Association of the FABP2 T54 Variant with Plasma Triglycerides and Insulin Resistance in a Multiethnic Population

To the Editor:

Fasting triglyceride concentrations and insulin resistance vary substantially according to patient ethnic origin (1, 2), but the role of genetic variants in these differences is not known. The fatty acid binding protein 2, intestinal (FABP2) gene encodes the intestinal fatty acid binding protein, which is involved in intestinal fatty acid uptake. Carriers of the T54 variant (c.163G>A; p.A54T) of FABP2 produce a modified, functional intestinal fatty acid binding protein that has high affinity for fatty acids. Thus carriers have higher triglyceride concentrations and insulin resistance than noncarriers (3). However, many of the studies in which this association was observed did not account for variations in health behaviors (e.g., physical activity and diet) and adiposity, which may also affect triglyceride concentrations and insulin resistance. Also, among individuals who consume a high-fat diet, T54 carriers may have higher lipids than noncarriers (4). We investigated the association of the FABP2 T54 variant with fasting triglyceride concentrations and insulin resistance in a multiethnic population, and by controlling for ethnicity, health behaviors, and adiposity we specifically focused on the explanatory power of this genetic variable. We also tested for interactions of the T54 variant with dietary variables.

Study participants were selected by stratified random sampling from 3 urban centers in Canada. The study population included a total of 972 persons of 3 ethnic origins, South Asian (n = 337), Chinese (n = 313), and European (n = 322). The mean (SD) age of this population was 49.6 (9.9) years; 51.5% were women (n = 501); 9.8% (n = 95) had confirmed type 2 diabetes; and 5.6% (n = 54) reported having had a cardiovascular disease episode (heart attack, stroke, or angina). Participants completed questionnaires on medical history, tobacco use, alcohol intake, physical activity, and diet. Study participants underwent an oral glucose tolerance test with a 75-g glucose load and provided blood samples for the analysis of fasting (8 h) triglycerides, glucose, and insulin. We used restriction iso-typing to genotype all participants for the FABP2 T54 variant and the homeostasis model assessment for insulin resistance (HOMA-IR) (5).

Multiple linear regression was used to measure the association of the T54 variant with triglycerides and insulin resistance after adjusting for age, sex, ethnicity, health behaviors (tobacco use, alcohol intake, physical activity, total fat intake, trans fat intake, protein intake, fiber intake, and total energy), and adiposity (body mass index and waist-to-hip ratio).

The T54 variant was present in 51.0% of all participants, and these individuals had significantly higher mean triglyceride concentrations than noncarriers (1.50 vs 1.42 mmol/L; P < 0.02). More T54 carriers than noncarriers were insulin resistant, although this difference was not statistically significant (HOMA-IR = 3.84 vs 3.41, P = 0.06). After adjustment for age, sex, and ethnicity, the T54 variant was not a significant determinant of triglyceride concentration or insulin resistance (Table 1); however, after adjustment for health behaviors and adiposity measurements, the T54 variant was significantly associated with triglyceride concentrations. This association did not differ significantly in study participants who were healthy compared with those who were undergoing treatment for high lipids or diabetes. The percentage variance in triglyceride concentrations that was attributable to the T54 variant was small (0.5%) compared to the percentage variances attributable to ethnicity (1.7%), health behaviors (4.9%), and adiposity (12.6%). After multivariate adjustment of the data, we found that the T54 variant was not significantly associated with insulin resistance. We observed no significant interactions between the T54 variant and dietary factors.

T54 prevalence, mean triglyceride concentrations, and insulin resistance were significantly higher in South Asians (60.2%, triglycerides = 1.58 mmol/L, HOMA-IR = 4.60) compared to Europeans (48.4%, triglycerides = 1.40 mmol/L, HOMA-IR = 3.08), and Chinese (43.8%, triglycerides = 1.39 mmol/L, HOMA-IR = 3.15). These differences were highly significant (overall P < 0.01; contrast P < 0.01), except for the difference between Europeans and Chinese (P > 0.29). Among South Asians, T54 carriers had significantly higher triglyceride concentrations than noncarriers (1.62 vs 1.52 mmol/L, P = 0.04) and tended to have higher insulin resistance (HOMA-IR = 4.85 vs 4.23, P = 0.18). Among Europeans, T54 carriers had higher triglyceride concentrations and insulin resistance than noncarriers, but the differences were not significant (1.43 vs 1.37 mmol/L, P = 0.31;
We did not observe this variation in the high triglyceride T54 variant accounted for little variation in the high triglyceride concentrations and insulin resistance found in this ethnic group.

**Table 1. Adjusted associations of the FABP2 T54 variant with mean triglycerides and mean insulin resistance.**

<table>
<thead>
<tr>
<th>T54 status</th>
<th>Triglycerides, mmol/L (95% CI)</th>
<th>HOMA-IR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncarriers</td>
<td>1.48 (1.41 to 1.55)</td>
<td>3.49 (2.98 to 3.99)</td>
</tr>
<tr>
<td>T54 carriers</td>
<td>1.53 (1.46 to 1.60)</td>
<td>3.70 (3.20 to 4.21)</td>
</tr>
<tr>
<td>Difference (β)</td>
<td>0.05 (−0.01 to 0.11) $P = 0.12$</td>
<td>0.22 (−0.23 to 0.67) $P = 0.34$</td>
</tr>
<tr>
<td>Variance explained</td>
<td>FABP2 T54, 0.25%; total variance, 10.83%</td>
<td>FABP2 T54, 0.09%; total variance, 8.03%</td>
</tr>
<tr>
<td>Noncarriers</td>
<td>1.42 (1.38 to 1.47)</td>
<td>2.82 (1.96 to 3.69)</td>
</tr>
<tr>
<td>T54 carriers</td>
<td>1.49 (1.44 to 1.54)</td>
<td>3.23 (2.36 to 4.10)</td>
</tr>
<tr>
<td>Difference (β)</td>
<td>0.06 (0.00 to 0.13) $P = 0.05$</td>
<td>0.40 (−0.07 to 0.89) $P = 0.10$</td>
</tr>
<tr>
<td>Variance explained</td>
<td>FABP2 T54, 0.53%; ethnicity, 1.74%; health behaviors, 4.92%; WHR, BMI, 12.59%; total variance, 25.65%</td>
<td>FABP2 T54, 0.38%; ethnicity, 2.10%; health behaviors, 3.76%; WHR, BMI, 12.10%; total variance, 24.45%</td>
</tr>
</tbody>
</table>

* Health behaviors include tobacco use (current smoker, previous smoker, reference = never), alcohol intake (1 drink/month to 5 drinks/week, >5 drinks/week, reference = never), physical activity (metabolic equivalents/day), total fat intake (g/day), trans fat intake (g/day), protein intake (g/day), fiber intake (g/day), total energy intake (kcal/day). Adiposity metrics included body mass index (BMI, kg/m²) and waist-to-hip ratio (WHR).

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References


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Quantification of Urinary Light Chains

To the Editor:

Monoclonal gammopathies are usually monitored with serum and/or urine protein electrophoresis (PEL) (1). In addition, quantitative immunoglobulins are often ordered for patients with large serum M-spikes. For patients with monoclonal light-chain diseases, diagnosis and monitoring can be a challenge, and free light-chain (FLC) quantification in serum has become an important additional test (2). Although there have been some conflicting reports, serum FLC should not replace urine PEL for monitoring patients with a urine M-spikes (3–5). The purpose of this study was to determine if measuring urine FLCs or urine total light chains (TLCs) is useful in addition to measuring urine PEL for monitoring patients, in a manner analogous to measuring quantitative immunoglobulin as a complement to measuring serum PEL.

Sequential waste urines (n = 336) were obtained from excess samples in which a monoclonal protein was detected by urine immunofixation electrophoresis (IFE). We performed PEL assays with agarose gel electrophoresis (REP, Helena Laboratories) after we increased the protein concentration in urine samples up to 200-fold to achieve a protein concentration of 20–80 g/L. IFE assays were performed with Helena reagent sets. The FLCs and TLCs were quantified on a Dade Behring BN II nephelometer, with separate antisera for $\kappa$ and $\lambda$ FLCs (The Binding Site) and $\kappa$ and $\lambda$ TLCs (Dade Behring). The limits of quantification of the urine TLC $\kappa$ and $\lambda$ assays are 7 and 4 mg/L, respectively, and 1 mg/L for both $\kappa$ and $\lambda$ FLC. The reference range for the urine TLC $\kappa:\lambda$ ratio was based on urine samples obtained from 54 healthy adult donors. These samples had total protein >100 mg/24 h, and we excluded 1 donor because of a highly increased TLC $\kappa:\lambda$ ratio. The reference range for the urine FLC $\kappa:\lambda$ ratio was based on urine samples from 91 healthy adult donors, and was the central 95% range.

Urine monoclonal protein was detected with IFE in all urine