Folate sensitive site at 10q23 and its expression as a deletion

SUMMARY A patient is reported for whom initial chromosome analysis indicated 45,X/46,XX/46,XX,10q— mosaicism. The clinical findings included hypothyroidism and a low red cell folate estimation. The deleted chromosome 10 was subsequently shown to be an extreme expression of the folate sensitive heritable fragile site at 10q23, and a possible association between this and the in vivo folate status of the patient is suggested.

A blood sample was received for chromosome analysis from a 61 year old woman who was suspected of mosaicism for Turner’s syndrome. She had been admitted to hospital following convulsions and was suffering from profound hypothyroidism, secondary to non-compliance with medication. While in hospital, it was noted that she had slight neck webbing, an increased carrying angle, and was of marginal intelligence. The blood sample was processed using a methotrexate synchronisation technique and chromosome analysis indicated mosaicism for Turner’s syndrome with a low level (8%) of 45,X cells, but also with a 46,XX,10q— cell line (10%). A total of 100 cells was counted for this and subsequent investigations.

As the breakpoint in the deleted chromosome 10 was at q23, it was considered that this cell line might be an example of the expression of the folate sensitive heritable fragile site in this region, even though breaks and gaps were not apparent, and a repeat was requested. This was received three months later. The sample was treated with methotrexate as before and also grown in medium 199 without folic acid and with 2% fetal bovine serum, our standard technique for fragile site detection. With the methotrexate treatment, 12% of cells indicated fragile 10q with 66% of these expressing as deleted chromosomes. With the low folate treatment, 21% of cells indicated fragile 10q with 33% of these expressing as deleted chromosomes. The fragile 10q site was also expressed in the 45,X cell line. It was concluded that the original 10q—cell line was indeed indicative of the heritable fragile site at 10q23, and the true karyotype was 45,X/46,XX. Although this laboratory has often detected heritable fragile sites during the course of routine cytogenetic investigations, their expression as deleted chromosomes at the high level (100%) found in the first blood sample was considered to be very unusual. Of further interest was the patient’s clinical discharge summary from the time of the first referral, which revealed that her red cell folate estimation was then only 201 µg/l, at the low borderline of the normal range (200 to 750 µg/l). She was subsequently prescribed multivitamin tablets which she may have been using when the repeat blood sample was taken.

It has been known for many years that folate deficiency can result in chromosome damage in vivo.1 Cases are also documented in which hypothyroid subjects were found to be folate deficient in the absence of any other contributory factors.2 Although we are aware of no previous evidence suggesting that the in vivo folate status may affect the type of expression of the fragile site, it seems possible in the case reported here. It is also of interest that treatment of the lymphocyte culture from this patient with the folate antagonist methotrexate increased the level of actual deletions at the fragile site, compared with culture in low folate medium.

The fragile site Xpter associated with mental retardation has already been shown to express as a deletion in as many as 30% of cells expressing the fragility.3 The variability seen in the type of expression of heritable folate sensitive sites may be influenced by the previous folate status of the individual patient.

E L Maltby* and S Higgin†
*Centre for Human Genetics,
117 Manchester Road, Sheffield; and
†the District General Hospital, Barnsley.

References

Correspondence and requests for reprints to Mrs E L Maltby, Centre for Human Genetics, 117 Manchester Road, Sheffield S10 5DN.