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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.

References

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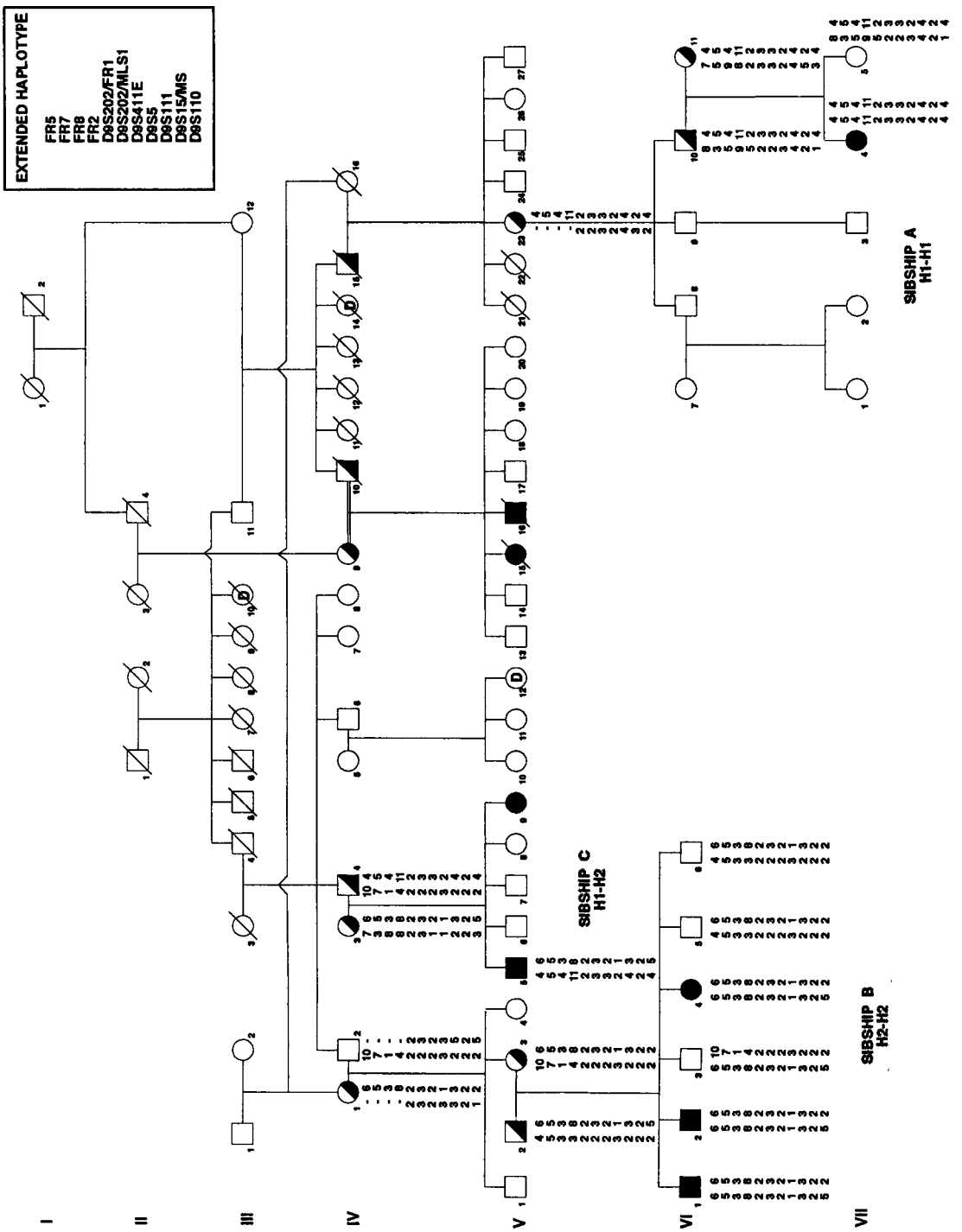

Fig. 1. Pedigree from the southeast of Spain.