

Detection of Imprinting and Heterogeneous Maternal Effects by Using Framingham Heart Study Data

Jingyuan Yang, Shili Lin

Department of Statistics, The Ohio State University

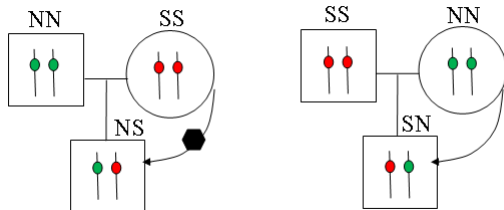
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Background

- Parent-of-Origin (POO) patterns: A characteristic follows either a maternal or paternal lineage, rather than following standard Mendelian inheritance patterns.
- Typical causes of POO patterns:
 - Maternal effect
 - Genomic imprinting
 - X inactivation
 - Transmission ratio distortion

Maternal Effect

The genotype of a mother is expressed in the phenotype of her offspring, which is usually attributed to maternally-produced molecules, such as mRNAs that are deposited in the egg cell, or antigens that are passed to the offspring during pregnancy.

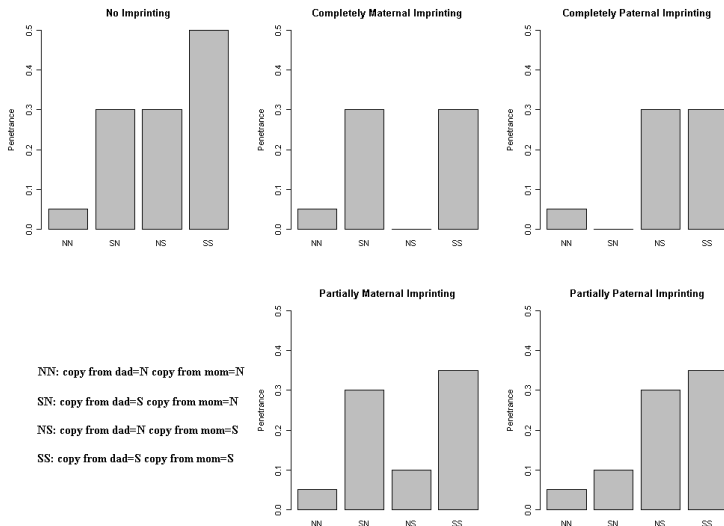


S stands for the minor allele of a SNP, carrying of which may increase the disease susceptibility; N denotes the normal allele.

Heterogeneous Maternal Effect: Maternal effect may vary among different mother-child pairs.

Genomic Imprinting

Unequal expression of the two parental alleles of a gene.



Data

High blood pressure in an adult is defined as:

- systolic pressure ≥ 140 mm Hg and/or
- diastolic pressure ≥ 90 mm Hg

In Framingham Heart Study data:

- 1036 out of 2760 individuals in the second generation have high blood pressure
- 379 out of 3997 individuals in the third generation have high blood pressure

For extended families, we select one nuclear family at random. Around 300 nuclear families were analyzed. Number of children in each nuclear family ranges from 1 to 8.

Aim and Method

Aim:

- Identify SNPs that have imprinting effect and/or heterogeneous maternal effect on high blood pressure.

Method:

- We use a likelihood-based method to achieve the above aim. The likelihood of each nuclear family can be decomposed into the probability of familial genotypes and the probability of getting high blood pressure given familial genotypes (penetrance). Logit link is used to relate the penetrance to the covariates (minor allele effect, imprinting effect and maternal effect).

Familial Genotype Combinations

Mother's genotype × Father's genotype	<i>M, F, C</i>	Origin of Child's Minor Allele	Maternal Effect
<i>NN</i> × <i>NN</i>	000	—	No
<i>SN</i> × <i>NN</i>	100	—	Yes
	101	M	Yes
<i>NN</i> × <i>SN</i>	010	—	No
	011	F	No
<i>SN</i> × <i>SN</i>	110	—	Yes
	111	M or F	Yes
	112	M and F	Yes
<i>SS</i> × <i>NN</i>	201	M	Yes
<i>NN</i> × <i>SS</i>	021	F	No
<i>SS</i> × <i>SN</i>	211	M	Yes
	212	M and F	Yes
<i>SN</i> × <i>SS</i>	121	F	Yes
	122	M and F	Yes
<i>SS</i> × <i>SS</i>	222	M and F	Yes

- Mother and father's genotype: *S* stands for minor allele of a SNP, *N* stands for otherwise.
- *M, F, C*: *M*, *F* and *C* denote the number of minor alleles carried by mother, father and child, each of which can take a value among 0, 1 or 2.
- Origin of Child's Minor Allele: If child doesn't carry any minor allele, — denotes that origin is undefined; Otherwise, *M* indicates the minor allele carried by the child is inherited from the mother; *F* indicates it is from the father.
- Maternal Effect: Maternal effect caused by the minor allele(s) of a specific SNP is absent if the mother doesn't carry any minor allele, which is denoted by "No"; "Yes" indicates maternal effect is possible.

Notation

- Suppose there are N nuclear families.
- The i th family has two parents and n_i children, $i = 1, 2, \dots, N$.
- Let M_i and F_i denote genotypes of the mother and the father in the i th family.
- $\mathbf{C}_i = (C_i^1, C_i^2, \dots, C_i^{n_i})$ denotes genotypes of the n_i children in the i th family.
- M_i , F_i and C_i^j can take values among 0, 1 or 2, indicating the number of the minor allele(s) at a SNP carried by the corresponding person, $j = 1, 2, \dots, n_i$.
- $\mathbf{D}_i = (D_i^1, D_i^2, \dots, D_i^{n_i})$ denotes siblings' disease status, with $D_i^j = 1$ indicating the j th child has high blood pressure and 0 indicating otherwise.

Likelihood

We model genotypes of all family members and disease status of all children jointly.

The likelihood for the i th family can be decomposed as

$$P(M_i, F_i, \mathbf{C}_i, \mathbf{D}_i) = P(\mathbf{D}_i | M_i, F_i, \mathbf{C}_i) P(M_i, F_i, \mathbf{C}_i) \\ = \prod_{j=1}^{n_i} P(D_i^j | M_i, F_i, C_i^j) \prod_{j=1}^{n_i} P(C_i^j | M_i, F_i) P(M_i, F_i)$$

Penetrance of high blood pressure is related to imprinting effect and maternal effect by logit link.

$$\text{logit}P(D_i^j = 1 | M_i, F_i, C_i^j) = \mathbf{X}'\boldsymbol{\theta} + \epsilon_i, \text{ where:}$$

- \mathbf{X}' is the design matrix with the covariates related to the j th offspring in the i th family coded in one row:
 $X_{j(i)} = \{1, I(C_i^j = 1), I(C_i^j = 2), I(C_i^j = 1 \text{ \& maternally-derived copy}), I(M_i = 1), I(M_i = 2)\}'$;
- $\boldsymbol{\theta} = \{\beta_0, \beta_1, \beta_2, \beta_{im}, \gamma_1, \gamma_2\}'$;
- $\epsilon_i \sim \text{Normal}(0, \sigma^2)$.

Interpretation of Parameters

- β_0 is the logit of phenocopy rate.
- β_1, β_2 measure the minor allele effects when the child carries one or two copies of minor alleles, respectively.
- β_{im} measures the imprinting effect. $\beta_{im} < 0$ indicates maternally imprinting and $\beta_{im} > 0$ indicates paternally imprinting.
- γ_1, γ_2 measure the maternal effects when the mother carries one or two copies of the minor alleles, respectively.
- ϵ_i is the deviation of maternal effect size from the average. It introduces correlation among the siblings within the same family.

Results






- 33682 SNPs on chromosome 1 were scanned by using our method. Genome-wide search is feasible if time allows.
- We use minimum p-value of testing $\beta_1 = 0$, $\beta_2 = 0$, $\beta_{im} = 0$, $\gamma_1 = 0$ and $\gamma_2 = 0$ being less than 0.0005 as the criterion to choose SNPs that are related to high blood pressure. 10 SNPs are identified using this criterion.
- Then use p-value of testing $\sigma = 0$ being less than 0.05 and reduced AIC value as the criterion to identify heterogeneity of maternal effect.
- Depending on how these 10 SNPs could affect the susceptibility of high blood pressure, they can be categorized into a Venn diagram.

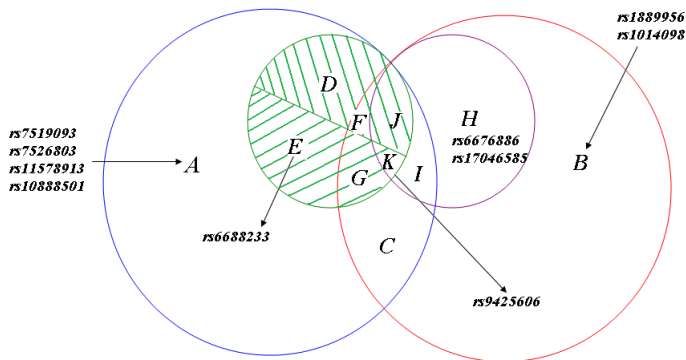
Parameter Estimates and AIC

SNP	$\hat{\beta}_1$ and p-value		$\hat{\beta}_2$ and p-value		$\hat{\beta}_{im}$ and p-value		$\hat{\gamma}_1$ and p-value		$\hat{\gamma}_2$ and p-value		<i>minp</i>
rs6688233	1.573	0.000	0.234	0.737	-1.609	0.011	0.377	0.385	0.747	0.341	0.0000
rs7519093	1.333	0.000	1.491	0.021	-1.406	0.067	-0.446	0.375	-0.496	0.568	0.0002
rs1889956	0.351	0.473	-0.733	0.167	-0.388	0.524	1.797	0.000	1.701	0.010	0.0002
rs1014098	-0.792	0.199	-2.555	0.040	-0.321	0.709	0.656	0.060	2.936	0.000	0.0003
rs6676886	1.639	0.000	0.578	0.255	-1.118	0.060	1.033	0.028	0.961	0.137	0.0003
rs7526803	1.543	0.000	0.718	0.177	-0.333	0.548	0.395	0.377	0.113	0.856	0.0004
rs11578913	1.369	0.000	0.796	0.156	-0.926	0.129	0.063	0.887	0.276	0.714	0.0004
rs10888501	0.918	0.033	2.440	0.000	1.149	0.108	-0.937	0.137	-1.402	0.068	0.0004
rs17046585	0.121	0.799	-0.251	0.605	-0.559	0.366	1.250	0.000	1.760	0.008	0.0005
rs9425606	-0.453	0.370	-1.202	0.071	-2.238	0.019	0.752	0.036	2.965	0.000	0.0005

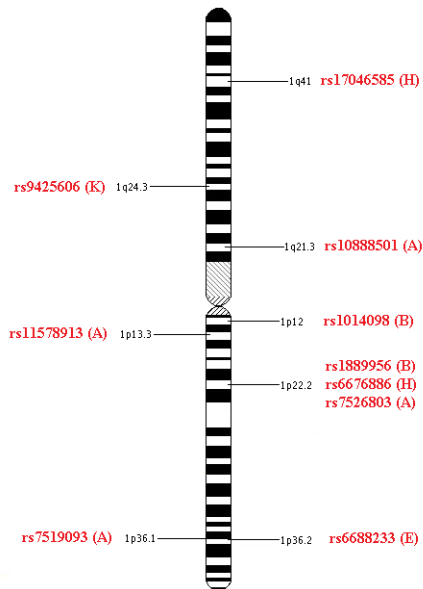
SNP	$\hat{\beta}_1$ and p-value		$\hat{\beta}_2$ and p-value		$\hat{\beta}_{im}$ and p-value		$\hat{\gamma}_1$ and p-value		$\hat{\gamma}_2$ and p-value		$\hat{\sigma}$ and p-value		AIC
rs1889956	0.351	0.473	-0.733	0.167	-0.388	0.524	1.797	0.000	1.701	0.010	-	-	1969.3
	0.470	0.399	-0.636	0.276	-0.496	0.472	1.889	0.001	1.736	0.019	1.037	0.0822	1970.4
rs1014098	-0.792	0.199	-2.555	0.040	-0.321	0.709	0.656	0.060	2.936	0.000	-	-	1538.5
	-0.483	0.617	-4.464	0.114	-1.149	0.379	0.789	0.340	4.413	0.063	5.523	0.000	1549.4
rs6676886	1.639	0.000	0.578	0.255	-1.118	0.060	1.033	0.028	0.961	0.137	-	-	1977.3
	1.679	0.002	0.623	0.284	-1.069	0.140	0.971	0.089	1.008	0.204	1.459	0.011	1975.2
rs17046585	0.121	0.799	-0.251	0.605	-0.559	0.366	1.250	0.000	1.760	0.008	-	-	1795.6
	0.472	0.487	-0.184	0.790	-1.084	0.234	1.422	0.008	2.462	0.043	2.021	0.095	1786.9
rs9425606	-0.453	0.370	-1.202	0.071	-2.238	0.019	0.752	0.036	2.965	0.000	-	-	1841.5
	-0.440	0.433	-1.252	0.096	-2.416	0.025	0.802	0.063	3.252	0.001	1.188	0.039	1842.0

Venn Diagram

-  Minor Allele Effect
-  Paternally Imprinting
-  Maternally Imprinting
-  Maternal Effect
-  Heterogeneous Maternal Effect



Locations of Detected SNPs



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