

Linkage Disequilibrium Mapping and Parkinson's Disease

Several investigators (1) have questioned the suggestion made by Polymeropoulos *et al.* (2) that a single nonsynonymous mutation changing G to A at position 209 in the α -synuclein gene, labeled G209A (an Ala53thr substitution), found in association with Parkinson's disease (PD) in four apparently unrelated Italian and Greek families, may be a cause of the disease. Lynch *et al.* proposed instead that the G209A mutation might be a neutral variant in linkage disequilibrium (LD) with another, causative, mutation. We show that the recently developed theory of LD mapping (3, 4) can be used to quantitatively assess Lynch's suggestion. LD mapping uses the number, i , of recombinants (affected individuals carrying a marker other than the one found associated with the disease) in a sample of n

chromosomes from affected individuals to estimate the recombination rate, c , between a presumptive disease locus and a linked marker. Several methods have been proposed to estimate c and to provide a confidence interval for that estimate (3, 4). For the data provided by Polymeropoulos *et al.* (2), $i = 0$ and $n = 4$ (each of the four affected families contributes one chromosome) and all available methods would choose the best estimate of c to be 0, meaning that G209A is the disease-causing mutation. The likelihood at different values of c relative to that at $c = 0$ indicates the recombination (MAP) distances on either side of the marker that could be reasonably excluded as possible locations for the putative mutation (5). To illustrate this result, we have applied a method that we developed for LD mapping to these data (2). Our method accounts for several demographic factors that might influence levels of disequilibrium, including population growth, genealogical associations, and sampling effects (4). The method provides the likelihood of the observed haplotype data for a given MAP distance c (the likelihood also depends on several demographic parameters). We found that, for these data, likelihoods were relatively insensitive to values of demographic parameters other than the population growth rate, r , in the recent past (5). The change in likelihood as a function of MAP distance can be determined (Fig. 1) for several different growth rates. Our results show that the relative probability of the haplotypes found in the sample described by Polymeropoulos *et al.*, given that the PD-causative mutation is separated from the G209A mutation by a MAP distance of $c > 0.001$ (in units of

percentage of recombinants per meiotic event, or Cm/100), is less than 0.05 (a difference in log likelihood of -3) if the population growth rate has been less than about 0.01, which is likely to have been the case. We conclude from our analysis that, if G209A is not the PD-causative mutation, then the causative mutation can reasonably be expected to reside at a MAP distance of no more than about $c = 0.001$ from the G209A mutation (roughly 100 KB, assuming 1 MB = 1 Cm) and is probably much closer.

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2. M. H. Polymeropoulos *et al.*, *ibid.* **276**, 2045 (1997).
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5. The program Disequilibrium Mapping Using Likelihood (DMLE) was used to perform the analysis and may be obtained on the Web at <http://mw511.biol.berkeley.edu/homepage.html>. A sample of 152 sequences of the α -synuclein gene from unrelated individuals living in southern Italy were examined as controls in the analysis of Polymeropoulos *et al.*, and none of these samples contained the G209A mutation. The best estimate of the frequency of G209A among normal (non-PD) chromosomes based on this sample is $p = 0$. The fraction of disease chromosomes sampled, f , is unknown for these data, and was varied from 0.001 to 0.00001, with little effect on the likelihood. The time of origin of the G209A mutation was assumed to be the time at which population growth began and was estimated as $t = (1/r)\log(N)$, where N is the current population size (assumed for our analyses to be 3×10^8).

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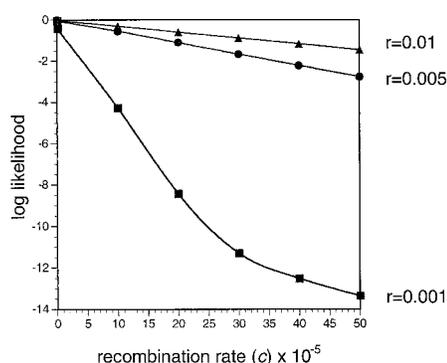


Fig. 1. Calculation of the log likelihood with use of data provided by Polymeropoulos *et al.* (2). We assumed a recombination rate of c between the PD-causing mutation and the G209A mutation in the α -synuclein gene and an exponential growth rate of the population. Three possible population growth rates are shown as $r = 0.01$ (Δ), $r = 0.005$ (\bullet), and $r = 0.001$ (\blacksquare).