

Bivariate Linkage Analysis of Cholesterol and Triglyceride Levels in Framingham Heart Study

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INTRODUCTION

* Triglyceride level and cholesterol level are two risk factors for cardiovascular diseases.

* These factors are often correlated.

* Are there any pleiotropic/clustered genes?

* A bivariate linkage analysis is done using a score statistic in Wang [2002]

* Data from cohort 1 and cohort 2 of the Framingham Heart Study were used.

DATA

* For cohort 1, participants' cholesterol level was measured up to 16 times and their triglyceride level was measured up to 3 times.

* For cohort 2 participants, both cholesterol and triglyceride were measured up to 5 times.

* These two cohorts together provided 22,040 cholesterol measures and 9,155 triglyceride measures (repeated measurements on an individual were included).

* These measures were age adjusted using simple regression of cholesterol or triglyceride level on age. When a single individual had multiple measures so that multiple residuals were obtained from the regression, the mean of these residuals was used as the quantitative phenotype for the analysis.

* All sibpairs from the same or different nuclear families were used.

* IBD sharing of the sibpairs on all markers was provided by GAW 13. To keep the number of sibpairs large, we considered only those markers for which IBD sharing was available for at least 1,000 sibpairs.

METHODS

Let x_i be a vector of 4 elements of the phenotypic data on the i th sibpair, i.e.,

$$x_i = \begin{pmatrix} x_{i1} \\ x_{i2} \\ x_{i3} \\ x_{i4} \end{pmatrix} = \begin{pmatrix} \text{cholesterol level for sib 1} \\ \text{cholesterol level for sib 2} \\ \text{triglyceride level for sib 1} \\ \text{triglyceride level for sib 2} \end{pmatrix}$$

The sample mean of $\{x_i\}$ is a vector of 0 since the elements of $\{x_i\}$ are regression residuals.

Σ_0 = the sample variance-covariance matrix of $\{x_i\}$ whose (i, j) th element is denoted by a_{ij} .

Define

$$w_i = (w_{i1}, w_{i2}, w_{i3}, w_{i4})^T = \Sigma_0^{-1} x_i$$

and

$$z_i = w_{i1}w_{i2}a_{11} + (w_{i1}w_{i3} + w_{i2}w_{i4})a_{13} + w_{i3}w_{i4}a_{33}.$$

Note: a_{11} and a_{33} are the variances of cholesterol level and triglyceride level, respectively, on sib 1's and a_{33} is the covariance between the two levels on sib 1's and a_{33} on sib 2's. When the sample size is large, $a_{11} = a_{22}$, $a_{33} = a_{44}$, and $a_{13} = a_{31}$.

Denote the proportion of alleles that are shared IBD between the i th sibpair by π_i . Let $\bar{\pi}$ and \bar{z} be the sample means of $\{\pi_i\}$ and $\{z_i\}$, respectively.

Define

$$b = \sum_{i=1}^N (\pi_i - \bar{\pi})(z_i - \bar{z})$$

where N is the total number of sibpairs. When the putative locus is not linked to any trait locus, the expectation of b is 0 and its variance is $s_b^2 = N s_\pi^2 s_z^2$, where s_π^2 and s_z^2 are the sample variances of $\{\pi_i\}$ and $\{z_i\}$, respectively. The score statistic S for the bivariate phenotypes is defined by

$$S = \begin{cases} b^2 / s_b^2 & \text{if } b > 0 \\ 0 & \text{otherwise} \end{cases}$$

Under the null hypothesis of no linkage, the asymptotic distribution of S is $0.5\chi_0^2 + 0.5\chi_1^2$ (Wang, 2002).

RESULTS

* Bivariate score statistic and univariate score statistic (Wang & Huang, 2002) were computed for all screened markers. They were listed in Table 1 along with their p -values for those markers with p -value < 0.005 .

* Shearman et al. [2000]: The highest multipoint variance component LOD scores were obtained on chromosome 7q (at 155 cM). On this locus, we also obtained a significant linkage ($p = 0.0020$); The numbers print in red in Table 1).

* At chromosome 16, they reported a LOD score 1.5 at 70 cM with multipoint mapping. We used single point calculation for IBD sharing and obtained a very significant linkage at 64 cM ($p = 0.0001$); The numbers print in red in Table 1).

* Our method identified a locus at 212 cM of chromosome 1 with $p = 0.0004$ and one at 140 cM of chromosome 8 ($p = 0.0006$), which were not identified by Shearman et al. (The numbers print in green in Table 1).

Table 1. Summary of markers that are significant at level 0.005 (p -value is in the parenthesis).

Chr.	Marker	p-telomere (cM)	Bivariate Score statistic	Univariate score statistic	
				Cholesterol	Triglyceride
1	Gata4B01	212	11.029(0.0004)	9.141(0.0013)	
1	GATA87F04	233	8.618(0.0017)	7.602(0.0029)	
3	3PTEL25	1		8.358(0.0019)	
3	036y68	37		10.445(0.0006)	
3	GATA128C02	112	6.799(0.0046)		
4	GATA24H01	78		6.670(0.0049)	
4	ATA2A03	93		7.665(0.0028)	
4	GATA2F11	105	7.534(0.0030)		
4	ATA26B08	130		7.159(0.0037)	
4	GATA2A04	19	7.119(0.0038)		
5	GATA21H09	139		7.682(0.0028)	
6	242zq5	166	7.776(0.0026)		
7	GGAA6D03	128	7.036(0.0040)		
7	GATA112F07	155	8.274(0.0020)	8.410(0.0019)	
8	GATA21C12	140	10.474(0.0006)	7.603(0.0029)	
12	GATA49D12	18		7.695(0.0028)	
12	GATA3F02	81		9.674(0.0009)	
14	GATA4B04	44		8.648(0.0016)	
16	ATA55A11	64	13.489(0.0001)	11.049(0.0004)	
21	GGAA3C07	13		7.043(0.0040)	

DISCUSSION

* A bivariate linkage analysis is done on cholesterol and triglyceride levels in Framingham study, using a method in Wang [2002].

* Only sibpairs are considered since the computation is much easier to implement.

* Bivariate analyses may be less powerful than univariate analyses when the polygenic correlation is in the same direction with the major gene correlation [Allison et al. 1998; Amos et al. 2001; Wang 2002].

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