

Incorporating Heterogeneity in Detecting NIMA Alleles as a Disease Factor and the Extension to Identify Gene Imprinting

Jingyuan Yang

Department of Statistics
The Ohio State University

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Outline

Relative Risk Model

Bayesian Logistic Model

Bayesian Mixed Model

Extension to Gene Imprinting

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- ▶ Non-Inherited Maternal Antigen (NIMA): Antigens in the offspring, which are not encoded by the inherited alleles but by the mother's alleles, and passed to the offspring through microchimerism.
- ▶ People suspect that NIMA may involve in the pathogenesis of Rheumatoid Arthritis (RA) through microchimerism, but studies using conventional methods (like MFG test) have not found a significant NIMA effect.
- ▶ One possible reason of the failure is that the original MFG test hasn't taken into account the **heterogeneity** in people's susceptibility to microchimerism.

Model

We model both affected and unaffected offsprings in the likelihood:

$$L(\theta | \mathbf{D}, \mathbf{G}_m, \mathbf{G}_c)$$

$$= \prod_{i=1}^N P(G_m^{(i)}, \mathbf{G}_c^{(i)}, \mathbf{D}^{(i)} | \theta)$$

$$\propto \prod_{i=1}^N \prod_{j=1}^{n_i} P(D_j^{(i)} | M^{(i)}, C_j^{(i)}, \theta)$$

$$\propto \prod_{i=1}^N \prod_{j=1}^{n_i} (P_{ij})^{I[D_j^{(i)}=1]} (1 - P_{ij})^{I[D_j^{(i)}=0]},$$

where P_{ij} denotes $P(D_j^{(i)} = 1 | M^{(i)}, C_j^{(i)}, \theta)$

$$= \alpha P(D_j^{(i)} = 1 | M^{(i)}, C_j^{(i)}, \text{NIMA})$$

$$+ (1 - \alpha) P(D_j^{(i)} = 1 | M^{(i)}, C_j^{(i)}, \text{No NIMA})$$

Model - Continued

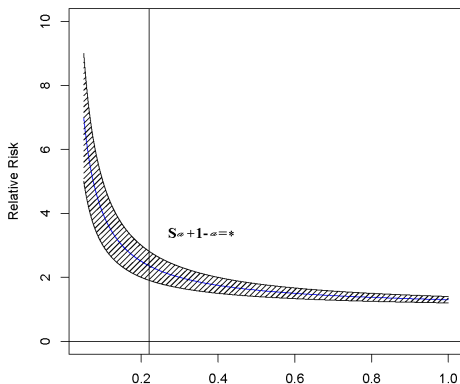
M	C	NIMA	Penetrance(Conditional)	Penetrance
0	0	No	P_0	P_0
1	0	No	P_0	$(1 - \alpha)P_0 + \alpha S_1 P_0$
		Yes	$S_1 P_0$	
0	1	No	P_1	P_1
1	1	No	P_1	$(1 - \alpha)P_1 + \alpha S_1 P_1$
		Yes	$S_1 P_1$	
2	1	No	P_1	$(1 - \alpha)P_1 + \alpha S_2 P_1$
		Yes	$S_2 P_1$	
1	2	No	P_2	$(1 - \alpha)P_2 + \alpha S_1 P_2$
		Yes	$S_1 P_2$	
2	2	No	P_2	$(1 - \alpha)P_2 + \alpha S_2 P_2$
		Yes	$S_2 P_2$	

Model - Continued

Comparing to the conventional MFG test, which assumes NIMA effect always present as long as the mother carries at least one copy of the disease allele, the proposed model would not underestimate the NIMA effect if alpha can be well-estimated.

Model - Continued

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Issues

- ▶ α and S_1, S_2 are confounding, only $S_1\alpha + 1 - \alpha$ and $S_2\alpha + 1 - \alpha$ are estimable.
- ▶ If we model the NIMA effect as an additive effect rather than multiplicative effect, and use EM algorithm to estimate α , then a large sample size is needed to get reasonable estimates.

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$$RA_{ij} \sim \text{Bernoulli}(P_{ij})$$

$$P_{ij} = PM_{ij} \times \alpha + PNM_{ij} \times (1 - \alpha)$$

$$\begin{aligned} \text{logit}(PM_{ij}) = & \beta_0 + \beta_1 I(C = 1) + \beta_2 I(C = 2) \\ & + \beta_3 I(M = 1) + \beta_4 I(M = 2) \end{aligned}$$

$$\text{logit}(PNM_{ij}) = \beta_0 + \beta_1 I(C = 1) + \beta_2 I(C = 2)$$

Prior:

$$\alpha \sim \text{Beta}(1, 1) \quad \beta_0 \sim U(-10, -2) \quad \beta_1 \sim U(-10, 10)$$

$$\beta_2 \sim U(-10, 10) \quad \beta_3 \sim U(-10, 10) \quad \beta_4 \sim U(-10, 10)$$

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Model the uncertainty of the NIMA effect as a random factor. There is report that people use quantitative-PCR to measure the amount of microchimerism. It's reasonable to believe that the NIMA effect is not all-or-none. Use Bayes factor to test whether the NIMA effect is significant.

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$$RA_{ij} \sim \text{Bernoulli}(P_{ij})$$

$$P_{ij} = \text{logit}(PM_{ij}) = \beta_0 + \beta_1 I(C = 1) + \beta_2 I(C = 2) + \beta_3 I(M = 1) + \beta_4 I(M = 2)$$

Prior:

$$\beta_0 \sim U(-10, -2) \quad \beta_1 \sim U(-10, 10) \quad \beta_2 \sim U(-10, 10)$$

$$\beta_3 \sim \text{Exp}(\lambda_1) \quad \beta_4 \sim \text{Exp}(\lambda_2)$$

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Imprinting (Parent-of-origin effect)

An epigenetic alteration of genes in which primarily the maternally or paternally inherited allele is expressed.

Introduces functional (expressional) **inequity** between 2 parental alleles of a gene.

Causes deviations from Mendelian law, therefore, conventional linkage analysis methods are not appropriate and require modification.

Model

Focus on the case that the offspring has only one copy of the allele, then it's feasible to track that the allele is transmitted from mother or father.

M	C
0	1
1	1
2	1

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⇒

M	F	C	Transmitted From
0	2	1	F
0	1	1	F
1	2	1	F
1	1	1	F or M
1	0	1	M
2	1	1	M
2	0	1	M

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Previous models can be extended to identify gene imprinting now.
Only need to make change on the parameter accounting for the one copy offspring disease allele effect:

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Only need to make change on the parameter accounting for the one copy offspring disease allele effect:

- ▶ Relative Risk Model: $P_1 \Rightarrow P_{1M}$ and P_{1F}
- ▶ Bayesian Logistic Model: $\beta_1 \Rightarrow \beta_{1M}$ and β_{1F}
- ▶ Bayesian Mixed Model: $\beta_1 \Rightarrow \beta_{1M}$ and β_{1F}

Issues

- ▶ For the case $(M, F, C) = (1, 1, 1)$, the copy of offspring disease allele can be transmitted from mother or father. Weinberg (1998, 1999) suggested either using EM algorithm to impute the missing transmission origin or omitting this category from analysis.
- ▶ Potential confounding problem. P_{1M} (or β_{1M}) are only present in the model when mother has at least one copy of the disease allele. Meanwhile, parameters account for maternal effect are also present when $M \geq 1$. Need to better address the question that how to detect imprinting (maternal effect) when maternal effect (imprinting) exists.