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Original Article

Frequencies of Genetic Polymorphisms of the Cholesterol and Statin Metabolic Pathway Genes among Healthy South Indian Tamil Population

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ABSTRACT

Background: Indians are genetically predisposed to Coronary Artery Disease (CAD), hence it is worth studying the effect of genetic polymorphisms which affect CAD development including Low- Density Lipoprotein Cholesterol (LDL-C) in our population. Studies have found that there is a considerable variation in the genetic makeup of Indians with distinct genetic groups having been identified-one such being Dravidian Tamil population. **Aim:**We aimed to determine the distribution of allele and genotype frequencies of genes associated with LDL-C lipid levels as well as those associated with statin metabolic pathway in 100 healthy South Indian Tamil volunteers. **Results:**The minor allele frequencies (MAFs) of the genetic polymorphisms of *HMGCR* rs5908, rs17238540 and rs12916 were 0.5, 3.5 and 41% respectively. The MAF of *LDLR* rs688, *CYP7A1* rs3808607, ABCB1 rs1128503, *SLCO1B1* rs4149056 were 26, 42, 41.5 and 7% respectively. The frequencies of the genetic polymorphisms studied show considerable variation from other Indian ethnic groups in 5 out of the 7 genetic polymorphisms studied. **Conclusion:** Considerable variations in frequencies of genetic polymorphisms were found between Tamil population and other major ethnic populations worldwide with respect to *HMGCR* rs17238540 and *LDLR* rs688.

Key words: Genetic polymorphisms, Genotype frequency, Tamilians, Healthy volunteers, LDL-C, Statin pathway.

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INTRODUCTION

Elevated levels of Low-Density Lipoprotein Cholesterol (LDL-C) is associated with an increased risk of coronary artery disease (CAD).[1] LDL-C levels are affected by genetic and environmental factors. The basal risk in the form of genetic variations is not modifiable, although they are to a good extent modulated by environmental factors. Exploring and characterizing these genetic variations for each population would provide the background information needed to conduct further studies on lipid abnormalities and their treatment. Lipid traits are up to 60% heritable.[2] Indians being predisposed to CAD,[3] it is essential to study the genetics of LDL-C to help predict CAD and to implement preventive measures in this high- risk population. Till now, 157 gene loci have been studied for association with blood lipid levels which could explain only 12-14% variation in the lipid levels.[4]

The clinical significance of genetic variants associated with lipid abnormalities depends on the frequency of genetic variants in the population of interest. Further, the normative data of frequency of single nucleotide polymorphism (SNP) is essential for planning and conducting genotype-phenotype association studies. The frequency distribution of SNPs in other population cannot be used for planning studies in Indian population due to their unique genetic constitution.[5]

In earlier studies, the frequencies of genetic polymorphisms of genes involved in lipid and statin pathways such as *ApoA, ApoB,*[6] *CETP,*[7] ABCB1,[8,9] and *CYP3A5*[10] have been established among healthy South Indian Tamil population in our laboratory. For the current study, SNPs were selected based on their role in statin and cholesterol metabolism. These variants have been associated with altered LDL-C response to statins or associated with toxicity in other populations. However, there is no data among South Indian Tamil patients. Genes such as *HMGCR*, *LDLR* and *CYP7A1* are involved in the cholesterol metabolic pathway. *HMGCR* codes for 3-hydroxy-3-methylglutaryl-CoA reductase which is the rate-limiting enzyme for cholesterol synthesis.[11] *LDLR* codes for low -density lipoprotein receptor, which is involved in endocytosis of LDL cholesterol.[12] *CYP7A1* belongs to Cytochrome 450 group of enzymes which catalyzes the rate limiting step in cholesterol catabolism to bile acids, the major route of cholesterol elimination from the body.[13] *ABCB1* encodes the membrane associated protein which is a member of the superfamily of ATP-binding cassette (ABC) transporters which is involved in efflux of statins.[14] The *SLCO1B1* codes for hepatic solute carrier organic anion transporter family member 1B1 which is responsible for uptake of bilirubin and its metabolites and drugs like statins.[15]

Hence in the current study, we aimed to determine the frequencies of genetic variations for other genes in the lipid pathway such as *HMGCR* (rs5908, rs17238540, rs12916), *LDLR* (rs688), *CYP7A1* (rs3808607), *ABCB1* (rs1128503), and *SLCO1B1* (rs4149056) in South Indian Tamil population. We also aimed to compare the studied genotype distributions with that of other ethnic populations.

MATERIALS AND METHODS

The study was approved by the Institute Ethics Committee (Human Studies) of Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India. Written informed consent was obtained from participants recruited for the study. The study was conducted among 100 apparently healthy volunteers of either gender, aged between 27 and 70 years. All study subjects belonged to South Indian Tamil ethnicity which was defined as people with history of their past three generations residing in the state of Tamil Nadu or Puducherry and speaking Tamil language as the mother tongue.

Five milliliters of blood for genotyping was collected from the forearm of the patient in sitting posture, using ethylenediamine tetra-acetic acid (EDTA) as the anticoagulant. The cellular layer including the buffy coat was separated using ultracentrifugation at 2500 rotations per minute (RPM) for 10 min, and stored at -20^{0}C, until extraction. DNA extraction was performed using standard phenol chloroform method. Genotyping was done with allelic discrimination assays, with the kits obtained from Applied BioSystems (ABI) USA. The assay kits were based on TaqMan Technology. Real-Time PCR platform ABI 7300 was used. The allelic call was read with the help of sequence manipulation suite (SMS) version 1.4. The genotyping results were confirmed by running the samples in triplicates (representative genotypes) and by Sanger sequencing.

Hardy-Weinberg equilibrium for the studied genotypes was tested using Chi-square test. Genotype frequencies from the current study were compared with data from other studies using Fisher's Exact Test or Chi-square test. P value less than 0.05 was considered significant. All statistical tests were done using GraphPad Instat v 3.0 (GraphPad Software Inc., San Diego, CA, USA).

RESULTS

The study subjects included 75 females and 25 males with a mean age of 45.5 ± 10.9 (SD). The genotype and allele frequencies established in this study are given in Table 1. *HMGCR rs5908* was found to be very rare in the study population with only one subject having a heterozygous variant genotype with the absence of homozygous variant genotype. *HMGCR* rs17238540 polymorphism was also less prevalent in our population with the frequency of 3.5%.The variant alleles of *HMGCR* rs12916, *CYP7A1* rs3808607 and *ABCB1* rs1128503 polymorphisms were found to be more prevalent. The variant genotype of *SLCO1B1* rs4149056 polymorphism was not found in our population. All genotypes except *LDLR* rs688 polymorphism did not show significant deviation from Hardy -Weinberg equilibrium.

Data of genotype and allele counts of the studied SNPs from North India[16] and other major ethnic groups retrieved from 1000 genomes project phase 3 population[17] are given in Table 2. The distribution of variant genotypes of *HMGCR* rs5908 observed in our population was significantly different only from North Indian population. However, distribution of *HMGCR* rs17238540 genotypes were significantly different from other populations except for CEU (Utah residents with Northern and Western European Ancestry), MXL (Mexican Ancestry in Los-Angeles, California), and Europeans from Norfolk-United Kingdom.[18] The distribution of *HMGCR* rs12916 genotypes was significantly different from that of CEU, YRI (Yoruba in Ibadan, Nigeria) and MXL population. The distribution of *LDLR* rs688 genotypes in the current study was distinctly different from the other populations except that of CHB (Han Chinese in Beijing, China). The distribution of genotypes of *CYP7A1* rs3808607 polymorphism was significantly different from a north Indian study which included patients from Punjab, Haryana and Chandigarh and also from YRI and JPT (Japanese in Tokyo, Japan)but not from other population of North India.[19] The distribution of *ABCB1* rs1128503 was significantly different from that of CEU and YRI population. The distribution of genotypes of *SLCO1B1* in our population was significantly different from that of GIH (Gujarati Indian in Houston), CEU, CHB, and YRI.

Table 1: Genotype and allelic frequencies of the studied genetic polymorphisms

Gene	SNP	Genotype (%)			Allele (%)		HWE p-value
HMGCR	1912 A>G (rs5908)	**AA**	**AG**	**GG**	**A**	**G**	
		99	1	0	99.5	0.5	0.95
	74655498T>G (rs17238540)	**TT**	**TG**	**GG**	**T**	**G**	
		93	7	0	96.5	3.5	0.71
	*372C>T (rs129 16)	CC	CT	TT	C	T	
		36	46	18	59	41	0.62
LDLR	1773 C>T (rs688)	**CC**	**CT**	**TT**	**C**	**T**	
		64	20	16	74	26	<0.0001*
CYP7A1	58500365G>T (rs3808607)	**GG**	**GT**	**TT**	**G**	**T**	
		22	40	38	42	58	0.07
ABCB1	87550285A>G (rs1128503)	**GG**	**AG**	**AA**	**G**	A	
		18	47	35	41.5	58.5	0.74
SLCO1B1	521 T>C (rs4149056)	**TT**	**CT**	**CC**	**T**	**C**	
		86	14	0	93	7	0.45

HWE - Hardy Weinberg Equilibrium p value.

*p value less than 0.05, significant deviation from Hardy Weinberg Equilibrium

Table 2: Comparison of genotype counts of Tamilian population with other populations

SNP	Population	N	Genotype count			Allele count		P value
HMGCR rs5908	**Tamilians**	**100**	**AA**	**AG**	**GG**	**A**	**G**	
			99	**(1**	**0)**	**199**	**1**	
	North Indians[16]	150	126	(22	2)	274	26	<0.0001*
	GIH[17]	103	103	0	0	206	0	0.49
	ITU#	102	102	0	0	204	0	0.49
	BEB#	86	85	(1	0)	171	1	1.00
	PJL#	96	93	(3	0)	189	3	0.36
	STU#	102	100	(2	0)	202	2	1.00
	CEU#	99	94	(5	0)	193	5	0.12
	CHB#	103	103	0	0	206	0	0.49
	YRI#	108	108	0	0	216	0	0.48
	JPT#	104	104	0	0	208	0	0.49
	MXL#	64	63	(1	0)	127	1	1.00
HMGCR rs17238540	**Tamilians**	**100**	**TT**	**GT**	**GG**	**T**	**G**	
			93	**(7**	**0)**	**193**	**7**	
	North Indians	150	150	0	0	300	0	0.001*
	GIH	103	103	0	0	206	0	0.006*
	ITU	102	102	0	0	204	0	0.006*
	BEB	86	86	0	0	172	0	0.01*
	PJL	96	96	0	0	192	0	0.01*
	STU	102	101	(1	0)	203	1	0.03*
	CEU	99	96	(3	0)	195	3	0.33
	CHB	103	103	0	0	206	0	0.006*
	YRI	108	88	(19	1)	195	21	0.02*
	JPT	104	104	0	0	208	0	0.006*
	MXL	64	59	(5	0)	123	5	1.00
	European[18]	23011	22010	(989	12)	45009	1013	0.19
HMGCR rs12916	**Tamilians**	**100**	**CC**	**CT**	**TT**	**C**	**T**	
			36	**46**	**18**	**118**	**82**	
	North Indians	150	64	63	23	191	109	0.56
	GIH	103	35	55	13	125	81	0.45
	ITU	102	33	39	30	105	99	0.15
	BEB	86	31	37	18	99	73	0.86
	PJL	96	25	52	19	102	90	0.31
	STU	102	33	49	20	115	89	0.85
	CEU	99	17	46	36	80	118	0.001*
	CHB	103	29	49	25	107	99	0.37
	YRI	108	7	28	73	42	174	<0.0001*
	JPT	104	26	58	20	110	98	0.22
	MXL	64	12	24	28	48	80	0.001*
LDLR rs688	**Tamilians**	**100**	**CC**	**CT**	**TT**	**C**	**T**	
			64	**20**	**16**	**148**	**52**	
	GIH	103	42	45	16	129	77	0.0009*
	ITU	102	35	52	15	122	82	<0.0001*
	BEB	86	38	36	12	112	60	0.004*
	PJL	96	36	40	20	112	80	0.0006*

Table 2: Comparison of genotype counts of Tamilian population with other populations

SNP	Population	N	Genotype count			Allele count		P value
	STU	102	41	45	16	127	77	0.0007*
	CEU	99	35	42	22	112	86	0.0002*
	CHB	103	74	23	6	171	35	0.06
	YRI	108	105	3	0	213	3	<0.0001*
	JPT	104	73	29	2	175	33	0.001*
	MXL	64	18	39	7	75	53	<0.0001*
CYP7A1 rs3808607	**Tamilians**	**100**	**GG**	**GT**	**TT**	**G**	**T**	
			22	**40**	**38**	**84**	**116**	
	North Indians[19]	200	29	101	70	159	241	0.13
	North Indians[16]	150	8	38	104	54	246	<0.0001*
	GIH	103	18	52	33	88	118	0.32
	ITU	102	23	52	27	98	106	0.18
	BEB	86	18	48	20	84	88	0.05
	PJL	96	13	42	41	68	124	0.30
	STU	102	27	46	29	100	104	0.34
	CEU	99	16	40	43	72	126	0.53
	CHB	103	23	44	36	90	116	0.89
	YRI	108	37	55	16	129	87	0.0006*
	JPT	104	30	53	21	113	95	0.01*
	MXL	64	5	31	28	41	87	0.056
ABCB1 rs1128503	**Tamilians**	**100**	**GG**	**AG**	**AA**	**G**	**A**	
			18	**47**	**35**	**83**	**117**	
	GIH	103	17	55	31	89	117	0.65
	ITU	102	15	53	34	83	121	0.73
	BEB	86	12	40	34	64	108	0.69
	PJL	96	22	46	28	90	102	0.57
	STU	102	18	42	42	78	126	0.63
	CEU	99	29	55	15	113	85	0.003*
	CHB	103	11	40	52	62	144	0.06
	YRI	108	78	29	1	185	31	<0.0001*
	JPT	104	18	47	39	83	125	0.93
	MXL	64	17	34	13	68	60	0.10
SLCO1B1 rs4149056	**Tamilians**	**100**	**TT**	**CT**	**CC**	**T**	**C**	
			86	**14**	**0**	**186**	**14**	
	GIH	103	99	4	0	202	4	0.01*
	ITU	102	90	11	1	191	13	0.63
	BEB	86	77	9	0	163	9	0.46
	PJL	96	90	5	1	185	7	0.07
	STU	102	93	9	0	195	9	0.24
	CEU	99	71	27	1	169	29	0.01*
	CHB	103	77	24	2	178	28	0.04*
	YRI	108	106	2	0	214	2	0.001*
	JPT	104	82	19	3	183	25	0.18
	MXL	64	54	10	0	118	10	0.77

#Data obtained from 1000 genome project; GIH- Gujarati Indian in Houston, TX, ITU-Indian Telugu in the UK, BEB-Bengali in Bangladesh, PJL-Punjabi in Lahore, Pakistan, STU-Sri Lankan Tamil in the UK, CEU-Utah residents with Northern and Western European Ancestry, CHB-Han Chinese in Beijing, China, YRI-Yoruba in Ibadan, Nigeria, JPT-Japanese in Tokyo Japan, MXL-Mexican Ancestry in Los-Angeles, California. Parentheses ( ) indicates genotypes were combined for analysis, due to low numbers. Genotype count from current study were compared with data from other studies using Fisher's Exact Test or Chi square test.

DISCUSSION

The present study has determined the normative data on allele and genotype frequencies for SNPs of five genes namely, *HMGCR* (rs5908, rs17238540, rs12916), *LDLR* (rs688), *CYP7A1* (rs3808607), *ABCB1* (rs1128503), and *SLCO1B1* (rs4149056). These genes are involved in the maintenance of plasma lipid levels and the metabolism of statin drugs. To the best of our knowledge this study is the first to describe this information for South Indian Tamil population. The normative data on allele and genotype frequencies are important for planning of any genetic study to estimate sample size and to understand the clinical implications of a genetic variation. Thus, the current study provides the background information needed for future studies on pharmacogenetics of lipid metabolism and statins among South Indian Tamil population.

Genetic variants of HMG-CoA reductase (*HMGCR*) have been widely studied for their effect on lipid levels and variations in therapeutic responses to different statins. *HMGCR* variants have been associated with diminished response to pravastatin and simvastatin but not to fluvastatin[20] and atorvastatin.[21] Further, they were also found to be associated with varied response between different ethnic groups.[22] Among the three SNPs studied in *HMGCR* gene, variant genotypes of rs12916 and rs17238540 are more common in the study population. In contrast, *HMGCR* rs5908 variant being in low frequency may have less clinical relevance for the study population, even if functionally significant. Functional studies on rs12916 and rs17238540 variants may have clinical relevance in elucidating the effect of these SNPs on lipid homeostasis.

The *HMGCR* rs17238540 was found to be associated with reduced efficacy of statins in terms of lowering plasma levels of total cholesterol (TC) and LDL-C. Individuals with heterozygous variant genotype (GT) had 19% lower reduction in LDL-C when treated with pravastatin.[23] In the GoDARTS study, individuals with *HMGCR* rs17238540 variant G allele were associated with failure to achieve lipid lowering target.[24] In a study by Poduri *et al.,* in North Indian population, the variant genotypes of *HMGCR* rs17238540 was associated with significantly higher LDL-C levels after atorvastatin therapy compared to wild type.[25] However, in a study by Thompson *et al*., this SNP was not associated with response to atorvastatin.[21] In few studies, *HMGCR* rs17238540 was not associated with baseline lipid values.[18,23,24] In the multi-ethnic study of atherosclerosis the *HMGCR* haplotypes,[26] and these genotypes among North Indians were associated with baseline lipid levels respectively.[25] It was also observed that the *HMGCR* rs17238540 might negate some of the observed pleiotropic effects of statins, such as improved endothelial function, decreased platelet aggregability and reduced vascular inflammation and was also found to be associated with stroke risk in the EPIC-Norfolk study.[27]

The *HMGCR* rs12916 locus has been associated with total cholesterol and LDL-C levels among Europeans as well as East Asians and South Asians in a genome wide study.[28] In candidate gene studies the mean percentage reduction in LDL-C with *HMGCR* rs12916 polymorphisms among Chinese were found to be highest for homozygous variant, least for wild genotype and intermediate for heterozygous individuals after treatment with statins[29] while, studies among North Indians revealed that variant genotypes of this polymorphisms were responsible for poor response to atorvastatin in terms of LDL-C lowering.[25] Given the high prevalence of this genetic polymorphism among Tamilians, it would be of interest to determine the effect of this polymorphism on the lipid levels in our population.

LDL receptor gene (LDLR) is a commonly studied genetic locus for dyslipidemias. Genetic variations in LDL receptor gene may greatly reduce or abolish the function of LDL receptor. This may lead to increase in circulating LDL-C levels and risk of CAD.[30] Although LDLR gene mutations are associated with familial hypercholesterolemia (FH), less dysfunctional variants have been associated with response to statin in non –FH individuals.[31] Studies by Haiyan Zhu and his colleagues have identified SNP *LDLR* rs688 to be present in 60% of Caucasians and associated with a significant 10% increase in total and LDL-cholesterol in pre-menopausal women.[32] This SNP has been recently shown to alter splicing efficiency, with the T allele being associated with increased total and LDL-cholesterol levels among premenopausal women.[33] Since this SNP is present in high frequency in the study population, and since it has not been studied among Indian population at large, more studies on the functional significance, of this SNP might yield useful information on the genetics of LDL-C in our population.

The genotype distribution of *CYP7A1* rs3808607 variants among Tamilian population was found to be similar to another study involving people from Lucknow region of North India,[19] whereas it was significantly different from the results obtained in a study among North Indian regions of Punjab, Haryana, and Chandigarh,[16] revealing the diversity even among North Indians. The genetic variants of *CYP7A1* rs3808607, *ABCB1* rs1128503, and *SLCO1B1* rs4149056, although similar to most other populations in frequency distribution, were found to occur at a higher frequency in the study population and may have clinical relevance if functional significance can be demonstrated in future studies.

CONCLUSION

The study has established the allele and genotype frequency distributions for *HMGCR* (rs5908, rs17238540, rs12916), *LDLR* (rs688), *CYP7A1* (rs3808607), *ABCB1* (rs1128503), and *SLCO1B1* (rs4149056) genetic variants among healthy subjects of South Indian Tamil population. The South Indian Tamil population is a unique ethnic group in terms of genetic polymorphisms in the cholesterol and statin metabolic pathways.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

ABBREVIATION USED

ApoA*:** Apolipoprotein A; ***ApoB*:** Apolipoprotein B; ***CETP*:** Cholesteryl ester transfer protein; ***ABCB1*:** ATP binding Cassette subfamily B member 1; ***CYP3A5*:** Cytochrome P450 family 3 subfamily A member 5; ***CYP7A1: Cytochrome P450 family 7 subfamily A member 1.

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