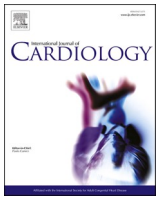
International Journal of Cardiology 413 (2024) 132402

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



PCSK9 gene variations in the clinical setting of premature cardiovascular disease: A critical appraisal

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ARTICLE INFO

Keywords:
PCSK9 gene
CAD
Prognosis
Risk factors

ABSTRACT

Introduction: Information about *PCSK9* gene variations and its association with cardiovascular (CV) disease is controversial. We aimed to evaluate 3 reported polymorphisms in *PSCK9* in a cohort of young patients with myocardial infarction with ST segment elevation (STEMI).
Methods: Retrospective study of consecutive patients with premature STEMI (2018–2023). 216 patients with STEMI due atherothrombotic coronary artery disease (CAD), confirmed by coronary angiogram, were included. We genotyped 3 polymorphisms in *PCSK9* (rs12117661, rs2483205, rs505151) in 207 patients (DNA unavailable in 9) and a control group ($N = 200$).
Results: Mean age 49.4 ± 6,6 years (82.4% men). Genotypes frequencies distribution in patient's and control's cohorts did not deviate from the expected by Hardy-Weinberg equilibrium and there were no significant differences between patients and controls. Among patients, we did not find any association between *PSCK9* genotypes and clinical variables (gender, age, CV risk factors, cholesterol levels, family history of premature CAD or number of coronary arteries affected).
Conclusion: We did not find any association between *PSCK9* genotypes (RS12117661, RS2483205 and RS505151) and any CV risk factors or the extent of CAD in a cohort of patients with premature STEMI. There were not differences in the genotype distribution between patients and controls.

1. Introduction

Nowadays, coronary artery disease (CAD) is considered the principal cause of mortality and morbidity worldwide [1]. CAD is a complex entity, resulting from numerous additive and interacting factors. Based in an individual genetic background and possible predisposition, individual's environment and lifestyle contributes to modulate the possible development and manifestations of the disease [2]. Therefore, clinical guidelines promote healthy lifestyle and encourage to treat all cardiovascular (CV) risk factors (CVRF) [3]. The main causal and modifiable classical CVRF are known to be high blood pressure (HBP), cigarette smoking, diabetes mellitus (DM) and apolipoprotein-B-containing lipoproteins, being low-density lipoprotein-cholesterol (LDLc) the most abundant one [3]. The LDL receptor plays a crucial role in regulating blood cholesterol levels by mediating the uptake of LDL particles from the bloodstream into cells.

As a result, abundant research about lipid disorders is available. The causal role of LDLc in the development of atherosclerotic CV disease has been proven beyond doubt by genetic, observational, and interventional studies [4]. Moreover, genetic dyslipidemias, such as familial

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https://doi.org/10.1016/j.ijcard.2024.132402
Received 18 January 2024; Received in revised form 23 July 2024; Accepted 26 July 2024
Available online 27 July 2024

hypercholesterolemia (FH) are considered directly a high-risk group of population with specific recommendation strategies in primary prevention [4,5]. In this regard, pathogenic variants in the proprotein convertase subtilisin/kexin type 9 gene (PCSK9) have been reported as the genetic cause of autosomal dominant FH [6]. Therefore, as in any other monogenic diseases, the atherosclerotic CV disease of these families related to LDLc can be solely explained by the reported single genetic variant classified as pathogenic.

Apart from, it has been proposed that some *PCSK9* gene variations could associate with the risk of developing CAD and cerebrovascular events in different populations. However, published provided results can be considered controversial. One of the main limitations of many studies that may explain the results variability is the lack of homogeneity in the studied cohorts, with different definitions and presentations of CAD. In this scenario, we aimed to evaluate the possible association with premature CAD and CVRF of 3 different *PSCK9* polymorphisms that have been associated with different gene expression or the risk of several cardiovascular traits. The study was based on a homogenous young Spanish cohort whose CAD presented with an acute CV event: a myocardial infarction with ST segment elevation (STEMI).

2. Methods

2.1. Study population

This is a retrospective study based on the patients form the CholeSTEMI registry [7,8], from 2018 to date. This study was approved by the local Ethical Committee (CEIMPA; registry number 2020/003). We recruited consecutive patients with premature STEMI and referred to our center for emergency cardiac catheterization. Only those patients with atherothrombotic CAD, confirmed by coronary angiogram, as the cause of the STEMI were included in this study. Premature CAD was defined as men younger than 55 years old, or women <60 years old, according to DLCN criteria [9,10]. All participants who wished to participate signed informed consent for genetic testing for additional investigational purposes.

We reviewed all available clinical data at admission: birth date, gender, age at STEMI, family history, classical cardiovascular risk factors (high blood pressure, tobacco consumption, diabetes mellitus and hypercholesterolemia), number of affected coronary arteries and laboratory levels of cholesterol (Total cholesterol, LDLc, high-density lipoprotein cholesterol (HDLc) and triglycerides).

2.2. Control cohort group

We compare the STEMI population with a representative control cohort of 200 individual's similar demographic characteristics (age 31–60 years, 54% male) from the same geographical area **(**suppl. Table 1**).** These healthy controls were recruited as part of the RENASTUR project to determine the prevalence of CV risk factors in our region [11].

2.3. Genetic evaluation

From the recruited cohort of 216 patients with premature STEMI, there was not enough quality DNA from 22 patients to perform the genetic analyses and had to be excluded from this study. Patients ($N = 194$) and control groups ($N = 200$) were genotyped for 3 polymorphisms in the *PCSK9* gene: rs12117661 (*PCSK1* promoter, g.55021673C > G), rs2483205 (*PCSK1* intronic, c.658-7C > T), and rs505151 (*PCSK1* missense, c.2009G > A, p.Gly670Glu). The three polymorphisms were selected based on studies that reported a significant association with cardiovascular traits (rs2483205 and rs505151). Rs12117661 was the SNP with the highest *PCSK9* expression difference between the genotypes according to the GTEx portal (https://gtexportal.org/home/).

The rs12117661 was genotyped by real time-PCR with a Taqman assay (Fisher Scientific, assay id. C_32221232_10). The other two SNPs were genotyped by restriction-enzyme digestion of PCR fragments followed by agarose gel electrophoresis to visualize the two allele-sizes (suppl. Fig. 1). PCRs were performed in 96 well plates. Briefly, for each sample 50 nG of genomic DNA was amplified (30 cycles 95 °C-30s, 64 °C-60s, 72 °C-60s) in a final volume of 30 μL, containing the two PCR primers, 1xTaq polymerase buffer with dNTPs and 1 unit of Taq polymerase (Eurx Mol Biol Products, Poland):

Rs2483205 C > T: PCR primers 5´GTGGGTGGGGACTGCCACC and 5´ TGGTTCTCTGGCTCTGCGGCAG, annealing temperature 64 °C, size of the amplified fragment 461 bp, digestion with TaqI (allele sizes, $T = 461$, $C = 283 + 178$ bp).

rs505151 G > A: PCR primers 5´ TACGCCGTAGACAACACGTGTGTAG and 5´ AAAGGCGGAAGCATCCCCATCC, annealing temperature 64 °C, size of the amplified fragment 266 bp, digestion with *Sau*96I (allele sizes, $A = 266$, $G = 200 + 66$ bp).

2.4. Statistical analysis

Statistical analysis was performed with STATA. Descriptive data for continuous variables are presented as mean ± SD and as frequencies or percentages for categorical variables. The Chi-square test and or Mann–Whitney *U* test was used to compare frequencies, whereas differences in continuous variables were evaluated with either Student's *t*-test or ANOVA. The normal distribution of the variables was checked by graphic methods using Q-Q (quantile-quantile plot) and the histogram. A p value below 0.05 was considered to be significant.

3. Results

Mean age of the 194 patients with premature STEMI included in this study was 49.4 ± 6,6 years. Most patients were men (82.4%). The most prevalent CV risk factor was smoking history (82.4%), followed by dyslipidemia (38%), high blood pressure (28.2%) and family history of premature CAD (24.5%). Only 8.3% of premature STEMI patients had diabetes mellitus. Mean total cholesterol levels at admission were 185.9 ± 43.1 mg/dl; LDLc 115.5 ± 41.3 mg/dl; HDLc 39.9 ± 10.9 mg/dl and triglycerides 166.9 ± 93.2 mg/dl. All parameters conform to the normal distribution. Only 43 patients (22.2%) were under lipid-lowering treatment before admission, receiving all of them statins. In addition to statins, 4 of these 44 patients received ezetimibe and 2 fibrates.

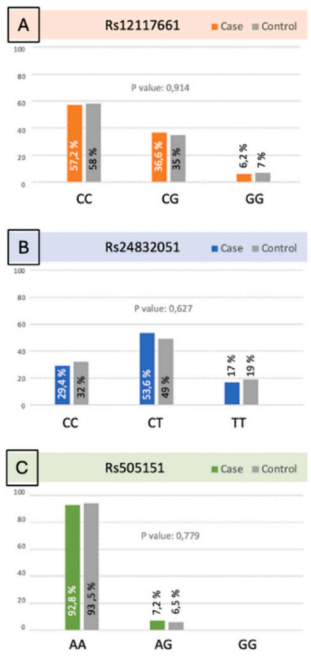
Most patients had only one coronary artery disease (61.6%), causative of the premature STEMI. However, surprisingly due to the age of the cohort, >1 in every 3 patients had additional coronary arteries affected by CAD, illustrating the conceal high CV-risk of this population.

Clinical general data obtained from the healthy control population can be consulted in Suppl. Table 1. The mean age was very similar (52 ± 6 years old). However, distribution among sex was more proportionate (54% men). Despite the slightly differences among CVRF between case and control populations, the control cohort was free of acute CV events.

The genotypes frequencies at the three *PCSK9* polymorphisms did not deviate from the expected according to the Hardy-Weinberg equilibrium in patients and controls. Moreover, the observed frequencies in our population were close to the reported among individuals of European ancestry (see www.ensemble.org). We did not find significant differences between the patient's and control's allele and genotype frequencies (Fig. 1).

There were no differences for the lipid values between the three SNP genotypes in both, patients and controls (Table 1 and Suppl. Table 1).

In addition, among evaluated patients with premature STEMI, we did not find no association between any specific *PSCK9* genotypes and any of the clinical variables analyzed of this population (gender, age, CV risk factors, family history of premature CAD or number of coronary arteries affected) nor laboratory cholesterol levels (Table 1).



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	CASES (n = 194)	CONTROLS (n = 200)	P value
Rs12117661			
CC	111 (57,2 %)	116 (58,0 %)	0,914
CG	71 (35,6 %)	70 (35,0 %)	
GG	12 (6,2 %)	14 (7,0 %)	
RS2483205			
CC	57 (29,4 %)	64 (32,0 %)	0,627
CT	104 (53,6 %)	98 (49,0 %)	
TT	33 (17,0 %)	38 (19,0 %)	
RS505151			
AA	180 (92,8 %)	187 (93,5 %)	0,779
AG	14 (7,2 %)	13 (6,5 %)	
GG	0 (0 %)	0 (0 %)	

Fig. 1. Distribution of the 3 studied polymorphisms in the *PCSK9* gene in patients and control cohorts.
Panel A) rs12117661; Panel B) rs2483205; Panel C) rs505151; Panel D) Table showing patients (cases) and control population data.

Table 1
Comparison of the 3 studied polymorphisms in the PCSK9 gene in patients with STEMI patients with cholesterol levels.

	Total Cholesterol mg/dl	LDL mg/dl	HDL mg/dl	TG mg/dl	Men	Women	No familial PCAD	Family history of PCAD	CAD of 1 vessel	CAD of >1 vessel	HBP	No HBP
RS12117661	p = 0,936	*p* = 0,885	*p* = 0,686	p = 0,687	p = 0,556		p = 0,343		p = 0,996		p = 0,674	
CC	185,42 ± 45,4	115,49 ± 43,2	40,05 ± 11,4	158,21 ± 76,0	58,86%	50,00%	57,14%	57,45%	57,50%	56,76%	55,36%	57,97%
CG	183,17 ± 41,0	114,56 ± 39,2	39,71 ± 9,9	163,30 ± 80,7	34,81%	44,44%	36,73%	36,17%	37,50%	35,14%	39,29%	35,51%
GG	185,92 ± 23,3	109,42 ± 17,5	42,67 ± 11,5	177,83 ± 86,6	6,33%	5,56%	6,12%	6,38%	5,00%	8,11%	5,36%	6,52%
RS2483205	*p* = 0,774	p = 0,754	p = 0,318	p = 0,467	p = 0,362		*p* = 0,786		p = 0,891		p = 0,800	
CC	183,75 ± 44,8	111,61 ± 43,9	41,58 ± 12,1	150,48 ± 78,2	29,75%	27,78%	29,93%	27,66%	28,33%	31,08%	23,21%	31,88%
CT	183,57 ± 43,4	115,53 ± 40,6	39,01 ± 11,0	165,07 ± 83,2	55,06%	47,22%	53,74%	53,19%	53,33%	54,05%	58,93%	51,45%
TT	189,48 ± 36,7	117,81 ± 34,8	40,94 ± 7,6	167,70 ± 59,7	15,19%	25,00%	16,33%	19,15%	18,33%	14,86%	17,86%	16,67%
RS505151	p = 0,923	p = 0,842	p = 0,805	p = 0,212	p = 0,086		p = 0,721		p = 0,367		p = 0,444	
AA	184,71 ± 41,9	114,61 ± 39,3	40,04 ± 11,0	163,24 ± 80,0	94,30%	86,11%	91,84%	95,74%	91,67%	94,59%	92,86%	92,75%
AG	183,57 ± 53,0	116,85 ± 56,2	40,79 ± 9,0	136,14 ± 43,0	5,70%	13,89%	8,16%	4,26%	8,33%	5,41%	8,33%	5,41%
GG	–	–	–	–	0%	0%	0%	0%	0%	0%	0%	0%

LDL: Low-density lipoprotein-cholesterol; HDL: high-density lipoprotein cholesterol; PCAD: premature coronary artery disease; CAD: coronary artery disease; HBP: high blood pressure.

4. Discussion

In this study of a homogenous cohort of young patients presenting with an acute CV event we did not find any association with the analyzed variations of *PCSK9* with any CV risk factor, cholesterol levels or the extend of the CAD. Moreover, we found a similar distribution for the evaluated polymorphisms in the *PCSK9* gene (rs12117661, rs2483205 and rs505151) in the STEMI population than in the control cohort, from the same geographical area and without acute CV events.

To date, several studies have tried to elucidate if some variations in the PCSK9 gene could in fact be considered as risk factors for CAD, with controversial results. For instance, the p.Glu670Gly variant (rs505151) has been considered one of the strongest predictors. It has been described as an independent determinant LDLc levels and the severity of CAD [12]. An interesting meta-analysis, including 5484 subjects from 13 studies, found that this polymorphism was associated with an elevated risk of CAD [13]. It was hypothesized that E670G hepatocytes' may have an enhanced ability to degrade the LDL receptor and, consequently, a decreased elimination of LDLc, leading to an increased risk of CAD [13]. The elevated CAD risk was also found in a Tunisian cohort [14].

However, this was not confirmed neither by *Kotowski et al* [15] nor by our findings. In fact, in another European cohort, the "attributable" risk associated with increased LDLc levels was not found among women [16]. On the other hand, the TT genotype of rs2483205 has been reported in association with CAD [17]. Moreover, a recent Spanish study among patients with already diagnosed CAD, reported that *PCSK9* rs2483205 T alleles conferred a risk of rapid clinical progression of CAD [18]. In our study, we not only found that the distribution of polymorphisms in the gene was the same between cases and controls (Fig. 1), but also that the LDL profile was better in the group supposedly considered "high risk" (*PCSK9* rs2483205 T alleles, sup. Table 1), contrary to previously described findings. Finally, it has been reported that RS12117661 polymorphisms can be associated with decreased LDLc levels and lower CAD in Greenland and European populations [19]. Our work did not confirm these results either.

There are possible ways to explain the difference between previous evidence and our study. Firstly, previous studies are very heterogeneous. They include either population of different origins (Europe, China, Greenland, *etc.*). Secondly, one of the main limitations to withdraw conclusions regarding genetic predisposition is obtaining a representative sample of the considered "affected population". In this regard, previous studies have an enormous variability in the definition and presentation of CAD, including patients with both acute and chronic coronary syndrome and without any difference between early and late coronary artery disease. Therefore, given the variability of the results in previously reported studies, assuming statements without sufficient evidence should be avoided, as should proclaiming dubious genetic markers as established genetic risks factors for CAD. In fact, the genetic evidence in monogenic diseases such as FH is clearly demonstrated, and therefore it has clinical utility. All carriers of pathogenic variants associated with FH are considered directly as high-risk patients [3]. Therefore, preventive strategies can be promptly started from genetic diagnosis, including PCSK9 inhibitors. Over the past few years, *Rosoff et al* have published very important studies about drug-Target Mendelian Randomization evaluating the Impact of PCSK9 and HMGCR Inhibition on Liver Function [20], Cognitive Function [21] and, recently, the Cardiovascular Impact in East Asian and European Populations [22]. Moreover, in the near future, they may also benefit from new emerging treatment strategies, including gene editing and the use of clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 complex-mediated delivery and adenine base editing (ABE) [23].

However, unlike in the scenario of FH, with clearly causal pathogenic variants of the disease and associated with high CV risk, clinicians should be critical of other genetic information or genetic "risk markers" that are yet to be confirmed and especially when translating these uncertainties or confounding factors into clinical practice. All reported associations should be replicated in large cohorts and from different populations. Based on the information provided in this study, none of the evaluated variants could be considered as a conclusive CV risk faction, at least in Spanish populations.

Finally, the main limitation of our study was the limited sample size and that it is a retrospective analysis from a single center. Moreover, we cannot rule out the presence of unknown genetic modifiers and environmental factors that could have affected the phenotype. However, the greatest strength of the study is having obtained a homogeneous and truly representative cohort in which to analyze the data, with rigorous and strict selection criteria that have allowed for the exclusive selection of young patients presenting with acute coronary syndrome with a confirmed atherothrombotic cause.

However, CAD is still considered to have an underlying inherited susceptibility in up to 40–60% of the patients [24]. While risk variants are less potent predictors of CAD, compared with biomarkers, they have the advantage of being constant, unaffected by lifestyle, age or medication [24]. As a result, more rigorous research into the variability of genetic markers to provide more insights into this field is strongly encouraged. Further studies are needed to elucidate the genetic mechanisms underlying the predisposition of premature CV beyond FH. More research about genetics in high-risk large populations is encouraged, avoiding publication vias of only positive results.

5. Conclusion

In this cohort of consecutive patients with premature CAD presenting with an acute CV event (STEMI) we did find any association of the evaluated polymorphisms in the PCSK9 gene (RS12117661, RS2483205 and RS505151) with classical CV risk factors, cholesterol levels or the extent of CAD. Moreover, different genotypes present the same distribution as the control cohort population form the same geographical area.

CRediT authorship contribution statement

Rebeca Lorca: Writing – review & editing, Writing – original draft, Conceptualization. **Andrea Aparicio:** Writing – review & editing, Software, Data curation, Conceptualization. **Luis Gutiérrez:** Writing – review & editing, Writing – original draft, Formal analysis. **Rut Álvarez-Velasco:** Writing – review & editing, Methodology, Formal analysis. **Francisco González-Urbistondo:** Writing – original draft, Visualization, Software. **Isaac Pascual:** Writing – review & editing, Writing – original draft, Validation, Supervision. **Juan Gómez:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Daniel Vazquez-Coto:** Writing – original draft, Software, Conceptualization. **Claudia Garcia-Lago:** Writing – original draft, Validation, Formal analysis, Conceptualization. **Pablo Avanzas:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Eliecer Coto:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision.

Acknowledgement

This research was funded by Instituto de Salud Carlos III (ISCIII) (grant number PI22/00705).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.132402.

This research was funded by Instituto de Salud Carlos III (ISCIII) (grant number PI22/00705).

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