Wolf-Hirschhorn locus is distal to *D4S10* on short arm of chromosome 4

C McKEOWN*, A P READ*, A DODGE*, O STECKO*, A MERCER†, AND R HARRIS*

From *the Department of Medical Genetics, St Mary's Hospital, Manchester; and †Regional Cytogenetics Laboratory, East Birmingham Hospital, Birmingham.

SUMMARY We report a family in which Wolf-Hirschhorn syndrome in two children with partial monosomy of the short arm of chromosome 4 is the result of unbalanced segregation of a reciprocal 4;12 translocation in the mother. Studies with the DNA probe G8 show that the translocation breakpoint in this family is distal to the *D4S10* locus. Previously reported cases of Wolf-Hirschhorn syndrome have involved the deletion of *D4S10*. These observations may prove helpful in the search for better genetic markers for Huntington's chorea, which maps close to *D4S10*.

Case reports

Wolf-Hirschhorn syndrome was diagnosed clinically in a 10 year old boy and his six month old sister. Two older brothers and both parents were clinically normal. A sister of the mother died at the age of five years. She was retarded and dysmorphic and never learned to walk. Family photographs show an appearance suggestive of Wolf-Hirschhorn syndrome.

Case 1 (fig 1), the proband, was small for gestational age, weighing 2.48 kg at term. He was noted to be dysmorphic at birth with microcephaly, hypertelorism, haemangioma on the glabella, cleft palate, and simple ears. He was hypotonic and developed convulsions in the first year of life. Initially he showed no auditory or visual awareness, but visual evoked responses and electroretinograms were normal and vision and hearing improved gradually. Physical growth followed the 10th centile and development was grossly retarded. He walked at three years two months. At nine years seven months his height and weight were still on the 10th centile but his head circumference was below the 2nd centile. He had marked hypertelorism and low set ears with unrolled helices and creases on the lobes. His hair was coarse with two whorls at the crown. His philtrum was short with a thin upper lip, a small jaw, a cleft of the soft palate, and widely spaced upper teeth. His hands were unremarkable apart from dislocatable thumbs and very flat nails. He had an umbilical hernia and shawl scrotum with

both testes descended. His feet showed hallux valgus and clinodactyly of the fifth toes. He walked aimlessly around making very little visual contact, had no speech, and was incontinent.

Case 2 (fig 2), the younger sister of the proband, was born at 38 weeks' gestation weighing 2.6 kg

FIG 1 Case 1.

Pregnancy was complicated by threatened abortion at 12 weeks, poor fetal movement, polyhydramnios, and intrauterine growth retardation. She was noted to look very like her brother (case 1). At two months she was very hypotonic with a high pitched cry. She did not smile and was unable to fix her gaze. Height, weight, and head circumference were all below the 3rd centile. She had a short neck, the anterior fontanelle was small, and there were two hair whorls. There was a downward slant of the palpebral fissures, hypertelorism, epicanthic folds, and strabismus. There was a large haemangioma on the glabella and eyelids. Her ears were low set with creases on the lobes. Her palate was high arched with broad alveolar ridges and her mouth was small and downturned with thin lips and short philtrum. She held her hands clenched but both thumbs were dislocatable. She had an umbilical hernia and clinodactyly of both fifth toes. Photographs of case 1 at the same age showed a strikingly similar appearance.

CYTOGENETIC FINDINGS

Chromosome analysis in cases 1 and 2 showed an abnormal chromosome 4. The mother was found to have a balanced translocation between chromosomes 4 and 12: 46,XX,t(4;12)(p16;p13·3) (fig 3),

FIG 2 Case 2.

FIG 3 Partial karyotype of mother of cases 1 and 2. The normal chromosomes are shown on the left and the derivative ones on the right. Arrows indicate the breakpoints.

which was also found in one of the phenotypically normal children. The father had normal chromosomes. The affected children had inherited the derivative chromosome 4 but the normal chromosome 12. They are therefore monosomic for the terminal region of 4p: 46,XY,der(4),t(4;12)mat. The breakpoint appeared to be in the distal part of band 4p16.

DNA STUDIES

DNA from peripheral blood lymphocytes of both parents and three of the children was tested with the G8 probe¹ which defines the *D4S10* locus. The family was uninformative for the *HindIII* polymorphisms detected by subclone pK082 of G8 (all members homozygous for the 17 kb and 3·7 kb bands), but informative for the *EcoRI* polymorphism detected by subclone pK083. The mother was homozygous for the 9·5 kb fragment, the father was homozygous for the 14·5 kb fragment, and all three children, including the affected child, were heterozygous (fig 4).

Discussion

Gusella *et al*² reported an apparent deletion of the

FIG 4 Southern blot of genomic DNA from family members digested with *EcoRI* and hybridised to subclone pK083 of the G8 probe.

D4S10 locus when they tested seven unrelated patients with Wolf-Hirschhorn syndrome. All seven were apparently homozygous for all G8 polymorphisms and all appeared hemizygous by gene dosage. In one case the affected child had inherited no paternal allele, which is proof of a deletion, provided that paternity is confirmed. In our family the affected child we tested has an unbalanced form of the maternal translocation resulting in monosomy for the terminal region of 4p. Nevertheless, he is heterozygous for the *EcoRI* polymorphism detected by G8 and has inherited a maternal allele of *D4S10*. Therefore, both the translocation breakpoint on chromosome 4 and the material whose deletion produces the Wolf-Hirschhorn phenotype must map distal to *D4S10*.

Under the microscope the 4p deletions in different patients with Wolf-Hirschhorn syndrome appear

quite variable in size, and in our family the abnormality was very small. It seems likely that the deletions studied by Gusella *et al*² were larger than ours, despite the similar phenotype. Clinically, both the children we report conformed closely to the features of Wolf-Hirschhorn 4p- syndrome as reviewed by Stengel-Rutkowski *et al*³ and Wilson *et al*,⁴ and the cytogenetic findings were consistent with monosomy for a small terminal region of 4p16→pter. There were no obvious features of the partial trisomy 12p⁵ which also resulted from the derivative chromosome 4.

This chromosomal region is of special interest because of the close linkage of *D4S10* with the Huntington's chorea locus.¹ Attempts to make bridging probes for gene tracking in HC have met difficulties, apparently because sequences mapping distal to G8 are not readily found in genomic libraries. The translocation breakpoint in our family will provide an extra landmark for mapping probes in 4p16 and, if one of the abnormal chromosomes can be isolated on a non-human background in a somatic cell hybrid, it may be possible to generate probes from the 4p terminal sequences, either by direct cloning or by the deletion cloning technique,⁶ which has proved so successful with Duchenne muscular dystrophy.

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Correspondence and requests for reprints to Dr C McKeown, Department of Medical Genetics, St Mary's Hospital, Hathersage Road, Manchester M13 0JH.