Supplementary Material

Rare variant association test in family based sequencing studies

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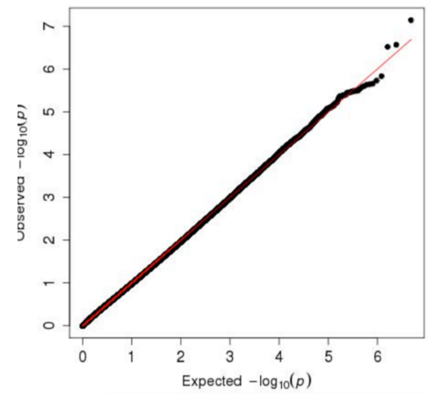
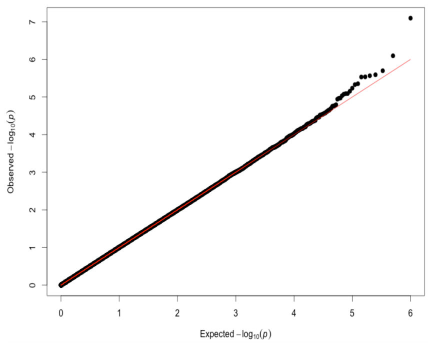
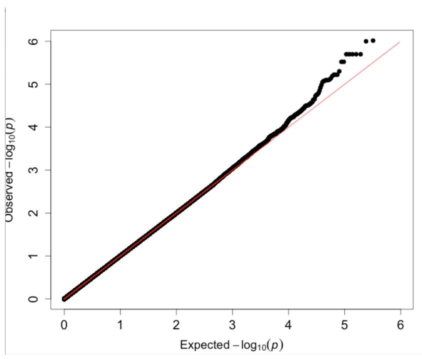


(a)

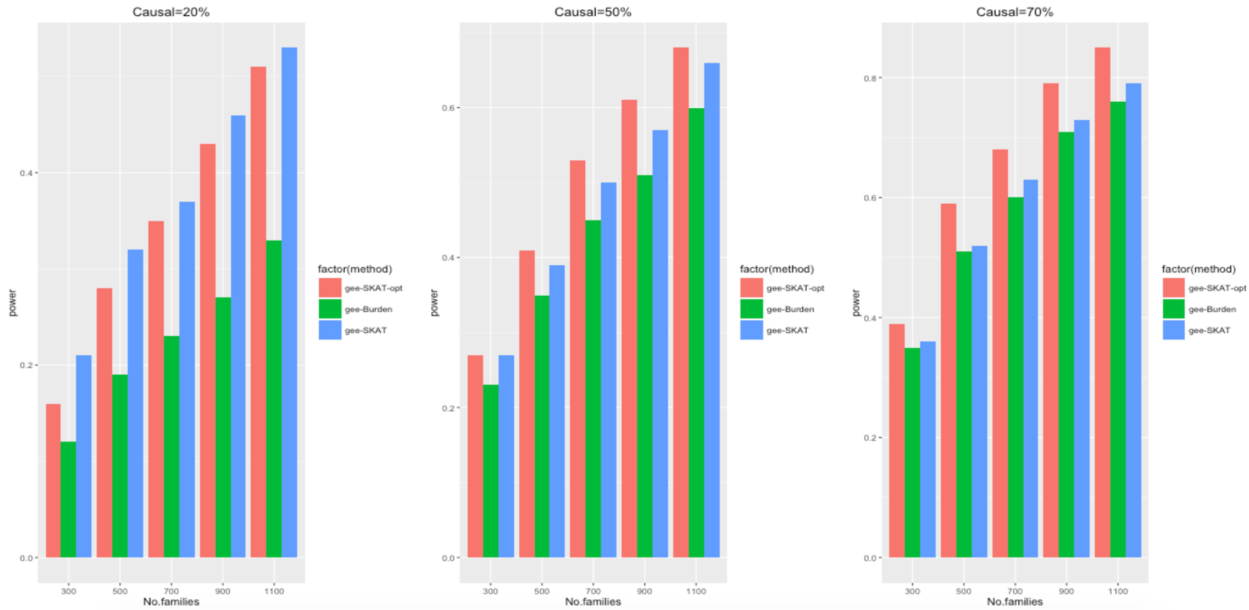


(b)

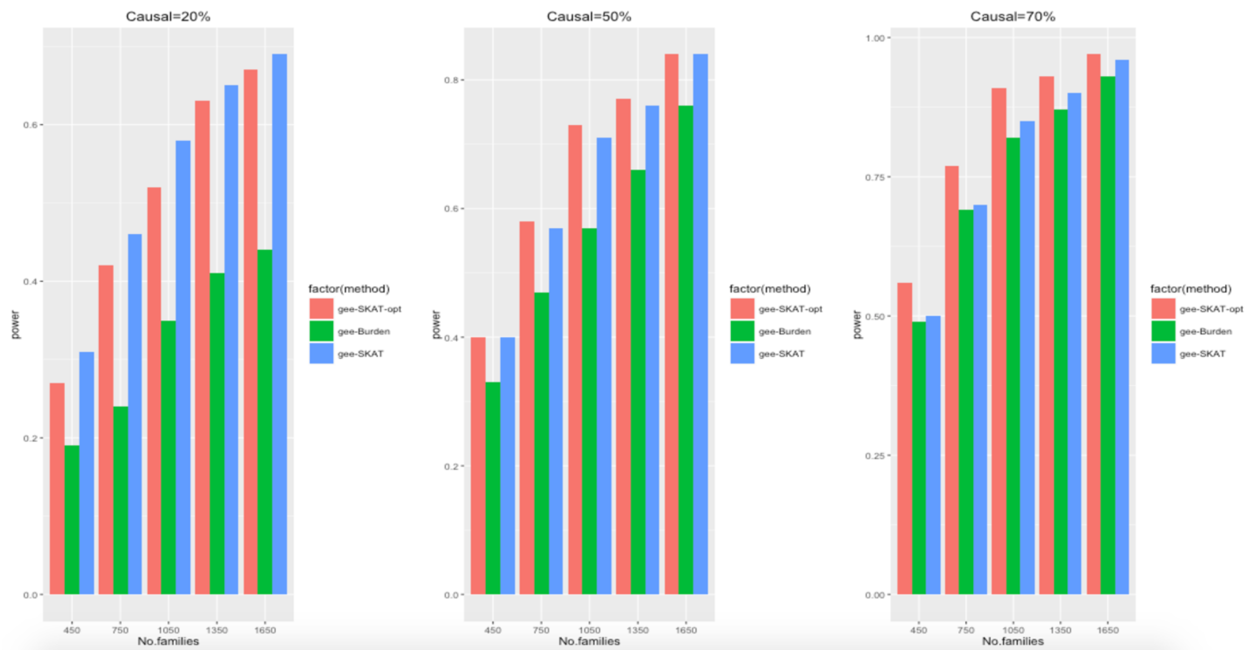


(c)

Supplementary Figure 1: QQ plot through permutation (a) and optimal test (b) from simulations under the null. (c) shows the results from simulation with a mixed sample of sib pairs and nuclear families.



Supplementary Figure 2: Power comparison with sib pair samples, in which half of the families have at least 1 sick child, while other families are unaffected.



Supplementary Figure 3: Power comparison with a mixed sample of sib pairs and nuclear families.

1 Null distribution of the GEE-KM statistic T

To derive the asymptotic distribution of the statistic T, as shown in equation (4), denote $\mathbf{A} = \mathbf{I}(\boldsymbol{\theta_0}) = -E(\frac{\partial \mathbf{U}}{\partial \boldsymbol{\theta}^T}) = \sum_{i=1}^{n} \mathbf{D_i^T V_i^{-1} D_i}$, where $\boldsymbol{\theta_0 = (\alpha_0, 0)'}$ is the true value of $\boldsymbol{\theta}$. Partition $\mathbf{A}$ as $\mathbf{A_{xx}}, \mathbf{A_{xz}}, \mathbf{A_{zx}}, \mathbf{A_{zz}}$ according to the dimensions of $\boldsymbol{\alpha}$ and $\boldsymbol{\beta}$. From a Taylor series expansion, we get $\boldsymbol{\tilde{\alpha} - \alpha_0} = \boldsymbol{A_{xx}^{-1} U_x(\theta_0)} + o_p(1)$, where $\boldsymbol{\tilde{\alpha}}$ is the MLE of $\boldsymbol{\alpha}$ under the null.
From a Taylor expansion of $\mathbf{U_z}(\boldsymbol{\tilde{\theta}})$, where $\boldsymbol{\tilde{\theta}} = (\boldsymbol{\tilde{\alpha}}, 0)'$, we have

$$
\begin{aligned}
\mathbf{U_z}(\boldsymbol{\tilde{\theta}_0}) =& [\mathbf{U_z}(\boldsymbol{\theta}_0) - \mathbf{A_z x}(\tilde{\boldsymbol{\alpha}} - \boldsymbol{\alpha}_0)] + o_p(1) \\
=& [-\mathbf{A_{zx} A_{xx}^{-1} U_x}(\boldsymbol{\theta_0}) + \mathbf{U_z}(\boldsymbol{\theta_0})] + o_p(\sqrt{n})
\end{aligned}
$$

Let $\mathbf{C} = (-\mathbf{A_{zx} A_{xx}^{-1}}, \mathbf{I})$, then $\mathbf{U_z} \approx CU(\boldsymbol{\theta}_0)$. Denote $\mathbf{B} = E(\mathbf{U}(\boldsymbol{\theta_0})\mathbf{U^T}(\boldsymbol{\theta_0})) = \sum_{i=1}^{n} \mathbf{D_i^T V_i^{-1}} Cov(\boldsymbol{y}_i) \mathbf{V_i^{-1} D_i}$. As $n \to \infty$, $\mathbf{B}^{1/2}\mathbf{U}(\boldsymbol{\theta_0}) \to N(0, \mathbf{I})$ in distribution.

$$
\begin{aligned}
T =& \mathbf{U_z^T W R W U_z} \\
=& \{\mathbf{B}^{1/2}\mathbf{U}(\boldsymbol{\theta}_0)\}^T \{\mathbf{B^{1/2} C^T W R W C B^{1/2}}\} \{\mathbf{B}^{1/2}\mathbf{U}(\boldsymbol{\theta}_0)\} \\
\to & \sum_{k=1}^{p} \lambda_k \chi^2_{k,1}
\end{aligned}
$$

where $(\lambda_1, \ldots, \lambda_p)$ are the eigenvalues of $\mathbf{B^{1/2} C^T W R W C B^{1/2}}$ and $\chi^2_{k,1}$ are independent χ^2_1 random variables. $Cov(\boldsymbol{y}_i)$ in $\mathbf{B}$ is estimated by $\{\boldsymbol{y}_i - \boldsymbol{\mu}_i(\boldsymbol{\theta}_0)_i\}\{\boldsymbol{y}_i - \boldsymbol{\mu}_i(\boldsymbol{\theta}_0)_i\}^T$

2 Asymptotic approximation of the optimal-test statistic

Following the original SKAT-O (Lee et al. 2012) derivation, denote $\mathbf{Z} = \mathbf{W C B^{1/2}}$, $\bar{z} = \mathbf{Z} \cdot \mathbf{1}_p / p, \mathbf{M} = \bar{z}(\bar{z}^T \bar{z})^{-1} \bar{z}^T$ and $\mathbf{Y} = \mathbf{B^{-1/2}} \mathbf{U}(\theta_0) \sim N(0, \mathbf{I})$, then

$$
T = \mathbf{Y^T Z}[(\mathbf{1} - \rho)\mathbf{I} + \rho \mathbf{1_p 1_p^T}]\mathbf{Z^T Y} = (\mathbf{1} - \rho)\mathbf{Y^T Z Z^T Y} + \rho p^2 \mathbf{Y^T \bar{z} \bar{z}^T Y}
$$

$$
\begin{aligned}
\mathbf{M Z Z^T M} =& \bar{z}(\bar{z}^T \bar{z})^{-1} \bar{z}^T \mathbf{Z Z^T} \bar{z}(\bar{z}^T \bar{z})^{-1} \bar{z}^T \\
=& \frac{1}{(\bar{z}^T \bar{z})^2} \bar{z}\bar{z}^T \mathbf{Z Z^T} \bar{z}\bar{z}^T = \frac{1}{(\bar{z}^T \bar{z})^2} \bar{z}(\mathbf{Z^T} \bar{z})^T (\mathbf{Z^T} \bar{z}) \bar{z}^T \\
=& \frac{\bar{z}\bar{z}^T}{(\bar{z}^T \bar{z})^2} (\mathbf{Z^T} \bar{z})^T (\mathbf{Z^T} \bar{z}) \\
=& \frac{\bar{z}\bar{z}^T}{(\bar{z}^T \bar{z})^2} \sum_{j=1}^{p} (\bar{z}^T \mathbf{Z}_{\cdot j})^2
\end{aligned}
$$

where $\mathbf{Z}_{\cdot j}$ is the jth column of $\mathbf{Z}$.

$$\begin{aligned}
T =&(\mathbf{1}-\rho)\mathbf{Y^T}\mathbf{Z}\mathbf{Z^T}\mathbf{Y}+\rho p^2\mathbf{Y^T}\bar{\mathbf{z}}\bar{\mathbf{z}}^{\mathbf{T}}\mathbf{Y}\\
=&(\mathbf{1}-\rho)\mathbf{Y^T}(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}(\mathbf{I}-\mathbf{M})\mathbf{Y}\\
&+\mathbf{2}(\mathbf{1}-\rho)\mathbf{Y^T}(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M}\mathbf{Y}\\
&+(\mathbf{1}-\rho)\mathbf{Y^T}(\mathbf{M}\mathbf{Z}\mathbf{Z^T}\mathbf{M}+\mathbf{M}\mathbf{Z}\mathbf{Z^T}-\mathbf{Z}\mathbf{Z^T}\mathbf{M})\mathbf{Y}+p^2\rho\mathbf{Y^T}\bar{\mathbf{z}}\bar{\mathbf{z}}^{\mathbf{T}}\mathbf{Y}
\end{aligned}$$

$$\begin{aligned}
&(\mathbf{1}-\rho)\mathbf{Y^T}(\mathbf{M}\mathbf{Z}\mathbf{Z^T}\mathbf{M}+\mathbf{M}\mathbf{Z}\mathbf{Z^T}-\mathbf{Z}\mathbf{Z^T}\mathbf{M})\mathbf{Y}+p^2\rho\mathbf{Y^T}\bar{\mathbf{z}}\bar{\mathbf{z}}^{\mathbf{T}}\mathbf{Y}\\
=&(1-\rho)\frac{\sum_{j=1}^{p}(\bar{z}^T\mathbf{Z}_{\cdot j})^2}{(\bar{z}^T\bar{z})^2}\mathbf{Y^T}\bar{\mathbf{z}}\bar{\mathbf{z}}^{\mathbf{T}}\mathbf{Y}+\rho p^2\mathbf{Y^T}\bar{\mathbf{z}}\bar{\mathbf{z}}^{\mathbf{T}}\mathbf{Y}\\
=&\gamma(\rho)\frac{1}{\bar{z}^T\bar{z}}\mathbf{Y^T}\bar{\mathbf{z}}\bar{\mathbf{z}}^{\mathbf{T}}\mathbf{Y}
\end{aligned}$$

where $\gamma(\rho)=\rho p^2\bar{z}^T\bar{z}+\frac{1-\rho}{\bar{z}^T\bar{z}}\sum_{j=1}^{p}(\bar{z}^T\mathbf{Z}_{\cdot j})^2$.

Denote $\varepsilon=\mathbf{Y^T}(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}(\mathbf{I}-\mathbf{M})\mathbf{Y}, \zeta=\mathbf{Y^T}(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M}\mathbf{Y}, \eta=\mathbf{Y^T}\bar{\mathbf{z}}\bar{\mathbf{z}}^{\mathbf{T}}\mathbf{Y}$, as $\mathbf{M}\bar{z}\bar{z}^T=\bar{z}(\bar{z}^T\bar{z})^{-1}\bar{z}^T\bar{z}\bar{z}^T=\bar{z}\bar{z}^T, (\mathbf{I}-\mathbf{M})\bar{\mathbf{z}}\bar{\mathbf{z}}^{\mathbf{T}}=\mathbf{0}$, ε and η are asymptotically independent (Craig's Theorem) under the null.
Since $\mathbf{Y}=\mathbf{B^{-1/2}}\mathbf{U}(\theta_{\mathbf{0}})\sim N(0,\mathbf{I})$, we have

$$\begin{aligned}
E(\zeta)=&E(\mathbf{Y^T}(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M}\mathbf{Y})\\
=&tr((\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M})=tr(\mathbf{M}(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T})\\
=&0\\
var(\zeta)=&var(\mathbf{Y^T}(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M}\mathbf{Y})\\
=&var\left\{\frac{1}{2}\mathbf{Y^T}\left[(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M}+((\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M})^{\mathbf{T}}\right]\mathbf{Y}\right\}\\
=&\frac{1}{4}2tr\left\{\left[(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M}+((\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M})^{\mathbf{T}}\right]^2\right\}\\
=&tr\left[(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M}\cdot((\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M})^{\mathbf{T}}\right]\\
=&tr(\mathbf{Z}\mathbf{Z^T}\mathbf{M}\mathbf{Z}\mathbf{Z^T}(\mathbf{I}-\mathbf{M}))\\
cov(\varepsilon,\zeta)=&cov(\mathbf{Y^T}(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}(\mathbf{I}-\mathbf{M})\mathbf{Y},\mathbf{Y^T}(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M}\mathbf{Y})\\
=&\frac{1}{2}cov(\mathbf{Y^T}(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}(\mathbf{I}-\mathbf{M})\mathbf{Y},\mathbf{Y^T}[(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M}+((\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M})^{\mathbf{T}}]\mathbf{Y})\\
=&tr\left\{(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}(\mathbf{I}-\mathbf{M})[(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M}+((\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M})^{\mathbf{T}}]\right\}\\
=&tr\left\{(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}(\mathbf{I}-\mathbf{M})(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M}\right\}+tr\left\{(\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}(\mathbf{I}-\mathbf{M})((\mathbf{I}-\mathbf{M})\mathbf{Z}\mathbf{Z^T}\mathbf{M})^{\mathbf{T}}\right\}\\
=&0
\end{aligned}$$

Similarly, we can show that $cov(\eta,\zeta)=0$. Let $\kappa=\varepsilon+2\zeta$, $T=(1-\rho)\kappa+\gamma(\rho)\eta$. ε and η are asymptotically independent under the null, ζ is asymptotically uncorrelated with ε and η. Since the Pearson correlation between η and κ is 0, we can approximate T as sum of two independent variables.