Chapitre 5 La contribution des niveaux de PCSK9 à la sévérité phénotypique de l'hypercholestérolémie familiale est indépendante du génotype du récepteur LDL

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The contribution of PCSK9 levels to the phenotypic severity of familial hypercholesterolemia is independent of LDL receptor genotype

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Résumé

L'HF est causée par des mutations génétiques dans le R-LDL, l'apo B ou la PCSK9. Bien qu'il ait été montré que les concentrations de PCSK9 sont corrélées avec les niveaux de C-LDL dans l'HF, la mesure dans laquelle les niveaux de PCSK9 modulent la sévérité phénotypique de cette maladie, et ce, indépendamment du génotype du R-LDL, reste à clarifier.

Objectif : Évaluer les associations entre le génotype du R-LDL et les concentrations plasmatiques de PCSK9, C-LDL et de Lp(a) dans une grande cohorte de patients avec HFHe génétiquement définie.

Méthodes : Un total de 292 sujets avec HFHe porteurs d'une des 9 mutations canadiennes-françaises dans le gène du R-LDL ont été recrutés. La cohorte comprenait 226 sujets porteurs d'une mutation récepteur-nul (RN) et 66 sujets porteurs d'une mutation récepteur-défectueux (RD). Des sujets contrôles (n=56) appariés aux sujets avec HFHe pour le sexe et l'indice de masse corporelle ont aussi été recrutés.

Résultats : Les concentrations de PCSK9 étaient plus élevées chez les sujets avec HFHe que chez les sujets contrôles (318 ± 107 ng/mL *vs* 203 ± 60 ng/mL ; $P<0,0001$). La force de l'association entre les niveaux de PCSK9 et de C-LDL était similaire entre les contrôles (r=0,37 ; $P=0,005$) et les sujets avec HFHe (r=0,31 ; $P<0,0001$). Une analyse de régression linéaire multiple a révélé que la corrélation positive entre les niveaux de PCSK9 et de C-LDL demeurait significative après ajustement pour le génotype du R-LDL dans le groupe avec HFHe.

Conclusion : Ces résultats suggèrent que la contribution des niveaux de PCSK9 à la sévérité phénotypique de l'HFHe est indépendante du génotype du R-LDL.

Title page

The contribution of PCSK9 levels to the phenotypic severity of familial hypercholesterolemia is independent of LDL receptor genotype

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Abbreviations

ApoB: apolipoprotein B;

BMI: body mass index;

CAD: coronary artery disease;

DR: defective-receptor;

EGF(A): epidermal growth factor precursor homology domain A;

FH: familial hypercholesterolemia;

HDL-C: HDL-cholesterol;

HeFH: FH heterozygotes;

LDL-C: LDL-cholesterol;

LDLR: LDL receptor;

Lp(a): Lipoprotein (a);

NR: negative-receptor;

PCR: polymerase-chain reaction;

PCSK9: proprotein convertase subtilisin/kexin type 9;

TG: triglyceride.

Abstract

Autosomal dominant familial hypercholesterolemia (FH) is caused by genetic mutations in the LDL receptor (LDLR), its ligand apolipoprotein (apo) B, or proprotein convertase subtilisin/kexin type 9 (PCSK9). Although PCSK9 levels have been shown to correlate with LDL-cholesterol (LDL-C) levels in FH, the extent to which PCSK9 levels modulate the phenotypic severity of this disease independent of LDLR genotype remains to be clarified.

Objective: To assess the relationship between LDLR genotype and the plasma levels of PCSK9, LDL-C, and lipoprotein (a) (Lp(a)) in a large cohort of genetically defined FH heterozygotes (HeFH).

Methods: A total of 292 HeFH carrying one of the nine French-Canadian mutations in the LDLR gene were recruited. The cohort included 226 carriers of a negative-receptor (NR) mutation and 66 carriers of a defective-receptor (DR) LDLR gene mutation. Fifty-six control subjects, who were matched with the HeFH subjects based on gender and body mass index, were also recruited.

Results: PCSK9 levels were higher in the HeFH group than in the control group (317.9 ± 107.1 ng/ml vs. 203.3 ± 59.8 ng/ml; $P<0.0001$). The strength of the association between PCSK9 and LDL-C levels was similar among controls ($r=0.37$; $P=0.005$) and HeFH ($r=0.31$; $P<0.0001$). Furthermore, a multiple linear regression analysis revealed that the positive correlation between PCSK9 and LDL-C levels remained significant after adjusting for LDLR genotype in the HeFH group.

Conclusion: These results suggested that the contribution of PCSK9 levels to the phenotypic severity in FH heterozygotes is independent of LDLR genotype.

Keywords: PCSK9, familial hypercholesterolemia, LDL-cholesterol.

Introduction

Autosomal dominant familial hypercholesterolemia (FH) is caused by genetic mutations in the LDL receptor (LDLR), its ligand apolipoprotein (apo) B, or proprotein convertase subtilisin/kexin type 9 (PCSK9).[1,2] Mutations in the LDLR gene disrupt the normal clearance of LDL particles from the plasma, causing a marked increase in LDL-cholesterol (LDL-C) levels.[1] Atherosclerotic coronary artery disease (CAD) usually occurs between the age of 35 and 55 years in untreated FH heterozygotes (HeFH).[3] The LDLR mutations have been classified based on biosynthetic and functional studies in fibroblasts derived from skin biopsy specimens.[4] Negative-receptor (NR) mutations are associated with <2% of the normal LDLR allele activity, whereas defective-receptor (DR) mutations exhibit between 2 and 30% of the normal allele activity.[4] In HeFH subjects who possess a single functional LDLR allele, the ability of LDLR to bind LDL particles is reduced by 20 to 50% compared with non-FH subjects. Previous studies have shown that CAD occurs earlier in HeFH carrying NR mutations compared with HeFH carrying DR variants.[5] In the Province of Quebec (Canada), nine mutations are responsible for 90% of the HeFH cases, as defined based on clinical and biochemical criteria.[6, 7]

PCSK9 is the ninth member of the proprotein convertase family[8] and is predominantly expressed in the liver, small intestine and kidneys.[9] Mechanistic studies have shown that PCSK9 interacts with the epidermal growth factor precursor homology domain A (EGF(A)) of LDLR at the cell surface and promotes its intracellular lysosomal degradation.[8, 10] High levels of PCSK9 decrease the LDLR density on the cell surface and therefore reduce LDL-C clearance, leading to an accumulation of LDL particles in the plasma.[11] LDL-C levels and PCSK9 levels are positively correlated in non-FH and untreated FH subjects,[12-15] and previous studies have shown that PCSK9 levels are higher in HeFH than in non-FH controls.[13-16] Although a recent report from a South African group suggested that the detrimental effect of PCSK9 levels on the FH phenotype is independent of LDLR genotype,[15] it is unclear whether this observation also applies to other FH groups.

Therefore, the primary objective of this study was to examine the extent to which LDLR genotype modulates the relationship between LDL-C and PCSK9 levels in a large French-Canadian cohort of genetically defined HeFH subjects. We also examined the relationship between PCSK9 levels and lipoprotein (a) (Lp(a)) levels in FH because hepatic apoB synthesis and secretion have been shown to be modulated by PCSK9.[17] We hypothesized that the relationship between PCSK9 and LDL-C levels in FH heterozygotes would be dependent on LDLR genotype.

Methods

Population

A total of 292 HeFH (133 men and 159 women) and 56 control subjects, matched as a group for gender and body mass index (BMI), were recruited in the Quebec City area to participate in the study. All eligible subjects were required to discontinue their use of lipid-lowering medications for at least 6 weeks before blood sample collection. Subjects with a previous history of cardiovascular disease, acute liver disease, hepatic dysfunction, persistent elevations of serum transaminases, secondary hyperlipidemia due to any cause, a recent history of alcohol or drug abuse, diabetes mellitus, a history of cancer or any other conditions that may interfere with optimal participation in the study were ineligible.

All the HeFH subjects were carriers of one of the nine previously identified French-Canadian mutations in the LDLR gene.[6] Of the 292 HeFH subjects that were included in the study, 183 had the >15 kb deletion at the 5' end of the gene,[3] 57 had the W66G mutation in exon 3,[18] 24 had the C646Y mutation in exon 14,[4] 17 had the Y468X mutation in exon 10,[19] 4 had the C347R mutation in exon 8,[6] 3 had the E207K mutation in exon 4,[4] 1 had the C152W mutation in exon 4,[6] 1 had the R329X mutation in exon 7,[6] and 2 had the 5 kb deletion in exons 2 and 3.[4] The >15 kb deletion and the R329X, Y468X and C646Y point mutations were considered to be NR mutations because the receptor encoded by these alleles exhibits <2% of the normal activity. The 5 kb deletion and the C152W, C347R, E207K and W66G point mutations were considered to be DR mutations because the receptor encoded by these alleles exhibits 2% to 30% of the normal activity.

The study was approved by the Laval University Medical Center ethical review committee, and informed consent was obtained from each patient. This trial was registered at clinicaltrials.gov as NCT02225340.

DNA analysis

All the FH patients were screened for nine mutations in the LDLR gene using genomic DNA; the two deletions were analyzed by Southern blotting,[20] and seven point mutations were analyzed by restriction enzyme fragment analysis.[6, 19] Genotyping of apoE was performed by PCR amplification of a 244 bp fragment of exon 4 of the apoE gene with oligonucleotides F4 and F6 and digestion of the resulting PCR fragments with the restriction enzyme Hhal.[21]

Plasma lipids, lipoproteins and apoproteins

Blood samples were collected after a 12-hour fast in tubes containing disodium EDTA (Na_2EDTA) and benzamidine (0.03%).[22] The samples were then immediately centrifuged at 4°C for 10 min at 3000 rpm to obtain plasma, which was stored at 4°C and processed within 5 days. Cholesterol and

triglyceride (TG) levels were determined in the plasma and lipoprotein fractions by enzymatic methods (Randox Co., Crumlin, UK) using an RA-500 analyzer (Bayer Corporation Inc., Tarrytown, NY) as previously described.[23] Plasma VLDL (d < 1.006/mL) was isolated by preparative ultracentrifugation, and the HDL fraction was obtained after precipitation of LDL in the infranatant (d > 1.006 g/mL) using heparin and MnCl. The cholesterol and TG content of the infranatant fraction was measured before and after the precipitation step to obtain the LDL-C level. Plasma apoB levels were measured using a Behring Nephelometer BN-100 (Behring Diagnostic, Westwood, MA) with reagents and calibrators (Dade Behring, Mississauga, ON) provided by the manufacturer.

Measurement of plasma PCSK9 and Lp(a) levels

Commercial ELISA kits were used to measure plasma PCSK9 levels (Circulex, CycLex Co, Nagano, Japan)[24] and Lp(a) levels (ALPCO Diagnostics, Salem, NH, US). The intra-assay coefficients of variation for the PCSK9 and Lp(a) measurements were estimated at 1.5 and 4%, respectively.

Statistical analysis

Comparisons between different groups were calculated using ANOVA and Student's t-test. A multiple regression linear analysis was performed to evaluate the independent contribution of PCSK9 to LDL-C variability after adjusting for age, LDLR mutation and BMI. Plasma PCSK9 levels were log-transformed to normalize their distribution. Spearman's correlation was used to assess the relationship between PCSK9 and Lp(a) levels. Differences with $P \leq 0.05$ were considered to be statistically significant. All the statistical analyses were performed using JMP software v10.0.0.

Results

The demographic, anthropometric and genotypic characteristics of the 292 HeFH (133 men and 159 women) and the 56 control subjects (28 men and 28 women) are presented in **Table 1**. The mean age was significantly higher in the control group than in the HeFH group (38.8 ± 13.0 y vs. 34.9 ± 13.2 y; P=0.04). The two groups had a similar gender distribution and a similar BMI (24.1 ± 2.1 kg/m^2 vs. 24.6 ± 4.2 kg/m^2; P=0.37). In the HeFH group, the >15 kb deletion at the 5' end of the gene and the W66G missense mutation in exon 3 were the most common mutations, representing 82.5% of all mutated alleles. Two hundred and twenty-six HeFH were carriers of a NR mutation, and 66 HeFH were carriers of a DR mutation. The distribution of apoE genotypes was similar among the NR and DR groups (data not shown).

The biochemical characteristics of the controls and HeFH are presented in **Table 2**. Compared with controls, HeFH had higher total cholesterol levels (+74%; P<0.0001), TG levels (+50%; P=0.001), LDL-C levels (+120%; P<0.0001), plasma apoB levels (+104%; P<0.0001), and PCSK9 levels (+56%; P<0.0001) as well as lower HDL-C levels (-24%; P<0.0001). The Lp(a) concentrations were not significantly different between the two groups. As illustrated in **Figure 1**, the LDL-C concentration

was significantly correlated with PCSK9 levels in both HeFH (r=0.31; *P*<0.0001) and controls (r=0.37; *P*=0.005).

The potential independent association of PCSK9 levels with the variability in LDL-C concentration among HeFH was assessed using multiple linear regression analysis. As shown in **Table 3**, age and PCSK9 levels were the most important predictors of LDL-C variance in HeFH, representing 13.6 and 8.1% of the total variance, respectively; furthermore, the type of LDLR mutation (DR vs. NR) and BMI accounted for 3.9 and 1.8% of the LDL-C variance, respectively. Interestingly, PCSK9 levels also significantly predicted LDL-C levels in the whole cohort (*P*<0.0001) independent of age, BMI, and the FH/control status and accounted for 5.2% of the LDL-C variance.

PCSK9 levels were significantly higher in HeFH than in controls (317.9 ± 107.1 vs. 203.3 ± 59.8 ng/mL; +56.4%; *P*<0.0001) (**Figure 2A**). NR carriers had significantly higher LDL-C levels than DR carriers (6.48 ± 1.59 mmol/L vs. 5.97 ± 1.44 mmol/L; +8.5%; *P*=0.02), but PCSK9 levels were not significantly different between these two groups (314.5 ± 107.7 ng/mL and 329.7 ± 105.0 ng/mL; *P*=0.31) (**Figure 2B**). The concentrations of Lp(a) and total apoB were positively correlated with PCSK9 levels in HeFH (Lp(a): r=0.14, *P*=0.01; apoB: r=0.35, *P*<0.0001) (**Figure 3**). Total apoB concentrations were positively correlated with PCSK9 levels in controls (r=0.40; *P*=0.002).

Discussion

The present study examined the extent to which PCSK9 levels correlated with LDL-C levels and LDLR genotype in a large cohort of genetically defined FH heterozygotes. Compared with non-FH controls, HeFH had higher plasma levels of LDL-C, TG, and apoB, whereas HDL-C levels were significantly lower in HeFH. No significant differences were observed in the plasma Lp(a) concentration between the two groups. Moreover, HeFH had an elevated plasma PCSK9 concentration compared with controls, and significant positive correlations were identified between the plasma levels of LDL-C, apoB and PCSK9 in the HeFH group. Plasma PCSK9 levels were also significantly higher in HeFH than in controls, but there were no differences in PCSK9 levels between NR and DR carriers in our cohort. PCSK9 levels among HeFH were associated with variations in LDL-C concentration independent of LDLR genotype, age, and BMI. Finally, we found a positive correlation between Lp(a) and PCSK9 levels in HeFH, suggesting that PCSK9 plays an important role in Lp(a) metabolism.

Previous studies have shown that plasma PCSK9 levels are higher in untreated FH subjects than in non-FH subjects.[13-15] Plasma PCSK9 levels are also positively correlated with LDL-C concentration in untreated heterozygous and homozygous FH subjects and in non-FH subjects,[12-16] a finding that is consistent with the results of the present study. In fact, PCSK9 has been shown to interact with the LDLR, thereby decreasing the LDLR density on the cell surface and ultimately reducing LDL-C

clearance; this leads to an accumulation of LDL particles in the plasma.[11, 25, 26] In agreement with previous studies,[14, 15] our results showed that because of its stimulatory effect on LDLR catabolism, high PCSK9 levels represent an independent contributing factor to the elevated LDL-C levels in FH heterozygotes, and this may contribute to the phenotypic severity of this disorder.

The impact of the LDLR genotype on plasma PCSK9 levels was also assessed in the present study. Previous studies have shown that the EGF(A) of the LDLR is critical for PCSK9 binding at the cell surface.[27] Therefore, any LDLR mutation that disrupts the EGF(A) could result in diminished binding and decreased clearance of PCSK9 via LDLR, leading to elevated plasma PCSK9 levels. Our results showed that plasma PCSK9 levels were significantly higher in HeFH compared with non-FH controls, a finding that supports the concept that LDLR plays a crucial role in PCSK9 clearance. However, there were no significant differences in PCSK9 levels between carriers of a NR mutation and carriers of a DR mutation, in whom EGF(A) integrity is preserved. Our data are consistent with those reported in previous studies that showed that HeFH patients carrying negative or defective LDLR defects had similar PCSK9 levels.[15] These results suggest that NR and DR carriers maintain a similar capacity to remove PCSK9 from the circulation either via the fully functional LDLR or via alternative LDLR-independent pathways, as has been suggested in previous reports.[28] The presence of a normal LDLR allele in HeFH could also offer some level of compensation, which may differ depending on the function of the mutated allele. Supporting *in vitro* studies are required to assess the variability in the uptake of LDL particles and PCSK9 based on LDLR functionality.

Our study demonstrated that PCSK9 levels had a greater impact on LDL-C variability than did LDLR genotype and BMI, with independent contributions of 8.1%, 3.9%, and 1.8%, respectively. The only factor with a greater impact on LDL-C concentration than PCSK9 levels was age. Our results are consistent with the analysis of the large multiethnic Dallas Heart study cohort,[29] in which PCSK9 levels were correlated with LDL-C concentration but accounted for less than 8% of the variance in LDL-C levels. These findings also support the concept that the impact of PCSK9 levels on plasma LDL-C levels is independent of the functionality of the LDLR mutation.

In the present study, a large variability in PCSK9 concentration, ranging from 119 to 757 ng/mL, was observed among HeFH. In the Dallas Heart Study cohort, 22% of the PCSK9 variability was explained by gender, LDL-C and TG levels, statin use, BMI and fasting glucose.[29] Mutations in the PCSK9 gene affect functionality and the plasma levels of its cognate protein. Subjects with gain-of-function mutations have higher plasma PCSK9 levels and higher plasma LDL-C levels,[26] whereas mutations causing a defective PCSK9 decrease the LDL-C concentration and CVD risk in non-FH subjects.[30, 31] Among the PCSK9 loss-of-function variants, R46L is the most prevalent and affects nearly 1/50 individuals.[31-33] This mutation is associated with decreased PCSK9 levels, LDL-C concentrations and CAD risk[29, 31] in non-FH subjects. A recent study by Saavedra *et al*.[34] showed that HeFH carrying the

R46L had lower LDL-C levels and a reduced CVD risk compared with non-carriers. In the Dallas Heart Study cohort, the addition of the variant R46L in the linear model predicting PCSK9 levels only slightly increased by 1% the predictive value of the model.[29] These findings suggest that PCSK9 genetic variants are likely to have a limited impact on variability of PCSK9 and LDL-C levels in our cohort.

Finally, significant positive correlations were found between the levels of Lp(a), apoB and PCSK9. A recent study by Alonso *et al*. suggested that Lp(a) levels are a significant predictor of CVD independent of the functionality of the LDLR mutation in HeFH.[35] It has been shown that PCSK9 impacts the synthesis of Lp(a) via apoB-100 synthesis. Experiments in mice showed that PCSK9 is a determinant of hepatic apoB synthesis by inhibiting the intracellular degradation of newly synthesized apoB and therefore increasing plasma apoB levels.[17, 36] In support of these findings, lomitapide, which inhibits microsomal triglyceride transfer protein and therefore blocks the assembly of apoB-containing particles, reduced Lp(a) levels by 15%.[37] AMG-145, an antibody against PCSK9, also causes a significant decrease in apoB and Lp(a) levels.[38] Therefore, the presence of a significant positive correlation between Lp(a) and PCSK9 levels in HeFH supports the hypothesis that Lp(a) production may be modulated by plasma PCSK9 levels.

This study encompasses several strengths and limitations. The large number of genetically defined FH subjects in the present study is one of the major strengths and increases our statistical power. In addition, the case-control design allowed us to compare the associations between PCSK9, Lp(a) and LDL-C between FH and non-FH control subjects. Data on circulating PCSK9 and lipid levels are presented on only a single blood sample, however, given that lipid profiles naturally experience day-to-day fluctuations, a better estimation would have been achieved via repeated sampling and calculations of means. Finally, we also stress that the association between PCSK9 and LDLR genotype is limited by the relatively small sample size of DR subjects and these will need to be replicated in studies with more subjects.

Conclusion

In summary, these findings confirmed the importance of PCSK9 as a determinant of LDL-C and Lp(a) levels in HeFH. PCSK9 levels had a greater impact on the variability in LDL-C concentration than did the functionality of the LDLR mutation in HeFH. Our results also suggested that the contribution of PCSK9 levels to the phenotypic severity in FH heterozygotes is independent of LDLR genotype.

Author contributions

All of the authors read and approved the final manuscript. PC, TCO and BL designed the research; AJT and JCH conducted the research; JPDC, PC, TCO, BL, and AJT analyzed the data; JPDC, PC, TCO, AJT, and BL wrote the paper; and PC had primary responsibility for the final content. The authors report no conflicts of interest related to this study.

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Tables

Table 5-1 Characteristics of the subjects

	Controls	**HeFH**	**Δ**	***P***
Subjects	56	292		
Age, years	38.8 ± 13.0	34.9 ± 13.2	-3.9	0.04
Sex				
Men, (%)	28 (50.0)	133 (46.0)	-4.0	0.54
Women, (%)	28 (50.0)	159 (54.0)	+4.0	0.54
BMI, kg/m^2	24.1 ± 2.1	24.6 ± 4.2	+0.5	0.37
Mutation				
Del15, (%)	-	183 (62.7)	-	-
W66G, (%)	-	57 (19.5)	-	-
C646Y, (%)	-	24 (8.2)	-	-
Y468X, (%)	-	17 (5.8)	-	-
C347R, (%)	-	4 (1.4)	-	-
Del5, (%)	-	2 (0.7)	-	-
E207K, (%)	-	3 (1.0)	-	-
R329X, (%)	-	1 (0.3)	-	-
C152W, (%)	-	1 (0.3)	-	-

Mean ± standard deviation. Percentages are indicated in parentheses. Δ represents the difference between HeFH and controls.

Table 5-2 Biochemical characteristics of the controls and HeFH

	Controls	**HeFH**	**Δ (%)**	***P***
Total cholesterol, mmol/L	4.65 ± 0.85	8.09 ± 1.70	+74	<0.001
Triglycerides, mmol/L	1.07 ± 0.62	1.57 ± 1.09	+50	0.001
LDL-C, mmol/L	2.90 ± 0.75	6.37 ± 1.57	+120	<0.001
HDL-C, mmol/L	1.40 ± 0.35	1.07 ± 0.29	-24	<0.001
ApoB, g/L	0.85 ± 0.22	1.73 ± 0.37	+104	<0.0001
PCSK9, ng/mL	203.3 ± 59.8	317.9 ± 107.1	+56	<0.0001
Lp(a), mg/dL	21.5 ± 19.7	23.3 ± 20.2	+8	0.54

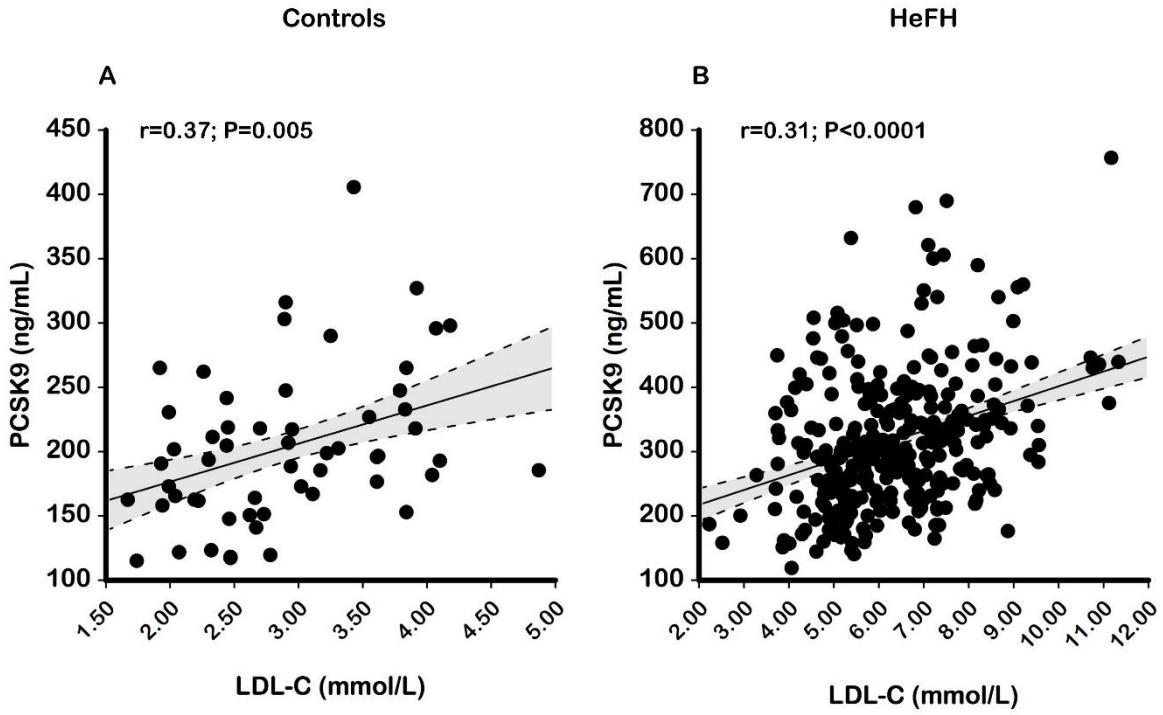
Mean ± standard deviation. Δ (%) represents the percent difference between the HeFH and controls.

Table 5-3 Multiple linear regression analysis showing the independent contribution of various factors to LDL-C variability in 292 FH heterozygotes

Independent variables	**Partial (R^2 x 100)**	***P***
Age	13.6	<0.0001
PCSK9 level	8.1	<0.0001
LDLR mutation	3.9	0.0008
BMI	1.8	0.02
Gender	0.0	0.95
Total	27.4	<0.001

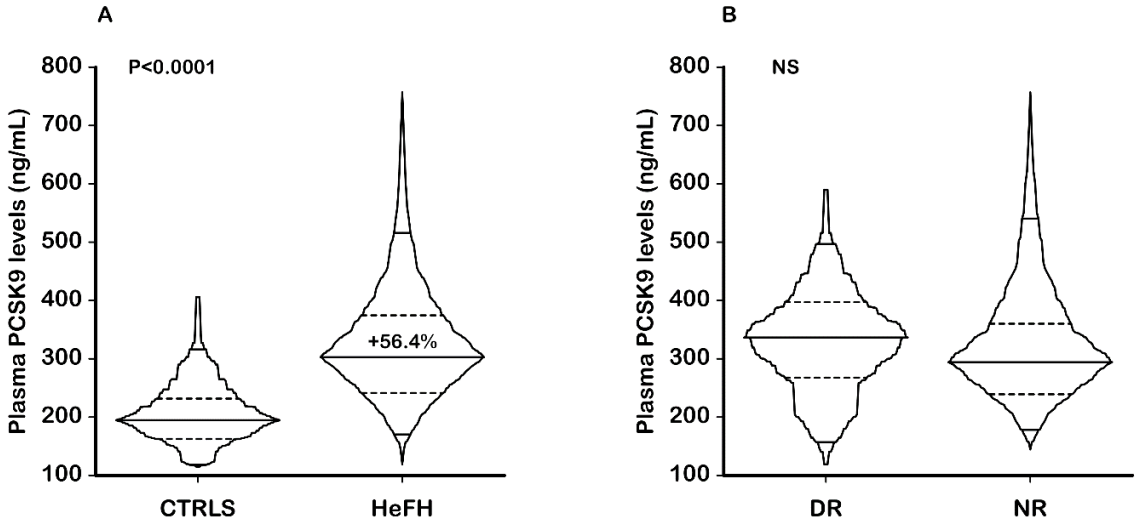
Figures

Figure 5-1 Correlation between PCSK9 and LDL-C levels in controls (A) and HeFH (B)



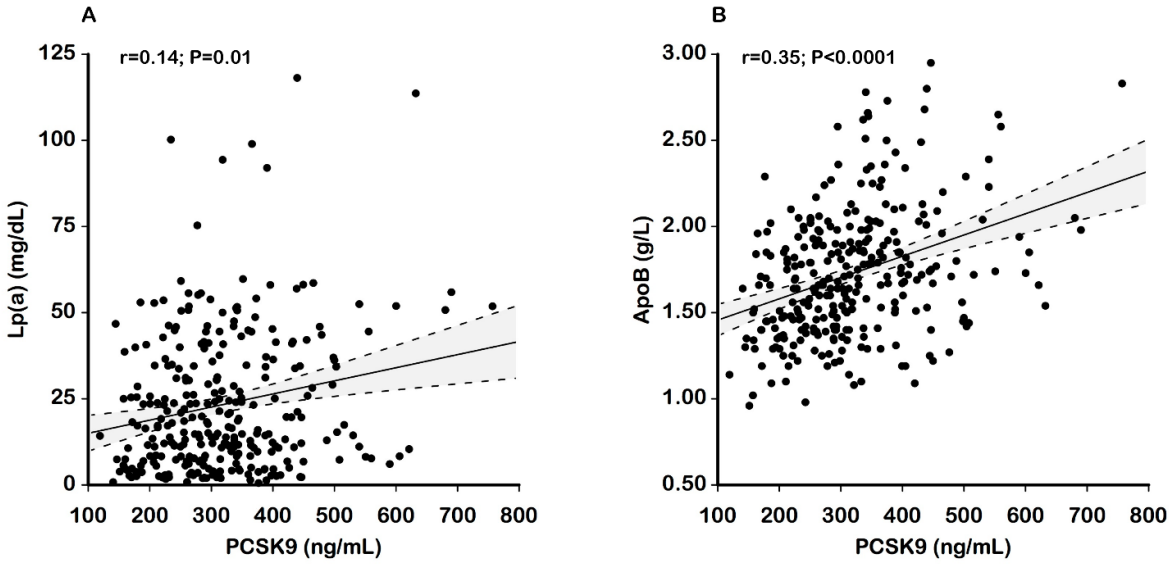
Correlation between PCSK9 and LDL-C levels in controls (A) and HeFH (B). The dotted lines indicate the 95% confidence intervals for the regression line. LDL-C: LDL-cholesterol; PCSK9: proprotein convertase subtilisin/kexin type 9.

Figure 5-2 Distribution of plasma PCSK9 levels in the HeFH and control groups (panel A). Distribution of plasma PCSK9 levels according to the functionality of the LDL receptor mutation in FH heterozygotes (panel B)



Panel A: Distribution of plasma PCSK9 levels in the HeFH and control groups. Panel B: Distribution of plasma PCSK9 levels according to the functionality of the LDL receptor mutation in FH heterozygotes. The line through the center of each Gaussian box-percentile is the group median. The dotted lines within each box indicate the 25th and 75th percentiles, and the small solid lines indicate the 10th and 90th percentiles. PCSK9: proprotein convertase subtilisin/kexin type 9; CTRLS: control subjects; HeFH: FH heterozygotes; NR: negative LDL receptor gene mutation; DR: defective LDL receptor gene mutation.

Figure 5-3 Correlations between Lp(a) levels (panel A), plasma apoB levels (panel B), and PCSK9 levels in HeFH



Correlations between Lp(a) levels (panel A), plasma apoB levels (panel B), and PCSK9 levels in HeFH. The dotted lines indicate the 95% confidence intervals for the regression lines. Lp(a): lipoprotein (a); apoB: apolipoprotein B; PCSK9: proprotein convertase subtilisin/kexin type 9.