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**ABSTRACT**

A clinical population of 39 families affected by fragile X syndrome, a sex-linked form of mental retardation, is described. Physical aspects, including such common features as prominent jaw and simple ears, are noted along with psychological aspects such as different mean IQs among various age groups. Findings of intellectual evaluation did not show any predictive relationship between number of fragile sites observed in chromosomal analysis and level of intellect. Levels of retardation extended from the mild to the profound range. It is noted that folic acid therapy may benefit the syndrome, although it is an extremely controversial topic. Tables and figures illustrate the data. (CL)

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## Fragile X Syndrome: A Common Etiology of Mental Retardation R. Curtis Rogers, M.D. and Richard J. Simensen, Ph.D

### Introduction

Fragile X syndrome is a well described X-linked or sex-linked form of mental retardation which has been estimated to affect one in every 1,000 to 1,350 males.<sup>1-3</sup> The syndrome can be confirmed cytogenetically by the occurrence of a fragile site on the long arm of the X chromosome at Xq27 (see Figure 1). There are 20 X-linked mental (XLMR) syndromes that have been described.<sup>4</sup> The fragile X (fra (X)) is felt by most authorities to constitute about 40% of all XLMR; thus, it is by far the most common of the XLMR syndromes. In a study by Webb in which she evaluated school children in England, she found a prevalence of fra (X) positive mental retardation in 1/1,350 males. Females were positive for fra (X) testing in 1/2,033, giving a total prevalence of the fragile X "gene" of 1/1,634 in the school children studied.<sup>3</sup> Using these estimates and a 3% prevalence of mental retardation in the general population, fra (X) syndrome may account for up to 10% of all MR. The prevalence of the fragile X syndrome in retarded males has ranged from 1.9% to 5.9%.<sup>5-8</sup> Fra (X) syndrome is therefore second only to Down Syndrome among etiologies of MR associated with cytotgenetic abnormalities.

Fragile X syndrome is usually associated with severe to profound MR with a frequency of 7% in severely retarded males.<sup>7</sup> Blomquist et al reported a prevalence of 4.5% in mildly retarded males.<sup>8</sup> Mental retardation affects roughly 80% of fra (X) positive males and at least 30% of fra (X) positive females. Behavioral disturbances have been frequently noted in the fra (X) syndrome.<sup>9-11</sup> Several studies have associated autism or autistic behaviors with this syndrome. Fra (X) syndrome is present in 7.7% of autistic males and 21.2% of fra (X) positive males exhibited autistic behaviors.<sup>12</sup> Speech problems are also common in fra (X) positive individuals.<sup>13</sup>

The clinical phenotype of the affected individuals is characteristic but may be highly variable or absent in some. Males are more likely to exhibit the typical physical features than are females, just as they are more likely to be severely mentally retarded. Commonly described findings include relative macrocephaly, large simple ears, high prominent forehead, prominent nose, a long narrow face, and macro-orchidism.

### Discussion of Patients

A total of 39 families affected with fra (X) syndrome have been studied by our Center. Based on the family pedigree, and clinical and laboratory findings females can be classified as unaffected, obligate carriers (an unaffected individual who must be transmitting the fra (X), or fra (X) positive). We have ascertained 67 fra (X) positive affected males, 35 fra (X) positive females, and 27 obligate carriers who are fra X negative.

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## Physical Aspects of the Study Population

The 67 fra (X) positive males had variable phenotypes but did, as a group, share some physical features. The male patient group was examined for the common physical features associated with fra (X) syndrome. The specific features and the percent of the males positive for these features are shown in Table 1. Over half of the fra (X) positive males had long, thin facies, midface hypoplasia, prominent jaw, simple ears, and macroorchidism. Compared to the general population the fra (X) positive males had head circumference that was greater than two standard deviations above the mean in 11.8%, ear length -43.3%, hand length -40.4%, and palm length -32.7% (Table 2). However, when compared to standards for the institutionalized mentally retarded males in South Carolina, very few of the fra (X) positive males had values lying above the mean plus two standard deviations. All of these males were retarded. The fra (X) expression ranged from 1 to 56 percent with an average of 21 percent. Thirty-five fra (X) positive females were identified with expressions of fragile sites ranging from 1 to 47 percent. The average expression was 15 percent. The facial features were much less consistent among fra (X) positive females. Approximately 1/4 of them had speech difficulties and 1/3 percent were mentally retarded.

A typical fra (X) syndrome pedigree is shown in Figure 2. Seven fra (X) positive males, ten known (fra (X) positive) or obligate carriers, and 9 other potential carriers were ascertained by pedigree and laboratory analysis. The fra (X) positive females are noted by a dot beside their pedigree symbol. All four of these women have MR. The family history shows the inheritance pattern call X-linked or sex-linked in which affected males pass the condition to their daughters (who may be fra X positive or negative by laboratory testing) who may then pass it to their sons.

## Psychological Aspects of the Study Population

The population for this investigation consisted of 60 male and 17 female patients with fragile X syndrome by chromosomal analysis. Among the male patients 21 are white, 39 black; 29 of the males are currently institutionalized in public facilities, primarily in South Carolina, while 31 are in community based programs and/or home placement. As one would anticipate, the intellectual level of the community based patients was superior to that of the institutionalized patients. The mean IQ of the institutionalized males was 23.31 while the community based males had a mean IQ of 37.70.

Since this is a sex chromosomal abnormality, it was felt that females would not demonstrate detrimental effects unless they were homozygous; however, such is not the case. Retardation seen in the female patients could be explained by the Lyon hypothesis of inactivation of one of the female's X chromosomes.

The majority of the patients were administered the Stanford-Binet Intelligence Scale, and a ratio IQ was calculated employing the corrected CA divisor for patients beyond 13 years of age. Six of the male subjects and 6 of the female subjects had been administered Weschler Scales. It is recognized that for psychological and/or educational purposes the two measures are non-interchangeable; however, for the purposes of establishing mental retardation and baseline intellectual data, it was assumed that there was sufficient correlation between the two measures that the data would not be adversely affected. The mean and range of intellectual abilities, percent of fragile X sites noted on chromosomal analysis, and chronological age at a time of intellectual assessment are shown in Table 3 and 4.

Early investigation of fragile X syndrome posited the construct that there was an inverse relationship between intellectual level and % of fragile sites on chromosomal analysis. As can be seen in Figure 3, which presents IQ and % of fragile sites among the male subjects, there is a wide upward trend, but regression analysis shows little reliability in the regression correlation performed with an  $r^2$  being less than .04. Figure 4 represents the data on the female patients. Among this population there was a slight downward trend, however, one should consider the relatively small N. The  $r^2$  in this group was also less than 0.4.

Of interest was the different mean IQ among various age groups. Male patients in the chronological age range of 3 years 0 months to 7 years 0 months had a mean IQ of 50 (N=6); those 7 years 1 month to 15 years 0 months had a mean IQ of 45.71, (N=7); while those in the 15 years 1 month to 21 years 0 months had a mean IQ of 45.71 (N=12). The rationale for the reduction in tested intellectual function remains obscure and provides direction for further investigation.

One could hypothesize that these differences are a result of testing artifact, early involvement with educational programs and infant stimulation, or a component of the disease entity. A prospective study employing these subjects as well as those identified in the future is planned. Further, a retrospective study viewing previous records of the patient will ensue. The concept of deterioration as a component of the syndrome can not be ruled out at this time. A similar analysis of the female patients is difficult due to the small N. There are only two female patients in the 3 to 7 year age range, one a 5 year 10 months old patient with a Stanford Binet IQ of 43.

Three obligate carriers, that is mothers of affected offspring who did not demonstrate any fragile X sites on chromosomal analysis, have also been evaluated. Intellect among these individuals was within the normal range, with IQ's of 98, 106, and 115. Clinical observations and physician reports of the remainder failed to yield a rationale for intellectual assessment.

Several of the affected male patients, two normal siblings and one obligate carrier, were administered the Halstead-Reitan

Neuropsychological Battery. The findings among the affected patient were consistent with diffuse neuropsychological dysfunction and performance in keeping with their level of mental retardation. There were no consistent lateralizing signs to indicate specific hemispheric involvement. The two normal siblings and the obligate carrier performed all tasks within normal limits.

In summary, the findings of intellectual evaluation of the affected patients did not show any predictive relationship between number of fragile sites observed in chromosomal analysis and level of intellect. The levels of mental retardation extend from the mild to profound range. Specific implications for further investigation were noted.

### TREATMENT

Folic acid therapy may hold promise as a treatment modality for the fra(X) syndrome, although this is currently an extremely controversial area. Hagerman et al. recently reported a double-blind crossover study of folic acid treatment in fra(X) positive males.<sup>14</sup> The patients were assessed with psychological, language and behavioral evaluations as well as subjective parent and caretaker reports. No statistically significant changes in the study group were seen except in prepubertal males who demonstrated improvement in intellect and behavior. While on treatment they demonstrated longer attention span, decreased hyperactivity, decreased aggressiveness, and decreased unusual hand movements. Our Center has also had reports from parents and teachers of improved intellectual performance and behavior in children who have fra(X) syndrome and are on treatment with folic acid.

### SUMMARY

Fragile X syndrome is a common identifiable X-linked etiology of mental retardation which may affect up to one in a thousand males. The affected males may have a characteristic phenotype but may be extremely variable in their appearance. The suspected diagnosis can be confirmed with cytogenetic testing. Folic acid may be of benefit in the treatment of prepubertal patients.

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TABLE 1

Fragile X positive males

CLINICAL DATA

<u>Physical finding</u>	<u>% positive for finding</u>
Long, thin facies	63.2
Prominent forehead	50.0
Midface hypoplasia	57.3
Prominent jaw	66.2
Soft ears	10.8
Simple helix	40.0
Simple anthelix	56.9
Hyperextensible hands	16.9
Soft or fleshy hands	29.2

TABLE 2

Fragile X positive males

ANTHROPOMETRIC DATA

<u>Measurement</u>	<u>% above mean +2SD of general population norms</u>
Head circumference	11.8
Ear length	43.3
Total hand length	40.4
Palm length	32.7

TABLE 3

Intellect, Percent Fragile Sites, and Age

N=60 males

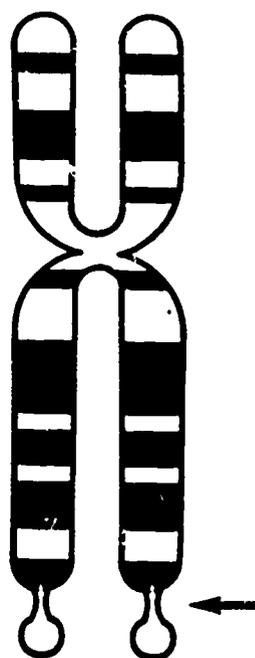
	<u>Mean</u>	<u>Range</u>
IQ	25.75	11--68
% Fragile Site	22.78	3--56
Age (years)	27.38	3-0-62-3

TABLE 4

Intellect, Percent Fragile Sites, and Age

N=17 female demonstrates

	<u>Mean</u>	<u>Range</u>
IQ	47.88	21--90
% Fragile Site	16.41	3--47
Age (years)	23.31	2-10--59-9

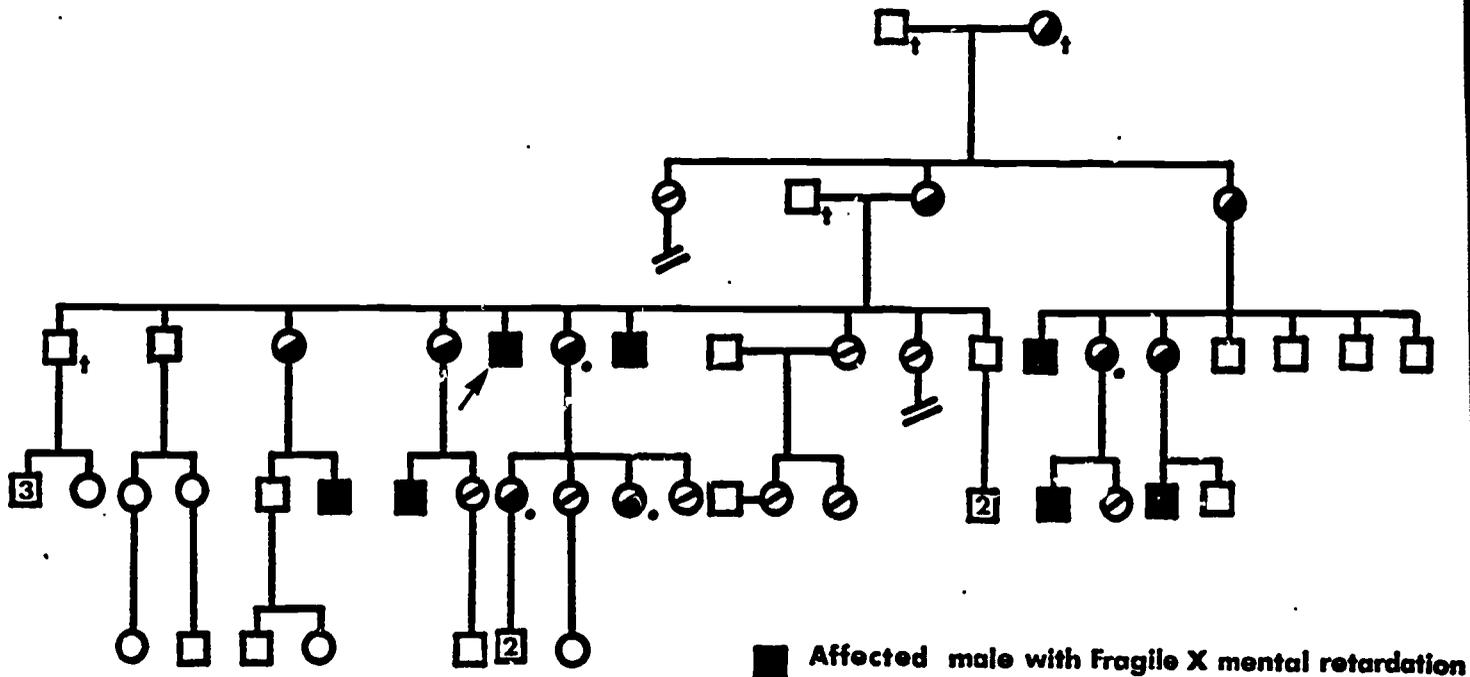


*Schematic drawing of the fragile X chromosome. Arrow points to the fragile site.*

Reprinted from The Fragile X Syndrome,  
Hagerman RJ and McBogg PM, Spectra  
Publishing Co., Inc., Dillon Colorado, 1983.

FIGURE 1

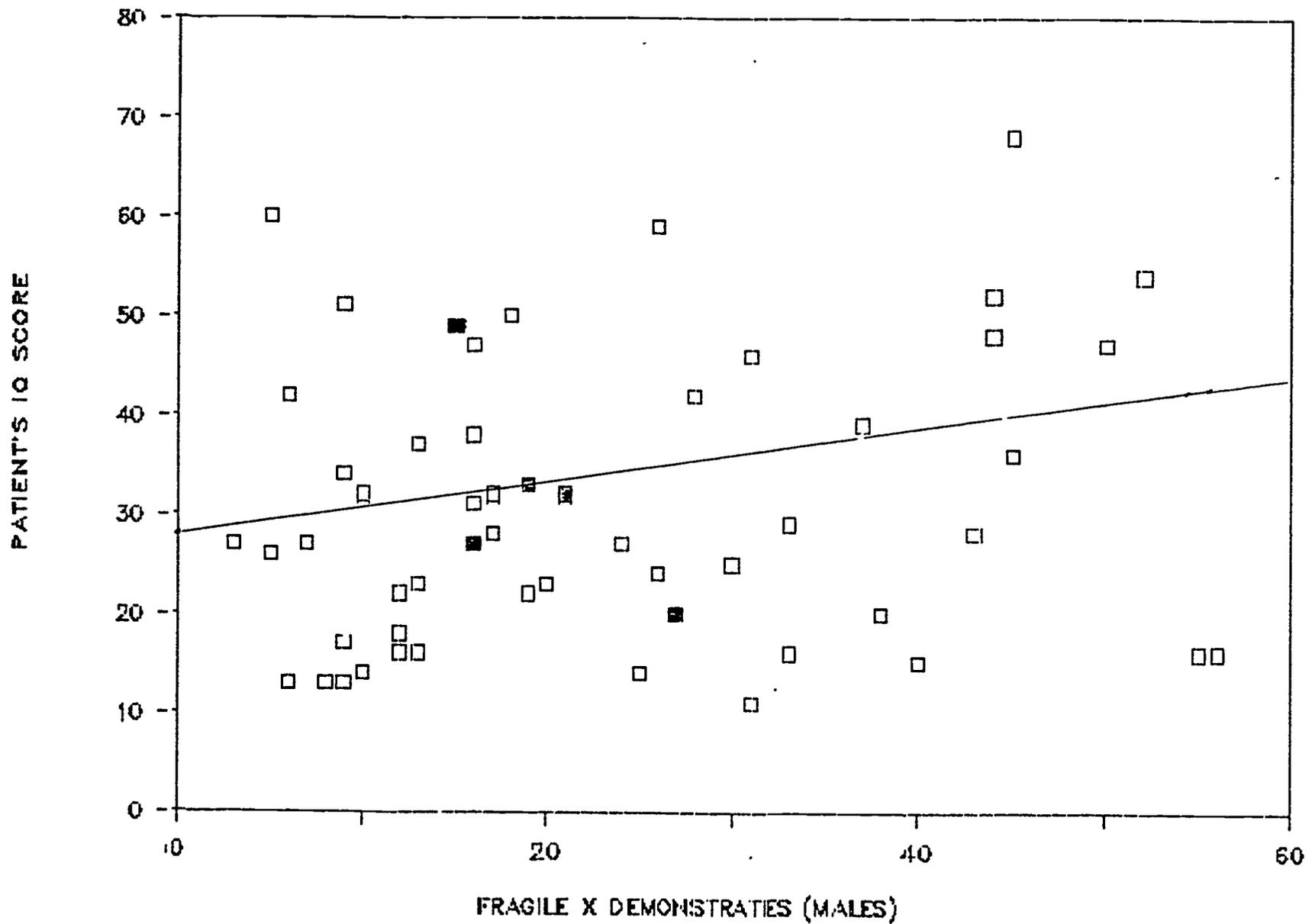
I  
II  
III  
IV  
V



- Affected male with Fragile X mental retardation
- ⊖ Potential carrier of Fragile X
- Obligate or known carrier

FIGURE 2

# FRAGILE SITES AND IQ SCORES

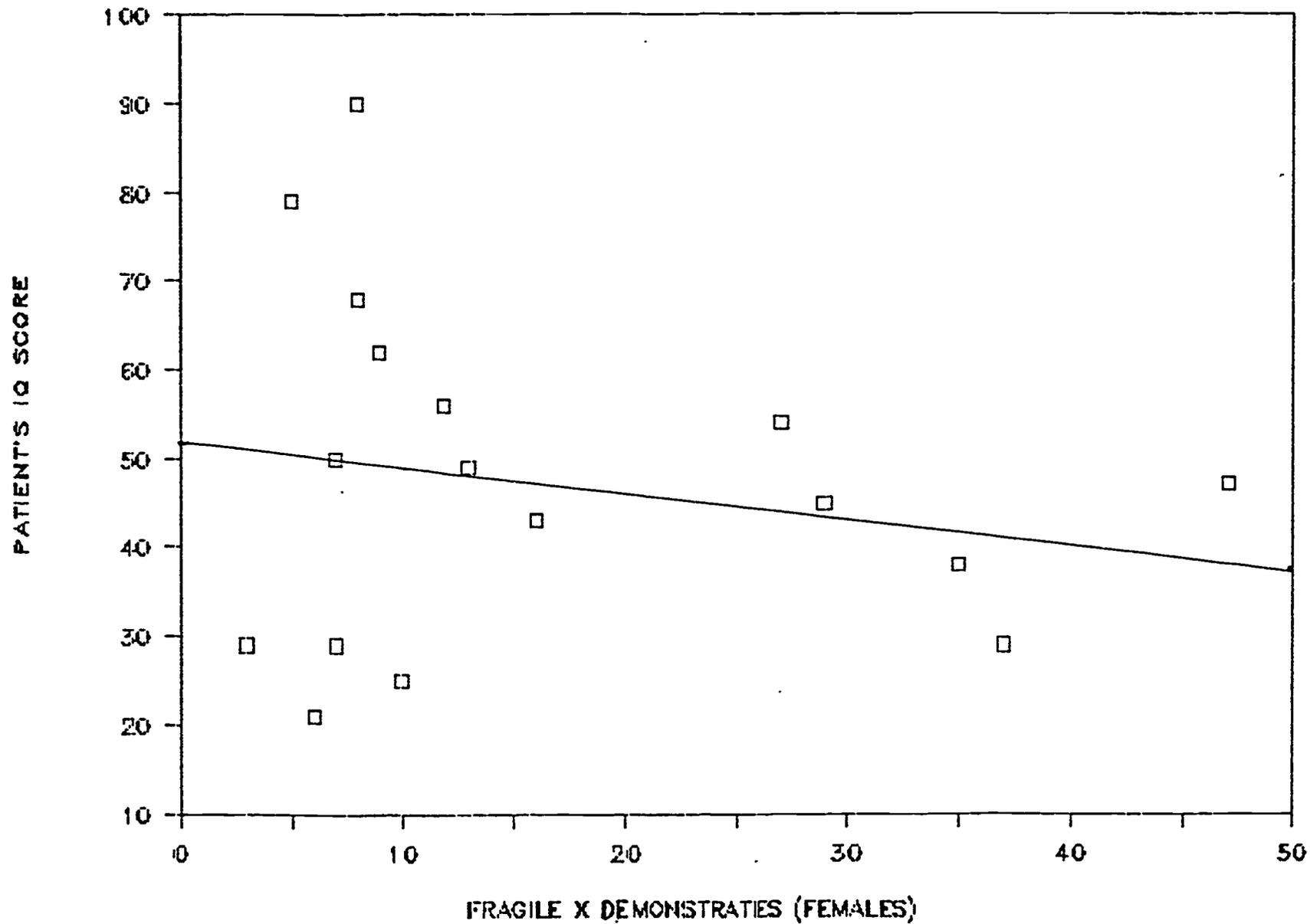


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FIGURE 3

14

# FRAGILE SITES AND IQ SCORES



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FIGURE 4

Paper presented at the Annual Convention of the  
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