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# Friedreich Ataxia in Louisiana Acadians: Demonstration of a Founder Effect by Analysis of Microsatellite-generated Extended Haplotypes

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## Summary

**Eleven Acadian families with Friedreich ataxia (FA) who were from southwest Louisiana were studied with a series of polymorphic markers spanning 310 kb in the D9S5-D9S15 region previously shown to be tightly linked to the disease locus. In particular, three very informative microsatellites were tested. Evidence for a strong founder effect was found, since a specific extended haplotype spanning 230 kb from 26P (D9S5) to MCT112 (D9S15) was present on 70% of independent FA chromosomes and only once (6%) on the normal ones. There was no evident correlation between haplotypes and clinical expression. The typing of an additional microsatellite (GS4) located 80 kb from MCT112 created a divergence of the main FA-linked haplotype, generating four minor and one major haplotype. A similar split was observed with GS4 in a patient homozygous for a rare 26P-to-MCT112 haplotype. These results suggest that GS4 is a flanking marker for the disease locus, although other interpretations are possible.**

## Introduction

Friedreich ataxia (FA) is a progressive neurodegenerative disorder, involving both the central and peripheral nervous systems, with autosomal recessive inheritance. The disease is characterized by gait ataxia, muscle weakness, areflexia of the lower limbs, dysarthria, and sensory disturbances. It is usually manifest, in its classical form, around puberty (Geoffroy et al. 1976; Harding 1981). Chamberlain et al. (1988) mapped the FA gene ("FRDA" in the Human Gene Mapping Workshop nomenclature) to chromosome 9 by virtue of its tight linkage to a dimorphic RFLP at locus D9S15 (detected by probe pMCT112). This was confirmed by Fujita et al. (1989), who showed that marker D9S5 is also tightly linked to FRDA. Both D9S5 and D9S15 appear extremely close to the FRDA locus, since no proven recombination events have been reported to date and the cumulative lod score ($Z$) at a recombination fraction ($\theta$) of 0 is greater than 80 for D9S15 and is greater than 50 for D9S5 (Chamberlain et al. 1989; Fujita et al. 1989, 1990; Wallis et al. 1990). A "recombinant" consanguineous family previously described by Fujita et al. (1990) later proved to have ataxia caused by autosomal recessive vitamin E deficiency (M. Pandolfo, personal communication).

By means of very informative markers including a microsatellite at MCT112, linkage disequilibrium was observed on extended D9S5-D9S15 haplotypes in a French outbred population (Fujita et al. 1990; Hanauer et al. 1990). Similar findings were reported for both a Quebec French population (Richter et al. 1989) and an Italian population (Pandolfo et al. 1990), while no significant disequilibrium was observed in a population of unspecified origin (Wallis et al. 1990). Overall, this reinforced the notion that D9S5 and D9S15 are less than 1 cM from the FRDA locus. Physical mapping has demonstrated that D9S5 and D9S15 are within 280 kb of each other (Fujita et al. 1991; Wilkes et al. 1991). The region that encompasses the two

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markers has been cloned as yeast artificial chromosomes (YACs) (Wilkes et al. 1991; Fujita et al., submitted).

Clusters of FA have been reported in Acadian populations of French ancestry, including the Acadians of southwest Louisiana (Cajuns). The disease was initially reported to have a slower progression in this population (Barbeau et al. 1984), suggesting possible genetic heterogeneity. Linkage analysis later showed linkage to D9S15 as for classical FA (Keats et al. 1989). We have thoroughly analyzed 11 FA families in the Acadian population by using a set of highly polymorphic markers (including three microsatellites) spanning 310 kb, to document evidence for a founder effect. We reasoned that in such an inbred population it should be possible to better use linkage disequilibrium studies to infer a more precise genetic localization of FRDA.

## Subjects and Methods

### *Families*

All patients in the 11 families analyzed conformed to the diagnostic criteria of Geoffroy et al. (1976) and Harding (1981). Age at onset was 8–18 years (average 11.8 years), and age when first wheelchair bound was 18–30 years (average 25.6 years). In 6 of the 11 families, parents showed distant consanguinity, from third to fifth cousins. Four families were related two by two, by third or fifth cousins.

### *Detection of RFLPs*

The *Msp*I two-allele polymorphism (probe MCT112) and the *Bst*XI three-allele polymorphism (probe 26P) were analyzed as in the work of Fujita et al. (1990). A *Dra*I polymorphism is detected by probe 26P that reveals two alleles, of 3.8 and 3.2 kb. The *Msp*I polymorphism detected with probe DR47 (D9S5) (Fujita et al. 1989) was analyzed by PCR amplification. Oligonucleotide primers were synthesized on the basis of end sequences of probe DR47 (Orzechowski et al. 1987) (see table 1) and were used to amplify a 1.7-kb fragment. PCR was carried out in a Perkin-Elmer thermocycler with 200 ng of DNA used as template. The reaction mixture consisted of 10 pmol of each primer, 200 mM of each dNTP, 50 mM KCl, 10 mM Tris-HCl (pH 8.2), and 1.5 mM $MgCl_2$ in a final volume of 20 μl. The samples were subjected to 25 cycles consisting of 1 min at 92°C, 1 min at 65°C, and 1 min at 72°C. One-half of each reaction was digested with *Msp*I in a final volume of 30 μl. Fragments were electrophoresed on 0.9% agarose gel and were visualized, after ethidium bromide staining, at 1.7 kb (allele 1) and 1.5 kb (allele 2).

### *Detection of Microsatellite Polymorphisms*

All microsatellite polymorphisms were typed by PCR using end-labeled oligonucleotide primer. Primer sequences are given in table 1. Amplification procedure and primer sequences of MCT112 microsatellite have been described elsewhere (Fujita et al. 1990). End-labeling was performed in a reaction containing 250 pmol primer, 20 pmol $\gamma^{32}$P-ATP at 5,000 Ci/mmol, 10 mM $MgCl_2$, 5 mM DTT, 50 mM Tris-HCl (pH 7.6), and 20 units T4 polynucleotide kinase. Primers D GS2, D GS4, and R GS1 were labeled for the GS2, GS4, and GS1 reactions, respectively. PCR reactions for GS2 were carried out in a Perkin-Elmer temperature cycler with 200 ng of genomic DNA as template, 10 pmol $^{32}$P end-labeled primer, 10 pmol

**Table 1**

**Sequence of Primers Used for PCR Amplification**

| Marker | Length of Amplified DNA (bp) | Repeat Sequence | PCR Primers[a] |
|---|---|---|---|
| GS1 ..... | 151 | (TAAA)6 | D 5′GCCTCTGCACTCCAGCCTGGGCAACAGAG-3′ |
| | | | R 5′-GATACCTGATAGCTATATAGCTATAAGC-3′ |
| GS2 ..... | 124 | (TG)11-(TT)-(TG)8 | D 5′-AATGAAATAGAATTTCACAGG-3′ |
| | | | R 5′-AACCCTTCTGTCAGACAAGGA-3′ |
| GS4 ..... | 131 | (TG)17 | D 5′-GGGAAGAGCAAATTCCCTGAACCCCG-3′ |
| | | | R 5′-CCTGGGCGACAGAGTGAGACTCG-3′ |
| DR47 ..... | ≈1,700 | . . . | D 5′-GCCTCAGTTCCCAGTTGACTGTTGGCC-3′ |
| | | | R 5′-GACCTGCAGGAGGTATCTCTTCCTTAC-3′ |

[a] D and R indicate direct and reverse primer, respectively.

cold primer, 200 mM of each dNTP, 50 mM KCl, 10 mM Tris-HCl (pH 8.2), 1.5 mM $MgCl_2$, and 2 units of *Taq* polymerase (Perkin Elmer Cetus) in a final volume of 50 µl. PCR for GS1 was performed in the same conditions but with 10 pmol of end-labeled RGS1 primer (which flanks the Alu sequence) and 25 pmol of DGS1 primer (within the Alu sequence). GS2 was amplified through 25 cycles each consisting of 1 min at 92°C for denaturation, 1 min at 55°C for annealing, and 15 s at 72°C for extension. GS4 was subjected to 30 cycles each consisting of 1 min at 94°C, 1 min at 65°C, and 1 min at 72°C, and GS1 was subjected to 30 cycles each consisting of 1 min at 94°C, 1 min at 50°C, and 1 min at 72°C. One microliter of each reaction was mixed with 9 µl of 90% formamide blue (bromo-phenol/xylene-cyanol), and 3 µl of this mix were loaded on a 8% polyacrylamide–50% urea sequencing gel. Gels were run at 1,800 V, in 2 × TBE, for 3 h and subsequently were exposed to Kodak X-AR films overnight.

In our numbering system, successive alleles differ by one dinucleotide repeat. The largest observed allele is allele 1 for GS2 and GS4. Alleles at GS4 have thus been numbered 1–13, although allele 3 has not yet been observed. The largest allele for MCT112/MS is allele 0, as it was discovered after our initial description of alleles 1–6 of this polymorphism (Fujita et al. 1990).

## Results

### Markers Used

All families were analyzed for the D9S5 locus by using the 26P probe that detects a three-allele *Bst*XI RFLP (Fujita et al. 1990), and some families were also tested for a *Dra*I RFLP (two alleles) detected by the same probe (G. Sirugo, unpublished data). The *Msp*I polymorphism detected with probe DR47 (D9S5) (Fujita et al. 1989) was investigated in five families (15 individuals) by PCR amplification (see Subjects and Methods). An additional *Hha*I polymorphism was detected on the same amplified product, but it appeared to be in a very strong linkage disequilibrium with the *Msp*I polymorphism and was not further tested.

The GS1 sequence corresponds to an end fragment of a YAC clone containing probe DR47 (Fujita et al., submitted). It was isolated and cloned following an Alu-vector amplification procedure (Breukel et al. 1990). GS1 is located between the D9S5 and D9S15 loci, 95 kb away from marker 26P (fig. 1). Sequence of the Alu repeat revealed that the polyA tail was associated with a (TAAA)6 repeat; this was tested for polymorphism by PCR using a radio-labeled primer outside the Alu sequence (see Subjects and Methods). Two rare alleles were found in addition to the prevalent allele 3. Only three families were found to carry the rarer alleles.

Locus D9S15 was analyzed for the *Msp*I RFLP and a microsatellite polymorphism MCT112/MS corresponding to probe MCT112 (Fujita et al. 1990; Wallis et al. 1990). The *Msp*I polymorphism was tested in 43 individuals only, as it showed very little informativeness in this population. The seven-allele MCT112 microsatellite was typed in all families.

Two new (CA)n microsatellites, GS2 and GS4, which flank MCT112 at about 60 and 80 kb, respectively, were similarly tested (fig. 2). These have been isolated and characterized from YAC clones (Fujita et al., submitted). In a French outbred population, GS2 showed five alleles (in partial linkage disequilibrium with MCT112 polymorphisms), and 12 alleles have been detected for GS4 to date. This latter polymorphism is in equilibrium with MCT112 (G. Sirugo, unpublished data). The relative positions of all markers used are indicated in figure 1.

### Family Studies

We analyzed 11 families with a total of 58 individuals, including 21 patients with Friedreich ataxia. Evident consanguinity is often present in our population

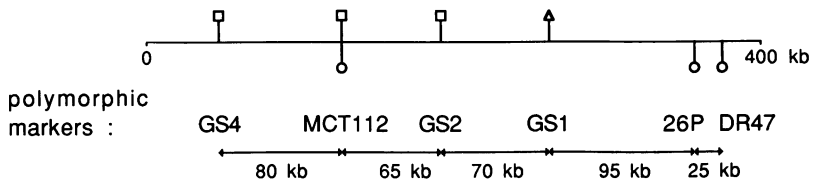


**Figure 1** Physical map of polymorphic markers used. Boxes indicate (CA)n microsatellites. Circles indicate RFLPs. The triangle corresponds to the (TAAA)6 repeat. Distances between markers are noted.

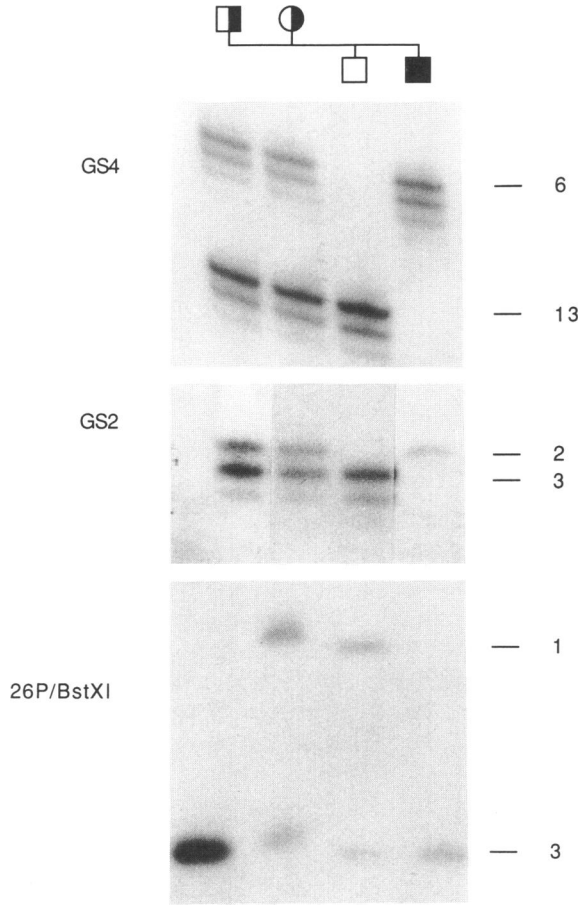


**Figure 2** GS4, GS2, and 26P/*Bst*XI allele segregation in part of FA family 1. In this family, the affected patient is homozygous for the haplotype in strong disequilibrium with the disease. The family tree is indicated on top, polymorphic markers are on the left, and allele numbers are on the right. For the microsatellite polymorphisms (GS4 and GS2), fainter bands due to polymerase slippage are seen below the allelic bands.

sample represented by various degrees of cousinship and most parents in the other families are believed to be distantly related (Barbeau et al. 1984; B. Keats, unpublished data). In families 2 and 5, FA is present in 3 and 2 sibships respectively (fig. 3).

Linkage disequilibrium between marker loci and FRDA was studied by constructing extended haplotypes. Forty-one "independent" chromosomes (18 normal chromosomes and 23 FA chromosomes) have been analyzed for the B-G-MS haplotype (where B indicates 26P/*Bst*XI polymorphism and where G and MS indicate the GS2 and MCT112 microsatellite polymorphisms, respectively) (table 2). Other two-allele RFLPs (the *Msp*I and *Dra*I at D9S5 and the *Msp*I at D9S15) were not studied in all families, as they did not define any new haplotype on FA chromosomes. Chromosomes were considered independent when there was no direct common inheritance. Distant consanguinity (third cousin once removed or more distant relationship) was not taken into account. Haplotypes were unambiguously deduced in all but three families. In two of these three families, most probable haplotypes were inferred by taking into account observed linkage disequilibrium between markers. We observed a striking overrepresentation of the B3 G2 MS2 haplotype C, accounting for 70% of the FA chromosomes, while only 1 of 18 normal chromosomes was found to carry the same haplotype (table 2). Fifteen other haplotypes were observed at low frequency (5 in FA chromosomes and 14 on normal chromosomes), and no further significant evidence for disequilibrium was found for these haplotypes. The GS1 polymorphism was studied in eight families. The rare alleles 1 and 2 were found in three families and were associated with minor B-G-MS haplotypes on FA chromosomes. In particular, in family 8 the patient was homozygous for both the rare A haplotype and the rare GS1 allele 1, most likely because of homozygosity by descent (not shown). Another patient (in family 2) was also homozygous for the rare haplotype F, while, as could be expected, patients were homozygous for the frequent haplotype C in six other sibships. It may be noted that in one branch of family 2 (fig. 3), patients are heterozygous despite consanguinity of their parents (fifth cousins). As this consanguinity is rather distant, this finding may well reflect lack of homozygosity by descent for the mutation, rather than a past recombination event.

The families were then typed for the highly polymorphic microsatellite GS4, located 80 kb from probe MCT112 (D9S15), outside the region spanned by the B-G-MS haplotype. So far, 12 alleles have been detected for this polymorphism in a Caucasian population. Seven of these were found on FA chromosomes in the Acadian families analyzed. A preferential but nonexclusive association was observed between haplotype C and allele 6 of GS4. This resulted in a splitting of haplotype C into four rare and one frequent extended haplotype (table 3) (one of the minor haplotypes was inferred, since it could not be strictly deduced). It is interesting to note that, in two families, FA patients who were homozygous for all previously typed polymorphisms were heterozygous for GS4. This specifically concerned both an FA patient in family 7 who was homozygous for the frequent haplotype

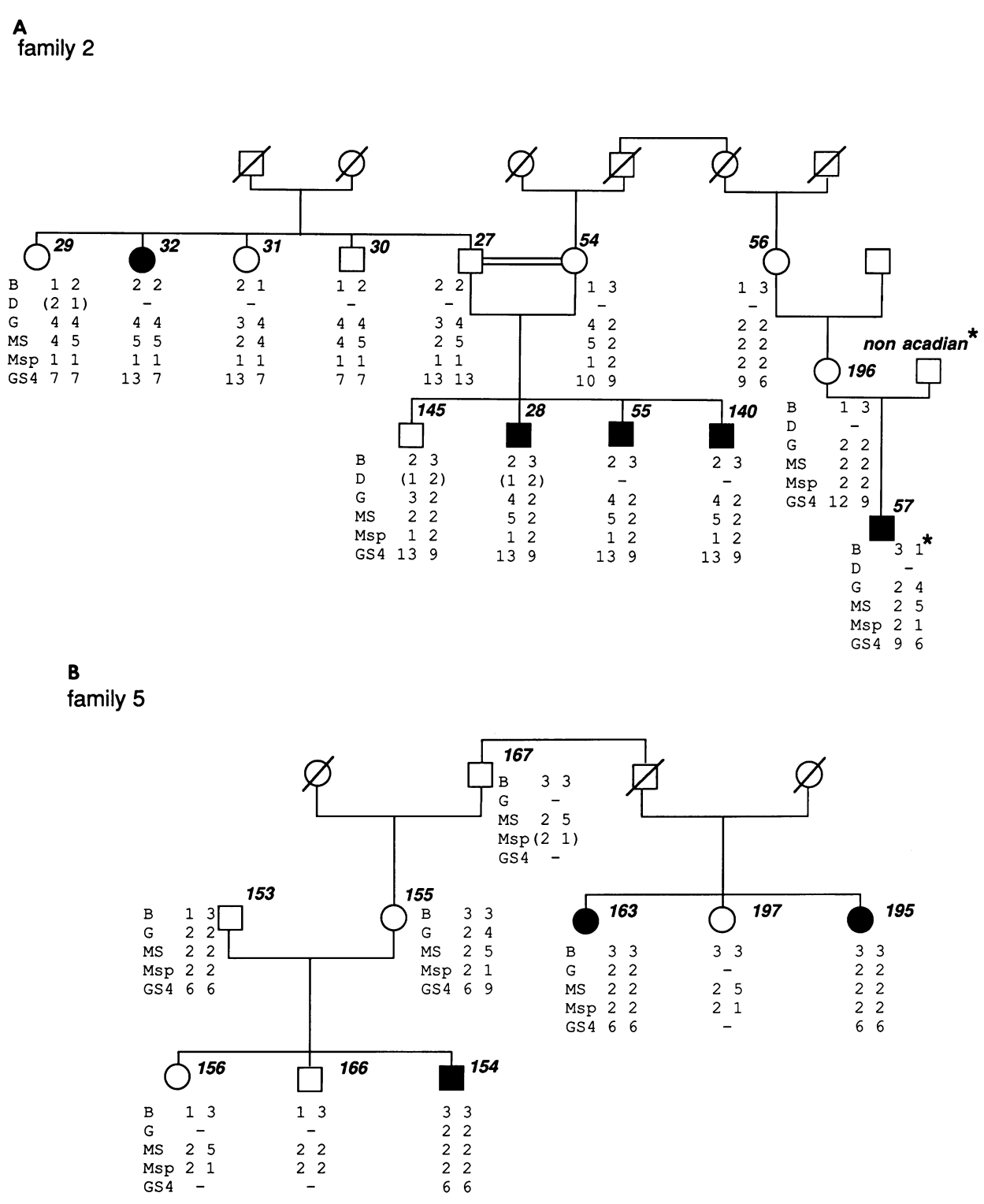


**Figure 3** Segregation of marker loci in two multigeneration FA pedigrees. Families 2 and 5 were analyzed for RFLPs at D9S5 (B, 26P/*Bst*XI; and D, 26P/*Dra*I) and at D9S15 (MS, MCT112 microsatellite; Msp, MCT112/*Msp*I RFLP). Segregation for GS2 (G) and GS4 microsatellites is also shown. In family 2, individuals 27 and 54 are fifth cousins. Parents of individual 32 are distantly related. The phase of the 26P/*Dra*I alleles is indicated in parentheses. The phase was inferred on the basis of linkage disequilibrium data in a large (about 130 independent chromosomes) outbred population sample where the rare allele 1 was always associated with allele 2 of 26P/*Bst*XI. Family 5 was analyzed at D9S5 only for the 26P/*Bst*XI RFLP.

**Table 2**

**Frequency of B-G-MS Extended Haplotype**

| Haplotype | B(26P) | G(GS2) | MS(MCT112) | Normal ($n$ = 18) | FA ($n$ = 23) |
|---|---|---|---|---|---|
| A ..... | 1 | 3 | 1 | 0 | 2[a] |
| B ..... | 2 | 2 | 2 | 1 | 1 |
| C ..... | 3 | 2 | 2 | 1 | 16 |
| D ..... | 2 | 5 | 4 | 1 | 1 |
| E ..... | 1 | 4 | 5 | 1 | 1 |
| F ..... | 2 | 4 | 5 | 1 | 2[a] |
| 10 others ... | | | | 13 | 0 |

[a] Found in a homozygous individual.

C and a patient in family 2 (individual 32; see fig. 3) who was homozygous for the rare F haplotype.

The very high frequency of haplotype C on FA chromosomes demonstrates a founder effect, and it is likely that most or all such chromosomes carry the same FA mutation. In order to see whether such predominant mutation could account for the proposed slower progression of the disease in this population, we compared age at onset and age when wheelchair bound for patients carrying two, one, or no haplotype C chromosomes ($n$ = 10, 9, and 2, respectively). No consistent differences were observed for these clinical parameters. For instance, average age when first wheelchair bound was 26.5 years (range 23–30 years) for homozygotes CC, and it was 25.2 years (range 20–30 years) for heterozygotes with a single haplotype C. Of possible interest, however, is the observation that the single patient homozygous for the rare A haplotype had the earliest age when first wheelchair bound (18 years) among the population studied.

**Table 3**

**Frequency of B-G-MS-GS4 Extended Haplotype**

| B-G-MS | GS4 | Normal ($n$ = 16) | FA ($n$ = 22) |
|---|---|---|---|
| A ..... | 8 | 0 | 2 |
| B ..... | 7 | 1 | 1 |
| C ..... | 1 | 0 | 1 |
| | 6 | 0 | 11 |
| | 7 | 0 | 1 |
| | 12[a] | 0 | 1 |
| | 9 | 0 | 1 |
| D ..... | 6 | 1 | 1 |
| E ..... | 6 | 0 | 1 |
| | 10 | 1 | 0 |
| F ..... | 7[a] | 0 | 1 |
| | 8 | 1 | 0 |
| | 13 | 0 | 1 |
| Others ..... | | 12 | 0 |

[a] Inferred haplotype.

## Discussion

To date, no recombination between the FA locus and marker loci D9S5 and D9S15 has been reported, precluding the ordering of the three loci. In an attempt to map the FRDA gene, we have explored a strategy based on both the study of linkage disequilibrium and identification of recombinant haplotypes. The linkage disequilibrium among markers in a chromosomal region reflects the evolutionary history of the markers in the population being studied, as well as the recombination frequency (Cox et al. 1988). Because of a founder effect, unusually high rates of a disease or of a specific associated haplotype are detected in some isolated populations (Fujiwara et al. 1989; Rozen et al. 1990). By analyzing such recent genetic isolates, it should be possible to interpret divergent haplotypes as recombinants with respect to an original founder haplotype, since the alleles at more distant loci eventually will be randomized by recombination (Lander and Botstein 1986). For this reason we chose to study FA in Louisiana Acadian (Cajun) families. Acadians are descendants of about 4,000 French-Canadians whom the British in the 18th century drove from the captured French colony of Acadia (now Nova Scotia and adjacent areas) and who settled in the fertile lands of southern Louisiana. The Acadian population size is approximately 500,000 (Brasseaux 1987). They form self- contained communities and speak their own patois. Geographical location as well as cultural cohesiveness, religion, and language have contributed to their genetic isolation.

In order to gain maximum informativeness, we have used, in addition to standard RFLPs, a set of multiallelic microsatellite (simple sequence repeats) polymorphisms. Three of them are associated with CA repeats, and a less polymorphic one is associated with a TAAA repeat at the end of an Alu sequence (Economou et al. 1990). Strong linkage disequilibrium between FA and the polymorphic markers was found in the Louisiana Acadian families analyzed. The striking disequilibrium observed between FA and the extended C haplotype (see table 2) demonstrates a founder effect for FA in the Acadian isolate. It should be noted that in an outbred French population sample the haplotype C was represented only in 9 (13%) of 72 FA chromosomes and in 5 (7%) of 71 normal chromosomes (G. Sirugo, unpublished data). The construction of more

extended haplotypes by adding the GS4 polymorphism resulted in a splitting of C, generating one major extended haplotype (C6) and four minor ones (C1, C7, C9, and C12). Because of this splitting effect, the disequilibrium between C6 and FA, although still strong, is weaker than that between FA and C alone (see table 3). The haplotype divergence and decrease in disequilibrium might be subjected to three different interpretations: detection of past recombination events between the FA locus and GS4, occurrence of neutral mutations in the GS4 repeat, or presence of several mutations originally associated with the same B-G-MS haplotype but different GS4 alleles.

Could sequence instability of the GS4 microsatellite explain the observed decrease of the disequilibrium? Little is known about stability of microsatellites. Detectable level of mutation has been demonstrated in minisatellites when their heterozygosity exceeds 90% (Jeffreys et al. 1988). However, this relationship may not apply to microsatellites, which may vary more because of slippage of DNA polymerase than because of unequal recombination events. Our own experience has indicated that the MCT112 and GS2 microsatellites are in strong disequilibrium either with nearby polymorphic markers or with one another in an outbred population sample, which implies great stability (Fujita et al. 1990; G. Sirugo, unpublished data). A similar effect was also observed in microsatellites at the 5′ end of the dystrophin gene (Oudet et al. 1991). On the other hand, 1 mutation event in 2,000 has been observed with other such sequences (N. Dracopoli, personal communication). GS4 has a higher heterozygosity and number of alleles than do average microsatellites (Love et al. 1990; Weber 1990). Since at present we have no data on nearby RFLPs, we cannot exclude the possibility that the GS4 sequence is more unstable than the two other CA repeats analyzed, GS2 and MCT112. Stability of the GS4 microsatellite is suggested by the finding of linkage disequilibrium between GS4 and FA in an outbred Caucasian population sample, mostly French ($P < .05$ that the allelic frequencies are the same on the normal and the FA chromosomes) (G. Sirugo, unpublished data). It should be noted that, if a 200-year-old founder effect is assumed and if about eight generations have passed since the establishment of the Louisiana Acadians in their new land, then the observed 16 chromosomes with haplotype C have been transmitted through, at most, 130 meiosis. Therefore, it seems unlikely that all four divergent haplotypes could have arisen by mutation. A second possibility is that the haplotype divergence at GS4 corresponds to different mutations present originally on haplotype C but linked to different GS4 alleles. However, given both the much greater haplotype diversity on normal chromosomes and the limited sample of FA chromosomes studied, it is unlikely that four additional mutations are present on haplotype C (which is infrequent on the normal chromosomes in both the Acadian and French populations). In addition, since the Louisiana Acadian population passed through a bottleneck, the number of different mutations is expected to be small. We thus favor the interpretation that at least some of the minor extended haplotypes C1, C7, C9, and C12 arose as recombinants derived from the major C6 extended haplotype.

We found further evidence of haplotype divergence in family 2, in which individual 32 is both homozygous for F, a rare haplotype among Louisiana Acadians, and heterozygous for GS4. The F haplotype was not observed on other FA chromosomes. The parents who transmitted the F haplotype with one FA mutation to their child are believed to be distantly related. It is therefore likely that the patient in this family is homozygous by descent, and the heterozygosity detected by GS4 might be interpreted as an ancient recombination event.

The identification of probable recombinant haplotypes on Acadian FA chromosomes would indicate that GS4 is a flanking marker of FRDA. Analysis of additional polymorphisms around the regions defined by GS4 and by probe 26P(D9S5) are required to confirm or reject this hypothesis.

The linkage disequilibrium data could be used for prediction of FA risk in Louisiana Acadians. If a gene frequency of 1/220 chromosomes (as estimated in Caucasian populations) is assumed, then the probability that a random chromosome with a C haplotype carries a FA mutation is about 5%, while it is approximately 0.1% for a random chromosome carrying a non-C haplotype (this is true only if Acadian ancestry is documented). These probabilities could be useful for calculating the risk of FA in a circumstance where one parent is known (from segregation analysis) to carry the FA mutation and where the other parent has no family history of FA.

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## References


Barbeau A, Roy M, Sadibelouiz M, Wilensky MA (1984) Recessive ataxia in Acadians and "Cajuns." Can J Neurol Sci 11:526–533

Brasseaux CA (1987) The founding of New Acadia: the beginnings of Acadian life in Louisiana, 1765–1803. Louisiana State University Press, Baton Rouge

Breukel C, Wijnen J, Tops C, Klift H, Dauwerse H, Khan M (1990) Vector-alu PCR: a rapid step in mapping cosmids and YACs. Nucleic Acids Res 18:3097

Chamberlain S, Shaw J, Rowland A, Wallis J, South S, Nakamura Y, von Gabain A, et al (1988) Mapping of mutation causing Friedreich's ataxia to human chromosome 9. Nature 334:248–250

Chamberlain S, Shaw J, Wallis J, Rowland A, Chow L, Farrall M, Keats B, et al (1989) Genetic homogeneity at the Friedreich ataxia locus on chromosome 9. Am J Hum Genet 44:518–521

Cox NJ, Bell GI, Xiang K-S (1988) Linkage disequilibrium in the human insulin/insulin-like growth factor II region of human chromosome 11. Am J Hum Genet 43:495–501

Economou EP, Bergen A, Warren AC, Antonarakis SE (1990) The polydeoxyadenylate tract of Alu repetitive elements is polymorphic in the human genome. Proc Natl Acad Sci USA 87:2951–2954

Fujita R, Agid Y, Trouillas P, Seck A, Tommasi-Davenas C, Driesel AJ, Olek K, et al (1989) Confirmation of linkage of Friedreich ataxia to chromosome 9 and identification of a new closely linked marker. Genomics 4:110–111

Fujita R, Hanauer A, Sirugo G, Heilig R, Mandel JL (1990) Additional polymorphisms at marker loci D9S5 and D9S15 generate extended haplotypes in linkage disequilibrium with Friedreich ataxia. Proc Natl Acad Sci USA 87:1796–1800

Fujita R, Hanauer A, Vincent A, Mandel JL, Koenig M (1991) Physical mapping of two loci (D9S5 and D9S15) tightly linked to Friedreich ataxia locus (FRDA) and identification of nearby CpG islands by pulse-field gel electrophoresis. Genomics 10:915–920

Fujita R, Sirugo G, Duclos F, Abderrahim H, le Paslier D, Cohen D, Brownstein BH, et al. A 530-kb YAC contig tightly linked to Friedreich ataxia locus contains 5 CpG clusters and a new highly polymorphic microsatellite (submitted)

Fujiwara TM, Morgan K, Schwartz RH, Doherty RA, Miller SR, Klinger K, Stanislovitis P, et al (1989) Genealogical analysis of cystic fibrosis families and chromosome 7q RFLP haplotypes in the Hutterite Brethren. Am J Hum Genet 44:327–337

Geoffroy G, Barbeau A, Breton G, Lemieux B, Aube M, Lepert C, Bouchard JP (1976) Clinical description and rotentgenologic evaluation of patients with Friedreich's ataxia. Can J Neurol Sci 3:279–287

Hanauer A, Chery M, Fujita R, Driesel AJ, Gilgenkrantz S, Mandel JL (1990) The Friedreich ataxia gene is assigned to chromosome 9q13-q21 by mapping of tightly linked markers and shows linkage disequilibrium with D9S15. Am J Hum Genet 46:133–137

Harding AE (1981) Friedreich's ataxia: a clinical and genetic study of 90 families with an analysis of early diagnostic criteria and intrafamilial clustering of clinical features. Brain 104:589–620

Jeffreys AJ, Royle NJ, Wilson V, Wong Z (1988) Spontaneous mutation rates to new length alleles at tandem-repetitive hypervariable loci in human DNA. Nature 332: 278–281

Keats JB, Ward LJ, Shaw J, Wickrenmasinghe A, Chamberlain S (1989) "Acadian" and "classical" forms of Friedreich ataxia are most probably caused by mutations at the same locus. Am J Med Genet 33:266–268

Lander ES, Botstein D (1986) Mapping complex genetic traits in humans: new methods using a complete RFLP linkage map. Cold Spring Harbor Symp Quant Biol 51: 49–61

Love JM, Knight A, McAleer MA, Todd JA (1990) Towards construction of a high resolution map of the mouse using PCR-analysed microsatellites. Nucleic Acids Res 18: 4123–4129

Orzechowski HD, Henning J, Winter P, Grzeschik KH, Olek K, Driesel AJ (1987) A human single copy DNA probe (DR47) detects a TaqI RFLP on chromosome 9 (D9S5). Nucleic Acids Res 15:6310

Oudet C, Heilig R, Hanauer A, Mandel J-L (1991) Nonradioactive assay for new microsatellite polymorphisms at 5′ end of the dystrophin gene, and estimation of intragenic recombination. Am J Hum Genet 49:311–319

Pandolfo M, Sirugo G, Antonelli A, Weitnauer L, Ferretti L, Leone M, Dones I, et al (1990) Friedreich ataxia in Italian families: genetic homogeneity and linkage disequilibrium with the marker loci D9S5 and D9S15. Am J Hum Genet 47:228–235

Richter A, Morgan JK, Poirier J, Mercier J, Chamberlain S, Mandel J-L, Melançon SB (1990) Friedreich's ataxia: linkage disequilibrium in the Quebec French Canadian population. Am J Hum Genet 47 [suppl]: A144 .40th Annual Meeting. The American Society of Human Genetics

Rozen R, Schwartz RH, Hilman BC, Stanislovitis P, Horn GT, Klinger K, Daigneault J, et al (1990) Cystic fibrosis mutations in North American populations of French ancestry: analysis of Quebec French-Canadian and Louisiana Acadian families. Am J Hum Genet 47:606–610

Wallis J, Williamson R, Chamberlain S (1990) Identification of a hypervariable microsatellite polymorphism within D9S15 tightly linked to the Friedreich's ataxia locus. Hum Genet 85:98–100

Weber JL (1990) Informativeness of human (dC-dA)n (dG-dT)n polymorphisms. Genomics 8:524–530

Wilkes D, Shaw J, Anand R, Riley J, Winter P, Wallis J, Driesel AG, et al (1991) Identification of CpG islands in a physical map encompassing the Friedreich's ataxia locus. Genomics 9:90–95