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A case of inv dup(8p) with early onset breast cancer

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A case of inv dup(8p) with early onset breast cancer

EDITOR—More than 50 cases have been described with inv dup(8p) which can be either di- or monocentric.[1–4] A rough estimate of the prevalence of both is 1/22 000-30 000 of the white population. Concurrently with the 8p duplication, markers at the tip of chromosome 8 are consistently deleted. All the cases described are associated with mental retardation, facial dysmorphism, brain defects and/or developmental delay. Allele loss and amplifications of regions of chromosome 8p are commonly reported in sporadic breast cancer,[5–7] and two recent papers have suggested linkage to 8p11-12 in familial breast cancer.[5–8] We report a case of 8p duplication and inversion in a woman who developed breast cancer at the age of 36, with a personal history of developmental abnormality and a family history of breast and other cancers. Because of the possible link between this chromosomal abnormality and a breast cancer predisposing gene on chromosome 8p, we analysed the chromosome in more detail. Our analysis suggests, however, that the cancers and the chromosomal abnormality are unrelated.

The patient (DD003-1EW) was born in 1951. She was considered to have had a birth injury resulting in hypoxic encephalopathy and cerebral palsy. At the age of 25 she had a left breast biopsy which was diagnosed as benign, and at the age of 36 (in 1987) she had an infiltrating ductal carcinoma of the right breast. In 1988 chromosome analysis was undertaken by G banding because of a suspected "developmental disorder of the brain". This showed an inversion and duplication of chromosome 8p. In her family, her mother is well, her maternal grandfather was reported to have had colon cancer, his sister (the patient's great aunt) to have had breast and colon cancers and his mother breast and pancreatic cancer, a son and grandson of the great aunt to have had leukaemia of unspecified type, and a granddaughter to have had breast cancer in her 30s. None of these family members could, however, be contacted.

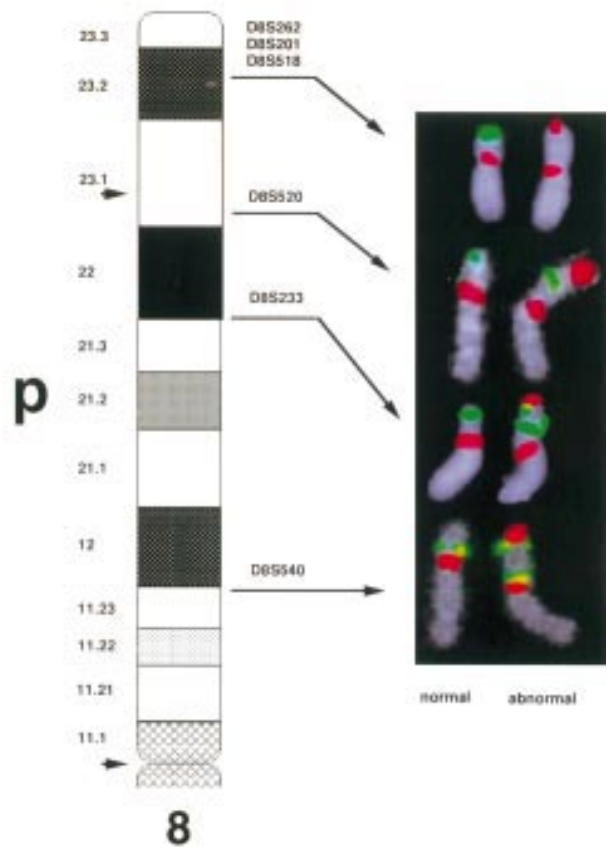

Figure 1 FISH analysis of different 8p YAC probes (green) in combination with a human chromosome 8 specific centromeric probe (red). (Yellow colour indicates overlap of the signals). (Left) Ideogram of 8p which shows the localisation of the probes. The duplicated and inverted portion of the rearranged chromosome 8p is indicated by arrowheads. (Right) Images obtained for the normal and rearranged chromosome 8 showing inv dup(8p). The following YAC probes were used from top to bottom: Y787_c_11,Y700_d_3,Y812_g_7,Y936_g_4.

An 8p+ karyotype was reported suggesting an inv dup(8p)(p11.2→p23.1) after routine G banding chromosome analysis. Metaphase chromosomes from EBV immortalised lymphoblasts from the patient were prepared after synchronisation with thymidine and incubation with colcemid by standard techniques. Fluorescence in situ hybridisation (FISH) studies performed with a whole chromosome 8 paint (Cambio) showed that the additional material present in the short arm of the rearranged chromosome 8 is derived from chromosome 8 (data not shown). To define the breakpoints of the rearrangement more accurately, dual colour FISH experiments were performed using total yeast DNA from YAC clones from chromosome 8 (HGMP Resource Centre, UK) together with a chromosome 8 specific centromeric probe (Boehringer Mannheim). By analysis of 20 metaphases each it could be shown that the short arm of the rearranged chromosome 8p is dicentric with most of the short arm duplicated (cen→p23.1) and inverted (fig 1). The telomeric region distal to p23.1 is deleted. The proximal breakpoint seems to be the centromere as the dicentric chromosome 8 shows a second centromere at the very end of the tip of the short arm.

Neither the breakpoints nor the telomeric deletion lay in regions associated with breast carcinomas, which frequently show allelic deletions in regions 8p11-p12 and 8p21-p22 in sporadic cases.[5 6] 8p12 is also found to be amplified in 10-15% of breast tumours.[7] For the NEFL marker (8p11-p12), a lod score of 2.5 was obtained by linkage analysis using families unlinked to *BRCA1* or *BRCA2* indicating the presence of a putative *BRCA3* gene.[5] Because samples from other family members of the index case were not available for linkage analysis, mutational analysis of *BRCA1* and *BRCA2* was performed in the proband but did not detect any mutation (data not shown).

In conclusion, the presented case of inv dup(8p) shows the genotype of other reported cases associated with developmental delay and/or mental retardation. The occurrence of breast cancer is probably coincidental and unrelated to the chromosome 8p rearrangement.

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Appendiceal carcinoma complicating adenomatous polyposis in a young woman with a de novo constitutional reciprocal translocation t(5;8)(q22;p23.1)

EDITOR—Familial adenomatous polyposis (FAP) is an autosomal dominant condition characterised by the presence of more than 100 adenomatous polyps in the colon and rectum. Polyps generally first appear in the second or third decade of life and are usually most numerous distally. Left untreated, colorectal cancer is virtually inevitable and generally arises in the fourth or fifth decade.[1] Adenocarcinoma of the appendix is an uncommon neoplasm and has only rarely been reported in association with FAP.[2]

The gene responsible for FAP, *APC*, was initially localised to the long arm of chromosome five (5q) by linkage.[3 4] This followed a case report describing carcinomas of the rectum and ascending colon, adenomatous polyposis, mental retardation, and various dysmorphic features in a 42 year old man with a constitutional deletion of 5q.[5] Most patients with FAP have normal karyotypes.[6] Mental retardation and dysmorphic features are unusual in such people but characterise those rare patients with cytogenetically visible 5q deletions and FAP.[5–12] The few reports detailing the clinical findings in patients with submicroscopic deletions of *APC* suggest that such people may be mentally normal.[13 14]

In this report we describe a patient with adenomatous polyposis, mental retardation, and an apparently balanced translocation t(5;8)(q22;p23.1) causing submicroscopic deletion of *APC* and *MCC*.

Clinical data were obtained by review of medical records. In addition, the patient was interviewed and examined by two of the authors (JF and AS) before her death. Cytogenetic studies were performed using standard techniques on a 72 hour peripheral blood culture with GTG banding, as previously reported.[6]

Slides for fluorescence in situ hybridisation (FISH) were obtained using the cell suspension retained after routine cytogenetic harvest. RNAse treatment, probe and chromosomal denaturation, and hybridisation conditions were as previously described[15] with the stringencies adjusted after assessment of the optimal conditions for each probe combination. The biotinylated probes were detected with

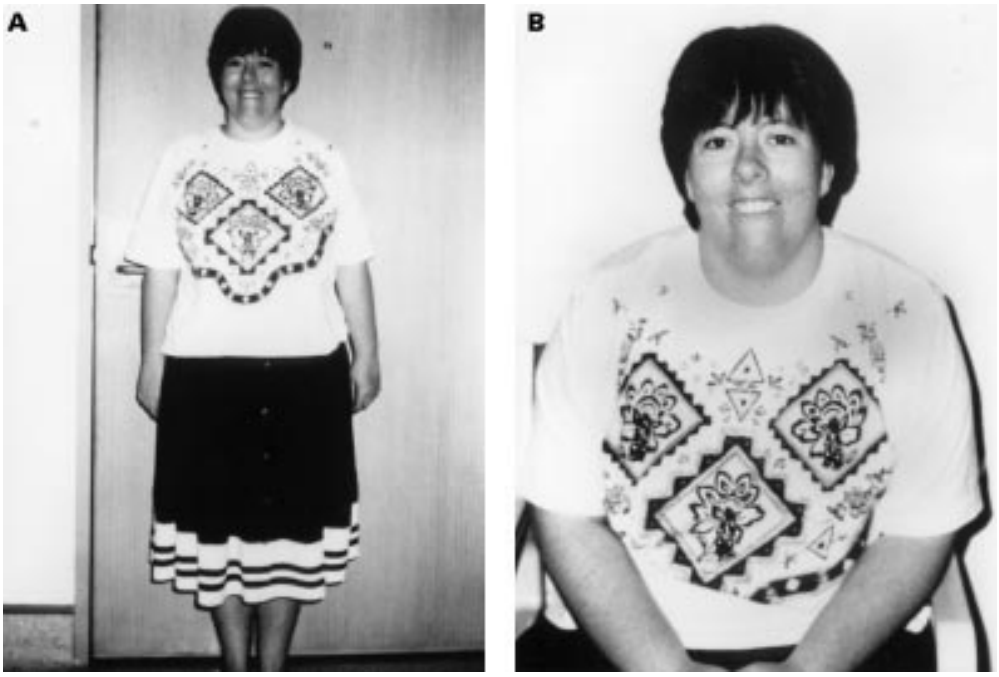

Figure 1 (A, B) The patient aged 26 years.