MATERIAL ADICIONAL

Methods of the supplementary data

Serum biomarker levels were measured using the ELISA technique (Enzyme-Linked ImmunoSorbent Assay) through the acquisition of commercial kits.[1-4]

The technique used for gene expression studies was the quantitative real-time polymerase chain reaction,[5] using the QuantStudio 7 Flex real-time polymerase chain reaction system (Applied Biosystems, United States). With this technique, the relative expression of the study genes was measured with regard to *GAPDH* expression, used as housekeeping gene. This change was evaluated in the messenger RNAand reverse transcribed to complementary DNA for use in the previous technique. The data have been analyzed through the delta Ct (threshold cycle) method, as previously described.[6,7]

For genetic studies, genomic DNA was extracted from peripheral blood using the REALPURE "SSS" kit (RBME04, REAL, Durviz S.L., Spain). All patients were genotyped for *IL6, CRP, TNFA, PCSK9, LDLR, SREBP2* and *APOB* single nucleotide polymorphisms (SNPs) by TaqMan assays. The list of SNPs selected in this study is detailed in table 1 of the supplementary data. Negative controls and duplicate samples were included to check the accuracy of the genotyping. Genotyping was performed in a QuantStudio 7 Flex real-time polymerase chain reaction system (Applied Biosystems, United States).

The modified Mantel-Haenszel chi-square test, or exact Fisher test, as appropriate, and the trend chi square test have been used in ordinal or continuous variables grouped in intervals. Differences in mRNA expression and serum levels of each gene/molecule between RCP and LSS patients were calculated by Student's t-test and further adjusted by sex, age, diabetes mellitus, smoking, and hypertension at study using ANCOVA. All genotype data were checked for deviation from Hardy–Weinberg equilibrium (HWE). First, comparisons were performed

considering each studied polymorphism independently. Both genotype and allele (and carrier when appropriate) frequencies were calculated and compared between "RCP and LSS patients by chi-square or Fisher tests when necessary (expected values below 5). Strength of association was estimated using odds ratios (OR) and 95% confidence intervals (95%CI). Subsequently, allelic combinations (haplotypes) of each gene were carried out. Haplotype frequencies were calculated by the Haploview v4.2 software (https://www.broadinstitute.org/haploview/haploview) and then compared by chi-square or Fisher tests between RCP and LSS patients. Strength of associations was estimated by OR and 95%CI. An OR > 1 is identified as a SNP that increases the risk and an OR < 1 as a SNP that reduces the risk. Then, results were adjusted by sex, age, diabetes mellitus, smoking, and hypertension at study using linear regression.

SUPPLEMENTARY DATA

Table 1 of the supplementary data

List of single nucleotide polymorphisms genotyped in the study.

Gene	Polymorphism
LDLR	rs1122608 rs6511720
PCSK9	rs11206510 rs2479409 rs11583680 rs2483205 rs2495477 rs562556
SREBP2	rs7288536 rs2228314
APOB	rs1042031 rs693
IL6	rs2069827 rs1800795 rs2069840
CRP	rs1205 rs1800947 rs1417938
TNF	rs1800629 rs3093661 rs1800610

	rs3093664

Apo, apolipoprotein; CRP, C reactive protein; IL6, interleukin-6; LDLR, low density lipoprotein receptor receptor; PCSK9, proprotein convertase subtilisin/kexin type 9; SREBP2, sterol regulatory element binding transcription factor 2; TNF, tumor necrosis factor.

Table 2 of the supplementary data

Genotype, allele and haplotype frequencies of *IL-6* in all the patients included in this study.

rs1800795 **Genotype** **/Allele**	**RCP** **% (n/N)**	**LSS** **% (n/N)**	***P***	**OR [95%CI]**
GG	36.21 (21/58)	50.41 (61/121)	-	Ref.
GC	44.83 (26/58)	38.84 (47/121)	.20	1.60 [0.78-3.31]
CC	18.97 (11/58)	10.74 (13/121)	**.046**	**2.70 [1.02-7.18]**
G	58.62 (68/116)	69.83(169/242)	-	Ref.
C	41.38 (48/116)	30.17 (73/242)	**.028**	**1.71 [1.06-2.75]**
Haplotype[a]	**RCP** **% (n/N)**	**LSS % (n/N)**	***P***	**OR [95% CI]**
GGC	43.10 (50/116)	41.32(100/242)	-	Ref.
GGG	15.51 (18/116)	28.51(69/242)	.08	0.57 [0.30-1.08]
GCC	21.56 (25/116)	16.94(41/242)	.41	1.30 [0.70-2.41]
GCG	14.66 (17/116)	5.37 (13/242)	**.02**	**2.75 [1.19-6.37]**
TCC	4.31 (5/116)	4.13 (10/242)	.85	1.12 [0.35-3.57]
TCG	0.86 (1/116)	3.73 (9/242)	.24	0.28 [0.03-2.33]

95%CI, confidence interval; LSS, long standing stable; N, total number of individuals successfully genotyped; OR, odds ratio; RCP, rapid clinical progressor.

OR (95%CI) and P-values were adjusted by sex, age, diabetes mellitus, smoking, and hypertension at study.

Significant results are highlighted in **bold**.

[a] The polymorphism order was rs2069827, rs1800795 and rs2069840.

Table 3 of the supplementary data

Genotype, allele and carrier frequencies of *TNF* rs3093664 polymorphism in all the patients included in this study.

rs3093664 **Genotype/** **Allele/Carriers**	**RCP** **% (n/N)**	**LSS** **% (n/N)**	***P***	**OR [95%CI]**
AA	94.74 (54/57)	81.82 (99/121)	-	Ref.
AG	5.26 (3/57)	17.36 (21/121)	.06	0.29 [0.08-1.04]
GG	0	0.83 (1/121)	-	-
A	97.37 (111/114)	90.5 (219/242)	-	Ref.
G	2.63 (3/114)	9.50 (23/242)	**.04**	**0.27 [0.08-0.92]**
G non-carriers	94.74 (54/57)	81.82 (99/121)	-	Ref.
G carriers	5.26 (3/57)	18.18 (22/121)	**.04**	**0.27 [0.07-0.95]**

95%CI, confidence interval; LSS, long standing stable; N, total number of individuals successfully genotyped; OR, odds ratio; RCP, rapid clinical progressor.

OR (95%CI) and p values were adjusted by sex, age, diabetes mellitus, smoking, and hypertension at study.

Significant results are highlighted in **bold**.

Table 4 of the supplementary data

Genotype and allele frequencies of *PCSK9* rs2483205 polymorphism in all the patients included in this study.

rs2483205 Genotype /Allele	**RCP % (n/N)**	**LSS % (n/N)**	***P***	**OR [95%CI]**
CC	18.97 (11/58)	39.83 (47/118)	-	Ref.
CT	60.34 (35/58)	43.22 (51/118)	**.003**	**3.39 [1.50-7.65]**
TT	20.69 (12/58)	16.95 (20/118)	**.03**	**3.12 [1.12-8.64]**
C	49.14 (57/116)	61.44 (145/236)	-	Ref.
T	50.86 (59/116)	38.56 (91/236)	**.01**	**1.83 [1.15-2.93]**

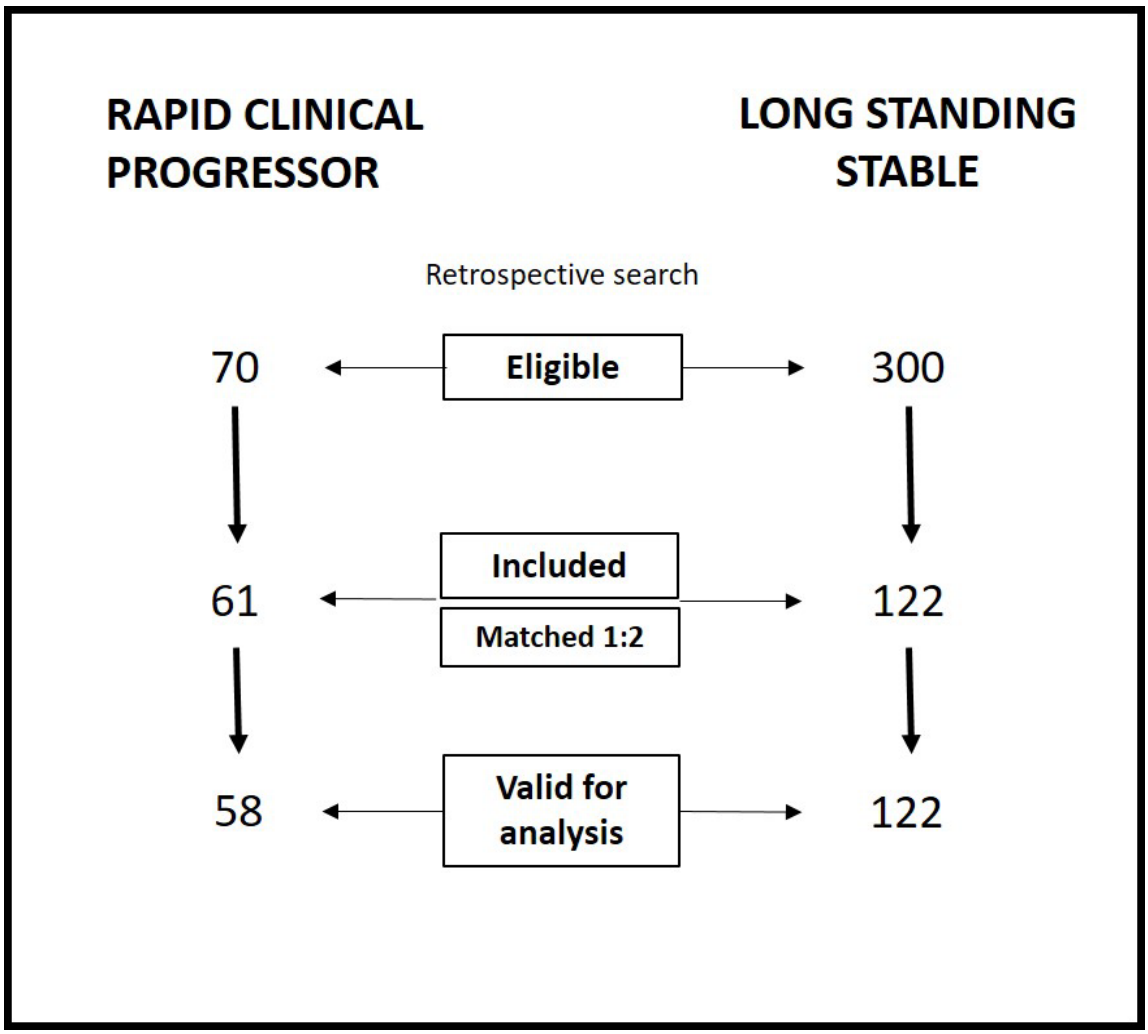
95%CI, confidence interval; LSS, long standing stable; N, total number of individuals successfully genotyped; OR, odds ratio; RCP, rapid clinical progressor.

OR (95%CI) and p values were adjusted by sex, age, diabetes mellitus, smoking, and hypertension at study.

Significant results are highlighted in **bold**.

FIGURE LEGENDS

Figure 1 of the supplementary data. Flowchart of the study. Caption: This figure illustrates the flowchart followed in the study. In a retrospective search we identified 70 patients from the Rapid clinical progressor group and 300 from the Long standing stable. 61 patients from the case group were finally included (9 refused to participate) and matched 1:2 by sex and age to 122 control patients. 3 of the case group samples were not properly processed and not valid for analysis.



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