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Inherited Deletion of Chromosome (21p-) in a Child with Congenital Malformation and Psychomotor Retardation

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Polymorphic variants of chromosome 21 short arms ($21p^+$, p^-, s^+, s^-, dNOR, secondary constriction, *etc.*) are common and are inherited as simple Mendelian traits. Deletion resulting in loss of genetic material leads to varying degree of malformations and mental retardation. Advances in banding techniques have enabled in detecting minor regions of chromosomes in delineating several deletion syndromes. Abnormalities of chromosome 21 (numerical and structural) are relatively more frequently associated with congenital malformation, mental retardation, fetal loss and infertility. Lejeune *et al.* reported the first case of partial monosomy of chromosome 21 resulting from ring 21(1). Later on deletion of shot arm of a G-group chromosome was reported by many workers(2-8). In this report a case of familial 21p- associated with congenital malformation and psychomotor retardation is described.

Case Report

The index patient, 8-month-old male child was the product of normal full term 3rd pregnancy, born to nonconsanguinous parents through breech delivery. His weight was 5 kg, height 67 cm and head circumference 40 cm. Other two siblings of ages 6 years (III–1) and 4 years (III–2) were female children (*Fig. 1*). The father and mother were 30 and 29 years, respectively at the time of proband's birth. The pregnancy and neonatal history were unremarkable. The child was referred for investigations with history of poor weight gain, severe hypotonia, delayed milestones, receding chin, low set ears, genu valgum (knock knees), bilateral edema, undes-

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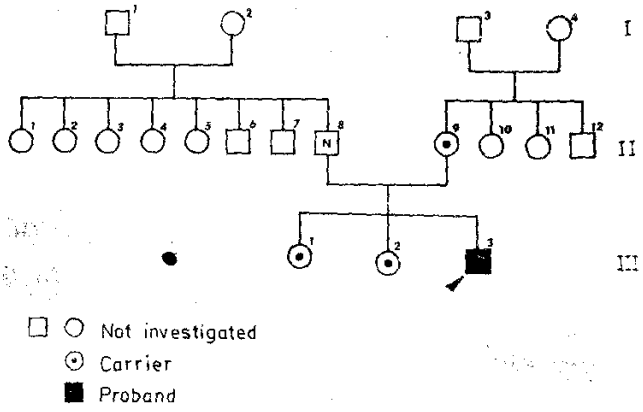

Fig. 1 Pedigree Chart

cended testes, hypogenitalism, high arched palate, prominent upper lip, long philtrum, epicanthial fold. His DO was 75 on DST (Development Screening Test, Indian Standard). These features were not suggestive of any known chromosomal syndromes. There was no family history of any malformation or mental subnormality.

Peripheral blood lymphocytes of the proband and other family members were cultured in E 10 medium (GIBCO, USA) supplemented with 10% fetal calf serum. Air dried metaphase chromosome preparations were made by standard procedure. Conventional Giemsa staining, G- and C-banding were done according to standard procedure. Ag-NOR staining followed by trypsin-Giemsa (GTG) banding was used to identify the precise location of the NOR on each acrocentric chromosome(9). Patterns of Ag-NOR staining, acrocentric associations were scored in proband, proband's sister and the parents.

Detailed chromosome analysis showed apparent deletion of chromosome 21, 46, XY, 21 p- (p cent → p ter) in proband. The deleted chromosome 21 was inherited from mother and was also found in two other female sibs. Karyotype of father was normal. 21p- in the proband is shown by different banding techniques (*Fig. 2*). In *Fig. 2* E, F, G, H shows association of 21p- with other acrocentric chromosomes (chromosome 14, 15, 21 and 22). *Figure 3* shows partial karyotype of chromosome 21, 22 and Y in proband and parents. The frequency and types of acrocentric associations (normal 21 and 21p-) with other D and G group chromosomes in the index family compared with appropriate control group is summarized in *Table I*. Interestingly the frequency of association was significantly less in proband compared to control. As expected the frequency of association was relatively less in sister of proband and mother compared to control and normal father. The association pattern of chromosome 21 with D group and G group was studied and it was found that the 21p- is taking part in association with other

TABLE I—*Frequency of Association of 21p- and Normal 21 with other D and G Group Chromosomes*

Subjects	No. of cells scored	No. of cells with assoc	D/21p-	D/21	G/21p-	G/21
			Per cent			
Proband	200	38.0*	4.0	15.0	1.0	6.0
Control	200	58.0	–	30.0	–	11.5
Sister	100	40.0	4.0	18.0	4.0	4.0
Mother	100	43.0	5.0	17.0	2.0	5.0
Father	100	62.0	–	28.0	–	12.0

*p = 0.01 statistical analysis by Chi-square (χ^2) test.

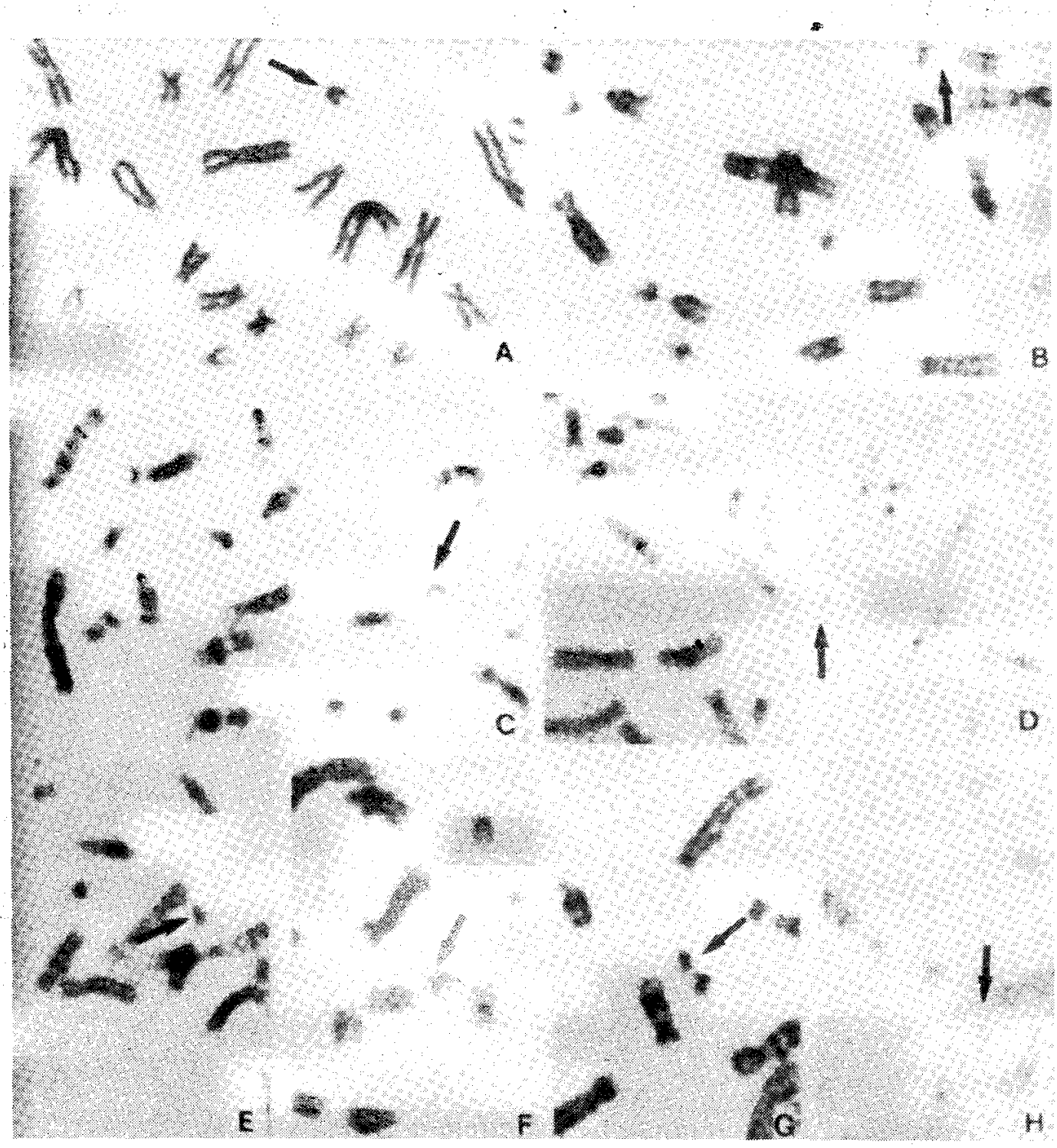

Fig. 2. A, Geimsa staining; B, G-banding; C, NOR-GTC banding;: D, C-banding showing (arrow) 21p-. E, F, G, H showing association of 21p- with chromosome 14, 15, 21 and 22, respectively.

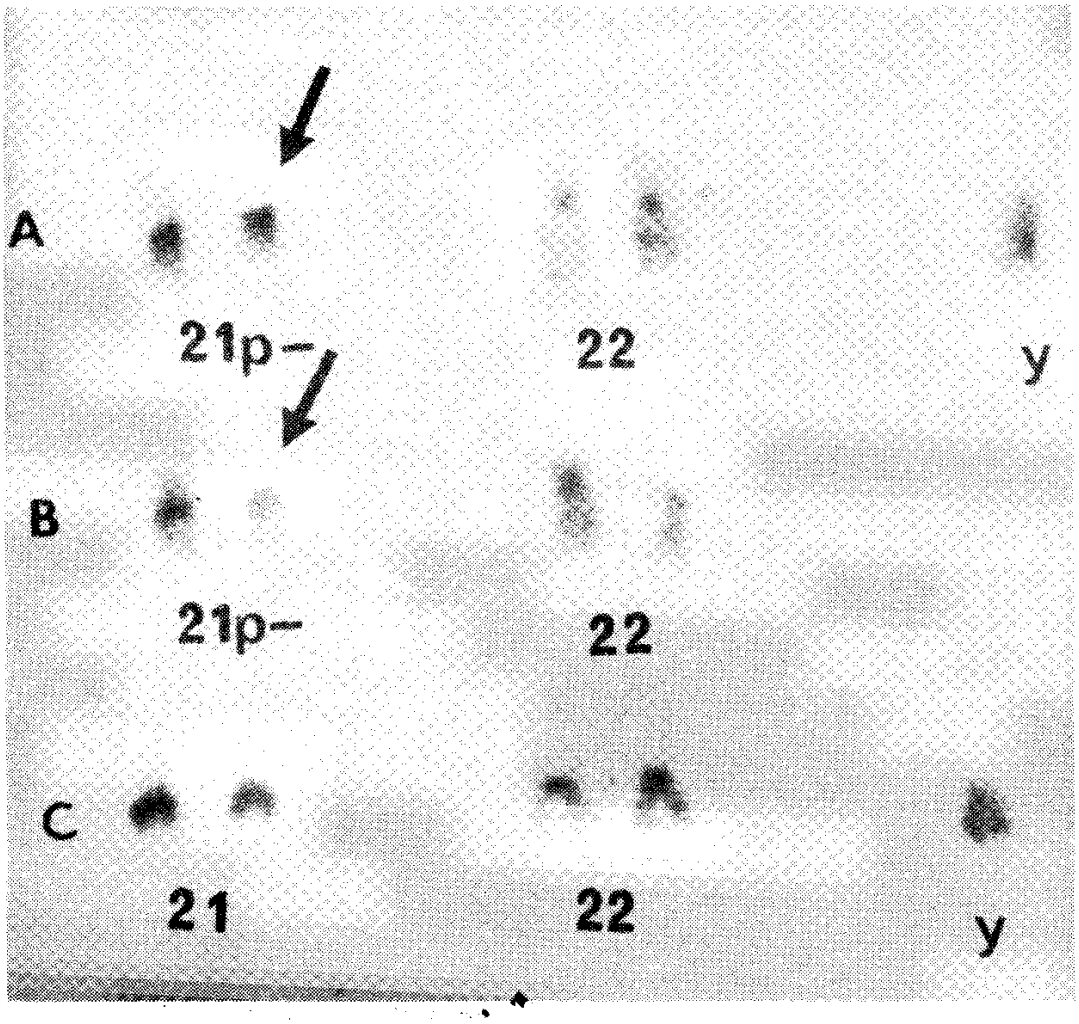

Fig. 3. Partial karyotype of A, Proband; B, Mother and C, Father showing 21p- (arrow).

acrocentric chromosomes, and this may be due to the presence of small amount of heterochromatin found in C-banding. Also the association of 21 with D and G group chromosomes was significantly less as compared to control. Thus, it can be concluded that this may be due to the loss of NOR as a result of deletion of short arm of chromosome 21.

Discussion

Very few cases of 21p- have been documented in the literature (*Table II*). The typical feature of 21p- syndrome has thus not been well characterized. As shown by many Robertsonian and other translocation and ring chromosomes, deletion of juxtacentromeric segment only of chromosome 21 has no impact on the phenotype except for possible reduced fertility in some male carriers(11). Recently, El-Badramany *et al.*, reported familial maniac depressive illness with deleted short arm of chromosome 21(8). It appears variants of chromosome 21 short arm are often benign. There are number of reports of heritable structural variations of the chromosome including the Gp- being associated within families with both normal and abnormal phenotypes(5,7). Apparently a complete absence of the short arm in acrocentric chromosome is without any deleterious phenotype effect as in persons with balanced centric fusion; t (Dq, 21q), t (21q, 22q) or t (21q, 21q)(6,7). In the present

TABLE II–*Summary of Reported Cases with 21p-**

	Cytogenetic findings	Clinical manifestation	Reference
1.	46, XY, 21q+/46, XY, 21 p- Mosaicism in a child with Down's syndrome	Down's syndrome	Atkin & Feingold(2)
2.	21p- maternal en double exemplaire chez un trisomique 21 46, XX, 21 p- 47, XX, der (21p- mat, + der (21p-) mat	Down's syndrome	de Grouchy(3)
3.	Deletion of short arm. satellites in acrocentric chromosoms 46, XX, 21 ps-	Unknown	Nielsen *et al.*(4)
4.	Down's syndrome and deletion of short arms of a G-chromosome	Down's syndrome	Ballantyn *et al.*(5)
5.	Absence of the short arm in acrocentric chromosomes is without any deleterious phenotype effect as in person with balanced centric fusion	Unknown	Rethore(6)
6.	Deletion of short arm in acrocentric chromosomes (gp- being associated within families with both normal and abnormal phenotypes	Unknown	Hsu *et al.*(7)
7.	Familial manic depression illness with deleted short arm of chromosome 21	Manic depression	El-Badramany *et al.*(8)
8.	Familial 21p- deletion associated with congenital malformation retardation 46, XX, 21p- : Mother 46, XY, 21 p- (mat) : Index patient 46, XY, 21 P- (mat) : Sisters of Index patient.	Congenital malformation and retardation	Present Report

*Compiled from Borgaonkar and Schinzel(10,11).

case, proband had mild mental retardation with other clinical manifestations whereas two sisters and mother were clinically normal. Our investigation is supported by Ballantyne and Hsu studies(5,7). The mechanism underlying the onset of clinical manifestation in males, but not in females due to deletion is not understood.

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