses examined	No. spots on	
		8	inv dup 8p		8	inv dup 8p
2	50/166	55[a] 13[b]	5[b]			
6	17/56	20[a]	5[b]	39/97	43[a] 10[b]	9[b]
9	28/80	33[a] 7[b]	4[b]			

[a] Spots clustered at 8p23
[b] Spots scattered along the whole chromosome

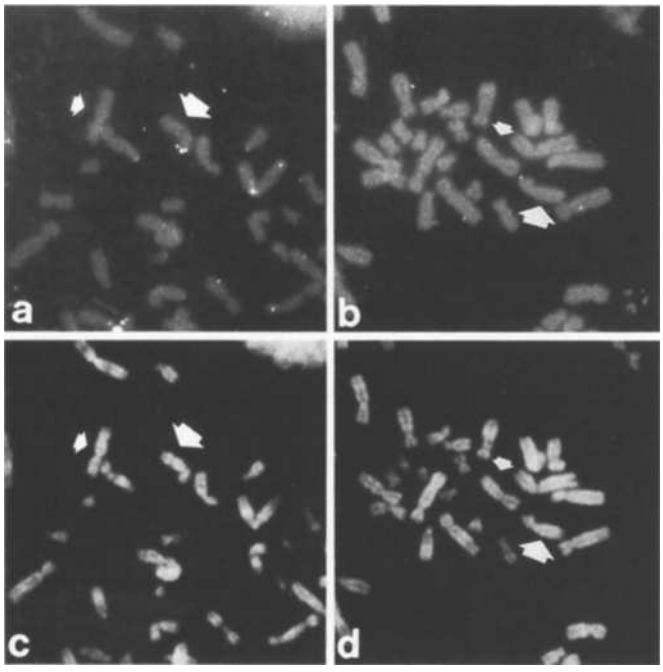

Fig. 2. a–d. Partial metaphases from case 2. **a, b** In situ hybridization with pSW50. **c, d** The same metaphases stained with DAPI. *Large arrows* indicate the normal chromosome 8; *small arrows* indicate the abnormal one

the 3.1-kb allele and the propositi show a D8S7/G80 ratio reduced to 50% of that of each parent (Table 4).

In each of the cases 6–9, one of the parents is heterozygous (Table 4) but all the propositi show only the 3.1-kb allele. The patients show a D8S7/G80 ratio reduced to 50% of that of the homozygous parent, whereas the ratio is close to 1 when they are compared with the heterozygous parent, in which only the 3.1-kb allele was used for densitometric analysis. These findings demonstrate the presence of only one allele at the D8S7 locus in all the patients.

At the LPL locus, the probe pG2LPL35 recognizes a *Hin*dIII RFLP with two alleles A1 and A2, of 8.7 and 17.5 kb, respectively (Fig. 4), with fequencies of 0.67 and 0.33. A constant band of 4.5 kb is also observed. In the three cases studied (cases 5, 8 and 9), densitometric analysis (data not shown) indicated that the LPL locus is duplicated.

Table 4. Results of the densitometric analysis. A comparison of D8S7/G80 ratios within each family

Case	D8S7/G80 ratio			Alleles		
	P/F	P/M	F/M	P	F	M
1	0.45	0.44	0.97	A1/–	A1/A1	A1/A1
2	0.50	0.50	1.02	A1/–	A1/A1	A1/A1
3	0.43	0.37	0.86	A1/–	A1/A1	A1/A1
4	0.57	0.46	0.81	A1/–	A1/A1	A1/A1
5	0.30	0.42	1.40	A1/–	A1/A1	A1/A1
6	1.05	0.58	0.55	A1/–	A1/A2	A1/A1
7	1.27	0.61	0.48	A1/–	A1/A2	A1/A1
8	0.37	–	–	A1/–	A1/A1	A1/A2
9	1.02	0.53	0.52	A1/–	A1/A2	A1/A1

P, Propositus; F, father; M, mother; A1, 3.1-kb fragment; A2, 2.4-kb fragment

Case 5 was not informative as to the origin of the anomaly. In case 8, the mother and father are homozygous respectively for A1 and A2. The child shows both alleles and densitometric analysis indicates a 2:1 ratio between A1 and A2. In case 9, the mother and father are homozygous for A2 and A1 respectively; in this case, a 2:1 ratio between A2 and A1 is observed in the child. Thus, in both the latter cases, the presence of a double dose of the maternal allele indicates a maternal origin of the anomaly.

Discussion

Kleczkowska et al. (1987) made an attempt to define a common clinical picture for inv dup 8p patients and stressed the changes that can be observed from childhood to adult phenotype. The synopsis of the symptoms more frequently observed in our patients, reported in Table 2, confirms the existence of a phenotype with characteristic facies (prominent forehead, broad nasal bridge, large mouth with everted lower lip, high arched palate and large, abnormally shaped ears), spine abnormalities, brain malformations and very poor expressive language in adult life. We consider that brain anomalies (agenesis of the corpus callosum, enlarged ventricles and cerebral atrophy) should be included among the relevant symptoms and be routinely investigated in these patients; indeed, singularly or in various combinations, they are present in

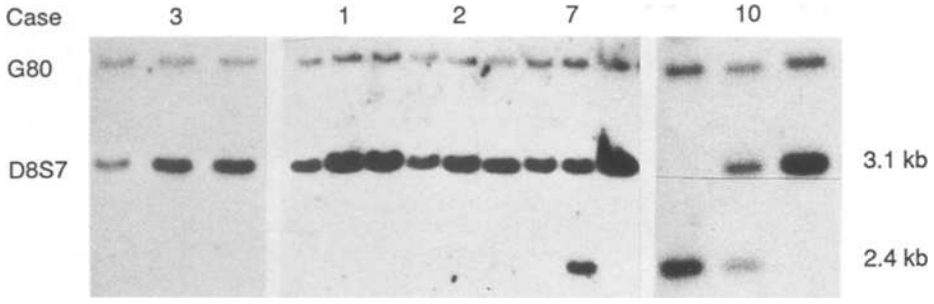

Fig. 3. Hybridization analysis of *Hin*dIII-digested DNA with probes G80 and D8S7 in cases 1, 2, 3, 7, 10. From the *left*: propositus, father mother

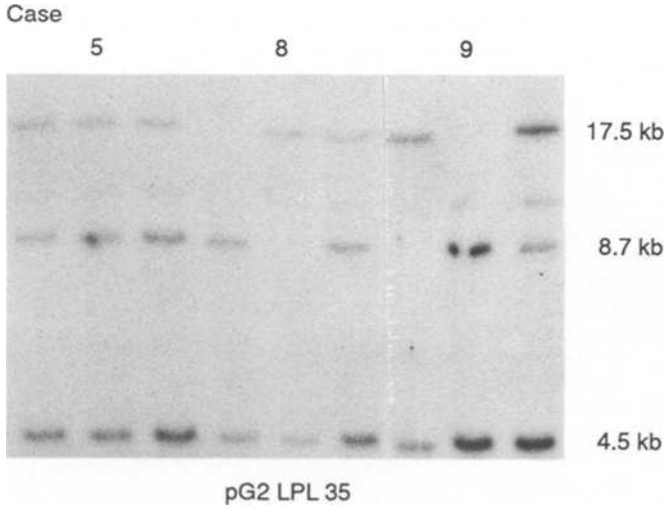

Fig. 4. Hybridization analysis of *Hin*dIII-digested DNA with probe pGL2LPL35 in cases 5, 8 and 9. From the *left*: mother, father propositus

all 16 patients studied by neonatal echography or by computerized tomograpy (CT). The absence of the corpus callosum is also a frequent finding in trisomy 8 mosaicism and in several cases of partial trisomy 8p (Schinzel 1984), and thus suggests that it is related to the trisomy for a gene located on the short arm of chromosome 8.

More detailed correlations between single symptoms and imbalances for 8p-specific regions are presently impossible because of the complexity of the inv dup 8p rearrangements with some regions being duplicated and others deleted (see also below), and because of the possible heterogeneity of the rearrangements. Our finding that D8S7 is deleted in all ten patients indicates that the rearrangement is homogeneous at least for the presence of a deletion within the distal band 8p23. The same deletion was found in a single case by Dill et al. (1987), whereas in a second case, Mitchell et al. (1991) demonstrated the deletion of the defensin gene, DEF1, that also maps on 8p23. Our in situ hybridization data with D8S11, performed only in case 6, suggest that this locus is included in the deleted region. Lack of information (Steinbrueck et al. 1992) on the relative distances between D8S7, D8S11 and DEF1 does not allow us to establish the size of the deletion.

With regard to the duplication, the cytognetic interpretations are not uniform, although bands 8p21 and 8p22 are always included in the duplicated region. GSR activity was increased in all our cases and in eight cases from the literature. Only one of the two patients reported by Jensen et al. (1982) had normal GSR activity. Thus 8p21.1, to which the GSR gene has been mapped, is included in the duplication in the vast majority of cases. We suggest that the assay of GSR should be performed routinely in all cases of inv dup 8p. Should the cytogenetic interpretation given by Jensen et al. (1982) be correct, their "patient 1" is indeed different from most reported inv dup 8p.

Analysis of polymorphisms was informative in cases 8, 9 (pG2LPL35) and 10 (pSW50); the finding of a maternal origin in all of them suggests that the chromosome abnormality is related to maternal age. Indeed, maternal ages at the patients' births in these cases were 37, 43 and 42 years, respectively.

Although the elucidation of the molecular mechanism producing these rearrangements will have to await cloning and sequencing of the breakpoints, it appears likely that direct and inverted repeats, spreaded along the short arm of chromosome 8, can cause illegitimate recombination. This mechanism of formation of large genetic changes has been demonstrated in several human cell lines (Monnat et al. 1992; Morris and Thacker 1993) and in some human diseases (reviewed by Hu and Worton 1992).

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