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Autosomal Fragile Site at 2q13 in a Proband with Mental Retardation

Toshio KUMADA[1], Tetsuji KADOTANI[2], Suzue KANATA[1], Yoko WATANABE[2], Noriko KUROSAKI[2] and Osam TOI[3]

1) *Department of Psychiatry, National Sanatorium Kamo Hospital, Kurose-cho, Kamo-gun, Hiroshima 724-06, Japan*
2) *The Kadotani Medical Research Foundation, 1248, Saijohigashi, Saijo, Higashihiroshima, Hiroshima 724, Japan*
3) *Chugoku Geinan Gakuen, Tadanoumi-cho, Takehara, Hiroshima 729-23, Japan*

ABSTRACT

Folate sensitive fragile site on chromosome 2q13 was detected in a female proband with mild hypertrichosis, negativism, speech disorder, and severe mental retardation. The same chromosomal aberration was also detected in her mother with normal phenotype. Spontaneous expression of fragile site on 2q13 was also observed.

Key words: *Fragile site, Mental retardation, Fra(2)(q13)*

Folate sensitive fragile site on chromosome Xq27 has been definitively associated with mental retardation and macro-orchidism (Brown, 1989[3]). However, the clinical significance of the other fragile sites has not been determined. During a chromosomal survey of mental retardates, a female proband and her mother were found to have a folate sensitive fragile site on chromosome 2q13. This article describes the clinical and cytogenetic details of the proband and her parents.

CASE REPORTS

The proband is a 33-year-old woman, 84 kg in weight, 164 cm in height. She was the first child of a 30-year-old mother and a 37-year-old father. She was born with forceps operation at overterm, without asphyxia or other clinical problems. Her infancy is unclear. At the age of 10, she appeared to have behavioral problems. She graduated from a special class of junior high school, and was soon institutionalized. She underwent bilateral ovphorectomy for polycystic ovaries at the age of 33. At the present time, remarkable clinical signs are mild hypertrichosis, negativism, speech disorder, and severe mental retardation (IQ = 35-20). The parents are phenotypically normal and have no history of abortion, stillbirth, exposure to the atomic bomb, or consanguinity. The mother is 63 years old, and had undergone an operation for polyp of the colon. Two siblings of the proband are phenotypically normal.

METHODS

The peripheral blood lymphocytes of the proband and her parents were isolated and cultured for 72 hours in complete Minimal Essential Medium (MEM) and MEM without folic acid (MEM-FA). 0.04 mg/ml of colchicine was added 2 hours before harvesting. Slides were made by flame-drying technique (Makino, 1975[10]). For the chromosomal analysis, the lymphocytes cultured in MEM-FA or MEM were observed by the Giemsa technique (Makino, 1975[10]). The locations of chromosomal aberrations were identified after G-banding (Kanata et al, 1988[8]).

RESULTS

About the proband, in 9 cells out of 110 cells cultured in MEM-FA, fragility on 2q13 was observed (Fig. 1). In one cell out of 130 cells cultured in MEM, the same breakage was also detected. The karyotype was given, therefore, as 46, XX, with fra(2)(q13).

About her mother, in 7 cells out of 100 cells cultured in MEM-FA, fragility on 2q13 was observed. In 5 cells out of 100 cells cultured in MEM, the same breakage was also detected (Fig. 2). The karyotype was given, therefore, as 46, XX, with fra(2)(q13).

About the father of the proband, no chromosomal abnormalities were detected.

DISCUSSION

Fra(2)(q13) was detected in the proband with mild hypertrichosis, negativism, speech disorder, and severe mental retardation. The same aberration was also detected in her mother with normal phenotype.

In several reports (Annerén and Gustavson, 1981[1]: Ferguson-Smith, 1973[4]: Shabtai et al, 1984[11]: Williams and Howell, 1976[16]), fragile

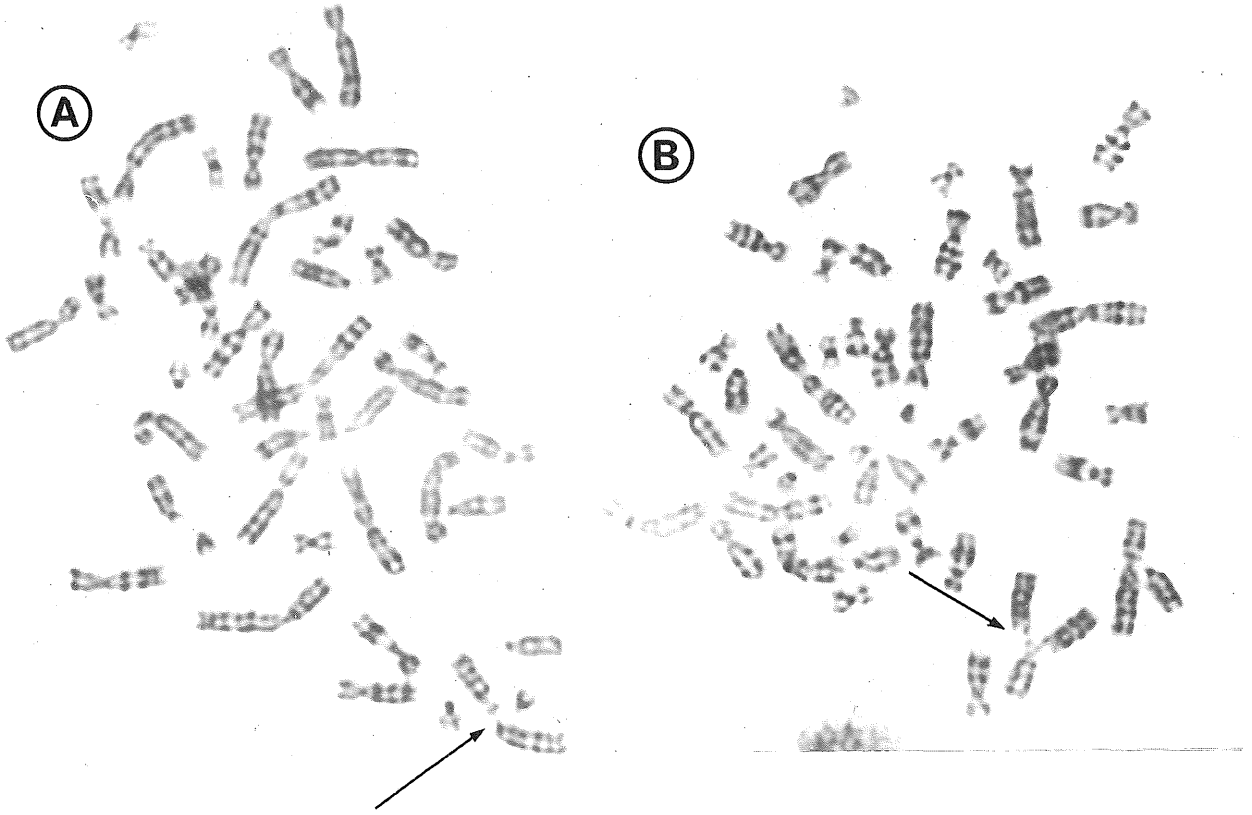

Fig. 1. Fra(2)(q13) in the lymphocytes of the proband, cultured in MEM-FA: ⓐ break, Ⓑ triradials.

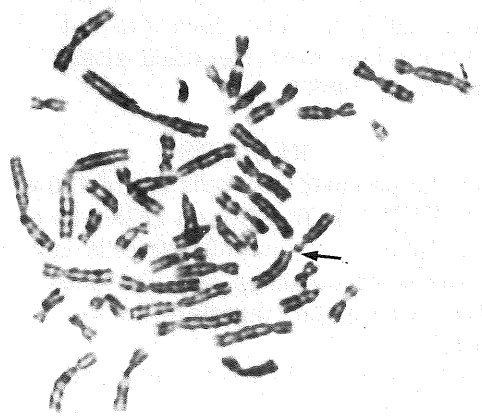

Fig. 2. Fra(2)(q13) in the mother's lymphocyte, cultured in MEM.

secondary constrictions close to the centromere on the long arm of chromosome no. 2 were detected in the cases with mental retardation, hyper-beta-lipoproteinemia, central nervous system malformation, cardiomyopathy, carcinoma, and/or Crohn's disease. These aberrations were also detected in normal cases (Annerén and Gustavson, 1981[1]: Ferguson-Smith, 1973[4]). It is not clear whether these aberrations are fra(2)(q13) or not.

Recently, fra(2)(q13) has been classified as a folate sensitive fragile site (Berger et al, 1985[2]) and detected in cases with autism, mental retardation, epilepsy, craniofacial dysmorphism, and/or cerebral hygroma (Fryns and Van Den Berghe, 1988[5]: Keshiaho et al, 1987[9]). Jayaker et al (1986[6]) reported that fra(2)(q13) was found in 2 cases out of 20 autistic children and no cases out of 20 normal controls. In the present study, however, fra(2)(q13) was detected also in the normal case. This throws a doubt on the clinical significance of fra(2)(q13). The normal carrier of fra(2)(q13) may constitute a similar existence to the normal carrier of fra(X)(q27) (Sherman et al, 1985[12]). The prevalence of autosomal folate sensitive fragile sites among mental retardates has been reported as higher than that among normal or consecutive populations (Kähkönen et al, 1989[7]: Sutherland 1982[13], 1985[14]). The clinical significance of fra(2)(q13) needs further study.

Keshiaho et al (1987[9]) reported the absence of fra(2)(q13) in the parents of 3 unrelated children with fra(2)(q13) and Fryns and Van Den Berghe (1988[5]) reported the absence of fra(2)(q13) in the parents of the brothers with fra(2)(q13). These authors suspected that the expression of fra(2)(q13) may be age dependent. The suspicion was not supported in the present study.

Fra(2)(q13) has been considered to be folate sensitive (Berger et al, 1985[2]). On the other hand, it was reported by Annerén and Gustavson (1981[1])

that the fragile secondary constriction on chromosome no. 2 was detected in the cells cultured in the medium Parker 199, which includes folic acid. In the present study, spontaneous breakage at 2q13 was observed in the cells cultured in MEM. However, this phenomena does not indicate that the breakage is not folate sensitive (Takahashi et al, 1988[15]). In the proband's cells, folate deficiency seems to have enhance the breakage at 2q13. About the mother, the observed cells are too few to conclude that folate deficiency does not enhance the breakage at 2q13.

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