Handbook of Cerebellar Diseases

edited by
Richard Lechtenberg

35

Genetics of Friedreich's Ataxia in the Spanish Population

Francisco Palau, José Lopez-Arlandis, Eugenia Monrós, Juan Vilchez, and Felix Prieto

Hospital Universitari La Fe, Valencia, Spain

Modern molecular biology techniques have improved the analysis of inherited diseases, including those for which the biochemical defect is unknown, thereby allowing us to find the location of the responsible genes or to describe tightly linked polymorphic marker loci that will be the starting points leading to cloning and isolation of the gene. Friedreich's ataxia is a typical case of an autosomal recessive neurologic disorder that has been clarified by the new genetic strategies. It is interesting to study different human populations to improve our knowledge of Friedreich's ataxia. In the present paper we describe some epidemiologic and molecular studies in the Spanish population.

EPIDEMIOLOGIC STUDIES

A formal genetic study was made of the Friedreich's ataxia series from the La Fe University Hospital, a level III hospital in Valencia on the Mediterranean coast of Spain. Thirty-eight patients from 35 families were analyzed. Twenty-eight individuals born in this geographic region were chosen for a segregational study. By using Weinberg's probands method, a segregation rate of 0.185, not statistically significant at the 0.25 value expected for a recessive trait, was calculated. The incidence of Friedreich's ataxia was estimated from an analysis of consanguineous marriages. The frequency of consanguineous marriages (C') expected among parents of children homozygous for a given mutant allele is known to depend on the frequency observed in the general population (C) and on the frequency (q) of the allele [1]. For first-cousin marriages, one can estimate the frequency of the allele (q) and therefore of the disease (q^2) according to the following formula derived from Dahlberg's formula (see Emery [1]):

$$q = C(1-C')/C(1-C') + 16(C'-C).$$

A consanguinity rate of 0.4% of the general population (C) in Valencia was estimated from the National Institute of Statistics and the dispensations given by the Catholic Church in the period 1960–1982. The Friedreich's ataxia consanguinity rate (C') in our series was 3.57%. We calculated a gene frequency of 1 in 127, an incidence at birth of 6.18 in 100,000, and a carrier rate of 1 in 64.

MOLECULAR ANALYSIS

The Friedreich's ataxia (FRDA) locus has been assigned to chromosome 9 by the demonstration of close linkage to two anonymous marker loci, D9S15 [2] and D9S5 [3]. In situ hybridization mapping of these marker loci subsequently ascribed the FRDA locus to the subchromosomal region 9q13-21.1 [4,5]. Using strict diagnostic criteria, Chamberlain et al. [6] showed locus homogeneity for the genetic defect by the analysis of several patient populations. To date, no recombination events have been described between these marker loci and FRDA. Confidence interval mapping would suggest that the disease locus lies within 1 megabase (Mb) of D9S15/D9S5; the marker loci have been shown to lie within <0.5 Mb of each other [7,8].

Evidence for linkage disequilibrium at the D9S15/D9S5/FRDA cluster has been reported in the French [9] and Italian [10] patient populations. This may reflect either close proximity to the disease locus or a small number of mutations giving rise to the disease phenotype in these populations, as manifest in the Cajun [6] and French Canadian [11] pedigrees. Interpretation of these data would favor the closer proximity of the FRDA locus to D9S15.

Linkage Studies

A genetic linkage analysis was performed in 16 families with 24 affected individuals. Four DNA polymorphisms were analyzed: MCT112/microsatellite [12] and MCT112/MspI restriction fragment length polymorphisms (RFLPs) [13] at the D9S15 marker locus, and DR47/TaqI [14] and 26P/BstXI [9] RFLPs at the D9S5 marker locus. Positive lod scores for both D9S15 ($z = 1.89$; $\theta = 0.04$) and D9S5 ($z = 3.68$; $\theta = 0.00$) were obtained [15] that suggest genetic homogeneity [6] in the Spanish population also. A slight but significant allelic association was observed between Friedreich's ataxia and the D9S15 locus. This finding suggests a small number of responsible mutations in the Spanish families. A genetic recombinant event was found between the disease locus and the D9S15 marker in a classic family. Multipoint analysis suggests that the order D9S15–Friedreich's ataxia–D9S5 describes the disease locus.

Analysis of Clinical Heterogeneity by Genetic Linkage Studies

Friedreich's ataxia shows a degree of heterogeneity that is more evident between families than within families. This clinical variability could suggest a genetic heterogeneity [16], but molecular studies in different populations have shown that every patient mutation is located on chromosome 9 [6]. Thus molecular analysis can help us to confirm that the clinical variability of Friedreich's ataxia is not an

expression of genetic heterogeneity. We performed linkage studies using D9S15 and D9S5 marker loci in two two-affected families, both with a child showing retained lower limb reflexes [17]. Identical individual haplotypes were obtained in each sibship, suggesting that this clinical difference was not due to genetic heterogeneity.

The Use of DNA Polymorphic Markers for Differential Diagnosis

Genetic recombination between a pathologic trait and DNA markers suggests that they do not show physical linkage on the same chromosome region. This fundamental biological event can be useful in the diagnosis of patients with a Friedreich's ataxia like syndrome if two or more affected sibs are available in the family. Construction of D9S15/D9S5 haplotypes will show two possible results: (1) If sibs have different haplotypes, the Friedreich's ataxia diagnosis can be discounted; (2) if they show the same haplotype, Friedreich's ataxia is probably a correct but not definitive diagnosis because no detection of recombinant events could be due to biological chance in that family.

REFERENCES

1. Emery AEH. Methodology in medical genetics: an introduction to statistical methods. Edinburgh: Chuchill Livingstone, 1986; 22.
2. Chamberlain S, Shaw J, Rowland S, Wallis J, South S, Nakamura Y, Gabain A von, Farrall M, Williamson R. Mapping of the mutation causing Friedreich's ataxia to chromosome 9. Nature 1988; 334: 248–50.
3. Fujita R, Agid Y, Trouillas P, Seck A, Tommasi-Davenas C, Driesel AJ, Olek K, Grzeschik K-H, Nakamura Y, Mandel JL. Confirmation of linkage of Friedreich's ataxia to chromosome 9 and identification of a new closely linked marker. Genomics 1989; 4: 110–11.
4. Shaw J, Litcher P, Driesel AJ, Williamson, Chamberlain S. Regional localization of the Friedreich ataxia locus to human chromosome 9q13-q21.1. Cytogenet Cell Genet 1990; 53: 221–4.
5. Hanauer A, Chery M, Fujita R, Driesel AJ, Gilgenfrantz S, Mandel JL. The Friedreich's ataxia gene is assigned to chromosome 9q13-21 by mapping tightly linked markers and shows linkage disequilibrium with D9S15. Am J Hum Genet 1990; 46: 133–7.
6. Chamberlain S, Shaw J, Wallis J, Rowland A, Chow L, Farrall M, Keats B, Ritcher A, Roy M, Melancon S, Deufel T, Berciano J, Williamson R. Genetic homogeneity at the Friedreich's ataxia locus on chromosome 9. Am J Hum Genet 1989; 44: 518–21.
7. Wilkes D, Shaw J, Anand R, Riley J, Winter P, Wallis J, Driesel AG, Williamson R, Chamberlain S. Identification of CpG islands in a physical map encompassing the Friedreich's ataxia locus. Genomics 1991; 9:90–5.
8. Fujita R, Hanauer A, Vincent A, Mandel J-L, Koening M. Physical mapping of two loci (D9S5 and D9S15) tightly linked to Friedreich ataxia locus (FRDA) and identification of nearby CpG islands by pulsed-field gel electrophoresis. Genomics 1991; 915–20.
9. Fujita R, Hanauer A, Sirugo G, Heilig R, Mandel JL. Additional polymorphisms at marker loci D9S5 and D9S15 generate extended haplotypes in linkage disequilibrium with Friedreich ataxia. Proc Natl Acad Sci USA 1990; 87: 1776–1800.

10. Pandolfo M, Sirugo G, Antonelli A, Weitnauer L, et al. Friedreich ataxia in Italian families: genetic homogeneity and linkage disequilibrium with the marker loci D9S5 and D9S15. Am J Hum Genet 1990; 47:228–35.
11. Richter A, Melançon S, Farral M, Chamberlain S. Friedreich's ataxia: confirmation of gene localization to chromosome 9 in the Quebec French Canadian population. HGM10. Cytogenet Cell Genet 1989; 51: 1066.
12. Wallis J, Williamson R, Chamberlain S. Identification of a hypervariable microsatellite polymorphism within D9S15 tightly linked to Friedreich's ataxia. Hum Genet 1990; 85: 98–100.
13. Carlsson M, Nakamura Y, Krapcho K, Fujimoto E, O'Connell P, Leppert M, Lathrop GM, Lalouel JM, White R. Isolation and mapping of a polymorphic DNA sequence pMCT112 on chromosome 9q (D9S15). Nucleic Acids Res 1987; 15: 10614.
14. Orzechoswski HD, Henning J, Winter P, Grzeschik KH, Olek K, Driesel AJ. A human single copy DNA probe (DR47) detects a TaqI RFLP on chromosome 9 (D9S5). Nucleic Acids Res 1987; 15: 6310.
15. Palau F, Lopez-Arlandis J, Vilchez J, Prieto F. Genetic studies of Friedreich ataxia in a Spanish population: epidemiological and molecular linkage analysis. Am J Hum Genet 1991; 49(Suppl): A1989.
16. Winter RM, Harding AE, Baraitser M, Bravery MB. Intrafamilial correlation in Friedreich's ataxia. Clin Genet 1981; 20: 419–27.
17. Vilchez JJ, Monrós E, Lopez-Arlandis JM, Sevilla T, Prieto F, Palau F. Clinical heterogeneity in Friedreich's ataxia is confirmed by molecular analysis. J Neurol 1992; 239(Suppl. 2): A292.