

Genetics of Autism: Association of Chromosomal Fragile Sites

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ABSTRACT Autism is a behavioural disorder in children with male predominance. The genetic basis of autism is now well established with twin and family studies. Association of autosomal fragile sites play an important role in the absence of any other genetic etiological factors. Fragile site at Xq27.3, which is a common defect among mentally retarded children also accounts for the major genetic etiological factor in autism. The genetic and clinical implication of Fragile X chromosome besides other chromosomal fragile sites with autism is discussed in the present study.

INTRODUCTION

Autism is a behavioural disorder in children characterized by qualitative impairment in reciprocal social interaction and communication. The prevalence in general population ranges from 0.04% to more than 0.1% (Gillberg et al. 1991) and boys are 3 to 4 times more commonly affected than girls. The association of cognitive and psychiatric conditions in families with autism establish the importance of genetic influence in the etiology of autism.

Autism has been known to be associated with genetic disorders like PKU, Neurofibromatosis, tuberous sclerosis and Fragile X Syndrome (Folstein and Rutter 1988; Gilberg and Fonsell 1984; Coleman and Gilberg 1985; Cohen et al. 1991).

There are some studies which points towards association of autosomal fragile sites with Autism (Arrieta et al. 1996). Herein we discuss the systematic study of 150 autistic children for the association of autosomal fragile sites and Fragile site at Xq27.3 region.

SUBJECT AND METHODOLOGY

The subjects for the present study were selected among the patients attending the child

guidance clinic unit of National Institute of Mental Health and Neurosciences, Bangalore, India. The subject group includes, 150 individuals showing characteristic abnormal functions in all the 3 areas i.e., social interaction, communication and restricted/repetitive behaviour, diagnosed to have autism as per the ICD-10 guidelines. The 150 subjects selected were from 140 families, among which 132 families had a single autistic child, while in 8 families, multiple sibs were affected. Twins were present in two families. The intellectual status among the subject group is presented in the table 1.

The karyotype studies include the lymphocyte culture for 72/96 hrs using TC 199 medium which is deficient in folic acid contents and high in pH, in order to express folate sensitive fragile sites and the use of folate antagonists like MTX and FudR in culture medium RPMI for the enhanced expression of fragile sites (Table 2). Atleast 100 cells were screened for each type of culture and a cut off point of 4% is taken as positive for fragile site association and cultures were repeated and observed by two different observes to avoid biased ascertainment (Chetan et al. 2001)

RESULTS

Among the 150 subjects analysed for various fragile sites. 12 individuals were found to be positive for Fragile 'X' chromosome. The percentage of expression varied from 4-30% of cells in different cultures (Table 3).

Other chromosomal fragile sites (3-14%) were noticed among 25 autistic individuals, which are negative for fragile X chromosome (Table 4).

DISCUSSION

Autism was first described and named by Leo Kanner after observing 11 children with common features (Kanner 1943). Genetic factor undoubtedly play a major etiologic role in autism, but how it is inherited and manifest remains unknown. The increased incidence in males, suggest that the possible involvement of the fragile X chromosome. There are sporadic reports of

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Table 1: Intellectual status among subject group (N=150)

Degree of mental impairment	Number of Individuals	
	Male	Female
No mental retardation	3	1
Dull normal intelligence	11	
Mild mental retardation	65	18
Mild-Moderate mental retardation	2	-
Moderate mental retardation	33	2
Severe mental retardation	2	1
Total	117	33

certain chromosome observation like duplication of 15 q 11-13 (Bunday et al. 1984; Baker et al. 1984), partial tetrasomy of chromosome 15 (Hotopt et al. 1995) deletion of 15 q12 (Kerbeshian et al. 1990), inv dup (15) (pter→q13) (Schinzel 1990). Complex chromosomal rearrangements like interstitial deletion of chromosome 17 (p11.2:p11.2) and monosomy for chromosome 5 (5pter→5p15.3) in a single individual (Vostanis et al. 1994), mosaicism for a duplication of the long arm of chromosome 18 and deletion of the short arm of chromosome 18 (Ghaiziuddin et al.

Table 2: Karyotype protocol employed in the present study

Medium	Fbs(MI)	pH	Duration	Inducer	Final Conc.	Duration
RPMI 1640	10-15	7.0 - 7.2	72 Hrs	-	-	-
Tc 199	5-8	7.4 - 7.6	72 Hrs	-	-	-
RPMI 1640	10-15	7.2 - 7.4	96 Hrs	Mtx	0.01 Mg/MI	Final 24 Hrs
RPMI 1640	10-15	7.2 - 7.4	96 Hrs	Fudr	10 ⁻⁷	Final 24 Hrs

Table 3: Details of fragile X expression in different culture conditions

S. No.	Sex	Age	Intellectual Status	Percentage of Fragile X Expression			
				TC-199	RPM/MT	RPMI/FudR	Repeat TC-199
1	Male	5 yr	No mental retardation	15%	7%	6%	20%
2	Male	6 yr	Mild mental retardation	23%	8%	5%	18%
3	Male	33 yr	Moderate mental retardation	11%	5%	4%	10%
4	Male	26 yr	Mild mental retardation	15%	6%	8%	11%
5	Male	9 yr	Mild mental retardation	9%	6%	5%	7%
6	Female	8 yr	Moderate mental retardation	4%	8%	6%	5%
7	Male	9 yr	Mild mental retardation	8%	4%	4%	9%
8	Male	7 yr	Mild mental retardation	5%	4%	4%	7%
9	Male	3.5 yr	Mild mental retardation	10%	6%	4%	12%
10	Male	17 yr	Moderate mental retardation	25%	8%	5%	22%
11	Male	12 yr	Moderate mental retardation	30%	7%	5%	27%
12	Male	12 yr	Moderate mental retardation	10%	4%	4%	10%

Table 4: Details of autosomal fragile sites seen among 25 autistic subjects

S.No.	Fragile Sites Observed	No. of Subjects Showing Fragile Sites	Nature of the Fragile Sites	Percentage Of Expression
1	2q31	4	Common fragile site	4-6%
2	2q33	3	Common fragile site	5-6%
3	4q31	2	Common fragile site	4-10%
4	5q21	4	Common fragile site	4%
5	5q31	3	Common fragile site	5-14%
6	6p23	1	Folate sensitive site	12%
7	6q26	1	Common fragile site	6%
8	12q24	1	Folate sensitive site	5%
9	13q21	1	Common fragile site	4%
10	Xq22	3	Common fragile site	4-5%
11	Xq26	2	Rare fragile site	3-4%

1993) have also been reported. In the present study, inversion of chromosome 9 (p13;q21) has been observed in three male autistic individuals (Arathi 1998).

Apart from these, common chromosomal polymorphic features like 9qh+, long Y, short Y and presence of constitutive fragile sites have also been reported among autistic children (Gillberg and Wahlstrom 1985).

Goldfine et al. (1985) in their study on 37 autistic individuals screened for the presence of fragile X chromosome, incidentally noted that 32.4% of the autistic individuals showed autosomal fragile sites like 1p31, 3p14, 3q21, 3q27, 6q26 and 16q22.

Arrieta et al. (1996) have seen high frequency of autosomal fragile sites like 2q13, 6p23, 12q13 in autistic children. They strongly believe that in the absence of any other etiology, fragile sites play an important role in the etiology of autism.

In another study (Li 1993), 104 autistic patients carried a total of 397 fragile sites and the 22 control individuals carried 112 fragile sites, 22 different fragile sites were detected in the autistic group and their mean frequency of expression varied from 1% to 8.58%. Fra 3q14 was the most frequent autosomal fragile site, being present in 92 autistic children and accounting for 23.17% of all ascertainment. The mean frequency of expression of this fragile site was 8.58%. The next common fragile site observed was Fra 6q27. Other fragile sites observed included 1p32, 1q32, 1q44, 2q32, 2q37, 6q21, 7q32, 8q22, 9q32, 10q22, 10q26, 12p12, 14q23, 14q24, 16q23, 16q24, 18q22, 18q23, Xp22 and Xq22.

Gillberg and Wahlstrom (1985), in their study on chromosomal abnormalities in infantile autism and other related childhood psychoses observed that 17% (8/46) of the children with Infantile autism showed Fra 16q23. Five out of the 8 children with Fra 16q23 also had other chromosomal variations like Fra 6q26, Fra Xp22, Fra Xq27 and 47, XYY. Other fragile sites like 6q26 and Xp22 were observed in 7% and 9% of the study group. The authors suggested that the presence of Fra 16q23 in percentages as high as 17% may indicate the possibility that it might be a biological marker in early childhood psychosis.

Jayakar et al. (1986) found that 2/20 individuals with autism or related disorders had fragile site at 2q13 in 36% and 6% of their cells. While one individual inherited the site from a healthy mother, in another individual, it was inherited from a healthy father. No casual link was suggested since the fragile site was found in phenotypically

normal first degree relatives of the affected individuals.

In the present study, 25 autistic subjects who were negative for fragile X chromosome showed fragile sites at 2q31, 2q33, 4q31, 5q21, 5q31, 6p23, 6q26, 12q24, 13q21, Xq22, Xq26 in 4-14% in percentages of cells (See Table 4). Some of the fragile X positive autistic subjects also showed fragile sites at 2p16, 2q11, 2q33, 2q36, 3p14, 4q31, 5p14, 5q21, 5q31, 6q26, 10q25, 11q14, 12q21, 12q24, 13q32 and Xq22 in one to two percent of cells. Many other folate sensitive, rare and common fragile sites were observed in percentages as low as 1 to 3%. These chromosomal fragile sites observed among the subject group in low percentages of expression are not high enough to suggest any significant association with autism, since they were not seen in repeated blood cultures among these subjects.

Two genetic conditions for which a strong association with autism exists viz., the fragile X chromosome (Brown et al. 1982; Blomquist et al. 1985; Brown et al. 1986; Wahlstrom et al. 1986; Cohen et al., 1991) and the other being tuberous sclerosis (Lotter 1974; Wing and Gould 1979; Coleman and Gillberg 1987). Various reports of association of tuberous sclerosis with autism show that percentages varying from 24% to 61% of tuberous sclerosis patients meet autism diagnosis criteria (Hunt and Dennis 1987; Smalley et al. 1991; Smalley et al. 1992; Hunt and Sheperd 1993; Gillberg et al. 1994). However, data also available showing figures with a range of 3% (Smalley et al. 1992) to 9% (Gillberg et al. 1994), for the association of autistic individuals with tuberous sclerosis.

Large scale studies on autistic individuals to establish the association revealed percentages as high as 13% of autistics being positive for fragile X chromosome. Wahlstrom et al. (1986) found a frequency of 13% in his study on 143 autistic individuals with 16 out of 112 boys screened being fragile X positive. Brown et al. (1986) in their study on 183 autistic males reported a similar frequency. While Fisch et al. (1986) reported a slightly lower frequency of 12.5% in their study on 144 autistic males (Table 5).

This prompted the undertaking of the present study so as to study the association between the fragile X chromosome and autism and its genetic implication. Further, there is no systematic study done in this regard in Indian population, hence, present study would help us in understanding the involvement of the fragile X chro-

Table 5: Various degree of Fragile X expression among autistic subjects reported in the literature

Reference	Autistics	Fra(X) +Ve	Per- centage
Watson et al. 1984	76	4	5
Jorgensen, et al. 1984	23	1	4
Chudley 1984	16	1	6
Mikkelsen 1984	20	1	5
Turner 1984	70	1	1
Blomquist et al. 1984	83	13	16
Mc.Gillivray et al. 1984	40	3	8
Blomquist et al. 1985	102	13	13
Mc.Gillivray et al. 1986	33	3	9
Wright et al. 1986	40	1	3
Wahlstrom et al. 1986	143	16	12
Fisch et al. 1986	144	18	13
Brown et al. 1986	183	24	13
Mandokoro et al. 1986	38	2	5
Matsuishi et al. 1987	38	2	5
Crowe et al. 1988	20	2	10
Mavrou et al. 1988	30	2	7
Payton et al. 1989	85	2	2
Wahlstrom et al. 1989	52	5	9
Ho & Kalousek et al. 1989	45	1	2
Cantu et al. 1990	67	1	1
Tranebjaerg & Kure 1991	32	2	7
Cohen et al. 1991	344	34	7
Present study	150	12	8

mosome among autistic individuals and for offering better genetic counseling services for the affected families.

Certain features common in both autism and Fragile X Syndrome like elongated face, large lop ears and high arched palate were noticed among autistic individuals with fragile X chromosome. Apart from these features, macro-orchidism, a very common finding in fragile X syndrome patients, was observed in only 3 out of the 11 autistic males with fragile X chromosome. Other features typical to fragile X syndrome like hype extensible joints, double jointedness, pectus deformity, mitral valve prolapse, bushy eyebrows etc. were also not observed in these individuals. Further, some features which are rare, among the fragile X syndrome patients, like anteverted, posteriorly placed ears, macrocephaly, microcephaly, short stature, low birth weight, were also observed in autistic subjects, there by phenotypic correlations becomes very difficult to establish the disease pattern.

In the present study of 150 autistic individuals screened for the presence of fragile X chromosome, 11 out of 117 males and 1 out of 33 females were found to be fragile X positive, bringing the percentage of autistic individuals with

fragile X chromosome to 8% (Arathi 1998). This observation is in accordance with the findings of various large scale studies done on autistic individuals reported from other parts of the world. It suggests that the frequency of occurrence of fragile X chromosome among autistic individuals is considerably high enough to suggest a positive association between autism and the presence of fragile X chromosome.

A second approach was also taken in which the frequency of fragile X individuals with autism was assessed to establish an association between autism and fragile X chromosome. The prevalence rates of autism among fragile X males varied widely from 5%-60% (Table 6). This wide range of variation can be attributed to varying sample sizes from 9 to 150 males and also to ascertainment bias (Brown et al. 1986). The lack of uniform diagnostic criteria for autism, could also be a reason.

Table 6: Proportion of autistic cases among Fragile X subjects

Reference	F(X) +Ve	Autism +ve	Per- centage
Brown et al. 1982	22	5	2
Fryns et al. 1984	30	5	1
Jacobs et al. 1983	9	2	2
Levitas et al. 1983	10	6	6
Brondum-Nielson. 1983	27	9	3
Fryns et al. 1984	21	3	1
Partington 1984	61	3	
Rhoades 1984	17	3	1
Simola 1984	41	5	1
Benezech & Noel 1985	28	15	5
Brown et al. 1986	150	24	1
Hagerman, Jackson et al. 1986	20	23	4
Borghgraef et al. 1987	23	9	3
Bregman et al. 1988	14	1	
Reiss & Freund 1990	17	3	1

Many males with fragile X syndrome, upto 90% exhibit various combinations of autistic behaviours and traits (Hagerman et al. 1986). Many of the autistic behaviours are prominent in younger males and show a decrease in frequency of severity with advancing age (Borghgraef et al. 1987; Reiss and Freund 1990). It has been reported that with increasing age, many fragile X males become more responsive to others, show less perseverative speech, and show less exaggerated responses to environmental changes (Borghgraef et al. 1987; Hagerman et al. 1986; Reiss and Freund 1990).

In-depth studies of autistic behaviour in fragile X individuals have noted both similarities and

discontinuities with autism and offer preliminary evidence for an unique fragile X behaviour phenotype. Individuals with fragile X chromosome and those with autism, both manifest poor eye contact, yet they seem to differ in certain aspects of this disorder (Cohen et al. 1989, 1991; Cohen et al. 1991).

Though problems of social relatedness, avoidance and anxiety have been noticed in fragile X syndrome males the superficial descriptions of the social interaction of fragile X males seem to be inconsistent, ranging from a pleasant and comfortable stance (Levitas et al. 1983) to a shy and anxious type with others (Nielson 1983). Unlike autistic individuals, most fragile X males relate well to others, including their parents, and only a few show the profound indifference characteristic of autism. Fragile X individuals may therefore be placed on a spectrum of socially avoidant behaviour that ranges in severity from autism at one extreme to shyness at the other extreme. Language problems are described in both fragile X syndrome males and autistic males. But some differences have been noted in the language problems associated with both the syndromes. Ferrier et al. (1991) found that related to males with fragile X syndrome, autistic subjects provided the greatest number of inappropriate communications, including echolalia. Echolalia was rarely present in Paul and colleague's (1987) study of older institutionalized males with fragile X syndrome, yet was frequently encountered in their autistic subjects. Thus echolalia seems problematic for autistic subjects where as males with fragile X syndrome are more apt to persevere on phrases, sentences or topics (Sudhalter et al. 1990).

All these studies indicate that both the disorders, in spite of having a few common behavioural characteristics, have certain variations in the features suggesting that autism is distinct from fragile X syndrome as far as phenotype – genotype correlations are compared. The genetic implications have played a major role in establishing etiology for fragile X syndrome, where in site at Xq27.3 region (FMR-1 mutation) is predominantly associated (Sujatha et al. 1998) as compared to few genetic etiological factors for autism, is evident from the present study.

SUMMARY

Autism was first described by Leo Kanner (1943) and its genetic nature was established following twin studies, which showed high

concordance rates among monozygotic twins. Autism was first reported to be associated with fragile X chromosome by Brown et al. (1982) which was supported by many other workers .

In the present study, 150 individuals belonging to either sexes and various age groups, diagnosed to have autism as per the ICD – 10 criteria were subjected to chromosomal analysis, with special emphasis on fragile X chromosome expression. Out of these 150 individuals, 11 males and 1 female were found to be positive for fragile X expression, bringing the percentage of occurrence of fragile X chromosome among autistic individuals to 8% , which confirms its genetic etiology as reported by others. Though other chromosomal fragile sites were observed in these individuals even in repeat cultures and in high frequency, their association needs to be confirmed from other sources of data concerning the genetic etiology of autism.

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