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Original Research Article

PCSK9 rs11591147 polymorphism and response to atorvastatin in patients with type 2 diabetes mellitus and/or hypertension

Smita Tripathi^{1*}, Ghan Shyam Pangtey², Animesh Ray³, Subhradip Karmakar⁴

¹Department of Biochemistry, Lady Hardinge Medical College, New Delhi, India

²Department of Medicine, Lady Hardinge Medical College, New Delhi, India

³Department of Medicine, AIIMS, Delhi, India

⁴Department of Biochemistry, AIIMS, Delhi, India

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*Correspondence:

Dr. Smita Tripathi,

Email: smitatripathi@rediffmail.com

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ABSTRACT

Background: The loss-of-function (LOF) variant rs11591147 of PCSK9 reduces PCSK9 activity and is expected to lower low-density lipoprotein cholesterol (LDL-C) and improve the response to statins, meaning a greater LDL-C reduction. However, studies are few and inconsistent. This study explored the association of the LOF variant with baseline lipid levels and the response to atorvastatin in statin-naïve patients.

Methods: Eligible patients with type 2 diabetes mellitus and/or hypertension from two tertiary care hospitals in Delhi (n=260) received atorvastatin for 10–12 weeks. The PCSK9 rs11591147 polymorphism was studied by PCR-restriction fragment length polymorphism (PCR-RFLP) and the lipid profile, including LDL-C, was measured before and after treatment.

Results: The frequency of the LOF T allele was 16.5%, with genotype frequencies of GG 66.9%, GT 33.1% and TT 0%. Baseline LDL-C was similar in both groups (GG 136.04±43.89 vs. GT 134.79±41.38 mg/dl; p=0.813), as was the percentage fall in LDL-C after atorvastatin (GG 28.7% vs. GT 26.9%; p=0.386). Genotype distribution deviated from Hardy–Weinberg equilibrium (p=0.001).

Conclusions: In this North Indian cohort, the LOF T allele was not associated with baseline LDL-C or with the response to atorvastatin. Larger studies, including TT homozygotes, are needed to confirm these findings.

Keywords: Allele, Atorvastatin, Loss of function, LDL-C, PCR-RFLP, PCSK9, SNP, Statins

INTRODUCTION

Proprotein convertase subtilisin/kexin type 9 (PCSK9), identified in 2003, is a key regulator of LDL-C metabolism through its role in the degradation of the low-density lipoprotein receptor (LDLR).¹ PCSK9 binds to the epidermal growth factor-like repeat A (EGF-A) domain of the LDLR. This prevents the receptor from recycling to the hepatocyte surface and directs it to lysosomal degradation, which reduces the number of LDLRs on hepatocytes and thereby increases circulating LDL-C.² The PCSK9 gene, located on chromosome 1p32.3, is highly polymorphic. Its

variants are classified as gain-of-function (GOF) or LOF, depending on their effect on PCSK9 activity. The rs11591147 variant (R46L; exon 1) is a well-characterized LOF variant that reduces PCSK9 activity and increases LDLR-mediated clearance of LDL-C.² Its frequency and effects differ considerably among populations, reflecting ethnic and genetic diversity in lipid metabolism.^{3–5} Statins remain the cornerstone of lipid-lowering therapy for the prevention of cardiovascular disease.⁶ Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, thereby reducing hepatic cholesterol synthesis. The resulting decrease in intracellular cholesterol activates

sterol regulatory element-binding protein 2 (SREBP-2), which upregulates both LDLR and PCSK9. While increased LDLR expression enhances plasma LDL-C clearance, PCSK9 promotes LDLR degradation, potentially attenuating the lipid-lowering effect of statins.^{7,8} This counter-regulatory mechanism may contribute to variability in LDL-C response to statin therapy.

A meta-analysis suggests that PCSK9 rs11591147 polymorphism is associated with differences in lipid levels and cardiovascular disease risk, although the size of the effect varies across populations.⁹ Pharmacogenetic studies have reported that LOF variants may be associated with a greater LDL-C reduction with statins, but the results are inconsistent across ethnic groups.^{10,11} Evidence on the effect of rs11591147 on statin response in Indian populations is limited.

This study determined the distribution of the PCSK9 rs11591147 polymorphism and evaluated its association with baseline lipid levels and with lipid changes after atorvastatin in North Indian patients with type 2 diabetes mellitus and/or hypertension.

METHODS

This observational study recruited 260 statin-naïve adults (≥ 18 years) with type 2 diabetes mellitus and/or hypertension, without prior cardiovascular disease, from two tertiary care hospitals in Delhi. Patients with a previously diagnosed dyslipidaemia, those on any lipid-lowering therapy, pregnant women and those unwilling to participate were excluded. Participants were started on moderate-intensity atorvastatin for primary prevention. Of these, 192 completed follow-up and were included in the response analysis.

The study was conducted from July 2022 to November 2023 in accordance with the New Drugs and Clinical Trials Rules (2019), Good Clinical Practice and ICMR (2017) guidelines. It was approved by the Institutional Ethics Committee (LHMC/IEC/2020/03/04 and AIIMS ND / Ref No: IEC-546/17.06.2022) and all participants gave written informed consent. A sample size of 200 was estimated using the Lemeshow formula, based on an expected LDL-C reduction of 30% with atorvastatin, to achieve 80% power at a 95% confidence level.¹²

Sample collection

Blood samples were collected at baseline, before starting atorvastatin and after 10–12 weeks of treatment. Lipid profiles were measured on an AU680 autoanalyzer (Beckman Coulter) and reported on the same day. For genetic analysis, baseline blood was collected in EDTA vacutainers. Genomic DNA was extracted from peripheral blood leukocytes within three days using a commercial kit (Qiagen, Germany), checked for quality and purity, stored at -20°C and analysed in batches.

PCR amplification and restriction fragment length polymorphism analysis of rs11591147

A 205 bp fragment of exon 1 of the PCSK9 gene, containing rs11591147, was amplified by PCR using the following primers:

Forward: 5'-CACGGCCTCTAGGTCTCCTC-3'

Reverse: 5'-AGGCCGTCCTCCTCGGTA-3'

The 10 μl reaction contained Platinum™ II Hot-Start PCR Master Mix (Invitrogen), 2 μL of template DNA and 2 μl of Platinum™ GC Enhancer. Cycling consisted of initial denaturation at 94°C for 5 min, 38 cycles of 95°C for 40 s, 60°C for 40 s and 72°C for 40 s and a final extension at 72°C for 10 min.

The PCR products were digested with RsaI (Thermo Scientific, USA), separated on a 2.5% agarose gel and visualised using a gel documentation system. The T allele abolishes the RsaI site, so the genotypes were identified from the fragments obtained: GG, 188 bp; GT, 205 bp and 188 bp; and TT, undigested 205 bp (Figure 1). The 17 bp fragment produced by digestion was too small to be resolved on the gel. Blinded duplicate testing was performed because sequencing could not be done.

Statistical analysis

Data were analysed using IBM SPSS Statistics version 23.0. Continuous variables were expressed as mean $\pm$ standard deviation (SD) and categorical variables as numbers and percentages. Normality was assessed with the Shapiro–Wilk test. Lipid values and percentage change ($\Delta\%$) were compared between genotypes using Student's t-test or the Mann–Whitney U test. Categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. Pre- and post-treatment lipid values were compared using the paired t-test or Wilcoxon signed-rank test, as appropriate. Genotype and allele frequencies were determined in all 260 participants and tested for Hardy–Weinberg equilibrium using the chi-square test; lipid response analyses included the 192 who completed follow-up. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics and lipid profile changes following atorvastatin treatment

Of the 260 participants enrolled (mean age 49.34 ± 9.82 years; 54.6% male), 192 completed follow-up and were included in the response analysis. Baseline total cholesterol was higher in participants receiving atorvastatin 20 mg/day (57%) than in those receiving 10 mg/day (43%) ($p = 0.01$). After treatment, total cholesterol, triglycerides and LDL-C fell significantly (all $p < 0.001$), whereas the increase in HDL-C was not significant (Table 1).

PCSK9 rs11591147 genotype distribution and atorvastatin response

The PCSK9 rs11591147 genotype distribution showed the presence of GG and GT genotypes, with no TT homozygotes identified (Table 2). The genotype distribution deviated from Hardy–Weinberg equilibrium ($\chi^2=10.2$, $p=0.001$), owing to the absence of TT

homozygotes (7.1 expected) and an excess of GT heterozygotes (86 observed vs. 71.8 expected).

Baseline and post-treatment lipid levels were comparable between GG and GT carriers and the percentage change ($\Delta\%$) after atorvastatin therapy did not differ significantly for any lipid parameter, including LDL-C (28.7% vs. 26.9%; $p=0.386$) (Table 3).

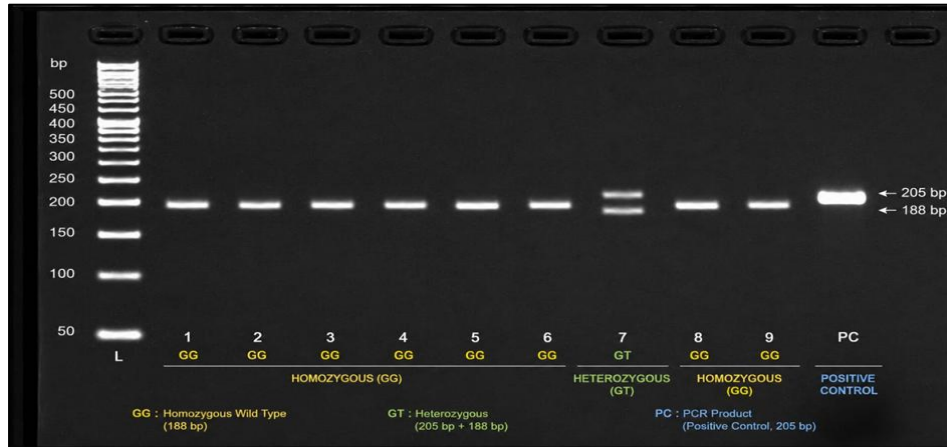


Figure 1: Agarose gel electrophoresis of PCSK9 exon 1 (rs11591147) after RsaI digestion. A 50 bp DNA ladder (L) is shown on the left. GG indicates homozygous wild type (188 bp), GT indicates heterozygous (205 bp + 188 bp) and PC represents the undigested positive control (205 bp). No homozygous mutant (TT) genotype was observed.

Table 1: Baseline and follow-up lipid profile in patients.

Parameter (mg/dl)	Baseline (Mean±SD)	Follow-up (Mean±SD)	Percent change (Mean±SD)	P value
Total cholesterol	186.23±44.14	153.90±40.74	-16.35±18.87	<0.001
HDL-C	43.53±11.37	44.91±12.48	4.21±30.47	0.180
Triglycerides	201.45±100.83	157.21±68.70	-11.90±55.33	<0.001
LDL-C	135.65±43.02	97.48±34.52	-24.72±22.85	<0.001

Table 2: Genotype and allele distribution of PCSK9 rs11591147.

Genotype/Allele	% (N)
Wild-type (GG)	66.9 (174)
Heterozygous (GT)	33.1 (86)
Mutant type (TT)	0 (0)
G allele	83.5
T allele	16.5

Table 3: Change in lipids in different genotypes of rs11591147.

Lipid parameter	Wild-type (GG)	Heterozygous (GT)	P value (between-group)	P value for $\Delta\%$ between groups
Baseline cholesterol (mean±SD)	185.17±44.40	188.52±43.81	0.291	0.639
Follow-up cholesterol (mean±SD)	153.48±39.67	154.77±43.21	0.980	
P value for change within group	<0.001	<0.001		
Baseline LDL-C (mean±SD)	136.04±43.89	134.79±41.38	0.813	0.386
Follow-up LDL-C (mean±SD)	96.99±35.73	98.60±31.98	0.740	
P value for change within group	<0.001	<0.001		
Baseline triglycerides (mean±SD)	192.79±92.71	220.04±114.94	0.098	0.081

Continued.

Lipid parameter	Wild-type (GG)	Heterozygous (GT)	P value (between-group)	P value for Δ% between groups
Follow-up triglycerides (mean±SD)	154.95±65.77	161.95±74.81	0.715	
P value for change within group	<0.001	<0.001		
Baseline HDL-C (mean±SD)	43.02±9.68	44.64±14.41	0.463	0.798
Follow-Up HDL-C (mean±SD)	44.62±9.55	45.52±17.16	0.799	
P value for change within group	0.187	0.547		

DISCUSSION

In this North Indian cohort, the loss-of-function rs11591147 T allele was common (16.5%), but GT patients did not differ from GG patients in baseline LDL-C or in the LDL-C response to atorvastatin. The T allele frequency was considerably higher than the 1–2% reported for South Asian populations in the 1000 Genomes Project, but lower than the 36.2% reported in a South Indian study.^{13,14} The genotype distribution deviated from Hardy–Weinberg equilibrium ($p=0.001$), with no TT homozygotes (about seven expected) and an excess of GT patients. Possible explanations include patient selection, chance and genotyping error.

Previous studies of rs11591147 have reported varied findings. Feng et al, reported a greater LDL-C reduction with statins in T allele carriers, but this was based on few carriers and was only borderline significant in a European cohort.¹⁰ The PROSPER study (Prospective Study of Pravastatin in the Elderly at Risk) found no effect of rs11591147 on pravastatin response, in agreement with our findings.¹¹ Contrary to our baseline result, Guella et al, found lower LDL-C and a lower risk of myocardial infarction in T allele carriers, but did not assess statin response.¹⁵

These differences may reflect differences in study population, statin type and dose and the zygosity of the carriers studied. A single T allele may have too small an effect size to alter treatment response and any effect may appear only in TT homozygotes, who were absent from this cohort. Type 2 diabetes mellitus and/or hypertension may also alter metabolic status and attenuate genotype-specific effects. Overall, the rs11591147 GT genotype alone is unlikely to be a useful predictor of statin response in this population.

Limitations

This study has some limitations. First, PCR-RFLP genotyping could not be confirmed by Sanger sequencing due to financial constraints, although blinded duplicate testing showed reproducible results. Second, the absence of TT homozygotes limited genotype-specific comparisons. Finally, statin response is influenced by multiple genetic and non-genetic factors and attributing it to a single PCSK9 SNP may be an oversimplification.

CONCLUSION

The PCSK9 rs11591147 T allele had an observed frequency of 16.5% in North Indian patients with diabetes mellitus and/or hypertension and all carriers were heterozygous. The T allele was not associated with baseline LDL-C or the response to atorvastatin, so its value as an independent predictor appears limited. Larger studies with sequencing-confirmed genotypes, including TT homozygotes, are needed to confirm these findings.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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