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Global distribution of Fatal familial insomnia: founder or recurrent mutations

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The mechanisms of geographic spread of hereditary disorders through predominantly founder effect or predominantly recurrent mutational events is not only of historic significance; it is important for understanding molecular mechanisms of disease spread and may ultimately influence the selection of methods for disease prevention. As reported in the recent issue of the Journal, Rodriguez-Martinez et al. [1] carried out a haplotype analysis of the *PRNP* D178N genetic variant associated with Fatal familial insomnia (FFI) by using seven single nucleotide polymorphisms (SNPs) for identification of disease haplotypes in 38 cases (27 probands) that occurred in three European countries. The study reports two founder FFI haplotypes. All Spanish cases and one family from the Tuscany region in Italy share a common haplotype, and all nine German patients and an Italian family from Veneto region share the second haplotype. The likelihood *G* goodness-of-fit test shows a difference in haplotype frequency distribution between Spanish FFI cases and Spanish controls. Based on these results, the authors conclude that two independent ancient *PRNP* D178N mutational events are responsible for most of the current FFI cases in Europe.

We find a number of serious issues related to the methodology and data interpretation that the authors used for drawing their conclusions. The *G* test merely evaluates a general hypothesis of whether observed haplotype frequency among patients deviates from the frequency in controls. The omnibus nature of the *G* test does not allow evaluating other scenarios like the presence of two or more founder mutations in the FFI patients. This lack of specificity in determining the D178N-carrying chromosomes is especially troubling because the haplotypes identified in this study are common in the background population (17% and 43%), while FFI is a rare disease.

The seven SNPs selected by Rodriguez-Martinez et al. only yield very limited amount of information as a haplotyping unit. The haplotype diversity value of these seven SNPs is 0.75 (calculated from their Table 3), which is equivalent to only one microsatellite marker. The authors rightfully indicate that SNPs have inherent advantage over microsatellites as a methodology for determining ancient founder effects (they are more stable, and a large number of SNPs are available). But, this argument is valid only when SNPs and haplotypes are carefully selected to represent a genome being inherited. A good illustration of such approach is a recent study by Stacey et al. [2], in which the breast cancer risk seven-SNP haplotype frequency was 53 of 53 among the *BARD1* C557S carriers, while it was 0 of 1,197 in controls.

In our view, Rodriguez-Martinez et al. failed to provide conclusive evidence to support the hypothesis that only two founder haplotypes are associated with all known FFI cases in the European populations. Therefore, D178N should be considered a predominantly recurrent mutation, as previously concluded based on microsatellite testing [3], until valid data are

obtained to conclude otherwise. Ancestral haplotype analysis based on SNPs is superior to micro-satellites, but to use all advantages of SNP-based analysis, the generated haplotype should represent the uniqueness of the founder disease-associated chromosome.

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