**SUPPLEMENTAL MATERIAL**

Following the notations similar to the main texts, we have a total number of individuals in the study population, enrolled from families with members from the -th family.The family-based genetic random filed (FGRF) method uses a conditional auto-regressive model. The matrix form the model is given by *Eq.* (3) in the main texts:

where is the phenotype vector of all individuals from all families in a sequential order; ; is a block diagonal matrix in which the -th block is a matrix with the element as ; ; is a matrix for pairwise genetic similarities among individuals.

**Modeling Within-family Correlation**

In *Eq*. (A1), is a matrix, each element of which is proportional to the correlation between the phenotypes of two individuals (e.g. and ). We further assume the phenotypic correlation among family members can be attributed to a mixture of components through the following decomposition:

;

where is a block matrix in which the -th block is a matrix with the element as the kinship coefficient between the -th and the -th members of family ; and are also block matrix representing phenotypic correlation due to shared environmental factors among family members, where the -th block of is a matrix with all elements as 1, featuring a compound symmetric structure, and the -th block of is a matrix with the element as 1 for parent-offspring pairs and as 0 otherwise. It is worthwhile to note that that the generalized estimating equations (GEE) were used for statistical inference, and is a working correlation matrix partially robust to its choice in terms of type-I error control. The statistical inference asymptotically remains valid even when the working correlation matrix is incorrectly specified.

**Estimation of Nuisance Parameters and**

The estimating equations with respect to and are:

where equals for quantitative phenotypes and for binary phenotypes. The estimators and are calculated iteratively. Given initial values of , we estimate by the Fisher’s Scoring Algorithm; given the estimated , we update by solving linear equations , . The iteration stops when convergence is reached.

**Asymptotic Distribution of score statistic for the FGRF-O**

In this section, we derive statistical inference for the FGRF-O modeled by *Eq.* (A1). Let be the matrix for -locus genotypes of individuals, and the minor allele frequency of each variant was centered at 0. We further denote , and . It follows that the score statistic

To derive the asymptotic distribution of the above test statistic, we write out the first order Taylor expansion of :

We further denote as in *Eq.* (A3) and . The first order Taylor expansion of is

 Plugging the *Eq.* (A5) to *Eq.* (A4),

It is easy to see that Therefore

It follows that

where , and . The null distribution of is given by the property of quadratic form.

where the s are i.i.d. Chi-square distributions with degree of freedom one; s are the eigen values of

**Asymptotic Distribution of score statistic for the FGRF-W and for the FGRF-B**

In this section, we derive statistical inference for the FGRF-W and the FGRF-B modeled by *Eq.* (8) of the main text. Similar to the above section, we define score functions for within-family and between-family summary statistics:

Following the same Taylor expansion steps in *Eq*. (A4) and *Eq*. (A5), we have

We further denote

It then follows:

**For the FGRF-W**

Therefore,

where , and .

**For the FGRF-B,**

We denote as the genotype matrix. Without loss of generality, we further assume the minor allele frequency of each variant is centered at 0 within each family (See *Eq.* (7) of the main text). The between-family similarity matrix = , where . It follows:

where c is a constant. By the result derived above,

where , and . The null distribution of is given by the property of quadratic form.

where the s are i.i.d. Chi-square distributions with degree of freedom one; s are the eigen-values of

**Small-sample Adjustment**

We also propose an analytical small-sample adjustment for the empirical variance estimator,

The adjustment was originally proposed by Guo, et al. (2005) for a different purpose.1 In our study, we observe that the score type tests are conservative in rare-variants analysis because the empirical variance estimators and rely on the i.i.d and mean 0 assumption of s and s. The variance estimates can be unstable when rare variants only exist in a small number of families, because and with or without the rare variants can be highly distinct. When the sample means of s and s deviate from 0, and can be over-estimated. The use of sample variance estimator and can improve the conservative type-I error.

REFERENCES

1. Guo, X., Pan, W., Connett, J.E., Hannan, P.J., and French, S.A. (2005). Small-sample performance of the robust score test and its modifications in generalized estimating equations. Stat Med 24, 3479-3495.