Canadian Journal of Cardiology 33 (2017) 1312–1318

Clinical Research

Scavenger Receptor LOX1 Genotype Predicts Coronary Artery Disease in Patients With Familial Hypercholesterolemia

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ABSTRACT

Background: Familial hypercholesterolemia (FH) is a monogenic disease associated with elevated low-density lipoprotein (LDL) cholesterol and oxidized LDL (oxLDL) leading to premature cardiovascular disease. Lectin-like oxLDL receptor-1 (LOX1) is one of the major contributors of oxLDL uptake and degradation in macrophages, which leads to foam cell formation and the development of atherosclerosis. This study investigated the effect of the rs11053646 genotype of the oxidized low-density lipoprotein receptor 1 (*OLR1*) gene on coronary artery disease (CAD) risk in a cohort of FH patients.

Methods: A total of 665 genetically confirmed heterozygous adult patients with FH were included in the analysis. We evaluated the association between the rs11053646 genotype (GG vs GC) and CAD.

Results: The GC genotype (K167N carriers) represented 12.9% of the study cohort (n = 86), whereas 87.1% of the participants were non-carriers (GG genotype) (n = 579). A significantly higher proportion of GC carriers experienced a CAD event (40.7%) than did GG carriers (29.0%; *P* = 0.03). The presence of a C allele remained significantly

RÉSUMÉ

Contexte : L'hypercholestérolémie familiale (HF) est une maladie monogénique liée à des taux élevés de cholestérol à lipoprotéines de basse densité (LDL) et de LDL oxydées (LDLox), conduisant à l'apparition prématurée de maladies cardiovasculaires. Le récepteur de type lectine (LOX-1) des LDLox est un des principaux facteurs contribuant à la captation et à la dégradation des LDLox dans les macrophages, ce qui entraîne la formation de cellules spumeuses et l'apparition d'athérosclérose. Cette étude a analysé l'effet du génotype rs11053646 du polymorphisme du gène du récepteur 1 des LDLox (*OLR1*) sur le risque de coronaropathie dans une cohorte de patients atteints d'HF.

Méthodologie : Un total de 665 patients adultes atteints de HF hétérozygote, confirmée par diagnostic génétique, ont été inclus dans l'analyse, qui a évalué l'association entre le génotype rs11053646 (GG vs GC) et le risque de coronaropathie.

Résultats : Le génotype GC (sujets porteurs de la variante K167N) représentait 12,9 % de la cohorte de l'étude (n = 86), tandis que 87,1 %

Familial hypercholesterolemia (FH) is an autosomal codominant monogenic disease characterized by extreme elevations in low-density lipoprotein cholesterol (LDL-C) and ectopic cholesterol depositions (tendinous xanthomas), as well as premature cardiovascular disease (CVD).[1,2] This disease results mainly from mutations in the LDL receptor (*LDLR*), apolipoprotein B (*APOB*), or proprotein convertase subtilisin/kexin-type 9 (*PCSK9*) genes.[3-5] FH is 1 of the most prevalent genetic diseases worldwide, with an estimated frequency of 1 in 250 individuals.[6,7] However, not all patients with FH present with the same CVD risk,[8] and common genetic variants can significantly contribute to the CVD risk and the modulation of the disease phenotype.[9-12]

Scavenger receptors (SRs) are a superfamily of membrane-bound receptors that can recognize modified lipoproteins (eg, oxidized LDL [oxLDL]) and other ligands (such as bacteria or apoptotic cells) and mediate their clearance.[13] There are 9 classes of SRs in humans,[14] but only 3 of them (SR-A1, SR-B2, and lectin-like oxLDL receptor-1 [LOX1]) constitute the major contributors of oxLDL uptake and degradation in macrophages.[15] Under normal conditions, the contribution of LOX1 in macrophage uptake and degradation of oxLDL is negligible.[16] However, in inflammatory states and in atherosclerosis, the expression of LOX1 is markedly upregulated, and its contribution to oxLDL removal is greatly increased.[16]

Received for publication June 8, 2017. Accepted July 25, 2017.

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See page 1317 for disclosure information.

http://dx.doi.org/10.1016/j.cjca.2017.07.480

associated with an increased CAD risk, even when the regression model was corrected for all traditional CAD risk factors (odds ratio, 3.05; 95% confidence interval, 1.63-5.70; *P* = 0.0005). The negative impact of carrying the C allele on CAD risk was similar in both sexes but was significantly more important in smokers as well as in younger patients with FH.

Conclusions: **Carrying the C allele of the rs11053646 variant of the *OLR1* gene was associated with an increased risk of CAD in heterozygous adult patients with FH, and this risk could be even greater in smokers as well as in younger patients.**

des participants étaient non porteurs de cette variante (génotype GG) (n = 579). Une proportion sensiblement plus élevée de sujets porteurs du génotype GC a présenté un épisode de coronaropathie (40,7 %), comparativement aux porteurs du génotype GG (29,0 %; *p* = 0,03). La présence de l'allèle C était associée de façon significative à un risque accru de coronaropathie, même après ajustement du modèle de régression pour tenir compte de tous les facteurs de risque usuels de coronaropathie (rapport de cotes : 3,05; intervalle de confiance à 95 % : de 1,63 à 5,70; *p* = 0,0005). Les répercussions négatives de la présence de l'allèle C sur le risque de coronaropathie étaient semblables entre les sexes, mais elles étaient sensiblement plus importantes chez les fumeurs, de même que chez les jeunes patients atteints de HF.

Conclusion : **La présence de l'allèle C de la variante rs11053646 du gène *OLR1* a été associée à un risque accru de coronaropathie chez les patients adultes atteints de HF hétérozygote, un risque qui pourrait être majoré chez les fumeurs et les sujets plus jeunes.**

In this context, endothelial dysfunction leads to monocyte recruitment and migration into the subendothelial space, where they differentiate into macrophages that express LOX1 receptors.[17,18] These macrophages can take up oxLDL particles, leading to the formation of foam cells that secrete molecules implicated in the development of primary atherosclerotic plaque (fatty streaks).[19]

The rs11053646 single-nucleotide polymorphism (SNP) in the oxidized low-density lipoprotein receptor 1 (*OLR1*) gene on chromosome 12 leads to a nonsynonymous modification of the LOX1 protein (K167N) in the ligand-binding domain. The results of a study by Tatsuguchi et al.[20] suggest that carrying the K167N variant (heterozygous or homozygous) is associated with a 3-fold increased risk of myocardial infarction. However, the association between this variant and CVD risk in the literature is not clear, because results from previous studies are inconsistent.[21,22]

In the context of FH, high plasma levels of LDL-C are associated with increased formation of oxidatively modified LDL, which plays an important and independent role in atherosclerosis development.[23-25] However, the contribution of the K167N polymorphism of SR LOX1 (*OLR1* gene) in patients with FH has never been studied.

The objectives of this study were to investigate the effect of the rs11053646 genotype of the *OLR1* gene on the risk of coronary artery disease (CAD) in a cohort of genetically confirmed patients with FH. Furthermore, because oxLDL is involved in the initial steps of atherosclerosis, we further investigated if this polymorphism was more strongly associated with risk in younger individuals as well as in smokers.

Methods

Study population and data collection

The patients with FH included in this cohort were followed at the Nutrition, Metabolism, and Atherosclerosis Clinic of the Institut de recherches cliniques de Montréal (IRCM). A flowchart of patient selection is presented in Figure 1. A total of 665 genetically confirmed heterozygous adult patients with FH were included in the present study. Only 3 individuals carried the CC genotype of rs11053646 and were excluded from the analysis. Details concerning FH-causing mutations and CAD events included in this study are presented in Supplemental Table S1. CAD events were self-reported by the patients at the time of the first consultation. Documentation concerning these events was obtained by requesting copies of relevant tests (eg, coronarography, stress test) and hospital visits. Concerning angina, diagnosis was confirmed using data from exercise stress testing, nuclear stress myocardial perfusion imaging, or stress echocardiography. Written informed consent, approved by the IRCM Institutional Review Board and ethical committees in accordance with the Helsinki Declaration, was obtained from all patients.

Biochemical analysis

The lipid profile was assayed after a 12-hour overnight fast and a 4-week washout of lipid-lowering medications. Lipoprotein concentrations were assayed by ultracentrifugation according to the reference method described by the National Heart, Lung, and Blood Institute.[26] Total cholesterol and triglyceride levels were measured using an enzymatic method (Abbott Biochromatic Analyzer model 100; Abbott Laboratories, Abbott Park, IL). Lipoprotein(a) concentration was measured using an enzyme-linked immunoassay kit (Macra EIA Kit; Strategic Diagnostics Industries, Newark, NJ) and apolipoprotein B was assayed by electroimmunoassay (Behringwerke; Marburg, Germany).

DNA analysis

The methodology used to analyze DNA has previously been described elsewhere.[11] Briefly, an automated 340A DNA extractor (Applied Biosystems, Foster City, CA) or QIAmp Blood Maxi Kit (Qiagen, Hilden, Germany) was used to extract DNA. A polymerase chain reaction−based method was used to detect the presence of W66G, E207K, Y468X, and C646Y *LDLR* mutations and Southern blot analysis or a semiquantitative polymerase chain reaction assay was used to detect *LDLR* deletions > 15 kb and > 5 kb.[11,27]

Exome chip genotyping

Genotypes were obtained using the Illumina HumanCoreExome-24, version 1-0A, microarray (Illumina,

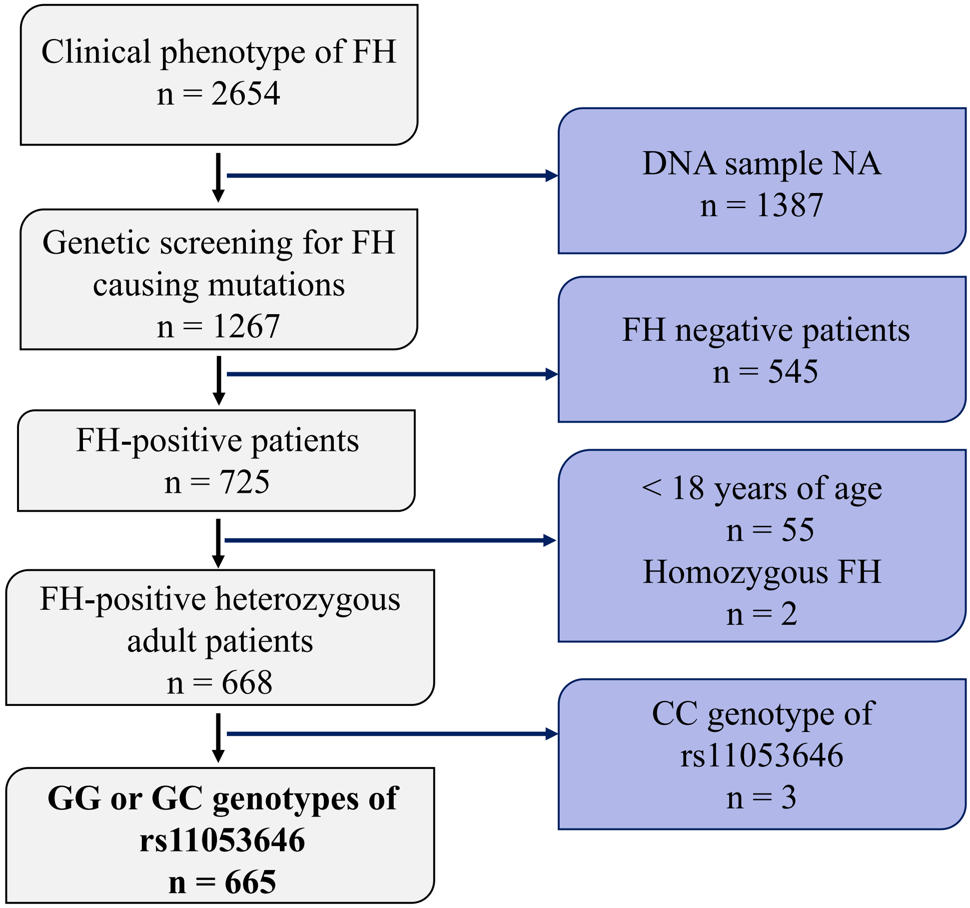

Figure 1. Flowchart of study. FH, familial hypercholesterolemia.

San Diego, CA). Quality control filtering was performed on the basis of sample-level checks (missingness, sex check, ethnicity check, and relatedness check) and variant-level checks (missingness and the Hardy-Weinberg equilibrium). The genotyping rate in the call set was 99.91%. Genomic coverage of variants was extended by prephasing and imputation to infer SNPs that were not directly genotyped using the 1000Genomes Phase 1, version 3 (November 23, 2010 subversion) reference panel. *OLR1* rs11053646 was directly genotyped.

Statistical analysis

Statistical analyses were performed using SPSS, version 20.0 (IBM Corp, Armonk, NY). We considered results significant with $P < 0.05$ and all P values were 2-sided. Continuous variables with a skewed distribution were normalized by log-transformation before the analysis and were expressed as median (interquartile range). Categorical variables are summarized as frequency (n [%]), whereas data for continuous normally distributed variables are presented as mean ± standard deviation (SD). Differences between the 2 genotypes of the rs11053646 SNP were compared with a Student unpaired 2-tailed t test for continuous variables, whereas the χ^2 or the Fisher exact test were used to compare categorical variables. The strength of association between the rs11053646 genotype and CAD events was evaluated using logistic regression analysis according to different models of correction.

Results

Description of the study cohort

A total of 665 heterozygous adult patients with FH with a known mutation in the *LDLR* gene were included in the present study. The clinical characteristics of the study population according to the rs11053646 genotype are shown in Table 1. The C allele, referring to the reverse strand, represents the alternative (minor) allele for this SNP (K167N carriers). Indeed, C allele carriers (GC) represented 12.9% of the study cohort (n = 86), whereas noncarriers (GG) represented 87.1% of the participants (n = 579). In summary, significantly more GC carriers presented a diagnosis of hypertension (26.7%) than did GG carriers (17.3%; P = 0.05). However, total cholesterol and non−LDL-C levels were lower in GC carriers (8.93 ± 1.67 mmol/L and 7.99 ± 1.64 mmol/L, respectively) than in GG carriers (9.41 ± 1.63 mmol/L; P = 0.01 and 8.43 ± 1.72 mmol/L; P = 0.03, respectively). No other differences were observed between these 2 groups.

C allele carriers are at higher CAD risk

Figure 2 presents the frequency of CAD events according to the rs11053646 genotype. A significantly higher proportion of

Table 1. Participant characteristics

OLR1 rs11053646 genotype	GG n = 579 (87.1%)	GC n = 86 (12.9%)	*P* value
Age (y)	40.5 ± 13.7	40.0 ± 15.5	0.76
Sex (women)	326 (56.3%)	55 (64.0%)	0.20
BMI (kg/m^2)	25.0 ± 4.7	24.4 ± 4.9	0.26
HTN (yes)	100 (17.3%)	23 (26.7%)	**0.05**
Diabetes (yes)	20 (3.5%)	2 (2.3%)	1.00
Smoking (past or current)	380 (65.6%)	49 (57.0%)	0.15
Previous statin drug use (yes)	439 (75.8%)	58 (67.4%)	0.11
LDL-C (mmol/L)	7.39 ± 1.44	7.09 ± 1.48	0.08
Total cholesterol (mmol/L)	9.41 ± 1.63	8.93 ± 1.67	**0.01**
HDL-C (mmol/L)	1.03 ± 0.31	1.02 ± 0.30	0.96
Triglycerides (mmol/L)	1.42 (1.05-2.01)	1.43 (1.08-1.93)	0.99
Lipoprotein(a) (μmol/L)	0.57 (0.21-1.18)	0.61 (0.21-1.75)	0.27
ApoB (g/L)	2.25 ± 0.50	2.21 ± 0.44	0.59
Non−HDL-C (mmol/L)	8.43 ± 1.72	7.99 ± 1.64	**0.03**

Data for continuous normally distributed variables are expressed as mean ± standard deviation. Continuous logarithmic variables (triglycerides, lipoprotein[a]) are expressed as median (interquartile range). Categorical variables are expressed as frequency, n (%). Data for lipids were collected without any lipid-lowering medication. C (referring to the reverse strand) represents the risk allele for rs11053646. N = 657 for age; n = 665 for sex, HTN, diabetes, smoking, and previous statin drug use; n = 647 for BMI; n = 637 for LDL-C; n = 646 for total cholesterol; n = 640 for HDL-C; n = 648 for triglycerides; n = 554 for lipoprotein(a); n = 524 for ApoB; and n = 631 for non−HDL-C. Bold type indicates *P* values ≤ 0.05.

ApoB, apolipoprotein B; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol.

GC carriers experienced at least 1 CAD event (40.7%) compared with GG carriers (29.0%; *P* = 0.03). If CAD events were studied separately (angina, myocardial infarction, coronary angioplasty, and coronary bypass surgery), the difference of frequency between GC and GG carriers was significant only for myocardial infarction (Supplemental Fig. S1).

Table 2 presents the association between CAD and the rs11053646 genotype according to 6 models of regression. The presence of the C allele remained significantly associated with an increased CAD risk, even when the regression model was corrected for the Montreal-FH-SCORE or a genetic risk score for CAD. Furthermore, this association remained significant when corrections were performed for all traditional CAD risk factors: age, sex, body mass index (BMI), hypertension, diabetes, smoking, previous use of statin drugs, total cholesterol, high-density lipoprotein (HDL)-C, and triglyceride levels (odds ratio [OR], 3.05; 95% confidence interval [CI], 1.63-5.70; *P* = 0.0005). When analysis was performed according to the type of *LDLR* mutation, no significant interaction between rs11053646 and the type of *LDLR* mutation was identified (Supplemental Table S2).

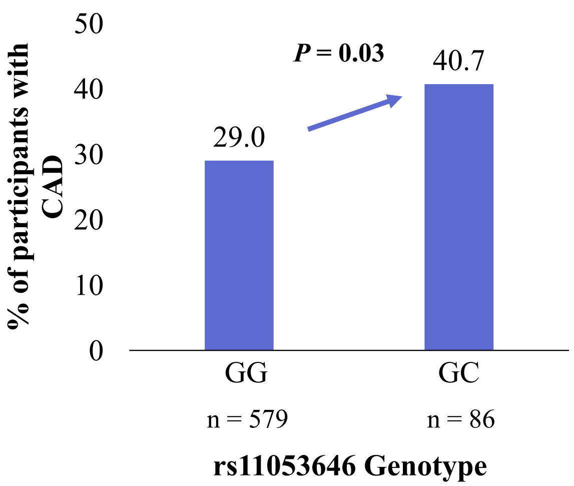

Figure 2. Coronary artery disease (CAD) frequency according to the rs11053646 genotype.

Table 2. CAD frequency according to the rs11053646 genotype

	Analysis		
Models	OR	95% CI	*P* value
Uncorrected	1.68	1.05-2.68	**0.03**
Corrected for age and sex	2.44	1.37-4.33	**0.002**
Corrected for all*	3.05	1.63-5.70	**0.0005**
Corrected for MFHS	2.47	1.38-4.44	**0.002**
Corrected for GRS_{CAD}	1.62	1.01-2.59	**0.04**
Corrected for MFHS and GRS_{CAD}	2.40	1.33-4.31	**0.003**

P value for logistic regression. C (referring to the reverse strand) represents the risk allele for rs11053646; n = 665. Bold type indicates *P* values ≤ 0.05.

BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; GRS, genetic risk score; HDL-C, high-density lipoprotein cholesterol; MFHS, Montreal-FH-SCORE; OR, odds ratio.

* Included age, sex, BMI, hypertension, diabetes, smoking, previous statin drug use, total cholesterol, HDL-C, and triglycerides.

The negative impact that carrying the C allele has on CAD risk is similar in both sexes but is more pronounced in smokers as well as in younger patients with FH. Subgroup analysis according to sex, age, and smoking status is presented in Table 3.

After stratification according to sex, carrying the C allele predicted CAD in women (OR, 2.12; 95% CI, 1.14-3.93; *P* = 0.02) but not in men (OR, 1.55; 95% CI, 0.74-3.28; *P* = 0.25) in an uncorrected model, whereas this association was significant in both women (OR, 2.52; 95% CI, 1.08-5.91; *P* = 0.03) and men (OR, 5.05; 95% CI, 1.89-13.48; *P* = 0.001) after correction for cardiovascular risk factors. When stratifying for age (older or younger than the median value of 39 years), carrying the C allele was strongly associated with CAD risk in the younger group (OR, 8.73; 95% CI, 3.38-22.57; *P* = 0.000008), whereas no association was seen in the older group (OR, 1.90; 95% CI, 0.83-4.32; *P* = 0.13) (*P* value is for the model corrected for cardiovascular risk factors). Finally, in the individuals who smoked (previous or current smokers), the presence of a C allele showed a significant association with CAD risk (OR, 4.87; 95% CI, 2.10-11.28; *P* = 0.0002), whereas no association was observed among the nonsmokers (OR, 2.12; 95% CI, 0.73-6.16; *P* = 0.17) (*P* value id for the model corrected for cardiovascular risk factors).

Discussion

Because of the lifelong burden of circulating LDL-C accumulation, patients with FH are strongly predisposed to premature CVD. Recent studies have identified several common genetic variants associated with cardiovascular risk, even in the context of this severe monogenic disease.[9-12] To our knowledge, this is the first study to report the association between the rs11053646 SNP (K167N) of the *OLR1* gene

Table 3. Subgroup analysis for CAD frequency according to the rs11053646 genotype

Models	OR	95% CI	*P* value
Women (n = 381)			
Uncorrected	2.12	1.14-3.93	**0.02**
Corrected for age	2.24	1.06-4.74	**0.04**
Corrected for all*	2.52	1.08-5.91	**0.03**
Men (n = 284)			
Uncorrected	1.55	0.74-3.28	0.25
Corrected for age	3.06	1.27-7.37	**0.01**
Corrected for all*	5.05	1.89-13.48	**0.001**
≤ 39 y (n = 344)			
Uncorrected	4.01	1.99-8.09	**0.0001**
Corrected for sex	4.37	2.09-9.15	**0.00009**
Corrected for all†	8.73	3.38-22.57	**0.000008**
> 39 y (n = 313)			
Uncorrected	1.29	0.63-2.65	0.48
Corrected for sex	1.68	0.80-3.54	0.17
Corrected for all†	1.90	0.83-4.32	0.13
Smokers (n = 429)			
Uncorrected	1.98	1.09-3.61	**0.03**
Corrected for age and sex	3.64	1.73-7.68	**0.001**
Corrected for all‡	4.87	2.10-11.28	**0.0002**
Nonsmokers (n = 236)			
Uncorrected	1.49	0.68-3.25	0.32
Corrected for age and sex	2.37	0.84-6.75	0.11
Corrected for all‡	2.12	0.73-6.16	0.17

P value for logistic regression. C (referring to the reverse strand) represents the risk allele for rs11053646. Bold type indicates *P* values ≤ 0.05.

BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; OR, odds ratio.

* Included age, BMI, hypertension, diabetes, smoking, previous statin drug use, total cholesterol, HDL-C, and triglycerides.

† Included sex, BMI, hypertension, diabetes, smoking, previous statin drug use, total cholesterol, HDL-C, and triglycerides.

‡ Included age, sex, BMI, hypertension, diabetes, previous statin drug use, total cholesterol, HDL-C, and triglycerides.

and CAD susceptibility in patients with FH. We demonstrated that carrying the C allele (amino acid N) significantly increased the risk of CAD in this cohort comprising 665 heterozygous adult patients with FH. This association remained significant even after corrections for other CVD risk predictors such as the Montreal-FH-SCORE or a polygenic risk score for CAD.[8,9] Discordant results have been reported concerning the association between the K167N variant and cardiovascular risk in the general population. However, several studies reported similar results, showing that carrying the risk allele of this SNP is significantly associated with the risk of myocardial infarction,[20] ischemic stroke,[28,29] intima media thickness,[30] and carotid plaque.[31]

In this French Canadian cohort of patients with FH, we found that 12.9% were heterozygous carriers of the K167N variant, whereas the rest of the cohort (87.1%) were noncarriers. This prevalence is similar but slightly lower than previously reported in the study of Brinkley et al.,[32] in which the GG (wild type) and GC (heterozygous) genotypes were 79% and 21%, respectively, in a multiethnic cohort. These results are also consistent with the study of Mango et al.,[33] who found that 12% of participants were GC carriers in a white cohort.[33]

The mechanism by which carrying the K167N variant leads to a less favourable CAD outcome is not understood. It has been shown that the LOX-1 receptor can be cleaved through some serine proteases and released in the circulation in a soluble form of the molecule (sLOX1).[34,35] Previous work suggests that serum sLOX1 would be a marker of atherosclerotic plaque instability and that the level of sLOX1 in blood may begin to rise even before the occurrence of a cardiovascular event.[36] A study from Brinkley et al.[32] in a population of 97 healthy older men and women demonstrated that plasma sLOX1 was significantly higher in K167N carriers (GC) than in noncarriers ($P = 0.004$), independent of age, sex, ethnic group, and BMI.[32] Also, the presence of CC LOX1 receptors has been associated with an increased inflammatory profile in macrophages.[30] Further mechanistic studies are needed to clarify the mechanisms by which this variant exerts a deleterious effect in patients with FH.

In the subgroup analysis, we found that the negative impact that carrying the risk allele C has on CAD risk is more pronounced in smokers as well as in younger patients with FH (< 40 years). Indeed, the LOX1 receptor would be implicated in early atherosclerotic lesions, because the formation of foamy macrophages is 1 of the first steps in the formation of atherosclerotic plaque.[17] Cigarette smoking is associated with increased oxidative stress and oxLDL generation,[37] particularly in the presence of hypercholesterolemia.[38] However, the exact mechanism by which smoking status is more deleterious in the GC genotype than in the GG genotype remains to be elucidated.

Strengths of our study include the fact that all lipid profiles were collected without any lipid-lowering treatment after a 4-week washout period and were measured using the reference method. Also, our FH cohort was homogeneous because all patients were white and carried a classic French Canadian *LDLR* mutation, which reduces the phenotype variability.

Limitations of our study include the fact that plasma or serum samples were not available for the measurement of circulating oxLDL or sLOX1 levels. Furthermore, the limited number of FH-causing mutations may decrease the generalizability of these results to other FH populations.

Conclusions

Carrying the C allele of the rs11053646 variant of the *OLR1* gene greatly increased CAD risk in heterozygous adult patients with FH, especially in smokers as well as in younger patients with FH. These results suggest that genetic screening for this SNP could help identify patients with FH who could benefit from more intensive CVD prevention. Further studies would be required to understand the underlying mechanism explaining the association between K167N and the increased CAD risk.

Acknowledgements

The authors want to thank Dr Jean Davignon, who created this large database of patients with FH over the time of his career in lipidology.

Funding Sources

This work was supported by The Fondation Leducq Transatlantic Networks of Excellence (Grant No. 13CVD03) and AMGEN Canada.

Disclosures

A.B. and R.D. received research grants from Merck Frosst, Amgen, Astra Zeneca, CIHR, and the Fondation Leducq. They have participated in clinical research protocols from Pfizer, Regeneron Pharmaceuticals, the Medecines Company, Amgen, Acasti Pharma, Novartis, Sanofi, Ionis Pharmaceuticals, AstraZeneca, and Merck Frosst. Both have served on advisory boards for Amgen and Sanofi and have received honoraria for symposia from Amgen and Sanofi. P.Q. has no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2017.07.480.