

Complex trait genetics: new methods yield a result for essential hypertension.

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Editorial

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Like many common maladies of middle age to late life, hypertension is a complex trait (1), which may encompass multiple syndromes with both hereditary and environmental determinants (2); even its heredity is likely to be polygenic. While parametric LOD-score¹ linkage and subsequent positional cloning have identified disease genes for such Mendelian traits as cystic fibrosis or Huntington's disease, and even for two unusual autosomal dominant forms of hypertension (3), the parametric LOD-score method may not be readily applicable to traits whose mode of inheritance is unknown, variable, or poorly understood.

The current report by Wu et al. appearing in this issue of *The Journal* (4) illustrates methodologic advances toward deciphering genetic origins of complex traits such as hypertension:

Model-free (or nonparametric) linkage. In contrast to parametric LOD-score linkage, which requires precise specification of the mode of trait inheritance, model-free methods rely only on allele sharing by first-degree relatives: if allelic variation at a locus plays a role in determination of a phenotype, then phenotypically similar relatives will share alleles at that locus more often than predicted by chance (1). In the study by Wu et al. (reference 4, see Fig. 3), squared trait difference in a quantitative phenotype (systolic blood pressure) between siblings was viewed as a function of number of alleles shared at the lipoprotein lipase (LPL) locus; a significant negative regression between allele sharing and trait difference squared constitutes linkage (or cosegregation) (5). Such methods raise statistical power issues: since many areas of the genome might be searched for cosegregation, one must correct for the possibility of multiple comparisons; indeed, some have argued that an appropriate significance level for definite nonparametric linkage be set as stringently as $P < 2.2 \times 10^{-5}$ (6). However, the appropriate level of stringency for nonparametric linkage in humans has not yet reached consensus.

"Candidate" genes (or loci). The human genome is vast, comprising ~ 3 billion DNA basepairs and containing > 50,000 genes (functional transcription units). Although genome-wide searches have found novel linkages in human complex traits (7), comprehensive searches remain labor-intensive and time-consuming; hence, a shrewd initial linkage strategy may be to focus on logical candidate loci whose allelic variation might reasonably be expected to influence the trait in question. Because hypertension, obesity, dyslipidemia, and insulin resistance frequently coexist (8), Wu et al. (4) examined the LPL locus for linkage to blood pressure. However, since the statistical confidence interval for linkage is characteristically distributed over a broad chromosomal region (reference 4, see Fig.

2), other nearby loci might be responsible for the observed blood pressure linkage.

Highly polymorphic microsatellite (simple sequence repeat) marker alleles. A practical marker locus must be polymorphic (or diverse) in alleles; indeed, the ideal marker is so polymorphic that each individual in a sibship or family is a heterozygote at that locus. Traditional RFLPs have few alleles and consequently low heterozygosity; in addition, they require substantial amounts of genomic DNA (~ 10 µg each). Weber and May (9) reported a new class of genomic polymorphisms: simple sequence repeats (example: the dinucleotide repeat CACACACA . . .), present in loci widely and abundantly dispersed in mammalian genomes, in which variation in repeat length creates substantial polymorphism. When specific DNA sequences flanking these repeats are exploited by PCR primers, locus specificity is coupled to length polymorphism, creating the most powerful genetic markers yet developed. Dense genetic maps of such marker loci are now available (10). An additional advantage of such PCR-scored polymorphisms is reduced genomic DNA requirement (~ 100 ng each). Typing parental DNA augments the power of nonparametric sibling linkage studies, since the origin (or descent) of each allele at a locus can be ascertained; hence, common alleles (frequent in the population), which might be identical in electrophoretic size (or "identical by state") in a sibship, can be verified to derive from a common ancestor (and thus be "identical by descent")(1).

The LPL locus on chromosome 8p22 becomes the third locus with documented (nonparametric) linkage to common variations in human blood pressure, others being the angiotensinogen locus on chromosome 1q42-q43 (11) and a marker locus on chromosome 1p36 with suggestive linkage (5).

Genetic studies, such as that of Wu et al. (4), have the compelling potential to slice through such "Gordian knots" as cause-or-effect relationships in complex traits with several phenotypic features. The frequent concordance of dyslipidemia, insulin resistance, obesity, and hypertension represents such a difficult cause-or-effect riddle. Unlike a phenotype, somatic cell genomic DNA sequence is, for most practical purposes, invariant in an individual after conception. If mutations in the LPL locus itself are ultimately found to cosegregate with blood pressure, then variations (either qualitative or quantitative) in LPL might prove to have some etiologic primacy in syndromes of combined dyslipidemia and hypertension.

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1. LOD stands for log[base 10] of the odds ratio for linkage. For example, a LOD score = 3 indicates a 1,000/1 odds ratio in favor of linkage.

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