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Association of Genetic Polymorphism of Gene ABCB1 with Statin resistance in cardiac patients from the tertiary care hospital of South Punjab, Pakistan

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Abstract

The present study aimed to determine the frequency distribution and association of genetic polymorphism with statin treatment in the population of Punjab, Pakistan. Atorvastatin therapy is associated with ABCB1 (ATP-binding cassette transporter) gene expression and LDL cholesterol reduction. Two common SNPs, rs2032582, rs1045642 of the ABCB1 gene, were selected, variants of which are associated with muscle toxicity. The hypothesis that there is a significant association between single nucleotide polymorphism (SNP) at 3435 T>C and 2677 G>A/T of the gene ABCB1 that affects statin therapy in cardiac patients of the tertiary care hospital of Punjab, Pakistan. **Methods**. For this,100 cardiac patients with percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS) who were undergoing treatment with statin (Atorvastatin) were selected. Lipid profile was determined using a commercial assay kit. The patients were analyzed for rs2032582 and rs1045642 allelic variants using an allele-specific primer extension polymerase chain reaction method followed by sequencing to confirm the mutation. The results were expressed in mean ± SEM, and in all cases, the difference was considered significant when $p<0.05$.**Results.** The present results showed allele variant AC at SNP rs1045642 (3435 T>C) showed a significant increase in total cholesterol ($p = 0.05$), reduction in HDL ($p=0.02$), and increase in

TG (p = 0.01), while a significant increase (p=0.042) in cholesterol was found in the CT variant. And, variants (AC, AT, CT) at SNP rs2032582 (2677 G>A/T) of ABCB1 showed a significant increase in TGs (P= 0.04, p=0.03, p= 0.008, respectively) and total cholesterol (p=0.02, p=0.04, p=0.04, respectively) with the increase in LDL cholesterol in AC (p =0.012) and AT (p=0.016). These results were found to be concordant with the chromatograms obtained by sequencing.
Conclusion: The failure of drug response and resistance draws the conclusion that not only single nucleotide polymorphism but epigenetic factors and other enzymes with transcriptional and translational factors are also responsible for the metabolism and side effects of Atorvastatin.

Introduction

Cardiovascular diseases (CVD), ranging from myocardial infarction to stroke and coronary artery diseases (CAD)are the leading cause of death worldwide. This demands effective medication to treat and reduce the risk of the progression of these pathologies (Nabel 2003, Balakumar, Maung-U et al. 2016). Since these cardiovascular diseases are related to hyperlipidemia, lipid-lowering drugs are the most widely used drugs across the world to treat hyperlipidemia.

The cholesterol-lowering characteristic of statins is known to inhibit the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase enzyme (Goldstein and Brown 2015). This enzymatic inhibition increases the level of low-density lipoprotein (LDL) receptors, thus enhancing the uptake and degradation of LDL-cholesterol (LDL-C), lowering the synthesis and accumulation of cholesterol, and reducing the secretion of plasma LDL (Brown and Goldstein 1986)

Statin induces a reduction in blood concentrations of LDL-C. In addition, it is also used to treat pulmonary vascular disorder (PVD) & hemorrhage in both primary & secondary prevention (Stone, Robinson et al. 2014). Rosuvastatin, atorvastatin, fluvastatin, lovastatin, simvastatin, pravastatin, and pitavastatin are some of the most commonly prescribed statins.

An inter-patient variation in the treatment outcome to reduce the rate of coronary artery disease has been shown in various populations (Yow, Hamzah et al. 2023). Despite clinical benefits of statin, several patients have stopped taking these medications for its adverse treatment outcomes with side effects. There has been reported countless side effects and a heightened hazard of clinical outcomes including muscular dystrophy, tendonitis, liver toxicity, type 2 diabetes mellitus, myopia, neurological dysfunction, brain damage, behavioral disorders, and, less frequently, migraine and stomach problems disruption, rash, and other side effects are the most prevalent statin side effects. (Lalatović, 2023;Park et al., 2025, Maji, Shaikh et al. 2013)

Based on genetic polymorphism, drug interaction, and metabolism vary individually with subsequent therapeutic effects. Reduction in the dose of simvastatin from 80mg to 40mg has been reported to contribute to a reduction in myotoxicity (FDA, 2011). Single nucleotide polymorphism was found to be one of the major underlying causes (Consortium, 2010) that may result in a reduction in effective cardiovascular risk. In addition to this, muscle weakness, cramps, fatigue, myalgia to life-threatening rhabdomyolysis have been reported (du Souich, Roederer et al. 2017, Selva-O'Callaghan, Alvarado-Cardenas et al. 2018)

The ABCB1 gene codes for P-glycoprotein (also known as multi drug resistance-1 gene) that transports and excrete a wide range of toxic xenobiotic agents out of cell (Leslie, Zarzour et al. 2025, Reiner 2014). Likewise, statins are eliminated from cells via this mechanism (Xu, Li et al. 2005). Atorvastatin therapy significantly associates

ABCB1 gene expression and associated with LDL cholesterol reduction (Rebecchi, Rodrigues et al. 2009).
Polymorphisms in ABCB1 play a vital role in the lipid-lowering response of statins (Hodges, Markova et al. 2011). Studies have demonstrated that the atorvastatin (Kajinami, Brousseau et al. 2004) and simvastatin (Fiegenbaum, da Silveira et al. 2005) therapy to the variant of ABCB1 belongs to SNP C3435T. This SNP is associated with a smaller reduction in LDL cholesterol compared to non-carriers. Variant alleles of SNPs 2677 G>A/T (rs2032582) and 3435C>T (rs1045642) are the two most studied in ABCB1 gene and have been associated with statins pharmacokinetics and statin tolerability (Becker, Visser et al. 2010, Hoenig, Walker et al. 2011).
A report from Indian population has shown that in atorvastatin-treated patients, carriers of variant allele for G2677T had 3 times more significant reduction of LDL-C as compared to those who carried the wild-type allele (Kadam, Ashavaid et al. 2016, Lalatović, Ždralević et al. 2023). Further, Fiegenbaum et al. (2005) have demonstrated that the 3435T variants at rs1045642 were linked with a decreased risk of myalgia for people treated with simvastatin compared to allele C (Fiegenbaum et al. 2005). According to another study, patients were more frequently found with T allele variants at rs1045642 who were on atorvastatin treatment. And, they were reported to have complaints of myalgia compared to those without the variant allele (Hoenig, Walker et al. 2011). These recent developments are considered for better CVD treatment outcomes and to reduce morbidity and mortality risk (guideline CG181 2023). Therefore, the present study explored for the first time the data for the presence of SNPs 2677 G>A/T (rs2032582) and 3435C>T (rs1045642) in the tertiary care hospital from the population of Punjab, Pakistan

Material and Methods

A total of 100 cardiac patients (both male and female) who were on statin therapy for the last year in various hospitals of the district Lahore were studied to evaluate the statin treatment response (statin resistance) after the approval of the ethical committee of the School of Biochemistry, Minhaj University Lahore, Pakistan. For more than a year, the cardiovascular patient's baseline biochemical characteristics and follow-ups of complaints were recorded as mean values towards two salts of statin (atorvastatin and rosuvastatin) treatment. Since lipid profile dysfunction and complaints were seen among atorvastatin patients (results not shown), their biochemical characteristics were finally recorded following completion of one year at the time of blood collection. The Blood samples were taken from these patients in properly labeled Ethylene Diamine Tetraacetic Acid (EDTA) tubes with 3 to 5 mL. Informed consent was provided to the patients or their families, and the collected data were kept confidential.
The age of the cardiovascular patients was 28 to 71 years, with a mean of 50.52 ± 12.25 years during sample collection.

Biochemical Analysis

Estimation of lipid profile

Lipid profiles, i-e, serum TC, HDL-C, TG, and LDL-C were determined using a commercial assay kit (Randox® kit, Randox Laboratories, United Kingdom). LDL-C =Total cholesterol - Triglycerides - HDL-C

Molecular Analysis

The DNA was extracted from fresh blood samples by using the Genomics DNA extraction kit (k0512-Thermo Scientific Genomics DNA purification kit: Thermo Fisher Scientific, Waltham, MA, USA). Following extraction, Agarose gel

electrophoresis was done to determine the quality of the DNA (Fig. 1). Further, the extracted DNA was also quantified by using nanodrop (NanoDrop™ 2000; Thermo Scientific, Wilmington, DE, USA) by using 1 µl of the extracted DNA samples. The absorbance measures ratio of A260/A280 was used as an indicator of DNA purity. The ratios A260/A280 results greater than 1.5 were considered for PCR

Primer designing

The primer 3 software was used to design the primers for the allelic variants of the ABCB1 gene retrieved from the website (http://frodo.wi.mit.edu).. One universal primer (Forward and Reverse) for SNP (I) rs2032582 and two allele-specific primers (only forward) with a product size of 212bp were designed. Similarly, for SNP (II) rs1045642, one primer set was universal (Forward and Reverse), and three allele-specific primers (only forward) were designed with a product size of 180bp. Primers with their melting points are shown in Table 1.

Sr. No	Primer ID	Primer Sequences (5′-3′)	Melting Temperature (Tm)
1	rs582-FA	5′-TTAGTTTGACTCACCTTCCCAGA-3′	64^0
2	rs582-FC	5′-TTAGTTTGACTCACCTTCCCAGC-3′	66^0
3	rs582-FT	5′-TTAGTTTGACTCACCTTCCCAGT-3′	64^0
4	rs582-RU	5′- GGTTCCAGGCTTGCTGTAAT -3′	58^0
5	rs642-FA	5′-CTCCTTTGCTGCCCTCACAA-3′	60^0
6	rs642-FC	5′-CTCCTTTGCTGCCCTCACAC-3′	62^0
7	rs642-FT	5′-CTCCTTTGCTGCCCTCACAT-3′	60^0
8	rs642-FG	5′-CTCCTTTGCTGCCCTCACAG-3′	62^0
9	rs642-RU	5′-TGTTTTCAGCTGCTTGATGG-3′	56^0

PCR Amplification

The extracted DNA was subjected to amplification through a thermal cycler. A total of 25µl reaction volume containing 12.5 µl 2X PCR Master Mix (WizPureTM, Republic of Korea), 1 µl of genomic DNA, 0.5 µl primer 1 (Forward), 0.5 µl primer 2 (Reverse), 10.5 µl dH2O for both SNPs was prepared. The PCR cycling conditions were as follows, with different annealing temperatures for two SNPs. Initial denaturation temperature 95^o °C for 8 minutes followed by 35 cycles, which contain denaturation temperature 95^o °C for 1 minute and 30 seconds, with various annealing temperatures (SNP-I rs20325582: 63 °C and for SNP-II rs1045642: 61 °C) for 1 minute and 30 seconds, and the elongation temperature was 72 °C for 1 minute and 30 seconds. The final elongation temperature was 72 °C for 10 minutes in a PCR thermal cycler (Simpli Amp™ Thermal Cycler, Catalog number: A24811).

Gel electrophoresis
The PCR amplified products of both SNPs were electrophoresed on a 1.5% agarose gel and stained with ethidium bromide and observed under a UV transilluminator (Gel Documentation System). The bands of both SNPs PCR amplified products were compared to a 100bp ladder for further analysis.

Sanger Sequencing
The purified products in an amount of 20µl of each sample were sent to Singapore through ABI Lahore for further sequencing by using the genetic analyzer ABI 3700 (Applied Biosystems). The Sanger sequencing was performed to confirm the allelic variants of the ABCB1 gene and to validate the gel-based approach to SNP identification. The purified products were sequenced using forward primers using the BigDye® Terminator v3.1 Cycle Sequencing kit according to the manufacturer's instructions. (Applied Biosystems, USA). The ABI PRISM sequencing analysis software version 3.7 was used to put the sequencing results together.Similarly, the Applied Bio-systems Chromas software 2424 (http://www.technelysium.com.au/chromas.html) and Bio Edit version 7 were used to analyze the data.

Statistical Analysis
Statistical analysis was performed using a two-way analysis of variance (ANOVA) followed by LSD (Least Significant Difference) with the help of Microsoft Office Excel 2010 and IBM SPSS Statistics for Windows version 23. The results were expressed in mean ± SEM, and in all cases, the difference was considered significant when $p < 0.05$.

Results
Integrity of DNA samples
Figure 1 shows the integrity of DNA samples, are the extracted DNA of cardiac patients and their quality from cardiac patients on statin treatment using a 0.8% agarose gel. Molecular marker (Molecular Marker; Thermo Scientific™ 100bp Plus DNA Ladder) was used to compare the integrity of samples shown in L1 to 12.

Amplification of allelic variants of rs1045642
Fig 2 shows amplification of allelic variants of rs1045642 with genetic marker and their electrophoresis results on a 1.5% agarose gel. M (Molecular Marker; Thermo Scientific™ 100bp Plus DNA Ladder); Left L4 (Variant A), L5 (variant T) and L6 (variant C), and L7 (variant G) with 180bp.

Amplification of allelic variants of rs2032582
Fig 3 shows amplification of allelic variants of rs2032582 with genetic marker and their electrophoresis results on 1.5% agarose gel. M (Molecular Marker; Thermo Scientific™ 100bp Plus DNA Ladder); Left L1, to L3 Variant A, L4 to L6 variant C and L7 and L8 T variant with 212bp.

Sanger sequencing
The amplified PCR products for SNP rs1045642 with allelic variants A, C and G (Figure 4 A – 4C respectively) and SNP rs2032582 with allelic variants (A, C, T) (Figure 5A -5C respectively) were confirmed by the Sanger sequencing method. The results of sequencing chromatograms demonstrated 100% concordance with the results of the gel electrophoresis method in the selected samples.

Genotype and allele frequency of SNP rs1045642 variants (A> T, C, G)
Table 1 shows genotype and allele frequency of SNP rs1045642 variants (A> T, C, G) among 100 cardiac patients 12% were heterozygous for AC variants, 48% for AG variants, 4% for AT variants, 4% for CT variants, 24% for CG variants and 8% for TG variants, Further, the wild type allele A was found to be 32% and Allele G was 40% and was found to be higher among all Alleles > Allele C (20%) > Allele T (8%)

Genotype and allelic variant frequencies of SNP rs2032582 (A>C, T)
Table 2 shows genotype and allelic variant frequencies of SNP rs2032582 (A>C, T). Among 100 cardiac patients, 36% were having heterozygous genotype for AC variants, 44% were heterozygous for AT variants and 20% were heterozygous for CT variants. Similarly, the allelic frequency for wild type Allele A was 41% and was found to be higher than Allele T (33%) and Allele C (27%).

Lipid profile of allelic variants of SNP rs1045642
Table 3 shows the lipid profile of allelic variants AC, AG, AT, CT, CG, TG of SNP rs1045642. Statistical analysis by paired-samples T test in allele variant A/C showed a significant increase in total cholesterol (p = 0.05), reduction in HDL (0.02) and increase in TG (0.01) with the insignificant change in LDL cholesterol. Increase in cholesterol was found in CT (p=0.042) variant while insignificant changes were found in all other variants in total cholesterol, LDL-cholesterol HDL-cholesterol and triglycerides.

Lipid profile of allelic variants of SNP rs2032582
Table 4 shows the lipid profile of allelic variants AC, AT, and CT of SNP rs2032582. Statistical analysis by paired-samples T test showed a significant increase in total cholesterol, p = 0.027, LDL-cholesterol (p= 0.012), triglycerides (p=0.04) and reduction in HDL cholesterol (0.02) in allele AC genotype variant. Allele AT. showed significant increase in total cholesterol, p = 0.048, LDL-cholesterol (p= 0.016), triglycerides (p=0.039) and insignificant change in HDL cholesterol (0.02) In addition, allele CT showed significant increase in cholesterol (0.041) and in triglycerides (p=0.008). However, HDL and LDL-cholesterol showed insignificant change.

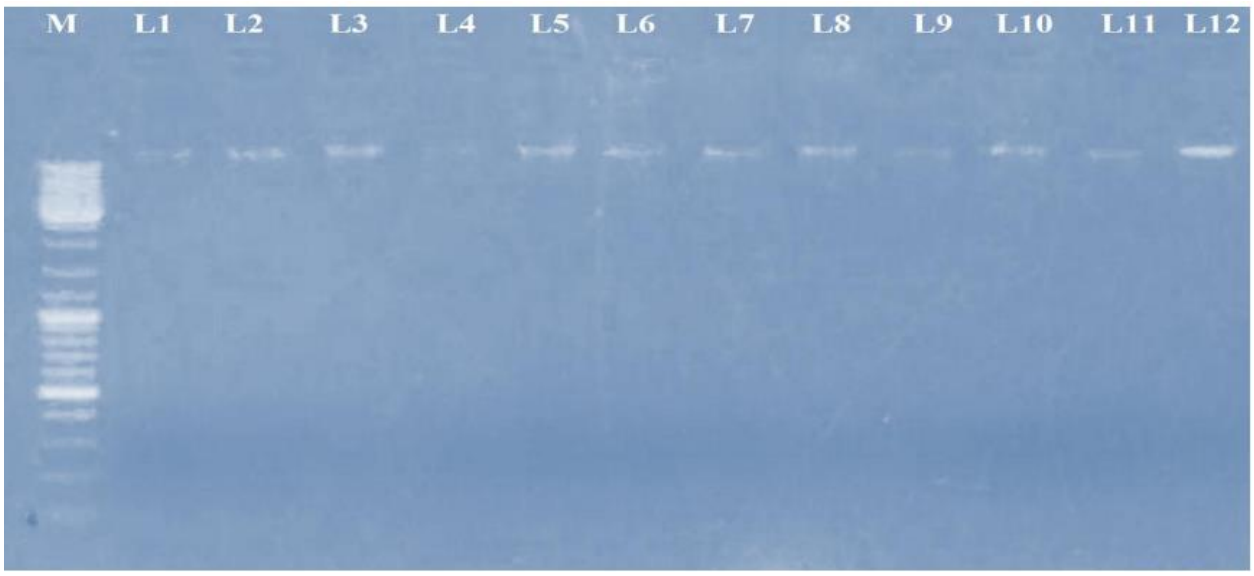

Figure 1: DNA extraction from blood samples of cardiovascular patients on Statin treatment. M is Molecular Marker (Molecular Marker), L1 to L12 shows DNA samples

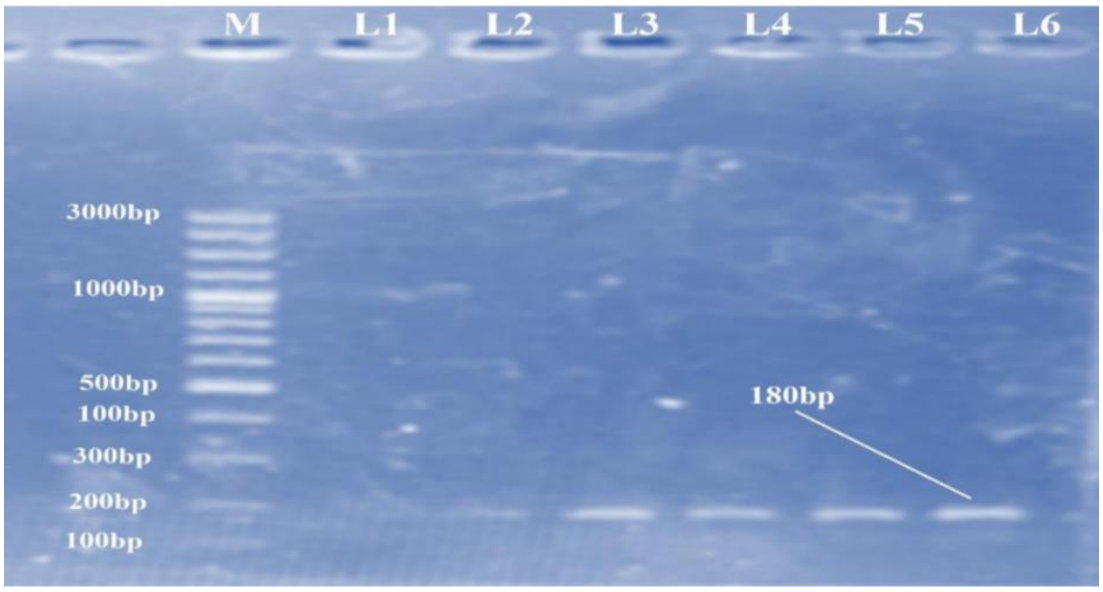

Figure 2: Amplification of allelic variants of rs1045642 with genetic marker. M (Molecular Marker; 100bp Plus DNA Ladder); Left L4 (Variant A), L5 (variant T) and L6 (variant C), and L7 (variant G) with 180bp

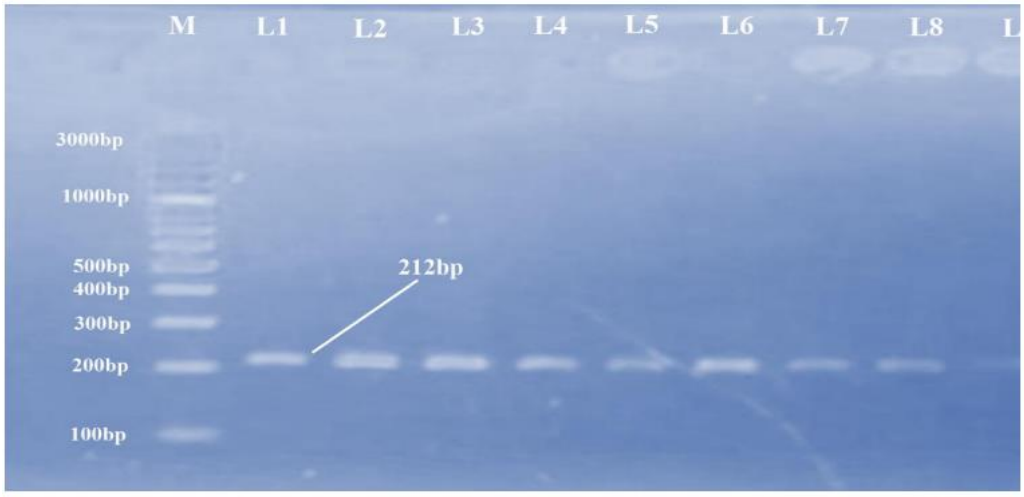

Figure 3: Amplification of allelic variants of rs2032582 with genetic marker. M (Molecular Marker; Left L1, to L3 Variant A, L4 to L6 variant C and L7 and L8 T variant with 212bp

The sequencing chromatogram (Figure 4A-4D) showing four different variants of a genetic marker (rs1045642) amplified with a particular allele-specific primer (A>C, G, T).

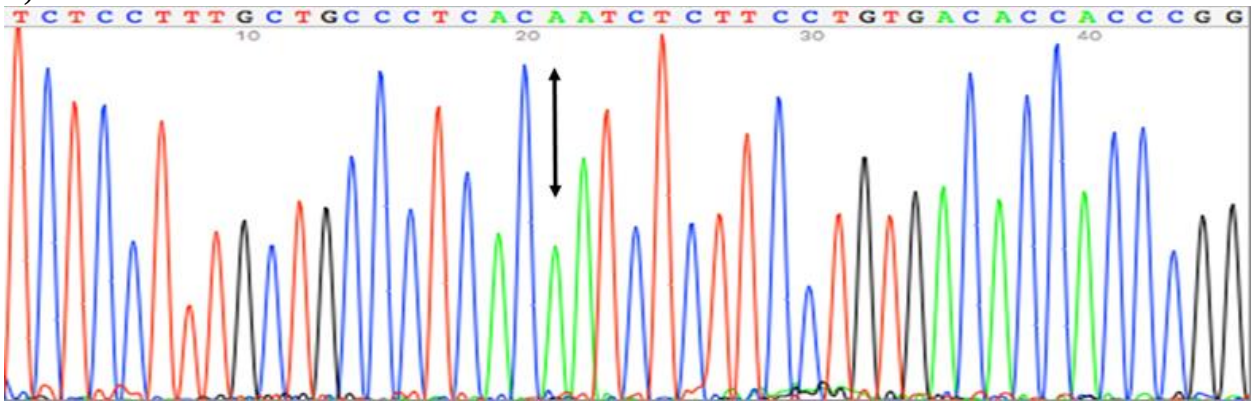

Figure 4A: ABCB1 (Variant A of rs1045642)

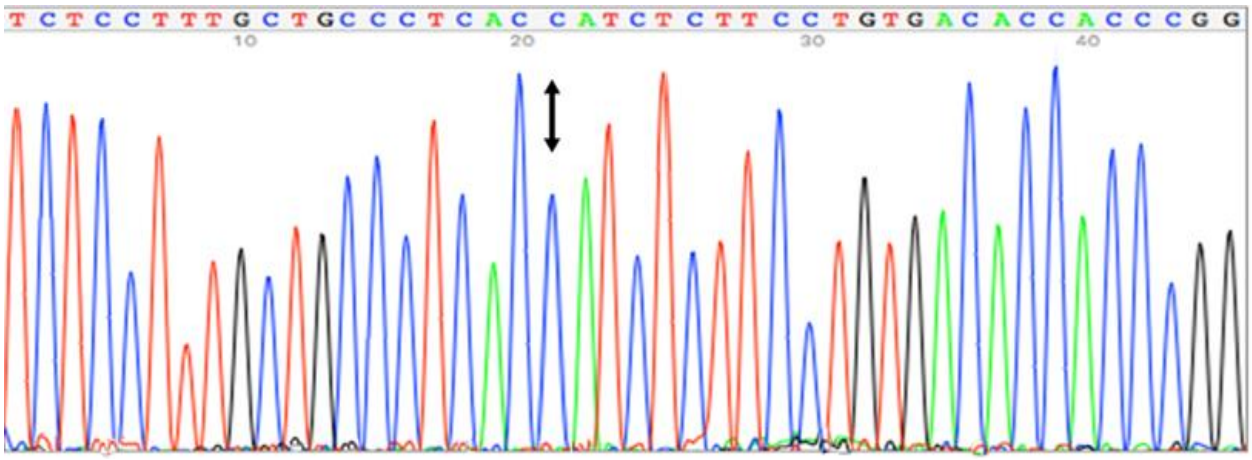

Figure 4B : ABCB1 (Variant C of rs1045642)

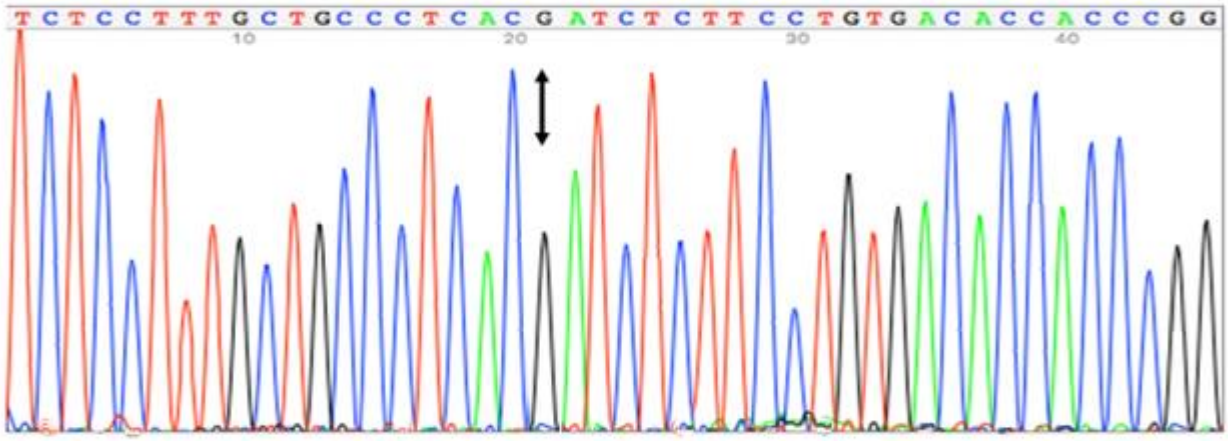

Figure 4C: ABCB1 (Variant G of rs1045642)

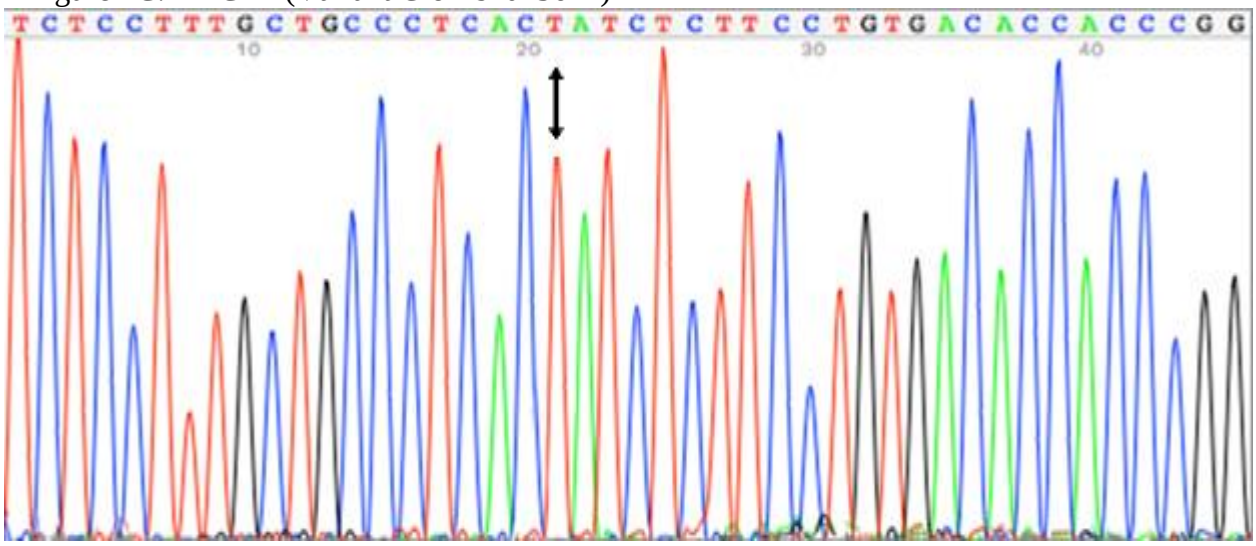

Fig 4D: ABCB1 (Variant T of rs1045642)

The sequencing chromatogram (Figure 5A-5C) showing three different variants of a genetic marker (rs2032582) amplified with a particular allele-specific primer (A> C, T).

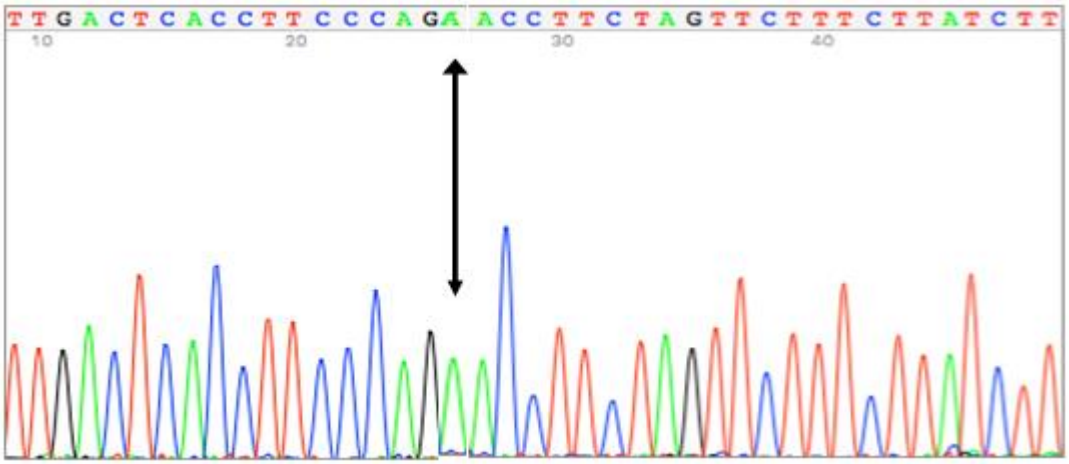

Figure 5A: ABCB1 (Variant A of rs2032582)

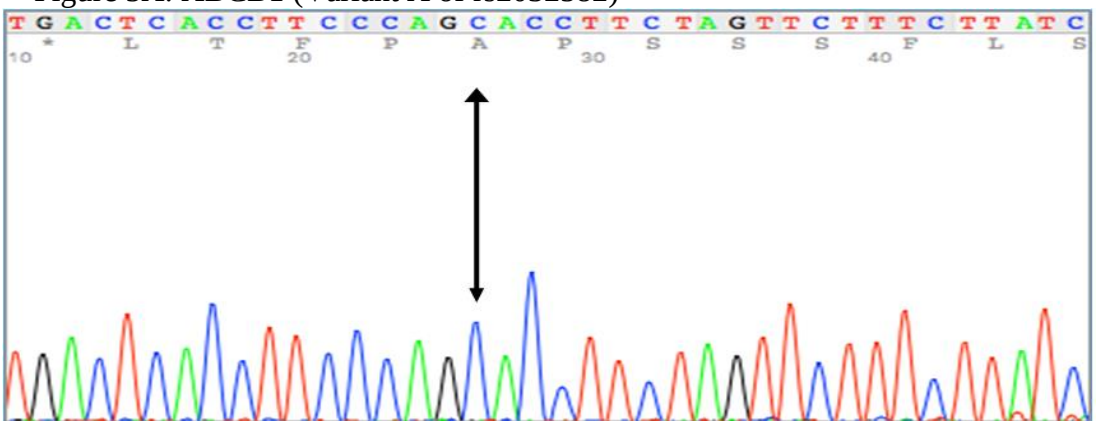

Figure 5B : ABCB1 (Variant C of rs2032582)

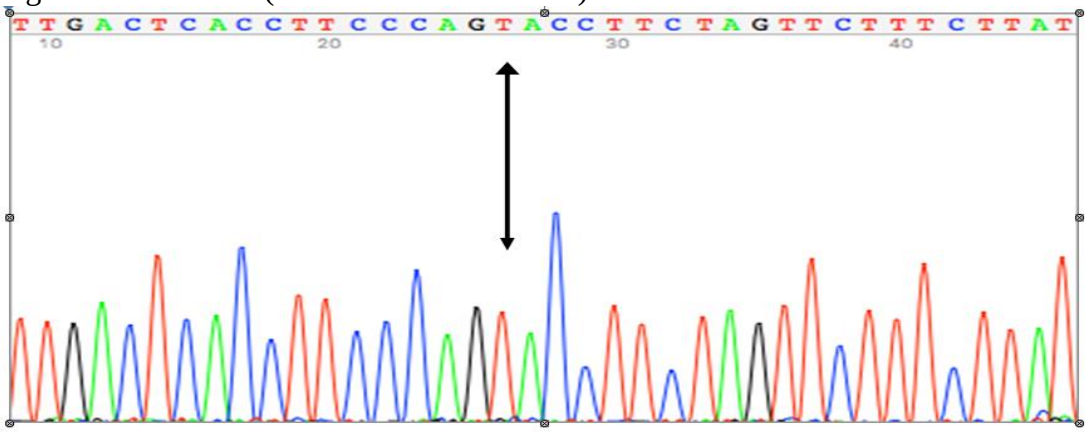

Figure 5C: ABCB1 (Variant T of rs2032582)

The Allele and genotype frequencies of genetic variant (SNP; rs1045642 of ABCB1 gene) in cardiac patients of the study group.

SNP; rs1045642 (A> T, C, G) Genotype	Number of Patients (n=100)	Genotype Frequency	Allele Frequency
AC	12	0.12	Allele A = 0.32
AG	48	0.48	Allele T = 0.08
AT	4	0.04	Allele C = 0.20
CT	4	0.04	Allele G = 0.40
CG	24	0.24	-
TG	8	0.08	-

Table 1: The allele and genotype frequencies of genetic variants (SNP, rs 1045642 of ABCB1 gene

The Allele and genotype frequencies of genetic variant (SNP; rs2032582 of ABCB1gene) in cardiac patients of the study group.

SNP; rs2032582 (A>C, T) Genotypes	Number of Patients (n=100)	Genotype Frequency	Allele Frequency
AC	36	0.36	Allele A = 0.41
AT	44	0.44	Allele C = 0.27
CT	20	0.20	Allele T = 0.33

Table 2: The allele and genotype frequencies of genetic variants (SNP rs 2032582 of ABCB1 gene

SNP rs1045642 (A> T, C, G) Genotype	AC	AG	AT	CT	CG	TG

	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up
Total Cholesterol	258 ± 10.3	306.8 ± 10.9	267.2 ± 14.5	285.2 ± 13.9	272 ± 19.8	222 ± 18.9	249.2 ± 18.9	299 ± 15.6	247 ± 15.2	222 ± 18.9	288 ± 21.3	179 ± 17.74
	0.050*		0.332		0.215		0.042*		0.484		0.120	
LDL Cholesterol	97.4 ± 5.7	96.9 ± 8.3	91.2 ± 6.2	99.6 ± 6.28	85.4 ± 5.9	82.0 ± 6.2	82 ± 6.5	101.4 ± 6.2	95..4 ± 3.9	91.4 ± 9.8	87.6 ± 7.8	93.6 ± 2.6
	0.965		0.493		0.682		0.160		0.720		0.514	
HDL	55 ± 3.2	32 ± 4.0	44 ± 5.1	43 ± 4.8	46 ± 3.5	47 ± 4.3	46 ± 3.9	51 ± 4.9	40 ± 3.9	46.8 ± 2.6	54.8 ± 8.0	45.0 ± 5.7
	0.02*		0.81		0.76		0.29		0.38		0.29	
Triglycerides	182.8 ± 11.3	212 ± 10.2	177.2 ± 12.6	199.2 ± 10.6	158.2 ± 13.7	143.4 ± 12.7	163.4 ± 14.1	190 ± 11.9	173.4 ± 11.3	174.4 ± 12.8	185.6 ± 12.7	186.6 ± 11.8
	0.01*		0.152		.253		.117		.962		0.91	

Table 3: Lipid Profile of Genetic Variant of ABCB1 Gene (SNP rs1045642) Experimental details are as described in the materials and methods section. Values are means± SEM for each group of 5 rats. The significance of the differences is indicated by *P<0.05

SNP: rs2032582 (A>C, T), Genotype	AC		AT		CT	
	Baseline	Follow up	Baseline	Follow up	Baseline	Follow up
Total Cholesterol	222.8± 11.6	271± 12.3	215.2±10.7	247.2±12.2	210±12.7	268±11.4
	0.027*		0.048*		0.041*	
LDL Cholesterol	84.4 ± 8.1	99.8 ± 5.1	62.6 ± 7.47	87.8 ± 6.8	82.6 ± 4.5	81.4 ± 5.7
	0.012		0.016		0.682	
HDL	55.6 ± 3.2	44.8± 5.1	49.2± 5.9	46 ± 3.5	49.6±6.1	46± 3.9
	0.02*		0.67		0.50	
Triglycerides	184±12.8	234 ± 10.8	188.2± 11	247± 11.3	188± 10.4	244.8± 10
	0.04*		0.039*		0.008**	

Table 4: Lipid profile of allelic variants of SNP rs2032582. Experimental details are as described in the materials and methods section. Values are means± SEM for each group of 5 rats. The significance of the differences is indicated by *P<0.05 ,**P<0.01, ***P<0.001.

Discussion

Statin is renowned for its remarkable effects as anti-hyperlipidemia drug but it has wage inter-individual response to treatment is still questionable. Statin intervenes cholesterol metabolism depends largely on genetic determinants has been largely reported.

According to our present results ABCB1 genotype variants show dramatic difference in lipid profile following statin (atorvastatin) treatment. In association with SNP at rs1045642 of ABCB1, haplotype analysis evaluating the A, T, C and G separately at 3435, only allele variant AC showed increase in triglycerides and total cholesterol with the reduction in HDL levels. However, except CT allele that showed increase in total cholesterol all other genotypes showed insignificant change in lipid profile. For all allele variants having SNP G2677A/T (rs2032582) showed significant increase in total cholesterol and triglycerides. Increase in LDL cholesterol was seen in both SNP variants AC and AT with the reduction in HDL in AC variant.

The mutations in ABCB1 represented by the chromatograms in our present study correspond to the lipid profile of the patients. These results clearly show little contribution in the reduction of LDL-cholesterol to statin therapy. Similar to our results, a study conducted in Boston by Mega and colleagues reported pravastatin has the ability to reduce LDL-C associated with G2677T/A variant in ABCB1, however, no association was seen in LDL reduction by atorvastatin (Mega, 2009). It was reported that the ABCB1 3435T variant in patients with atorvastatin-induced myopathy were significantly higher compared to controls on atorvastatin without myopathy in a 98-patient study

Concomitant to our results, it was reported that the C3435T SNP variant of ABCB1 is associated with a significantly smaller reduction in LDL cholesterol following both atorvastatin (Kajinami et al., 2004) and simvastatin (Fiegenbaum et al., 2005) treatment. Further evidences from a case–control study of atorvastatin myopathy reported no difference in ABCB1 3435T allele. (Hermann et al., 2006). The most common silent polymorphism, which is associated with variable responses is the C3435T on exon 26 has been reported different significantly amongst different populations (Kulsoom, 2015; Jamroziak et al., 2009). However, in a prospective trial simvastatin 20mg daily given for 6 months reduced statin myopathy in patients compared to controls in ABCB1 TTT haplotypes (Fiegenbaum et al., 2005).

Additional evidences from the reports published by Thompson et al., (2005) suggests that the C3435T SNP is in linkage disequilibrium with the G2677T variant (Thompson et al., 2005) that may consequently affect statin pharmacokinetics (Soranzo, 2004). It was reported earlier that simvastatin, lovastatin, and atorvastatin were P-glycoprotein inhibitors, whereas pravastatin was not (Bogman, 2001). It was reported that rosuvastatin has the most potent and significant effects to reduce LDL-C, with 5 mg of rosuvastatin being equivalent to up to 10 mg of atorvastatin, up to 40 mg of simvastatin, and up to 80 mg of pravastatin, respectively (Olsson, 2002 ; Shah, 2019). In contrast, Kadam et al., (2016) reported atorvastatin therapy reduced LDL cholesterol in Indian population, when 177 hypercholesterolaemic patients were genotyped to study allele polymorphism in ABCB1 (2677G>T, 3435C>T) against atorvastatin response (Kadam, Ashavaid et al. 2016)

In a case–control study, no association was found between ABCB1 2677T and atorvastatin blood levels reported by (DeGorter et al., 2013). Further, Mega et al., 2009 demonstrated that the non-GC mutant alleles of the G2677T/A and C3435T

haplotypes are associated with smaller pravastatin induced reduction in LDL cholesterol levels compared to controls (Mega et al., 2009). Hoenig et al reported a significantly higher frequency of the ABCB1 3435T variant in patients with atorvastatin-induced myopathy compared to controls on atorvastatin without myopathy in a 98-patient study (Hoenig., et al. 2011).

Clinical research findings are not yet conclusive for ABCB1 variants, therefore, to test statin toxicity, routine clinical use of ABCB1 genotyping is not currently recommended. There is no doubt that the ABCB1 plays an important role in the transport of statin, therefore it is suggested that the multigene guidance could conclude the statin therapy including ABCB1 variants (Kitzmiller et al., 2016). Because the genes that are known for absorption, distribution, metabolism and excretion of statins fall into four classes and encode cytochrome P450 enzymes (CYP2D6, CYP3A4, and CYP3A5) (Willrich, 2009), the mitochondrial enzyme glycine amidinotransferase (GATM), cell influx transporters (SLCO1B1), and cell efflux transporters (ABCB1 and ABCG2), therefore, the role of number of transcriptional factors and inhibitory factors can be suggested to have cumulative role for the mechanism of action and side effects of statin (Turner, 2019). This may alter translation of many dependent proteins that could contribute to its side effects in individuals.

Conclusion

It can be concluded that not only single nucleotide polymorphism but epigenetic factors and other enzymes with transcriptional and translational factors are also responsible for the metabolism of statin that could contribute its side effects, Further, nanotechnology should be implicated to go beyond cellular and physicochemical barriers to achieve therapeutic targets with minimum side effects.

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