Published in final edited form as:

Liver Int. 2009 May ; 29(5): . doi:10.1111/j.1478-3231.2008.01965.x.

Heritability of serum γ -glutamyltransferase level: genetic analysis from the Framingham Offspring Study

Jing-Ping Lin¹, Christopher J. O'Donnell², Caroline S. Fox², and L. Adrienne Cupples³

¹Office of Biostatistics, Division of Prevention and Population Sciences, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA

²Framingham Heart Study, National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA

³Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA

To the Editor:

Serum γ -glutamyltransferase (GGT) has been widely used as an index of liver dysfunction. Recent studies have shown that high serum GGT is a risk factor for coronary heart disease, type 2 diabetes, metabolic syndrome, alcohol intake, blood pressure and total and high-density lipoprotein cholesterol (1–3).

Human GGT genes are mapped on chromosome 22q11 (4). Family studies have revealed that serum GGT variation is significantly determined by genetic factors, with heritability estimates as high as 35% (5). We carried out a 10 cM genome-wide linkage analysis for quantitative trait loci (QTL) of serum GGT in a community-based Caucasian cohort: the Framingham Heart Study.

The Framingham Heart Study is a population-based study (6). Within the study, 330 largest extended families were selected for a 10-cM-density genome-wide scan (399 microsatellite markers), with 1702 individuals being genotyped. GGT was only measured during the second examinations of the offspring. The microsatellite genotyping was carried out at the Marshfield Mammalian Genotyping Service (<http://research.marshfieldclinic.org/genetics/>).

Variation in GGT from known factors was identified and removed by regression modelling incorporated into SOLAR (7) to enhance the ability of linkage analysis. The covariates selected ($P < 0.05$) and incorporated into both the heritability estimation and the linkage analyses are listed in Table 1.

The variance component method was also used for heritability estimate and linkage analysis of GGT, using the random microsatellite DNA markers covering the entire genome. Because the variance-component method is based on the assumption of a multivariate normal distribution, violations of this assumption may result in inaccurate results (8). We found that GGT had high kurtosis and thus used a logarithm of the odds (LOD) score adjustment method implemented in SOLAR to ensure more reliable results.

The basic characteristics of the clinical covariates of the study sample (50% male) are displayed in Table 1. The skewness and kurtosis of GGT was 2.64 ± 0.04 and 8.83 ± 0.81 respectively. The heritability estimate for GGT, after adjusting for the covariates, was $31 \pm 6\%$. The proportion of variation because of all covariates included in the model was 22%. From the multipoint linkage analysis of GGT, several maximum LOD scores between 1 and 2 were obtained: 1.54, 1.73, 1.14, 1.28, 1.29 and 1.20 on chromosomes 3, 8, 9, 10, 13 and 15 respectively.

In our study, the heritability of GGT was estimated to be 31%, indicating that a substantial portion of the variation in serum GGT was attributable to additive genetic factors. This is consistent with a previous finding (5). We agree that in both studies, common environmental factors may have had an influence on the heritability estimate. In the linkage study, we identified several chromosomal regions with LOD scores between 1 and 2. None of them were located on the chromosomes where the genes encoding the GGT isoenzymes reside. No obvious candidate genes were found in the above-mentioned chromosomal regions.

A power study for linkage on the 330 Framingham families with traits measured only in the Offspring Cohort, similar to our study, was performed using *SOLAR*. The power was estimated to be 97, 84 and 62% to detect a QTL heritability of 30% using a LOD score cut-off of 1, 2 or 3, respectively, as significant (<http://www.framinghamheartstudy.org/>). The results of the simulation studies imply that this study sample has the power to detect only large QTL effects.

Overall, we used the Framingham 330 largest families to identify QTL of serum GGT levels and confirmed that there was a significant genetic component in determining serum GGT variation. Instead of a major gene effect, there may be several genes, different from the gene of GGT isoenzymes, with small effects in controlling the variation of serum GGT concentrations.

Acknowledgments

We thank Jim Tomlin from the Center for Information Technology, NIH, for data management assistance. This work was supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195).

References

1. Lee DH, Jacobs DR Jr, Gross M, et al. Gamma-glutamyltransferase is a predictor of incident diabetes and hypertension: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Clin Chem*. 2003a; 49:1358–66. [PubMed: 12881453]
2. Rosalki SB, Zilva JF. Serum gamma-glutamyltransferase and alcoholism. *Lancet*. 1977; 3:1183–4. [PubMed: 73099]
3. Arnesen E, Huseby NE, Brenn T, et al. The Tromso Heart Study: distribution of, and determinants for, gamma-glutamyltransferase in a free-living population. *Scand J Clin Lab Invest*. 1986; 46:63–70. [PubMed: 2869572]
4. Figlewicz DA, Delattre O, Guellaen G, et al. Mapping of human gamma-glutamyl transpeptidase genes on chromosome 22 and other human autosomes. *Genomics*. 1993; 17:299–305. [PubMed: 8104871]
5. Bathum L, Petersen HC, Rosholm JU, et al. Evidence for a substantial genetic influence on biochemical liver function tests: results from a population-based Danish twin study. *Clin Chem*. 2001; 47:81–7. [PubMed: 11148181]
6. Dawber, TR. *The Framingham Heart Study: The Epidemiology of Athero-sclerotic Diseases*. Harvard University Press; Cambridge, MA: 1980.
7. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet*. 1998; 62:198–211.
8. Allison DB, Neal MC, Zannolli R, et al. Testing robustness of the likelihood-ratio test in a variance-component-trait loci-mapping procedure. *Am J Hum Genet*. 1999; 65:531–44. [PubMed: 10417295]

Table 1

Characteristics of the 1306 individuals with γ -glutamyltransferase and covariates measured and used in the heritability estimate and linkage analysis

Variable	Mean $\pm$ SD	Range
GGT (mg/dl)	165.1 $\pm$ 141.7	10.0–990.0
Age (years)	41.3 $\pm$ 10.3	17.0–72.0
Height (in.)	66.4 $\pm$ 3.9	56.0–77.5
Weight (pound)	161.0 $\pm$ 34.1	87.0–289.0
Total cholesterol (mg/dl)	198.5 $\pm$ 38.1	97.0–418.0
Triglycerides (mg/dl)	99.9 $\pm$ 82.6	10.9–928.7
Total serum protein (mg/dl)	72.3 $\pm$ 4.4	54.0–87.0
Albumin (mg/dl)	44.7 $\pm$ 3.2	29.0–56.0
Smoking (no./day)	59.5 $\pm$ 34.8	0.0–95.0
Alcohol (oz./week)	3.8 $\pm$ 5.2	0.0–48.0

GGT, γ -glutamyltransferase; SD, standard deviation.