

A Comparison of Three Affected-Sib-Pair Scoring Methods To Detect HLA-Linked Disease Susceptibility Genes

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Two widely used affected-sib-pair scoring procedures (the Green and Woodrow [1977] procedure, and the method of forming all possible affected-sib-pairs) are compared with a new method for their relative efficiency in detecting the presence of an HLA-linked disease susceptibility gene. Their relative performance is investigated by extensive computer simulations over a large number of disease transmission models. On the average, the new procedure appears to outperform the Green and Woodrow method and the "all-possible-pairs" method.

Key words: affected-sib-pairs, linkage detection, HLA, computer simulation

INTRODUCTION

Most HLA-associated diseases are transmitted in a non-Mendelian fashion. In many of these there exists evidence implicating the effect of a linked disease susceptibility (DS) locus, although the exact causal relationships are obscure. Since these diseases are non-Mendelian and often show variation in age-of-onset, traditional linkage analysis with large extended pedigrees is difficult and prone to erroneous inference if the transmission parameters are misspecified [Suarez and Van Eerdewegh, 1981]. Accordingly, a variety of sib-pair methods have been elaborated to detect the presence of DS loci [Green and Woodrow, 1977; Suarez, 1978; Suarez et al, 1978; Fishman et al, 1978].

Perhaps the simplest method is to disassemble multiplex sibships by forming all possible pairs of affected sibs. The distribution of shared HLA haplotypes is then inventoried and the sib-pairs are treated, for statistical purposes, as if they are independent. This may inflate the contribution of large multiplex sibships. However,

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it is conceivable that this practice of dismantling large multiplex sibships into all possible pairs may represent an efficient method for detecting the presence of a DS locus. Indeed, this speculation was recently heightened when an analysis of multiplex sibships, segregating for affective disorder [Suarez and Croughan, 1982], gave evidence for the presence of an HLA-linked susceptibility locus by the above method, but failed to adduce any convincing evidence by the method of Green and Woodrow [1977]. While subsequent analysis [Suarez and Reich, 1984] of an additional 15 multiplex sibships has failed to confirm the presence of an HLA-linked susceptibility locus—by either method—the discrepancy noted earlier remains intriguing.

Since the two procedures are equivalent for sibships that contain exactly one affected-sib-pair, the difference between the methods is due to the way larger multiplex sibships are scored. In this paper we offer a modification of the all-possible pairs procedure which is well suited to unusually large multiplex sibships. The method proposed here allows sibships of various sizes to be combined in forming the test statistic, while preserving computational simplicity so that no more than paper and pencil are required. In what follows, three scoring procedures—the original Green and Woodrow (GW) method, the method of forming all-possible-pairs (PAIRS) and the proposed weighted pairs (WP) modification [Suarez and Hodge, 1979]—are compared via computer simulation for a large number of transmission models.

MODELS AND METHODS

Sibship Statistics

The GW statistic [Green and Woodrow, 1977] is the number of haplotypes repeats at the marker locus among the S affected sibs in a sibship. Its expected value, under the null hypothesis (H_0) of no linkage ($\theta = 1/2$) between the marker and the DS loci, is $E(\text{GW}) = (2S - 4 + 2^{-S+2})$, while its variance is $\sigma^2(\text{GW}) = 2^{-S+2}(1 - 2^{-S+1})$. To compute the PAIRS statistic we form all $S(S-1)/2$ possible pairs of affected sibs, scoring each pair 2, 1, or 0 according to their identity by descent (IBD) status at the marker locus:

$$\text{PAIRS} = \sum_{\substack{i=1 \\ i < j}}^S \sum_{j=2}^S X_{ij},$$

where X_{ij} is the IBD score between the i^{th} and j^{th} sibs. Under H_0 , the X_{ij} 's are nonindependent, identically distributed, binomial $B(2, 1/2)$ random variables. The expected value of PAIRS is

$$E(\text{PAIRS}) = \sum_{i < j} \sum E(X_{ij}) = \frac{S(S-1)}{2}$$

and the variance is $\sigma^2(\text{PAIRS}) = S(S-1)/4$ (see Appendix). We note that, despite the fact that the $S(S-1)/2$ pairs are not statistically (nor genetically) independent, the variance and the mean of the random variable PAIRS are identical to those we would obtain had we used independent pairs. If a geometric representation of the IBD

configuration is used [Suarez et al, 1982], PAIRS is simply the number of lines connecting the S affected sibs.

The WP statistic is a modification of the PAIRS statistic [Suarez and Hodge, 1979]. The IBD configuration of a given family can be inferred from sib pair's IBD information if, for each parental side, the IBD is provided on the (S-1) sibs of a randomly chosen offspring. Rather than arbitrarily choosing one sib to be paired with the remaining sibs, we consider, in turn, each of the S affected sibs and compute the average IBD score of an offspring with his/her (S-1) sibs. Let I and S-I be the paternal side IBD partitioning of these S sibs; similarly, let J and S-J be the partitioning on the maternal side; then

$$WP = \frac{1}{S} (I(I-1) + (S-I)(S-I-1) + J(J-1) + (S-J)(S-J-1)) = \frac{2}{S} \times PAIRS.$$

The WP-statistic can also be interpreted as the IBD of a randomly chosen pair of sibs

$$\left(PAIRS \div \binom{S}{2} \right)$$

times the number of "independent" pairs, (S-1). The mean and variance of WP are easily derived from the mean and variance of the PAIRS random variable:

$$E(WP) = S-1 \text{ and } \sigma^2(WP) = \frac{S-1}{S}.$$

Combining the statistics computed on N different families, we generate the standardized random variables

$$Z_{GW} = \frac{\frac{\sum_k GW_k - \sum_k E(GW_k)}{k}}{\left(\frac{\sum_k \sigma^2(GW_k)}{k} \right)^{1/2}},$$

$$Z_{PAIRS} = \frac{\frac{\sum_k PAIRS_k - \sum_k E(PAIRS_k)}{k}}{\left(\frac{\sum_k \sigma^2(PAIRS_k)}{k} \right)^{1/2}}, \text{ and } Z_{WP} = \frac{\frac{\sum_k WP_k - \sum_k E(WP_k)}{k}}{\left(\frac{\sum_k \sigma^2(WP_k)}{k} \right)^{1/2}}.$$

Although the random variable PAIRS has a lattice distribution, we will not introduce a continuity correction for either PAIRS or WP, since the distance between successive

points with positive probability mass is not constant. For the sake of fairness, we have removed the continuity correction in GW, resulting in a statistic slightly more powerful than the one proposed by Green and Woodrow [1977]. We now appeal to the Central Limit Theorem, and consider Z_{GW} , Z_{PAIRS} , and Z_{WP} to be approximately normally distributed under the hypothesis H_0 of no linkage.

Major Locus Transmission of Disease Susceptibility

The genetic transmission of the disease phenotype was modeled by the generalized single major locus model. This model assumes that the disease susceptibility locus contains two alleles, A and a, with respective population frequencies of p and $q=(1-p)$. Each of the three genotypes, AA, Aa, and aa is allowed to be incompletely penetrant. Their respective penetrances are denoted as f_1 , f_2 , and f_3 . In the general model the f_i 's are allowed to assume any value between 0 and 1 [Suarez et al, 1976, 1977], although for the simulations reported here the penetrances were constrained such that $f_1 \leq f_2 \leq f_3$. To maintain comparability for simulations that involve different penetrance combinations, the gene frequency is fixed at

$$q = \frac{[(f_2 - f_1)^2 - (f_1 - 2f_2 + f_3)(f_1 - 0.1)]^{1/2} - f_2 + f_1}{f_1 - 2f_2 + f_3},$$

for $2f_2 \neq f_1 + f_3$, which guarantees that for all analyses the frequency of the disease phenotype in the population (ie, $p^2f_1 + 2pqf_2 + q^2f_3$) is held constant at 10%.

Disease Transmission With a Heritable Polygenic Component

For the generalized single major locus model, the sources of incomplete penetrance are nonfamilial and, accordingly, do not contribute to the covariances between relatives. In other words, the probability that an individual is affected depends only on his or her genotype, and not on parental phenotypes.

In the mixed model [Morton and MacLean, 1974; Lalouel and Morton, 1981], we allow for the variation within a genotype to be familial. Thus, if the liability distribution x (which denotes the underlying continuous scale determining disease status) is written as the sum of the effect of the major locus g and a residual component ζ , ie, $x = g + \zeta$, we have that ζ is correlated between relatives. The term ζ may be partitioned into polygenic and environmental components, and if there is an effect due to a shared rearing environment for sibs, the sib correlation (r_{oo}) and parent-offspring correlation (r_{po}) for ζ will differ. We will assume that the joint distribution of ζ 's between mates is uncorrelated, and that all marginals have mean 0 and variance 1.

Disease status is determined by a threshold value T , so that an individual is affected if his or her liability $x \geq T$, and unaffected otherwise. Letting g_1 , g_2 , and g_3 denote the mean liability of the genotypes AA, Aa, and aa, respectively, we may define T_i as $T - g_i$, $i = 1, 2, 3$. Then, an individual of genotype i is affected if his or her score on ζ is above T_i (since the score on x is then greater than $T_i + g_i = T$). If the penetrance for genotype i is f_i , then T_i may be calculated as that value for which the area to the right of T_i is f_i for the standard Gaussian distribution.

Simulation

In simulation studies, the distribution of sibship size is often modeled as either a Poisson or negative binomial process. However, unpublished analysis (Wette,

personal communication) of two large combined sets of normal controls reported by Mayo et al [1973] showed that a geometric distribution with its single parameter t gave the most parsimonious fit. For these data the maximum likelihood estimate of t is $\hat{t} = 1/\bar{y} = 0.4551$, where \bar{y} is the mean sibship size. Because the geometric distribution has no memory, it is convenient to use it in a simulation study of multiplex sibships where families that contain no children, or only a single child, are not of interest. Accordingly, the distribution of sibship sizes for families that contain at least two children ($m \geq 2$) is here modeled as a geometric with $t = 0.4551$, ie, $P(y=m) = t(1-t)^{m-2}$, $m = 2, 3, \dots$. An upper truncation above ten was subsequently enforced by rejecting families with more than ten children.

For each family, sibship size was determined as above. The distribution of disease phenotypes under each unique DS locus parameter combination g, f_i was then generated as follows. The genotype of the first parent at the DS locus was determined by consulting a random number generator whose distribution is uniform over the range 0 to 1. If the number selected was $\leq q$, then the first allele assigned was a , otherwise A is assigned. This process was repeated to complete the first parent's genotype. Next, the disease status of the parent was determined by again consulting the random number generator. If the generated number was $\leq f_i$, given that the parent has the i^{th} genotype, then the parent is taken to be affected. This three-step procedure was repeated to determine the genotype and phenotype of the second parent.

Since for practical purposes the HLA complex is completely informative with respect to linkage, we assign marker haplotypes such that each parent is uniquely heterozygous. Recombination between the DS locus and the marker was likewise determined by consulting the random number generator. Two recombination fractions (θ) were used in this study, namely, $\theta = 0$ and $\theta = 0.2$. When $\theta = 0$, recombination never takes place, and the DS locus is completely linked to the marker. At the alternative value of θ , recombination randomly takes place in 20% of meioses.

Once the parents were simulated, the offsprings' genotypes were generated according to Mendelian expectations, and their phenotypes were determined in the same manner as the parents' phenotypes.

For the mixed model, a vector of genotypes g was sampled as above. Next, a vector of observations ζ was sampled from a $(m + 2)$ multivariate normal distribution with a mean vector of 0's and a variance-cov matrix Σ ,

$$\Sigma = \begin{pmatrix} 1 & 0 & r_{po} & r_{po} & \dots & r_{po} \\ & 1 & r_{po} & r_{po} & \dots & r_{po} \\ & & 1 & r_{oo} & \dots & r_{oo} \\ & & & \dots & r_{oo} & \\ & & & & & 1 \end{pmatrix}$$

where the first two components correspond to the parents and the next m to their offspring. For each penetrance f_i , a threshold value T_i was defined as $T_i = \phi_c^{-1}(f_i)$, where ϕ_c is the complimentary distribution function of the standard normal random variable. That is, the probability of observing a value greater than T_i is f_i . Finally, for an individual with genotype k , if the value of ζ_k was greater than the corresponding T_k , then the individual was taken to be affected; otherwise the individual was unaffected. For the simulation reported here, the background correlation between

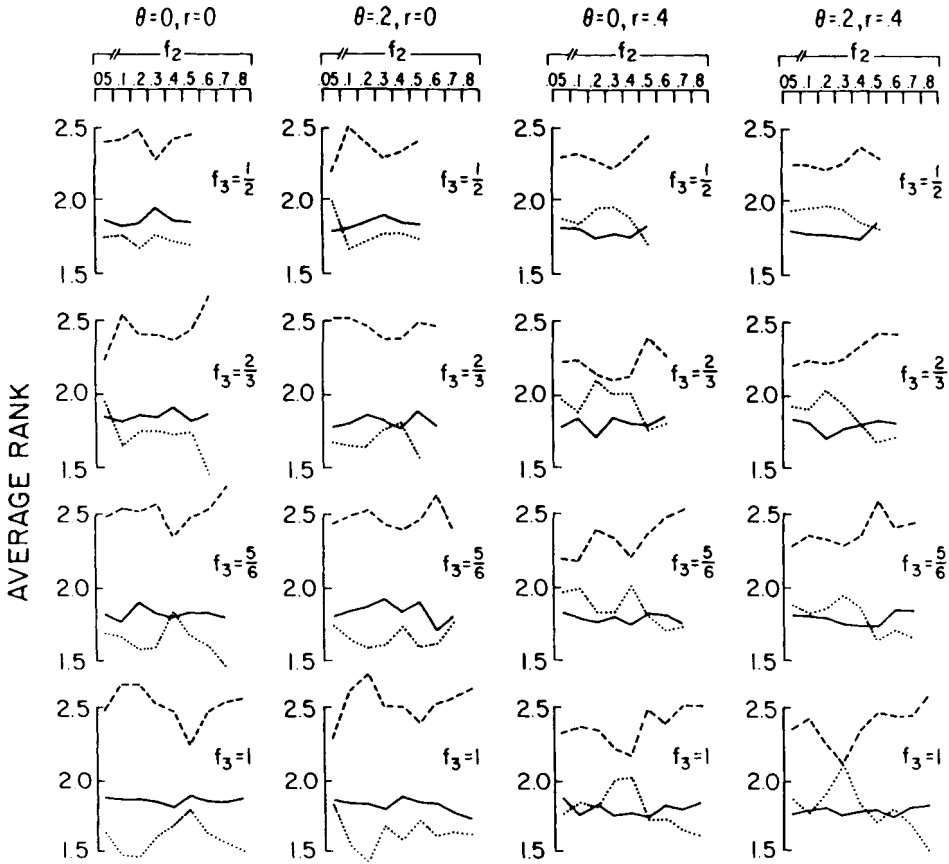


Fig. 1. Average finishing rank for three affected-sib-pair scoring procedures: GW (----), WP (—), and PAIRS (....). All simulations shown in these panels were generated with $f_1 = 0.05$, and 100 replications were taken for each penetrance (f_i), recombination (θ), and heritable background (r) combination.

parent and offspring was set equal to that between sibs. Two values of $r_{po} = r_{oo}$ were used. In half of the simulations the correlation was set to zero, thereby reducing the mixed model to the single major locus model. For the other half of the simulations, the correlation was set equal to 0.4, which represents a substantial heritable polygenic background.

Sequential Sampling

Families were randomly simulated and only those containing two or more affected sibs were retained for further analysis. We decided in advance that rather than fix the number of ascertained families for each computer run, sampling would continue until one of the three scoring methods achieved the predetermined significance level of $P \leq 0.005$ (ie, $Z \geq 2.576$). For each simulation, as one of the sib pair statistics reached or exceeded this critical level, we recorded the Z-scores for the remaining two methods and assigned ranks of 1, 2, or 3 according to finishing

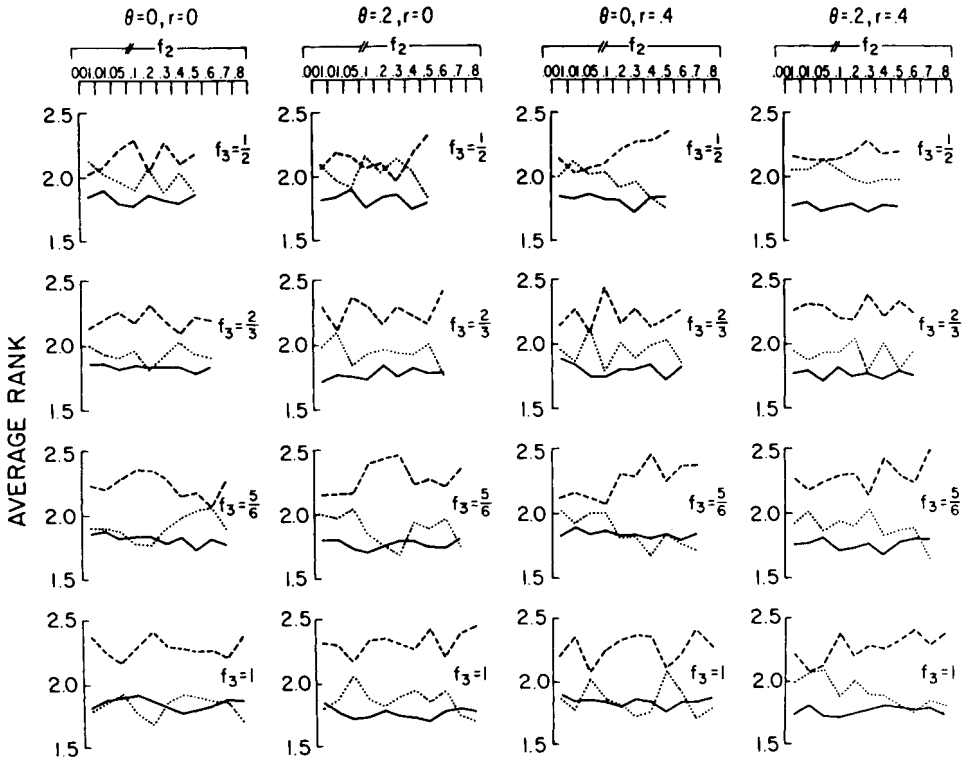


Fig. 2. Average finishing rank for three affected-sib-pair scoring procedures: GW (---), WP (—), and PAIRS (....) All simulations shown in these panels were generated with $f_1 = 0.001$, and 100 replications were taken for each penetrance (f_i), recombination (θ), and heritable background (r) combination.

position. Two-way ties were recorded by assigning a mean rank depending on whether the tie was for first or second place. For each parameter set $\{q, f_i, \theta, r\}$ 100 replicate simulations were performed, and the 100 rankings were averaged.

RESULTS

Simulations were carried out for 68 different penetrance combinations and four combinations of θ and r , thereby giving rise to 272 separate parameter sets. Figures 1 and 2 record the results from the approximately 500 CPU hours of simulation.

The most striking characteristic of the mean rankings is that, compared to either PAIRS or WP, the GW scoring procedure does not perform well, especially when $f_1 = 0.05$. Moreover, it is noteworthy that as transmission approaches quasidominance (ie, as $f_2 \rightarrow f_3$), GW's relative performance is poorest. Mean rankings for the PAIRS statistic, on the other hand, tend to mirror those for GW, and, compared to WP, both exhibit wide fluctuations from one parameter set to the next.

Comparing the mean ranking for PAIRS versus those for WP, it is seen that when $f_1 = 0.05$ the PAIRS statistic tends to perform better, especially when there is

no polygenic background. This is interesting because when $f_1 = 0.05$ the population contains more "sporadic" cases, that is, phenotypes whose disease is not attributable to the effects of the at-risk a allele. Accordingly, the genetic variance due to the DS locus is smaller when $f_1 = 0.05$ than when $f_1 = 0.001$. However, when a heritable background is introduced into the model, WP tends to outperform PAIRS regardless of the penetrance of the AA homozygote.

For all of the scoring methods, no noticeable effect on mean rankings can be discerned as the recombination fraction increases from $\theta = 0$ to $\theta = 0.2$.

Compared to the GW and PAIRS scoring procedures, WP performs better not because it most often reaches a correct decision first, but because it rarely reaches a correct decision last. This was determined by allowing the simulations to continue to run even after one of the methods attained the critical Z-score. Accordingly, for each replication, the number of families required to reach a decision was determined for each method. For illustration, Table I reports, for each scoring method, the mean number of families and the standard deviation for the parameter sets $f_1 = 0.001$, $f_2 = 0.001 \rightarrow 0.7$, $f_3 = 5/6$, $\theta = 0$, $r = 0$. While not invariant, the usual situation is that the WP procedure requires the fewest average number of families and, additionally, tends to have the lowest variance. This is evident when the mean number of first, second, and third place ranks are obtained for the ten parameter combinations given in Table I (Table II). Whereas WP finishes first less frequently than either of the other two methods, it rarely finishes third. As a result of its stable behavior, and because the other two methods tend to "flip-flop" between finishing first and finishing last, the WP procedure tends to achieve the overall lowest rank.

Another way this can be seen is by comparing the "average waiting time" for the second and third finishing methods to reach a correct decision. Consider, for instance, the case $f_2 = 0.3$ from Table I. For this parameter set, when PAIRS was first to reach $Z \geq 2.576$, WP required, on average, 1.43 additional families to reach the decision, while GW required 3.76 additional families. When GW was first to reach the decision, PAIRS required an average of 5.73 further families, whereas WP only required an average of 1.57 additional families.

While we were primarily interested in evaluating the various scoring methods for their relative efficiency to detect linkage when it is present, we also were interested in determining whether they were equally robust in rejecting linkage when it is absent. Accordingly, we carried out three further simulations for the penetrance vector $f_1 = 0.001$, $f_2 = 0.5$, $f_3 = 1.0$ and set θ to $1/2$ (ie, no linkage). For these three simulations the number of ascertained families was fixed at $N = 10$, $N = 25$, and $N = 100$, respectively, and 10,000 replicates were taken for each.

Table III gives the results of these simulations. None of the three scoring methods, regardless of the number of families ascertained, yielded mean Z-scores significantly different from zero, nor variances significantly different from unity. However, the distribution of Z-scores for WP was significantly skewed to the right for $N = 10$ ($P < 0.001$) and $N = 25$ ($P < 0.05$), while for PAIRS the distribution was significantly skewed to the right for all three N 's ($P < 0.0001$ for $N = 10$ and $N = 25$ and $P < 0.05$ for $N = 100$) and significantly kurtotic for $N = 10$ ($P < 0.05$). These departures from normality are reflected in Table III where the number of false-positive replications is recorded for four critical Z-scores. Since 10,000

TABLE I. Mean and Standard Deviation for the Number of Families Required To Detect the Presence of a Disease Susceptibility Locus (at $p \leq 0.005$) for 100 Replicates of Each of Ten Penetrance Combinations $f_1 = 0.001$, $f_2 = 0.001 \rightarrow 0.7$, $f_3 = 0.833^*$

Scoring method	Number of Ascertained Multiplex Families		Rank	
	Mean	S.D.	Mean	S.D.
$f_2 = 0.001$				
GW	6.30	3.63	2.24	0.90
WP	6.11	3.67	1.86	0.49
PAIRS	6.58	5.10	1.90	0.93
$f_2 = 0.01$				
GW	6.57	3.78	2.21	0.92
WP	6.36	3.66	1.88	0.45
PAIRS	6.56	3.90	1.90	0.96
$f_2 = 0.05$				
GW	8.93	6.90	2.30	0.88
WP	8.77	7.20	1.82	0.46
PAIRS	9.26	8.48	1.88	0.93
$f_2 = 0.1$				
GW	12.38	8.17	2.37	0.89
WP	10.97	8.16	1.84	0.43
PAIRS	11.90	10.06	1.78	0.93
$f_2 = 0.2$				
GW	18.25	12.41	2.37	0.88
WP	17.16	11.60	1.87	0.44
PAIRS	17.19	12.35	1.78	0.92
$f_2 = 0.3$				
GW	19.52	12.99	2.31	0.89
WP	18.38	11.65	1.79	0.42
PAIRS	19.68	12.93	1.90	0.94
$f_2 = 0.4$				
GW	18.72	13.14	2.17	0.92
WP	17.61	12.57	1.84	0.38
PAIRS	18.55	12.83	1.99	0.97
$f_2 = 0.5$				
GW	17.41	11.17	2.20	0.84
WP	16.05	10.13	1.74	0.50
PAIRS	15.92	10.38	2.05	0.98
$f_2 = 0.6$				
GW	14.37	9.32	2.09	0.93
WP	14.30	9.15	1.83	0.46
PAIRS	14.58	9.88	2.07	0.96
$f_2 = 0.7$				
GW	12.81	7.11	2.30	0.87
WP	11.95	6.44	1.79	0.43
PAIRS	11.99	6.88	1.91	0.95

*Linkage to the marker is complete and there is no heritable polygenic background. Although differences are not great, the average lower mean and variance achieved by the WP procedure results in an overall superior rank.

TABLE II. Average Finishing Position for the Three Scoring Procedures Pooled Over the Ten Penetrance Combinations Reported in Table I

Method	Rank			Mean
	1	2	3	
GW	30.7	13.0	56.3	2.256
WP	19.9	77.6	2.5	1.826
PAIRS	49.4	9.4	41.2	1.918

TABLE III. Results From 10,000 Replicate Simulations on Three Different Family Sample Sizes When Linkage Is Absent*

Method	P values ^a											
	10 ^b				25 ^b				100 ^b			
	0.050	0.025	0.005	0.001	0.050	0.025	0.005	0.001	0.050	0.025	0.005	0.001
GW	489	281	59	21	471	248	66	12	504	272	65	10
WP	548	303	73	19	471	253	64	13	530	285	73	12
PAIRS	576	328	91	28	545	310	92	23	587	304	71	15

*The generating parameters where ($f_1 = 0.001$, $f_2 = 1/2$, $f_3 = 1$, $\theta = 0$, and $r = 0$). Random expectations for the number of false-positives at $P = 0.05$, 0.025 , 0.005 , and 0.001 are, respectively, 500, 250, 50, and 10.

^aUppertail test.

^bNumber of ascertained multiplex families.

replications were simulated, 500, 250, 50, and 10 false positives are expected for the four respective P values. In most cases these expectations are exceeded—especially by the PAIRS statistic.

DISCUSSION

For non-Mendelian diseases the affected-sib-pair approach has proved useful in detecting susceptibility genes linked to the major histocompatibility complex. However, the best strategy for the analysis of multiplex sibships is difficult to determine. Recently a number of workers have suggested that more precise inferences regarding mode of transmission could be made if information from unaffected sibs and parental phenotypes were incorporated into the affected-sib-pair methodology [Alter and Quevedo, 1979; Weitkamp, 1981], although the best way to accomplish this remains unclear [Suarez et al, 1982, 1983a,b].

The simulations reported here indicate that when analysis is restricted to just the affected members of a sibship, the widely used Green and Woodrow [1977] scoring procedure is unduly conservative. On the other hand, the practice of dismantling large multiplex sibships into all possible affected pairs, while conceptually simple, appears to give rise to an unacceptably large type I error. On balance, it appears that the scoring procedure developed here represents a reasonable compromise. The extensive simulations indicate that the WP statistic is well suited to detect an incompletely penetrant HLA-linked disease susceptibility locus. Finally, by comparison with either the GW or the PAIRS scoring procedure, the WP statistic performs

better in the presence of a heritable multifactorial component and is not given to wide fluctuations across divergent transmission models.

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APPENDIX

Assume S affected sibs, then $PAIRS \equiv \sum_{i < j}^S \sum^S X_{ij}$, where X_{ij} is the IBD score (2, 1, or 0) at the marker locus between the i^{th} and j^{th} sibs. The null hypothesis H_0 ,

of course, is that the marker and the disease susceptibility loci are unlinked ($\theta = 1/2$). Then $X_{ij} \sim B(2, 1/2)$ and $E(X_{ij}) = 1, \forall ij$. Accordingly,

$$E(\text{PAIRS}) = \sum_{i < j}^S \sum_{i < j}^S E(X_{ij}) = \frac{S(S-1)}{2}.$$

Since the random variables X_{ij} are not independent, it is easier to use a different expression for PAIRS in order to compute the variance. Treating separately the paternal and maternal contribution to the IBD scores, we partition the S sibs into two groups of sizes I and $(S-I)$ on the paternal side and similarly into two groups of size J and $(S-J)$ on the maternal side. Under H_0 , I and J are independent binomial random variables $B(S, 1/2)$. As easily seen,

$$\begin{aligned} \text{PAIRS} &= \frac{I(I-1) + (S-I)(S-I-1)}{2} + \frac{J(J-1) + (S-J)(S-J-1)}{2} \\ &= \left(I - \frac{S}{2} \right)^2 + \frac{S(S-2)}{4} + \left(J - \frac{S}{2} \right)^2 + \frac{S(S-2)}{4}. \end{aligned}$$

Accordingly,

$$\begin{aligned} \sigma^2(\text{PAIRS}) &= 2 \left\{ E \left[\left(I - \frac{S}{2} \right)^2 + \frac{S(S-2)}{4} \right]^2 - \left(\frac{S(S-1)}{4} \right)^2 \right\} \\ &= 2 \left\{ E \left[\left(I - \frac{S}{2} \right)^4 \right] + \frac{S(S-2)}{2} E \left[\left(I - \frac{S}{2} \right)^2 \right] - \frac{S^2(2S-3)}{16} \right\}. \end{aligned}$$

The 4th and 2nd central moments of the binomial $B(S, 1/2)$ are equal to $S(3S-2)/16$ and $S/4$, respectively. After substitution we get

$$\sigma^2(\text{PAIRS}) = 2 \frac{S(S-1)}{8} = \frac{S(S-1)}{4}.$$