A Variant in the LRRFIP1 Gene Is Associated with Adiposity and Inflammation

Melanie Plourde\(^1\), Marie-Claude Vohl\(^1\), Claire Bellis\(^5\), Melanie Carless\(^5\), Thomas Dyer\(^5\), Guillaume Dolley\(^1\)-\(^3\), André Marette\(^6\), Jean-Pierre Després\(^6\)-\(^7\), Claude Bouchard\(^8\), John Blangero\(^5\) and Louis Pérusse\(^1\)-\(^3\),\(^7\)

Introduction

Obesity is one of the most important health challenges of the 21st century worldwide. This complex multifactorial disease results mostly from genetic and environmental influences plus interaction effects between genes and behaviour. Genome-wide association studies (GWAS) of large population-based samples identified early approximately 10 loci with genome-wide significant \((P < 5 \times 10^{-8})\) association in or near \(FTO\), \(MC4R\), \(TMEM18\), \(GNPDA2\), \(BDNF\), \(NEGR1\), \(SH2B1\), \(ETV5\), \(MTC2\), and \(KCTD15\) \((1)\) consistently associated with BMI. Recently, Speliotes et al. increased the number of such loci to a total of 32, including the 10 loci previously documented \((1)\). However, the susceptibility genes identified through GWAS explained only a small fraction of the variance in BMI or obesity risk. Thus, the 32 loci found to be associated with BMI only accounted for 1.45% of the variance of this trait \((1)\). Several factors have been proposed to explain this missing heritability, including the influence of low-frequency or rare variants not accounted for in most arrays used in GWAS, the

Conclusion: This gene may therefore represent a potential interesting target to investigate in further functional studies on adiposity and inflammation.

Disclosure: M.P., M.-C.V., C.B., M.C., T.D., G.D., A.M., J.-P.D., J.B., and L.P. have no statement to disclose. C.B. receives honoraria from Weight Watchers and Pathway Genomics. See the online ICMJE Conflict of Interest Forms for this article. Additional Supporting Information may be found in the online version of this article.

Received: 1 July 2011 Accepted: 17 May 2012 First published online by Nature Publishing Group on behalf of The Obesity Society 26 July 2012. doi:10.1038/oby.2012.181

Inflammation is an important factor linking abdominal obesity with insulin resistance and related cardiometabolic risk. A genome-wide association study of adiposity-related traits performed in the Quebec Family Study (QFS) revealed that a single-nucleotide polymorphism (SNP) in the \(LRRFIP1\) gene \((rs11680012)\) was associated with abdominal adiposity \((P = 4.6 \times 10^{-5})\).

**Objective:** The objective of this study was to assess the relationship between polymorphisms in \(LRRFIP1\) gene and adiposity (BMI, fat mass (FM), waist circumference (WC), and computed tomography - derived areas of total, subcutaneous and visceral abdominal adipose tissue) and markers of inflammation (C-reactive protein (CRP) and interleukin-6).

**Design and Methods:** Using Sequenom, 16 tag SNPs in the \(LRRFIP1\) gene, capturing 78% of the genetic variation, were genotyped in 926 participants of the QFS.

**Results:** Eight SNPs \((rs7575941, rs3769053, rs11689421, rs3820808, rs11680012, rs3806505, rs6739130, and rs11686141)\) showed evidence of association with at least two adiposity phenotypes and plasma levels of one marker of inflammation. The strongest evidence of association was observed with \(rs11680012\), which explained 1.8 – 3.4% of the variance in areas of abdominal adiposity and 2.0% of the variation in CRP levels. Carriers of the rare allele of \(rs11680012\) had ~30% more abdominal adiposity \((P \text{ values between } 2.7 \times 10^{-4} \text{ and } 3.8 \times 10^{-5})\) and 75% higher CRP levels \((P = 1.6 \times 10^{-5})\) than the common allele in age and sex adjusted data. \(Rs11680012\) is a G/C SNP converting an arginine into a threonine and this amino acid substitution may potentially alter exonic splicing.

**Conclusion:** This gene may therefore represent a potential interesting target to investigate in further functional studies on adiposity and inflammation.
presence of gene–gene and gene–environment interaction effects or the presence of many more common variants with very small effect sizes that cannot be detected by most GWAS, which led some authors to suggest that the heritability is not missing, but rather hidden (2). It has also been recommended that population studies with more sophisticated adiposity phenotype should be conducted in order to reduce heterogeneity and explore pleiotropic effects (3).

For instance, measurement of abdominal adiposity by computed tomography scans provides information regarding the true magnitude of this fat depot, abdominal obesity being more closely associated with related metabolic complications than the total amount of excess body fat (4). For instance, there are evidence supporting a molecular link between obesity, particularly excess abdominal adiposity, and inflammation. Therefore, it is important to identify the genes and sequence variants specifically associated with abdominal adiposity and its related metabolic complications.

The Toll-like receptor (TLR) gene was recently proposed as one potential molecular link between obesity, inflammation, and insulin resistance (5). Indeed, a polymorphism within TLR-4 was associated with increased total body fat, visceral fat, liver fat, and decreased insulin sensitivity in nondiabetic white (5). One regulator of the TLR pathway signalling is the leucine rich repeat (in Flii) interacting protein 1 (LRRFIP1, ID 9208) gene (6). One characteristic of the leucine rich repeated (LRR) motifs is that they are expressed mostly in adult heart and skeletal muscle tissues and are involved in protein–protein interactions. As a consequence, they could possibly participate in many biologically important processes such as hormone–receptor interactions, enzyme inhibition, cell adhesion, and cellular trafficking (7), thereby modulating adiposity and inflammation.

Hence, since obesity is a complex disease that is commonly associated with an inflammatory state (8), the objective of this study was to assess whether there was a relationship between LRRFIP1 gene polymorphisms and adiposity phenotypes with an emphasis on abdominal adiposity and relevant plasma inflammatory markers.

Methods and Procedures

Participants
Subjects were participants of the Quebec Family Study (QFS), a project investigating the genetics of obesity and its comorbidity in French–Canadian families (9). This cohort represents a mixture of random sampling and ascertainment through obese (BMI >32 kg/m²) probands. All procedures were approved by the institutional review board of the Medical Ethics Committee of Laval University, and all subjects gave their informed written consent to participate in this study.

Measures
Height, body weight, and waist circumference (WC) were measured following standardized procedures (10). Measurement of abdominal adipose tissue areas was performed by computed tomography with a Siemens Somatom scanner. Briefly, participants were examined in the supine position with both arms stretched above head. The scan was performed at the abdominal level (L4 and L5 vertebrae) using an abdominal scout radiograph to standardize the position of the scan to the nearest millimetre. Total adipose tissue area (TAT) was calculated by delineating the abdominal scan with a graph pen and then by computing the TAT with an attenuation range of −190 to −30 Hounsfield units (11,12). Visceral adipose tissue area (VAT) was measured by drawing a line within the muscle wall surrounding the abdominal cavity. Subcutaneous adipose tissue area (SAT) was calculated by subtracting VAT from TAT. Body fat mass (FM) was determined from body density measurements obtained by underwater weighing and conversion of density to percentage body fat was performed with the Siri equation (13).

Blood samples were obtained after a 12-h fast and were kept frozen at −80 °C until further analysis. Interleukin-6 (IL-6) concentrations were assessed using an enzyme-linked immunoabsorbant assay from available commercial kits (B-Bridge International, San Jose, CA and R&D System, Minneapolis, MN) whereas C-reactive protein (CRP) concentrations were measured using the Behring latex-enhanced high-sensitivity assay on a Behring BN-100 nephelometer (Dade Behring, Mississauga, Ontario, Canada) using the manufacturers’ procedure (14). Subjects with CRP values equal to or higher than 10 mg/ml were excluded based on previous studies suggesting that values above this threshold may be more likely resulting from major infection or trauma (15).

Genotyping
A GWAS was conducted on 928 lymphocyte-derived DNA samples of the QFS cohort using the Illumina 610-Quad chip containing 620,901 markers including 582,591 autosomal single-nucleotide polymorphisms (SNPs). The average global coverage of the 610-Quad chip, i.e., the fraction of SNPs that are tagged by the SNPs found on the chip is 93% (based on the CEU (European-derived) reference HapMap population). After exclusion of copy number variations, SNPs called in <95% of the subjects, SNPs not in Hardy–Weinberg (P < 10⁻⁴) and those with a minor allele frequency <1%, a total of 543,714 SNPs were analyzed for association with the phenotypes. Association of each SNP with the phenotypes adjusted for age and sex was tested using the measured genotype approach implemented in the software program SOLAR (16). This approach accounts for the non-independence among family members by incorporating a residual polygenic component.

Further gene-specific genotyping was conducted on 926 QFS subjects and genotypes were obtained using the Sequenom MassARRAY assays that combine primer extension reaction chemistry with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (17). Using the CEU (European-derived) reference HapMap population (HapMap data Rel 24/phaseII Nov08, on NCBI B36 assembly, dbDNP b126), tag SNPs were selected with Hapview version 4.2 (18) with a Hardy–Weinberg P value cut-off of 0.001 and a minor allele frequency cut-off of 0.001. Four SNPs coming from our GWAS results (rs11680012, rs3806505, rs6739130, and rs11686141) were also genotyped. Primers and probes were selected using NCBI and are presented in Supplementary Table S1 online. Analysis was restricted to SNPs passing quality filters, excluding SNPs with success rate <95%, minor allele frequency <1% or deviation from Hardy–Weinberg equilibrium (P < 10⁻³).

Moreover, we have used PolyPhen software to predict whether SNPs in protein-coding regions that cause amino acid variants (non-synonymous cSNP) could potentially change three-dimensional structure and function of the protein. These predictions are based on
straightforward empirical rules which are applied to the sequence, phylogenetic, and structural information characterizing the substitution (19). ESEfinder (http://exon.cshl.edu/ESE) was used to facilitate rapid analysis of exon sequences to identify serine/arginine-rich proteins and to predict whether exonic mutations disrupt such elements (20).

### Statistics

Calculations of allele frequencies and tests of SNP data for Mendelian inconsistencies and Hardy–Weinberg equilibrium were performed using PLINK software (version 1.07; http://pngu.mgh.harvard.edu/purcell/plink/) (21). Measures of linkage disequilibrium between SNPs were determined using Haplovew version 4.2 (18). Haplotype blocks were generated with the subject genotype data in Haplovew using the confidence interval method. All phenotypes were adjusted for age, age squared and sex after an inverse normal transformation to ensure normality of the distribution. The single marker association analyses were performed using mixed linear model (MLM) methods (22,23) implemented in the GWAF Package (24). In MLM-based methods, population structure and SNP genotype are fit as fixed effects, whereas kinship among individuals is incorporated as the variance-covariance structure of the random effect for the individuals. The methods utilizes a variance-components framework to combine phenotypic means model and estimates of additive genetic, residual genetic, and residual environmental variances from a variance-covariance matrix into a single likelihood model. The evidence of association is evaluated by maximizing the likelihood of twice the difference of the log likelihoods between the null and the alternative hypotheses \(2\ln(L_1 - L_0)\). Using Hapmap data, we selected 12 tag SNPs using Haplovew (Cambridge, MA) capturing 76% of the gene variation. In addition, four SNPs (rs11680012, rs3806505, rs6739130, and rs11686141) from the GWAS array and not in linkage disequilibrium with any of the selected tag SNPs were also genotyped for all participants. The study sample included 926 individuals. Their characteristics are presented in Table 1. Participants' mean age was 41.9 ± 17.6 years. Women accounted for 56.5% of the study sample. The mean BMI value was of 27.8 ± 7.6 kg/m². Measurements of CT abdominal adipose tissue areas were available for 669 participants (Table 1). WC and VAT were significantly lower in women than in men. In contrast, men had lower TAT, SAT, and %FAT values together with lower plasma CRP than women (1). If we take into account the correlations among the phenotypes tested (by calculating the mean correlation among the phenotypes, which is 0.69), the Bonferroni adjusted \(P\) value for an overall \(z\) level of 0.05 would be 0.011. Haplotype analyses were performed using the HBAT command in the FBAT (Family-based association tests) software. In these analyses, we used the empirical variance estimator option (-e) as our primary hypothesis.

### Results

Results of the GWAS revealed that one SNP (rs11680012) in an exon of \(LRRFIP1\) gene suggest and association with TAT (\(P = 4.6 \times 10^{-6}\)), SAT (\(P = 2.6 \times 10^{-5}\)), and VAT (\(P = 2.0 \times 10^{-5}\)) (data not shown). Using Hapmap data, we selected 12 tag SNPs using Haplovew (Cambridge, MA) capturing 76% of the gene variation. In addition, four SNPs (rs11680012, rs3806505, rs6739130, and rs11686141) from the GWAS array and not in linkage disequilibrium with any of the selected tag SNPs were also genotyped for all participants. Hence, a total of sixteen SNPs in the \(LRRFIP1\) gene (listed in Table 2 by position) allowed coverage of 78% of the gene variation. Minor allele frequencies were calculated from unrelated participants and ranged from 1.80 to 40.73% (Table 2). All the genotyped SNPs were in Hardy–Weinberg equilibrium (Table 2). We performed power calculations to assess the likelihood of detecting an association between SNPs and a trait and found that with our sample size, we have 80% power to detect an association at the 0.05 significance level for a SNP accounting for ~3% of the phenotypic variation in the obesity-related traits. The LD pattern of the 16 \(LRRFIP1\) SNPs genotyped in the subjects included in the present study in shown in Figure 1. The Lewontin’s standardized

---

### Table 1 Characteristics of the Quebec Family Study (QFS) participants

<table>
<thead>
<tr>
<th>Phenotypes</th>
<th>Total</th>
<th>Mean ± SD</th>
<th>Men</th>
<th>Mean ± SD</th>
<th>Women</th>
<th>Mean ± SD</th>
<th>(P) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>926</td>
<td>41.9 ± 17.6</td>
<td>403</td>
<td>41.4 ± 17.6</td>
<td>523</td>
<td>42.2 ± 17.6</td>
<td>0.484</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>918</td>
<td>27.8 ± 7.6</td>
<td>400</td>
<td>27.6 ± 6.6</td>
<td>518</td>
<td>27.9 ± 8.3</td>
<td>0.447</td>
</tr>
<tr>
<td>% FAT</td>
<td>736</td>
<td>28.3 ± 10.8</td>
<td>327</td>
<td>23.2 ± 9.3</td>
<td>409</td>
<td>32.3 ± 10.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>888</td>
<td>89.0 ± 18.3</td>
<td>395</td>
<td>94.0 ± 17.0</td>
<td>493</td>
<td>85.1 ± 18.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TAT (cm²)</td>
<td>669</td>
<td>407.5 ± 224.1</td>
<td>284</td>
<td>354.8 ± 201.3</td>
<td>385</td>
<td>446.4 ± 232.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SAT (cm²)</td>
<td>669</td>
<td>291.1 ± 172.3</td>
<td>284</td>
<td>223.1 ± 137.4</td>
<td>385</td>
<td>341.2 ± 178.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>VAT (cm²)</td>
<td>669</td>
<td>116.4 ± 80.1</td>
<td>284</td>
<td>131.8 ± 86.4</td>
<td>385</td>
<td>105.1 ± 73.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CRP (mg/ml)</td>
<td>785</td>
<td>3.3 ± 5.6</td>
<td>341</td>
<td>2.5 ± 4.6</td>
<td>444</td>
<td>3.9 ± 6.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>780</td>
<td>3.0 ± 13.8</td>
<td>342</td>
<td>2.1 ± 2.5</td>
<td>447</td>
<td>3.7 ± 18.2</td>
<td>0.103</td>
</tr>
</tbody>
</table>

%FAT, percent body fat; CRP, C-reactive protein; IL-6, Interleukin-6; SAT, subcutaneous adipose tissue area; TAT, total adipose tissue area; VAT, visceral adipose tissue area; WC, waist circumference.

* \(P\) value for difference between men and women.
TABLE 2 List of LRRFIP1 gene SNP, genotype and minor allele frequency (MAF)

<table>
<thead>
<tr>
<th>N of unrelated participants</th>
<th>rs number</th>
<th>Position (bp)</th>
<th>Genotype</th>
<th>MAF (%)(a)</th>
<th>HW (P values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>586</td>
<td>rs3769090</td>
<td>238,286,529</td>
<td>C/T</td>
<td>17.92</td>
<td>0.1633</td>
</tr>
<tr>
<td>608</td>
<td>rs6740706</td>
<td>238,203,248</td>
<td>T/C</td>
<td>18.59</td>
<td>0.3438</td>
</tr>
<tr>
<td>604</td>
<td>rs1565853</td>
<td>238,294,975</td>
<td>T/C</td>
<td>40.73</td>
<td>0.6353</td>
</tr>
<tr>
<td>608</td>
<td>rs3820813</td>
<td>238,296,646</td>
<td>A/G</td>
<td>18.75</td>
<td>0.2561</td>
</tr>
<tr>
<td>602</td>
<td>rs3769085</td>
<td>238,297,116</td>
<td>A/C</td>
<td>17.28</td>
<td>1.0000</td>
</tr>
<tr>
<td>606</td>
<td>rs3769080</td>
<td>238,306,260</td>
<td>C/T</td>
<td>12.38</td>
<td>0.7918</td>
</tr>
<tr>
<td>608</td>
<td>rs3820808</td>
<td>238,312,544</td>
<td>C/G</td>
<td>5.92</td>
<td>0.6107</td>
</tr>
<tr>
<td>610</td>
<td>rs3769072</td>
<td>238,312,683</td>
<td>C/G</td>
<td>22.53</td>
<td>0.8695</td>
</tr>
<tr>
<td>610</td>
<td>rs11689421</td>
<td>238,315,428</td>
<td>T/C</td>
<td>5.57</td>
<td>0.6105</td>
</tr>
<tr>
<td>610</td>
<td>rs3754720</td>
<td>238,319,199</td>
<td>C/T</td>
<td>1.80</td>
<td>1.0000</td>
</tr>
<tr>
<td>610</td>
<td>rs7575941</td>
<td>238,331,787</td>
<td>G/T</td>
<td>5.90</td>
<td>0.6106</td>
</tr>
<tr>
<td>610</td>
<td>rs3769053</td>
<td>238,335,531</td>
<td>T/C</td>
<td>7.87</td>
<td>0.7064</td>
</tr>
<tr>
<td>610</td>
<td>rs11680012</td>
<td>238,337,164</td>
<td>G/C</td>
<td>5.41</td>
<td>1.0000</td>
</tr>
<tr>
<td>606</td>
<td>rs3806505</td>
<td>238,341,188</td>
<td>A/G</td>
<td>8.42</td>
<td>0.2472</td>
</tr>
<tr>
<td>610</td>
<td>rs6739130</td>
<td>238,354,108</td>
<td>A/G</td>
<td>11.48</td>
<td>0.2571</td>
</tr>
<tr>
<td>606</td>
<td>rs11686141</td>
<td>238,354,297</td>
<td>A/G</td>
<td>7.43</td>
<td>0.3887</td>
</tr>
</tbody>
</table>

SNP, single-nucleotide polymorphism.

\(a\)MAF calculated in unrelated study participants.

FIGURE 1 Linkage disequilibrium (LD) pattern of the 16 single-nucleotide polymorphisms (SNPs) genotyped in the LRRFIP1 gene. The Lewontin’s standardized disequilibrium coefficient (\(D'\) value \times 100) of each SNP pair is shown in the squares. Empty squares indicate \(D' = 1\).
The disequilibrium coefficient (D’ values) is shown in the squares as pairwise measures of LD. The LD pattern reveals four haplotype blocks: blocks 1 and 2 encompassing three SNPs each and blocks 3 and 4 encompassing two SNPs each.

**LRRFIP1** gene expresses 5 protein isoforms: NM_001137550.1, NM_001137551.1, NM_001137552.1, NM_001137553.1, and NM_004735.3. Rs11680012 polymorphism changes an arginine residue for a threonine residue in LRRFIP1 isoform 3 protein (NM_001137552.1; R690T), in isoform 4 protein (NM_004735.3; R666T) and in isoform 5 protein (NM_001137553.1; R634T). Using PolyPhen-2 software, consequence of the exon G/C polymorphism of rs11680012 on the functionality of the three proteins was evaluated. This polymorphism was predicted to be benign on the three-dimensional structure and function of the proteins. However, a splicing site might be altered by this polymorphism as predicted by ESEfinder. Indeed, a new splice site SF2/ASF IgM-BRCA1 may exist in G/C carriers of rs11680012 since the score for the G allele was lower than 0.1 whereas the score was of 2.66 for the C allele.

Table 3 presents the results of single SNPs association analyses for SNPs showing evidence of association with at least one of the phenotypes tested. Analyses were performed in the combined sample of men and women as no evidence of gene by sex interaction was found for any of the SNP-trait combinations. Eight out of the sixteen **LRRFIP1** SNPs were found to be associated with percent body fat, abdominal fat (TAT, SAT, VAT), and CRP levels. Three SNPS (rs3769053, rs11680012, and rs3806505) showed evidence of association after adjustment for multiple testing ($P < 10^{-4}$) and the strongest evidence of association ($P$ values) was observed with rs11680012 for %FAT ($3.8 \times 10^{-6}$), TAT ($3.5 \times 10^{-5}$), SAT ($1.6 \times 10^{-5}$), and CRP ($1.6 \times 10^{-5}$). The rs11680012 SNP was associated with increased adiposity and CRP levels (positive $\beta$ values) and explained 1.8–3.4% of the phenotypic variance (Table 3).

Table 4 presents the least square mean estimates $\pm$ SD for the three SNPs showing evidence of association after Bonferroni correction. Carriers of the rare C/C allele of rs3769053, rs11680012, and rs3806505 showed evidence of association after adjustment for multiple testing ($P < 3.9 \times 10^{-4}$) and the strongest evidence of association ($P$ values) was observed with rs11680012 for %FAT ($2.7 \times 10^{-4}$), TAT ($2.7 \times 10^{-4}$), SAT ($1.6 \times 10^{-5}$), and CRP ($1.6 \times 10^{-5}$). The rs11680012 SNP was associated with increased increased adiposity and CRP levels (positive $\beta$ values) and explained 1.8–3.4% of the phenotypic variance (Table 3).
rs11680012 had ~29% higher abdominal adiposity levels compared with G/G homozygotes (Table 4). Carriers of the rare A/G allele of rs3806505 had ~20% higher abdominal adiposity compared with A/A homozygotes whereas carriers of the rare G allele of rs6739130 had between 12% and 32% higher abdominal adiposity levels compared with A/A homozygotes (Table 4).

Results of haplotype analyses are presented in Table 5. Haplotypes derived from the SNPs of the four blocks shown in Figure 1 were analyzed retaining only haplotypes with a frequency of at least 1%. Significant evidence of association was observed with two most common haplotypes for SNPs of blocks 2, 3, and 4. Two haplotypes (TGT and CTC) from SNPs rs11689421, rs7575941, and rs3769053...
of block 2 showed significant association with CRP levels (global $P = 0.03$). Two other haplotypes (GA and CG) from SNPs rs11680012 and rs3806505 which showed the strongest associations in single marker tests also showed association with adiposity with %FAT, abdominal fat (TAT, SAT, VAT), and CRP levels (global $P = 0.008$). Finally, haplotypes AA and GG from SNPs rs679130 and rs11686141 were also associated with adiposity (%FAT, TAT, and SAT) and CRP levels (global $P = 0.009$).

### Discussion

The aim of this study was to evaluate the relationship between LRRFIP1 gene polymorphisms, obesity indices with a focus on abdominal adiposity, together with two markers of inflammation, plasma IL-6, and CRP levels. A GWAS approach first revealed that rs11680012 of the LRRFIP1 gene was associated with abdominal adiposity phenotypes ($P$ values ranging from $2.0 \times 10^{-5}$ to $4.6 \times 10^{-6}$).

To our knowledge, this is the first time that the LRRFIP1 gene is reported to be associated with abdominal adiposity phenotypes.

The LRRFIP1 gene expresses five protein isoforms that vary in length—from a short 80 kDa isoform named FLAP1 to a full-length 160 kDa isoform (6). The G/C polymorphism of rs11680012 is the only one altering the amino acid sequence among the 16 SNPs studied. In silico analysis reveals that splicing site might be altered by this polymorphism. Moreover, rs11680012 results in the substitution of an amino acid, an arginine for a threonine in LRRFIP1 protein isoforms 3, 4, and 5 which are the three short protein isoforms. FLAP1 protein has several functions including serving as a regulator of TLR pathway signalling, a transcriptional repressor and a MyD88-interacting protein (25-27). Moreover, it was recently reported that activation of the FLAP1 protein may lead to a cascade of signalling events culminating in the production of tumor necrosis factor-$
\alpha$ and other marker of inflammation related to extracellular treats (28). This signalling pathway relies primarily on NF-$\kappa$B for proinflammatory marker of inflammation production (29). TLR is considered a molecular link between obesity, inflammation, and insulin resistance (5). A polymorphism within TLR4 was associated with higher total body fat, visceral fat, liver fat, and lower insulin sensitivity in nondiabetic white (5). Since FLAP1 was shown to relieve the FliiH-mediated inhibition of TLR signalling (25), we hypothesize that the mutation in rs11680012 can potentially affect RNA splicing and regulation of TLR pathway signalling. However, functional studies are needed to confirm this hypothesis.

Another potential explanation for the association between LRRFIP1 and inflammation may relate to the LRRFIP1 proteins’ potential to be phosphorylated on one or more motifs (four motifs of serine and one of tyrosine) (6). In primary monocyte cell lines, LRRFIP1 was shown to be phosphorylated in response to immunologic stimuli and the level of phosphorylation was regulated by stimuli impacting TLR responses (6). Moreover, in the same cell lines, LRRFIP1 was found predominantly dispersed in the cytoplasm but when cells were stimulated with a specific antibody for the 120/160 kDa isoform to produce an immune response, LRRFIP1 translocated to lysosomal structures to modulate the response to the stressor agent (6).

One limitation of this study is that we did not replicate our results in another independent cohort and this is explained by the fact that we do not have access to other samples with the same set of phenotypes for replication. However, we have screened the literature and the Genetic Association Data Base (http://geneticassociationdb.nih.gov/) to interrogate GWAS on BMI and related traits in association with LRRFIP1 gene and more specifically with rs11680012 SNP, but no hit was found.

Overall, our results support the hypothesis of an association between LRRFIP1 gene SNPs and obesity indices, abdominal adiposity, and plasma markers of inflammation. However, these results need to be replicated in independent studies. In addition, functional studies are needed to confirm whether splice isoforms impact protein 3, 4, and 5 functions, especially among carriers of the G/C polymorphism of rs11680012. To the best of our knowledge, this is the first time that the LRRFIP1 gene variants are shown to be associated with adiposity and inflammation phenotypes. This gene is an interesting target gene for further investigation particularly as it appears to be involved in TLR signalling, a pathway that is thought to provide a molecular link between obesity and inflammation.

### Acknowledgment

This work was supported by the Canadian Institute of Health Research (CIHR). M.P. was supported by a Fonds de la recherche sur la santé du Québec Postdoctoral Fellowship Award. J.-P.D. is the Scientific Director of the International Chair on Cardiometabolic Risk. C.B. is partially funded by John W. Barton Sr. Chair in Genetics and Nutrition. M.-C.V. holds a Canada Research Chair in Genomics Applied to Nutrition and Health and A.M. holds a CIHR/Pfizer Research Chair on the pathogenesis of insulin resistance and cardiovascular disease.

### References


学霸图书馆

www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：

图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具