

Short reports

5p14 deletion associated with microcephaly and seizures

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Revised version received 24 March 1999
Accepted for publication 1 September 1999



Figure 1 Photographs of the proband (reproduced with permission).

Abstract

We report on a father and son who have an interstitial deletion of 5p14. The father is clinically and mentally normal while the son has significant clinical involvement including microcephaly, seizures, and global developmental delay. The extent of the 5p14 deletion was determined using fluorescence in situ hybridisation (FISH). The deletion in this present family is smaller than a deletion previously described in a multigenerational family that lacks any clinical phenotype. This report shows that a 5p14 deletion does not always lead to a normal phenotype.

(J Med Genet 2000;37:125-127)

Keywords: interstitial deletion; chromosome 5; fluorescence in situ hybridisation; cri du chat syndrome

Deletions of 5p are normally associated with a diagnosis of cri du chat syndrome. Clinical features of this syndrome include a cat-like cry at birth, microcephaly, mental and developmental delay, growth delay, and craniofacial features that include microcephaly, hypertelorism, and micrognathia.^{1,2} The extent of the 5p deletion can vary from a small terminal deletion to the entire short arm.^{3,4} Through the molecular

analysis of 5p deletions in patients that do not fit the cri du chat syndrome phenotype, it has become clear that there is a critical region within 5p15.2 that is involved in the facial features and severe mental retardation associated with the syndrome.^{4,5} A region within 5p15.3 appears to be involved in the cat-like cry.^{5,6} The involvement of other regions of 5p in the overall cri du chat syndrome phenotype is less clear.

In 1986, a three generation family with six members having an interstitial deletion of 5p14 was described.⁷ They were all completely asymptomatic. This suggested that a deletion of 5p14 is not associated with a clinical phenotype. Since 5p14 is a Giesma dark, late replicating band, it is thought that this chromosomal region may have a low number of genes⁸ and the report of this family supported this hypothesis. Patients with clinical involvement have been described with interstitial deletions including 5p14, but in every case additional material from 5p13 or 5p15.1 was also deleted.^{9,10} Taken together, these reports suggest that deletions of 5p15.1 and 5p13 can result in some level of mental retardation and dysmorphic facial features, but that a deletion of 5p14 is benign.

Case report

The proband is a 3 year old male with healthy, unrelated parents. The pregnancy was uneventful. There was no history of drug or alcohol usage during the pregnancy. He was born by caesarean section because of breech presentation. Jaundice was noted and the child was diagnosed with hyperbilirubinaemia owing to ABO incompatibility. A mild aortic stenosis was reported but did not require surgery. The

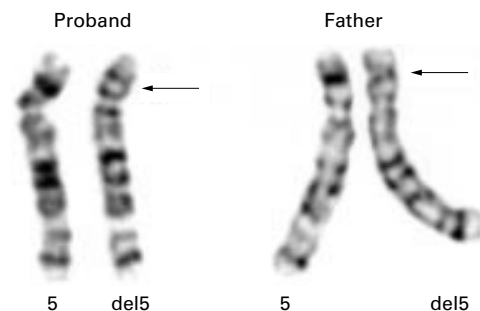


Figure 2 Partial karyotype of the son and father.

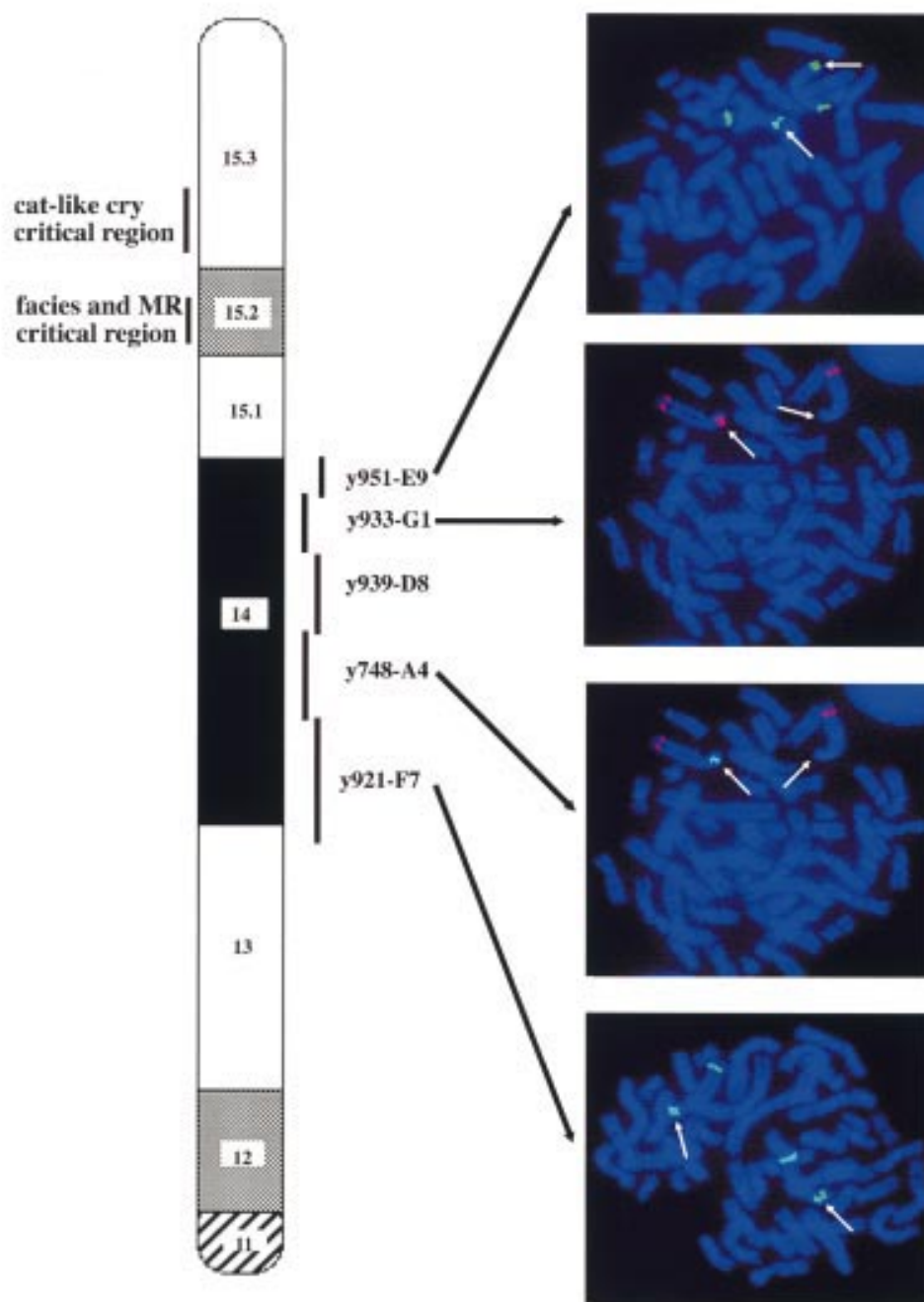


Figure 3 FISH analysis of the proband. An ideogram of 5p with the locations of the four YAC clones used in the analysis is shown. Representative FISH pictures are shown to the right. The large white arrows point to the short arms of chromosome 5 where a signal might be expected to be located.

birth weight (2990 g), length (51 cm), and head circumference (35.5 cm) were all within normal parameters. He crawled at 14 months but was not able to walk. He did not say any words. At 17 months of age, he developed seizures which were of the generalised tonic-clonic type. A CT scan after one of the seizures was reported to be normal. At 19 months of age, developmental delay was reported. At that time, the proband's head circumference was 46 cm, on the 2nd centile for his age. His weight and height were on the 25th and 10th centile, respectively. Plagiocephaly was noted as well as some midfacial hypoplasia and misshapen ears.

He is presently on phenobarbital for the seizure disorder. Fig 1 shows a picture of the proband.

Chromosome and molecular analyses were performed to rule out fragile X and Angelman syndrome, respectively. A karyotype of 46,XY,del(5)(p14) was reported. Chromosome analyses of both parents were performed. The mother had a normal karyotype while the father's karyotype was identical to his son's. Partial karyotypes of the father and the son are shown in fig 2. A skin biopsy on the father was performed and an extremely low level of mosaicism was noted: 46,XY (1%) / 46,XY,del(5)(p14) (99%).

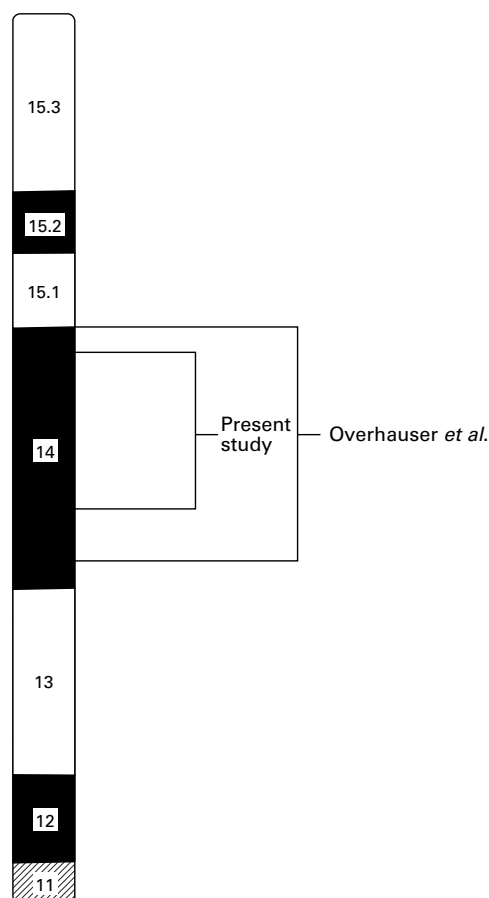


Figure 4 5p14 deletion comparisons. An ideogram of 5p is shown. The location of the deletion in the family described by Overhauser *et al* and the deletion in this present study are shown.

Results

To map the extent of the deletion in the father and the son more precisely, FISH analysis was performed using YAC clones that map to distinct regions of 5p.¹¹ Fig 3 shows the locations of the YAC clones that were used in the analysis. For each hybridisation, at least 20 metaphase spreads were analysed. The location of the distal breakpoint was localised to 5p14.3 between YAC clones y951-E9 and y933-G1. The proximal breakpoint was localised to 5p14.1 between YAC clones y748-A4 and y92-F7. Similar analyses were performed on metaphase spreads from the father and identical results were observed.

The clinical presentation of the proband is in significant contrast to a previous report of a three generation family with a 5p14 deletion in which all of the members with 5p deletions were asymptomatic. Because molecular or FISH studies or both have been performed on the deletions in both pedigrees, it is possible to compare directly the locations of the deletions. As fig 4 shows, the three generation family report by Overhauser *et al* completely encompasses the deletion described in this report.

Therefore, the disparate phenotypes cannot be explained by partial overlaps of the deletions as is the case in previous reports.^{9,10} Although the phenotypic presentation of the father and son who have the exact same 5p deletion is different, the difference might be the result of mosaicism in the father. Although the level of the normal karyotype was very low, it is impossible to determine the level of mosaicism in critical tissues such as the brain.

It is of interest to note that in the pedigree described by Overhauser *et al*,⁷ the inheritance of the deletion was always from a female. In the present report, the inheritance is from a male. It is possible that part of the reason for the different clinical presentations in the two families is because of a parent of origin/genomic imprinting effect. Possible genomic imprinting effects were investigated when the parental origin of de novo deletions leading to cri du chat syndrome was determined. In two studies, a preponderance of paternally derived deletions (80-90%) was reported.^{5,12} However, no difference in clinical severity was found between the paternally derived deletions and the maternally derived deletions.

In the light of this case report, it is clear that a deletion of 5p14 can lead to a clinical phenotype. Therefore, an accurate prognosis cannot be made if a 5p14 deletion is observed during prenatal analysis. The detailed characterisation of additional patients with 5p14 deletions will help to determine the extent of the clinical phenotype that is associated with interstitial deletions of 5p.

This work was supported by a grant from NIH HD33447 to JO.

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