

The *MYLIP* p.N342S polymorphism is associated with response to lipid-lowering therapy in Brazilian patients with familial hypercholesterolemia

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Background A previous study reported that the myosin regulatory light chain interacting protein (MYLIP) might serve as a novel therapeutic class for treating dyslipidemia. It contributes to variations in the levels of circulating low-density lipoprotein cholesterol (LDL-C), promoting the degradation of LDL-LDLR, thus limiting absorption. The effect of genetic variation in the *MYLIP* gene in a disease scenario characterized by mutations in the *LDLR* gene has not been previously evaluated.

Objective The aim of this study was to assess the effect of the p.N342S variant on the response to lipid-lowering therapy in Brazilian patients with heterozygous familial hypercholesterolemia (FH).

Patients and methods A total of 156 patients with heterozygous FH were followed up for 12 months and received lipid-lowering therapy (different doses of atorvastatin with the addition of ezetimibe in over half the patients of each genotype group). Cholesterol data were assessed, and analysis of the *MYLIP* rs9370867 (p.N342S) genotypes was carried out by melting curve analysis.

Results Baseline total cholesterol and baseline LDL-C levels were not different between genotypes. After 1 year of treatment, LDL-C responses (expressed as mg/dl and as %) were significantly different among genotypes (AA: -79 ± 68

and -39 ± 27 , GA: -60 ± 79 and -27 ± 32 , and GG: -30 ± 83 and -15 ± 38 ; $P=0.02$ and 0.005 , respectively). In addition, FH patients carrying the AA genotype were more likely to achieve LDL-C levels of less than 130 mg/dl after 1 year of treatment (75.0%) compared with patients with the GG and GA genotypes (34.5 and 34.8%, respectively; $P=0.001$).

Conclusion Our study indicates that *MYLIP* p.N342S might be a pharmacogenetic marker for lipid-lowering therapy in patients with FH. *Pharmacogenetics and Genomics* 24:548–555 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Statins, competitive inhibitors of HMG-CoA reductase, are widely prescribed to reduce cardiovascular morbidity and mortality. Although several types of statins and nonstatin lipid-lowering drugs are available, a proportion of dyslipidemic patients actually do not achieve therapeutic goals [1].

Familial hypercholesterolemia (FH) is an autosomal dominant disease caused primarily by mutations in the *LDLR* gene. FH patients, despite being a high-risk group for cardiovascular disease, are usually undertreated [2].

The identification of new markers of treatment response would allow for more effective treatment delivery, reducing the risk for cardiovascular disease in this population.

Current studies provide evidence that genetic factors, such as polymorphisms in the *APOE*, *SLCO1B1*, *CYP3A4*, *CYP3A5*, *KIF6*, *CETP*, *HMGCR*, and *ABCB1* genes, can contribute to interindividual variations in response to lipid-lowering statin therapy and/or toxicity from statins. However, the total variability due to genetic variants is still unknown [3–12].

The myosin regulatory light chain interacting protein (MYLIP; also known as IDOL) has been indicated as a possible target for a new and useful strategy in the pharmacological treatment of dyslipidemia. The protein is coded for by the *MYLIP* gene and works as a regulator of the low-density lipoprotein receptor (LDLR) pathway for cellular cholesterol absorption [13]. Recent studies

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have identified *MYLIP* genomic regions to be associated with low-density lipoprotein cholesterol (LDL-C) levels [14–16]. Later, a study identified a nonsynonymous polymorphism (p.N342S, rs9370867) as the accounting basis for the functional variation observed in previous studies. Furthermore, it has been shown that the N342 allele is associated with higher levels of LDLR degradation and decreased LDL-C uptake [17].

In this scenario, the main aim of this study was to evaluate the effect of p.N342S on the response to lipid-lowering therapy in Brazilian patients with FH.

Patients and methods

Clinical and laboratory evaluation of patients

This study included 156 index Brazilian patients with a heterozygous FH phenotype ascertained by the Lipid Clinic, Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil. These patients were diagnosed on the basis of biochemical and clinical data [18,19] and were followed up for at least 12 months, from January 2006 to December 2012, while receiving lipid-lowering therapy. Patients were categorized into self-declared ‘racial/color’ subgroups, according to the criteria used by the Brazilian Census, as White, Brown (*Pardo* in Portuguese), or Black [20]. The Institutional Ethics Committee approved the study protocol (CAPPesq numbers 022/11 and 191/04), and written informed consent was obtained from all participants before entering the study.

Treatment was administered by the attending physician without any knowledge of the kind of genetic defect causing the FH phenotype. Atorvastatin dosage and coadministration of ezetimibe, an adjuvant cholesterol-lowering medication, were at physician discretion, to attain the greatest possible LDL-C reduction. All patients were assessed at least three times during follow-up. Plasma total cholesterol (TC) and LDL-C levels were measured using enzymatic methods during the following periods: at baseline (first value), at the initiation of atorvastatin use (immediately before), and, on average, after 1-year of treatment onset (the first two measured values were not necessarily the same).

Genetic analyses

Genomic DNA was extracted from the peripheral blood of patients following a standard salting-out procedure. Coding sequences of the *LDLR* gene (18 exons) were amplified by PCR. PCR products were bidirectionally sequenced using the ABI Terminator Sequencing Kit and the ABI 3500XL Sequencer (Applied Biosystems, Foster City, California, USA) according to the manufacturer’s instructions. In addition, the *APOB* and *PCSK9* genes were sequenced and the multiplex ligation-dependent probe amplification technique was used to identify *LDLR* gene deletions/insertions. *LDLR* gene mutations were classified according to their probable

functional class as previously reported in the literature. For multivariable analysis, we grouped individuals with null or a defective mutation into the same group and compared them with individuals with no identified mutation (we defined this variable as the presence of an *LDLR* mutation) [21–24]. Genotypes for the *MYLIP* rs9370867 (p.N342S, c.G1025A) polymorphism were detected by PCR followed by high-resolution melting (HRM) analysis using the Rotor Gene 6000 instrument (Qiagen, Courtaboeuf, France) [25]. Amplification of the fragment was performed using the sense 5′-TTGTGGACCTCGTTTCAAGA-3′ and antisense 5′-GCTGCAGTTCATGCTGCT-3′ (80 bp) primers for rs9370867. A 40-cycle PCR was carried out under the following conditions: denaturation of the template DNA in the first cycle at 94°C for 120 s, denaturation at 94°C for 20 s, annealing at 53.4°C for 20 s, and extension at 72°C for 22 s. PCR was performed using a 10- μ l reactive solution (10 mmol/l tris-HCl, 50 mmol/l KCl, pH 9.0, 2.0 mmol/l MgCl₂, 200 μ mol/l of each dNTP, 0.5 U Taq DNA polymerase, 200 nmol/l of each primer, 10 ng genomic DNA template) with the addition of fluorescent DNA-intercalating SYTO9 (1.5 μ mol/l; Invitrogen, Carlsbad, California, USA).

In the HRM phase, the Rotor Gene 6000 measured the fluorescence at each 0.1°C temperature increase in the range of 73–85°C. Melting curves were generated from the decrease in fluorescence with the increase in the temperature and, on analysis, nucleotide changes resulted in three different curve patterns. Samples from the three observed curves were analyzed using bidirectional sequencing as a validation procedure (ABI Terminator Sequencing Kit and ABI 3500XL Sequencer; Applied Biosystems). The GG, GA, and AA genotypes for rs9370867 were easily discernible by HRM analysis. In addition, 15% of the samples were reanalyzed as a quality control measure and gave identical results [26].

Statistical analysis

The χ^2 -test or Fisher’s exact test (if an expected cell frequency was <5) was used for comparative analysis of the general characteristics and the LDL-C status according to *MYLIP* rs9370867 genotypes. The χ^2 -test was also used for estimating Hardy–Weinberg equilibrium [27]. The Shapiro–Wilk test showed that cholesterol data had a normal distribution. Analysis of variance (ANOVA) was carried out to compare the age, BMI, baseline cholesterol data, and cholesterol responses according to genotypes. If ANOVA identified a significant difference ($P \leq 0.05$), Tukey’s post-hoc test was performed, and the different significance levels for these hypothesis tests are shown in the tables as superscript codes. TC and LDL-C responses, expressed in mg/dl, were calculated by subtracting the time zero value from the 1-year follow-up value. The proportion change of TC and the proportion change of LDL-C, expressed as

percentages, were calculated as follows: (1-year follow-up treatment value – time zero)/time zero value. For multivariate analysis, baseline cholesterol data were adjusted for age, sex, and race (defined as White or non-White). LDL-C and TC responses and 1-year treatment data were also adjusted for baseline value, atorvastatin doses, and ezetimibe use. Regression models were developed using *MYLIP* genotypes in an additive model (0, 1, or 2 for AA, GA, and GG, respectively). Logistic regression multivariate analysis was carried out to evaluate factors associated with not achieving target LDL-C levels (LDL-C < 130 mg/dl vs. LDL-C ≥ 130.0 mg/dl; this value was defined arbitrarily). We also tested the effect of *MYLIP* genotypes in a multiple linear regression model including the following variables: number of variant alleles for *MYLIP* rs9370867 (0, 1, or 2 for GG, GA, or AA, respectively), age, sex, BMI, race, smoking status, atorvastatin dose, ezetimibe use, baseline LDL-C level, and the presence of *LDLR* mutations (null plus defective mutations vs. no mutation). All statistical analyses were carried out using SPSS software (version 16.0; IBM, New York, New York, USA), with the level of significance set at a *P*-value of 0.05 or lower.

Results

Characteristics of studied FH patients

Of the 156 patients (mean age 52.5 ± 14.5), 106 (67.9%) were female and 50 (32.1%) were male. All patients received atorvastatin for at least 12 months (mean ± SD 14 ± 3 months of follow-up on therapy). The current dose of atorvastatin and the use of 10 mg/day ezetimibe according to the *MYLIP* polymorphism are shown in Table 1. Only 10 (6.4%) patients had their doses modified during follow-up, and none of the study participants discontinued the drug. All dosage changes among the study participants were to up-titrate atorvastatin to a higher dosage in individuals who did not receive the maximum dosage at the first medical visit. All prescriptions were made at the physician discretion, who had no knowledge of the *MYLIP* genotype or the type of *LDLR* mutation.

Frequencies of the *MYLIP* rs937086 genotypes

The frequency of the *MYLIP* rs937086 A variant allele was 39.7%, and the distribution of the genotypes was 18.6% (*n* = 29) for the AA genotype, 42.3% (*n* = 66) for the GA genotype, and 39.1% (*n* = 61) for the GG genotype. The genotypic distribution for the *MYLIP* rs937086 polymorphism was in accordance with Hardy–Weinberg equilibrium ($\chi^2 = 2.12$, *P* = 0.14). Table 1 shows the genotypic distribution for the *MYLIP* rs937086 polymorphism according to race.

Baseline characteristics according to *MYLIP* rs937086 genotypes

Table 1 shows the baseline characteristics of the study participants according to genotype. The variables age,

Table 1 Baseline characteristics of FH patients according to *MYLIP* rs9370867 genotypes

Variables	Genotypes			<i>P</i> -value
	GG (<i>n</i> = 61)	GA (<i>n</i> = 66)	AA (<i>n</i> = 29)	
Age (years)	56.7 ± 15.3	49.44 ± 13.4	50.4 ± 13.1	0.14
Sex, female (%)	62.3	69.7	75.9	0.40
Race/color (%)				
White (<i>n</i> = 119)	31.9	47.1	21.0	< 0.01
Non-White (<i>n</i> = 37)	62.2	27.0	10.8	
BMI (kg/m ²)	26.9 ± 6.2	27.9 ± 5.1	26.2 ± 3.2	0.40
Smoking (%)				
No	51.7	75.0	73.3	
Ex-smoker	44.8	14.3	6.7	< 0.01
Yes	3.5	10.7	20.0	
Total cholesterol (mg/dl)	343 ± 88	340 ± 78	332 ± 85	0.84
LDL-C (mg/dl)	262 ± 84	265 ± 78	260 ± 84	0.93
HDL-C (mg/dl)	46 ± 11	46 ± 11	48 ± 9	0.75
Triglycerides (mg/dl)	151 ± 76	152 ± 82	162 ± 109	0.86
Atorvastatin current dose (%)				
20 mg/day	4.9	10.6	13.8	0.95
40 mg/day	27.9	27.7	20.7	
60 mg/day	1.6	0	3.4	
80 mg/day	66.6	66.7	62.1	
Presence of ezetimibe	59.0	57.6	51.7	0.80
10 mg/day (%)				
Presence of <i>LDLR</i> mutation (%)*	67.2	60.6	62.0	0.73

Baseline cholesterol data are adjusted for age, sex, and race. Race/color was categorized as White and non-White (Intermediate plus Black; details in the Patients and methods section).

ANOVA test was performed for continuous variables and the χ^2 -test or Fisher's exact tests were performed for categorical variables.

ANOVA, analysis of variance; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; *LDLR*, low-density lipoprotein receptor; *MYLIP*, myosin regulatory light chain interacting protein.

*Probable functional *LDLR* gene mutation classes were classified according to previously reported data in the literature (detail in the Patients and methods section).

sex, BMI, baseline cholesterol level, and the presence of *LDLR* mutations were not significantly different according to genotypes. White patients more frequently had GA and AA genotypes, whereas patients who smoked more frequently had the AA genotype.

Cholesterol data and response to lipid-lowering therapy according to *MYLIP* rs937086 genotypes

Table 2 shows data on cholesterol and response to lipid-lowering therapy. After 1-year of treatment, LDL-C values were different among *MYLIP* rs937086 genotypes adjusted for age, sex, race, baseline value, atorvastatin doses, and ezetimibe use (*P* = 0.04, ANOVA test). In the Tukey's post-hoc test, patients carrying the AA genotype were found to have lower LDL-C levels (134 ± 50 mg/dl) compared with patients carrying the GG genotype (174 ± 71 mg/dl). In addition, FH patients carrying the AA genotype had a greater LDL-C response (–79 ± 68 mg/dl) and a higher frequency of LDL-C less than 130.0 mg/dl (75.0%) compared with GG genotype carriers (–30 ± 83 mg/dl and 34.5%; *P* = 0.02 and 0.001, respectively). The proportion change of LDL-C, expressed in percentage (%), was also different among genotypes (Table 2). In addition, LDL-C values according to the *MYLIP* polymorphism and time periods

Table 2 Cholesterol data and responses to lipid-lowering therapy of FH patients according to MYLIP rs9370867 genotypes

Variables	Genotypes			P-value
	GG (n = 61)	GA (n = 66)	AA (n = 29)	
1-year treatment TC (mg/dl)	250 ± 83	231 ± 68	207 ± 52	0.07
1-year treatment LDL-C (mg/dl)	174 ± 71 ^a	165 ± 61 ^{a,b}	134 ± 50 ^b	0.04
TC response (mg/dl)	-38 ± 89 ^a	-66 ± 86 ^b	-86 ± 78 ^c	0.04
LDL-C response (mg/dl)	-30 ± 83 ^a	-60 ± 79 ^b	-79 ± 68 ^c	0.02
Proportion change in TC (%)	-12 ± 31 ^a	-22 ± 25 ^b	-28 ± 21 ^b	0.04
Proportion change in LDL-C (%)	-15 ± 38 ^a	-27 ± 32 ^b	-39 ± 27 ^c	0.005
Treatment 1-year status (LDL-C < 130 mg/dl) (%)	34.5	34.8	75.0	0.001

TC and LDL-C responses, expressed in mg/dl, were calculated by the 1-year value - time zero value. Proportion change in TC and proportion change in LDL-C, expressed in %, were calculated as follows: (1-year treatment value - time zero value)/time zero value.

Cholesterol data and cholesterol responses were adjusted for age, sex, race, baseline value, atorvastatin doses, and ezetimibe use.

If the ANOVA test identified a significant difference ($P \leq 0.05$), Tukey's post-hoc test was performed, and the values with different superscript letters are significantly different.

For the variable 'Treatment 1-year status', the χ^2 -test was performed on the basis of a two-row by three-column contingency table.

ANOVA, analysis of variance; FH, familial hypercholesterolemia; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; MYLIP, myosin regulatory light chain interacting protein; TC, total cholesterol.

are shown in Supplemental Figure 1 (Supplemental digital content 1, <http://links.lww.com/FPC/A773>).

Figures 1 and 2 show stratified analyses for the presence of the *LDLR* mutation. Both LDL-C response ($P = 0.02$) and the frequency of patients with LDL-C levels less than 130.0 mg/dl ($P = 0.002$) statistically differed according to the rs937086 genotype in the patient group with the *LDLR* mutation ($n = 99$). In the group of patients without the *LDLR* mutation ($n = 57$), the P -value was either borderline ($P = 0.11$) or significant ($P = 0.04$; Figs 1 and 2).

Furthermore, the presence of the G allele was associated with a greater odds of not achieving the LDL-C target in a multivariate model [odds ratio (OR) = 2.08 per G allele, 95% confidence interval (CI) = 1.11-3.90, $P = 0.02$]. No interaction between *MYLIP* rs937086 and atorvastatin dose was found (OR = 2.53, 95% CI = 0.20-31.90, $P = 0.47$), whereas a trend toward a significant interaction was observed between *MYLIP* rs937086 and the presence of *LDLR* mutations (OR = 2.70, 95% CI = 0.96-7.60, $P = 0.06$; Table 3). In a multiple linear regression model, we showed that the number of variant alleles for *MYLIP* rs9370867 (GG = 0, GA = 1, and AA = 2) was significant in terms of the LDL-C response (Supplementary Table 1, Supplemental digital content 2, <http://links.lww.com/FPC/A774>).

In a stratified analysis by race, we were able to identify significant differences even with small sample sizes. In the White group ($n = 119$), the presence of the G allele

was associated with a greater odds of not achieving the LDL-C target in a multivariate model (OR 1.98 per G allele, 95% CI 1.22-3.21, $P = 0.006$; Supplementary Table 2, Supplemental digital content 3, <http://links.lww.com/FPC/A775>). In addition, patients with the AA genotype had a greater LDL-C response (-87 ± 73 mg/dl) compared with patients with the GG genotype (-24 ± 89 mg/dl; $P = 0.04$; ANOVA plus Tukey's tests, data not shown).

Discussion

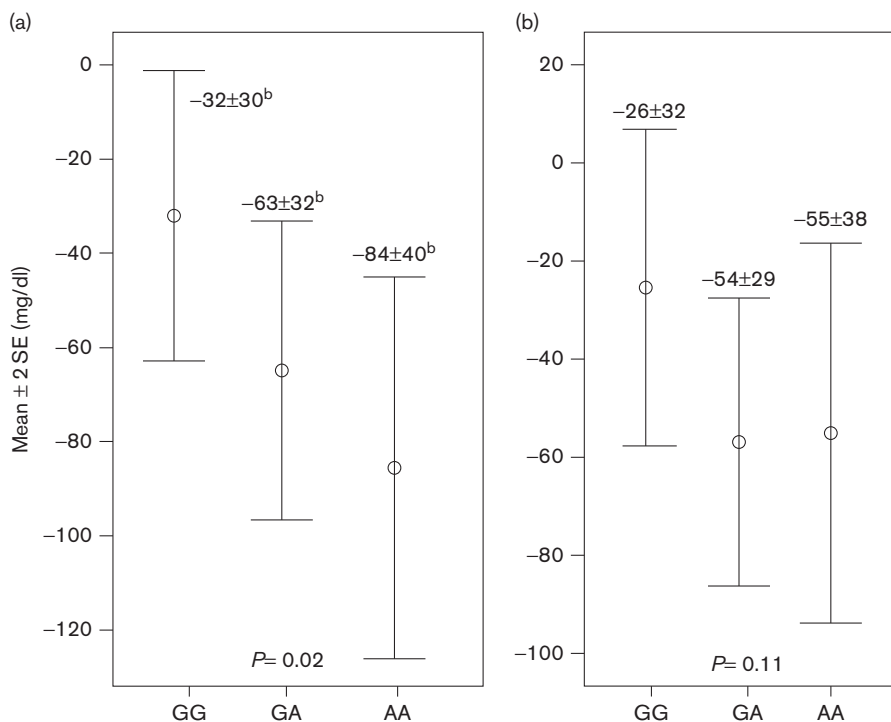
The main findings of the present study were that patients carrying the homozygous genotype for p.N342S (AA genotype) had lower LDL-C mean levels after 1-year of treatment, a higher LDL-C response, and a higher frequency of LDL-C levels less than 130.0 mg/dl compared with patients carrying the GG or GA genotypes. These genetic associations are functionally based on previous data that showed the G allele (N342) to be associated with more potent ubiquitination and degradation of the LDLR and decreased LDL uptake [17]. Consequently, the differential effects of the G and A alleles on LDLR and LDL-C levels are very consistent with our observations on the response to lipid-lowering therapy.

LDLR has a pivotal role in LDL-C uptake into cells, and a better example is that mutations in the *LDLR* gene cause FH, which is characterized by reduced hepatic LDL clearance. MYLIP is a post-transcriptional regulator of LDLR abundance, which is induced by transcription factors when cellular cholesterol levels rise [13,28,29]. In contrast, atorvastatin, other than being a potent HMG-CoA reductase inhibitor, is an upregulator of *LDLR* gene expression [30]. As our cohort was composed of patients with a heterozygous FH phenotype, and assuming that most of them had only one functional allele on the *LDLR* gene, one could suggest that post-transcriptional action and different allelic activities of MYLIP may be more evident in this clinical scenario. Interestingly, the association between the *MYLIP* genotype and the presence or absence of an *LDLR* mutation was marginally significant ($P = 0.06$).

In addition, we were able to carry out stratified analyses according to the *LDLR* mutation and race. We observed the same results irrespective of the group being compared; AA genotype carriers had higher response to lipid-lowering therapy. In these analyses, even with the sample size being small, the effect of the *MYLIP* variant on the response to treatment was clear.

Further, using an additive model, the number of *MYLIP* alleles was associated with LDL-C response as a continuous variable or with higher odds of not achieving an arbitrarily determined LDL-C cutoff (130 mg/dl). In these models, male sex was a factor associated with a worse response. Smoking and race variables were not

Fig. 1



LDL-C response (mg/dl) according to genotype for the *MYLIP* polymorphism and the presence of the *LDLR* mutation. (a) Patients with the *LDLR* mutation ($n=99$) and (b) patients without the *LDLR* mutation ($n=57$). If the analysis of variance test identified a significant difference, Tukey's post-hoc test was performed, and values with different superscript letters are significantly different. LDL-C, low-density lipoprotein cholesterol; *LDLR*, low-density lipoprotein receptor; *MYLIP*, myosin regulatory light chain interacting protein.

significant predictors of the study outcome, although being differently distributed according to the genotype.

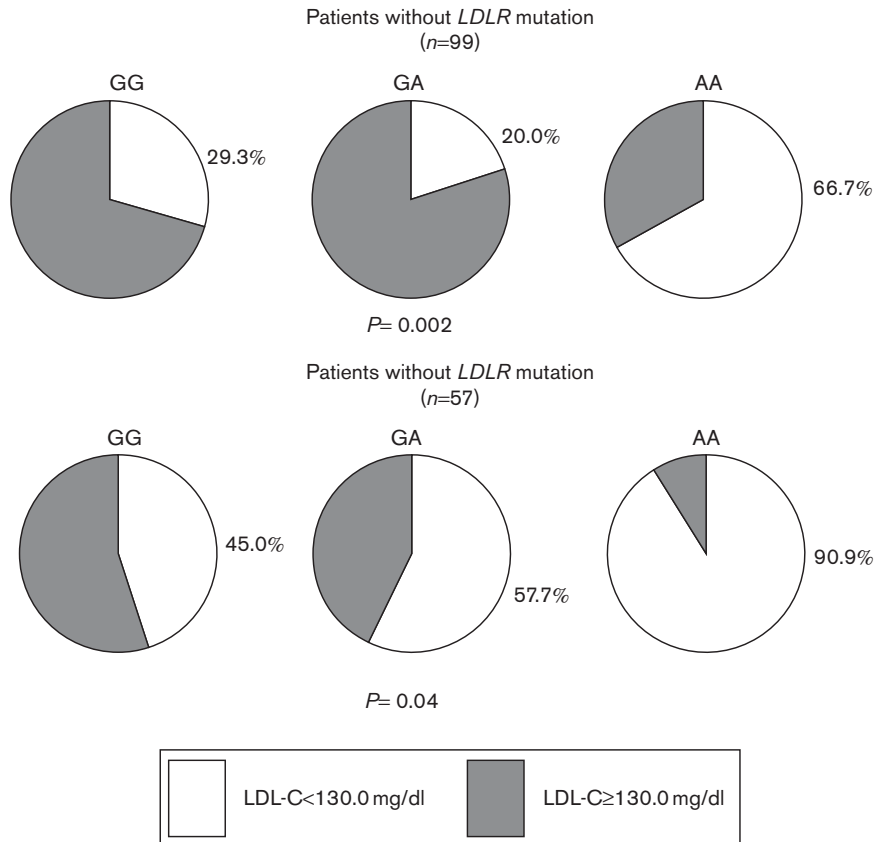
Genomewide association studies identified the *MYLIP* region to be associated with cholesterol levels [14–16]. Other recent studies demonstrated the association of the p.N342S polymorphism with cholesterol levels in a Mexican dyslipidemic sample and a possible contribution of *MYLIP* variants to circulating LDL-C levels [17,31]. In addition, other studies have reported an association of *MYLIP* polymorphisms with phenotypes such as blood pressure and obesity [32–34]. Interestingly, patients from our sample had equal baseline TC and LDL-C levels according to *MYLIP* genotypes. One possibility is that the severity of FH may not allow us to identify a possible difference in the baseline measures. In the same sense, our group did not identify this association in Brazilian participants from the general population or in patients who underwent coronary angiography because of suspected coronary artery disease [26].

Here, we were able to observe a significant pharmacogenetic effect of an *MYLIP* polymorphism on lipid-lowering therapy. A previous study has reported an additional association with subgenomewide significance ($P < 1 \times 10^{-6}$) for rosuvastatin-related LDL-C reduction at the *MYLIP* locus [35]. All patients in our study took

atorvastatin as the lipid-lowering therapy. Nonetheless, it is tempting to suggest that the effectiveness of statin, including inhibition of HMG-CoA reductase and upregulation of LDLR activity, might be dependent on changes in the *MYLIP*–*LDLR* scenario due to the *MYLIP* genetic variant.

Some aspects and study limitations must be pointed out. First, our sample size was relatively small. However, we were able to observe significant variations in the lipid profile because of the nature of our sample (FH patients), thus increasing the power of the analysis. Second, our study enrolled only clinically diagnosed FH patients; thus, further studies should assess *MYLIP* as a pharmacogenetic marker in patients with dyslipidemia from the general population. Third, it is not possible to completely exclude the influence of atorvastatin dose, including dose modifications for some patients, even with these frequencies being no different according to genotypes. In addition, a standard protocol to select the atorvastatin dose and ezetimibe use was not used. However, we added these as covariates in the multivariate models and the findings remained the same. Fourth, we were not able to verify information on objective measures of lifestyle changes throughout the course of follow-up, or on medication adherence. Nonetheless, we do not believe

Fig. 2



Frequencies of patients with LDL-C less than 130.0 mg/dl according to genotype for the MYLIP polymorphism and the presence of the LDLR mutation. The χ^2 -test was performed using a two-row by three-column contingency table. LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; MYLIP, myosin regulatory light chain interacting protein.

Table 3 Logistic regression multivariate analysis of factors associated with not achieving target LDL-C levels (LDL-C ≥ 130.0 mg/dl)

Variables	OR (95% CI)	P-value
MYLIP rs9370867 G allele	2.08 (1.11–3.90)	0.02
Sex (male)	3.21 (1.19–8.65)	0.02
Age	0.99 (0.95–1.02)	0.63
BMI	1.03 (0.94–1.11)	0.54
Smoking	1.12 (0.32–3.83)	0.86
Atorvastatin dose	1.01 (0.98–1.03)	0.57
Ezetimibe use	1.29 (0.44–3.70)	0.64
Baseline LDL-C	1.01 (0.99–1.01)	0.28
Presence of LDLR mutations	6.14 (1.91–19.71)	0.002
MYLIP rs9370867 × presence of LDLR mutations ^a	2.70 (0.96–7.60)	0.06
MYLIP rs9370867 × atorvastatin dose ^a	2.53 (0.20–31.90)	0.47

MYLIP rs9370867 G allele means 0, 1, or 2 G alleles for AA, GA, or GG, respectively.

LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; MYLIP, myosin regulatory light chain interacting protein.

^aThese variables are interaction analyses of two variables.

that imbalances in these variables significantly bias our conclusions. This was a single-center study, and all participants received the same (blinded to genotype status) medical assistance, nutritional and lifestyle orientations,

and pharmacist assistance. Finally, our study did not include replication and other factors could still be evaluated, for example, the type of dyslipidemia, other markers associated with the pharmacogenomics of statins, the type of hypolipidemic drugs, concomitant medications, cost-effectiveness, age, sex, and ethnicity [36–40].

Conclusion

Our findings indicate that the MYLIP variant might be a pharmacogenetic marker for lipid-lowering therapy. Furthermore, genetic associations reported in this study are functionally based on previous data, and they reaffirm that pharmacologic modulation of MYLIP activity might be a potential strategy that could be translated into dyslipidemia treatment.

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Conflicts of interest

R.D.S. has the following conflicts of interest to declare: honoraria or consulting fees from Astra Zeneca, Aegerion, Amgen, Biolab, Bristol Myers Squibb, Merck, Pfizer, Sanofi, Regeneron, Genzyme, Novo-Nordisk, Lilly, Boehringer Ingelheim, Novartis, and Nestle. For the remaining authors, there are no conflicts of interest.

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