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SUPPLEMENTAL DATA

Cholesterol 7 alpha-hydroxylase (*CYP7A1*) gene polymorphisms are associated with increased LDL-cholesterol levels and the incidence of subclinical atherosclerosis

Table S1. Information of the studied polymorphisms

Gene symbol	Chromosome	Chromosome position	SNP (rsID-number) [a,b]	Minor Allele	Location in gene
CYP7A1	8q11-12	58476006	rs2081687 *T/C*	*T*	Enhancer region
CYP7A1	8q11-12	58479765	rs9297994 *G/A*	*G*	Enhancer region
CYP7A1	8q11-12	58480178	rs10107182 *C/T*	*C*	Enhancer region
CYP7A1	8q11-12	58485902	rs10504255 *G/A*	*G*	Enhancer region
CYP7A1	8q11-12	58497880	rs1457043 *C/T*	*C*	Promoter region
CYP7A1	8q11-12	58499507	rs8192870 *T/G*	*T*	Promoter region
CYP7A1	8q11-12	58500365	rs3808607 *G/T*	*G*	Promoter region

[a] Single Nucleotide Polymorphisms (rsID-number) in database dbSNP; [b] Given name according to NCBI, Current Build 156 (released September 21, 2022) https://www-ncbi-nlm-nih-gov.pbidi.unam.mx:2443/snp/rs2081687.

Table S2. Allele and genotype frequencies of *CYP7A1* gene polymorphisms in Subclinical Atherosclerosis (SA) and healthy controls

Polymorphic Site (rsID-number)	SA n=416, n (%)	Controls n=1046. n (%)	*P
rs2081687 *C/T*			
Allele			
C	661 (79.4)	1787 (85.4)	7X10^{-4}
T	171 (20.5)	305 (14.5)	
Genotype			
CC	262 (62.9)	759 (72.5)	
CT	137 (32.9)	269 (25.7)	
TT	17 (4)	18 (1.7)	0.007
rs9297994 *G/A*			
Allele			
A	667 (80.1)	1798 (85.9)	1X10^{-3}
G	165 (19.8)	294 (14.0)	
Genotype			
AA	266 (63.9)	767 (73.3)	
AG	135 (32.4)	264 (25.2)	
GG	15 (3.6)	15 (1.4)	0.008
rs10107182 *C/T*			
Allele			
T	665 (79.9)	1796 (85.8)	7X10^{-4}
C	167 (20)	296 (14.1)	
Genotype			
TT	264 (63.4)	765 (73.1)	
TC	137 (32.9)	266 (25.4)	
CC	15 (3.6)	15 (1.4)	0.008
rs10504255 *A/G*			
Allele			
A	665 (79.9)	1803 (86.1)	2X10^{-4}
G	167 (20)	289 (13.8)	
Genotype			
AA	265 (63.7)	774 (73.9)	
AG	135 (32.4)	255 (24.3)	
GG	16 (3.8)	17 (1.6)	0.002
rs1457043 *C/T*			
Allele			
T	583 (70)	1567 (74.9)	0.007
C	249 (29.9)	525 (25.0)	
Genotype			
TT	207 (49.7)	582 (55.6)	
TC	169 (40.6)	403 (38.5)	
CC	40 (9.6)	61 (5.8)	0.009
rs8192870 *G/T*			
Allele			
G	658 (79)	1763 (84.2)	
T	174 (20.9)	329 (15.7)	7X10^{-3}
Genotype			
GG	258 (62.0)	737 (70.4)	
GT	142 (34.1)	289 (27.6)	
TT	16 (3.8)	20 (1.9)	0.031
rs3808607 *G/T*			
Allele			
T	589 (70.7)	1579 (75.4)	

G	243 (29.2)	513 (24.5)	0.009
Genotype			
TT	211 (50.7)	590 (56.4)	
GT	167 (40.1)	399 (38.1)	
GG	38 (9.1)	57 (5.5)	0.009

Data are shown as n and frequency expressed as percentage. *chi-square test.

NS: No significant

Table S3. Characteristics of the patients with SA and individuals control.

Characteristics	SA patients (n=325)	Controls (n=937)	*P*
Age (years)	58 ± 9.13	51 ± 8.8	<0.001
BMI (kg/m2)	28.5 ± 3.82	28.1 ± 3.9	0.109
Gender n (%) Male	248 (76.3)	380 (40.5)	<0.001
Female	77 (23.6)	557 (59.4)	<0.001
Hypertension, Yes, n (%)	109 (33.5)	160 (17)	<0.001
Smoking, Yes, n (%)	75 (23)	211 (22.5)	0.835
Blood pressure (mmHg) Systolic	120 [110-131]	111 [103-121]	<0.001
Blood pressure (mmHg) Diastolic	74 [68-81]	70 [64-76]	<0.001
Glucose (mg/dL)	90 [85-97]	88 [83-95]	0.115
Total cholesterol (mg/dL)	199 [175-219]	190 [167-211]	0.012
HDL-C (mg/dL)	44 [37-51]	45 [36-55]	0.101
LDL-C (mg/dL)	124 [105-146]	116 [96-135]	<0.0001
Triglycerides (mg/dL)	150 [116-202]	141 [105-196]	0.178

SA, Subclinical Atherosclerosis. Data were collected at recruitment. Gender, hypertension, and smoking are expressed as n (frequency), and *P* values was calculated to chi-square. Other variables are expressed as Mean ± SD or median [25th-75th interquartile interval] for normally or non-normally distributed variables and groups were compared by t-test or Mann-Whitney U-test, respectively.

Table S4. Association of the *CYP7A1* polymorphisms with subclinical atherosclerosis (AS) without DM2, accordance to the inheritance models.

SNP(rsID) / Models	Genotype	SA patients n=325 (n(%))	Controls n=937 (n(%))	OR (95%CI)	pC
rs2081687 *T/C*					
Co-dominant	*CC* *CT* *TT*	199 (0.612) 113 (0.348) 13 (0.040)	674 (0.719) 246 (0.262) 17 (0.018)	1.47(1.08-2.01)	0.039
Dominant	*CC* *CT* + *TT*	199 (0.612) 126 (0.388)	674 (0.719) 263 (0.281)	1.48 (1.09-2.01)	0.011
Recessive	*CC* + *CT* *TT*	312 (0.960) 13 (0.040)	920 (0.982) 11 (0.018)	1.44 (0.61-3.37)	0.409
Over-dominant	*CC* + *TT* *CT*	212 (0.652) 113 (0.348)	696 (0.738) 246 (0.262)	1.44 (1.06-2.96)	0.022
Additive	--------	---------	-----------	1.40 (1.08-1.83)	0.013
rs9297994 *G/A*					
Co-dominant	*AA* *AG* *GG*	203 (0.625) 111 (0.341) 11 (0.034)	681 (0.727) 242 (0.258) 14 (0.015)	1.51 (1.11-2.07)	0.028
Dominant	*AA* *AG* + *GG*	203 (0.625) 122 (0.375)	681 (0.727) 256 (0.273)	1.52 (1.12-2.06)	0.008
Recessive	*AA* + *AG* *GG*	314 (0.966) 11 (0.034)	923 (0.985) 14 (0.015)	1.37 (0.52-2.06)	0.522
Over-dominant	*AA* + *GG* *AG*	214 (0.658) 111 (0.341)	695 (0.742) 242 (0.258)	1.49 (1.09-2.04)	0.012
Additive	--------	---------	-----------	1.44 (1.09-1.89)	0.009
rs10107182 *C/T*					
Co-dominant	*TT* *TC* *CC*	201 (0.619) 113 (0.348) 11 (0.034)	679 (0.725) 244 (0.260) 14 (0.015)	1.53(1.12-2.09)	0.024
Dominant	*TT* *TC* + *CC*	201 (0.619) 124 (0.381)	679 (0.725) 258 (0.275)	1.53 (1.13-2.08)	0.006
Recessive	*TT* + *TC* *CC*	314 (0.966) 11 (0.034)	923 (0.985) 14 (0.015)	1.37 (0.52-3.52)	0.519
Over-dominant	*TT* + *CC* *TC*	212 (0.652) 113 (0.348)	693 (0.740) 244 (0.260)	1.50 (1.10-2.05)	0.012
Additive	--------	---------	-----------	1.45 (1.10-1.91)	0.008
rs10504255 *G/A*					
Co-dominant	*AA* *AG* *GG*	202 (0.621) 111 (0.341) 12 (0.037)	688 (0.734) 233 (0.249) 16 (0.017)	1.57 (1.15-2.15)	0.015
Dominant	*AA* *AG* + *GG*	202 (0.621) 123 (0.379)	688 (0.734) 249 (0.266)	1.58 (1.16-2.14)	0.004
Recessive	*AA* + *AG* *GG*	313 (0.963) 12 (0.037)	921 (0.983) 16 (0.017)	1.38 (0.55-3.45)	0.497
Over-dominant	*AA* + *GG* *AG*	214 (0.658) 111 (0.341)	704 (0.751) 233 (0.249)	1.55 (1.13-2.11)	0.006
Additive	--------	---------	-----------	1.47 (1.12-1.93)	0.005
rs1457043 *C/T*					
Co-dominant	*TT* *CT* *CC*	159 (0.489) 135 (0.415) 31 (0.095)	511 (0.545) 369 (0.394) 57 (0.061)	1.35 (0.78-2.34)	0.561
Dominant	*TT* *CT* + *CC*	159 (0.489) 166 (0.511)	511 (0.545) 426 (0.455)	1.10 (0.83-1.47)	0.509
Recessive	*TT* + *CT* *CC*	294 (0.905) 31 (0.095)	880 (0.939) 57 (0.061)	1.32 (0.78-2.24)	0.315

Over-dominant	*TT + CC* *CT*	190 (0.585) 135 (0.415)	568 (0.606) 369 (0.394)	1.02 (0.76-1.37)	0.918
Additive	--------	---------	-----------	1.12 (0.89-1.40)	0.343
rs81922870 *T/G*					
Co-dominant	*GG* *GT* *TT*	197 (0.606) 116 (0.357) 12 (0.037)	654 (0.698) 264 (0.282) 19 (0.020)	1.44 (1.06-1.97)	0.066
Dominant	*GG* *GT + TT*	197 (0.606) 128 (0.394)	654 (0.698) 283 (0.302)	1.43 (1.06-1.93)	0.021
Recessive	*GG + GT* *TT*	313 (0.963) 12 (0.037)	918 (0.980) 19 (0.020)	1.07 (0.44-2.60)	0.881
Over-dominant	*GG + TT* *GT*	209 (0.643) 116 (0.357)	673 (0.718) 264 (0.282)	1.43 (1.05-1.95)	0.022
Additive	--------	---------	-----------	1.33 (1.02-1.74)	0.037
rs3800867 *G/T*					
Co-dominant	*TT* *GT* *GG*	163 (0.501) 133 (0.409) 29 (0.089)	519 (0.554) 365 (0.390) 53 (0.057)	1.30 (0.74-2.28)	0.673
Dominant	*TT* *GT + GG*	163 (0.501) 162 (0.499)	519 (0.554) 418 (0.446)	1.08 (0.81-1.44)	0.601
Recessive	*TT + GT* *GG*	296 (0.911) 29 (0.089)	884 (0.943) 53 (0.057)	1.27 (0.73-2.20)	0.411
Over-dominant	*TT + GG* *GT*	192 (0.591) 133 (0.409)	572 (0.610) 365 (0.390)	1.01 (0.76-1.36)	0.927
Additive	--------	---------	-----------	1.10 (0.87-1.38)	0.442

SNP, single nucleotide polymorphism, SA, Subclinical Atherosclerosis, OR, odds ratio, CI, confidence interval, *pC*, corrected *P* value. *The inheritance models were design based in the minor allele. Co-dominant model that compares the subgroup of homozygous individuals carrying the minor allele with homozygotes of the major allele. Dominant model compares the subgroup of homozygous individuals carrying the major allele with the subgroup conformed by heterozygotes and minor allele homozygotes. Recessive model compares the subgroup conformed by heterozygotes and major allele homozygotes *vs* homozygotes of the minor allele. Over-dominant model compares the subgroup conformed by homozygotes of the major allele and homozygotes of the minor allele *vs* heterozygotes. Additive model compares the subgroup major allele carriers with both, heterozygotes and minor allele homozygotes. All models were analyzed by logistic regression including gender, age, hypertension, and smoking habit as confounding variables.

Table S5. Allele (af) frequencies of the *CYP7A1* polymorphisms in different populations.

SNP/Alleles	Mexican		Caucasian*		Asian*		African*		References
rs2081687 *T/C*									
	(n=1046)		(n=503)		(n=504)		(n=661)		
Allele	n	af	n	af	n	af	n	af	
C	1787	85.4	639	63.5	763	75.7	1001	75.7	Present study[A]
T	305	14.5[A]	367	36.5	245	24.3	321	24.3	NCBI*
rs9297994 *G/A*									
	(n=1046)		(n=503)		(n=504)		(n=661)		
Allele	n	af	n	af	n	af	n	af	
A	1798	85.9	636	63.2	761	75.5	1276	96.5	Present study[B]
G	294	14.0 [B]	370	36.8	247	24.5	46	4.6	NCBI*
rs10107182 *C/T*									
	(n=1046)		(n=503)		(n=504)		(n=661)		
Allele	n	af	n	af	n	af	n	af	
T	1796	85.8	636	63.2	761	75.5	1286	97.3	Present study[C]
C	296	14.1 [C]	370	36.8	247	24.5	36	2.7	NCBI*
rs10504255 *G/A*									
	(n=1046)		(n=503)		(n=504)		(n=661)		
Allele	n	af	n	af	n	af	n	af	
A	1803	86.1	639	63.5	765	75.9	1276	96.5	Present study[D]
G	289	13.8 [D]	367	36.5	243	24.1	46	3.5	NCBI*
rs1457043 *C/T*									
	(n=1046)		(n=503)		(n=504)		(n=661)		
Allele	n	af	n	af	n	af	n	af	
T	1567	74.9	561	55.8	401	38.9	547	41.4	Present study[E]
C	525	25.0 [E]	445	44.2	607	60.2	775	58.6	NCBI*
rs8192870 *T/G*									
	(n=1046)		(n=503)		(n=504)		(n=661)		
Allele	n	af	n	af	n	af	n	af	
G	1763	84.2	634	63.0	748	74.2	1132	85.6	Present study[F]
T	329	15.7 [F]	372	37.0	260	25.8	190	14.4	NCBI*
rs3808607 *G/T*									
	(n=1046)		(n=503)		(n=504)		(n=661)		
Allele	n	af	n	af	n	af	n	af	
T	1579	75.5	578	57.5	501	49.7	516	39.0	Present study[G]
G	513	24.5 [G]	428	42.5	507	50.3	806	61.0	NCBI*

SNP, Single nucleotide polymorphism; *NCBI, National Center for Biotechnology Information (https://www.ensembl.org/index.html (accessed on 17 September 2023)).

[A,B,C,D,E,F,G] The distribution of the of the rs2081687 *T*, rs9297994 *G*, rs10107182 *C*, rs10504255 *G*, rs1457043 *C*, rs8192870 *T*, and rs3808607 *G* alleles was low in Mexican mestizos compared to Asian, and Caucasian populations.

[A,E,G] The distribution of the rs2081687 *T*, rs1457043 *C*, and rs3808607 *G* alleles in our population was low compared to African population.

[B,C,D] The distribution of the of the rs9297994 *G*, rs10107182 *C*, and rs10504255 *G* alleles in Mexican mestizos population was higher compared to African population.

[F] The distribution of the rs8192870 *T* allele in Mexican Mestizos was similar compared to African population.