Biostatistics (2009), **1**, 1, *pp.* i–iv
doi:10.1093/biostatistics/bio000

Supplementary Material for "Identifying Genetic Marker Sets Associated with Phenotypes via an Efficient Adaptive Score Test"

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APPENDIX

A. Distribution of the Test Statistic Under a Local Alternative

In this section, we derive the distribution of $\widehat{Q}_{\mathcal{A}}$ under the local alternative $H_{1n} : \boldsymbol{\beta}_0 = n^{-1/2}\mathbf{b}_0$ with the true parameter value for $\boldsymbol{\alpha}$ being $\boldsymbol{\alpha}_0$ and $\boldsymbol{\theta}$ being $\boldsymbol{\theta}_{H_{1n}} = (\boldsymbol{\alpha}_0^{\mathrm{T}}, n^{-1/2}\mathbf{b}_0^{\mathrm{T}})^{\mathrm{T}}$. Recall that

$$\bar{\mathbf{S}}(\boldsymbol{\theta}) = \begin{bmatrix} \bar{\mathbf{S}}_u(\boldsymbol{\theta})_{p_u\times 1} \\ \bar{\mathbf{S}}_v(\boldsymbol{\theta})_{p\times 1} \end{bmatrix} = n^{-1}\sum_{i=1}^{n} \mathcal{G}_1(\boldsymbol{\theta}^{\mathrm{T}}\mathbf{W}_i)\left\{Y_i - \mu(\boldsymbol{\theta}^{\mathrm{T}}\mathbf{W}_i)\right\}\mathbf{W}_i$$

Let $\boldsymbol{\theta}_{H_0} = (\boldsymbol{\alpha}_0^{\mathrm{T}}, \mathbf{0}_{p\times 1}^{\mathrm{T}})^{\mathrm{T}}$ and consider the parameter space for $\boldsymbol{\theta}$ as $\Omega_{H_{1n}} = \{(\boldsymbol{\alpha}^{\mathrm{T}}, n^{-1/2}\mathbf{b}^{\mathrm{T}})^{\mathrm{T}}, \|\boldsymbol{\alpha} - \boldsymbol{\alpha}_0\| + \|\mathbf{b}\| \leqslant \mathcal{C}\}$ for some constant $\mathcal{C}$. Let $\widehat{\mathbb{C}}_{ww}(\boldsymbol{\theta})$ be the empirical version of

$$\mathbb{C}_{ww} = \begin{bmatrix} \mathbb{C}_{uu} & \mathbb{C}_{uv} \\ \mathbb{C}_{vu} & \mathbb{C}_{vv} \end{bmatrix} = \begin{bmatrix} E\left\{\mathcal{G}_2(\boldsymbol{\alpha}_0^{\mathrm{T}}\mathbf{U})\mathbf{U}\mathbf{U}^{\mathrm{T}}\right\} & E\left\{\mathcal{G}_2(\boldsymbol{\alpha}_0^{\mathrm{T}}\mathbf{U})\mathbf{U}\mathbf{V}^{\mathrm{T}}\right\} \\ E\left\{\mathcal{G}_2(\boldsymbol{\alpha}_0^{\mathrm{T}}\mathbf{U})\mathbf{V}\mathbf{U}^{\mathrm{T}}\right\} & E\left\{\mathcal{G}_2(\boldsymbol{\alpha}_0^{\mathrm{T}}\mathbf{U})\mathbf{V}\mathbf{V}^{\mathrm{T}}\right\} \end{bmatrix}$$

obtained by replacing expectations by averages over the data. For the initial estimator, we consider $\widehat{\boldsymbol{\beta}} = \widehat{\boldsymbol{\beta}}_{\mathrm{RQL}}(\widehat{\lambda})$, where $\widehat{\boldsymbol{\theta}}_{\mathrm{RQL}}(\lambda) = \{\widehat{\boldsymbol{\alpha}}_{\mathrm{RQL}}(\lambda)^{\mathrm{T}}, \widehat{\boldsymbol{\beta}}_{\mathrm{RQL}}(\lambda)^{\mathrm{T}}\}^{\mathrm{T}}$ is the solution to $\bar{\mathbf{S}}(\boldsymbol{\theta}) - \lambda(\mathbf{0}^{\mathrm{T}}, \boldsymbol{\beta}^{\mathrm{T}})^{\mathrm{T}} = 0$ and the tuning parameter $\widehat{\lambda}$ satisfies $\widehat{\lambda} \to \lambda_0 \geqslant 0$ as $n \to \infty$.

We first derive asymptotic properties of $\widehat{\boldsymbol{\theta}}_{\mathrm{RQL}}(\widehat{\lambda})$. By a uniform law of large numbers (Pollard, 1990), $\bar{\mathbf{S}}(\boldsymbol{\theta}) - \widehat{\lambda}(\mathbf{0}^{\mathrm{T}}, \boldsymbol{\beta}^{\mathrm{T}})^{\mathrm{T}} \to \mathbf{S}(\boldsymbol{\theta}) = E\{\bar{\mathbf{S}}(\boldsymbol{\theta})\}$ and $\widehat{\mathbb{C}}_{ww}(\boldsymbol{\theta}) = \partial\bar{\mathbf{S}}(\boldsymbol{\theta})/\partial\boldsymbol{\theta}^{\mathrm{T}} \to \mathbb{C}_{ww}(\boldsymbol{\theta}) = \partial E\{\bar{\mathbf{S}}(\boldsymbol{\theta})\}/\partial\boldsymbol{\theta}^{\mathrm{T}}$, uniformly in $\boldsymbol{\theta} \in \Omega_{H_{1n}}$ in probability, as $n \to \infty$. Thus under H_{1n}, for any

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$\mathcal{C}_n = O_p(n^{-1/2})$, $\sup_{\boldsymbol{\theta}^*:\|\boldsymbol{\theta}^*-\boldsymbol{\theta}_{H_{1n}}\|\leqslant\mathcal{C}_n} \left\|\widehat{\mathbb{C}}_{ww}(\boldsymbol{\theta}^*) - \mathbb{C}_{ww}\right\| \to_p 0$ as $n \to \infty$. The uniform convergence implies that under H_{1n}, $\widehat{\boldsymbol{\theta}}_{\text{RQL}}(\widehat{\lambda}) - \boldsymbol{\theta}_{H_{1n}} \to$ and $\widetilde{\boldsymbol{\alpha}}_{\text{QL}} - \boldsymbol{\alpha}_0 \to 0$ in probability, as $n \to \infty$. For the asymptotic distribution of $\widehat{\boldsymbol{\theta}}_{\text{RQL}}(\widehat{\lambda})$, by a Taylor series expansion,

$$n^{1/2}\{\widehat{\boldsymbol{\theta}}_{\text{RQL}}(\widehat{\lambda}) - \boldsymbol{\theta}_{H_{1n}}\} = \left\{\widehat{\mathbb{C}}_{ww}(\widehat{\boldsymbol{\theta}}^{\dagger}) + \begin{pmatrix} \mathbf{0}_{p_u\times p_u} & \mathbf{0}_{p_u\times p} \\ \mathbf{0}_{p\times p_u} & \widehat{\lambda}\mathbb{I}_{p\times p}\end{pmatrix}\right\}^{-1} n^{1/2}\left\{\bar{\mathbf{S}}(\boldsymbol{\theta}_{H_{1n}}) - \widehat{\lambda}(\mathbf{0}^{\mathrm{T}}, \boldsymbol{\beta}_0^{\mathrm{T}})^{\mathrm{T}}\right\},$$

for some $\widehat{\boldsymbol{\theta}}^{\dagger}$ such that $\|\widehat{\boldsymbol{\theta}}^{\dagger} - \boldsymbol{\theta}_{H_{1n}}\| \leqslant \|\widehat{\boldsymbol{\theta}}_{\text{RQL}}(\widehat{\lambda}) - \boldsymbol{\theta}_{H_{1n}}\|$. It then follows from the consistency of $\widehat{\boldsymbol{\theta}}_{\text{RQL}}(\widehat{\lambda})$ and the uniform consistency of $\widehat{\mathbb{C}}_{ww}(\boldsymbol{\theta})$ that

$$n^{1/2}\{\widehat{\boldsymbol{\theta}}_{\text{RQL}}(\widehat{\lambda}) - \boldsymbol{\theta}_{H_{1n}}\} = \{\mathbb{C}_{ww}^{(\lambda_0)}\}^{-1} n^{1/2}\bar{\mathbf{S}}(\boldsymbol{\theta}_{H_{1n}}) + o_p(1), \text{ where } \mathbb{C}_{ww}^{(\lambda_0)} = \begin{pmatrix} \mathbb{C}_{uu} & \mathbb{C}_{uv} \\ \mathbb{C}_{vu} & \mathbb{C}_{vv} + \lambda_0\mathbb{I}_{p\times p}\end{pmatrix}.$$

Thus letting $\mathbb{B}_v^{(\lambda_0)} = [-\{\mathbb{C}_{v|u} + \lambda_0\mathbb{I}_{p\times p}\}^{-1}\mathbb{C}_{vu}\mathbb{C}_{uu}^{-1}, \{\mathbb{C}_{v|u} + \lambda_0\mathbb{I}_{p\times p}\}^{-1}]$, we have $n^{1/2}\widehat{\boldsymbol{\beta}}_{\text{RQL}}(\widehat{\lambda}) = \mathbf{b}_0 + \mathbb{B}_v^{(\lambda_0)} n^{1/2}\bar{\mathbf{S}}(\boldsymbol{\theta}_{H_{1n}}) + o_p(1)$. Similarly,

$$n^{1/2}(\widetilde{\boldsymbol{\alpha}}_{\text{QL}} - \boldsymbol{\alpha}_0) = \mathbb{C}_{uu}^{-1} n^{1/2}\bar{\mathbf{S}}_u(\boldsymbol{\theta}_{H_0}) + o_p(1) = \mathbb{C}_{uu}^{-1}\left\{n^{1/2}\bar{\mathbf{S}}_u(\boldsymbol{\theta}_{H_{1n}}) + \mathbb{C}_{uv}\mathbf{b}_0\right\} + o_p(1). \quad \text{(A.1)}$$

Next, for the distribution of $\widetilde{\mathbf{S}}_v$, by a Taylor series expansion and (A.1),

$$\begin{aligned} \widetilde{\mathbf{S}}_v &= n^{1/2}\bar{\mathbf{S}}_v\{(\widetilde{\boldsymbol{\alpha}}_{\text{QL}}^{\mathrm{T}}, \mathbf{0}_{p\times 1}^{\mathrm{T}})^{\mathrm{T}}\} = n^{1/2}\bar{\mathbf{S}}_v(\boldsymbol{\theta}_{H_{1n}}) - n^{1/2}[\mathbb{C}_{vu}, \mathbb{C}_{vv}]\begin{pmatrix} \widetilde{\boldsymbol{\alpha}} - \boldsymbol{\alpha}_0 \\ -n^{-1/2}\mathbf{b}_0 \end{pmatrix} + o_p(1) \\ &= -\mathbb{C}_{vu}\mathbb{C}_{uu}^{-1} n^{1/2}\bar{\mathbf{S}}_x(\boldsymbol{\theta}_0) + n^{1/2}\bar{\mathbf{S}}_v(\boldsymbol{\theta}_{H_{1n}}) + \left(\mathbb{C}_{vv} - \mathbb{C}_{vu}\mathbb{C}_{uu}^{-1}\mathbb{C}_{uv}\right)\mathbf{b}_0 + o_p(1) \\ &= \mathbb{A}_v n^{1/2}\bar{\mathbf{S}}(\boldsymbol{\theta}_{H_{1n}}) + \mathbb{C}_{v|u}\mathbf{b}_0 + o_p(1). \end{aligned}$$

On the other hand, by the central limit theorem, $n^{1/2}\bar{\mathbf{S}}(\boldsymbol{\theta}_{H_{1n}}) \to \boldsymbol{\varepsilon}_w$ in distribution as $n \to \infty$, where $\boldsymbol{\varepsilon}_w \sim N(\mathbf{0}, \sigma^2\mathbb{C}_{ww})$. Therefore, as $n \to \infty$,

$$\begin{bmatrix} \widetilde{\mathbf{S}}_v \\ n^{1/2}\widehat{\boldsymbol{\beta}}_{\text{RQL}}(\widehat{\lambda}) \end{bmatrix} \to \begin{bmatrix} \mathbf{s}_0 + \mathbb{A}_v\boldsymbol{\varepsilon}_w \\ \mathbf{b}_0 + \mathbb{B}_v^{(\lambda_0)}\boldsymbol{\varepsilon}_w \end{bmatrix} \quad \text{in distribution.}$$

Furthermore, $\widehat{\boldsymbol{\kappa}} \to \boldsymbol{\kappa}$ in probability as $n \to \infty$. It follows from the continuous mapping theorem that under H_{1n}, $\widehat{Q}_{\mathcal{A}} = n\|\widetilde{\mathbf{S}}_v \odot \widehat{\mathbf{Z}}\|_2^2$ converges in distribution to $\mathcal{Q}_{\mathcal{A}}(\mathbf{b}_0) = \|(\mathbf{b}_0 + \mathbb{B}_v^{(\lambda_0)}\boldsymbol{\varepsilon}_w) \odot (\mathbf{s}_0 + \mathbb{A}_v\boldsymbol{\varepsilon}_w) \oslash \kappa\|_2^2$, as claimed.

REFERENCES

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Fig. 1. Estimated marginal log-odds ratio of the SNPs (open circles) along with their 95% confidence intervals (thick solid lines). Show also are the SNP's p-values if they are less than 0.05.

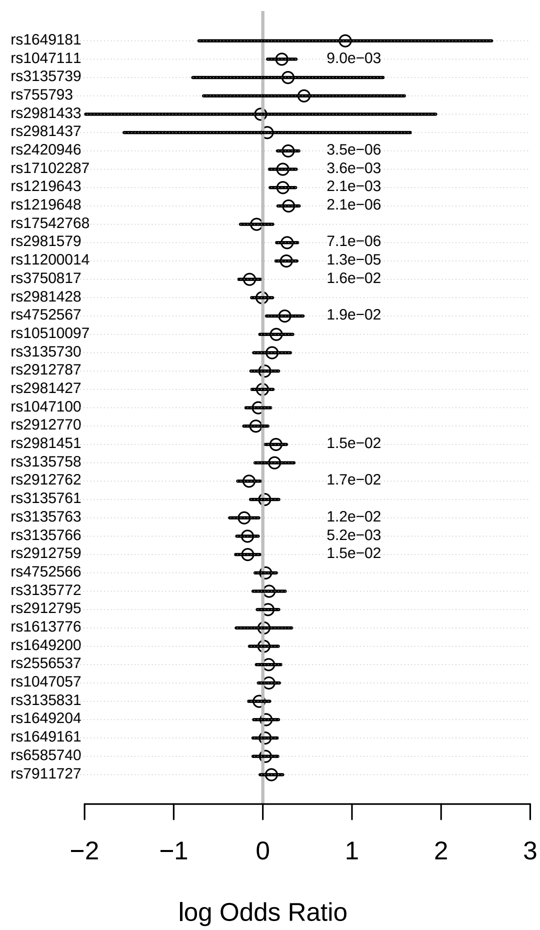
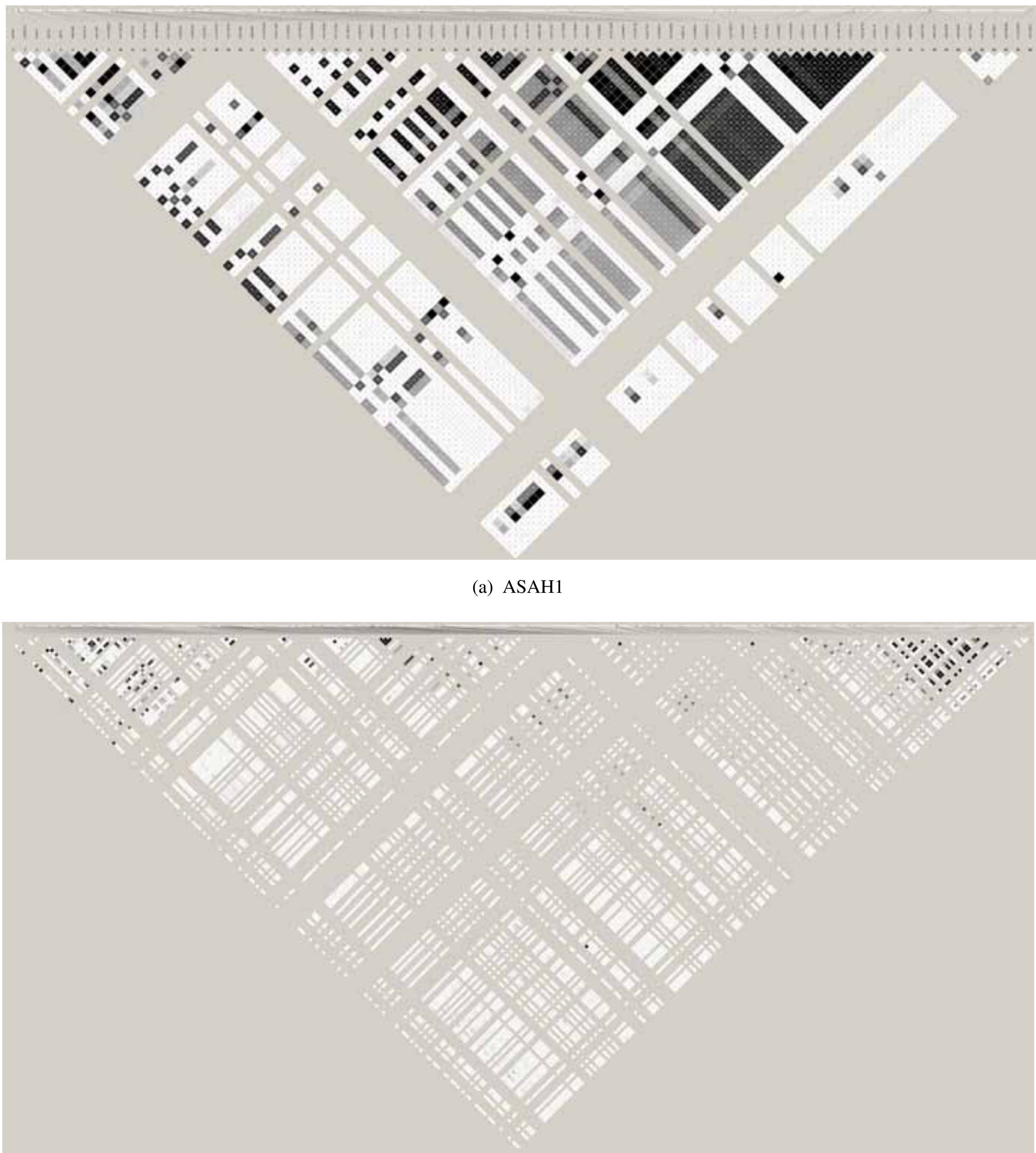


Fig. 2. LD structure of the 86 SNPs of the ASAH1 gene and the 232 SNPs of the FGFR2 gene from the Hapmap.



(a) ASAH1

(b) FGFR2