ELECTRONIC LETTER

Pure terminal duplication of the short arm of chromosome 19 in a boy with mild microcephaly

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Duplication of chromosome 19, partial or complete, has rarely been described. Trisomy of its short arm (19p) was briefly reported in abstract form by Byrne *et al*[1] in 1980 in a newborn patient with dysmorphism and intrauterine growth retardation and in 1992 by Salbert *et al*[2] in a dysmorphic newborn male. The delineation of these two patients was hampered by deletion of the terminal band of chromosome 13 in the first case and partial deletion of distal chromosome 3q in the second case.

Figure 1 Index patient aged 21 months. Note mild facial dysmorphism and sparse hair.

CASE REPORT

The infant presented here is the first and only child of non-consanguineous parents. The family history is unremarkable apart from epilepsy in the maternal grandmother. The pregnancy was uneventful with no intrauterine growth retardation. The mother and the father were aged 28 and 35 years at the time of birth. He was born at 41 weeks of gestation by spontaneous delivery. He sat alone at 6 months, walked at 17 months, and spoke a few words at 21 months. Mild psychomotor delay and head circumference at −3 SD were the reason for referral at 20 months. Craniofacial features included sparse hair, short nose, anteverted nostrils, low set ears, and a long upper lip (fig 1). His behaviour was hyperkinetic with a short attention span. Karyotype was 46,XY. Parental G banded karyotypes on peripheral blood lymphocytes were also normal. However, since the patient had microcephaly and dysmorphic signs we investigated the possibility of a submicroscopic chromosomal rearrangement by multitelomeric FISH analysis[3–5] using the Vysis ToTelVysion Probe Panel.

Three copies of the 19p arm probe clone 129F16/SP6[6] were observed: two hybridised to their normal location on 19p and the third on the telomere of the chromosome 14 long arm. All the other subtelomeric probes were present in two copies and hybridised at their correct location. It keeping with this, one of the chromosomes 14 had hybridisation signals from both the 14q (telomeric IGHV segments[7]) and the 19p probes (fig 2).

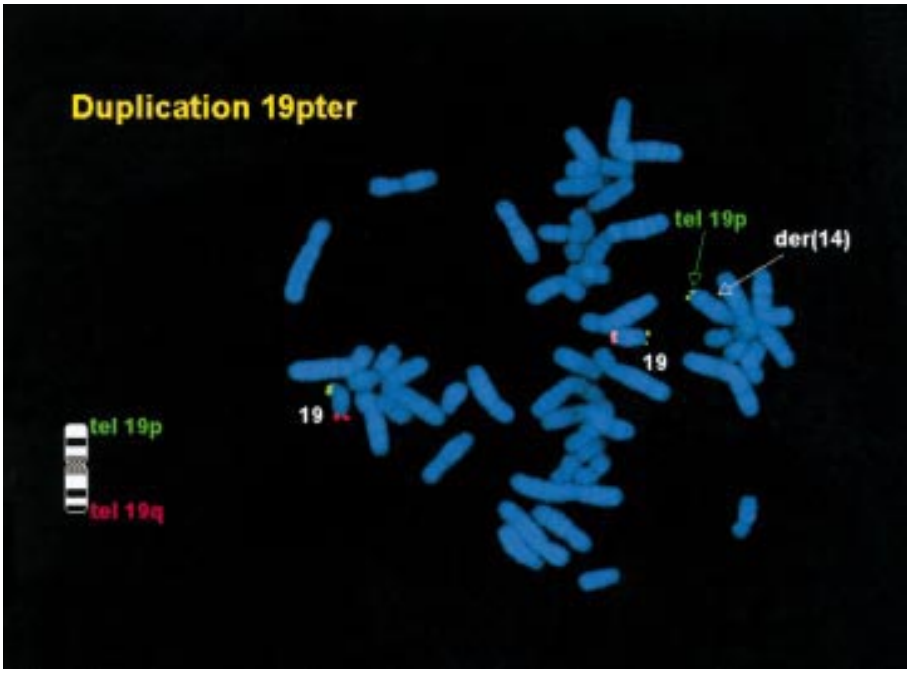

Figure 2 FISH analysis of peripheral lymphocytes: note three signals for the 19p marker.

Table 1 Clinical hallmarks of reported cases

	Byrn *et al*[1]	Salbert *et al*[2]	Our patient
Short stature (or IUGR)	++	++	–
Mental retardation	++	++	+
Microcephaly	++	NS	– 3 SD
Malformed ears	+	+ (pointed helices)	+ (low set ears)
Sparse hair	Not mentioned	+	+
Eye abnormalities	Upward slanting palpebral fissures	Short palpebral fissures	
Nose abnormalities	Anteverted nostrils	Prominent, broad nasal tip	Short nose
Limb abnormalities	4th-5th toe syndactyly	Proximally set thumbs, club feet	–
Cytogenetic abnormalities	dup 19p13.3-pter del 13q32-qter	dup 19p13.2-pter del 3q29-qter	dup 19 p13.3-pter
Additional findings	Heart defect, seizures, ambiguous genitalia	Hypotonia, short neck, telecanthus	

The karyotype of the infant may therefore be defined as 46,XY.ish der(14)t(14;19)(q32.3;p13.3)(IGHV+;129F16/SP6+). The parents have a normal hybridisation pattern for the 19pter and 14qter probes: 46,XX or 46,XY.ish (14q32.3(IGHV × 2, 19p13.3(129F16/SP6) × 2).

DISCUSSION

From this analysis it can be concluded that this patient has an unbalanced karyotype with partial trisomy of chromosome 19 without any apparent corresponding monosomy 14. This is, therefore, to the best of our knowledge, the first "pure" small distal 19p duplication reported to date. If we now compare the clinical features of our patient with those of the two previously mentioned reports, we see some similarities (table 1).

The patient reported by Byrne *et al*[1] had major intrauterine growth retardation with severe dysmorphic signs at birth, including severe microcephaly, upward slanting palpebral fissures, fused eyelids, malformed ears, ambiguous genitalia, and bilateral syndactyly of the 4th and 5th toes. He developed seizures. He was found to be partially trisomic for 19p and partially monosomic for 13q while his mother had a reciprocal translocation 46,XX,t(13;19)(q32;p13.3). The second patient, a neonate reported in 1992,[2] had dysmorphic facial features including sparse hair, normally set ears with pointed helices, short palpebral fissures, prominent and broad nasal tip, thin upper lip, retrognathia, short neck, proximally set thumbs, and bilateral club feet. He had partial trisomy 19p and deletion of the terminal band of chromosome 3q on karyotyping performed on peripheral lymphocytes.

Anteverted nostrils and sparse hair were also observed in our patient. Apart from these, the phenotype was essentially mild microcephaly, mild dysmorphic features, and mild developmental delay. When checking de Vries criteria[8] in our patient, we reached only a score of 1 point for microcephaly and 3 points if we included facial dysmorphism. In any case, the cut off score of 4 was not reached which means that the patient under discussion would not have been eligible for FISH with multitelomeric probes if these criteria were applied.

In conclusion, an apparently pure de novo duplication of the terminal short arm of chromosome 19 from 19p13.3 to 19ter causes mild delay and mild to moderate microcephaly (-3 SD). It is not associated with significant facial dysmorphism and is readily detectable by FISH multielomeric analysis. This case under discussion provides evidence that a recognisable phenotype is apparently not always present when a small terminal duplication of the chromasome 19 short arm is present. More generally, we suggest that this finding should encourage clinicians not to restrict the indication for FISH with subtelomeric probes to patients with moderate to severe mental retardation and/or multiple congenital anomalies.[3 8 9]

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