

FRAGILE Xq-27 ASSOCIATED WITH SCHIZOPHRENIA AND FAMILIAL PSYCHOSIS IN A MALE

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SUMMARY

A 31 years old man with history of familial psychiatric disorder was investigated. Chromosomal analysis in peripheral lymphocyte blood culture showed normal karyotype with 46, XY chromosomal complement. However, the cells treated with 5-Fluoro-deoxy-uridine (FUdR) and Caffeine showed fragile Xq-27 (4.0%) and nonspecific autosomal breakages (42.0%). The present case suggests a probable association between chromosomal fragility and non-mental retardation psychopathology. Further cytogenetic studies in cases with familial psychiatric disorders will enable us with a better understanding of the pathogenesis and further help in counselling the families.

The fragile X is the second most common chromosome abnormality among the mentally retarded, after trisomy-21. Though trisomy-21 is usually a sporadic event, but the fragile X is transmissible and is the most common Mendelian factor responsible for mental retardation (Sutherland and Hecht, 1985). The fragile X may also predispose to behavioural problem and abnormal physical features. This syndrome is common and affects nearly 1 in 2000 Males (Nussbaum and Ledbetter, 1986). The belief that the fragile Xq site is an obligatory feature of the disease has generated the idea that direct and possible causal relationship exist between the chromosomal aberration and the disease (Sutherland and Hecht, 1985). Schizophrenia is a severe mental illness occurring with a prevalence of approximately 1.5 per thousand with an early onset in life (Sherrington et al., 1988; Kennedy et al., 1988; I.C.M.R. Bulletin, 1988). The etiology of a number of psychiatric disorders including schizophrenia, is unknown. However, it is generally accepted that there is probably some genetic factor/s involved in schizophrenia (Say et al., 1977). The chromosomal fragility could be one of the probable causes leading to the psychopathology.

CASE REPORT

The propositus 31 years old (II, 5) is an apparently healthy normal person working in a textile industry. His mother is 67 years old and his father died at age 62 (of unknown cause). He has two sisters and four brothers. Two of his brothers (II, 4 & 8) and one of his nephew (III, 1) also have symptoms of psychosis/schizophrenia. They were not available for investigation. Occasionally the propositus suffers from convulsions and epilepsy. He was referred for unusual psychological disturbance and apparently normal. The marriage is non-consanguineous (See Pedigree Fig. 1).

Psychiatric diagnosis based on ICD-9 is 295.7-Schizo-affective psychosis. Neurological diagnosis was not done for the patient, since it was not applicable. The patient is not mentally retarded. There is family history of psychological illness and mental retardation with two of his brothers being affected with schizophrenia and one of his nephews being severely mentally retarded with psychosis. Chromosomal analysis was not possible in any of these affected individuals.

MATERIAL AND METHODS

Peripheral lymphocyte blood cultures were set up in RPMI-1640 (Hi Media, India)

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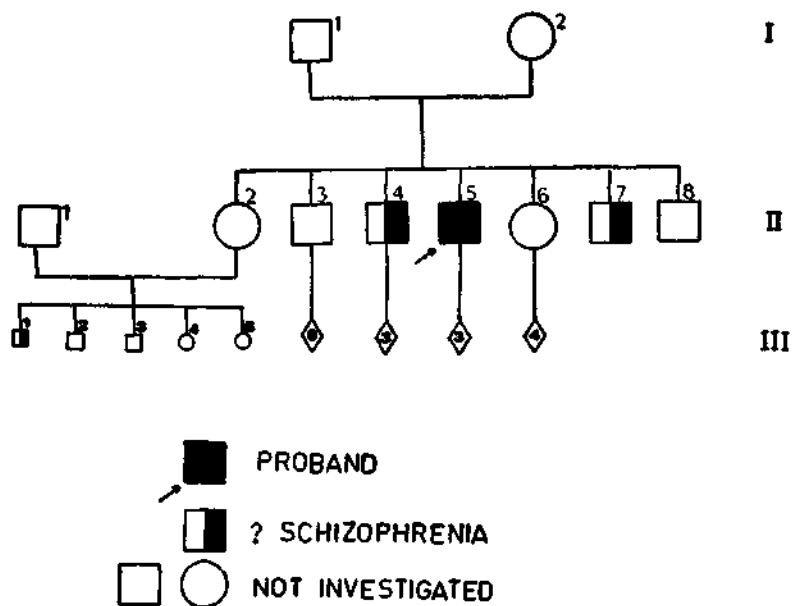


Fig. 1. Pedigree.

supplemented with 5% fetal calf serum (Gibco). Cultures were incubated at 37°C for 96 hours. FUdR at final concentration of 10^{-7} M was added for the last 24 hours of culture and 6 hours prior to harvest 500 ug/ml Caffeine was added. Cultures were harvested after 96 hours of incubation. Parallel normal control cultures were also set up from a male in our laboratory.

Air dried metaphase chromosome preparations were made by the standard procedure. Slides were stained with Giemsa. Unbanded metaphase plates were first

scanned for fragile sites and then G-banding was done to confirm the particular fragile sites.

RESULTS

The frequencies of common autosomal fragile site and fragile Xq-27 induced in peripheral lymphocytes by FUdR and Caffeine were calculated. The different types of induced fragile sites and its frequencies are summarised in Table 1. Some of the fragile sites observed, are shown in Fig. 2. Fragile Xq-27 in proband was found to be 4.0%

TABLE 1. The frequencies of fragile sites in proband and normal control (induced & uninduced)

Individual	No. of Metaphase scored	No. of Metaphase showing fragile sites	Autosomal fragile sites	Xq-27
Proband control	120	15(12.5)	15* (12.5)	—
Proband induced FUdR + Caffeine	100	42(42.0)	38** (38.0)	4
Normal control	140	6(4.3)	6(4.3)	—
Normal induced FUdR + Caffeine	100	22(22.0)	22(22.0)	—

Figures in parentheses show percent value out of total number of metaphase scored.

* $p < 0.05$, ** $p < 0.001$



Fig 2. Showing fragile sites at (a) Chr. No. 2, (b) Chr. No. 3 and (c) Xq 27 inducible by FUDR and caffeine combined.

compared to none in the normal control. The chromosomal abnormality associated with schizophrenia and psychiatric disorder in some reported cases has been summarised

TABLE 2. Summary of reported cases of chromosomal abnormality associated with schizophrenia and other psychiatric disorders

Cytogenetic findings	References
Chromosome variants (C-band heteromorphism) in chromosome 1, 2, 3, 9	Say et al., 1977
Rare heritable autosome fragile site at 19p1.3	Chodriker et al., 1987
Balanced translocation 5q11-13	Detera-Wadleigh et al., 1988
A familial 5q11-2-q13.3 segmental trisomy cosegregating with multiple anomalies	Wood et al., 1988
Partial trisomy of 5q11.2-13	Kennedy et al., 1988
Susceptibility locus on chromosome 5	Sherrington et al., 1988
Evidence against susceptibility locus on chromosome 5	Kennedy et al., 1988
Autosomal and sex chromosomal (Xq-27) fragile sites induced (See Table 1)	Present report

in Table 2. The frequency of fragile sites (induced or spontaneous) was found to be significantly higher in proband as compared to normal control individual.

DISCUSSION

Fragile X syndrome is relatively common type X-linked mental retardation distinguished by the expression of a fragile site at Xq-27 when cells from affected individuals are cultured under conditions of thymidylate stress (Sutherland, 1979; Glover, 1981; Tommerup et al., 1981). FUDR with Caffeine has been reported to enhance the expression of common fragile sites as well as fragile X in peripheral blood lymphocytes (Yunis and Soreng, 1984). Many workers (Glover, 1981) failed to find an effect of Caffeine on fragile-X expression peripheral blood lymphocyte culture. However, its effect on fragile-X is equivocal and may depend on the experimental laboratory condition (Abruzzo et al., 1986).

The non random occurrence of fragile Xq-27 (4.0%) in the present schizophrenic patient are seen to be more prone in induced than in non induced cultures. Nagesh Rao et al. (1988) have discussed the frequency of fragility in eight healthy control by inducing

them with FUDR and Caffeine separately where they have shown that with FUDR the frequency was 24.5% and with Caffeine 23.0%. In the present study fragility was induced with FUDR and Caffeine together and frequency was found to be 42.0%. The frequency of fragility was more in proband as compared to the healthy control (42.0% vs 22.0%).

Random and non random fragile sites have been found by many workers with and without inducing chemicals (See Table 2). Chromosomal aberrations as one of the major causes for mental retardation is well known. The pathogenesis of schizophrenia due to chromosomal abnormality is not well established. Sporadic, non specific chromosomal aberrations, reported in some families (Say et al., 1977; Wood et al., 1988; Kennedy et al., 1988; Detera-Wadleigh et al., 1988) could be coincidental and needs to be confirmed unequivocally. Two groups of scientists have reported new information on genetics of schizophrenia (Barnes, 1988; Lander, 1988). The results of the first group indicate that seven families appear to carry a single dominant gene for schizophrenia on chromosome 5. The second research team finds no such evidence for genetic defect on the long arm of chromosome no. 5 in a large multigenerational families. The present observation also leads us to conclude that fragility might be a probable cause or presumably a coincidental occurrence with the pathogenesis. Enhanced expression of fragile sites by specific chemicals in families with familial psychological disorders such as schizophrenia, manic depressive illness etc. might enable us to understand the etiology of some common psychological disorders.

Acknowledgements

This work was supported by grants from the Indian Council of Medical Research, New Delhi.

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