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PharmGKB: very important pharmacogene – HMGCR

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Keywords

HMGCR; 3-hydroxy-3-methylglutaryl coenzyme A reductase; PharmGKB; pravastatin; statin

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase enzyme (EC 1.1.1.88) catalyzes the NADP-dependent conversion of HMG-CoA to mevalonate in the rate-limiting step of cholesterol biosynthesis, and is the target of the statin family of cholesterol lowering drugs. In addition, this pathway also produces isoprenoid intermediates, which act as lipid attachments for intracellular signaling molecules such as Rho, Ras, and Rac [1]. The inhibition of these small GTP-binding proteins is thought to mediate the pleiotropic effects of statins [2]. Given its importance in regulating mevalonate production for both sterol and nonsterol end products, HMGCR is very tightly regulated by transcriptional, posttranscriptional, and posttranslational mechanisms [1]. The *HMGCR* gene is found on chromosome 5q13.3–q14 [3] and is comprised of 20 exons spanning approximately 25 kb. The 4475 bp transcript encodes an 888 amino acid protein which is widely expressed throughout the body. Alternative splicing of exon 13 has been described, but it is unknown whether this variant is translated into a protein [4–6]. In the Pravastatin Inflammation/CRP Evaluation (PRINCE) trial of 1536 individuals treated with 40 mg/day pravastatin for 24 weeks, Chasman *et al.* [7] reported a significant association between two common and tightly linked intronic single nucleotide polymorphisms (SNPs 12 A/T and 29 T/G) and reduced pravastatin efficacy as measured by smaller total cholesterol and LDL-cholesterol reductions. These two SNPs define haplotype 7 (H7), one of the 10 major haplotypes identified in this predominantly Caucasian population. H7 was later redefined by Krauss *et al.* [8], who discovered that the H7 haplotype includes an additional intronic SNP, rs3846662, otherwise known as SNP 20144, thus defining the H7 haplotype as carriers of SNPs 12, 29, and 20144 [8]. In addition to the original observation in the PRINCE population, the association between H7 and statin response has also been reported in two additional independent populations, The Cholesterol and Pharmacogenomics (CAP) and the Genetics of Diabetes Audit and Research in Tayside Scotland Database (GoDARTS); however, this association failed to replicate in the Atorvastatin Comparative Cholesterol Efficacy and Safety Study (ACCESS), Assessment of Lescol in Renal Transplantation (ALERT), Prospective Study of Pravastatin in the Elderly at Risk, or Treatment to New Targets (TNT) studies [8–13]. Recently, alternative splicing of exon 13 of the *HMGCR*

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transcript, *HMGCR13*(-), has been identified as marker of statin response as its expression is correlated with the magnitude of plasma total cholesterol, LDL-cholesterol, apolipoprotein (apo) B and triglyceride reductions with statin treatment [6]. As SNP 20144 has been shown to directly influence production of the *HMGCR13*(-) transcript [5,6], *HMGCR* alternative splicing is likely one of the molecular mechanisms contributing to the association among H7, H2, and statin response.

Despite the failure to replicate in several populations, the identification of an association between H7 and statin response in three independent populations, together with molecular data of a functional effect of the *HMGCR* H7 haplotype provides strong evidence that this genotypic relationship with statin response is valid.

Supplemental digital content for the *HMGCR* gene (PA189) and very important pharmacogene is available at <http://www.pharmgkb.org/search/annotatedGene/hmgcr/>

Important variants

<http://www.pharmgkb.org/search/annotatedGene/hmgcr/variant.jsp>

HMGR: SNP 12 (rs17244841)

Also known as SNP 12, the estimated allele frequencies of this variant in the predominantly Caucasian PRINCE population (88.7%) are $A = 0.965$ and $T = 0.035$. Complete details of genotypic frequencies are shown in the Table 1. In a study of 1536 individuals, SNP 12 was significantly associated with the mean change in both total and LDL-cholesterol. Heterozygous individuals had a 21.8% reduction in total cholesterol lowering and a 19.0% reduction in LDL-cholesterol lowering after pravastatin treatment as compared with individuals homozygous for the major (A) allele. There was no genotype effect on HDL-cholesterol changes. These effects remained significant after multiple testing, were not associated with baseline differences, and the LDL-cholesterol effect became stronger after ethnic stratification [7]. SNP 12 was also reported to be significantly associated with reduced total and LDL-cholesterol response to simvastatin treatment, 6 weeks of 40 mg/day, in the CAP population, comprised of 335 African Americans and 596 Caucasians. Although similar allele frequency and effect sizes were reported between the PRINCE and CAP populations, the relationship was observed only in the African American subset of the CAP cohort [8]. In contrast, this association was not identified in the ALERT population of 707 Caucasian fluvastatin treated renal transplant patients [12].

HMGR: SNP 29 (rs17238540)

Rs17238540, also known as SNP 29, is found in tight linkage disequilibrium ($r^2 > 0.9$) with SNP 12, with identical allele frequencies reported in the PRINCE population, $T = 0.965$ and $G = 0.035$ [7]. The GoDARTS Caucasian population reported a similar minor allele frequency of 0.033 ($N = 1601$), whereas the ACCESS trial reported a minor allele frequency of 0.0 in Asians ($N = 36$), 0.085 in African Americans ($N = 160$), 0.027 in Caucasians (2454), and 0.029 in Hispanics ($N = 85$). Association between SNP 29 and attenuated statin response has been reported in three independent populations. In the PRINCE trial, similar to SNP 12, SNP 29 was also significantly associated with the mean change in both total and LDL-cholesterol response to pravastatin [7]. Heterozygous individuals had a 22.3% reduction in total cholesterol lowering and a 19.0% reduction in LDL-cholesterol lowering after pravastatin treatment as compared with individuals homozygous for the major allele. In the CAP trial, African American SNP 29 carriers had reduced total cholesterol and LDL-cholesterol lowering, 14.1 and 12.2%, respectively, in response to simvastatin treatment compared with SNP 29 noncarriers [8]. Similarly, the GoDARTs study of 1601 Caucasians treated with a variety of different statins (predominantly simvastatin) also reported SNP 29

heterozygotes had a 13% smaller reduction in total cholesterol and a 27% smaller reduction in triglycerides compared with noncarriers [9]. The association between SNP 29 and LDL-cholesterol reduction with statin treatment was not replicated in either the ACCESS, ALERT, PROSPER or TNT studies [10–13]. The ACCESS trial reported no significant association between SNP 29 and LDL-cholesterol reduction in 293 genotyped Caucasian individuals treated with pravastatin for 24 weeks. The trial also included 1902 individuals treated with atorvastatin, 477 individuals with fluvastatin, 476 individuals with lovastatin, and 468 individuals with simvastatin, however no other associations between SNP29 and statin efficacy were reported [10]. The ALERT study included 707 Caucasian fluvastatin treated (40–80 mg/day) renal transplant recipients, and while no significant SNP 29 effect was found, the data suggested trends in the same direction as those reported in the PRINCE trial [12]. Lastly, in 2891 elderly (aged 70–82) pravastatin treated (40 mg/day) Caucasians comprising the PROSPER trial, no association was found between SNP 29 and either LDL-cholesterol response to pravastatin or coronary heart disease or cardiovascular disease event rates. However, the SNP29 allele frequency was notably more rare in the PROSPER population (1.9% carrier) compared with the PRINCE population [13]. Lastly, the TNT study included 5745 individuals with European ancestry treated with atorvastatin, 10–80 mg/day. Although no association between SNP 29 and LDL-cholesterol response to atorvastatin was identified, the authors were unable to rule out if a lack of replication was due to a statin specific effect [11].

Despite this lack of replication, SNP 29 has also been reported to be associated with baseline lipid levels [8]. Most recently, this SNP was found to be associated with greater total and LDL-cholesterol in a population of 265 North Indian patients with coronary artery disease [15]. In addition, it has also been associated with insulin resistance in women with polycystic ovary syndrome [14] suggesting that this SNP may be important in non-lipid phenotypes as well.

HMGR: SNP 20144 (rs3846662)

Also known as SNP 20144, rs3846662 occurs in the CAP population (Caucasian $n = 596$, African American $n = 326$) at a frequency of A = 0.615 and G = 0.385, however, the allele frequency varies greatly between racial groups as the 'A' allele is significantly more prevalent in the Caucasians compared with the African Americans [8]. Although this SNP by itself is not significantly associated with statin response, it is one of three SNPs, which defines HMGR haplotype 7 (H7), that has been shown to be associated with reduced simvastatin and pravastatin response. In addition, SNP 20144 regulates alternative splicing of *HMGR* exon 13 to produce a transcript in which exon 13 has been completely omitted. A genome-wide association study *HMGR* SNP, rs12654264, in tight linkage disequilibrium with the SNP 20144 ($r^2 > 0.8$) has been reported in multiple independent populations to be associated with endogenous variation in plasma LDL-cholesterol [5,16,17].

Important haplotypes

<http://www.pharmgkb.org/search/annotatedGene/hmgr/haplotype.jsp>

HMGR: H7

Identified by Chasman *et al.* [7], *HMGR* H7 was originally defined by SNPs 12 and 29, and found to be associated with reduced total cholesterol and LDL-cholesterol response to pravastatin therapy [7]. However, with additional resequencing and genotyping of tag SNPs spanning the entire *HMGR* gene, Krauss *et al.* [8] found that the H7 haplotype also includes SNP 20144. Although the original two-SNP definition of H7 did not offer

additional information than either SNP 12 or SNP 29 alone, the three-SNP definition has added value over the SNPs alone as SNP 20144 is found in two different haplotypes, H7 and H2. In the CAP population, African American H7 carriers had a 20.5% smaller reduction of total cholesterol and 24.4% smaller reduction of LDL-cholesterol in response to simvastatin treatment compared with noncarriers, $P = 0.002$ and 0.0009 , respectively. The H7 haplotype is found in 3% of Caucasians and 6% of African Americans [8]. Alternative splicing of exon 13 of the *HMGCR* transcript is likely one of the molecular mechanisms underlying the association between H7 and statin response. Through in-vitro statin incubation experiments of immortalized lymphocyte cell lines derived from the CAP individuals, Medina *et al.* reported that SNP 20144 is associated with statin-induced expression of the *HMGCR* transcript without exon 13, *HMGCR13(-)*, a finding that was independently validated using expression constructs [5,6]. In addition, greater in-vitro statin-induced *HMGCR13(-)* expression was found to be significantly related to smaller in-vivo reductions of plasma total cholesterol, LDL cholesterol, apoB and triglycerides. Furthermore, artificial enrichment of the *HMGCR13(-)* transcript via siRNA resulted in cells with reduced statin sensitivity, suggesting that the association between H7 with attenuated statin response is due to variation in the production of an *HMGCR* isoform with reduced statin sensitivity [6].

HMGCR H7 has also been found to be associated with baseline lipid levels in both the CAP and The Multi-Ethnic Study of Atherosclerosis (MESA) populations. CAP African American H7 carriers had lower baseline total cholesterol, LDL-cholesterol and apoB compared to noncarriers [8]. In the MESA population consisting of 597 African Americans, 627 Chinese Americans, 612 European Americans and 108 Hispanic Americans, a haplotype containing SNPs 12, 20144 and 29 was reported to be associated with significantly lower levels of triglycerides in the African American and Hispanic American ethnic groups within MESA population [18].

HMGR: H2

Originally identified by Krauss *et al.* [8], *HMGCR* haplotype 2 is defined as the combination of common alleles across 11 tag SNPs within *HMGCR*, and is found at a frequency of 0.32 in African Americans and 0.02 in Caucasians. H2 carriers had 10.3% smaller reductions of total cholesterol and 10.0% smaller reductions of LDL-cholesterol in the African American subset of the CAP population, P less than 0.05. Although this relationship was not as prominent as the H7 haplotype, notably, individuals who carry both the H2 and H7 *HMGCR* haplotypes have even further reductions in the LDL-cholesterol response compared to either H2 or H7 carriers alone [8]. As H2/H7 carriers are effectively SNP 20144 homozygotes who also carry SNPs 12 and 29, and SNP 20144 is a known genetic determinant of *HMGCR* exon 13 alternative splicing, it is likely that the relationship between both H2 and H7 with statin response is driven by regulation of exon 13 alternative splicing [6].

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Table 1

HMGCR variant allele frequencies

	Population	Individual group	Chromosome number	Allele		Reference
				Major	Minor	
SNP 12 (rs17244841) major allele = A, minor allele = T	PRINCE	Caucasian (88.7%)	2662	0.933	0.067	[7]
	ALERT	Caucasian (97.6%)	1320	0.955	0.045	[12]
		European American	948	0.967	0.033	[14]
SNP 29 (rs17238540) major allele = T, minor allele = G	PRINCE	Caucasian (88.7%)	2662	0.933	0.067	[7]
	Go-DARTS	European (Scotland)	5188	0.97	0.03	[9]
	CAP	African American	652	0.926	0.074	[8]
		European American	1192	0.968	0.032	
	ACCESS	Asian	72	1	0	[10]
		African American	320	0.915	0.085	
SNP 20144 (rs3846662) major allele = G, minor allele = A		Caucasian American	4908	0.972	0.028	
		Hispanic	170	0.971	0.029	
	ALERT	Caucasian (97.6%)	1172	0.952	0.048	[12]
	PROSPER	European (Scotland)	11566	0.981	0.019	[13]
		North Asian Indian	830	0.928	0.072	[15]
		European American	948	0.969	0.031	[14]
Haplotype 2 carrier vs. noncarrier	PARC	African American	46	0.826	0.174	[8]
		European American	46	0.391	0.609	
	CAP	African American	652	0.873	0.127	[8]
		European American	1192	0.475	0.525	
		European American	948	0.412	0.588	[14]
	HapMap	CEU-Caucasian	120	0.458	0.542	
Haplotype 7 carrier vs. noncarrier		HCb-Asian	90	0.567	0.433	
		JPT-Asian	90	0.533	0.467	
		YRI-Sub-Saharan African	120	0.933	0.067	
	CAP	African American	652	0.68	0.32	[8]
		European American	1192	0.98	0.02	
		European American	948	0.956	0.044	[14]
	CAP	African American	652	0.94	0.06	[8]

Population	Individual group	Chromosome number	Allele		Reference
			Major	Minor	
	European American	1192	0.97	0.03	[14]
	European American	948	0.969	0.031	

ACCESS, Atorvastatin Comparative Cholesterol Efficacy and Safety Study; ALERT, Assessment of Lescol in Renal Transplantation; CAP, Cholesterol and Pharmacogenomics; CEU, Utah residents with ancestry from northern and western Europe; Go-DARTS, Genetics of Diabetes Audit and Research in Tayside Scotland Database; HCB, Han Chinese in Beijing, China; JPT, Japanese in Tokyo, Japan; PARC, Pharmacogenomics and Risk of Cardiovascular Disease; PRINCE, Pravastatin Inflammation/CRP Evaluation; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; YRI, Yoruba in Ibadan, Nigeria.