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Single-Marker and Two-Marker Association Tests for Unphased Case-Control Genotype Data, with a Power Comparison

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Abstract

In case-control Single Nucleotide Polymorphism (SNP) data, the Allele frequency, Hardy Weinberg Disequilibrium (HWD) and Linkage Disequilibrium (LD) contrast tests are three distinct sources of information about genetic association. While all three tests are typically developed in a retrospective context, we show that prospective logistic regression models may be developed that correspond conceptually to the retrospective tests. This approach provides a flexible framework for conducting a systematic series of association analyses using unphased genotype data and any number of covariates. For a single stage study, two single-marker tests and four two-marker tests are discussed. The true association models are derived and they allow us to understand why a model with only a linear term will generally fit well for a SNP in weak LD with a causal SNP, whatever the disease model, but not for a SNP in high LD with a non-additive disease SNP. We investigate the power of the association tests using real LD parameters from chromosome 11 in the HapMap CEU population data. Among the single-marker tests, the allelic test has on average the most power in the case of an additive disease; but, for dominant, recessive and heterozygote disadvantage diseases, the genotypic test has the most power. Among the six two-marker tests, the Allelic-LD contrast test, which incorporates linear terms for two markers and their interaction term, provides the most reliable power overall for the cases studied. Therefore, our result supports incorporating an interaction term as well as linear terms in multi-marker tests.

Keywords

Allele frequency contrast test; LD contrast test; HWD contrast test; Genome-wide Association

INTRODUCTION

A genome-wide association study with case-control data aims to localize disease susceptibility regions in the genome. Single Nucleotide Polymorphism (SNP) markers, which are usually diallelic, have been used to cover the whole genome. Two categories of tests have been applied to these data: single-marker association tests, which examine association between affection status and the data one SNP at a time, and multi-marker association tests, which examine association between affection status and multiple SNP data simultaneously.

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For single-marker association tests, we can consider the allelic frequency contrast test (allelic test) [Sasieni 1997], and the Hardy Weinberg Disequilibrium (HWD) contrast test [Song and Elston 2006]. In genome-wide association studies, the allelic test has been predominantly used (e.g. The Wellcome Trust Case Control Consortium [2007]). However, this test often fails on account of a relatively strict correction for multiple comparisons, because it does not take advantage of marker linkage disequilibrium (LD) structure efficiently, and/or it is not suitable for detecting rare disease variants. For these reasons, multi-marker association tests may have more power than single-marker association tests. Such tests include the haplotype-based test [Schaid 2004; Schaid, et al. 2002], Hotelling's T^2 test [Chapman, et al. 2003; Clayton, et al. 2004; Xiong, et al. 2002] and the LD contrast test [Nielsen, et al. 2004; Wang, et al. 2007; Zaykin, et al. 2006]. The original LD-contrast test requires phased genotype data, but Zaykin et al. [2006] proposed the composite-LD contrast test that does not require phased genotype data. From now on in this paper, when it applies to unphased data, we use the term “LD contrast test” to denote the composite-LD contrast test.

Several authors have proposed that either of the HWD and LD contrasts be jointly tested with the allele frequency contrast [Song and Elston 2006; Zheng, et al. 2008; Zheng, et al. 2007]. Recently, Won and Elston [2008] described the allele frequency, HWD and LD contrasts as three distinct sources of information about case-control differences and suggested performing these tests in a joint or multi-stage manner. While these three sources of information are often close to being independent, they are only strictly independent under limiting conditions [Won and Elston 2008]. This fact has restricted a systematic use of the three tests, because extra work is required to adjust for their correlations.

The allele frequency, HWD and LD contrast tests are typically developed in what has been termed a retrospective context; i.e. case-control status is considered fixed and the genotypes are considered random. However, for case-control data, epidemiologists typically take advantage of the properties of the odds ratio and use the prospective logistic regression model, making the case-control status the random variable dependent on the predictors (i.e. genotypes and covariates) which are considered fixed [Prentice and Pyke 1979]. This prospective modeling tends to allow for greater flexibility, especially when adjusting for covariates. It also provides a natural way to adjust for any correlations between the tests or other covariates and can be extended to quantitative traits. The allele frequency contrast test has been performed in a prospective logistic regression model [Longmate 2001]. However, there is little discussion in the literature concerning the prospective modeling of the other two tests.

Here, for unphased case-control data, we discuss how the allelic, HWD and LD contrasts tests may be combined, either pairwise or all three together, in the retrospective context. We then show that these joint tests correspond very closely to analogous tests based on certain prospective models. Using these general models, various specific models and their corresponding tests are presented. After deriving “true” models in terms of the penetrances of a single disease SNP and the LD structure, we look for the best test in terms of power. Lastly, under the assumption that LD among two markers and the disease locus is similar to that among three markers, we compare the power of each test using the SNP data on chromosome 11 of the HapMap CEU (Utah residents with ancestry from northern and western Europe) population data.

METHODS

Notation and Assumptions

We assume that there is a single diallelic disease SNP in the genomic region being considered, but we allow multiple disease SNPs to exist that are not in LD with any SNP in the region. We suppose there are two diallelic SNP markers, A and B, having alleles $\{A_1,A_2\}$ and $\{B_1,B_2\}$, respectively, where A_1 and B_1 are the minor alleles. Let X and Y denote random variable for genotypes of markers *A* and *B* coded as follows:

$$X=\begin{cases} 1 & \text{for } A_1A_1 \\ 0 & \text{for } A_1A_2 \\ -1 & \text{for } A_2A_2 \end{cases}, Y=\begin{cases} 1 & \text{for } B_1B_1 \\ 0 & \text{for } B_1B_2 \\ -1 & \text{for } B_2B_2 \end{cases}.$$

The random variables X and Y for the i-th individual are denoted by X_i and Y_i. I_{case} and I_{ctrl} denote the sets of cases and controls. We assume a multinomial distribution for unphased genotype data in the general population and denote their probabilities as in TABLE I. Note that we make minimal assumptions about the general population sampled; in particular, we do not assume HWE in the population. The allele frequencies of A_1 and B_1 are given by $p_A=p_{A_1A_2}+\frac{1}{2}p_{A_1A_2}$ and $p_B=p_{B_1B_2}+\frac{1}{2}p_{B_1B_2}$. We use μ_X, σ_X^2 and $\sigma_{X,Y}$ to denote the expected value of X, the variance of X and the covariance of X and Y, respectively. Note that $\mu_X = 2P_A - 1$ and $\mu_Y = 2P_B - 1$. We similarly assume a multinomial distribution for cases and controls, denoting any parameters associated with these populations respectively by the subscripts "case" and "ctrl". The HWD parameter for marker A and the composite LD parameter for alleles A_1 and B_1 of markers A and B are respectively given by [Weir 1996;Zaykin 2004]

$$d_A=p_{A_1A_1}-p_A^2$$
$$D_{AB}=\left(g_{(1,1)}+\frac{1}{2}g_{(1,0)}+\frac{1}{2}g_{(0,1)}+\frac{1}{4}g_{(0,0)}\right)-p_Ap_B=\frac{1}{4}\sigma_{X,Y}.$$

The HWD parameter $d_A$can also be expressed in a different form. It can be shown that $\sigma_X^2=\mu_{X^2}-(\mu_X)^2=2\left(p_A+p_{A_1A_1}\right)-4p_A^2$. Under HWE (i.e. $p_A^2=p_{A_1A_1}$), this become $\sigma_{X|HWE}^2=2p_A(1-p_A)$. Thus the the HWD parameter can be expressed by $d_A=\frac{1}{2}\left(\sigma_X^2-\sigma_{X|HWE}^2\right)$ This means that the HWD parameter, d_A, is half the the deviation of the variance from the variance expected under HWE.

Tests in the Retrospective Context

The allele frequency and HWD contrast tests for marker A and the LD contrast test for markers A and B test the equalities, between cases and controls, of the parameters, P_A, d_A and Δ, respectively. Suppose we have n_{case} cases and n_{ctrl} controls. Since $\widehat{p}_A=\frac{1}{2}\left(\bar{X}+1\right)$, the test statistic for the allele frequency contrast can be written $T_{AF}^2=\frac{\left(\bar{X}_{case}-\bar{X}_{ctrl}\right)^2}{S_{X|case}^2+S_{X|ctrl}^2}$, where $S_{X|case}^2=\frac{1}{n_{case}}\Sigma_{i\in I\,case}\left(X_i-\bar{X}_{case}\right)^2$ and $S_{X|ctrl}^2=\frac{1}{n_{ctrl}}\Sigma_{i\in I\,ctrl}\left(X_i-\bar{X}_{ctrl}\right)^2$. This corresponds to the univariate version of Hotelling's [1931] T^2 test. Estimates for the HWD and LD parameters d_A and Δ of a population from a sample with size *n* are obtained by $\widehat{d}_A=\frac{1}{2}\left(\frac{1}{n}\Sigma_i(X_i-\mu_X)^2-\frac{\mu_X(1-\mu_X)}{2}\right)$ and $\widehat{\Delta}=\frac{1}{2n}\Sigma_i(X_i-\mu_X)(Y_i-\mu_Y)$. Then the T^2 statistics for the

HWD and LD contrast tests are given by $T^2_{HWD} = \frac{(\hat{d}_{A|case} - \hat{d}_{A|ctrl})^2}{\widehat{Var}(\hat{d}_{A|case}) + \widehat{Var}(\hat{d}_{A|ctrl})}$ and $T^2_{LD} = \frac{(\hat{d}_{case} - \hat{d}_{ctrl})^2}{\widehat{Var}(\hat{d}_{case}) + \widehat{Var}(\hat{d}_{ctrl})}$. It can be easily verified that, under the assumption of known and μ_X and μ_Y,

$$\mathrm{Var}(\hat{d}_A) = \frac{1}{4n}\sigma^2_{X^2} \text{ and } \mathrm{Var}(\hat{\Delta}) = \frac{1}{4n}\left(\sigma^2_{XY} + \mu_X\sigma^2_Y + \mu_Y\sigma^2_X\right). \quad (1)$$

In practice, when μ_X and μ_Y are unknown, we may replace them by the consistent estimates $\bar{X}$ and $\bar{Y}$. Other tests exist that utilize allele frequency, HWD and LD contrasts. However, these tests are in form and perform similarly.

The joint test of allele frequency and HWD contrasts between cases and controls tests the null hypothesis H_0: $(P_{A|case}\ d_{A|case}) = (P_{A|ctrl}\ d_{A|ctrl})$. Note the important point that the parameter vector $(P_A\ d_A)$ determines the genotype distribution and therefore this test is equivalent to the genotypic test. We denote this test the Allelic-HWD contrast test. In the following, M′ denote the transpose of a column vector, M. Letting $Z_i \equiv (X_i\ X_i^2)'$, the sample mean $\bar{Z}$ is a sufficient statistic for $(P_A\ d_A)'$. Thus the Allelic-HWD contrast test can be performed by comparing $\bar{Z}_{case}$ and $\bar{Z}_{ctrl}$. The T^2 statistic for this test is given by

$$T^2 = \frac{n_{case}n_{ctrl}}{n_{case}+n_{ctrl}}\left(\bar{Z}_{case} - \bar{Z}_{ctrl}\right)' S_{T^2} \ominus \left(\bar{Z}_{case} - \bar{Z}_{ctrl}\right), \quad (2)$$

where $S_{T^2} = \frac{1}{n_{case}+n_{ctrl}-2}\left(\Sigma_{i\in I_{case}}\left(Z_i - \bar{Z}_{case}\right)\left(Z_i - \bar{Z}_{case}\right)' + \Sigma_{i\in I_{ctrl}}\left(Z_i - \bar{Z}_{ctrl}\right)\left(\bar{Z}_i - \bar{Z}_{ctrl}\right)'\right)$ and $\ominus$ denotes a generalized inverse. Under the null hypothesis, T^2 asymptotically follows the chi-square distribution with degrees of freedom equal to the rank of S_{T^2}. Similarly, we can build a joint test of the allele frequency contrasts of two markers and their LD contrast, which tests the null hypothesis H_0: $(P_{A|case}\ P_{B|case}\ \Delta_{case}) = (P_{A|ctrl}\ P_{B|ctrl}\ \Delta_{ctrl})$. We denote this test the Allelic-LD contrast test. Letting $Z_i = (X_i\ Y_i\ X_iY_i)'$, $\bar{Z}$ is a sufficient statistic for $(P_A\ P_B\ \Delta)'$. Thus, the Allelic-LD contrast test can be performed using a version of Hotelling's T^2.

Therefore, it can be seen that the additional case-control differences that can be captured by the HWD and LD contrast tests, given the allele frequency contrast(s), are equivalent to the differences in quadratic and interaction terms, respectively. The joint test for the case-control difference in allele frequency and HWD of two markers and their LD (the Allelic-HWD-LD contrast test) can be constructed, in a similar manner, by contrasting the mean vector of $Z_i = \left(X_i \quad Y_i \quad X_iY_i \quad X_i^2 \quad Y_i^2\right)'$ between cases and controls.

Prospective Single-marker and Two-marker Association Models and Tests

Tests of regression coefficients in a logistic model with case control data, possibly with covariates, are known to be valid and widely used when covariates need to be included in the model as we mentioned earlier. In fact, the score test statistic is of the same form as (2), but with S_{T^2} replaced by the similar matrix

$$\frac{1}{n_{case}+n_{ctrl}}\sum_{i=1}^{n_{case}+n_{ctrl}}\left(Z_i - \bar{Z}\right)\left(Z_i - \bar{Z}\right)' = \frac{n_{case}+n_{ctrl}-2}{n_{case}+n_{ctrl}}S_{T^2} + \frac{n_{case}n_{ctrl}}{(n_{case}+n_{ctrl})^2}\left(\bar{Z}_{case} - \bar{Z}_{ctrl}\right)\left(\bar{Z}_{case} - \bar{Z}_{ctrl}\right)'.$$

This implies that the T^2 and score test statistics are asymptotically equivalent as the null and the alternative hypothesis approach each other (i.e. they become a Pitman sequence [Davidson and MacKinnon 1987]). Because the likelihood ratio test (LRT) for a logistic model is also very close to the score test for the same model, we expect all three tests, the T^2 test, score test and LRT, to behave similarly.

A single marker model for the Allelic-HWD contrast test incorporating covariates is

$$\log\left(\frac{\mu}{1-\mu}\right)=\beta_0+\beta_X \mathrm{X}+\beta_0+\beta_{X^2}\mathrm{X}^2+(\text{covariates}), \tag{3}$$

where we suppress the index i and μ denotes the probability that an individual is affected. Similarly, the two marker model for the Allelic-HWD-LD contrast test incorporating covariates is

$$\log\left(\frac{\mu}{1-\mu}\right)=\beta_0+\beta_X \mathrm{X}+\beta_Y \mathrm{Y}++\beta_{XY}\mathrm{XY}++\beta_{X^2}\mathrm{X}^2+\beta_{Y^2}\mathrm{Y}^2+(\text{covariates}). \tag{4}$$

Based on these two models or a reduced form of them, we can set up various types of association tests that examine the significance of all or a subset of the regression coefficients. Six models and their global hypotheses that may be tested in a single stage analysis are numbered and presented in TABLE II and, for each of these hypotheses, we can set up the corresponding score test or LRT. For genome-wide association analysis, we can perform a single marker test with every single SNP and/or a two-marker test with every consecutive pair of SNPs.

The models in TABLE II are specific genotype-based models and it may be helpful to review the relationship between these genotype-based models and haplotype-based models. Let H_{ij} be the number of (A_i,B_j) haplotypes an individual has. Then the haplotype-based model for two markers, taking H_{22} as a baseline, is written as

$$\log\left(\frac{\mu}{1-\mu}\right)=\beta_0+\beta_{12}\mathrm{H}_{12}+\beta_{21}\mathrm{H}_{21}+\beta_{11}\mathrm{H}_{11}+(\text{covariates}), \tag{5}$$

and the haplotype-based test is set up as a global test of their effects, that is a test of H_0: $(\beta_{12}\ \beta_{21}\ \beta_{11})' = \mathrm{O}$. Ignoring covariates, the saturated haplotype-based model has four parameters for main effects (i.e. we rewrite model (5) to include $\beta_{22}H_{22}$ instead of β_0) and six parameters for their first-order interaction effects. This model, with a total of ten parameters, is equivalent to the genotype-based model that includes the six terms in (4), together with the higher order terms X_2Y, XY_2, X_2Y_2 and an extra term for phase [Schaid 2004]. Therefore, each test in TABLE II and the haplotype-based test examine the case-control differences summarized in a different way. In particular, for two-marker data, Test 2–3 is comparable to the haplotype-based test because both of them are generally 3-degree-of-freedom tests [Conti and Gauderman 2004].

Multi-stage analysis, which utilizes the allele frequency, HWD and LD contrasts in sequential stages of the analysis, can be created by using a sequence of the tests in TABLE II in a prospective model. Suppose, for example, that SNPs have been selected for genotyping by an allele frequency contrast test based on pooled DNA samples. Then the HWD contrast test adjusted for the information which is used in the first stage can be performed by the test of H_0:$(\beta_X{}^2|\beta_X)=0$ in the model of Test 1–2, whether the second test is to

be applied to the same or a new sample of persons. Therefore, based on these marker association models, using this framework in a multi-stage study we can perform the allele frequency, HWD and LD contrast tests and their joint tests in a more systematic and convenient way.

Penetrance Model and True Marker Association Model

We can obtain true marker association models from knowing the genotype penetrances and the LD structure among the disease and marker alleles. The tests in TABLE II do not require HWE in the general population, but we will consider true marker association models under the assumption of HWE in the general population. Let the disease SNP have alleles $\{D_1,D_2\}$, where D_1 is the minor allele. Let D denote the disease genotype variable coded as

$$D=\begin{cases} 1 & \text{for } D_1D_1 \\ 0 & \text{for } D_1D_2 \\ -1 & \text{for } D_2D_2 \end{cases}.$$

We write the penetrance model as:

$$\mu=P(\text{affected}|D)=\gamma_0+\gamma_D D+\gamma_{D^2} D^2. \quad (6)$$

Note that for simplicity of exposition this is not written on a logit scale. Consider the four disease models: additive, dominant, recessive and heterozygote (dis)advantage. These can be obtained by constraining the coefficients of the penetrance model (6) as indicated in TABLE III. In the following, we assume that the homozygote with the major allele D_2 has the lowest risk. This implies that the minor allele is the disease susceptibility allele for the additive, dominant and recessive diseases, and that we are considering a heterozygote disadvantage disease. Nevertheless, the same test statistics are appropriate, and their power will be similar, for the diseases in which the homozygote with the major allele D_2 has the highest risk.

Now consider the LD structure between a single marker locus and a disease locus in the general population. Let p_D denote the disease allele frequency and D_{XD} denote the LD of the marker allele A_1 and the disease allele. The LD structure implies that $E(D|X) = aX + b$ and $E(D^2|X) = -a^2X^2 + abX + c$, where $a=\left(\frac{1}{p_A}+\frac{1}{1-p_A}\right)D_{XD}$, $b=\left(\frac{1}{p_A}-\frac{1}{1-p_A}\right)D_{XD}-(1-2p_D)$ and $c=1-2p_D\left(\frac{1}{p_A}-\frac{1}{1-p_A}\right)D_{XD}+2\left(p_D+\frac{D_{XD}}{p_A}\right)\left(p_D-\frac{D_{XD}}{1-p_A}\right)$ (see **Appendix A**). Given the true disease model and the LD structure, we can set up the true single-marker association model between the phenotype and single-marker data *X*, as follows:

$$\begin{aligned}\mu &= P(\text{affected}|X)=\sum_{D=-1,0,1} P(\text{affected}|D)\,P(D|X)=\gamma_0+\gamma_D E(D|X)+\gamma_{D^2} E\left(D^2|X\right) \\ &=\left(-ab\gamma_{D^2}+a\gamma_D\right)X-a^2\gamma_{D^2}X^2+\left(\gamma_{D^2}c+\gamma_D b+\gamma_0\right). \end{aligned} \quad (7)$$

This true association model, which has the same form as the penetrance model (6), allows us to understand how the disease model and the LD structure affect the SNP association pattern. It clearly implies that a marker allele that is in LD with the disease allele would be observed in the cases and controls as if it were a disease SNP with a particular disease model. Now, in the model (7), as D_{XD} approaches 0, the coefficients of both the linear and quadratic terms go to 0. However, the ratio of the coefficient of the linear term to that of the

quadratic term in model (7) is $(1-2p_A)+\left((1-2p_D)-\frac{\gamma_D}{\gamma_{D^2}}\right)\frac{1}{D_{XD}}$. When $(1-2p_D)-\frac{\gamma_D}{\gamma_{D^2}}\neq 0$, as D_{XD} approaches 0, the absolute value of the ratio approaches infinity. Thus as the LD decreases, the coefficient of the quadratic terms generally approaches 0 faster than does that of the linear term, and the association model becomes similar to that of an additive disease.

However, if $(1-2p_D)-\frac{\gamma_D}{\gamma_{D^2}}=0$ holds for the disease model, it can be shown that $\mu_{X|case} = \mu_{X|ctrl} = \mu_X$ (**Appendix B**). This implies that a test based on a model with only a linear term, such as the allelic test, cannot identify the association at all when it is applied to any SNP correlated with the disease SNP, even the disease SNP itself. This condition holds only in over- or under-dominant disease models.

For given LD parameters and allele frequencies, the true two-marker association model can be obtained in a similar way to the single-marker case as follows:

$$\begin{aligned}\mu=\mathrm{P}(\text{affected}|X,Y) &= \sum_{\mathrm{D}=-1,0,1}\mathrm{P}(\text{affected}|\mathrm{D})\,\mathrm{P}(\mathrm{D}|X,Y)\\ &=\gamma_0+\gamma_{\mathrm{D}}\mathrm{E}(\mathrm{D}|X,Y)+\gamma_{\mathrm{D}^2}\mathrm{E}\left(\mathrm{D}^2|X,Y\right),\end{aligned} \tag{8}$$

which is a full model with 9 polynomials of X and Y, or a reduced form of this model. While the regression coefficients cannot be expressed simply in general, we may easily write out E(D|X, Y) and E(D^2|X, Y) for computational purposes (see **Appendix A**).

Consider a disease allele on a multi-dimensional LD structure, by which we mean that E(D|X, Y) deviates from a linear combination of the variables X and Y. This often happens when there is high three-locus LD among the three SNPs. The case $E(D|X, Y) = \beta_X X + \beta_Y Y + \beta_{XY} XY + \beta_0$ with a relatively large absolute value of β_{XY} is a “simple” multi-dimensional LD structure. In this case, the true marker association model for an additive disease is written as $\mu = P(\text{affected}|X, Y) = \gamma_D(\beta_X X + \beta_Y Y + \beta_{XY} XY) + \gamma_0$. This implies that tests that include the contrast of an interaction term (i.e. Tests 2–5, Test 2–3 and the LD contrast test) may gain power by taking into account the multi-dimensional LD structure. On the other hand, tests that do not take into account the multi-dimensional LD structure (any single marker tests, Test 2–2 and Test 2–4) might have less power. The haplotype-based test also takes multi-dimensional LD structure into account, and its gain in power in a multi-dimensional LD structure has been observed by Nielsen et al. [2004].

We can consider the models in TABLE II as reduced, full, or extended in comparison to the true model. However, the models in TABLE II and the true association models are written with different link functions (the logit and identity functions, respectively); whereas the identity link function simplifies exposition for the relationship between the disease model and the association model, the logit link function is more convenient for data analysis. For small effect sizes the two link functions should yield similar models. Therefore, our true marker association models are sufficient to provide an intuition about which predictors will be important components of the logistic model.

Finding the most powerful test among the tests in TABLE II is not straightforward because the test under the full true model, which examines contrasts of all the predictor variables in the full model, is not always the most powerful. When a reduced model explains the data parsimoniously, its corresponding test becomes more powerful than the corresponding tests under the full model because of the smaller number of degrees of freedom. Therefore, we compared various association tests with different penetrance models and LD structures - which together determine the true association model.

Power Computation

As mentioned earlier, the T^2 test in a retrospective model and the score test and LRT in a prospective logistic model are expected to perform similarly. We first derive the theoretical power calculated from the noncentrality parameter of the T^2 test and compare this with the empirical power of the T^2 test, score test and LRT. The noncentrality parameter of the T^2 test for Test 2–5 is

$$\lambda = \frac{n_{case} n_{ctrl}}{n_{case} + n_{ctrl}} (\mu_{case} - \mu_{ctrl})' \Sigma \ominus (\mu_{\text{case}} - \mu_{\text{ctrl}}),$$

where $\mu_{case} = (\mu_{X|case}\ \mu_{Y|case}\ \mu_{XY|case}\ \mu_{X^2|case}$

$$\Sigma = \frac{n_{\text{case}}}{n_{\text{case}} + n_{\text{ctrl}}} \Sigma_{\text{case}} \frac{n_{\text{ctrl}}}{n_{\text{case}} + n_{\text{ctrl}}} \Sigma_{\text{ctrl}},$$

$$\Sigma_{case} = \begin{pmatrix} \sigma^2_{X|case} & \sigma_{X,Y|case} & \sigma_{X,XY|case} & \sigma_{X,X^2|case} & \sigma_{X,Y^2|case} \\ & \sigma^2_{Y|case} & \sigma_{Y,XY|case} & \sigma_{Y,X^2|case} & \sigma_{Y,Y^2|case} \\ & & \sigma^2_{XY|case} & \sigma_{XY,X^2|case} & \sigma_{XY,Y^2|case} \\ & & & \sigma^2_{X^2|case} & \sigma_{X^2,Y^2|case} \\ & & & & \sigma^2_{Y^2|case} \end{pmatrix} \text{ and } \quad \Sigma_{ctrl} = \begin{pmatrix} \sigma^2_{X|ctrl} & \sigma_{X,Y|ctrl} & \sigma_{X,XY|ctrl} & \sigma_{X,X^2|ctrl} & \sigma_{X,Y^2|ctrl} \\ & \sigma^2_{Y|ctrl} & \sigma_{Y,XY|ctrl} & \sigma_{Y,X^2|ctrl} & \sigma_{Y,Y^2|ctrl} \\ & & \sigma^2_{XY|ctrl} & \sigma_{XY,X^2|ctrl} & \sigma_{XY,Y^2|ctrl} \\ & & & \sigma^2_{X^2|ctrl} & \sigma_{X^2,Y^2|ctrl} \\ & & & & \sigma^2_{Y^2|ctrl} \end{pmatrix}.$$

Here, and Σ_{case} Σ_{ctrl} are symmetric, so we only indicate the diagonal and above diagonal elements. The number of degrees of freedom,*r* is the rank of Σ. Given the penetrance model and LD structure, we can derive the entries of μ_{case},μ_{ctrl},Σ_{case} and Σ_{ctrl} (**see Appendix C**). The noncentrality parameters for the other tests in TABLE II can be obtained by using the corresponding sub-matrices of ($\mu_{\text{case}} - \mu_{\text{ctrl}}$) and ($\Sigma_{\text{case}} + \Sigma$). Then the power of the significance level test with noncentrality parameter λis given by

$$(\text{POWER}) = 1 - F_{\chi^2_\lambda}\left(\chi^2_{1-\alpha}\right),$$

where $F_{\chi^2_\lambda}$ is the cumulative density function of a chi-square distribution with noncentrality parameter λ and degrees of freedom *r*, and $\chi^2_{1-\alpha}$ is the 1 − α quantile of a central chi-square distribution with *r* degrees of freedom.

We compared this theoretical power of the T^2 test with the empirical power of the T^2 test, score test and LRT. For each of the four disease models, we generated 100,000 replicate datasets, performed Test 1–2 on each dataset with each of the three test statistics and obtained their empirical power from the 100,000 replicate datasets. Specifically, the parameters were set as follows: p_D =0.2, p_A = 0.3, D_{XD} = 0.048 (D′ = 0.8) K = 0.05, (5%), and μ_{base} = 0.04 (4%), where K is the disease prevalence and μ_{base} is the baseline risk. By fixing K and μ_{base} instead of the effect size, for each region and each disease model we can condition on a constant attributable risk calculated as K − μ_{base}. The coefficients γ_{D^2}, γ_D and γ_0 are determined by the disease model, the prevalence K and baseline risk μ_{base} using the constraints shown in TABLE III and the following equations:

$$K = \gamma_{D^2}\left\{p_D^2 + (1 - p_D)^2\right\} + \gamma_D\left\{p_D^2 + (1 - p_D)^2\right\} + \gamma_0$$
$$\mu_{base} = \gamma_0 - \gamma_D + \gamma_{D^2}.$$

The significance level was set toα = 0.05/500,000 for a genome-wide association study with 500K independent SNPs. Each dataset compromised 2,000 cases and 2,000 controls (*n* =

$n_{case} = n_{ctrl}$ =2,000) for the additive, dominant and heterozygote disadvantage diseases, and 500 cases and 500 controls (n = 500) for a recessive disease so that its power would not be too high. Empirical power was obtained by the ratio of the number of rejected replicates to the total number of replicates.

The theoretical power of the T^2 test was close to the empirical power of the score, LRT and T^2 tests (TABLE IV) while the three test statistics led to almost identical (but very small), departure from nominal Type I error [Data not shown]. The T^2 test is slightly more powerful than the other two, while the LRT is slightly more powerful than the score test. The power under a recessive disease showed relatively greater inconsistencies because of the smaller sample size. Therefore the theoretical power of the T^2 test can be a good estimate for any of the three tests. For the purpose of comparing the power of the tests in TABLE II and any other association tests, it is sufficient to compare the theoretical power of the corresponding T^2 test.

RESULTS

Power Comparisons

The theoretical power of the HWD contrast test, LD contrast test and haplotype-based test can be computed from their noncentrality parameters. The noncentrality parameters for the HWD contrast test and the LD contrast test are given by $\lambda_{\mathrm{HWD}}=\frac{\left(d_{\mathrm{A|case}}-d_{\mathrm{A|ctrl}}\right)^2}{\mathrm{Var}\left(\hat{d}_{\mathrm{A|case}}\right)+\mathrm{Var}\left(\hat{d}_{\mathrm{A|ctrl}}\right)}$ and $\lambda_{\mathrm{LD}}=\frac{(\Delta_{\mathrm{case}}-\Delta_{\mathrm{ctrl}})^2}{\mathrm{Var}\left(\hat{\Delta}_{\mathrm{case}}\right)+\mathrm{Var}\left(\hat{\Delta}_{\mathrm{ctrl}}\right)}$, where the denominators are given in (1). The noncentrality parameter of the haplotype-based test, λ_{HAP}, can be also computed (see **Appendix D**). These three noncentrality parameters are given under the assumption that the true minor allele frequencies of markers A and B (p_A,p_B) are known, or that the haplotype frequencies are determined with certainty, in both cases and controls. The theoretical power from these noncentrality parameters somewhat overestimate the power in a real situation because the variances in the denominators of the noncentrality parameters would be greater. Therefore, our theoretical power comparisons of these three tests and the tests in TABLE II may give results which are a little favorable to these three tests.

We compared power among the single-marker tests and among the two-marker tests. For the single-marker tests, we present the power as a function of the LD (Lewontin's D′) between marker and disease allele (**Fig. 1**). Test 1–1 (the allelic test) always had more power than Test 1–2 (the genotypic test) or the HWD contrast test in the case of an additive disease. But in the other disease models, Test 1–2 had more power than the allelic test when LD is high. The HWD contrast test had less power for all four disease models. However, although the HWD contrast test performed poorly by itself, when it was combined with the allele frequency test to be Test 1–2, power was maximized.

For the two-marker tests, two cases of LD structure were considered for each disease model: a case with low multi-dimensional LD (LD structure 1) and one with high multi-dimensional LD (LD structure 2), as defined in the legend to TABLE IV. In LD structure 1, Test 2–2, which examines the allele frequencies of the two markers, had the most power except in the case of a recessive disease (TABLE V). However, in LD structure 2, the haplotype-based test, Test 2–5 and Test 2–3 had more power than Test 2–2 by taking into account the multi-dimensional LD. The LD contrast test, like the HWD contrast test, performed poorly alone but, when it was combined with the allele frequency contrast test, power was maximized. Our findings were not materially affected by different values of the prevalence or sample size [Data not shown].

For a given disease model, none of the tests were found to be the most powerful in both cases of LD structure. Therefore, specifying the LD structure that the markers and a real disease SNP take on would suggest the best test for a particular association study, were it known. If we assume that the LD structure among the marker and disease SNPs is similar to that among the marker SNPs, we can compute and compare the power of each test given that LD structure by estimating the necessary parameters from the marker LD structure.

Power Comparisons Based on Real Data

We estimated LD parameters and marker allele frequencies from the HapMap CEU population data [The International HapMap Project 2005]. These data consist of 120 haplotypes estimated from 30 parent-offspring trios. We split chromosome 11 into mutually exclusive consecutive regions containing 3 SNPs each. For each region we estimated the LD and allele frequency parameters. We excluded regions where the minor allele frequencies of three consecutive markers were less than 0.1, leaving 4,648 regions. Following the method in Nielsen et al.'s [2004] simulation, we chose the disease SNP to be the one with the smallest allele frequency, assuming the disease allele would have a smaller allele frequency than the ascertained marker SNPs. Parameters other than the LD parameters were set to be the same as before, i.e. n = 2,000 (500 for recessive),K=0.05, μ_{base} =0.04,α=0.05/500,000. For each region, we computed the power of the single marker tests based on the first of the non-disease SNPs, and we computed the power of the two marker tests based on the two non-disease SNPs. Then the mean power over all regions was computed (TABLE VI).

In a comparison of the single marker-tests, while Test 1–1 was the most powerful on average for an additive disease, Test 1–2 was the most powerful on average for the other three disease models. Comparing among the two-marker tests, the most powerful tests on average were: Test 2–2 for an additive disease, Test 2–3 for a dominant disease, and Test 2–5 for a recessive or heterozygote disadvantage disease. However, among these tests, Test 2–3 had relatively consistent power. It had greater overall average power than the haplotype-based test except for an additive disease, but it nevertheless had comparable power to the haplotype-based test. As seen before, the purely HWD contrast test and LD contrast test had the lowest power.

DISCUSSION

In this paper, we have represented the case-control HWD and LD contrasts, given the allele frequency contrast(s), as a quadratic term and an interaction term, respectively. Accordingly, we have written single-marker and two-marker association models with the predictors expressed as simple polynomials. The joint tests of the allele frequency, HWD and LD contrasts may be performed by testing the regression coefficients in a prospective marker association model. By considering these models in the prospective context, the allele frequency, HWD and LD contrasts can be utilized and understood better as follows. First, we gain some intuition as to how these contrasts are related to the disease model and LD structure. For example, the observation that the HWD contrast test has power only in the case of a non-additive disease is obvious in a prospective model because the HWD contrast corresponds to a quadratic term. Second, we can test the three contrasts more systematically in a multi-stage analysis by adopting a sequential test or any other testing procedures developed in regression modeling. Third, these contrasts can easily be tested together with other covariates. Therefore, under this framework population stratification can be modeled by any method that uses covariates for ancestry, as was developed in the context of the allele frequency contrast test [Price, et al. 2006; Pritchard, et al. 2000]. Last, the tests can be easily extended to quantitative traits.

By using the LD structures actually observed in HapMap data, we concluded that Test 2–3, which has an extra interaction term as well as linear terms, provides reliable power in any disease model. This suggests that, in tests involving more than two markers, it may be reasonable to include interaction terms as well as linear terms. Of course, it is difficult to speculate as to which of the many possible interaction terms should be included. In fact, multi-marker models with interaction terms have been presented by several authors [Conti and Gauderman 2004; Cordell and Clayton 2002; Devlin, et al. 2003]. Conti and Gauderman [2004] compared various two-marker tests, some of which are equivalent to the tests in TABLE II. They introduced a modified interaction term and gained comparable power to the haplotype-based test. In this paper, we compared a different set of two-marker tests under a more comprehensive set of disease models. We also show how the interaction term may be interpreted as an LD contrast. Therefore, our results provide further support for the inclusion of interaction terms in multi-marker tests.

Interaction variables have been also included in association models for the purpose of evaluating a biological interaction, or epistasis [Cordell 2002; Wu, et al. 2008; Zhao, et al. 2006]. They are built for unlinked markers in two regions each of which has been shown to be associated with a disease. As opposed to this, our model concerns relatively close markers that may be in pairwise-LD or multi-dimensional LD. Of course, close markers may also have biological interaction, and distinguishing between these two possibilities to identify the true disease pattern is an area for future research. However, localization of disease SNPs is the first step in a genome-wide study, and here we have been concerned with the inclusion of interaction terms to increase power at this screening step.

We showed theoretically that the model with a linear term will fit well for a SNP in weak LD with a causal SNP, whatever the disease model, except a special case. However, for non-additive diseases, as the LD between a disease and marker SNP increases, a test that includes an extra quadratic term has more power than a test that does not. Therefore, as the markers become denser, a test that includes the quadratic term may be preferable. Although the power of the HWD and LD contrast tests were by themselves very low, when combined with the allele frequency contrast(s), the joint tests gained power. Therefore we conclude that it is not advisable for HWD or LD contrast tests to be used alone when conducting a whole genome-wide association study, but rather they should be used in conjunction with the allele frequency contrast test.

Our results showed that in most cases our genotype-based tests have greater power than a haplotype based test. The practical benefit of genotype-based tests is that they do not require phase inference. Estimating haplotypes for a genome-wide association study not only introduces another source of variation in the test, but it also entails significantly more analysis time. However, it should be noted that we only considered two-locus haplotypes and our power comparisons using HapMap data are valid under the assumption that a disease SNP would be part of the same LD pattern as neighboring marker SNPs. Specifying a more realistic distribution for a disease allele and its LD structure with marker alleles – perhaps, for example, using coalescent theory [Zöllner and Pritchard 2005] - could provide a fairer comparison of the tests in real data analysis.

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TABLE I

Probabilities for unphased genotypes

	A_1A_1	A_1A_2	A_2A_2	
B_1B_2	$g_{(1,1)}$	$g_{(0,1)}$	$g_{(-1,1)}$	p_{B1B1}
B_1B_2	$g_{(1,0)}$	$g_{(0,0)}$	$g_{(-1,0)}$	p_{B1B2}
B_2B_2	$g_{(1,-1)}$	$g_{(0,-1)}$	$g_{(-1,-1)}$	p_{B2B2}
	p_{A1A1}	p_{A1A2}	p_{A2A2}	1

TABLE II

Single-marker and two-marker association tests with corresponding models and hypotheses

Test	Model	Null hypothesis (H_0)	Test Description
Single-marker association			
Test 1–2	$log\left(\frac{\mu}{1-\mu}\right) = \beta_0 + \beta_X X + \beta_{X^2} X^2$	$(\beta_X\ \beta_{X^2} = 0$	Allelic-HWD contrast test (Genotypic test)
Test 1–1	$log\left(\frac{\mu}{1-\mu}\right) = \beta_0 + \beta_X X$	$(\beta_X) = 0$	Allele frequency contrast test (Allelic test)
Two-marker association			
Test 2–5	$log\left(\frac{\mu}{1-\mu}\right) = \beta_0 + \beta_X X + \beta_Y Y + \beta_{X^2} X^2 + \beta_{Y^2} Y^2 \beta_{XY} XY$	$(\beta_X\ \beta_Y\ \beta_{XY}\ \beta_{X^2}\ \beta_{Y^2}) = 0$	Joint Allelic-HWD-LD contrast test
Test 2–4	$log\left(\frac{\mu}{1-\mu}\right) = \beta_0 + \beta_X X + \beta_Y Y + \beta_{X^2} X^2 + \beta_{Y^2} Y^2$	$(\beta_X\ \beta_Y\ \beta_{X^2}\ \beta_{Y^2}) = 0$	Joint Allelic-HWD contrast test
Test 2–3	$log\left(\frac{\mu}{1-\mu}\right) = \beta_0 + \beta_X X + \beta_Y Y + \beta_{XY} XY$	$(\beta_X\ \beta_Y\ \beta_{XY}) = 0$	Joint Allelic-LD contrast test
Test 2–2	$log\left(\frac{\mu}{1-\mu}\right) = \beta_0 + \beta_X X + \beta_Y Y$	$(\beta_X\ \beta_Y) = 0$	Joint Allelic contrast test

TABLE III

Constraints for disease models

Disease Model	Constraint
Additive	$\gamma_D^2 = 0$
Dominant or Recessive	$\gamma_D^2 = \pm\gamma D$
Heterozygote (Dis)advantage	$\gamma_D = 0$

TABLE IV

Comparisons of Theoretical and Empirical Power of Test 1–2

	Theoretical Power	Empirical Power		
	T^2 test	T^2 test	LRT	Score test
Additive	0.532	0.533	0.527	0.523
Dominant	0.366	0.366	0.361	0.359
Recessive	0.734	0.741	0.736	0.708
Heterozygote Disadvantage	0.284	0.283	0.277	0.275

For each of the four disease models, parameters are set as follows: $p_D = 0.2, p_A = 0.3$, K = 0.05, $D_{XD} = 0.048 (D' = 0.8), n = 2{,}000$ (500 for recessive), $\alpha = 0.05/500{,}000$. Empirical power is obtained by the ratio of the number of rejected replicates to the total 100,000 replicates.

TABLE V

Power comparisons of two-marker tests

	Test 2–5	Test 2–4	Test 2–3	Haplotype-based	Test 2–2	LD contrast
(LD structure 1)						
Additive	0.775	0.813	0.851	0.842	**0.890**	0.000
Dominant	0.695	0.736	0.774	0.749	**0.819**	0.000
Recessive	0.823	**0.845**	0.746	0.784	0.717	0.001
Heterozygote Disadvantage	0.617	0.653	0.673	0.621	**0.711**	0.000
(LD structure 2)						
Additive	0.962	0.758	**0.970**	0.948	0.850	0.007
Dominant	0.921	0.673	**0.926**	0.887	0.769	0.003
Recessive	0.851	0.647	0.910	**0.945**	0.618	0.206
Heterozygote Disadvantage	**0.845**	0.584	0.831	0.773	0.656	0.001

For both LD structure 1 and LD structure 2 the parameters are set as follows: n = **2,000 (500 for recessive), K = 0.05,** μ_{base} **= 0.04,** α **= 0.05/500,000,** p_A **= 0.2,** p_D **= 0.1,** p_B **= 0.2,** D_{XD} **= 0.045 (**D'_{XD} **= 0.56),** D_{YD} **= 0.047(**D'_{YD} **= 0.59),** D_{XY} **= 0.028(**D'_{XY} **= 0.18)**. For LD structure 1, the three locus LD, D_{Xdy}, was 0.01, and for LD structure 2, D_{XDY} was 0.035. Bold numbers in each row indicate the maximum power over all two-marker tests in that row.

TABLE VI

Mean of Power over Chromosome 11 of CEU HapMap Data

	Single-marker Test			Two-marker Test					
Disease Model	**Test 1–2**	**Test 1–1**	**HWD contrast**	**Test 2–5**	**Test 2–4**	**Test 2–3**	**Test 2–2**	**Haplotype-based**	**LD contrast**
Additive	0.423	**0.457**	0.000	0.575	0.586	0.604	**0.632**	0.625	0.019
Dominant	**0.361**	0.347	0.001	0.505	0.513	**0.518**	0.505	0.488	0.003
Recessive	**0.519**	0.415	0.255	**0.687**	0.677	0.672	0.572	0.624	0.278
Heterozygote Disadvantage	**0.423**	0.241	0.163	**0.587**	0.580	0.546	0.367	0.344	0.058

For both single-marker and two-marker tests, the parameters are set as follows: **n = 2,000 (500 for recessive), K = 0.05,** μ_{base} **= 0.04, α = 0.05/500,000.** Bold numbers in each row indicate the maximum power in that row.