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Perspectives

Anecdotal, Historical And Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

LODs Past and Present

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INFORMATION on linkage in the human is accumulated as a succession of samples, each of which may be small relative to the amount of data required to detect linkage. Analysis within a sample of pedigrees may be complex, with untested individuals, incomplete penetrance, and multiple loci. Despite these obstacles, several hundred disease loci have been mapped, in many cases with sufficient accuracy to permit positional cloning of a gene whose product was unknown. Now polygenic disease is being attacked with some success in maps that include hundreds of markers per chromosome and that pave the way for sequencing large parts of the genome. These developments testify to the power of intellectual curiosity to overcome intractable problems and may rank among the most significant applications of genetics to human welfare.

Linkage before LODs: FELIX BERNSTEIN was one of the pioneers in what is now called genetic epidemiology (CROW 1993). He is perhaps best known for his analysis of the *ABO* locus and bioassay of racial admixture, but he was also the first to realize that linkage could be detected in human pedigrees by taking the product of frequencies that must be in coupling or repulsion, whatever the phase of linkage (BERNSTEIN 1931). Various modifications of this method were made by WIENER (1932), HOGBEN (1934), and HALDANE (1934), but they were superseded by the maximum likelihood u scores of FISHER (1935) and FINNEY (1940). Although this elegant method is fully efficient in the limit for loose linkage, it has several disadvantages. Only the asymptotic distribution is known, but many linkage samples are small. FISHER's scores are difficult to compute except in simple two-generation cases and do not accommodate matings of known phase. They are not efficient for close linkage and do not give a good estimate of the recombination fraction. Finally, insufficient attention was paid to the low prior probability that two random loci are linked, which implies that a conservative significance level must be used to provide reasonable assurance that a statistically significant linkage is real. For these reasons the u-score approach was abandoned in the fifties.

Another approach was pioneered by PENROSE (1935) for sib pairs with unspecified parents. This did not become popular in the search for major loci because it neglects information in the phenotypes of parents and relatives, does not give an estimate of recombination, and is unreliable when multiple pairs are drawn from the same sibship. However, sib-pair methods have recently been revived for complex inheritance and for disease of late onset where the parents are rarely available.

In this early period only three autosomal linkages were discovered: between the Lutheran blood group (*LU*) and ABH secretion (*SE*) by MOHR (1951); one form of ellipticytosis (*EL1*) and the Rhesus blood group (*RH*) by LAWLER (1954); and the nail patella syndrome (*NPS1*) with the *ABO* blood group (RENWICK and LAWLER 1955; RENWICK and SCHULZE 1965). All these markers had high penetrance, precise diagnosis, and good survival, so that large pedigrees could be collected. Blood groups were markers of choice, despite dominance of antigenic factors. The next period would be characterized by markers with codominance and by analysis based on calculated probabilities.

LODs before linkage: Since its introduction by NEYMAN and PEARSON (1928), the likelihood ratio has been accepted as the optimal basis for statistical decisions. It is defined on the ith sample S_i as $\lambda_i = P(S_i|H_1)/P(S_i|H_0)$, where H_0 and H_1 are alternative hypotheses. The likelihood ratio is to statistics as the microscope is to cytogenetics. Because probabilities for independent samples are multiplicative and a likelihood ratio may be called *odds*, it was natural for BARNARD (1949) to introduce the logarithm of the likelihood ratio and to call this quantity a LOD (logarithms of odds). Therefore, if $z_i = \log \lambda_i$ is the LOD for the ith sample, then the LOD for a set of independent samples is $Z = \Sigma_{i=1}^{n} z_i$. In this formulation of LODs, the probabilities are conditional and the prior probabilities are unspecified. BARNARD was also interested in "average LODs" in which $\Pi\lambda_i$, the product of the λ_i, is integrated over a prior distribution under H_1 to give a weighted mean Λ that loses the convenience of additivity but appeals to Bayesians (SMITH 1959). In genetics the term "LOD" invariably refers to the z_i, which are often called *LOD*

scores to contrast them with other scoring procedures. They have three useful properties. First, for any prespecified alternative H_1 they give a conservative estimate of significance,

$$P(Z > \log A | H_0 < 1/A). \quad (1)$$

Second, if common logarithms are used (as they are by convention in genetics) and if H_1 differs from H_0 by m efficiently estimated parameters, then in the limit for large samples under H_0

$$(2 \ln 10) Z = \chi^2 \quad (\text{d.f.} = m) \quad (2)$$

(NEYMAN and PEARSON 1928). Third, if H_0 and H_1 are jointly exhaustive and mutually exclusive and if the prior distribution is correctly specified, the posterior probability of H_1 is

$$P(H_1 | S) = \frac{\Lambda[P(H_1)/P(H_0)]}{1 + \Lambda[P(H_1)/P(H_0)]} \quad (3)$$

where $P(H_1)/P(H_0)$ is called the prior (or "forward") odds (BARNARD 1949).

These three properties have led to different applications of LODs. One of these was a consequence of World War II, during which a refugee from the Nazis undertook to optimize the statistical procedure by which a consignment of bombs was selected or rejected by test explosion of a random sample. If the sample were too large, too few bombs would be left for the war. If the sample were too small, men and planes would be wasted on duds. This led ABRAHAM WALD to sequential analysis, whereby two hypotheses specifying acceptable and nonacceptable parameters are discriminated with tolerable errors by the smallest mean number of observations. Military secrecy delayed publication of his work until 1947 (WALD 1947), the year in which HALDANE and SMITH (1947) first applied LODs to analysis of linkage.

Linkage before DNA: Two developments in the fifties accelerated linkage mapping. The first was the application of starch gel electrophoresis to detect genetic variation in proteins (SMITHIES 1955, 1995). Many of these systems were polymorphic, and codominance of alleles was the rule. The laboratories in London and Copenhagen that had initially dominated studies of human linkage adopted isozymes and continued to lead the field. The Galton Laboratory had been headed by R. A. FISHER, who saw the promise of blood groups as linkage markers (FISHER 1935). He was succeeded by LIONEL PENROSE, with J. B. S. HALDANE as Weldon Professor. Younger members of the Galton Laboratory included C. A. B. SMITH, SYLVIA LAWLER, JAMES RENWICK, and later PETER COOK and SUSAN POVEY, all of whom shared enthusiasm for linkage. Their close collaborators included R. R. RACE and RUTH SANGER in blood groups and PATRICIA JACOBS in cytogenetics. ELIZABETH ROBSON provided a bridge between these enthusiasts and the isozyme research of HARRY HARRIS, the next Galton professor, whom she succeeded.

JAN MOHR (1951) at the Institute for Human Genetics in Copenhagen was the discoverer of the first autosomal linkage, of the Lutheran blood group to the Lewis blood group, that was subsequently shown to be an interaction between the *LE* and *SE* loci (the latter being the marker he detected). German and Scandinavian law on child support favors genetic markers that can be used in paternity cases, and so there was a strong tradition of blood grouping and later isozyme typing in Denmark. The head of the Institute, TAGE KEMP, was a pioneer in human population genetics, and the institute provided a stable base for the long-term linkage studies that MOHR undertook after he succeeded KEMP. It is unlikely that the patience required for such research with no immediate payoff (like the work of WATSON and CRICK at the same time) would be supported by research grants today.

The increasing volume of linkage data demanded a method of analysis that would escape the limitations of *u* scores, of which I first became aware when confronted by pedigrees of Pelger-Huet anomaly and elliptocytosis in Japan (MORTON *et al.* 1954; FUJII *et al.* 1955) and to which I was attracted as my interests shifted from Drosophila to human genetics. During this time and my years at the University of Wisconsin, JAMES CROW was a fount of encouragement and stimulation. One of my colleagues in the Atomic Bomb Casualty Commission was JAMES RENWICK, seconded from the medical corps that served the Commonwealth army of occupation and their troops at war in Korea. On our return from Japan we became more interested in linkage, leading RENWICK to join the Galton Laboratory and me to write a Ph.D. thesis on LODs (MORTON 1955), at that time a subject of great interest among statisticians because of WALD's (1947) book on sequential analysis, and among human geneticists because of a paper by HALDANE and SMITH (1947) on linkage of colorblindness and hemophilia. The appeal of sequential analysis was its simplicity and efficiency, conjoined with the fact that linkage detection often depended on a succession of samples, after each of which linkage could be accepted, rejected, or subjected to further test. This corresponded exactly with a sequential sampling rule to accept H_1 for $Z > \log A$ and to accept H_0 for $Z < \log B$, where H_1 specifies a probability in terms of recombination frequency $\theta < 0.5$ and H_0 assumes no linkage ($\theta = 0.5$). Increasing the size of a sample makes the test more conservative and the average sample size larger. For simplicity, WALD developed his theory in terms of a preassigned value of θ, and for many years some statisticians assumed that his bound on the type I error applied to every value of θ except the one that maximizes the likelihood (CHOTAI 1984), but this misunderstanding has been laid to rest (COLLINS and MORTON 1991). The first paper derived a number of LODs for two-generation families and tabulated the *z* scores (MORTON 1955). In a short time LODs were used to

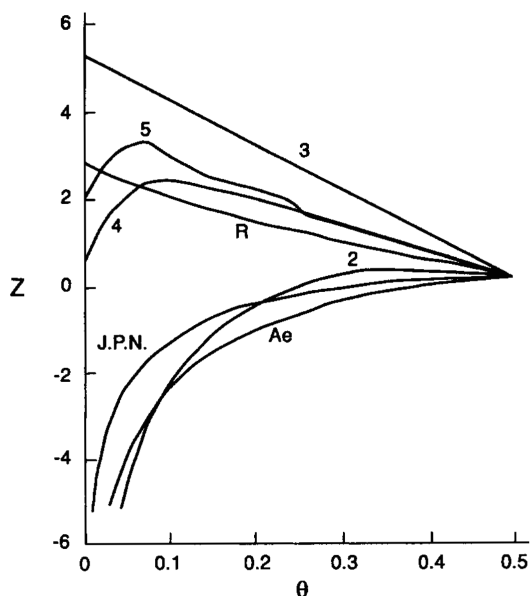

FIGURE 1.—LODs for elliptocytosis and *RH*. Pedigrees 3, 4, 5, and R are *EL1*, closely linked to *RH*. Pedigrees 2, Ae and J.P.N. are unlinked *EL2* and *EL3*.

disprove earlier claims of autosomal and partial sex linkage, the two reports from the Galton Laboratory were confirmed (MORTON 1957), and elliptocytosis was shown to involve dominant alleles at different loci in different pedigrees (MORTON 1956). One locus, close to *RH*, determines the protein band 4.1, while the others are α spectrin (*SPTA1*) and β spectrin (*SPTB*). These proteins are essential for the integrity of the erythrocyte membrane. Linkage heterogeneity of this type due to one of several mechanisms is common for human disease. To demonstrate the first example (Figure 1), I used the chi-square test derived from Equation 2, $(2 \ln 10)(\Sigma_{n=1}^{m} \hat{z}_i - \hat{Z})$, where $\hat{z}_i$ is the maximum LOD in the *i*th sample, $\hat{Z}$ is the maximum LOD overall, and there are $m - 1$ d.f. The α test of C. A. B. SMITH (1963) is more powerful. It takes the likelihood ratio as

$$\lambda_i = \frac{\alpha P(S_i|H_1) + (1 - \alpha)P(S_i|H_0)}{P(S_i|H_0)}$$
$$= \alpha P(S_i|H_1)/P(S_i|H_0) + 1 - \alpha \quad (4)$$

where α is the proportion of families linked to the marker. Because θ and α are both estimated, it is necessary to make some allowance when testing linkage for the extra degree of freedom (LANDER and LINCOLN 1988; RISCH 1989).

There is nothing in likelihood ratio theory that mandates a particular choice of logarithms. Following SMITH (1953), I used common logarithms (base 10) that are now universally accepted. Some mathematicians have expressed a preference for natural logarithms (base e), but the advantage of a factor of 2 over a factor of 4.6 is too tenuous to counterbalance the confusion that such a change would cause in a practice that has lasted for forty years.

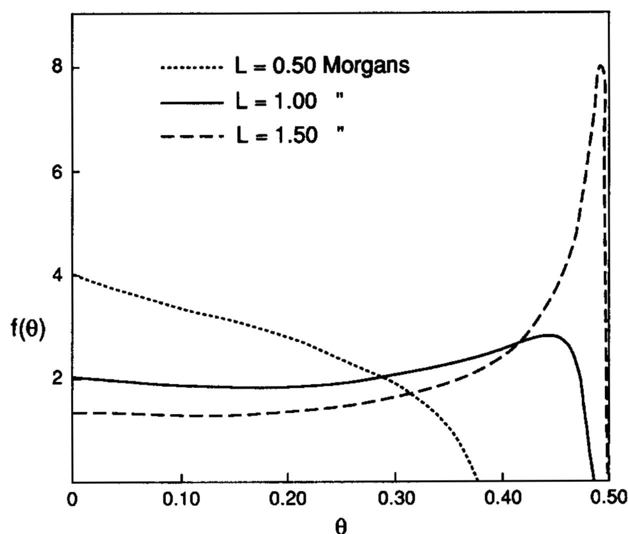

FIGURE 2.—The distribution of the recombinant fraction θ for chromosomes of length *L*.

Early studies presented a standard LOD table with values of θ from 0 to 0.5, from which the likelihood could be recovered. As the volume of data grew this became impractical, and today it is usual to report only the maximum likelihood estimate θ and corresponding LOD if θ ≠ 0.5, but otherwise a smaller value (usually 0.3), so that the equivalent number of meioses and recombinants can be estimated. Thus the distinction between sequential and nonsequential tests has diminished but may be reinforced for polygenic traits, where one sample is usually insufficient to assert linkage.

SMITH (1954) and RENWICK (1968) were the first to recognize the importance of sex differences in recombination, which are greater in the human than in the mouse, and to develop methods to factor LODs by sex. Because of their work, it is now usual and should be mandatory to present sex-specific LODs, so that maps may be constructed for both sexes and their differences studied in relation to condensation, coiling, protein binding, and other factors. Sex differences affect risks in genetic counseling and optimal analysis for high-resolution mapping.

The Galton Laboratory has maintained a strong interest in Bayesian statistics, the impact of which has been equivocal. HALDANE and SMITH (1947) suggested "chiefly from a comparison with the known linkage values of Drosophila" that the recombination fraction for linked genes has a nearly uniform distribution from 0 to 0.5. No assumption was or need be made about the distribution on the physical map, but it is now known that regions of high recombination tend to have a high density of CpG islands. Analytic treatment shows that the distribution is only roughly uniform, with an excess of small values of θ if the chromosome is small (Figure 2). At a time when there were no data in the human and the chromosome number was thought to be 48, I suggested that the prior probability of synteny for two random

autosomal loci was about 0.05 (MORTON 1955), and subsequent data refined this to 0.054 (RENWICK 1969). With the uniform approximation or a more exact one, the average odds Λ may be calculated, leading to inference about the posterior probability of linkage that appeals strongly to Bayesians. Alternatively, if $\rho(\theta)$ is the power of the test when the true recombination value is θ and $g(\theta)$ is the prior probability of θ given synteny, then $\int_0^{1/2} g(\theta)\rho(\theta)d\theta$ is the expected value of Λ, which can be used to select a significance level that is "reasonable" in the sense that a large proportion of statistically significant results will be true (MORTON 1955). The approach is more appealing to frequentists, who distrust Bayesian assumptions. For two random loci a value of $Z > 3$ and therefore $\alpha < 0.001$ is appropriate if sample size is adequate to detect close linkage. However, in smaller samples (such as most single pedigrees) this condition is not met (SKOLNICK *et al.* 1984; RISCH 1991), and therefore the Bayesian calculation may be favored. However, if there is linkage in some families, the prior probability does not correspond to a uniform distribution but more closely to Equation 4, and so the calculations are error-prone (GÉNIN *et al.* 1995). Although R. A. FISHER thought he had annihilated Bayesians, he was wrong. They continue to be dissatisfied with significance tests and to defend some formulation of posterior probability that may be useful in some cases. There is even a computer program (SIGMA) that attempts to construct maps from subjective probabilities, exploding the linear chromosome into a tree diagram that purports to give subjective order free of genetic and physical distances (BISHOP 1994; POVEY *et al.* 1994).

The success of LOD scores has obscured the seminal paper of C. A. B. SMITH (1953), which was largely concerned with probabilities for sib pairs and extension of FISHER's scores to pedigrees, with one section devoted to autozygosity mapping. LODs were introduced and their advantages were noted, but application was limited to matings of known phase and to trios and pairs of sibs with untested parents for the special case of a rare gene and a codominant marker. He was concerned about the computation of LODs, a problem of the utmost seriousness in Britain from 1950 to 1975 because of the protection afforded to computers manufactured in the United Kingdom. Unfortunately, domestic computers seldom worked and had poor compilers. A generation of researchers was sacrificed to protectionism, and scientific computing in Britain still suffers from the check to confidence and originality suffered in that period. Under this stimulus, RENWICK did his linkage computing in Baltimore (RENWICK and BOLLING 1967), and JOHN EDWARDS turned to New York (FALK and EDWARDS 1970). The first portable computer program for computing LODs in general pedigrees (LIPED) was developed by OTT (1974).

By the end of the seventies gene mappers were accustomed to meet every two years at workshops. About 300 loci had been assigned to the human autosomes (HUMAN GENE MAPPING 1979), and there were LODs for about half of them. Linkage had been complemented by expression of a human protein in somatic cell hybrids and *in situ* hybridization of radioactive probes (RUDDLE *et al.* 1972), although these physical methods gave lower resolution. Linkage maps were constructed by multiple pairwise LODs, in the most favorable case spanning 13 loci (RAO *et al.* 1979). Integration of genetic and physical data was crude and largely subjective. A database of LODs had been published (KEATS 1981), but the database on physical assignment was a card index with no linkage data. The stage was set for an advance that would strain these resources to the breaking point.

The DNA revolution: SOUTHERN (1975) demonstrated that specific DNA sequences could be separated by gel electrophoresis. This soon led to use of restriction fragment length polymorphisms as linkage markers (SOLOMON and BODMER 1979; BOTSTEIN *et al.* 1980), succeeded by markers defined on the polymerase chain reaction (PCR). The Centre d'Etude du Polymorphisme Humain (CEPH) provided DNA from large families to international collaborators, and soon they had linkage data on thousands of markers (DAUSSET *et al.* 1990). Several multilocus computer programs were developed to handle these samples and pedigrees of disease genes, all based on the assumption of no interference or typing errors (OTT 1991). Despite continued improvement, these programs cannot cope with strong interference, substantial error frequencies, dense maps, and innumerable datasets that can be summarized by LODs. It has been shown that multiple pairwise LODs give more accurate maps in the presence of typing errors (BUETOW 1991). The LODSOURCE database has been incorporated into a location database that includes locus content, clonal and other physical data, and can integrate all these sources into a summary map (MORTON *et al.* 1992), which the genome database (GDB) cannot do (PEARSON *et al.* 1991). In desperation, gene mappers have turned to consensus reports of single-chromosome workshops that practice electoral science. Therefore, the current standard of the Human Genome Initiative is a consensus map in which the position of each locus is supported by at least one member of a workshop, but the evidence (if any) on which this location is based is not accessible to other scientists. LODs provide a vehicle to summarize linkage data from unlimited numbers of pedigrees, formats, and data files.

Although linkage is not capable of high resolution, it is the best method to give connectivity to physical maps and to assign an approximate position to disease loci that can be refined by allelic disequilibrium and physical maps, prior to cloning and sequencing. Much of the information on linkage markers generated through disease mapping is neither published nor made public through Internet, but could be captured

through LODs, and locus-oriented multiple pairwise mapping can cope with thousands of loci per chromosome. There is no longer any motive to reconstruct the map by crude seriation or stepwise addition, nor to select by necessarily subjective criteria a small set of gold star loci for an index map. Instead, map integration must be used to improve dense but locally unreliable maps by reference to a location database that includes accumulated LODs as well as physical data. Only in this way can an enormously expensive mapping effort be used efficiently to characterize disease genes and to validate YAC and other contigs preparatory to sequencing.

An interesting recent development has been the resurrection of nonparametric sib-pair methods for polygenic inheritance, one of which is based on the asymptotic distribution (Equation 2) of a LOD for identity by descent (RISCH 1990; HOLMANS 1993). This and other nonparametric methods are robust to ascertainment bias (and therefore lend themselves to meta-analysis of multiple samples), but are less reliable than conventional LODs in small samples or with related sib pairs (COLLINS and MORTON 1995). Some investigators use weak significance levels to continue sampling, on the basis of their intuition that power is less than for major loci but the likely number of minor genes is great. The resultant error rate has not been determined, and the power of nonparametric methods against an appropriate genetic model is unknown.

Among genetic models the two-allele, two-locus model has seen greatest use, with a linked "major" locus and an unlinked "modifier" that is a surrogate for more complex inheritance (MORTON *et al.* 1992). Allelic association is represented by coupling frequencies: if c_i is the coupling frequency for the ith allele A_i with frequency p_i, then $p_i c_i$ is the frequency of haplotypes bearing A_i and an allele at the major locus for disease susceptibility, the total frequency of susceptibility alleles at that locus being $q = \Sigma p_i c_i$. Therefore, a single model tests both linkage and allelic association. To do this within the framework of statistical tests requires that Equations 1 and 2 be extended: if a genetic model specifies m nuisance parameters Ω_0 under H_0 describing gene frequencies and genotypic effects and $m + r$ parameters Ω_1 under H_1, and if the parameters are efficiently estimated under each hypothesis, then Equation 1 holds with $r = 1$, while Equation 2 holds for all r.

This approach and alternatives are being discussed vehemently, as is the optimal sampling strategy. The more the search for polygenes depends on replicate samples, the more closely it conforms to sequential sampling. The LODs that were proposed to detect linkage forty years ago, when the human gene map was only a dream, have proven their fitness to survive in a changed environment. It rests with alternatives to demonstrate equal viability.

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