Longitudinal Differences in Familial Combined Hyperlipidemia Quantitative Trait Loci

To the Editor:

Familial combined hyperlipidemia (FCHL), associated with premature cardiovascular disease, is the most common genetic hyperlipidemia with an estimated prevalence of 1%. The complex genetic background of FCHL is slowly being dissected through genome screens and positional candidate association studies. However, it has also been argued that although numerous studies have been conducted and reported, there are many conflicting results and a true understanding of the genetics remains largely unknown. Previously in this journal, we reported 4 quantitative trait loci (QTL) for apolipoprotein B (apoB), cholesterol, and triglycerides with \( P < 0.001 \) in 22 FCHL pedigrees from Maastricht, in The Netherlands. The original QTL study was based on the premise that because FCHL is defined by increased serum levels of cholesterol, apoB, and triglycerides in families, QTL analyses of these quantitative traits in FCHL families might identify important genetic loci for this disorder. This letter reports QTL analyses of 5-year follow-up data in the same individuals.

Longitudinal studies show that the lipid phenotype within individual FCHL patients changes over time. This expected intraindividual variability in cholesterol, triglyceride, and apoB levels may also change the heritabilities of these traits, thus affecting the locations and levels of significance of the reported QTL. However, one might expect that true QTL that are not false-positives would exhibit consistent chromosome locations, although the levels of significance might vary somewhat. To assess the impact of longitudinal lipid variability on our previous QTL, we recruited all of the Maastricht FCHL family members who participated in the original study and used the same research protocol and QTL analysis strategy used in the original study. The protocol of the current study was approved by the appropriate institutional ethics committees.

Unfortunately, 17 subjects from the original QTL analyses were lost to follow-up. The Table shows the characteristics of those who remained in the longitudinal study both at baseline in 1999 and in the follow-up in 2004. Nonparametric Mann–Whitney 2 sample tests found no significant differences in the baseline 1999 body mass index (BMI) and plasma trait values between the whole sample and those 17 lost to follow-up, providing confidence that there was no bias introduced by removing these 17 people from the study. However, their exclusion from the 1999 QTL analysis did influence the levels of significance of the original QTL to some extent. The cholesterol QTL on chromosome 12p13 had a marked reduction in the level of significance with their removal (“1999” versus “1999”; Figure, panel A), making a direct comparison of that QTL from the abbreviated 1999 data with the follow-up 2004 data difficult. The original QTL for the other traits were not affected so markedly by the loss of these 17 subjects (panels B, C, and D), allowing their direct comparison in the location and significance levels with the QTL derived from the 2004 data. The QTL for triglycerides in the abbreviated data set measured in 1999 at 4p15-16 was very similar in shape and location to the one generated after the 5-year follow-up \( Z_{\text{max}} = 2.7 \) at 40 cm, \( P = 0.003 \), panel B). The overlap between these longitudinal QTL suggests that the region on 4p15-16 might be narrowed to one between 35 and 45 cm for further studies. There was a greater reduction in the level of significance of the QTL for apoB at 17p11-q21 \( Z_{\text{max}} = 1.7 \) at 64 cm, \( P = 0.04 \), panel C). The QTL at 1p21-31 for apoB remained highly significant for the longitudinal data collected in 2004 \( Z_{\text{max}} = 3.8 \) at 137 cm, \( P = 0.00007 \), panel D), with the QTL having nearly the same shape.

In the early 1980’s, Brunzell and colleagues reported that lipid phenotypes in FCHL can change over time, likely because of the interplay of genetic and environmental factors prompting our assessment of the consistency of our QTL. Given the loss to follow-up, 3 of the 4 previously reported QTL were eligible for analysis. We were especially encouraged by the consistency in the location and level of significance of the QTL for apoB at 1p21-31 and the QTL for triglycerides at 4p15-16. The nonparametric QTL analysis applied to these traits may have mitigated the influence of any outliers in the original and follow-up analyses, thus keeping the true QTL consistent.

The present study supports the validity of this QTL approach for gene localization of FCHL-related quantitative traits over time and prioritizes the 1p21-31 region for fine mapping and positional candidate association studies.

Acknowledgments

This work was supported in part by National Institutes of Health grant HL 28481.

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5. Naoumova RP, Bonney SA, Eichenbaum-Voline S, Patel HH, Jones B, Jones EL, Amey J, Copilla S, Neuwirth CK, Allotey R, Seed M, Betteridge DJ, Galton DJ, Cox NJ, Bell GI, Scott J, Shoulders CC. Confirmed locus on chromosome 1p and candidate loci on 6q and 8p for...
Medians and Interquartile Ranges of Baseline and Follow-Up FCHL Traits

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>Intraindividual Variation†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females</td>
<td>24/30</td>
<td>24/30</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>45.5 (28.3–51.3)</td>
<td>49.5 (34.0–57.0)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.8 (23.6–30.5)</td>
<td>27.7 (23.9–30.5)</td>
<td></td>
</tr>
<tr>
<td>ApoB, g/L</td>
<td>1.16 (0.97–1.4)</td>
<td>1.12 (0.97–1.3)</td>
<td>8.3 (5.1–17.9)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.3 (4.7–6.7)</td>
<td>5.3 (4.4–6.1)</td>
<td>11.0 (5.7–17.7)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.3 (1.0–2.2)</td>
<td>1.6 (1.1–3.0)</td>
<td>21.9 (8.3–33.6)</td>
</tr>
</tbody>
</table>

*P=0.06, Wilcoxon test for paired samples.
†Calculated for each individual as SD (value1999, value2004)/mean (value1999, value2004)×100.

QTL analyses with 5-year interval for cholesterol (A), triglycerides (B), and apoB (C and D). The “1999-original” curves represent the significant QTL as presented in the original report; the “1999” curve is composed of the same measurements as “1999-original,” but without the 17 subjects who were lost in follow-up; the “2004” curve is composed of the same population as “1999,” but with measurements taken with a 5-years interval.

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Arterioscler Thromb Vasc Biol. 2006;26:e118-e119
doi: 10.1161/01.ATV.0000221232.79877.c7

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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