and large familial correlations (as reflected by $h^2_{pg}$, which is as large as .6), our QTL fine-mapping approach not only remains powerful but also is valid and robust (fig. 1). Under the parameters simulated, the correlation between full sibs is .36, and that between a parent and a child is .27, when $h^2_{pg} = .5$ (plot *B* in fig. 1). Finite population sizes and familial correlations may lower the power of our QTL fine-mapping approach, especially when the marker is extremely close (<0.2 cM) to the true QTL position. However, the effect is very small. In particular, when the distance of the peak from the true QTL position is >0.5 cM, our power of QTL fine mapping is little affected. Recall that the purpose of our QTL fine-mapping approach is to narrow a large genomic region found in regular linkage analyses to a small region of ~1 cM, for further physical mapping to clone the QTL. With finite population sizes and familial correlations, our approach can have >95% probability to correctly position the QTL to a region <0.8 cM (fig. 1).

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## Reply to Deng and Chen

*To the Editor:*

The simulations done by Deng and Chen (2000), in response to my letter (Terwilliger 2000), are completely consistent with one of the points that I was trying to make. The pointwise mean and variance of the distribution of the test statistics are slightly inflated in extreme samples from small populations, so that, when such analyses are performed over much larger genomic regions, as in a genome scan, these seemingly minor pointwise effects can be dramatic. This is the real danger in such studies, which could lead to a potential sea of false positives in the literature, swamping the likely dearth of true-positive findings (see Weiss and Terwilliger, in press). The effects of "extreme sampling" are going to be much greater when the frequency of the phenotype is <10% (which is very common for a disease phenotype) and/or the effective population size is smaller (e.g., because of rapid population expansion and/or more-extreme isolation), as seen in the schizophrenia study by Hovatta et al. (1999). But, even under this "best-case scenario," Deng and Chen showed that there is an inflation of mean and variance of their statistics under $H_0$, even for $P \leqslant .05$, and, when one gets closer to the critical values needed in a genomewide sense (which must be more, not less, strict than those used in linkage analysis—$P < .0001$), the inflation must be larger still (also see Terwilliger and Göring 2000 and Terwilliger, in press). Furthermore, under the model that I described, the familial correlations in phenotype could have absolutely nothing to do with genetic factors at all (like "ability to speak Finnish" in a sample of Americans); yet the same problems would result, because familial phenotypes correlate with familial substrata of the population, leading to potentially increased rates of false evidence of both Hardy-Weinberg and linkage disequilibrium, compared with what is seen in random samples from the whole population.

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## Interpretation of Linkage Data for a Huntington-Like Disorder Mapping to 4p15.3

*To The Editor:*

Kambouris et al. (2000) report on the mapping of a neurodegenerative disorder on the basis of a sibship of 10 individuals whose parents are first cousins. Using a model of autosomal recessive inheritance, linkage analysis detects a maximum two-point LOD score ($Z_{max}$) of 3.03 at recombination fraction ($\theta$) 0.

The authors of the report postulate the genetic interval as a 7-cM region bounded by *D4S2366* and *D4S2983,* because all affected individuals are homozygous for the two markers (*D4S431* and *D4S394*) in between. Figure 1 in their article demonstrates a haplotype analysis in which the parents (III:2 and III:3), although first cousins, share very few alleles in the putative linked region.

First, the marker order presented in the report's figure 2*b* contradicts that presented in its haplotype analysis (fig. 1) and in the multipoint analysis (fig. 2*a*). The Marshfield sex-averaged linkage map places *D4S2366* between *D4S431* and *D4S394*. The haplotype and multipoint analyses place *D4S2366* centromeric to *D4S431* and *D4S394*. Since the parents share no alleles for *D4S2366,* interposing *D4S2366* between *D4S431* and *D4S394* would abolish this region of putative homozygosity by descent among the affected individuals. It appears more likely that it is by chance alone that the two parents share a "2" allele for *D4S431* and a "1" allele for *D4S394*. For example, the Foundation Jean Dausset CEPH genotype database reveals that the most common allele (205 bp) for *D4S394* has a frequency of 41%. Thus, if allele 1 for *D4S394* in the report's figure 1 is the 205-bp allele, the chances are 41% that parent III:2 inherited the 1 allele from the unrelated parent (II:1). Without genotype data for the parents and/or siblings of III:2 and III:3, identity by descent cannot be assumed.

Kambouris et al. make the assumption that the disorder is recessive, apparently because of the consanguinity in the family. Although they report $Z_{max} = 3.03$ at $\theta = 0$, under the assumption of 50% penetrance, the two-point LOD scores were likely calculated under a model of 100% penetrance. The two-point LOD scores would be expected to be lower under a model of 50% penetrance (two-point LOD score 2.7 at $\theta = 0$ for the four fully linked markers). The data could also support a model of autosomal dominance with reduced penetrance with the disorder segregating with the red haplotype, if the disease is not penetrant in parent III:2 and individual IV:8. The same argument could be made for parent III:3 and individual IV:10 and the purple haplotype. Testing a dominant model assuming 90% penetrance demonstrated a $Z_{max}$ of 1.94 at $\theta = 0$, with marker *D4S412* (data not shown).

Even if it were assumed that the mode of inheritance is truly autosomal recessive, homozygous genotypes among the affected individuals are not absolutely required. If the linkage to this region is true, and if the red and purple haplotypes contain noncomplementing mutated alleles, the genetic interval would actually be defined by the telomeric recombination event in IV:2 and the centromeric recombination events in IV:4—that is, by *D4S3023* and *D4S1599,* defining a nonrecombinant region of 15 cM.

Finally, Kambouris et al. note that only chromosome 4 markers were genotyped. Testing markers at the already mapped locus on chromosome 20, for a similar Huntington-like disorder, would certainly seem pertinent. A two-point LOD score of 3.3 (not 3.0) is the generally accepted criterion for a 5% significance level (Lander and Schork 1994). A complete genome screen may well reveal another locus in which the parents are heterozygous for a common haplotype with a more convincing region of homozygosity.

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