Published in final edited form as:
Genet Epidemiol. 2010 April ; 34(3): 232–237. doi:10.1002/gepi.20453.

Variance-Components Methods for Linkage and Association Analysis of Ordinal Traits in General Pedigrees

G. Diao[1,*] and **D. Y. Lin**[2]

[1] Department of Statistics, George Mason University, Fairfax, Virginia

[2] Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina

Abstract

Many complex human diseases such as alcoholism and cancer are rated on ordinal scales. Well-developed statistical methods for the genetic mapping of quantitative traits may not be appropriate for ordinal traits. We propose a class of variance-component models for the joint linkage and association analysis of ordinal traits. The proposed models accommodate arbitrary pedigrees and allow covariates and gene-environment interactions. We develop efficient likelihood-based inference procedures under the proposed models. The maximum likelihood estimators are approximately unbiased, normally distributed, and statistically efficient. Extensive simulation studies demonstrate that the proposed methods perform well in practical situations. An application to data from the Collaborative Study on the Genetics of Alcoholism is provided.

Keywords

complex diseases; family studies; IBD sharing; LOD score; maximum likelihood; probit model; SNPs

INTRODUCTION

Variance-component (VC) models [Amos, 1994; Amos et al., 1996; Almasy and Blangero, 1998; Abecasis et al., 2000; Epstein et al., 2003; Diao and Lin, 2005, 2006a] are widely used in the genetic analysis of quantitative traits in family studies. This approach is attractive because it accommodates any type of pedigree, allows both linkage and association analysis, and tends to be more powerful than competing approaches. Many human conditions and complex diseases such as cancer and behavioral and psychiatric disorders are measured on ordinal scales. For example, in the Collaborative Study on the Genetics of Alcoholism (COGA) [Begleiter et al., 1995], alcohol dependence was measured on an ordinal scale with four levels (pure unaffected, never drank, unaffected with some symptoms, and affected). Direct applications of the VC models for quantitative traits to ordinal trait data may yield misleading results.

While methods for mapping quantitative trait loci have been well developed, the methodological literature on genetic analysis of ordinal traits is very limited. Feng et al. [2004] proposed a latent-variable proportional odds model for the linkage analysis of ordinal traits. Zhang et al. [2006] and Wang et al. [2006] proposed score tests under logistic regression models, while Baksh et al. [2007] derived a likelihood ratio test. These tests are

[*]Correspondence to: Guoqing Diao, Department of Statistics, George Mason University, MS 4A7, 4400 University Drive, Fairfax, VA 22030–4444. gdiao@gmu.edu.

restricted to nuclear families and the approach by Baksh et al. [2007] may not be effective in dealing with spurious association induced by population stratification. None of these tests utilizes parental phenotypic information. More important, these tests assume that the phenotypes within a family are independent given the covariates and the genotypes at a disease susceptibility locus. This assumption is likely false as complex diseases are often influenced by multiple genetic factors and the ordinal traits within a family may also be correlated due to common environmental factors. Violation of this assumption may result in significant loss of power [Lange et al., 2002].

In this article, we propose a class of VC models for the joint linkage and association analysis of ordinal traits in family studies. The variance-covariance part of the models accounts for within-family correlations. The proposed models allow covariates and gene-environment interaction terms and are applicable to arbitrary pedigrees. We develop efficient likelihood-based estimation and testing procedures. We have implemented the new methods in an efficient and reliable computer program, which is freely available for public use. Extensive simulation studies demonstrate that the proposed methods perform well in practical situations. We provide an application to the aforementioned COGA data.

METHODS

Suppose that the data contain n families or general pedigrees, with n_i individuals in the ith pedigree. Consider a (possibly multiallelic) candidate gene coded by $\mathbf{Z}_{ij}$ for the jth individual of the ith pedigree, which may incorporate both additive and dominant effects. To avoid detecting spurious association induced by population admixture, we decompose the marker genotype score $\mathbf{Z}_{ij}$ into orthogonal between- and within-family components: $\mathbf{b}_{ij}$ is the expected genotype score conditional on family data, and $\mathbf{w}_{ij}$ is the deviation from this expectation [Fulker et al., 1999; Abecasis et al., 2000; Cardon and Abecasis, 2000].

We consider an ordinal trait comprising of K categories. Let Y_{ij} be the trait value for the jth individual in the ith pedigree, and $\mathbf{X}_{ij}$ be the corresponding environmental factors or covariates. We propose the following class of VC models:

$$g(P(Y_{ij} \le k|\mathbf{Z}_{ij}, \mathbf{X}_{ij}, R_{ij}))=\alpha_k+\beta_{\mathrm{b}}^{\mathrm{T}}\mathbf{b}_{ij}+\beta_{\mathrm{w}}^{\mathrm{T}}\mathbf{w}_{ij}+\gamma^{\mathrm{T}}\mathbf{X}_{ij}+R_{ij},\ k=1,\ldots,K-1 \quad (1)$$

where g is a known link function, α_k is the intercept parameter corresponding to category k, β_{b} and β_{w} pertain to the between-family and within-family genetic effects, γ is a set of fixed covariates effects, R_{ij} is a random effect due to the major gene (after accounting for marker association) and other genes at unlinked loci. In this formulation, association is characterized by the mean structure whereas linkage is represented by the covariance structure; β_{b} accounts for all the spurious association between genotype score and phenotype, and β_{w} provides a direct measure of the additive genetic effect. We can also accommodate gene-environment interactions in model (1).

Write $\mathbf{R}_i = (R_{i1}, \ldots, R_{in_i})^{\mathrm{T}}$. The random effects $\mathbf{R}_i$ represent the within-pedigree correlations of the ordinal traits. The most popular choice for the distribution of $\mathbf{R}_i$ is the multivariate normal distribution with mean zero and variance-covariance matrix $\sum_i=\sigma_m^2\sum_{mi}+2\sigma_p^2\sum_{pi}$, where Σ_{mi} contains the proportions of alleles at the major locus that are identical by decent among the relative pairs in the ith family, Σ_{pi} is the matrix of kinship coefficients which depend only on the relatedness of the relative pairs, and σ_m^2 and σ_p^2 are the phenotypic variances explained by linkage with the candidate marker and other genes at unlinked loci, respectively. Several computer programs, such as GENEHUNTER [Kruglyak et al., 1996],

SOLAR [Almasy and Blangero, 1998], and MERLIN [Abecasis et al., 2002], are available for computing Σ_{mi} and Σ_{pi}.

Let $\boldsymbol{\theta}$ denote the complete set of parameters $\alpha_1, \ldots, \alpha_{K-1}$, $\boldsymbol{\beta}_b$, $\boldsymbol{\beta}_w$, γ, σ_m^2, and σ_p^2. The likelihood function for $\boldsymbol{\theta}$ is given by

$$L(\theta)=\prod_{i=1}^{n}\int_{\mathbf{R}_i}\prod_{j=1}^{n_i}\prod_{k=1}^{K}\pi_{ijk}(R_{ij})^{I(Y_{ij}=k)}\varphi(\mathbf{R}_i)\mathrm{d}\mathbf{R}_i \tag{2}$$

where $\pi_{ijk}(R_{ij}) = P(Y_{ij} = k|\mathbf{Z}_{ij}, \mathbf{X}_{ij}, R_{ij})$, and $\varphi(\mathbf{R}_i)$ is the density function for $\mathbf{R}_i$. As there is no closed form for the likelihood function, we use the adaptive Gaussian quadrature approximation [Pinheiro and Bates, 1995]. Our experience indicated that an adaptive Gaussian quadrature with 10 points would provide a very accurate approximation. We then maximize the likelihood function directly through the efficient quasi-Newton algorithm described by Press et al. [1992]. The maximum likelihood estimator, denoted by $\hat{\boldsymbol{\theta}}$, is consistent, asymptotically normal, and asymptotically efficient, and its covariance matrix can be estimated by the inversed Fisher information matrix of (2) [McCulloch and Searle, 2001]. The asymptotic efficiency implies that $\hat{\boldsymbol{\theta}}$ is the most efficient estimator among all valid estimators of $\boldsymbol{\theta}$ and therefore likelihood-based test statistics are the most powerful among all valid test statistics.

It is natural to postulate that there exists an underlying latent variable, denoted by Y_{ij}^*, with $Y_{ij}^* \in (\alpha_{k-1}, \alpha_k]$ corresponding to the kth level for Y_{ij}, where $-\infty = \alpha_0 < \alpha_1 < \cdots < \alpha_K = \infty$. We consider the following probit VC model for Y_{ij}^*

$$Y_{ij}^*= -(\beta_b^{\mathrm{T}}\mathbf{b}_{ij}+\beta_w^{\mathrm{T}}\mathbf{w}_{ij}+\gamma^{\mathrm{T}}\mathbf{X}_{ij}+R_{ij})+\varepsilon_{ij} \tag{3}$$

where ε_{ij} is standard normal. Model (3) is equivalent to model (1) with the inverse Gaussian link function. Alternatively, one may consider the logistic model in which the link function is a logit function. Probit VC model, however, is particularly attractive since it connects naturally to the standard VC models for quantitative traits and the likelihood is easy to evaluate; see Appendix for an alternative expression of the likelihood function.

We can perform various hypothesis testing under model (3). For the linkage analysis, we exclude the association components in (3) and test the null hypothesis H_0: $\sigma_m^2=0$ against the alternative hypothesis H_0: $\sigma_m^2>0$. We can assess whether there is association between the candidate marker and the ordinal trait by testing the null hypothesis H_0: $\boldsymbol{\beta}_w = \mathbf{0}$. Similar to the QTDT, the proposed model allows us to test for the presence of population admixture, H_0: $\boldsymbol{\beta}_b = \boldsymbol{\beta}_w$ vs. H_1: $\boldsymbol{\beta}_b \neq \boldsymbol{\beta}_w$. If there is no population admixture, we can replace $\boldsymbol{\beta}_b^{\mathrm{T}}\mathbf{b}_{ij}+\beta_w^{\mathrm{T}}\mathbf{w}_{ij}$ in (3) with $\boldsymbol{\beta}^{\mathrm{T}}\mathbf{Z}_{ij}$ and test the null hypothesis of no association H_0:$\boldsymbol{\beta} = 0$. For each hypothesis test, we calculate the likelihood ratio statistic

$$\mathrm{LR}= -2[\log L(\tilde{\boldsymbol{\theta}}) - \log L(\hat{\boldsymbol{\theta}})]$$

where $\tilde{\boldsymbol{\theta}}$ is the restricted maximum likelihood estimator of $\boldsymbol{\theta}$ under the null hypothesis. For testing linkage, the distribution of LR is approximately a half-and-half mixture of a χ_1^2 variable and a point mass at 0 [Self and Liang, 1987]. For testing association or the presence of population admixture, LR is approximately χ^2 distributed with the degrees of freedom being the dimension of $\boldsymbol{\beta}_w$.

RESULTS

SIMULATION STUDIES

We conducted extensive simulation studies to assess the performance of the proposed linkage and association tests for ordinal traits. We assumed an additive disease gene, *Q*, with two alleles Q_1 and Q_2 and simulated a diallelic marker locus *M* with two alleles M_1 and M_2. We generated population admixture by mixing in equal proportions families from two populations, *A* and *B*, with different QTL and marker allele frequencies: in population *A*, $p_{Q_1} = p_{M_1} = 0.4$; in population *B*, $p_{Q_1} = p_{M_1} = 0.6$. For each simulation, we generated 10,000 data sets, each with 100 nuclear families. Each family consisted of 2, 3, or 4 siblings with probabilities 0.3, 0.4, and 0.3, respectively. The parental genotypes were assumed to be known. We first generated the latent variables from the model

$$Y_{ij}^{*}=\beta Z_{ij} - X_{1ij}+X_{2ij}+g_{ij}+e_{ij} \quad (4)$$

where Z_{ij} is the QTL genotype score, X_{1ij} is a binary variable with 0.5 probability of being 1, X_{2ij} is a standard normal random variable, and g_{ij} and e_{ij} are independent zero-mean normal variables with variances σ_p^2 and σ_e^2, respectively. We then generated the ordinal traits with four levels {0, 1, 2, 3} according to the distribution of alcohol dependence observed in the COGA study.

We first assessed the type I error and power of the proposed linkage test of H_0: $\sigma_m^2=0$ with ordinal traits. For comparisons, we also considered the standard VC linkage test for quantitative traits proposed by Amos [1994]. We set σ_p^2 and σ_e^2 to 0.6 and 0.4, respectively. While fixing β at 1.63, we varied the recombination fraction between the marker locus and the QTL from 0 to 0.5. Figure 1 presents the type I error and power of the linkage tests at the nominal significance levels of 5, 1, and 0.1%. The new method provides accurate control of the type I error and is substantially more powerful than the method of Amos [1994]. At the true QTL, the powers of the new linkage test are 83.5, 63.0, and 34.4% at the nominal significance levels of 5, 1, and 0.1%, respectively, as compared to 74.8, 52.6, and 25.9% for Amos' test.

Next, we carried out simulation studies for the association analysis with ordinal traits. We considered the same model for data generation as in the above linkage analysis except that different values for β, σ_p^2, and σ_e^2 were used. We introduced linkage disequilibrium (LD) between the QTL and marker locus in the parental chromosomes. In each population, LD is measured by $D = p_{M_1Q_1} - p_{M_1}p_{Q_1}$, where $p_{M_1Q_1}$ is the frequency of haplotype M_1Q_1. The maximum of *D* is $D_{\max} = \min(p_{M_1}, p_{Q_1}) - p_{M_1}\, p_{Q_1}$, and the standardized LD coefficient is $D' = D/D_{\max}$. Values $D' = 0$ and $D' = 1$ correspond to LD and complete LD between the QTL and marker locus, respectively. When there is no LD in either population, LD exists in the pooled population with $D' = 0.04$. The marker locus is tightly linked to the QTL with a

recombination fraction of 0, but we considered different levels of D'. The values of β, σ_p^2, and σ_e^2 are 0.645, 0.6, and 1.2, respectively.

We assessed the performance of the proposed association test of H_0:$\beta_w = 0$ and compared it with the QTDT for quantitative traits proposed by Abecasis et al. [2000], the score test adjusting for covariates proposed by Wang et al. [2006], and the likelihood ratio test proposed by Baksh et al. [2007]. The results of these studies are presented in Table I. The new method is robust to spurious association induced by population admixture and provides accurate control of the type I error. The new method is more powerful than the QTDT and the score test by Wang et al. [2006]. The association test by Baksh et al. [2007] is very sensitive to population admixture and the type I error is very wrong.

We also evaluated the properties of the maximum likelihood estimator of the marker effect on the ordinal trait. Table II summarizes the results. The proposed estimator appears to be unbiased. The standard error estimator, that is, square root of the variance estimator, reflects accurately the true variation, and the confidence intervals have proper coverage probabilities.

Finally, we considered the same models as above for data generation but sampled only those sibships with one or more individuals with ordinal trait in the fourth level. Table III presents the results with such ascertained families. The proposed methods still provide accurate control of the type I error and are more powerful than the QTDT. The type I error of the test by Baksh et al. [2007] continues to be inflated.

COGA STUDY

Alcoholism is a disease that tends to run in families and results in part from genetic risk factors. COGA is a large-scale, multi-center collaboration with the goal of identifying genes that affect the susceptibility to alcohol dependence. The data provided to Genetic Analysis Workshop 14 consist of 1,614 individuals from 143 families with family sizes ranging from 5 to 32. The alcohol dependence measure was based on DSM-III-R and Feighner [Hasin, 2003], coded as ALDX1. This measure was expressed on an ordinal scale with four categories: pure unaffected, never drank, unaffected with some symptoms, and affected. The relative frequencies of these four categories were 0.205, 0.021, 0.311, and 0.463.

Preliminary analysis revealed that gender was associated with ALDX1; more males developed alcohol dependence than females. Figure 2 presents the gender-specific bar plots of the ordinal trait ALDX1. Previous linkage analysis showed a linked region on chromosome 14 [Palmer et al., 1999]. We performed association analysis under model (3) using 172 SNPs on chromosome 14 from Illumina and included gender as a covariate in the model. We also considered the QTDT with an equal space coding.

Figure 3 displays the LOD scores from the proposed probit VC method and the QTDT. The LOD scores were obtained by dividing the original likelihood ratio statistics by 2 log 10. The LOD score curves from the probit VC method and the QTDT reach their peaks at the same location of 0 cM for SNP rs1972373, with peak values 3.4 and 2.9, respectively. The corresponding *P*-values are 7.5×10^{-5} and 2.6×10^{-4}, respectively. These results are consistent with those of Wang et al. [2006], who reported a *P*-value of 3.8×10^{-4} for SNP rs1972373. The proposed method yielded the most significant result among the three approaches. With the Bonferroni correction for multiple testing, the probit VC method still declared significant association between the SNP marker and ALDX1 at the nominal significance level of 0.05, with an adjusted *P*-value of 0.013.

DISCUSSION

We have developed VC models for the joint linkage and association analysis of ordinal traits in family studies. The new methods accommodate extended pedigrees with missing genotype data, account for within-family correlations, allow covariates and gene-environment interactions, and avoid the spurious association introduced by population admixture. As demonstrated by the simulation studies and real data analysis, the proposed methods can greatly improve the power of mapping genes influencing ordinal traits over the existing linkage and association tests.

We have implemented an efficient and reliable algorithm for the new methods in a cost-free computer program. The computing time is not of concern even though numerical approximation of the likelihood function is involved. For the COGA data with the largest family size 32, it took less than 1 min on a Dell PowerEdge server to perform the proposed association tests at one locus. With sibship sizes ranging from 2 to 4 in the simulation studies, the analysis at one position takes only 1 sec.

Many human complex diseases exhibit variable ages of onset. There may exist genetic factors that not only influence the risk of developing a particular disease but also influence the severity of the disease. One particular example is the COGA study. Using the same data set, Li et al. [2005] and Diao and Lin [2006b] detected significant association between SNP rs1972373 on chromosome 14 and the age at onset of ALDX1. The power can potentially be increased by modeling the age of onset and disease severity simultaneously. Further investigation is warranted.

In the excellent review of family-based association tests for quantitative traits by Ewens et al. [2008], it was shown theoretically that regression-based tests including only the within-family component in the regression model are generally not robust against population admixture. We expect these results to be true for ordinals traits as well. Our proposed methods, however, include both the between- and with-family components in the regression model. By the arguments of Abecasis et al. [2000], the between-family genetic effect $\boldsymbol{\beta}_b$ explains all the spurious association due to population admixture. As expected, the simulation studies demonstrate that the proposed test statistics are robust against population admixture.

Several groups of investigators, including Van Steen et al. [2005] and Ionita-Laza et al. [2007] proposed to use both components, but strictly separate the between-and within-family components in the construction of the test statistic for quantitative traits. These approaches are shown to be robust to spurious effects and can achieve power comparable to population-based approach. It would be worthwhile to develop similar procedures for family-based association analysis of ordinal traits.

Acknowledgments

Contract grant sponsor: National Institutes of Health; Contract grant number: GM31575.

This research was supported by the National Institutes of Health. The authors are grateful to the COGA investigators and Jean W. MacCluer for providing the COGA data from GAW14, which was supported in part by the NIH grant GM31575. We also thank Dr. Fazil Baksh for providing us his computer program AsTeC.

References

Abecasis GR, Cardon LR, Cookson WOC. A general test of association for quantitative traits in nuclear families. Am J Hum Genet 2000;66:279–292. [PubMed: 10631157]

Abecasis GR, Cherny SS, Cookson WO, Cardon LR. Merlin-rapid analysisof dense genetic maps using sparse gene flow trees. Nat Genet 2002;30:97–101. [PubMed: 11731797]

Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. Am J Hum Genet 1998;62:1198–1211. [PubMed: 9545414]

Amos CI. Robust variance-components approach for assessing genetic linkage in pedigrees. Am J Hum Genet 1994;54:535–543. [PubMed: 8116623]

Amos CI, Zhu DK, Boerwinkle E. Assessing genetic linkage and association with robust components of variance approaches. Ann Hum Genet 1996;60:143–160. [PubMed: 8839128]

Baksh MF, Balding DJ, Yyes TJ, Whittaker JC. Family-based association analysis with ordinal categorical phenotypes, covariates and interactions. Genet Epidemiol 2007;31:1–8. [PubMed: 17096343]

Begleiter H, Reich T, Hesselbrock V, Porjesz B, Li TK, Schuckit MA, Edenberg HJ, Rice JP. The Collaborative Study on the Genetics of Alcoholism. Alcohol Health Res World 1995;19:228–236.

Cardon LR, Abecasis GR. Some properties of a variance components model for fine-mapping quantitative trait loci. Behav Genet 2000;30:235–243. [PubMed: 11105397]

Diao G, Lin DY. A powerful and robust method for mapping quantitative trait loci in general pedigrees. Am J Hum Genet 2005;77:97–111. [PubMed: 15918154]

Diao G, Lin DY. Improving the power of association tests for quantitative traits in family studies. Genet Epidemiol 2006a;30:301–313. [PubMed: 16607624]

Diao G, Lin DY. Semiparametric variance-component models for linkage and association analysis of censored trait data. Genet Epidemiol 2006b;30:570–581. [PubMed: 16858699]

Epstein MP, Lin XH, Boehnke M. A Tobit variance-component method for linkage analysis of censored trait data. Am J Hum Genet 2003;72:611–620. [PubMed: 12587095]

Ewens WJ, Li M, Spielman RS. A review of family-based tests for linkage disequilibrium between a quantitative trait and a genetic marker. PLoS Genet 2008;4:e1000180. [PubMed: 18818728]

Feng R, Leckman JF, Zhang HP. Linkage analysis of ordinal traits for pedigree data. PNAS 2004;101:16739–16744. [PubMed: 15548606]

Fulker DW, Cherny SS, Sham PC, Hewitt JK. Combined linkage and association sib-pair analysis for quantitative traits. Am J Hum Genet 1999;64:259–267. [PubMed: 9915965]

Genz A. Numerical computation of multivariate normal probabilities. J Comput Graph Stat 1992;1:141–149.

Hasin D. Classification of alcohol use disorders. Alcohol Res Health 2003;27:5–17. [PubMed: 15301396]

Ionita-Laza I, McQueen MB, Laird NM, Lange C. Genomewide weighted hypothesis testing in family-based association studies, with an application to a 100K scan. Am J Hum Genet 2007;81:607–614. [PubMed: 17701906]

Kruglyak L, Daly M, Reeve-Daly M, Lander ES. Parametric and nonparametric linkage analysis: a unified multi-point approach. Am J Hum Genet 1996;58:1347–1363. [PubMed: 8651312]

Lange C, DeMeo DL, Laird NM. Power and design considerations for a general class of family-based association tests: quantitative traits. Am J Hum Genet 2002;71:1330–1341. [PubMed: 12454799]

Li Y, Martin ER, Zhang L, Allen AS. Application of a rank-based genetic association test to age-at-onset data from the Collaborative Study on the Genetics of Alcoholism study. BMC Genet 2005;S53(6 Suppl 1)

McCulloch, CE.; Searle, SR. Generalized, Linear, and Mixed Models. New York: Wiley; 2001.

Palmer LJ, Katrina JT, Burton PR. Genome-wide linkage analysis using genetic variance components of alcohol dependency-associated censored and continuous traits. Genet Epidemiol 1999;17:S283–S288. [PubMed: 10597450]

Pinheiro JC, Bates DM. Approximations to the log-likelihood function in the nonlinear mixed-effects model. J Comput Graph Stat 1995;4:12–35.

Press, WH.; Teukolsky, SA.; Vetterling, WT.; Flannery, BP. Numerical Recipes in C: The Art of Scientific Computing. 2. New York: Cambridge University Press; 1992.

Self SG, Liang KL. Asymptotic properties of maximum likelihood estimators and likelihood ratio tests under nonstandard conditions. J Am Statist Assoc 1987;82:605–610.

Van Steen K, McQueen MB, Herbert A, Raby B, Lyon H, DeMeo DL, Murphy A, Su J, Datta S, Rosenow C, Christman M, Silverman EK, Laird NM, Weiss ST, Lange C. Genomic screening and replication using the same data set in family-based association testing. Nat Genet 2005;37:683–691. [PubMed: 15937480]

Wang XQ, Ye YQ, Zhang HP. Family-based association test for ordinal traits adjusting for covariates. Genet Epidemiol 2006;30:728–736. [PubMed: 17086513]

Zhang HP, Wang XQ, Ye YQ. Detection genes for ordinal traits in nuclear families and a unified approach for association studies. Genet 2006;172:693–699.

APPENDIX: LIKELIHOOD FUNCTION FOR THE PROBIT VC MODEL

For the probit VC model, we can represent the likelihood function for $\boldsymbol{\theta}$ in a computationally more convenient way. Let $\boldsymbol{Y}_i^*=(Y_{i1}^*,\ldots,Y_{in_i}^*)^{\mathrm{T}}$, $\mathbf{b}_i=(\mathbf{b}_{i1}^{\mathrm{T}},\ldots,\mathbf{b}_{in_i}^{\mathrm{T}})^{\mathrm{T}}$, $\mathbf{w}_i=(\mathbf{w}_{i1}^{\mathrm{T}},\ldots,\mathbf{w}_{in_i}^{\mathrm{T}})^{\mathrm{T}}$, and $\mathbf{X}_i=(\mathbf{X}_{i1}^{\mathrm{T}},\ldots,\mathbf{X}_{in_i}^{\mathrm{T}})^{\mathrm{T}}$. Then $\boldsymbol{Y}_i^*$ follows a multivariate normal distribution with mean $\boldsymbol{\mu}_i = -(\mathbf{b}_i\boldsymbol{\beta}_{\mathrm{b}} + \mathbf{w}_i\boldsymbol{\beta}_{\mathrm{w}} + \mathbf{X}_i\gamma)$ and variance-covariance matrix $\mathbf{V}_i=\sigma_m^2\sum_{mi}+2\sigma_p^2\sum_{pi}+\mathbf{I}_i$, where $\mathbf{I}_i$ is the n_i-dimensional identity matrix. Thus, the likelihood function for the ith family can be expressed as

$$L_i(\boldsymbol{\theta})=\int_{\alpha_{Y_{i1}-1}}^{\alpha_{Y_{i1}}}\cdots\int_{\alpha_{Y_{in_i}-1}}^{\alpha_{Y_{in_i}}}(2\pi)^{-n_i/2}|\mathbf{V}_i|^{-1/2}\times\exp\{-\frac{1}{2}(\mathbf{y}-\boldsymbol{\mu}_i)^{\mathrm{T}}\mathbf{V}_i^{-1}(\mathbf{y}-\boldsymbol{\mu}_i)\}\mathrm{d}\mathbf{y}$$

which can be approximated by a subroutine for computing multivariate normal probabilities given by Genz [1992]. The likelihood function for n families is $L(\boldsymbol{\theta})=\prod_{i=1}^{n}L_i(\boldsymbol{\theta})$.

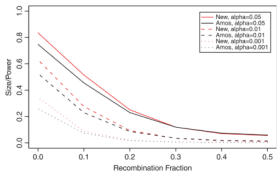

Fig. 1.
Type I error and power of the new linkage test versus Amos' test at the nominal significance level α.

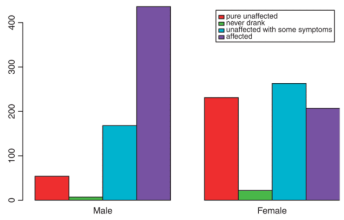

Fig. 2.
Bar plot of the ordinal trait ALDX1 by gender in the COGA study.

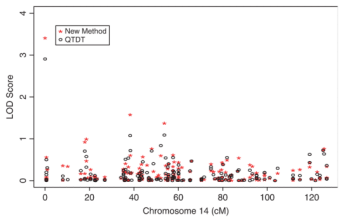

Fig. 3.
LOD scores based on the new method and the QTDT for the ordinal trait ALDX1 on chromosome 14 in the COGA study.

TABLE I

Type I error and power (%) of the association tests

	New			QTDT			Wang et al.			Baksh et al.		
D′	**α = 5%**	**1%**	**0.1%**	**5%**	**1%**	**0.1%**	**5%**	**1%**	**0.1%**	**5%**	**1%**	**0.1%**
0.00	5.27	1.08	0.11	5.18	1.03	0.12	5.41	1.04	0.08	9.37	2.79	0.47
0.25	13.07	3.81	0.60	12.04	3.52	0.58	12.80	3.63	0.56	32.4	15.56	5.25
0.50	36.21	16.95	4.48	33.12	14.88	3.85	35.41	15.88	4.03	71.33	49.81	25.00
0.75	67.84	43.88	18.97	63.07	39.31	16.03	65.86	41.93	17.13	94.26	85.12	64.40
1.00	91.03	75.62	49.72	88.23	70.86	42.7	89.51	72.64	44.37	99.57	98.25	92.84

TABLE II

Summary statistics for the estimation of the marker effects

D'	Bias	SE	SEE	CP (%)
0.00	−0.001	0.148	0.146	93.7
0.25	0.002	0.148	0.147	94.1
0.50	0.004	0.149	0.147	93.9
0.75	0.006	0.149	0.149	94.1
1.00	0.008	0.150	0.150	94.5

Note: Bias is the difference between the sampling mean of the parameter estimator and the true parameter value; SE is the sampling standard error of the parameter estimator; SEE is the mean of the standard error estimator; and CP is the coverage probability of the 95% confidence interval.

TABLE III

Type I error and power (%) of the association tests in ascertained families

	New			QTDT			Wang et al.			Baksh et al.		
D′	**α = 5%**	**1%**	**0.1%**	**5%**	**1%**	**0.1%**	**5%**	**1%**	**0.1%**	**5%**	**1%**	**0.1%**
0.00	5.10	1.02	0.10	4.85	0.99	0.10	5.08	0.92	0.06	6.40	1.45	0.22
0.25	13.09	4.07	0.68	12.01	3.62	0.58	12.31	3.54	0.52	22.09	8.69	1.92
0.50	35.92	16.88	4.75	33.40	15.27	4.10	34.30	15.72	4.06	55.94	32.69	12.65
0.75	66.81	43.7	19.09	63.03	39.41	15.92	64.80	40.48	15.81	87.12	69.97	42.41
1.00	89.59	74.54	48.41	87.17	69.74	42.16	87.96	70.46	42.21	98.16	93.42	78.79