# Supplementary Information, Non-centrality Parameters

Consider $N$ sib-pairs each consists of an affected sibling and a normal sibling. For convenience, assume that the first sibling is affected, and the second sibling is normal in each sib-pair. Let us denote $A_1 =$*(the first sibling is affected)*, $U_2 =$*(the second sibling is unaffected)*. For "haplotype/allele coding", the coding vector of the affected sibling in the $i$-th sib-pair is $X_i^{(A)} = (z_{i11}^{(A)}, \cdots, z_{i1(n_1-1)}^{(A)}, \cdots, z_{iJ1}^{(A)}, \cdots, z_{iJ(n_J-1)}^{(A)})^\tau$. Similarly, $Y_i^{(U)} = (z_{i11}^{(U)}, \cdots, z_{i1(n_1-1)}^{(U)}, \cdots, z_{iJ1}^{(U)}, \cdots, z_{iJ(n_J-1)}^{(U)})^\tau$ is the coding vector of the normal sibling. Denote the variance-covariance matrix of $X_i^{(A)} - Y_i^{(U)}$ by $\Sigma_{hap} = \mathrm{Var}(X_i^{(A)} - Y_i^{(U)}|A_1, U_2) = \mathrm{Var}(X_i^{(A)}|A_1, U_2) - \mathrm{Cov}(X_i^{(A)}, Y_i^{(U)}|A_1, U_2) - \mathrm{Cov}(Y_i^{(U)}, X_i^{(A)}|A_1, U_2) + \mathrm{Var}(Y_i^{(U)}|A_1, U_2)$. The elements of the above variance-covariance matrices are given in Appendices A, B, and C: $\mathrm{Var}(X_i^{(A)}|A_1, U_2)$ and $\mathrm{Var}(Y_i^{(U)}| A_1, U_2)$ in Appendix A, and $\mathrm{Cov}(X_i^{(A)}, Y_i^{(U)}|A_1, U_2)$ in Appendices B and C. Using quantities of $\mathrm{E}\,(z_{ijk}^{(A)}|A_1, U_2)$ and $\mathrm{E}\,(z_{ijk}^{(U)}|A_1, U_2)$ in the Appendix of the manuscript, $\mathrm{E}\,(X_i^{(A)} - Y_i^{(U)}|A_1, U_2)$ can be calculated. The non-centrality parameter $\lambda_H$ of Hotelling's statistics $T_H$ is given by $\lambda_H = N\,\mathrm{E}\,(X_i^{(A)} - Y_i^{(U)}|A_1, U_2)^\tau[\Sigma_{hap}]^{-1}\,\mathrm{E}\,(X_i^{(A)} - Y_i^{(U)}|A_1, U_2)$.

For "genotype coding", the coding vector of the affected sibling in the $i$-th sib-pair is $X_{ij}^{(A)} = (x_{ij1}^{(A)}, \cdots, x_{ij(n_j-1)}^{(A)}, x_{ij12}^{(A)}, \cdots, x_{ij1n_j}^{(A)}, \cdots, x_{ij(n_j-1)n_j}^{(A)})^\tau, j = 1, \cdots, J$. Similarly, $Y_{ij}^{(U)} = (x_{ij1}^{(U)}, \cdots, x_{ij(n_j-1)}^{(U)}, x_{ij12}^{(U)}, \cdots, x_{ij1n_j}^{(U)}, \cdots, x_{ij(n_j-1)n_j}^{(U)})^\tau$ is the coding vector of the normal sibling. Let $a_{jkl}$ and $\bar{a}_{jkl}$ be the frequencies of genotype $H_{jk}H_{jl}$ in affected and unaffected siblings given in the Appendix of the manuscript. Then,

$$\mathrm{E}\,[X_{ij}^{(A)}|A_1, U_2] = (a_{j11}, \cdots, a_{j(n_j-1)(n_j-1)}, a_{j12}, \cdots, a_{j1n_j}, \cdots, a_{j(n_j-1)n_j})^\tau, \quad (1)$$

$$\mathrm{E}\,[Y_{ij}^{(U)}|A_1, U_2] = (\bar{a}_{j11}, \cdots, \bar{a}_{j(n_j-1)(n_j-1)}, \bar{a}_{j12}, \cdots, \bar{a}_{j1n_j}, \cdots, \bar{a}_{j(n_j-1)n_j})^\tau. \quad (2)$$

Using $\mathrm{E}\,[X_{ij}^{(A)}|A_1, U_2]$ and $\mathrm{E}\,[Y_{ij}^{(U)}|A_1, U_2]$, one may calculate expectation $\mathrm{E}\,(\overline{X}^{(A)} - \overline{Y}^{(U)}|A_1, U_2) = (\mathrm{E}\,[X_{i1}^{(A)} - Y_{i1}^{(U)}|A_1, U_2]^\tau, \cdots, \mathrm{E}\,[X_{iJ}^{(A)} - Y_{iJ}^{(U)}|A_1, U_2]^\tau)^\tau$. Let $\Sigma_{geno} = \mathrm{Cov}(X_i^{(A)} - Y_i^{(U)}|A_1, U_2) = \mathrm{Var}(X_i^{(A)}|A_1, U_2) - \mathrm{Cov}(X_i^{(A)}, Y_i^{(U)}|A_1, U_2) - \mathrm{Cov}(Y_i^{(U)}, X_i^{(A)}| A_1, U_2) + \mathrm{Var}(Y_i^{(U)}|A_1, U_2)$ be the variance covariance matrix of $X_i^{(A)} - Y_i^{(U)}$. Then the non-centrality parameter $\lambda_G$ of Hotelling's statistics $T_G$ is given by $\lambda_G = N\,\mathrm{E}\,[\overline{X}^{(A)} - \overline{Y}^{(U)}|A_1, U_2]^\tau[\Sigma_{geno}]^{-1}\,\mathrm{E}\,[\overline{X}^{(A)} - \overline{Y}^{(U)}|A_1, U_2]$. The elements of the above variance-covariance matrices are given in Appendices D and E: $\mathrm{Var}(X_i^{(A)}|A_1, U_2)$ and $\mathrm{Var}(Y_i^{(U)}| A_1, U_2)$ in Appendix D, and $\mathrm{Cov}(X_i^{(A)}, Y_i^{(U)}\ |A_1, U_2)$ in Appendix E.

# Appendix A

Consider the "haplotype/allele coding". The variance-covariance matrices

$$\begin{aligned}
\mathrm{Var}(X_i^{(A)}|A_1,U_2) &= \mathrm{Var}\Big[(z_{i11}^{(A)},\cdots,z_{i1(n_1-1)}^{(A)},\cdots,z_{iJ1}^{(A)},\cdots,z_{iJ(n_J-1)}^{(A)})^\tau|A_1,U_2\Big],\\
\mathrm{Var}[Y_i^{(U)}|A_1,U_2] &= \mathrm{Var}\Big[(z_{i11}^{(U)},\cdots,z_{i1(n_1-1)}^{(U)},\cdots,z_{iJ1}^{(U)},\cdots,z_{iJ(n_J-1)}^{(U)})^\tau|A_1,U_2\Big].
\end{aligned}$$

The variance of number of alleles $H_{jk}$ in affected sibling and unaffected sibling can be calculated as follows

$$\begin{aligned}
\mathrm{Var}(z_{ijk}^{(A)}|A_1,U_2) &= \mathrm{E}\,[(z_{ijk}^{(A)})^2|A_1,U_2]-[\mathrm{E}\,(z_{ijk}^{(A)}|A_1,U_2)]^2\\
&= 4a_{jkk}+\sum_{l\neq k}a_{jkl}-\Big[2a_{jkk}+\sum_{l\neq k}a_{jkl}\Big]^2,\\
\mathrm{Var}(z_{ijk}^{(U)}|A_1,U_2) &= \mathrm{E}\,[(z_{ijk}^{(U)})^2|A_1,U_2]-[\mathrm{E}\,(z_{ijk}^{(U)}|A_1,U_2)]^2\\
&= 4\bar{a}_{jkk}+\sum_{l\neq k}\bar{a}_{jkl}-\Big[2\bar{a}_{jkk}+\sum_{l\neq k}\bar{a}_{jkl}\Big]^2.
\end{aligned}$$

Similarly, the covariance between the number of alleles $H_{jk}$ and the number of alleles $H_{jl}$, $l\neq k$, in affected sibling and unaffected sibling can be calculated as

$$\begin{aligned}
\mathrm{Cov}(z_{ijk}^{(A)},z_{ijl}^{(A)}|A_1,U_2) &= \mathrm{E}\,(z_{ijk}^{(A)}z_{ijl}^{(A)}|A_1,U_2)-\mathrm{E}\,(z_{ijk}^{(A)}|A_1,U_2)\,\mathrm{E}\,(z_{ijl}^{(A)}|A_1,U_2)\\
&= P(G_{ij}^{(A)}=H_{jk}H_{jl}|A_1,U_2)-\Big[2a_{jkk}+\sum_{k'\neq k}a_{jkk'}\Big]\Big[2a_{jll}+\sum_{l'\neq l}a_{jll'}\Big]\\
&= a_{jkl}-\Big[2a_{jkk}+\sum_{k'\neq k}a_{jkk'}\Big]\Big[2a_{jll}+\sum_{l'\neq l}a_{jll'}\Big],\\
\mathrm{Cov}(z_{ijk}^{(U)},z_{ijl}^{(U)}|A_1,U_2) &= \mathrm{E}\,(z_{ijk}^{(U)}z_{ijl}^{(U)}|A_1,U_2)-\mathrm{E}\,(z_{ijk}^{(U)}|A_1,U_2)\,\mathrm{E}\,(z_{ijl}^{(U)}|A_1,U_2)\\
&= \bar{a}_{jkl}-\Big[2\bar{a}_{jkk}+\sum_{k'\neq k}\bar{a}_{jkk'}\Big]\Big[2\bar{a}_{jll}+\sum_{l'\neq l}\bar{a}_{jll'}\Big].
\end{aligned}$$

For $j\neq g$, assume that markers $H_j$ and $H_g$ flank disease locus $D$ in an order of $H_jDH_g$. Let $P(H_{jk}DH_{gh})$ be frequencies of haplotype $H_{jk}DH_{gh}$. The frequencies of other haplotypes are denoted, accordingly. For the $i$-th sib-pair, let $G_{iD}^{(U)}$ be disease genotype of the unaffected sibling, and $G_{iD}^{(A)}$ be disease genotype of the affected sibling. To calculate covariance between $z_{ijk}^{(A)},z_{igh}^{(A)}$, denote for $j\neq g,k\neq k',h\neq h'$,

$$\begin{aligned}
g_{kkhh}^{(A,jg)} &= \mathrm{E}\Big[1_{(G_{ij}^{(A)}=H_{jk}H_{jk})}1_{(G_{ig}^{(A)}=H_{gh}H_{gh})}|A_1,U_2\Big]\\
&= P[G_{ij}^{(A)}=H_{jk}H_{jk},G_{ig}^{(A)}=H_{gh}H_{gh},A_1,U_2,(2\text{ IBD})\cup(1\text{ IBD})\cup(0\text{ IBD})]/P(A_1,U_2)\\
&= \Big[\frac{1}{4}\sum_{s,t\in\{D,d\}}f_{st}\bar{f}_{st}P[G_{ij}^{(A)}=H_{jk}H_{jk},G_{ig}^{(A)}=H_{gh}H_{gh},G_{iD}^{(A)}=st,G_{iD}^{(U)}=st]
\end{aligned}$$

$$
\begin{aligned}
&+\frac{1}{2}\sum_{s,t,q\in\{D,d\}} f_{st}\bar{f}_{tq}P[G_{ij}^{(A)}=H_{jk}H_{jk},G_{ig}^{(A)}=H_{gh}H_{gh},G_{iD}^{(A)}=st,G_{iD}^{(U)}=tq]\\
&+\frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} f_{st}\bar{f}_{qr}P[G_{ij}^{(A)}=H_{jk}H_{jk},G_{ig}^{(A)}=H_{gh}H_{gh},G_{iD}^{(A)}=st,G_{iD}^{(U)}=qr]\Big]/P(A_1,U_2)\\
=\ &\Big[\frac{1}{4}\sum_{s,t\in\{D,d\}} f_{st}\bar{f}_{st}P(H_{jk}sH_{gh})P(H_{jk}tH_{gh})+\frac{1}{2}\sum_{s,t,q\in\{D,d\}} f_{st}\bar{f}_{tq}P(H_{jk}tH_{gh})P(H_{jk}sH_{gh})P_q\\
&+\frac{1}{4}\sum_{s,t\in\{D,d\}} f_{st}P(H_{jk}sH_{gh})P(H_{jk}tH_{gh})\bar{A}\Big]/P(A_1,U_2)
\end{aligned}
$$

$$
\begin{aligned}
g_{kkhh'}^{(A,jg)}\ =\ &\mathrm{E}\left[1_{(G_{ij}^{(A)}=H_{jk}H_{jk})}1_{(G_{ig}^{(A)}=H_{gh}H_{gh'})}|A_1,U_2\right]\\
=\ &P[G_{ij}^{(A)}=H_{jk}H_{jk},G_{ig}^{(A)}=H_{gh}H_{gh'},A_1,U_2,(2\text{ IBD})\cup(1\text{ IBD})\cup(0\text{ IBD})]/P(A_1,U_2)\\
=\ &\Big[\frac{1}{4}\sum_{s,t\in\{D,d\}} f_{st}\bar{f}_{st}P[G_{ij}^{(A)}=H_{jk}H_{jk},G_{ig}^{(A)}=H_{gh}H_{gh'},G_{iD}^{(A)}=st,G_{iD}^{(U)}=st]\\
&+\frac{1}{2}\sum_{s,t,q\in\{D,d\}} f_{st}\bar{f}_{tq}P[G_{ij}^{(A)}=H_{jk}H_{jk},G_{ig}^{(A)}=H_{gh}H_{gh'},G_{iD}^{(A)}=st,G_{iD}^{(U)}=tq]\\
&+\frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} f_{st}\bar{f}_{qr}P[G_{ij}^{(A)}=H_{jk}H_{jk},G_{ig}^{(A)}=H_{gh}H_{gh'},G_{iD}^{(A)}=st,G_{iD}^{(U)}=qr]\Big]/P(A_1,U_2)\\
=\ &\Big[\frac{1}{4}\sum_{s,t\in\{D,d\}} f_{st}\bar{f}_{st}\Big(P(H_{jk}sH_{gh})P(H_{jk}tH_{gh'})+P(H_{jk}tH_{gh})P(H_{jk}sH_{gh'})\Big)\\
&+\frac{1}{2}\sum_{s,t,q\in\{D,d\}} f_{st}\bar{f}_{tq}\Big(P(H_{jk}sH_{gh})P(H_{jk}tH_{gh'})+P(H_{jk}tH_{gh})P(H_{jk}sH_{gh'})\Big)P_q\\
&+\frac{1}{4}\sum_{s,t\in\{D,d\}} f_{st}\Big(P(H_{jk}sH_{gh})P(H_{jk}tH_{gh'})+P(H_{jk}tH_{gh})P(H_{jk}sH_{gh'})\Big)\bar{A}\Big]/P(A_1,U_2)
\end{aligned}
$$

$$
\begin{aligned}
g_{kk'hh}^{(A,jg)}\ =\ &\mathrm{E}\left[1_{(G_{ij}^{(A)}=H_{jk}H_{jk'})}1_{(G_{ig}^{(A)}=H_{gh}H_{gh})}|A_1,U_2\right]\\
=\ &P[G_{ij}^{(A)}=H_{jk}H_{jk'},G_{ig}^{(A)}=H_{gh}H_{gh},A_1,U_2,(2\text{ IBD})\cup(1\text{ IBD})\cup(0\text{ IBD})]/P(A_1,U_2)\\
=\ &\Big[\frac{1}{4}\sum_{s,t\in\{D,d\}} f_{st}\bar{f}_{st}P[G_{ij}^{(A)}=H_{jk}H_{jk'},G_{ig}^{(A)}=H_{gh}H_{gh},G_{iD}^{(A)}=st,G_{iD}^{(U)}=st]\\
&+\frac{1}{2}\sum_{s,t,q\in\{D,d\}} f_{st}\bar{f}_{tq}P[G_{ij}^{(A)}=H_{jk}H_{jk'},G_{ig}^{(A)}=H_{gh}H_{gh},G_{iD}^{(A)}=st,G_{iD}^{(U)}=tq]\\
&+\frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} f_{st}\bar{f}_{qr}P[G_{ij}^{(A)}=H_{jk}H_{jk'},G_{ig}^{(A)}=H_{gh}H_{gh},G_{iD}^{(A)}=st,G_{iD}^{(U)}=qr]\Big]/P(A_1,U_2)\\
=\ &\Big[\frac{1}{4}\sum_{s,t\in\{D,d\}} f_{st}\bar{f}_{st}\Big(P(H_{jk}sH_{gh})P(H_{jk'}tH_{gh})+P(H_{jk}tH_{gh})P(H_{jk'}sH_{gh})\Big)\\
&+\frac{1}{2}\sum_{s,t,q\in\{D,d\}} f_{st}\bar{f}_{tq}\Big(P(H_{jk}sH_{gh})P(H_{jk'}tH_{gh})+P(H_{jk}tH_{gh})P(H_{jk'}sH_{gh})\Big)P_q\\
&+\frac{1}{4}\sum_{s,t\in\{D,d\}} f_{st}\Big(P(H_{jk}sH_{gh})P(H_{jk'}tH_{gh})+P(H_{jk}tH_{gh})P(H_{jk'}sH_{gh})\Big)\bar{A}\Big]/P(A_1,U_2)
\end{aligned}
$$

$$
\begin{aligned}
g^{(A,jg)}_{kk'hh'} &= \mathrm{E}\left[1_{(G^{(A)}_{ij}=H_{jk}H_{jk'})}1_{(G^{(A)}_{ig}=H_{gh}H_{gh'})}|A_1,U_2\right] \\
&= P[G^{(A)}_{ij}=H_{jk}H_{jk'},G^{(A)}_{ig}=H_{gh}H_{gh'},A_1,U_2,(2\text{ IBD})\cup(1\text{ IBD})\cup(0\text{ IBD})]/P(A_1,U_2) \\
&= \Big[\frac{1}{4}\sum_{s,t\in\{D,d\}} f_{st}\bar{f}_{st}P[G^{(A)}_{ij}=H_{jk}H_{jk'},G^{(A)}_{ig}=H_{gh}H_{gh'},G^{(A)}_{iD}=st,G^{(U)}_{iD}=st] \\
&\quad+\frac{1}{2}\sum_{s,t,q\in\{D,d\}} f_{st}\bar{f}_{tq}P[G^{(A)}_{ij}=H_{jk}H_{jk'},G^{(A)}_{ig}=H_{gh}H_{gh'},G^{(A)}_{iD}=st,G^{(U)}_{iD}=tq] \\
&\quad+\frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} f_{st}\bar{f}_{qr}P[G^{(A)}_{ij}=H_{jk}H_{jk'},G^{(A)}_{ig}=H_{gh}H_{gh'},G^{(A)}_{iD}=st,G^{(U)}_{iD}=qr]\Big]/P(A_1,U_2) \\
&= \Big[\frac{1}{4}\sum_{s,t\in\{D,d\}} f_{st}\bar{f}_{st}\Big(P(H_{jk}sH_{gh})P(H_{jk'}tH_{gh'})+P(H_{jk}tH_{gh})P(H_{jk'}sH_{gh'}) \\
&\qquad+P(H_{jk}sH_{gh'})P(H_{jk'}tH_{gh})+P(H_{jk}tH_{gh'})P(H_{jk'}sH_{gh})\Big) \\
&\quad+\frac{1}{2}\sum_{s,t,q\in\{D,d\}} f_{st}\bar{f}_{tq}\Big(P(H_{jk}sH_{gh})P(H_{jk'}tH_{gh'})+P(H_{jk}tH_{gh})P(H_{jk'}sH_{gh'}) \\
&\qquad+P(H_{jk}sH_{gh'})P(H_{jk'}tH_{gh})+P(H_{jk}tH_{gh'})P(H_{jk'}sH_{gh})\Big)P_q \\
&\quad+\frac{1}{4}\sum_{s,t\in\{D,d\}} f_{st}\Big(P(H_{jk}sH_{gh})P(H_{jk'}tH_{gh'})+P(H_{jk}tH_{gh})P(H_{jk'}sH_{gh'}) \\
&\qquad+P(H_{jk}sH_{gh'})P(H_{jk'}tH_{gh})+P(H_{jk}tH_{gh'})P(H_{jk'}sH_{gh})\Big)\bar{A}\Big]/P(A_1,U_2).
\end{aligned}
$$

For $k=1,\cdots,n_j-1$ and $h=1,\cdots,n_g-1$, $j\neq g$, the covariance

$$
\begin{aligned}
\mathrm{Cov}(z^{(A)}_{ijk},z^{(A)}_{igh}|A_1,U_2) &= \mathrm{E}\,[z^{(A)}_{ijk}z^{(A)}_{igh}|A_1,U_2]-\mathrm{E}\,[z^{(A)}_{ijk}|A_1,U_2]\,\mathrm{E}\,[z^{(A)}_{igh}|A_1,U_2] \\
&= 4g^{(A,jg)}_{kkhh}+2\sum_{h'\neq h}g^{(A,jg)}_{kkhh'}+2\sum_{k'\neq k}g^{(A,jg)}_{kk'hh}+\sum_{k'\neq k}\sum_{h'\neq h}g^{(A,jg)}_{kk'hh'} \\
&\quad-\Big[2a_{jkk}+\sum_{k'\neq k}a_{jkk'}\Big]\Big[2a_{ghh}+\sum_{h'\neq h}a_{ghh'}\Big].
\end{aligned}
$$

Similarly, for $k=1,\cdots,n_j-1$ and $h=1,\cdots,n_g-1$, $j\neq g$, the covariance

$$
\begin{aligned}
\mathrm{Cov}(z^{(U)}_{ijk},z^{(U)}_{igh}|A_1,U_2) &= \mathrm{E}\,[z^{(U)}_{ijk}z^{(U)}_{igh}|A_1,U_2]-\mathrm{E}\,[z^{(U)}_{ijk}|A_1,U_2]\,\mathrm{E}\,[z^{(U)}_{igh}|A_1,U_2] \\
&= 4\bar{g}^{(U,jg)}_{kkhh}+2\sum_{h'\neq h}\bar{g}^{(U,jg)}_{kkhh'}+2\sum_{k'\neq k}\bar{g}^{(U,jg)}_{kk'hh}+\sum_{k'\neq k}\sum_{h'\neq h}\bar{g}^{(U,jg)}_{kk'hh'} \\
&\quad-\Big[2\bar{a}_{jkk}+\sum_{k'\neq k}\bar{a}_{jkk'}\Big]\Big[2\bar{a}_{ghh}+\sum_{h'\neq h}\bar{a}_{ghh'}\Big].
\end{aligned}
$$

where $\bar{g}^{(U,jg)}_{kkhh}$, $\bar{g}^{(U,jg)}_{kkhh'}$, $\bar{g}^{(U,jg)}_{kk'hh}$ and $\bar{g}^{(U,jg)}_{kk'hh'}$ are expected genotype frequencies in normal sibling as follows

$$
\begin{aligned}
\bar{g}^{(U,jg)}_{kkhh} &= \mathrm{E}\Big[1_{(G^{(U)}_{ij}=H_{jk}H_{jk})}1_{(G^{(U)}_{ig}=H_{gh}H_{gh})}|A_1,U_2\Big], \\
g^{(U,jg)}_{kkhh'} &= \mathrm{E}\Big[1_{(G^{(U)}_{ij}=H_{jk}H_{jk})}1_{(G^{(U)}_{ig}=H_{gh}H_{gh'})}|A_1,U_2\Big],
\end{aligned}
$$

$$g_{kk'hh}^{(U,jg)} = \mathrm{E}\left[1_{(G_{ij}^{(U)}=H_{jk}H_{jk'})}1_{(G_{ig}^{(U)}=H_{gh}H_{gh})}|A_1,U_2\right],$$
$$g_{kk'hh'}^{(U,jg)} = \mathrm{E}\left[1_{(G_{ij}^{(U)}=H_{jk}H_{jk'})}1_{(G_{ig}^{(U)}=H_{gh}H_{gh'})}|A_1,U_2\right].$$

To calculate $\bar{g}_{kkhh}^{(U,jg)}, \bar{g}_{kkhh'}^{(U,jg)}, \bar{g}_{kk'hh}^{(U,jg)}$ and $\bar{g}_{kk'hh'}^{(U,jg)}$, one may use the formulae of $g_{kkhh}^{(A,jg)}, g_{kkhh'}^{(A,jg)}, g_{kk'hh}^{(A,jg)}$ and $g_{kk'hh'}^{(A,jg)}$ by substituting $f_{st}$ using $\bar{f}_{st}$.

# Appendix B

The conditional covariance

$$\begin{aligned}\mathrm{Cov}(Y_i^{(U)}, X_i^{(A)}|A_1,U_2) &= \mathrm{E}\,[Y_i^{(U)}X_i^{(A)\tau}|A_1,U_2] - \mathrm{E}\,[Y_i^{(U)}|A_1,U_2]\,\mathrm{E}\,[X_i^{(A)\tau}|A_1,U_2] \\ &= \frac{\mathrm{E}\,[Y_i^{(U)}X_i^{(A)\tau}1_{A_1}1_{U_2}]}{P(A_1,U_2)} - \mathrm{E}\,[Y_i^{(U)}|A_1,U_2]\,\mathrm{E}\,[X_i^{(A)\tau}|A_1,U_2].\end{aligned}$$

For "haplotype/allele coding", the expectations $\mathrm{E}\,[Y_i^{(U)}|A_1,U_2]$ and $\mathrm{E}\,[X_i^{(A)\tau}|A_1,U_2]$ are given by two quantities $\mathrm{E}\,(z_{ijk}^{(A)}|A_1,U_2)$ and $\mathrm{E}\,(z_{ijk}^{(U)}|A_1,U_2)$ in the Appendix of the manuscript. To get $\mathrm{E}\,[Y_i^{(U)}X_i^{(A)\tau}1_{A_1}1_{U_2}]$, we will calculate $\mathrm{E}\,[z_{ijk}^{(U)}z_{ijk}^{(A)}1_{A_1}1_{U_2}]$ and $\mathrm{E}\,[z_{ijk}^{(U)}z_{ijl}^{(A)}1_{A_1}1_{U_2}], l \neq k$ in this Appendix. In Appendix C, we will calculate expectation $\mathrm{E}\,[z_{ijk}^{(U)}z_{igh}^{(A)}1_{A_1}1_{U_2}]$ for $j \neq g$. Notice

$$\begin{aligned}&\mathrm{E}\,[z_{ijk}^{(U)}z_{ijk}^{(A)}1_{A_1}1_{U_2}] \qquad (3)\\ &= \mathrm{E}\left[\Big(2\cdot 1_{(G_{ij}^{(U)}=H_{jk}H_{jk})} + \sum_{l\neq k} 1_{(G_{ij}^{(U)}=H_{jk}H_{jl})}\Big)\Big(2\cdot 1_{(G_{ij}^{(A)}=H_{jk}H_{jk})} + \sum_{l\neq k} 1_{(G_{ij}^{(A)}=H_{jk}H_{jl})}\Big)1_{A_1}1_{U_2}\right].\end{aligned}$$

Since the siblings can share 2, 1, and 0 gene identical by descent (IBD) at the disease locus $D$ with probabilities 1/4, 1/2, and 1/4, respectively, the expectation

$$\begin{aligned}&\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk})}1_{(G_{ij}^{(A)}=H_{jk}H_{jk})}1_{A_1}1_{U_2}]\\ &= P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jk}H_{jk}, A_1, U_2, (2\text{ IBD}) \cup (1\text{ IBD}) \cup (0\text{ IBD})]\\ &= \frac{1}{4}\sum_{s,t\in\{D,d\}} \bar{f}_{st}f_{st}P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jk}H_{jk}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = st]\\ &\quad + \frac{1}{2}\sum_{s,t,q\in\{D,d\}} \bar{f}_{st}f_{tq}P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jk}H_{jk}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = tq] \qquad (4)\\ &\quad + \frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} \bar{f}_{st}f_{qr}P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jk}H_{jk}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = qr]\\ &= \frac{1}{4}\sum_{s,t\in\{D,d\}} \bar{f}_{st}f_{st}P(H_{jk}s)P(H_{jk}t) + \frac{1}{2}\sum_{s,t,q\in\{D,d\}} \bar{f}_{st}f_{tq}P(H_{jk}t)P(H_{jk}s)P(H_{jk}q)\\ &\quad + \frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} \bar{f}_{st}f_{qr}P(H_{jk}s)P(H_{jk}t)P(H_{jk}q)P(H_{jk}r).\end{aligned}$$

For $l \neq k$, one may calculate expectation

$$
\begin{aligned}
&\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk})}1_{(G_{ij}^{(A)}=H_{jk}H_{jl})}1_{A_1}1_{U_2}] \\
&= P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jk}H_{jl}, A_1, U_2, (2\text{ IBD}) \cup (1\text{ IBD}) \cup (0\text{ IBD})] \\
&= \frac{1}{4}\sum_{s,t\in\{D,d\}} \bar{f}_{st} f_{st} P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jk}H_{jl}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = st] \\
&\quad + \frac{1}{2}\sum_{s,t,q\in\{D,d\}} \bar{f}_{st} f_{tq} P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jk}H_{jl}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = tq] \\
&\quad + \frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} \bar{f}_{st} f_{qr} P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jk}H_{jl}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = qr] \\
&= \frac{1}{2}\sum_{s,t,q\in\{D,d\}} \bar{f}_{st} f_{tq} \cdot 2P(H_{jk}t)P(H_{jk}s)P(H_{jl}q) \\
&\quad + \frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} \bar{f}_{st} f_{qr} P(H_{jk}s)P(H_{jk}t)\Big[P(H_{jk}q)P(H_{jl}r) + P(H_{jk}r)P(H_{jl}q)\Big].
\end{aligned} \tag{5}
$$

Similarly, one has the following expectation

$$
\begin{aligned}
&\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jl})}1_{(G_{ij}^{(A)}=H_{jk}H_{jk})}1_{A_1}1_{U_2}] \\
&= \frac{1}{2}\sum_{s,t,q\in\{D,d\}} \bar{f}_{st} f_{tq} \cdot 2P(H_{jl}s)P(H_{jk}t)P(H_{jk}q) \\
&\quad + \frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} \bar{f}_{st} f_{qr} \Big[P(H_{jk}s)P(H_{jl}t) + P(H_{jk}t)P(H_{jl}s)\Big]P(H_{jk}q)P(H_{jk}r).
\end{aligned} \tag{6}
$$

For $l \neq k$, one may calculate expectation

$$
\begin{aligned}
&\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jl})}1_{(G_{ij}^{(A)}=H_{jk}H_{jl})}1_{A_1}1_{U_2}] \\
&= P[G_{ij}^{(U)} = H_{jk}H_{jl}, G_{ij}^{(A)} = H_{jk}H_{jl}, A_1, U_2, (2\text{ IBD}) \cup (1\text{ IBD}) \cup (0\text{ IBD})] \\
&= \frac{1}{4}\sum_{s,t\in\{D,d\}} \bar{f}_{st} f_{st} P[G_{ij}^{(U)} = H_{jk}H_{jl}, G_{ij}^{(A)} = H_{jk}H_{jl}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = st] \\
&\quad + \frac{1}{2}\sum_{s,t,q\in\{D,d\}} \bar{f}_{st} f_{tq} P[G_{ij}^{(U)} = H_{jk}H_{jl}, G_{ij}^{(A)} = H_{jk}H_{jl}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = tq] \\
&\quad + \frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} \bar{f}_{st} f_{qr} P[G_{ij}^{(U)} = H_{jk}H_{jl}, G_{ij}^{(A)} = H_{jk}H_{jl}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = qr] \\
&= \frac{1}{4}\sum_{s,t\in\{D,d\}} \bar{f}_{st} f_{st} \Big[P(H_{jk}s)P(H_{jl}t) + P(H_{jk}t)P(H_{jl}s)\Big] \\
&\quad + \frac{1}{2}\sum_{s,t,q\in\{D,d\}} \bar{f}_{st} f_{tq} \Big[P(H_{jk}t)[P(H_{jl}s)P(H_{jl}q)] + P(H_{jl}t)[P(H_{jk}s)P(H_{jk}q)]\Big] \\
&\quad + \frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} \bar{f}_{st} f_{qr} \Big[P(H_{jk}s)P(H_{jl}t) + P(H_{jk}t)P(H_{jl}s)\Big]\Big[P(H_{jk}q)P(H_{jl}r) + P(H_{jk}r)P(H_{jl}q)\Big].
\end{aligned} \tag{7}
$$

For $l_1 \neq l_2$, $l_1 \neq k$ and $l_2 \neq k$, one may calculate expectation

$$\begin{aligned}
&\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jl_1})}1_{(G_{ij}^{(A)}=H_{jk}H_{jl_2})}1_{A_1}1_{U_2}] \\
&= P[G_{ij}^{(U)} = H_{jk}H_{jl_1}, G_{ij}^{(A)} = H_{jk}H_{jl_2}, A_1, U_2, (2 \text{ IBD}) \cup (1 \text{ IBD}) \cup (0 \text{ IBD})] \\
&= \frac{1}{4}\sum_{s,t\in\{D,d\}} \bar{f}_{st}f_{st}P[G_{ij}^{(U)} = H_{jk}H_{jl_1}, G_{ij}^{(A)} = H_{jk}H_{jl_2}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = st] \qquad (8)\\
&\quad +\frac{1}{2}\sum_{s,t,q\in\{D,d\}} \bar{f}_{st}f_{tq}P[G_{ij}^{(U)} = H_{jk}H_{jl_1}, G_{ij}^{(A)} = H_{jk}H_{jl_2}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = tq] \\
&\quad +\frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} \bar{f}_{st}f_{qr}P[G_{ij}^{(U)} = H_{jk}H_{jl_1}, G_{ij}^{(A)} = H_{jk}H_{jl_2}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = qr] \\
&= \frac{1}{2}\sum_{s,t,q\in\{D,d\}} \bar{f}_{st}f_{tq}\cdot 2P(H_{jk}t)P(H_{jl_1}s)P(H_{jl_2}q) \\
&\quad +\frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} \bar{f}_{st}f_{qr}\Big[P(H_{jk}s)P(H_{jl_1}t) + P(H_{jk}t)P(H_{jl_1}s)\Big]\Big[P(H_{jk}q)P(H_{jl_2}r) + P(H_{jk}r)P(H_{jl_2}q)\Big].
\end{aligned}$$

By using equations (4), (5), (6), (7), and (8), we may calculate $\mathrm{E}\,[z_{ijk}^{(U)}z_{ijk}^{(A)}1_{A_1}1_{U_2}]$ in (3). If $k \neq l$, then

$$\begin{aligned}
&\mathrm{E}\,[z_{ijk}^{(U)}z_{ijl}^{(A)}1_{A_1}1_{U_2}] \\
&= \mathrm{E}\,\Big[\Big(2\cdot 1_{(G_{ij}^{(U)}=H_{jk}H_{jk})} + \sum_{m\neq k} 1_{(G_{ij}^{(U)}=H_{jk}H_{jm})}\Big)\Big(2\cdot 1_{(G_{ij}^{(A)}=H_{jl}H_{jl})} + \sum_{n\neq l} 1_{(G_{ij}^{(A)}=H_{jl}H_{jn})}\Big)1_{A_1}1_{U_2}\Big] \\
&= 4\,\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk})}1_{(G_{ij}^{(A)}=H_{jl}H_{jl})}1_{A_1}1_{U_2}] + 2\,\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk})}1_{(G_{ij}^{(A)}=H_{jl}H_{jk})}1_{A_1}1_{U_2}] \\
&\quad +2\sum_{n\neq k,l}\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk})}1_{(G_{ij}^{(A)}=H_{jl}H_{jn})}1_{A_1}1_{U_2}] + 2\,\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jl})}1_{(G_{ij}^{(A)}=H_{jl}H_{jl})}1_{A_1}1_{U_2}] \qquad (9)\\
&\quad +2\sum_{m\neq k,l}\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jm})}1_{(G_{ij}^{(A)}=H_{jl}H_{jl})}1_{A_1}1_{U_2}] + \sum_{m\neq k,l}\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jm})}1_{(G_{ij}^{(A)}=H_{jl}H_{jm})}1_{A_1}1_{U_2}] \\
&\quad +\sum_{m\neq k,l}\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jm})}1_{(G_{ij}^{(A)}=H_{jl}H_{jk})}1_{A_1}1_{U_2}] + \sum_{m\neq k,l}\sum_{n\neq m,k,l}\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jm})}1_{(G_{ij}^{(A)}=H_{jl}H_{jn})}1_{A_1}1_{U_2}] \\
&\quad +\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jl})}1_{(G_{ij}^{(A)}=H_{jl}H_{jk})}1_{A_1}1_{U_2}] + \sum_{n\neq k,l}\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jl})}1_{(G_{ij}^{(A)}=H_{jl}H_{jn})}1_{A_1}1_{U_2}].
\end{aligned}$$

First, one may calculate the expectation

$$\begin{aligned}
&\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk})}1_{(G_{ij}^{(A)}=H_{jl}H_{jl})}1_{A_1}1_{U_2}] \\
&= P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jl}H_{jl}, A_1, U_2, (2 \text{ IBD}) \cup (1 \text{ IBD}) \cup (0 \text{ IBD})] \\
&= \frac{1}{4}\sum_{s,t\in\{D,d\}} \bar{f}_{st}f_{st}P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jl}H_{jl}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = st] \\
&\quad +\frac{1}{2}\sum_{s,t,q\in\{D,d\}} \bar{f}_{st}f_{tq}P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jl}H_{jl}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = tq] \qquad (10)\\
&\quad +\frac{1}{4}\sum_{s,t,q,r\in\{D,d\}} \bar{f}_{st}f_{qr}P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jl}H_{jl}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = qr]
\end{aligned}$$

$$= \frac{1}{4} \sum_{s,t,q,r \in \{D,d\}} \bar{f}_{st} f_{qr} P(H_{jk}s) P(H_{jk}t) P(H_{jl}q) P(H_{jl}r).$$

For $n \neq k, l$, one may have the following expectation

$$\begin{aligned}
&\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk})} 1_{(G_{ij}^{(A)}=H_{jl}H_{jn})} 1_{A_1} 1_{U_2}] \\
&= P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jl}H_{jn}, A_1, U_2, (2 \text{ IBD}) \cup (1 \text{ IBD}) \cup (0 \text{ IBD})] \\
&= \frac{1}{4} \sum_{s,t \in \{D,d\}} \bar{f}_{st} f_{st} P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jl}H_{jn}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = st] \\
&\quad + \frac{1}{2} \sum_{s,t,q \in \{D,d\}} \bar{f}_{st} f_{tq} P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jl}H_{jn}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = tq] \qquad (11) \\
&\quad + \frac{1}{4} \sum_{s,t,q,r \in \{D,d\}} \bar{f}_{st} f_{qr} P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ij}^{(A)} = H_{jl}H_{jn}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = qr] \\
&= \frac{1}{4} \sum_{s,t,q,r \in \{D,d\}} \bar{f}_{st} f_{qr} P(H_{jk}s) P(H_{jk}t) \Big[ P(H_{jl}q) P(H_{jn}r) + P(H_{jl}r) P(H_{jn}q) \Big].
\end{aligned}$$

For $m \neq k, l$, one may have the following expectation

$$\begin{aligned}
&\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jm})} 1_{(G_{ij}^{(A)}=H_{jl}H_{jl})} 1_{A_1} 1_{U_2}] \\
&= P[G_{ij}^{(U)} = H_{jk}H_{jm}, G_{ij}^{(A)} = H_{jl}H_{jl}, A_1, U_2, (2 \text{ IBD}) \cup (1 \text{ IBD}) \cup (0 \text{ IBD})] \\
&= \frac{1}{4} \sum_{s,t \in \{D,d\}} \bar{f}_{st} f_{st} P[G_{ij}^{(U)} = H_{jk}H_{jm}, G_{ij}^{(A)} = H_{jl}H_{jl}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = st] \\
&\quad + \frac{1}{2} \sum_{s,t,q \in \{D,d\}} \bar{f}_{st} f_{tq} P[G_{ij}^{(U)} = H_{jk}H_{jm}, G_{ij}^{(A)} = H_{jl}H_{jl}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = tq] \qquad (12) \\
&\quad + \frac{1}{4} \sum_{s,t,q,r \in \{D,d\}} \bar{f}_{st} f_{qr} P[G_{ij}^{(U)} = H_{jk}H_{jm}, G_{ij}^{(A)} = H_{jl}H_{jl}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = qr] \\
&= \frac{1}{4} \sum_{s,t,q,r \in \{D,d\}} \bar{f}_{st} f_{qr} \Big[ P(H_{jk}s) P(H_{jm}t) + P(H_{jk}t) P(H_{jm}s) \Big] P(H_{jl}q) P(H_{jl}r).
\end{aligned}$$

For $m \neq k, l, n \neq m, k, l$, one may have the following expectation

$$\begin{aligned}
&\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jm})} 1_{(G_{ij}^{(A)}=H_{jl}H_{jn})} 1_{A_1} 1_{U_2}] \\
&= P[G_{ij}^{(U)} = H_{jk}H_{jm}, G_{ij}^{(A)} = H_{jl}H_{jn}, A_1, U_2, (2 \text{ IBD}) \cup (1 \text{ IBD}) \cup (0 \text{ IBD})] \\
&= \frac{1}{4} \sum_{s,t \in \{D,d\}} \bar{f}_{st} f_{st} P[G_{ij}^{(U)} = H_{jk}H_{jm}, G_{ij}^{(A)} = H_{jl}H_{jn}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = st] \\
&\quad + \frac{1}{2} \sum_{s,t,q \in \{D,d\}} \bar{f}_{st} f_{tq} P[G_{ij}^{(U)} = H_{jk}H_{jm}, G_{ij}^{(A)} = H_{jl}H_{jn}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = tq] \qquad (13) \\
&\quad + \frac{1}{4} \sum_{s,t,q,r \in \{D,d\}} \bar{f}_{st} f_{qr} P[G_{ij}^{(U)} = H_{jk}H_{jm}, G_{ij}^{(A)} = H_{jl}H_{jn}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = qr]
\end{aligned}$$

$$= \frac{1}{4} \sum_{s,t,q,r \in \{D,d\}} \bar{f}_{st} f_{qr} \Big[ P(H_{jk}s)P(H_{jm}t) + P(H_{jk}t)P(H_{jm}s) \Big] \Big[ P(H_{jl}q)P(H_{jn}r) + P(H_{jl}r)P(H_{jn}q) \Big].$$

Using equations (5), (6), (7), (8), (10), (11), (12), and (13), we may calculate terms of equation (9).

# Appendix C

For $j \neq g$, the expectation

$$\begin{aligned} & \mathrm{E}\,[z_{ijk}^{(U)} z_{igh}^{(A)} 1_{A_1} 1_{U_2}] && (14) \\ & = \mathrm{E}\,\Big[ \Big( 2 \cdot 1_{(G_{ij}^{(U)} = H_{jk}H_{jk})} + \sum_{k' \neq k} 1_{(G_{ij}^{(U)} = H_{jk}H_{jk'})} \Big) \Big( 2 \cdot 1_{(G_{ig}^{(A)} = H_{gh}H_{gh})} + \sum_{h' \neq h} 1_{(G_{ig}^{(A)} = H_{gh}H_{gh'})} \Big) 1_{A_1} 1_{U_2} \Big]. \end{aligned}$$

Suppose that blocks/markers $H_j$ and $H_g$ flank disease locus $D$ in an order $H_j D H_g$. The expectation

$$\begin{aligned} & \mathrm{E}\,[1_{(G_{ij}^{(U)} = H_{jk}H_{jk})} 1_{(G_{ig}^{(A)} = H_{gh}H_{gh})} 1_{A_1} 1_{U_2}] \\ & = P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ig}^{(A)} = H_{gh}H_{gh}, A_1, U_2, (2 \text{ IBD}) \cup (1 \text{ IBD}) \cup (0 \text{ IBD})] \\ & = \frac{1}{4} \sum_{s,t \in \{D,d\}} \bar{f}_{st} f_{st} P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ig}^{(A)} = H_{gh}H_{gh}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = st] \\ & \quad + \frac{1}{2} \sum_{s,t,q \in \{D,d\}} \bar{f}_{st} f_{tq} P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ig}^{(A)} = H_{gh}H_{gh}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = tq] && (15) \\ & \quad + \frac{1}{4} \sum_{s,t,q,r \in \{D,d\}} \bar{f}_{st} f_{qr} P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ig}^{(A)} = H_{gh}H_{gh}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = qr] \\ & = \frac{1}{4} \sum_{s,t \in \{D,d\}} \bar{f}_{st} f_{st} P(H_{jk}sH_{gh}) P(H_{jk}tH_{gh}) + \frac{1}{2} \sum_{s,t,q \in \{D,d\}} \bar{f}_{st} f_{tq} P(H_{jk}tH_{gh}) P(H_{jk}s) P(qH_{gh}) \\ & \quad + \frac{1}{4} \sum_{s,t,q,r \in \{D,d\}} \bar{f}_{st} f_{qr} P(H_{jk}s) P(H_{jk}t) P(qH_{gh}) P(rH_{gh}). \end{aligned}$$

If $h' \neq h$, the expectation

$$\begin{aligned} & \mathrm{E}\,[1_{(G_{ij}^{(U)} = H_{jk}H_{jk})} 1_{(G_{ig}^{(A)} = H_{gh}H_{gh'})} 1_{A_1} 1_{U_2}] \\ & = P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ig}^{(A)} = H_{gh}H_{gh'}, A_1, U_2, (2 \text{ IBD}) \cup (1 \text{ IBD}) \cup (0 \text{ IBD})] \\ & = \frac{1}{4} \sum_{s,t \in \{D,d\}} \bar{f}_{st} f_{st} P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ig}^{(A)} = H_{gh}H_{gh'}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = st] \\ & \quad + \frac{1}{2} \sum_{s,t,q \in \{D,d\}} \bar{f}_{st} f_{tq} P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ig}^{(A)} = H_{gh}H_{gh'}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = tq] && (16) \\ & \quad + \frac{1}{4} \sum_{s,t,q,r \in \{D,d\}} \bar{f}_{st} f_{qr} P[G_{ij}^{(U)} = H_{jk}H_{jk}, G_{ig}^{(A)} = H_{gh}H_{gh'}, G_{iD}^{(U)} = st, G_{iD}^{(A)} = qr] \\ & = \frac{1}{4} \sum_{s,t \in \{D,d\}} \bar{f}_{st} f_{st} \Big[ P(H_{jk}sH_{gh}) P(H_{jk}tH_{gh'}) + P(H_{jk}tH_{gh}) P(H_{jk}sH_{gh'}) \Big] \end{aligned}$$

$$+\frac{1}{2}\sum_{s,t,q\in\{D,d\}}\bar{f}_{st}f_{tq}\Big[P(H_{jk}tH_{gh})P(H_{jk}s)P(qH_{gh'})+P(H_{jk}tH_{gh'})P(H_{jk}s)P(qH_{gh})\Big]$$
$$+\frac{1}{4}\sum_{s,t,q,r\in\{D,d\}}\bar{f}_{st}f_{qr}P(H_{jk}s)P(H_{jk}t)\Big[P(qH_{gh})P(rH_{gh'})+P(rH_{gh})P(qH_{gh'})\Big].$$

If $k\neq k'$, the expectation

$$\begin{aligned}
&\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk'})}1_{(G_{ig}^{(A)}=H_{gh}H_{gh})}1_{A_1}1_{U_2}]\\
&=P[G_{ij}^{(U)}=H_{jk}H_{jk'},G_{ig}^{(A)}=H_{gh}H_{gh},A_1,U_2,(2\text{ IBD})\cup(1\text{ IBD})\cup(0\text{ IBD})]\\
&=\frac{1}{4}\sum_{s,t\in\{D,d\}}\bar{f}_{st}f_{st}P[G_{ij}^{(U)}=H_{jk}H_{jk'},G_{ig}^{(A)}=H_{gh}H_{gh},G_{iD}^{(U)}=st,G_{iD}^{(A)}=st]\\
&\quad+\frac{1}{2}\sum_{s,t,q\in\{D,d\}}\bar{f}_{st}f_{tq}P[G_{ij}^{(U)}=H_{jk}H_{jk'},G_{ig}^{(A)}=H_{gh}H_{gh},G_{iD}^{(U)}=st,G_{iD}^{(A)}=tq] \qquad (17)\\
&\quad+\frac{1}{4}\sum_{s,t,q,r\in\{D,d\}}\bar{f}_{st}f_{qr}P[G_{ij}^{(U)}=H_{jk}H_{jk'},G_{ig}^{(A)}=H_{gh}H_{gh},G_{iD}^{(U)}=st,G_{iD}^{(A)}=qr]\\
&=\frac{1}{4}\sum_{s,t\in\{D,d\}}\bar{f}_{st}f_{st}\Big[P(H_{jk}sH_{gh})P(H_{jk'}tH_{gh})+P(H_{jk}tH_{gh})P(H_{jk'}sH_{gh})\Big]\\
&\quad+\frac{1}{2}\sum_{s,t,q\in\{D,d\}}\bar{f}_{st}f_{tq}\Big[P(H_{jk}tH_{gh})P(H_{jk'}s)P(qH_{gh})+P(H_{jk'}tH_{gh})P(H_{jk}s)P(qH_{gh})\Big]\\
&\quad+\frac{1}{4}\sum_{s,t,q,r\in\{D,d\}}\bar{f}_{st}f_{qr}\Big[P(H_{jk}s)P(H_{jk'}t)+P(H_{jk}t)P(H_{jk'}s)\Big]P(qH_{gh})P(rH_{gh}).
\end{aligned}$$

If $k\neq k', h\neq h'$, the expectation

$$\begin{aligned}
&\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk'})}1_{(G_{ig}^{(A)}=H_{gh}H_{gh'})}1_{A_1}1_{U_2}]\\
&=P[G_{ij}^{(U)}=H_{jk}H_{jk'},G_{ig}^{(A)}=H_{gh}H_{gh'},A_1,U_2,(2\text{ IBD})\cup(1\text{ IBD})\cup(0\text{ IBD})]\\
&=\frac{1}{4}\sum_{s,t\in\{D,d\}}\bar{f}_{st}f_{st}P[G_{ij}^{(U)}=H_{jk}H_{jk'},G_{ig}^{(A)}=H_{gh}H_{gh'},G_{iD}^{(U)}=st,G_{iD}^{(A)}=st]\\
&\quad+\frac{1}{2}\sum_{s,t,q\in\{D,d\}}\bar{f}_{st}f_{tq}P[G_{ij}^{(U)}=H_{jk}H_{jk'},G_{ig}^{(A)}=H_{gh}H_{gh'},G_{iD}^{(U)}=st,G_{iD}^{(A)}=tq]\\
&\quad+\frac{1}{4}\sum_{s,t,q,r\in\{D,d\}}\bar{f}_{st}f_{qr}P[G_{ij}^{(U)}=H_{jk}H_{jk'},G_{ig}^{(A)}=H_{gh}H_{gh'},G_{iD}^{(U)}=st,G_{iD}^{(A)}=qr]\\
&=\frac{1}{4}\sum_{s,t\in\{D,d\}}\bar{f}_{st}f_{st}\Big[P(H_{jk}sH_{gh})P(H_{jk'}tH_{gh'})+P(H_{jk}tH_{gh})P(H_{jk'}sH_{gh'}) \qquad (18)\\
&\qquad\qquad+P(H_{jk}sH_{gh'})P(H_{jk'}tH_{gh})+P(H_{jk}tH_{gh'})P(H_{jk'}sH_{gh})\Big]\\
&\quad+\frac{1}{2}\sum_{s,t,q\in\{D,d\}}\bar{f}_{st}f_{tq}\Big[P(H_{jk}tH_{gh})P(H_{jk'}s)P(qH_{gh'})+P(H_{jk'}tH_{gh})P(H_{jk}s)P(qH_{gh'})\\
&\qquad\qquad+P(H_{jk}tH_{gh'})P(H_{jk'}s)P(qH_{gh})+P(H_{jk'}tH_{gh'})P(H_{jk}s)P(qH_{gh})\Big]
\end{aligned}$$

$$+\frac{1}{4}\sum_{s,t,q,r\in\{D,d\}}\bar{f}_{st}f_{qr}\Big[P(H_{jk}s)P(H_{jk'}t)+P(H_{jk}t)P(H_{jk'}s)\Big]\Big[P(qH_{gh})P(rH_{gh'})+P(rH_{gh})P(rqH_{gh'})\Big].$$

# Appendix D

For "genotype coding", the coding vector of the affected sibling in the $i$-th sib-pair is $X_{ij}^{(A)}=(x_{ij1}^{(A)},\cdots,x_{ij(n_j-1)}^{(A)},x_{ij12}^{(A)},\cdots,x_{ij1n_j}^{(A)},\cdots,x_{ij(n_j-1)n_j}^{(A)})^\tau, j=1,\cdots,J$. Similarly, $Y_{ij}^{(U)}=(x_{ij1}^{(U)},\cdots,x_{ij(n_j-1)}^{(U)},x_{ij12}^{(U)},\cdots,x_{ij1n_j}^{(U)},\cdots,x_{ij(n_j-1)n_j}^{(U)})^\tau, j=1,\cdots,J$ is the coding vector of the normal sibling in the $i$-th sib-pair. Using the expectations $\mathrm{E}\,[X_{ij}^{(A)}|A_1,U_2]$ and $\mathrm{E}\,[Y_{ij}^{(U)}|A_1,U_2]$ given in equations (1) and (2), one may calculate the following variance-covariance matrices

$$\begin{aligned}
\mathrm{Var}(X_{ij}^{(A)}|A_1,U_2) &= diag(a_{j11},\cdots,a_{j(n_j-1)(n_j-1)},a_{j12},\cdots,a_{j1n_j},\cdots,a_{j(n_j-1)n_j})\\
&\quad -\mathrm{E}\,[X_{ij}^{(A)}|A_1,U_2]\,\mathrm{E}\,[X_{ij}^{(A)}|A_1,U_2]^\tau,\\
\mathrm{Var}(Y_{ij}^{(U)}|A_1,U_2) &= diag(\bar{a}_{j11},\cdots,\bar{a}_{j(n_j-1)(n_j-1)},\bar{a}_{j12},\cdots,\bar{a}_{j1n_j},\cdots,\bar{a}_{j(n_j-1)n_j})\\
&\quad -\mathrm{E}\,[Y_{ij}^{(U)}|A_1,U_2]\,\mathrm{E}\,[Y_{ij}^{(U)}|A_1,U_2]^\tau.
\end{aligned}\tag{19}$$

The covariances between $x_{ijk},x_{ijkk'}$ and $x_{igh},x_{ighh'}$ are given by

$$\begin{aligned}
\mathrm{Cov}(x_{ijk}^{(A)},x_{igh}^{(A)}|A_1,U_2) &= g_{kkhh}^{(A,jg)}-a_{jkk}a_{ghh},\\
\mathrm{Cov}(x_{ijk}^{(A)},x_{ighh'}^{(A)}|A_1,U_2) &= g_{kkhh'}^{(A,jg)}-a_{jkk}a_{ghh'},\\
\mathrm{Cov}(x_{ijkk'}^{(A)},x_{igh}^{(A)}|A_1,U_2) &= g_{kk'hh}^{(A,jg)}-a_{jkk'}a_{ghh},\\
\mathrm{Cov}(x_{ijkk'}^{(A)},x_{ighh'}^{(A)}|A_1,U_2) &= g_{kk'hh'}^{(A,jg)}-a_{jkk'}a_{ghh'}.
\end{aligned}\tag{20}$$

Similarly,

$$\begin{aligned}
\mathrm{Cov}(x_{ijk}^{(U)},x_{igh}^{(U)}|A_1,U_2) &= \bar{g}_{kkhh}^{(U,jg)}-\bar{a}_{jkk}\bar{a}_{ghh},\\
\mathrm{Cov}(x_{ijk}^{(U)},x_{ighh'}^{(U)}|A_1,U_2) &= \bar{g}_{kkhh'}^{(U,jg)}-\bar{a}_{jkk}\bar{a}_{ghh'},\\
\mathrm{Cov}(x_{ijkk'}^{(U)},x_{igh}^{(U)}|A_1,U_2) &= \bar{g}_{kk'hh}^{(U,jg)}-\bar{a}_{jkk'}\bar{a}_{ghh},\\
\mathrm{Cov}(x_{ijkk'}^{(U)},x_{ighh'}^{(U)}|A_1,U_2) &= \bar{g}_{kk'hh'}^{(U,jg)}-\bar{a}_{jkk'}\bar{a}_{ghh'}.
\end{aligned}\tag{21}$$

Using results of equations (19), (20) and (21), one may calculate $\mathrm{Var}(X_i^{(A)}|A_1,U_2)$ and $\mathrm{Var}(Y_i^{(U)}|A_1,U_2)$ for genotype coding method.

# Appendix E

In this appendix, we calculate the following covariance matrix for "genotype coding"

$$\begin{aligned}\mathrm{Cov}(Y_i^{(U)}, X_i^{(A)}|A_1, U_2) &= \mathrm{E}\,[Y_i^{(U)} X_i^{(A)^\tau}|A_1, U_2] - \mathrm{E}\,[Y_i^{(U)}|A_1, U_2]\,\mathrm{E}\,[X_i^{(A)^\tau}|A_1, U_2] \\ &= \frac{\mathrm{E}\,[Y_i^{(U)} X_i^{(A)^\tau} 1_{A_1} 1_{U_2}]}{P(A_1, U_2)} - \mathrm{E}\,[Y_i^{(U)}|A_1, U_2]\,\mathrm{E}\,[X_i^{(A)^\tau}|A_1, U_2].\end{aligned}$$

The probability $P(A_1, U_2)$ is given in the Appendix of the manuscript, and the components of expectations $\mathrm{E}\,[X_i^{(A)}|A_1, U_2]$ and $\mathrm{E}\,[Y_i^{(U)}|A_1, U_2]$ are given in equations (1) and (2). For $\mathrm{E}\,[Y_i^{(U)} X_i^{(A)^\tau} 1_{A_1} 1_{U_2}]$, we notice the following results: the expectation $\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk})}\ 1_{(G_{ij}^{(A)}=H_{jk}H_{jk})} 1_{A_1} 1_{U_2}]$ is given by (4); For $l \neq k$, the expectation $\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk})}\ 1_{(G_{ij}^{(A)}=H_{jk}H_{jl})} 1_{A_1} 1_{U_2}]$ is given by (5); For $l \neq k$, $\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jl})} 1_{(G_{ij}^{(A)}=H_{jk}H_{jk})}$ $1_{A_1} 1_{U_2}]$ is given by (6); For $l \neq k$, $\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jl})}\ 1_{(G_{ij}^{(A)}=H_{jk}H_{jl})} 1_{A_1} 1_{U_2}]$ is given by (7); For $l_1 \neq l_2$, $l_1 \neq k$, $l_2 \neq k$, $\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jl_1})}\ 1_{(G_{ij}^{(A)}=H_{jk}H_{jl_2})} 1_{A_1} 1_{U_2}]$ is given by (8); For $l \neq k$, $\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk})} 1_{(G_{ij}^{(A)}=H_{jl}H_{jl})} 1_{A_1} 1_{U_2}]$ is given by (10); For $l \neq k, n \neq k, l$, $\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk})} 1_{(G_{ij}^{(A)}=H_{jl}H_{jn})} 1_{A_1} 1_{U_2}]$ is given by (11); For $l \neq k, m \neq k, l$, $\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jm})} 1_{(G_{ij}^{(A)}=H_{jl}H_{jl})} 1_{A_1} 1_{U_2}]$ is given by (12); For $l \neq k, m \neq k, l, n \neq m, k, l$, $\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jm})} 1_{(G_{ij}^{(A)}=H_{jl}H_{jn})} 1_{A_1} 1_{U_2}]$ is given by (13). In addition, $\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk})} 1_{(G_{ij}^{(A)}=H_{gh}H_{gh})}\ 1_{A_1} 1_{U_2}]$ is given by (15); $\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk})} 1_{(G_{ij}^{(A)}=H_{gh}H_{gh'})} 1_{A_1} 1_{U_2}]$ is given by (16); $\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk'})}\ 1_{(G_{ij}^{(A)}=H_{gh}H_{gh})} 1_{A_1} 1_{U_2}]$ is given by (17); Finally, $\mathrm{E}\,[1_{(G_{ij}^{(U)}=H_{jk}H_{jk'})} 1_{(G_{ij}^{(A)}=H_{gh}H_{gh'})} 1_{A_1} 1_{U_2}]$ is given by (18).