Balanced reciprocal whole arm translocation t(3;9): analysis by fluorescence in situ hybridisation

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Abstract

A patient with Turner phenotype was found to carry two de novo chromosome aberrations: a 45,X line and a whole arm reciprocal translocation t(3;9). Fluorescence in situ hybridisation on metaphase cells using α satellite DNA for chromosome 3 and β satellite and 'classical' satellite DNA for chromosome 9 showed that the centromeric region of chromosome 3 was retained in the 3q9q translocation derivative, as was the secondary constriction heterochromatin of chromosome 9. No signals were observed in the 3p9p derivative with the three probes. This suggests that the breakpoints were on 3p11 and 9q11. The karyotype was 45,X,t(3;9)(3qter→3p11::9q11→9qter; 9pter→9q11::3p11→3pter).

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Constitutional whole arm reciprocal translocations are rare. To our knowledge only a few cases have been reported.¹⁻⁶ Most of them were found in phenotypically normal subjects and some in patients with reproductive failure.^{4,6} In contrast, whole arm translocations are not uncommon in cancer cells where fluorescence in situ hybridisation (FISH) has been used to obtain more information on the breakpoints and involvement of centromeric DNA sequences in the chromosome rearrangements.^{7,8}

We report a patient with 45,X Turner syndrome and a whole arm reciprocal translocation t(3;9) where in situ hybridisation studies, combined with cytogenetic analysis, allowed us to define the breakpoints and the origin of centromeres in the derivative chromosomes.

Case report

A 19 year old female was referred because of short stature and absence of secondary sexual characteristics. She was the eighth child of healthy, unrelated parents. At birth, oedema of the hands and feet was noted and at 10 years of age the parents were concerned about her short stature. Physical examination showed a height of 1.36 m, multiple naevi, a short neck, broad chest with widely spaced nipples, cubitus valgus, and shortening of the fourth metacarpal and metatarsal bones. Intelligence was average. Cytogenetic studies of peripheral blood with G banding showed two chromosome aberrations: 45,X and a whole arm reciprocal

translocation between chromosomes 3 and 9 (fig 1). The proposed karyotype was 45,X,t(3;9)(3p9p;3q9q). C banding showed that 9qh heterochromatic region was retained on the der(3q9q); however, the precise breakpoints at the centromeres or on p or q could not be defined.

Chromosome studies of both parents were normal.

FLUORESCENCE IN SITU HYBRIDISATION

The chromosome specific DNA probes were obtained commercially (Oncor, Gaithersburg, MD). For chromosome 3 the α satellite probe which hybridises to alphoid DNA located at the centromere of chromosome 3 was used. Since the chromosome 9 α satellite probe was not commercially available, we used the β satellite probe which hybridises to highly repeated β satellite DNA located in the pericentric heterochromatin and the "classical" satellite probe which hybridises to the short repeats related to AATGG also located in pericentric heterochromatin.

FISH was done on unbanded slides using standard methods (Oncor) to allow simultaneous observation of chromosomes and hybridised probe.

Twelve metaphase cells were analysed for detection of fluorescent signal and five suitable metaphases were photographed.

Results

The α satellite probe for chromosome 3 showed strong specific hybridisation to the centromeric region of the normal chromosome 3 and the centromeric region of der(3q9q) (fig 2), while no signal was visible on der(3p9p). However, β satellite and "classical" satellite DNA probes showed specific hybridisation with the pericentric region of the normal

Figure 1 Partial karyotype of the patient. (A) normal chromosome 3. (B) 3q9q derivative translocation chromosome. (C) Normal chromosome 9. (D) 3p9p derivative translocation chromosome.

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Figure 2 Metaphase hybridised with α satellite probe for chromosome 3 showing specific hybridisation to the centromeric region of the normal chromosome 3 and the derivative (3q9q).

chromosome 9 and with the pericentric region of der(3q9q). No signal was observed on der(3p9p) (fig 3). The karyotype was then 45,X,t(3;9)(3qter→3p11::9q11→9qter;9pter→9q11::3p11→3pter).

Discussion

The patient reported here is interesting because she carries two de novo chromosome aberrations, one resulting from a non-disjunction event and one from rupture and rearrangement of two non-homologous chromosomes producing a rare whole arm reciprocal translocation. The abnormal phenotype was consistent with the 45,X constitution. No other abnormalities were observed suggesting that the reciprocal translocation was balanced.

Whole arm reciprocal translocations are

uncommon as a constitutional chromosome aberration although they have been observed in cancer cells involving preferentially chromosomes 1,7,9,12, 17, and Y.^{7,8} In situ hybridisation studies have shown in some cases that the translocation chromosome retained centromeric alphoid sequences from both chromosomes involved, suggesting that the breakpoints were within the centromeric regions, resulting in a hybrid centromere. In other cases, only one of the probes showed signal on the translocated chromosome indicating that only one centromeric region was retained and that the localisation of the breakpoints was in one or the other arm of the chromosomes involved.

In our patient, FISH showed that der(3q9q) retained the centromeric region of chromosome 3 which was absent in der(3p9p). However, the signals from the pericentric heterochromatin of chromosome 9 were also present in the 3q9q translocation chromosome and absent in chromosome 3p9p. These results suggest that the breakpoint in chromosome 3 was on 3p11 because the centromere was retained with the long arm in the same derivative translocation chromosome. We then infer that the centromere of chromosome 9 was retained on the 3p9p translocation chromosome although no alphoid sequences were available to show this. In addition, all the 9qh region was on the 3q9q translocation chromosome suggesting that the breakpoint on chromosome 9 must be at 9q11 very near to the centromere. This is consistent with the propensity to breakage reported for 9qh in different conditions.^{9,10}

In conclusion, the study of this patient emphasises how the combination of classical cytogenetic techniques with the resolution power of FISH allows the definition with more accuracy of the breakpoints and the origin of centromeres in this type of translocation.

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Figure 3 Metaphase hybridised with β satellite probe for chromosome 9 showing specific hybridisation to the pericentric region of the normal chromosome 9 and the derivative (3q9q).

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