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LETTER

Genotype-phenotype correlations in Wolf-Hirschhorn syndrome

In a recent issue of the journal, Wieczorek *et al*.[1] reported on a clinical, cytogenetic and molecular analysis of 13 Wolf-Hirschhorn syndrome (WHS) patients. They found that congenital malformations, such as cleft lip/palate and congenital heart defects (CHD), were present only in patients carrying a deletion larger than 10 Mb. In particular, CHDs were missing in patients with deletions smaller than 16 Mb. A submicroscopic deletion, from D4S43 (33c6 cosmid probe) to the telomere was described in two patients: the deletion size, in both cases, was assessed to be between 2.2 and 2.8 Mb. All the patients presented with microcephaly.

Although we agree with many of Wieczorek *et al*.'s conclusions, some observations seem to be in order. In a similar study on 16 WHS patients,[2] we found five patients with a deletion smaller than 10 Mb and four patients with a cryptic deletion varying from 4.4 to 2.8 Mb, that was detected by molecular probes only. The karyotype was established by means of prometaphase chromosome analysis (850 bands), or by FISH with a set of overlapping cosmid probes spanning the 4p16.3 chromosome region. We found that 3.5 Mb represents some sort of discriminating size with regard to the occurrence of congenital malformations: the 4.4 Mb deleted patient presented with cleft palate and hypospadias, while the five patients with a deletion smaller than 10 Mb presented with a midline defect (two with cleft palate, three with hypospadias), with renal abnormalities (four) and with CHD (three). It is worth noting that the head circumference was normal (25th centile) in the patient with a 2.8 Mb deletion, in which the D4S43 locus was preserved.

Regarding the assessment of the deletion size of 2.2–2.8 Mb described by Wieczorek *et al*.[1] in two patients that were deleted from at least the D4S43 locus to the telomere, we are in disagreement. As demonstrated by Baxendale *et al*.,[3] D4S43 lies 2.9 Mb from the telomere. Since these authors did not test by overlapping probes the interval between the D4S43 and D4S182 loci (described as deleted and not deleted, respectively), it is most likely that both patients carry a deletion much larger than described. We think that it is very important to verify whether a small deletion does not affect head circumference, since these genotype-phenotype correlations should allow a proper selection of apparently nondeleted WHS patients, who are potentially crucial in the search for a WHS gene.

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References

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2 Zollino M *et al*: Genotype-phenotype correlations and clinical diagnostic criteria in Wolf-Hirschhorn syndrome. *Am J Med Genet* 2000; **94**: 254–261.
3 Baxendale S *et al*: A cosmid contig and high resolution restriction map of the 2 megabase region containing the Huntington's disease gene. *Nat Genet* 1993; **4**: 181–186.