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Reply

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Sir,

Foncin et al. suggest that estimation of posterior probabilities by Bayesian analysis, along with the data obtained from haplotype homozygosity, would permit a quantitative evaluation of the probability of ancient recombination events in patients homozygous by descent. The authors illustrate their study with a Calabrian family segregating Alzheimer's disease, following an autosomal dominant pattern. For human diseases following an autosomal recessive inheritance, as Friedreich's ataxia (FA) does, identification of common ancestors of the proband's parents, in order to perform Bayesian calculations and to infer the probability that the proband is homozygous by descent, does not seem a useful methodology. The probability α for an FA patient to be homozygous by descent depends upon the coefficient of inbreeding, F, and the gene mutation frequency, q, by the formula $\alpha = Fq/Fq + (1 - F)q^2$ [1]. This probability is high for patients with first-cousin parents (F = 1/16) and second-cousin parents (F = 1/64), but becomes smaller than q for older cousinship relations. For example, in patients from third-cousin parents, the F value is 1/256, whereas the FA gene (FRDA) mutation frequency is 1/220. In such a case, the probability of the child to share identical FRDA mutations is 0.46, whereas the probability to be homozygous by chance is 0.54. Based on these data, we think that systematic search for all ancestors till detecting a common couple is not the rule in autosomal recessive diseases.

In the 18 families we analyzed, two parents were first cousins and four parents were second cousins. In the remaining 12 families, consanguinity was not evident, parents did not share common surnames, and only three originated from the same rural area. Specific genealogical investigations were not carried out for the above-mentioned reasons. In that way, we have had the opportunity to study a very large pedigree from the southeast of Spain where FA segregates in four distinct sibships (fig. 1). The common origin of all parents and ancestors, the multiple coincidence of surnames, even between apparently unrelated members, and the presence of consanguineous marriages were all indications of inbreeding, which is frequent in rural areas, and suggested a priori the presence of only one FRDA segregating mutation. Nevertheless, genetic analysis of members of three affected sibships showed segregation of two different FRDA-linked haplotypes, named H1 and H2. Sibship A was homozygous for haplotype H1, whereas the patient from sibship B was homozygous for haplotype H2. The patient from sibship C was heterozygous for H1 and H2. The analyzed marker loci cross the FRDA gene candidate region [2, 3], and no ancient crossing over between H1 and H2 involving FRDA locus was observed. Although many factors suggested homozygosity by descent, we think that the best explanation is that two different mutations are segregating in this pedigree.

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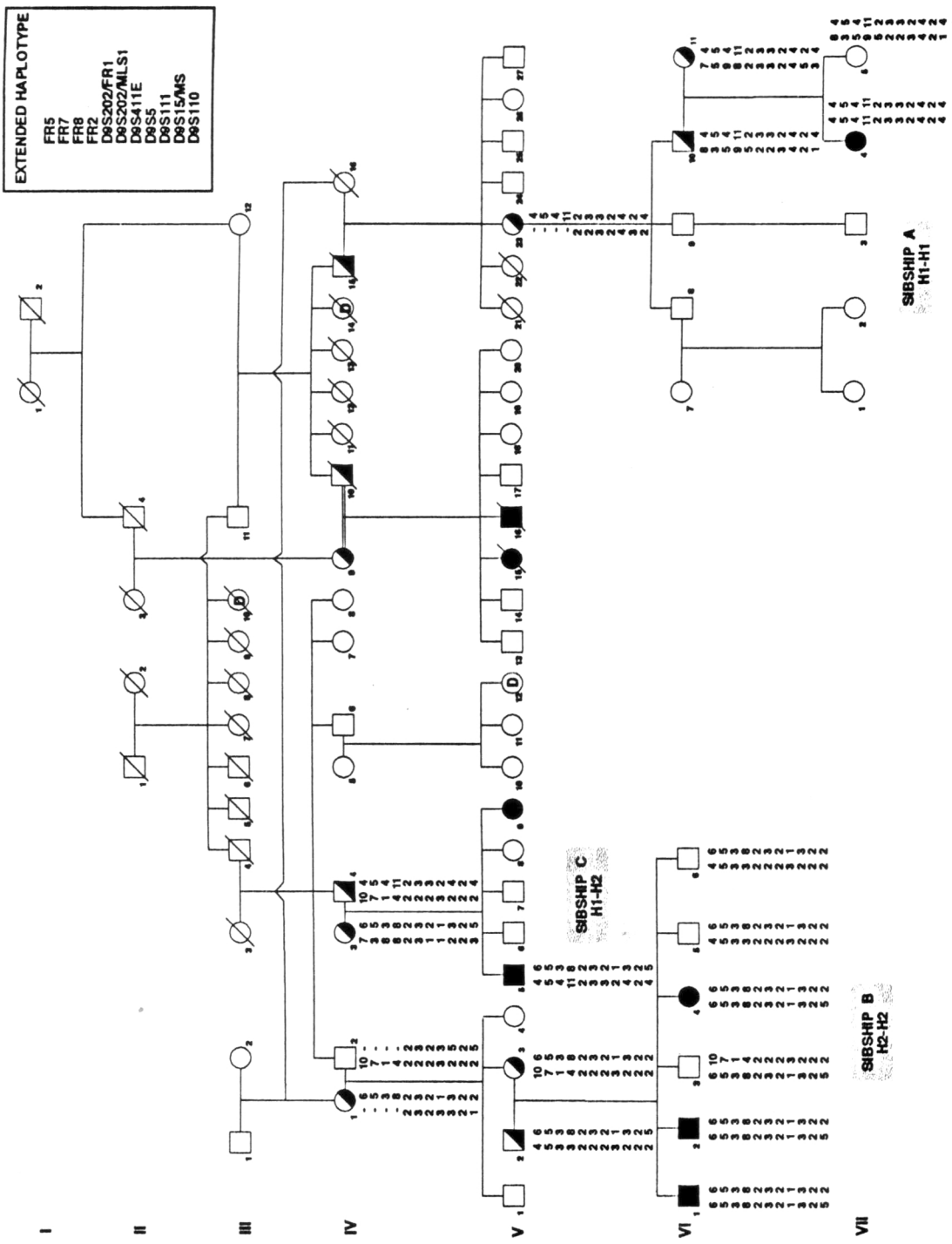

Fig. 1. Pedigree from the southeast of Spain.

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Detection of Homozygosity by Descent

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Sir,

We read with interest the recent paper by Monrós et al. [1] dealing with recombination events in patients affected with Friedreich's ataxia and (putatively) homozygous by descent. We share with the authors, although in a different setting, namely that of dominant disease [2], the opinion that genes (and haplotyes) identical by descent could be a powerful tool in positional cloning.

Fundamentally, Monrós et al. endeavour to evaluate Bayesian [3] a posteriori probabilities for their patients in 20 families of being homozygous by descent. They discuss extensively the *conditional* probabilities drawn from molecular genetics data (homozygosity for haplotypes). Bayesian probabilities, however, are not formally introduced, and a priori probabilities remain either implied (in the case of known consanguinity) or undefined (in the case of the 12 families without known consanguinity). In order to evaluate a priori probabilities, we would need, in addition to the gene frequency stated in the paper, to know how and to what extent family studies were conducted: were systematic attempts made to identify all the ancestors up to which generation?, by which methods (family history taking, or use of municipal and parish records)?, do the families originate from the same geographical area?, and do they share surnames [4]? Granted that the Spanish surname structure might tend to decrease its information content, a similar structure in Calabria did not prevent us [5], using surnames as elements of a priori probabilities, to assign a 0.7 probability to the identity by descent of mutations carried by two apparently unrelated individuals, whose common (carrier) ancestor was later identified as a woman born in 1715.

We believe that a Bayesian meta-analysis of data provided in the paper by Monrós et al. combined with population data allowing an estimation of a priori probabilities would permit a quantitative evaluation of the probability of recombination in the vicinity of the FRDA locus in their material. Population genetics may be as important as molecular genetics in the many-facetted work that eventually leads to positional cloning.

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