Statistical Validation of Endophenotypes Using a Surrogate Endpoint Analytic Analogue

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Brief outline

- Validation of surrogate endpoints
- Validation of endophenotypes
  - PHE (Proportion of heritability explained by the endophenotype)
- Estimation and variance of PHE
- Simulation design and results

Clinical vs. surrogate endpoint

- Clinical endpoint: reflecting how a patient feels, functions, or survive; should be
  - sensitive to treatment effects, and
  - clinically relevant.
- Surrogate endpoint: biomarkers intended to substitute for a clinical endpoint

Why surrogate endpoint?

- In many medical studies, the clinical endpoint is inaccessible due to **cost, time and difficulty of measurement**. A valid surrogate endpoint is then measured in place of the biologically definitive or clinically most meaningful endpoint.

Validation of surrogate endpoints

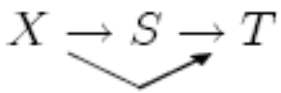
- Prentice's landmark definition [1989]
  - $f(S \mid X) = f(S) \Longleftrightarrow f(T \mid X) = f(T)$
    - T: clinical endpoint, S: surrogate endpoint, X: treatment variable
  - Validation of Prentice's definition involves the following two criteria:

    $f(T \mid S) \neq f(T)$ and $f(T \mid S, X) = f(T \mid S)$
    - Surrogate S could capture the dependence of T and X.
  - Good for

    $X \rightarrow S \rightarrow T$

Validation of surrogate endpoints (cont'd)

- More complex situation



- PTE proposed by Freedman et al.[1992]
  - The proportion of the treatment effect (on the primary endpoint) explained by the surrogate
  - $PTE = 1 - \frac{\beta_{TS}}{\beta_T}$
  - $g[E(T)] = \alpha_T + \beta_T X$ vs. $g[E(T)] = \alpha_{TS} + \beta_{TS} X + \gamma_{TS} S$
- A good surrogate is one that explains a large proportion of that effect.

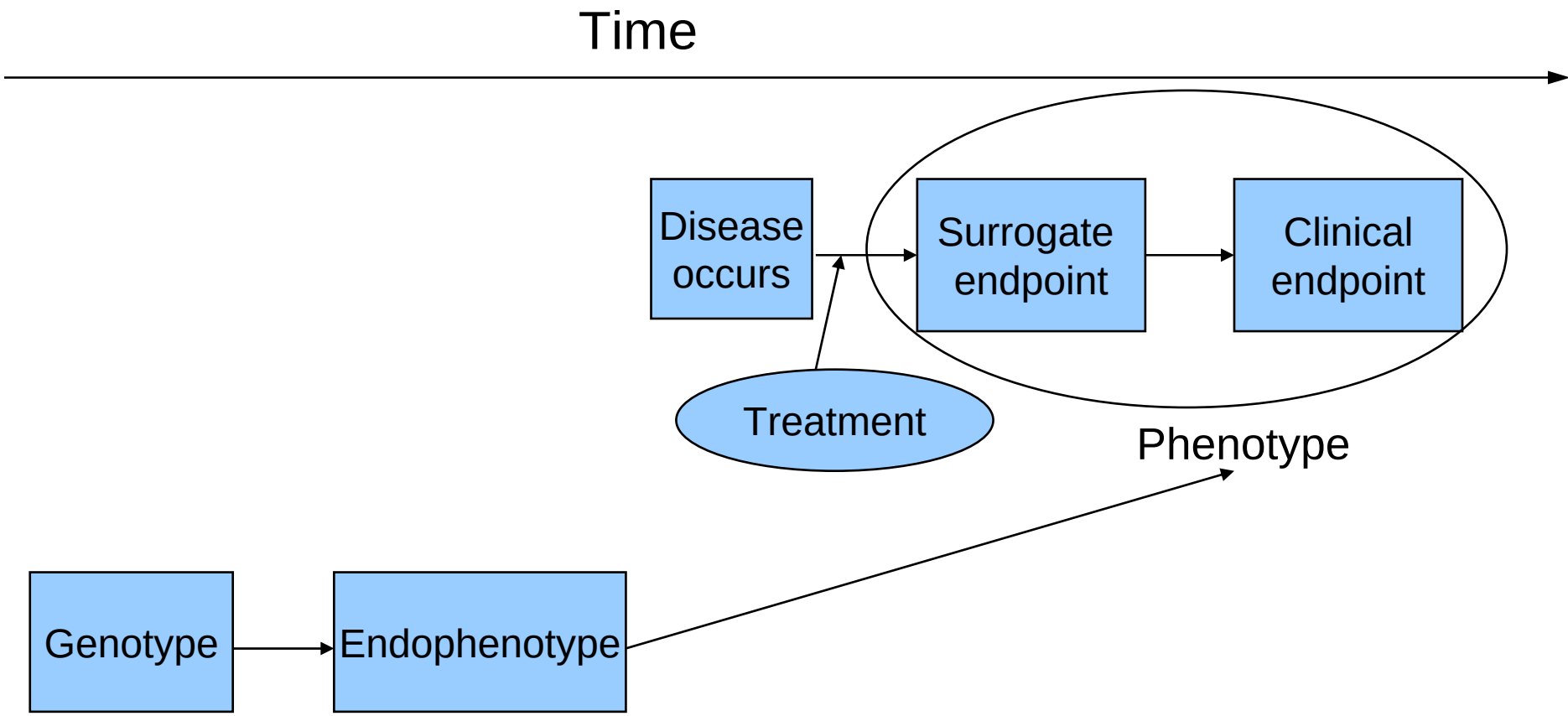
What is endophenotypes?

- Provide a means for identifying the “downstream” traits of clinical phenotypes, as well as the “upstream” consequences of genes.
- The hypothetical constructs that could mark the path between the genotype and the phenotype.

Why endophenotpe?

- Use endophenotype to assist in detecting the underlying genotype
- The endophenotype is closer to the underlying gene than the phenotype. Hopefully, the genetic analysis using the endophenotype is more likely to success than using the phenotype.

Surrogate endpoint vs. endophenotype



Defining endophenotype using the ideas from surrogate endpoint

- Both the endophenotype and the surrogate endpoint lie in a biological pathway.
- The key: verification of existence of the pathway

  genotype – endophenotype – phenotype

Two differences

- The endophenotype is expected to be closer to the genotype than the phenotype does, though the surrogate endpoint intends to substitute the primary endpoint.
- The genotype information is usually unknown, whereas treatment status in validating a surrogate is known.

Validation of endophenotype

- Definition
  - $f(E \mid G) = f(E) \Rightarrow f(P \mid G) = f(P)$
    - P: phenotype of interest, E: candidate endophenotype, G: underlying gene
  - If the condition, $f(P \mid E, G) = f(P \mid E)$, holds, then above definition holds.
  - The endophenotype mediates all of the effect of genotype on phenotype
    - $G \rightarrow E \rightarrow P$

Two features

- “imply” replaces “if and only if” statement in Prentice's definition of surrogate endpoints.
  - places the endophenotype in higher upstream of the pathway from the genotype to the phenotype
- Need to know genotype, which is typically unknown.
  - Use “heritability” to replace the association between phenotype and genotype
  - After adjusting for endophenotype, the heritability becomes null.

Validation of endophenotype (cont'd)

- Check the condition $f(P \mid E, G) = f(P \mid E)$
  - $$\begin{aligned} P_{ij} &= \alpha + \gamma E_{ij} + \tau Z_{ij} + G_{ij} + \varepsilon_{ij}, \\ \varepsilon_{ij} &\sim \text{Normal}(0, \sigma_R^2), \\ G_{ij} &\sim \text{Normal}(0, [\sigma_A^2 + \sigma_D^2 + \sigma_C^2]), \\ \text{Cov}(G_{ij}, G_{ik}) &= 2\phi_{ij,ik}\sigma_A^2 + \Delta_{ij,ik}\sigma_D^2 + \lambda_{ij,ik}\sigma_C^2 \ , \ j \neq k, \end{aligned}$$
  - The heritability of P_{ii} , conditional on E_{ij} is
    $$h_{P|E} = \frac{\sigma_A^2 + \sigma_D^2}{\sigma_A^2 + \sigma_D^2 + \sigma_C^2 + \sigma_R^2}$$
  - The significance of rejecting the hypothesis h = 0 indicates the fulfillment of the condition

Proportion of heritability explained by the endophenotype (PHE)

- More complex situation
  - 
- Define

$$\mathrm{PHE} = 1 - \frac{h_{P|E}}{h_P}$$

  - $h_{P|E}$ = the heritability from the model using the candidate endophenotype (E) as one covariate
  - h_P = the heritability from the model NOT using the candidate endophenotype as one covariate
  - the greater the PHE value, the more likely E is an endophenotype.

Estimation of PHE

- Variance component analysis can be performed using the SOLAR computer package. ($h_{P|E}$ and h_P are obtained)
- The variance estimator of the estimated PHE ($\widehat{\mathrm{PHE}} = 1 - \left(\hat{h}_{P|E}/\hat{h}_P\right)$)
  - Delta method

Delta method

- $h_{P|E} = h_1^{(1)} + h_2^{(1)}$ and $h_P = h_1^{(2)} + h_2^{(2)}$
- $$\begin{aligned}\operatorname{var}\left(\widehat{\mathrm{PHE}}\right) \approx & \frac{1}{\mathrm{E}^2(\hat{h}_P)}\left\{\operatorname{var}\left(\hat{h}_1^{(1)}\right) + \operatorname{var}\left(\hat{h}_2^{(1)}\right) + 2\operatorname{cov}\left(\hat{h}_1^{(1)}, \hat{h}_2^{(1)}\right)\right\} \\ & + \frac{\mathrm{E}^2(\hat{h}_{P|E})}{\mathrm{E}^4(\hat{h}_P)}\left\{\operatorname{var}\left(\hat{h}_1^{(2)}\right) + \operatorname{var}\left(\hat{h}_2^{(2)}\right) + 2\operatorname{cov}\left(\hat{h}_1^{(2)}, \hat{h}_2^{(2)}\right)\right\} \\ & - 2\frac{\mathrm{E}(\hat{h}_{P|E})}{\mathrm{E}^3(\hat{h}_P)}\left\{\operatorname{cov}\left(\hat{h}_1^{(1)}, \hat{h}_1^{(2)}\right) + \operatorname{cov}\left(\hat{h}_1^{(1)}, \hat{h}_2^{(2)}\right)\right. \\ & \left. + \operatorname{cov}\left(\hat{h}_2^{(1)}, \hat{h}_1^{(2)}\right) + \operatorname{cov}\left(\hat{h}_2^{(1)}, \hat{h}_2^{(2)}\right)\right\}.\end{aligned}$$

Estimate of robust covariance

- Idea: obtain approximate expression of $h_i^{(j)}$'s
  - Generalized estimating equations (GEE) for covariance
  - Fisher scoring algorithm
  - Some matrix operation

Hypothesis testing

- One-sided test

$$\begin{cases} H_0 : \mathrm{PHE} = a \\ H_1 : \mathrm{PHE} > a \end{cases}$$

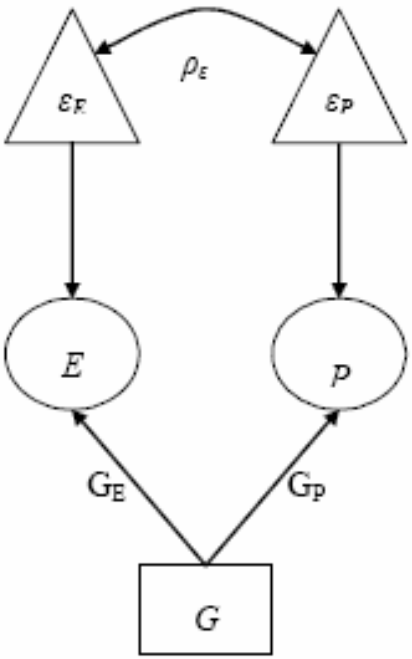
- *a*=0, 0.25, 0.5, 0.75
- Reject H_0 if the lower bound of the one-sided confidence interval of PHE,

$$\widehat{\mathrm{PHE}} - Z_{1-\alpha} \times \sqrt{\widehat{\mathrm{var}}(\widehat{\mathrm{PHE}})}$$

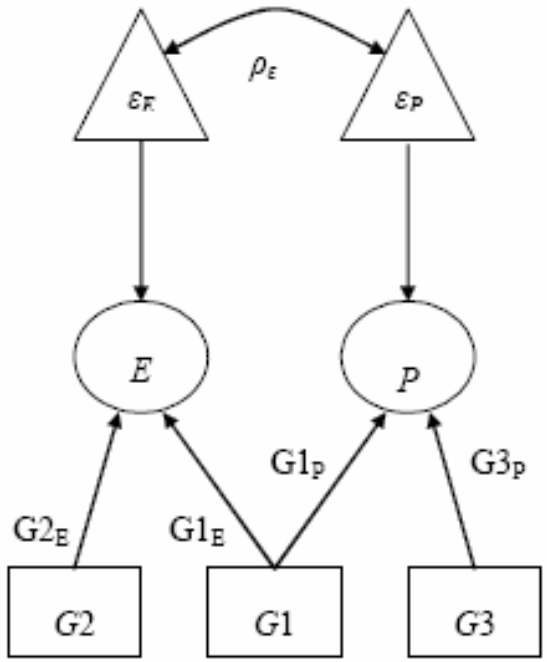
is greater than *a*

Simulation study

- Design



Scenario I



Scenario II

- Tools
  - SIMULATE
  - SOLAR
  - R language

Results

TABLE A1. Simulation results based on scenario I (1)

No. of families	h_P [a]	h_E^2 [a]	ρ_e [b]	h^2 [c]	PHE [d]	$s.e$ [e]	$s.e(delta)$ [f]	$s.e(Fieller)$ [g]	$S.W-pvalue$ [h]
200	0.42	0	0	0.405	−0.002	0.009	0.025	0.029	< 0.001
			0.5	0.473	−0.201	0.138	0.215	0.271	< 0.001
		0.15	0	0.337	0.202	0.079	0.128	0.154	< 0.001
			0.5	0.269	0.322	0.158	0.151	0.234	0.039
		0.42	0	0.183	0.562	0.138	0.107	0.204	0.698
			0.5	0.075	0.816	0.149	0.087	0.118	< 0.001
		0.74	0	0.053	0.875	0.125	0.084	0.094	< 0.001
			0.5	0.028	0.937	0.093	0.075	0.088	< 0.001

TABLE A2. Simulation results based on scenario I (2)

No. of families	h_P [a]	h_E^2 [a]	ρ_e [b]	h^2 [c]	PHE [d]	$s.e$ [e]	$s.e(delta)$ [f]	$s.e(Fieller)$ [g]	$S.W-pvalue$ [h]
500	0.42	0	0	0.422	−0.0004	0.002	0.007	0.008	< 0.001
			0.5	0.481	−0.173	0.071	0.117	0.122	< 0.001
		0.15	0	0.339	0.189	0.042	0.074	0.076	0.001
			0.5	0.282	0.331	0.081	0.084	0.088	0.282
		0.42	0	0.187	0.552	0.084	0.066	0.068	0.012
			0.5	0.076	0.817	0.092	0.050	0.052	0.003
		0.74	0	0.048	0.889	0.079	0.048	0.049	< 0.001
			0.5	0.017	0.959	0.053	0.045	0.046	< 0.001

Results (cont'd)

TABLE B2. Simulation results based on scenario II with P>E (2)

No. of families	$h(G1_E)/h(G1_P)$[a]	$h(G2_E)/h(G3_P)$[b]	ρ_ϵ^c	h^c	PHE[d]	$s.e$[e]	$s.e(delta)$[f]	$s.e(Fieller)$[f]	$S.W-pvalue$[g]
500	0/0.42	0.3/0.17	0	0.595	−0.0003	0.0017	0.0039	0.0039	< 0.001
			0.5	0.659	−0.127	0.038	0.058	0.059	< 0.001
	0.15/0.42	0.25/0.17	0	0.539	0.091	0.025	0.046	0.046	< 0.001
			0.5	0.588	−0.003	0.054	0.069	0.070	0.108
	0.42/0.42	0.12/0.17	0	0.432	0.267	0.051	0.055	0.056	0.367
			0.5	0.471	0.202	0.068	0.063	0.064	0.186
	0.51/0.42	0.04/0.17	0	0.388	0.344	0.053	0.053	0.054	0.084
			0.5	0.418	0.287	0.073	0.060	0.061	0.170
	0.74/0.42	0.05/0.41	0	0.672	0.185	0.038	0.034	0.034	0.805
			0.5	0.762	0.074	0.044	0.035	0.035	0.394
	0.74/0.42	0.08/0.41	0	0.681	0.175	0.038	0.033	0.034	0.495
			0.5	0.770	0.067	0.044	0.035	0.035	0.206
	0.79/0.42	0.08/0.41	0	0.664	0.192	0.041	0.034	0.034	0.681
			0.5	0.755	0.075	0.048	0.036	0.036	0.034

Results (cont'd)

TABLE C2. Simulation results based on scenario II with P<E (2)

No. of families	$h(G1_E)/h(G1_P)$[a]	$h(G2_E)/h(G3_P)$[b]	ρ_ϵ^c	h^c	PHE[d]	$s.e$[e]	$s.e(delta)$[f]	$s.e(Fieller)$[f]	$S.W-pvalue$[g]
500	0/0.42	0.7/0.17	0	0.589	−0.00003	0.0019	0.0043	0.0043	< 0.001
			0.5	0.647	−0.091	0.028	0.046	0.046	< 0.001
	0.15/0.42	0.59/0.17	0	0.553	0.069	0.025	0.047	0.048	0.170
			0.5	0.616	−0.054	0.046	0.068	0.069	0.089
	0.42/0.42	0.23/0.17	0	0.446	0.243	0.049	0.056	0.057	0.990
			0.5	0.519	0.126	0.069	0.066	0.067	0.654
	0.62/0.42	0.23/0.17	0	0.405	0.313	0.058	0.056	0.057	0.249
			0.5	0.483	0.177	0.074	0.064	0.065	0.932
	0.74/0.42	0.08/0.17	0	0.337	0.431	0.069	0.051	0.052	0.730
			0.5	0.413	0.295	0.079	0.059	0.060	0.001
	0.74/0.42	0.21/0.17	0	0.388	0.340	0.065	0.056	0.056	0.980
			0.5	0.445	0.242	0.075	0.061	0.062	0.146

Result summary

- PHE
  - scenario I
    - The higher the heritability of E due to G, the lower the heritability of P conditional on E and the closer the PHE values to 1.
    - ρ_ϵ is either 0 or 0.5, the trend is still kept.
  - scenario II
    - The higher the heritability of E due to G1, the higher the PHE values. It is consistent with scenario I.
    - The higher the heritability of P due to G3 or the heritability of E due to G2, the lower the PHE values.
    - The involvement of ρ_ϵ leads the PHE values to be disrupted. That is, it reduces the efficiency to use the PHE values for searching a useful endophenotype.

Result summary (cont'd)

- The accuracy of the estimator of s.e. of PHE
  - When the heritability of E due to the disease gene is lower than the heritability of P due to the shared gene, s.e. tend to be overestimated.
  - When the heritability of E due to the disease gene is higher than the heritability of P due to the shared gene, s.e. tend to be underestimated.
  - The overestimators and the underestimators are small.
  - C.I.'s are not too wide make inferences.

Results for hypothesis testing

- Test

$$\begin{cases} H_0 : \mathrm{PHE} = a \\ H_1 : \mathrm{PHE} > a \end{cases}$$

- Evaluate cutpoints = 0, 0.25, 0.50, 0.75
- Normality?

Results with table

TABLE A3. Simulation results based on scenario I (3)

				delta method				Fieller method			
No. of families	h_P [a]	h_E^2	ρ_z [b]	$D0.00$ [c]	$D0.25$ [c]	$D0.50$ [c]	$D0.75$ [c]	$F0.00$ [d]	$F0.25$ [d]	$F0.50$ [d]	$F0.75$ [d]
200	0.42	0	0	0	0	0	0	0	0	0	0
			0.5	0	0	0	0	0.01	0.005	0	0
		0.15	0	0.55	0	0	0	0.395	0.01	0.01	0.01
			0.5	0.715	0.195	0.01	0	0.56	0.115	0.01	0
		0.42	0	0.99	0.815	0.255	0	0.95	0.71	0.19	0
			0.5	0.995	0.98	0.825	0.365	0.99	0.945	0.8	0.34
		0.74	0	1	1	0.945	0.52	1	0.995	0.9	0.515
			0.5	1	1	0.99	0.78	0.995	0.99	0.99	0.765

TABLE A4. Simulation results based on scenario I (4)

				delta method				Fieller method			
No. of families	h_P [a]	h_E^2	ρ_z [b]	$D0.00$ [c]	$D0.25$ [c]	$D0.50$ [c]	$D0.75$ [c]	$F0.00$ [d]	$F0.25$ [d]	$F0.50$ [d]	$F0.75$ [d]
500	0.42	0	0	0	0	0	0	0	0	0	0
			0.5	0	0	0	0	0	0	0	0
		0.15	0	0.935	0	0	0	0.89	0	0	0
			0.5	0.975	0.28	0	0	0.945	0.24	0	0
		0.42	0	1	0.985	0.26	0.005	1	0.98	0.22	0.005
			0.5	1	1	0.995	0.4	1	1	0.985	0.39
		0.74	0	1	1	1	0.74	1	1	1	0.725
			0.5	1	1	1	0.97	1	1	1	0.965

Results with table (cont'd)

TABLE B4. Simulation results based on scenario II with P>E (4)

				delta method				Fieller method			
No. of families	$h(G1_E)/h(G1_P)$[a]	$h(G2_E)/h(G3_P)$[b]	ρ_ϵ^c	$D0.00$[d]	$D0.25$[d]	$D0.50$[d]	$D0.75$[d]	$F0.00$[e]	$F0.25$[e]	$F0.50$[e]	$F0.75$[e]
500	0/0.42	0.3/0.17	0	0	0	0	0	0	0	0	0
			0.5	0	0	0	0	0	0	0	0
	0.15/0.42	0.25/0.17	0	0.71	0	0	0	0.665	0	0	0
			0.5	0.02	0	0	0	0.015	0	0	0
	0.42/0.42	0.12/0.17	0	1	0.09	0	0	1	0.085	0	0
			0.5	0.905	0.03	0	0	0.885	0.03	0	0
	0.51/0.42	0.04/0.17	0	1	0.53	0	0	1	0.5	0	0
			0.5	0.985	0.24	0	0	0.985	0.22	0	0
	0.74/0.42	0.05/0.41	0	1	0	0	0	1	0	0	0
			0.5	0.6	0	0	0	0.585	0	0	0
	0.74/0.42	0.08/0.41	0	1	0	0	0	1	0	0	0
			0.5	0.59	0	0	0	0.565	0	0	0
	0.79/0.42	0.02/0.41	0	0.995	0	0	0	0.995	0	0	0
			0.5	0.67	0	0	0	0.645	0	0	0

Results with table (cont'd)

TABLE C4. Simulation results based on scenario II with P<E (4)

				delta method				Fieller method			
No. of families	$h(G1_E)/h(G1_P)$[a]	$h(G2_E)/h(G3_P)$[b]	ρ_ϵ^c	$D0.00$[d]	$D0.25$[d]	$D0.50$[d]	$D0.75$[d]	$F0.00$[e]	$F0.25$[e]	$F0.50$[e]	$F0.75$[e]
500	0/0.42	0.7/0.17	0	0	0	0	0	0	0	0	0
			0.5	0	0	0	0	0	0	0	0
	0.15/0.42	0.59/0.17	0	0.4	0	0	0	0.32	0	0	0
			0.5	0	0	0	0	0	0	0	0
	0.42/0.42	0.23/0.17	0	0.99	0.03	0	0	0.99	0.02	0	0
			0.5	0.575	0	0	0	0.54	0	0	0
	0.62/0.42	0.23/0.17	0	1	0.32	0	0	1	0.345	0	0
			0.5	0.805	0.015	0	0	0.76	0.01	0	0
	0.74/0.42	0.08/0.17	0	1	0.895	0.02	0	1	0.86	0.01	0
			0.5	0.97	0.31	0	0	0.96	0.27	0	0
	0.74/0.42	0.21/0.17	0	1	0.515	0	0	1	0.47	0	0
			0.5	0.93	0.075	0	0	0.9	0.075	0	0

Results (cont'd)

- Construct rules - Three criteria
  - The first criterion that lower bound of 95% one-sided confidence interval is larger than 0 is the potential evidence for searching the endophenotype.
  - The second criterion that lower bound of 95% one-sided confidence interval is larger than 0.25 is the moderate evidence for searching the endophenotype.
  - The third criterion that lower bound of 95% one-sided confidence interval is larger than 0.50 is the stronger evidence for searching the endophenotype.

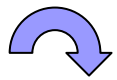
Results (cont'd)

- Construct rules - Three steps (use idea of power)
  - First step : check if ρ_ϵ is 0
    - Not hold : be careful to use
    - hold : go to second step
  - Second step : check if the lower bound of 95% one-sided confidence interval is larger than 0.25
    - hold :
      - the single disease gene & endophenotype-based effect isn't worse than the phenotype-based effect
      - both the influence of other genes be small relatively & endophenotype-based effect is better than the phenotype-based effect.
    - Not hold: go to third step
  - Third step : check if the lower bound of 95% one-sided confidence interval is larger than 0
    - hold :
      - the single disease gene & endophenotype-based effect isn't better than the phenotype-based effect.
      - other genes of either phenotype or endophenotype can be large relatively & endophenotype-based effect isn't worse than the phenotype-based effect.
    - Not hold : there is a high probability that it isn't a useful endophenotype.

Estimate of robust covariance

$$
\begin{aligned}
& \operatorname{cov}\left(\hat{\mathbf{h}}^{(t)}, \hat{\mathbf{h}}^{(t^*)}\right) \\
\approx\ & \left\{\sum_{i=1}^{I}\left(\frac{\partial \mathbf{V}_i^{(t)}}{\partial \mathbf{h}^{(t)}}\right)^T \left(\mathbf{W}_i^{(t)}\right)^{-1}\left(\frac{\partial \mathbf{V}_i^{(t)}}{\partial \mathbf{h}^{(t)}}\right)\right\}^{-1} \times \\
& \left\{\sum_{i=1}^{I}\left(\frac{\partial \mathbf{V}_i^{(t)}}{\partial \mathbf{h}^{(t)}}\right)^T \left(\mathbf{W}_i^{(t)}\right)^{-1}\left(\mathbf{S}_i^{(t)}-\mathbf{V}_i^{(t)}\right)\left(\mathbf{S}_i^{(t^*)}-\mathbf{V}_i^{(t^*)}\right)^T \left(\mathbf{W}_i^{(t^*)}\right)^{-1}\left(\frac{\partial \mathbf{V}_i^{(t^*)}}{\partial \mathbf{h}^{(t^*)}}\right)\right\} \times \\
& \left\{\sum_{i=1}^{I}\left(\frac{\partial \mathbf{V}_i^{(t^*)}}{\partial \mathbf{h}^{(t^*)}}\right)^T \left(\mathbf{W}_i^{(t^*)}\right)^{-1}\left(\frac{\partial \mathbf{V}_i^{(t^*)}}{\partial \mathbf{h}^{(t^*)}}\right)\right\}^{-1}
\end{aligned}
$$

$$t, t^* = 1, 2,$$



Let $h^{(t)} = \left(h_1^{(t)} \ , h_2^{(t)} \ , h_3^{(t)} \ , h_4^{(t)} \right)$

$$S_{\beta^{(t)}} \left(\beta^{(t)}, h^{(t)} \right) = \sum_{r=1}^{R} \left(\frac{\partial X_r^{(t)} \beta^{(t)}}{\partial \beta^{(t)}} \right)' Cov^{-1} \left(P_r \right) \left(P_r - X_r^{(t)} \beta^{(t)} \right) = 0$$

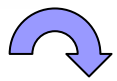
where $P_r = (P_{r1} \ , \ \cdots \ , P_{rn_r})'$, and $X_r^{(t)} = \left(x_{r1}^{(t)} \ , \ \cdots \ , x_{rn_r}^{(t)} \right)'$.

The correlation parameter $h^{(t)}$ may be estimated by simultanously solving

$$S_{\beta^{(t)}} \left(\beta^{(t)}, h^{(t)} \right) = 0$$

and

$$S_{h^{(t)}} \left(\beta^{(t)}, h^{(t)} \right) = \sum_{r=1}^{R} \left(\frac{\partial V_r^{(t)}}{\partial h^{(t)}} \right)' W^{-1(t)} \left(S_r^{(t)} - V_r^{(t)} \right) = 0$$



$$S_{h^{(t)}}\left(\beta^{(t)}, h^{(t)}\right) = \sum_{r=1}^{R}\left(\frac{\partial V_r^{(t)}}{\partial h^{(t)}}\right)' W^{-1(t)}\left(S_r^{(t)} - V_r^{(t)}\right)$$

$$\frac{S_{h^{(t)}}\left(\beta^{(t)}, h^{(t)}\right)}{\partial h^{(t)}}$$

$$= \sum_{r=1}^{R}\left[\left(\frac{\partial V_r^{(t)}}{\partial h^{(t)}}\right)'\left(\frac{\partial W^{-1(t)}}{\partial h^{(t)}}\right)\left(S_r^{(t)} - V_r^{(t)}\right) + \left(\frac{\partial V_r^{(t)}}{\partial h^{(t)}}\right)' W^{-1(t)}\left(-\frac{\partial V_r^{(t)}}{\partial h^{(t)}}\right)\right]$$

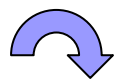
$$= \sum_{r=1}^{R}\left[\left(\frac{\partial V_r^{(t)}}{\partial h^{(t)}}\right)'\left(-W^{-1(t)}\frac{\partial W^{(t)}}{\partial h^{(t)}}W^{-1(t)}\right)\left(S_r^{(t)} - V_r^{(t)}\right) + \left(\frac{\partial V_r^{(t)}}{\partial h^{(t)}}\right)' W^{-1(t)}\left(-\frac{\partial V_r^{(t)}}{\partial h^{(t)}}\right)\right].$$

Using Taylor's expansion, we have

$$\widehat{h}^{(k)} - h^{(k)}$$

$$= \left(\sum_{r=1}^{R}\left[\left(\frac{\partial V_r^{(t)}}{\partial h^{(t)}}\right)'\left(-W^{-1(t)}\frac{\partial W^{(t)}}{\partial h^{(t)}}W^{-1(t)}\right)\left(S_r^{(t)} - V_r^{(t)}\right) + \left(\frac{\partial V_r^{(t)}}{\partial h^{(t)}}\right)' W^{-1(t)}\left(-\frac{\partial V_r^{(t)}}{\partial h^{(t)}}\right)\right]\right)^{-1}$$

$$\times \left(\sum_{r=1}^{R}\left(\frac{\partial V_r^{(t)}}{\partial h^{(t)}}\right)' W^{-1(t)}\left(S_r^{(t)} - V_r^{(t)}\right)\right)$$



LOD-score curve

- The LOD-score curve
  - Under either scenario I or scenario II, the LOD-score curve are related with the total numbers of family members and the heritability of the trait due to the disease gene mainly. (Similar results have shown in other papers)

$$(\text{fam},\ h(G1_E), h(G1_P), h(G2_E), h(G3_P),\ \rho_\epsilon)$$