

Fried syndrome is a distinct X linked mental retardation syndrome mapping to Xp22

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Abstract

In 1972, Fried described a large Scottish family affected by X linked mental retardation (XLMR), hydrocephalus, and mild facial dysmorphism. The phenotype has considerable similarity to the MASA syndrome, which results from mutations of the L1CAM gene in Xq28, and this family has since been assumed to be an example of this condition. We have reinvestigated the family for linkage to X chromosome markers, and obtained additional clinical information on surviving affected subjects. The phenotype in these patients has evolved into a distinctive syndrome, with severe mental retardation (MR), spastic diplegia, ventricular dilatation, and calcification of the basal ganglia. Linkage to Xq28 markers has been excluded, suggesting that Fried syndrome is not allelic with MASA syndrome. Two point and multipoint linkage analysis indicates that the gene for this condition lies within the interval KAL-DXS989 in Xp22. We propose the designation Fried syndrome to emphasise the disorder's distinctive phenotype.

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More than 20 years ago, Fried¹ described a Scottish family (here referred to as family J) with X linked mental retardation or hydrocephalus or both. There were five mentally retarded males in one generation and a sixth affected male (who had died) in a previous generation. The degree of mental retardation varied from moderate to severe and there were two cases of hydrocephalus, one suspected to be the result of aqueductal stenosis. All affected males had delayed motor development and difficulty in walking as adults. At the time of this initial description DNA analysis was not possible, and from 1973 to 1993 the family remained uninvestigated. However, Fried's description of the affected males in this family, with mental retardation, hydrocephalus, and spasticity, later suggested strong similarities to MASA syndrome² (mental retardation, aphasia, shuffling gait, adducted thumbs). In this condition, ventricular dilatation and spasticity are also present, as in family J. MASA syndrome was later localised by linkage to Xq28,³ and eventually shown to be allelic to X linked hydrocephalus (HSAS), both conditions resulting from mutations in the neural cell

adhesion molecule L1CAM.⁴ Despite a suggestion by Fried and Sanger⁵ in 1973 that the disorder in family J might be linked to the Xg blood group (now known to be in Xp22.33), the family has since been extensively cited as an example of MASA syndrome or X linked hydrocephalus.⁶⁻¹¹ We have now restudied the family and localised the XLMR gene in family J to a 17 cM interval in Xp22. This result is consistent with the blood group linkage data, and refutes the idea that this family has MASA syndrome. Additional clinical features not apparent at the time of the original description also show that this condition appears to be a new form of syndromic mental handicap, which we propose should be referred to as Fried syndrome.

Methods

CLINICAL DETAILS

The pedigree is shown in fig 1. Three affected males are still living in different hospitals in Scotland. Clinical reassessment was only possible on one person (III.26), although new information was also obtained about III.35 and III.41.

Case 1 (III.26, III.17 in Fried¹) was born in 1947 after a normal delivery although his mother had been admitted to hospital with oedema one week before delivery. He developed normally at first, but at 9 months suddenly regressed and developed loss of muscle tone with associated muscle wasting. Subsequent development was slow; he walked at 3 years and talked at 4 years. He required special education and was irritable and very difficult to manage at home. He was eventually admitted to a mental hospital at 22 years. His IQ was 39 (Binet). He had kyphosis with mild scoliosis and mild pes planus. His facial appearance was felt to be normal, although in 1995 (aged 48) his features appeared somewhat coarse (fig 2A, B). By the age of 31, he had difficulty in walking; weakness, sensory loss, and impaired coordination in both legs with an extensor plantar reflex on the right side were found. One year later he was wheelchair bound. A skull x ray two years later showed bilateral symmetrical calcification of the basal ganglia. When examined in 1995, he had increased tone in his arms and legs, lower limb weakness, bilateral extensor plantar reflexes, and sustained bilateral ankle clonus. A CT scan at this time showed extensive calcification of the basal ganglia and enlarged lateral ventricles (fig 2C).

Case 2 (III.35, III.24 in Fried¹) was born in 1936 after a normal pregnancy and delivery.

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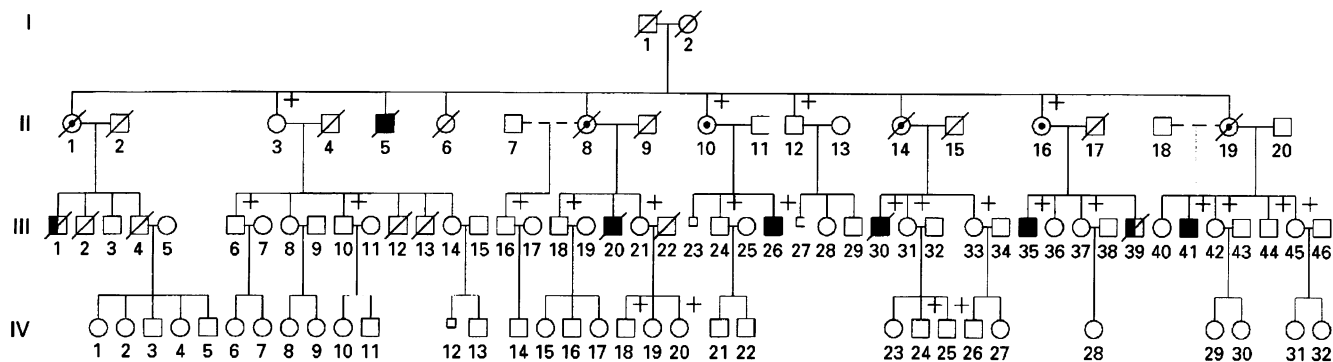


Figure 1 Pedigree of X linked mental retardation family 7. Males with MR are denoted by filled black symbols, and the two males reported to have had hydrocephalus (III.1 and III.39) by half shaded symbols. Obligate carrier females are represented by symbols with a dot. Blood was obtained from those subjects marked with a cross.

He had delayed developmental milestones and did not walk until 2 years of age. He attended a special school from the age of 8 years and was admitted to a mental hospital aged 45 with an IQ of approximately 45. His facial appearance was normal apart from the mildly dysplastic ears mentioned by Fried.¹ At the age of 47 he was referred to a neurologist because of weakness and confusional episodes, and found to have bilaterally increased limb reflexes and thinning of the interosseous muscles in the hands.

Case 3 (III.41, III.29 in Fried¹) was born in 1951. Neurological examination at the age of 20 had shown an abnormal gait and spastic diplegia with exaggerated limb reflexes. Further examination at the age of 40 showed kyphosis, mild choreiform movements, a wide based, flat footed gait, and wasting of the small muscles of the hands. He had poor speech. A skull *x* ray in 1995 showed calcification of the basal ganglia (fig 3).

The three cases described all had a normal 46,XY karyotype and had been found to be cytogenetically negative for the Xq27.3 fragile site (FRAXA).

There were also five affected males who had died in this family.

(1) II.5 (II.3 in Fried¹).

(2) III.1 was severely handicapped, noted to have a large head in infancy, and never walked. He died aged 15 from meningitis, although his death certificate stated "congenital hydrocephalus".

(3) III.20 (III.13 in Fried¹) was mentally handicapped with scoliosis and spastic diplegia. He died aged 33 from a suspected heart attack.

(4) III.30 (III.21 in Fried¹) was born in 1938 after a normal pregnancy although labour was prolonged and he was delivered by forceps. His milestones were delayed; he was unable to sit up until 8-9 months and did not walk unaided until 2½ years. He attended school but never learned to read or write. He was admitted to a mental hospital on a permanent basis at the age of 16. His legs were reported to be thin and he had kyphoscoliosis, bilateral genu valgum, pes planus, and a clumsy gait. No information is available about his cause of death.

(5) III.39 (III.27 in Fried¹) was born in 1955 and died in 1959. He had hydrocephalus as described by Fried.¹

The phenotype of the affected males, therefore, appears to be moderate to severe mental retardation with ventricular dilatation, and in survivors a progressive spastic diplegia (this is not dissimilar to the MASA phenotype). Wasting of the small muscles of the hand was also apparent in two of the three living affected males. The facial dysmorphism is mild; III.26 (fig 2A, B) has a long face with long ears and coarse facial features; some felt he resembled males with fragile X syndrome. Although increased OFC was present in infancy in the two males reported to have had hydrocephalus, the other mentally retarded males had normal head circumferences. Of the two males who had recent investigations (CT scan and *x* ray) both had marked calcification of the basal ganglia, and III.26 had enlarged lateral ventricles.

None of the obligate carrier females was known to have any manifestations of the disorder and all were of normal intelligence.

DNA was obtained from subjects marked with a cross (fig 1). Initially, because of the suggested diagnosis of MASA syndrome, linkage analysis using markers in Xq28 in the region of L1CAM was undertaken. When linkage to Xq28 was excluded, other regions of the X chromosome were screened using microsatellite markers. The sources for the markers used (microsatellite repeats except where specified) were as follows: DXS996,¹² DXS1224,¹² DXS987,¹² DXS1053,¹² DXS999,¹² DXS1229,¹² DXS1052,¹² DXS989,¹² DXS237,¹³ KAL,¹⁴ DXS207,¹⁵ DXS418,¹⁶ DXS1683,¹⁷ DXS1234,¹⁸ 5'DYS-II,¹⁹ DXS426,²⁰ AR,²¹ DXS3,²² DXS297 (*Xmn*I),²³ FMR1,²⁴ DXS296 (*Taq*I),²⁵ DXS305 (*Pst*I),²⁶ F8C (IVS13),²⁷ F8C (IVS19, *Hind*III),²⁸ F8C (*Bcl*I).²⁹

LINKAGE ANALYSIS

Two point analysis was carried out using the MLINK component of LINKAGE³⁰ with a mutation rate arbitrarily set at 1×10^{-5} and a corresponding gene frequency of 3×10^{-5} . Subjects who had died (II.5, III.20, and III.30) were coded as affected and complete penetrance was assumed. For microsatellite

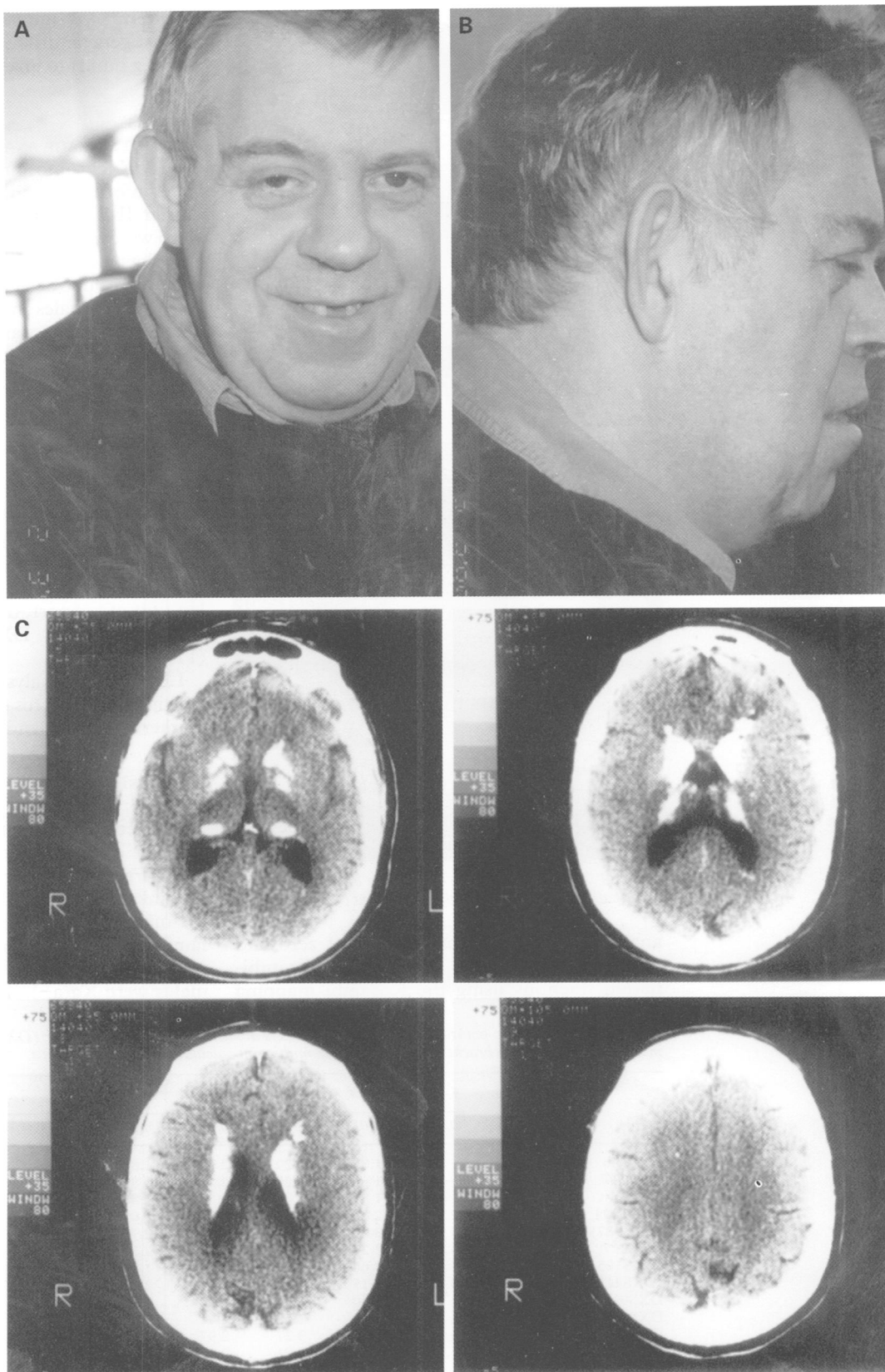


Figure 2 (A, B) III.26 at 47 years of age. (C) CT scan of III.26 showing bilateral calcification of the basal ganglia and lateral ventricular dilatation.

markers, equal allele frequencies were assumed, and for dimorphic markers, the published frequencies were used. The results of the pairwise analysis are shown in table 1.

Multipoint analysis was carried out with LINKMAP³⁰ using the map DXS996 - 1.0 - DXS237 - 3.3 - KAL - 7.6 - DXS1224 - 3.7 - DXS207 - 2.6 - DXS999 - 4.8 - DXS1229 -

8.0 - DXS989 - 7.4 - DXS1234 - 8.3 - 5'DYS - 22.5 - DXS426 - 6.5 - AR - 15.4 - DXS3 - 56.9 - DXS98 - 12.5 - DXS297 - 3.5 - FMR1 - 0.6 - DXS296 - 11.6 - F8C (genetic distances from Fain *et al*³¹). Fifteen overlapping five point analyses (four marker loci and the disease locus) were performed as recommended by Terwilliger and Ott.³² For the LINKMAP

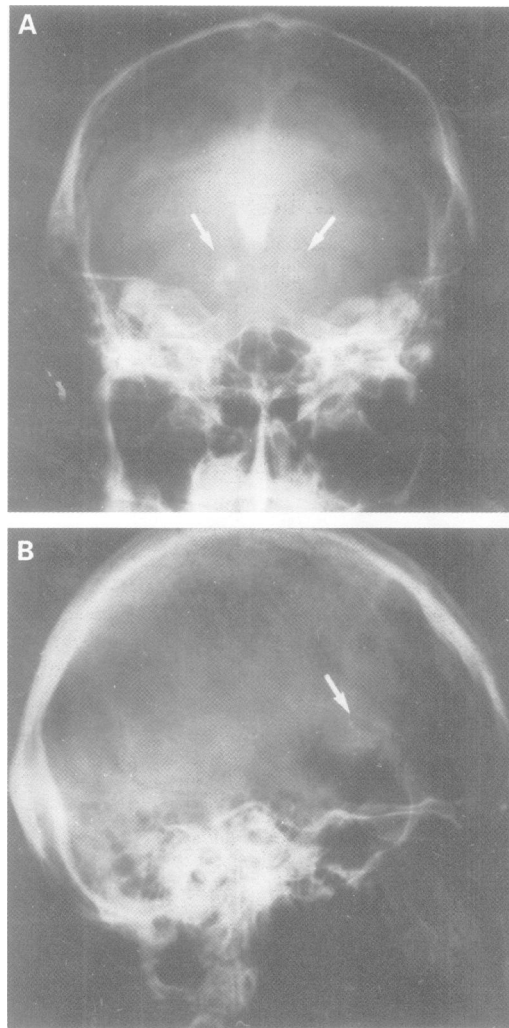


Figure 3 Skull x rays of III.41 showing bilateral calcification of the basal ganglia (indicated by arrows).

analysis, mutation rates were set at zero and genetic distances were converted to recombination fractions using the Kosambi mapping

function.³³ Multipoint lod scores were plotted against genetic distance (using DXS996 as the starting point) to give the graph shown in fig 4.

Results

DNA AND LINKAGE ANALYSIS

Of 33 X chromosome markers analysed, 26 were informative, in that either the possible carrier II.3 or the obligate carriers II.10 and II.16 were heterozygous. I.2 was assumed to be an obligate carrier because of the status of II.5. (If II.5 had not been affected, the father of the six carrier females in generation II could have been a gonadal mosaic for normal and mutant alleles, who transmitted the mutation to five out of six daughters.) Positive two point lod scores (table 1) were obtained in the interval DXS1224 (Xp22.31) to DXS1052 (Xp22.13), with a maximum lod score of 4.22 at DXS418 (Xp22.1). Markers from DXS1224 to DXS1683 showed no recombination with the disease gene. Using a confidence level of 2 lod score units (likelihood ratio of 100:1), the Fried syndrome interval is defined as KAL-DXS989 (26.7 cM). Using a less stringent 1 lod unit of support, the 90% confidence interval lies between DXS1224 and DXS1229 (17.2 cM).

LINKMAP analysis produced maximum multipoint lod scores of 4.26, with the adjacent markers DXS207 and DXS999 (fig 4).

Discussion

Family J was originally described in 1972, but the genetic cause of their mental retardation was not clearly defined for over 20 years. In 1973, Fried and Sanger⁵ had suggested possible linkage between the Xg blood group and the mental retardation gene segregating in the family. Four out of five affected males were Xg(a+) and five out of seven unaffected males were Xg(a-). These results produced a

Table 1 Results of two point linkage analysis. Markers are listed in chromosome order (DXS996, Xp-F8C, Xq). All markers except those in brackets were used in the multipoint calculation

| Locus | Lod scores at θ of: | | | | | | | Zmax | θ_{max} |
|---------------------------|----------------------------|--------|-------|-------|-------|-------|-------|------|----------------|
| | 0.0 | 0.01 | 0.05 | 0.1 | 0.2 | 0.3 | 0.4 | | |
| DXS996 | -∞ | 1.85 | 2.29 | 2.25 | 1.83 | 1.24 | 0.57 | 2.30 | 0.06 |
| DXS237 | -∞ | 1.85 | 2.29 | 2.25 | 1.83 | 1.24 | 0.57 | 2.30 | 0.06 |
| KAL | -∞ | 1.97 | 2.39 | 2.33 | 1.88 | 1.25 | 0.54 | 2.40 | 0.06 |
| DXS1224 | 2.31 | 2.28 | 2.16 | 1.99 | 1.62 | 1.17 | 0.63 | 2.31 | 0.00 |
| (DXS987) | 4.04 | 3.99 | 3.76 | 3.46 | 2.75 | 1.91 | 0.95 | 4.04 | 0.00 |
| DXS207 | 3.26 | 3.21 | 3.00 | 2.71 | 2.10 | 1.42 | 0.68 | 3.26 | 0.00 |
| (DXS1053) | 1.69 | 1.66 | 1.53 | 1.36 | 1.00 | 0.62 | 0.23 | 1.69 | 0.00 |
| (DXS418) | 4.22 | 4.15 | 3.89 | 3.54 | 2.78 | 1.91 | 0.93 | 4.22 | 0.00 |
| DXS999 | 1.83 | 1.80 | 1.67 | 1.50 | 1.12 | 0.71 | 0.28 | 1.83 | 0.00 |
| DXS1229 | 1.77 | 1.73 | 1.59 | 1.41 | 1.04 | 0.65 | 0.25 | 1.77 | 0.00 |
| (DXS1052) | 3.56 | 3.51 | 3.27 | 2.97 | 2.30 | 1.56 | 0.75 | 3.56 | 0.00 |
| (DXS1683) | 2.36 | 2.33 | 2.21 | 2.05 | 1.67 | 1.21 | 0.66 | 2.36 | 0.00 |
| DXS989 | -∞ | 2.45 | 2.89 | 2.84 | 2.38 | 1.69 | 0.83 | 2.90 | 0.06 |
| DXS1234 | -∞ | 0.46 | 1.60 | 1.88 | 1.76 | 1.31 | 0.67 | 1.90 | 0.12 |
| 5' DYS | -∞ | -3.83 | -1.21 | -0.25 | 0.41 | 0.50 | 0.32 | 0.50 | 0.27 |
| DXS426 | -∞ | -4.98 | -2.40 | -1.47 | -0.80 | -0.51 | -0.24 | 0.00 | 0.50 |
| AR | -∞ | -4.65 | -2.00 | -0.99 | -0.19 | 0.07 | 0.11 | 0.11 | 0.37 |
| DXS3 | -∞ | -5.19 | -2.51 | -1.45 | -0.55 | -0.18 | -0.03 | 0.00 | 0.50 |
| DXS98 | -∞ | -6.71 | -3.32 | -1.95 | -0.79 | -0.31 | -0.11 | 0.00 | 0.50 |
| DXS297 | -∞ | -3.03 | -1.61 | -1.02 | -0.52 | -0.29 | -0.13 | 0.00 | 0.50 |
| FMR1 | -∞ | -10.70 | -5.87 | -3.85 | -1.96 | -0.99 | -0.40 | 0.00 | 0.50 |
| DXS296 | -∞ | -3.57 | -1.71 | -1.10 | -0.78 | -0.64 | -0.31 | 0.00 | 0.50 |
| (DXS305) | -∞ | -2.89 | -1.54 | -1.04 | -0.73 | -0.59 | -0.32 | 0.00 | 0.50 |
| (F8C/F814) | -∞ | -3.30 | -1.42 | -0.79 | -0.43 | -0.42 | -0.32 | 0.00 | 0.50 |
| F8C/IVS13 | -∞ | -13.46 | -7.30 | -4.75 | -2.39 | -1.17 | -0.44 | 0.00 | 0.50 |
| (F8C/IVS19, HindIII RFLP) | -∞ | -3.30 | -1.42 | -0.79 | -0.43 | -0.42 | -0.31 | 0.00 | 0.50 |

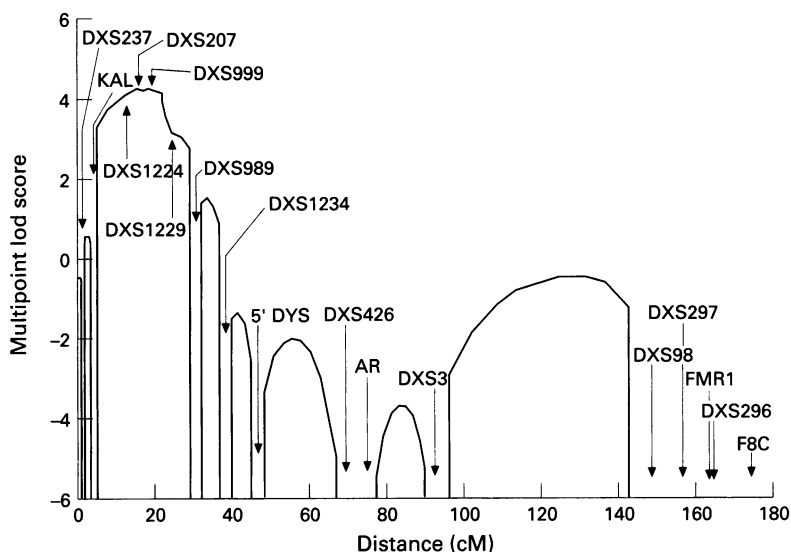


Figure 4 Results of LINKMAP analysis in family J. DXS996 (not shown) was used as the reference point (0 cM). The maximum multipoint lod score was 4.26 with the marker DXS207. The shoulder between the markers DXS999 and DXS1229 may be a consequence of combining information from two five point analyses. Alternatively, it may reflect differences in informativeness of markers in this region.

maximum likelihood ratio of linkage, between Fried syndrome and Xg, of 20.2 at $\theta=0.11$ (corresponding to a lod score of 1.3). Despite this, the weakness of the evidence for Xg linkage, along with the phenotype which had been described, allowed others to believe that the affected males had MASA syndrome. The presence of two males with hydrocephalus, and the discovery that one form of X linked spastic paraplegia (SPG1) is also caused by L1CAM mutations,⁴ added further weight to the assumption that the MASA/HSAS/SPG1 locus was involved in family J. The present study, however, maps the XLMR locus in this family to the interval DXS989-KAL (Xp22).

Thus two lines of evidence refute the diagnosis of MASA/HSAS in family J: (1) the locus maps to distal Xp and not distal Xq. (2) Further evaluation of the phenotype shows new features absent from MASA syndrome but present in Fried syndrome. In particular, two affected males had marked calcification of the basal ganglia. This is not seen in the MASA/HSAS syndromes, though the other clear radiological feature of ventricular enlargement (as in III.26) is seen in MASA families.³⁴ In addition, although the affected males in family J have poor speech, they are not aphasic, and none had adducted thumbs. Other features present in family J include spastic diplegia, kyphoscoliosis, and wasting of the small muscles in the hands.

The evidence thus indicates that the family described here has a mental retardation/spastic diplegia syndrome owing to mutation of a gene in distal Xp. The results vindicate the original largely ignored suggestion of Fried and Sanger⁵ that the syndrome is linked to Xg, since the PBDX gene,³⁵ which encodes Xg, lies at the left hand edge of the multipoint lod diagram in fig 4, 16-18 cM from our maximum likelihood location for XLMR Fried syndrome (cf Fried and Sanger's maximum likelihood at $\theta=0.11$).

The phenotype of Fried syndrome appears sufficiently distinctive that other families, if they exist, should be recognisable. However, the possibility that the condition could be allelic with other XLMR syndromes mapped to Xp22 requires consideration. Two other mental retardation syndromes with skeletal abnormalities also map to the same region as that of family J: Coffin-Lowry syndrome (CLS)³⁶ and Snyder-Robinson syndrome.³⁷ Arrested hydrocephalus is a feature of CLS and several males have been described with calcification of the ligamenta flava.^{38,39} Though mental retardation, ventricular dilatation, and kyphoscoliosis are shared between Fried syndrome and CLS, none of the characteristic dysmorphisms of CLS is present in family J. An allelic relationship between these disorders therefore seems rather unlikely on clinical grounds, though when complete mutational analysis of the recently identified CLS gene⁴⁰ is possible, this point may be clarified. For most other XLMR syndromes, the confidence limits for the gene locations are large, making suspected allelism difficult to confirm. The presence of distinctive basal ganglia calcification in family J inclines us to believe that they have a new, recognisable, syndromic XLMR disorder. Identification of other families with Fried syndrome should be aided by this observation, particularly if subjects with XLMR are reassessed radiologically in middle age.

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