Supplemental Material

The N342S MYLIP polymorphism is associated with high total cholesterol and increased LDL-receptor degradation in humans

by Daphna Weissglas-Volkov et al.

Supplementary Methods

Mexican dyslipidemic cases and controls

A total of 2,822 Mexican dyslipidemic cases and controls were recruited at INCMNSZ in Mexico City, as described in detail previously (1,2). Briefly, the inclusion criteria were fasting serum TGs > 2.3 mmol/L (200 mg/dL) for the cases and < 1.7 mmol/L (150 mg/dL) for the controls (3). Exclusion criteria were type 2 diabetes mellitus or morbid obesity (body mass index > 40 kg/m^2), and the use of lipid lowering drugs for the controls. For the association analysis with the binary TC trait, the Third Report of The National Cholesterol Education Program (NCEP) cut point of high TC was employed (3). Accordingly, the subjects were classified as high-TC if their serum TC levels were ≥ 6.2 mmol/L (240 mg/dL) (n=492) and normal TC if their serum TC levels were < 6.2 mmol/L in the absence of lipid lowering medication (n=2,233). The subjects were also classified as combined hyperlipidemia if their serum TC and TG levels were ≥ 6.2 mmol/L and 2.3 mmol/L, respectively (n=350), and as controls if TC and TG levels were < 6.2 mmol/L and 1.7 mmol/L, respectively, in the absence of lipid lowering medication (n= 1,356).

Individual Ancestry (IA) Analyses

In order to adjust for the admixed Mexican ancestry (4,5) individual ancestry (IA) estimates were used as a covariate in the regression analyses. IA was estimated using 82 ancestry informative markers (AIMs), i.e. SNPs that discriminate between the parental subpopulations that were evenly distributed along the genome (6). These AIMs were selected based on a published list of European/Amerindian AIMs (7) and were used to calculate IA estimates using the STRUCTURE 2.2 software (8), as we described previously (6). The AIMs were not available for the 512 additional dyslipidemic study samples that were further genotyped for rs9370867. Therefore, their IA estimates were imputed based on TC levels using the following model: AI_i

$=\alpha+\beta_{TC}Y_{i,}$, where the intercept α and the slope β were estimated by regressing the AI estimates from the sample with AIMs (n=2,310) against the rank of TC residuals adjusted for age, sex, and hypertriglyceridemia affection status.

Supplementary References

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Figure legends

Supplementary Figure S1. Trait distributions in the Mexican subjects that were sequenced for the *MYLIP* gene and in the Mexican dyslipidemic cases and controls. Frequency distributions of LDL-C values in the low-LDL resequencing sample (A) and in the high-LDL resequencing sample (B). Frequency distributions of standardized TC (C) and non-HDL-C (D) residuals corrected for age, sex and hypertriglyceridemia affection status in the dyslipidemic study sample.

Supplementary Figure S2. LD across the *MYLIP* gene (±50 kb) in the Mexican and European ancestries. LD was calculated in r^2 using the 60 Mexican-American founders (Left panel) and 60 CEU founders with European ancestry (Right panel) of the HapMap project. The red points represent the *MYLIP* gene. The Caucasian genome-wide significant variants are indicated in black and the most significantly associated SNP in Mexicans in blue.

Supplementary Figure S3. Analysis of the effect of MYLIP point mutations on LDLR degradation. (A) Immunoblot of HEK293T whole cell lysate co-transfected with LDLR and MYLIP expression plasmids with either isoleucine (I202) or leucine (L202) at residue 202. The ratio of MYLIP:LDLR expression vector was altered while maintaining a constant amount of total DNA transfected. (B) Immunoblot of HEK293T whole cell lysate co-transfected with LDLR and MYLIP expression plasmids with either valine (V339) or isoleucine (I339) at residue 339. The ratio of MYLIP:LDLR expression vector was altered while maintaining a constant amount of total DNA transfected. (C) Quantification of LDLR expression in HEK293T whole cell lysate following co-transfection with LDLR and either N342 or S342 MYLIP expression plasmids. The ratio of MYLIP:LDLR expression vector was altered while maintaining a constant amount of total DNA transfected. Data are expressed as mean±SEM (n=4/group). (D) Immunoblot of HEK293T whole cell lysate co-transfected with LDLR and FLAG-tagged WT (N342/V339/I202), C387A ring domain mutant (RING MUT), I339 or L202. The thin white line indicates that the lanes were run on the same gel but were noncontiguous. (E) Amino-acid sequence alignment of MYLIP homologs at position 342; N stands for asparagine and S for serine. (F) Immunoblot of HEK293T whole cell lysate following co-transfection with LDLR and

mouse MYLIP S342, N342 or RING MUT expression constructs as indicated. (G) Immunoblot of HEK293T cell surface protein isolated by biotinylation following transfection with LDLR and MYLIP N342 (WT), S342, I339 or RING MUT expression constructs as indicated.

Supplementary Table S1. Clinical characteristics of the Mexican subjects that were sequenced for the *MYLIP* gene and of the Mexican dyslipidemic case/control study sample.

Trait	Study Sample[A]			
	Low-LDL	High-LDL[B]	Hypertriglyceridemic	Normotriglyceridemic
N (% Females)	56 (70%)	66 (83%)	1,290 (49%)	1,532 (54%)
Age, years	41.2±1.58	45.4±1.61	41.3±0.33	42.8±0.28
LDL-C, mmol/L	1.83±0.04	5.06±0.12	3.33±0.05	3.13±0.02
TC, mmol/L	3.52±0.07	7.07±0.13	5.67±0.03	4.87±0.03
TG,mmol/L	0.97±0.02	1.37±0.03	3.21±0.01	1.11±0.01
apoB, g/L	62.84±2.14	139±3.32	121.3±0.74	96.2±0.62
BMI, kg/m^2	27.55±0.48	26.7±0.61	29.2±0.11	27.0±0.11
Amerindian ancestry estimates	0.49±0.03	0.46±0.03	0.50±0.01	0.52±0.01

Trait values represent the marginal means evaluated at the average age and sex ± SEM.
[A] The coding sequence of the MYLIP gene was sequenced in the Mexican subjects with low LDL-C and high LDL-C, and the GWA associated region of the MYLIP gene was fine mapped in the Mexican dyslipidemic case/control study sample.
[B]Marginal means ± SEM were calculated in a linear mixed effects model using the kinship library in R to adjust for family relations.

Supplementary Table S2. Sequence variants identified in the coding and exon-intron boundaries of *MYLIP*.

Variant[a]	Position[b]	Location (Type)	Major, minor allele[c]	Low-LDL		High-LDL	
				Genotype count[d]	MAF	Genotype count[d]	MAF[e]
rs3765234	16237477	5'UTR	G/T	0/2/48	0.020	0/1/59	0.008
I202L	16251370	Exon 4 (Non-synonymous)	A/C	0/2/54	0.018	0/2/62	0.019
rs2072783	16251876	Intron4 (-34bp)	A/G	4/19/30	0.250	7/21/35	0.283
rs34627146	16252059	Exon 5 (Synonymous)	G/A	0/1/52	0.010	0/3/61	0.028
L338L	16253293	Exon 6 (Synonymous)	C/T	0/1/54	0.009	0/1/63	0.009
V339I	16253294	Exon 6 (Non-synonymous)	G/A	0/2/53	0.009	0/0/64	0.000
rs9370867	16253304	Exon 6 (Non-synonymous)	G/A	4/26/25	0.306	7/23/34	0.264
rs1060901	16253452	Exon 6 (Synonymous)	C/T	0/6/49	0.056	0/1/63	0.009
rs2072781	16255328	3'UTR	T/C	0/7/46	0.067	0/5/61	0.045
C.*871T>C	16255833	3'UTR	T/C	0/0/53	0.000	0/1/60	0.010
rs2205795	16256037	3'UTR	G/T	4/29/22	0.343	5/28/33	0.318
rs2205794	16256155	3'UTR	G/A	0/2/53	0.019	0/0/66	0.000

All variants had at least a 90% genotype call rate and were in Hardy-Weinberg equilibrium ($P > 0.05$). [a]The unknown coding variants are called according to the amino-acid position and/or substitution, and the unknown 3'UTR variants are called according to the HGVS nomenclature guidelines (http://www.hgvs.org/mutnomen/). [b]Basepair position is indicated according to the human reference sequence NCBI36/hg18. [c]Alleles are shown in + strand relative to the human reference sequence. [d]Genotype count of the homozygote rare/heterozygote/homozygote common alleles. [e]Minor allele frequency in unrelated founder individuals.

Supplementary Table S3 Sequencing variants investigated in the Mexican normotriglyceridemic study samples

Variant	LDL-C mmol/L[a]		ALL		Low-LDL		High-LDL	
	C/C	R/X	Genotype count[b]	MAF	Genotype count[b]	MAF	Genotype count[b]	MAF
V339I	3.15±0.02	3.65±1.09	0/3/1073	0.001	0/1/265	0.002	0/2/379	0.003
rs1060901	3.04±0.04	2.99±0.13	1/32/415	0.037	0/13/120	0.046	1/10/127	0.043
rs2205794	3.01±0.04	2.82±0.23	0/13/423	0.014	0/5/131	0.018	0/4/126	0.015

[a]C/C represent the mean ± SEM in homozygotes of the common allele and R/X the mean in carriers of the rare allele. [b]Genotype count of the homozygote rare/heterozygote/homozygote common alleles.

Supplementary Table S4. Association results for the *MYLIP* region with TC and non-HDL-C in the Mexican dyslipidemic study sample.

SNP	BP	SNP	Major/	MAF		High TC Status				TC residuals				Non HDL-C residuals				Best GWA tag[F]	
	Position	type[A]	Minor[B]	High TC	Normal TC	Effect (SE)[C]	P	P.ADJ[D]	P.CON[E]	Effect (SE)[C]	P	P.ADJ[D]	P.CON[E]	Effect (SE)[C]	P	P.ADJ[D]	P.CON[E]	SNP	r^2
rs2876407	16186458	g	G/A	0.15	0.14	1.04 (0.12)	7.21E-01	9.16E-01	5.37E-01	0.03 (0.04)	5.48E-01	6.84E-01	4.36E-01	0.01 (0.04)	8.13E-01	9.32E-01	6.98E-01		
rs2294279	16187091	i	C/T	0.15	0.14	1.04 (0.12)	7.21E-01	9.16E-01	5.38E-01	0.03 (0.04)	5.48E-01	6.73E-01	4.34E-01	0.01 (0.04)	8.12E-01	9.20E-01	6.95E-01		
rs2294274	16187924	g	G/A	0.27	0.28	1 (0.09)	9.95E-01	8.90E-01	9.70E-01	0.01 (0.03)	6.94E-01	7.98E-01	6.78E-01	0 (0.03)	9.52E-01	8.68E-01	9.65E-01		
rs9396642	16189453	g	G/T	0.3	0.3	0.97 (0.09)	7.38E-01	7.01E-01	9.56E-02	-0.02 (0.03)	5.10E-01	4.99E-01	1.06E-01	0 (0.03)	9.93E-01	9.99E-01	4.40E-01		
rs9477033	16193568	i	T/C	0.28	0.28	1 (0.09)	9.79E-01	8.97E-01	9.41E-01	0.01 (0.03)	6.86E-01	7.97E-01	6.64E-01	0 (0.03)	9.69E-01	8.85E-01	9.87E-01		
rs9477035	16194229	i	T/C	0.28	0.28	1 (0.09)	9.79E-01	8.97E-01	9.41E-01	0.01 (0.03)	6.86E-01	7.97E-01	6.64E-01	0 (0.03)	9.69E-01	8.85E-01	9.87E-01		
rs2294270	16195213	g	A/G	0.15	0.14	1.04 (0.12)	7.21E-01	9.16E-01	5.37E-01	0.03 (0.04)	5.48E-01	6.84E-01	4.36E-01	0.01 (0.04)	8.13E-01	9.32E-01	6.98E-01		
rs2294268	16195835	i	T/C	0.43	0.42	1.03 (0.08)	7.57E-01	9.93E-01	5.95E-01	0.03 (0.03)	3.94E-01	5.53E-01	3.15E-01	0.01 (0.03)	8.60E-01	9.88E-01	7.60E-01		
rs4716044	16196372	i	G/A	0.43	0.42	1.03 (0.08)	7.61E-01	9.89E-01	5.98E-01	0.03 (0.03)	3.97E-01	5.57E-01	3.17E-01	0.01 (0.03)	8.63E-01	9.84E-01	7.63E-01		
rs12194627	16196709	i	T/A	0.28	0.28	1 (0.09)	9.85E-01	8.92E-01	9.44E-01	0.01 (0.03)	6.94E-01	8.06E-01	6.71E-01	0 (0.03)	9.61E-01	8.78E-01	9.81E-01		
rs16877617	16197064	i	A/G	0.17	0.14	1.19 (0.11)	1.30E-01	5.67E-01	3.87E-01	0.06 (0.04)	1.50E-01	4.82E-01	3.60E-01	0.03 (0.04)	4.84E-01	8.79E-01	7.96E-01		
rs7744733	16199621	g	C/A	0.29	0.32	0.84 (0.09)	**4.48E-02**	2.01E-01	6.78E-01	-0.09 (0.03)	**3.35E-03**	**1.52E-02**	7.61E-02	-0.08 (0.03)	**9.25E-03**	**2.64E-02**	1.04E-01	rs3757354	0.6
rs9396643	16200972	g	T/G	0.33	0.3	1.12 (0.09)	1.71E-01	5.35E-01	2.23E-01	0.04 (0.03)	2.13E-01	4.62E-01	5.23E-01	0.04 (0.03)	1.87E-01	3.51E-01	8.17E-01	rs9370867	0.4
rs16877620	16201404	i	G/T	0.29	0.32	0.83 (0.09)	**3.98E-02**	1.87E-01	6.46E-01	-0.09 (0.03)	**4.22E-03**	**2.05E-02**	1.06E-01	-0.08 (0.03)	**1.11E-02**	**3.25E-02**	1.39E-01	rs3757354	0.6
rs9477042	16203568	i	G/C	0.01	0.01	1.51 (0.47)	3.89E-01	4.03E-01	2.78E-01	0.17 (0.15)	3.27E-01	3.35E-01	2.59E-01	0.12 (0.15)	4.75E-01	4.81E-01	4.02E-01		
rs6459447	16205265	i	C/T	0.31	0.3	1.03 (0.09)	7.64E-01	9.31E-01	5.53E-01	0.04 (0.03)	2.06E-01	3.34E-01	1.64E-01	0.03 (0.03)	4.12E-01	5.52E-01	3.55E-01		
rs6459448	16206269	g	G/A	0.41	0.38	1.14 (0.08)	1.13E-01	2.16E-01	7.81E-01	0.05 (0.03)	8.51E-02	1.35E-01	6.89E-01	0.06 (0.03)	6.77E-02	9.79E-02	4.62E-01	rs3757354	0.3
rs6921677	16206923	g	T/C	0.12	0.11	1.17 (0.12)	2.02E-01	6.44E-01	7.61E-01	0.04 (0.05)	4.25E-01	8.62E-01	9.64E-01	0.01 (0.05)	7.82E-01	8.35E-01	7.13E-01		
rs11966052	16206969	g	A/G	0.29	0.32	0.83	**3.83E-02**	1.78E-01	6.41E-01	-0.09	**2.98E-03**	**1.37E-02**	7.01E-02	-0.08	**7.90E-03**	**2.30E-02**	9.23E-02	rs3757354	0.6

						(0.09)				(0.03)				(0.03)					
rs9383114	16207259	i	T/A	0.38	0.36	1.1 (0.08)	2.57E-01	4.27E-01	4.32E-01	0.03 (0.03)	2.85E-01	4.07E-01	7.77E-01	0.04 (0.03)	1.99E-01	2.67E-01	8.88E-01		
rs6912988	16208633	i	T/C	0.38	0.36	1.1 (0.08)	2.55E-01	4.25E-01	4.38E-01	0.03 (0.03)	2.89E-01	4.12E-01	7.73E-01	0.04 (0.03)	2.08E-01	2.77E-01	9.07E-01		
rs10949343	16209236	i	T/C	0.38	0.36	1.1 (0.08)	2.44E-01	4.07E-01	4.47E-01	0.03 (0.03)	2.87E-01	4.08E-01	7.74E-01	0.04 (0.03)	2.07E-01	2.76E-01	9.07E-01		
rs11751891	16209734	g	C/A	0.01	0.01	1.19 (0.41)	6.74E-01	8.11E-01	6.39E-01	-0.03 (0.15)	8.15E-01	7.01E-01	8.46E-01	-0.07 (0.15)	6.53E-01	5.72E-01	6.77E-01		
rs12192575	16210281	g	C/T	0.38	0.36	1.1 (0.08)	2.53E-01	4.19E-01	4.21E-01	0.03 (0.03)	2.92E-01	4.06E-01	7.41E-01	0.04 (0.03)	2.12E-01	2.81E-01	9.17E-01		
rs7749877	16210781	i	G/A	0.4	0.37	1.13 (0.08)	1.49E-01	2.65E-01	6.34E-01	0.04 (0.03)	1.52E-01	2.31E-01	9.24E-01	0.05 (0.03)	1.18E-01	1.64E-01	6.70E-01		
rs1474582	16212610	g	A/G	0.44	0.4	1.21 (0.08)	**1.66E-02**	**4.75E-02**	9.01E-01	0.06 (0.03)	**2.76E-02**	**5.34E-02**	5.70E-01	0.07 (0.03)	**1.98E-02**	**3.36E-02**	3.16E-01	rs9370867	0.4
rs7749556	16214288	i	A/G	0.01	0.01	1.44 (0.51)	4.49E-01	5.73E-01	3.87E-01	0.05 (0.15)	7.51E-01	8.60E-01	6.60E-01	-0.01 (0.15)	9.29E-01	8.44E-01	9.98E-01		
rs2294262	16216946	g	C/T	0.07	0.1	0.73 (0.15)	**4.11E-02**	1.58E-01	2.02E-01	-0.03 (0.05)	5.27E-01	8.83E-01	1.00E+00	-0.02 (0.05)	6.54E-01	9.45E-01	9.32E-01		
rs9477044	16216987	i	C/T	0.26	0.3	0.81 (0.09)	**2.24E-02**	1.16E-01	5.44E-01	-0.1 (0.03)	**3.77E-03**	**2.11E-02**	1.16E-01	-0.08 (0.03)	**2.37E-02**	6.77E-02	2.49E-01	rs3757354	0.8
rs2294261	16217142	g	C/A	0.32	0.26	1.32 (0.09)	**1.26E-03**	**1.32E-02**	7.13E-01	0.08 (0.03)	**2.03E-02**	6.90E-02	6.77E-01	0.08 (0.03)	**2.08E-02**	**5.34E-02**	8.94E-01	rs9370867	0.5
rs6913929	16218165	i	T/C	0.33	0.27	1.31 (0.09)	**2.00E-03**	**1.64E-02**	5.60E-01	0.08 (0.03)	**2.18E-02**	7.88E-02	8.43E-01	0.07 (0.03)	**2.30E-02**	6.12E-02	8.74E-01	rs9370867	0.7
rs2327949	16218424	g	G/A	0.32	0.36	0.83 (0.09)	**2.62E-02**	9.05E-02	6.16E-01	-0.11 (0.03)	**6.56E-04**	**2.45E-03**	**2.66E-02**	-0.09 (0.03)	**3.02E-03**	**7.39E-03**	**4.95E-02**	rs3757354	0.9
rs2480	16221712	g	T/C	0.34	0.28	1.36 (0.08)	**2.57E-04**	**3.80E-03**	6.51E-01	0.09 (0.03)	**7.00E-03**	**3.04E-02**	6.95E-01	0.08 (0.03)	**1.26E-02**	**3.64E-02**	9.81E-01	rs9370867	0.5
rs11969250	16222685	g	A/G	0.24	0.27	0.86 (0.09)	1.14E-01	3.67E-01	9.05E-01	-0.02 (0.03)	6.15E-01	9.79E-01	4.47E-01	-0.02 (0.03)	5.45E-01	8.10E-01	6.54E-01	rs2327951	0.4
rs9370865	16223774	g	T/G	0.25	0.28	0.87 (0.09)	1.15E-01	3.57E-01	8.85E-01	-0.01 (0.03)	6.55E-01	9.97E-01	4.04E-01	-0.02 (0.03)	5.24E-01	7.69E-01	6.68E-01	rs2327951	0.4
rs10484357	16224727	g	G/A	0.09	0.09	1.07 (0.14)	6.15E-01	8.53E-01	3.20E-01	0 (0.05)	9.93E-01	6.04E-01	7.24E-01	-0.01 (0.05)	7.80E-01	5.00E-01	9.81E-01		
rs6459450	16232539	i	C/T	0.39	0.31	1.46 (0.08)	**4.97E-06**	**5.40E-04**	1.19E-01	0.11 (0.03)	**3.43E-04**	**8.50E-03**	4.48E-01	0.1 (0.03)	**2.08E-03**	**1.77E-02**	5.01E-01	rs9370867	0.8
rs3757354	16235386	g	C/T	0.33	0.38	0.8 (0.09)	**9.62E-03**	**3.72E-02**	5.07E-01	-0.08 (0.03)	**5.36E-03**	**1.58E-02**	1.73E-01	-0.07 (0.03)	**1.39E-02**	**2.93E-02**	2.05E-01	rs3757354	1
rs909562	16238312	g	A/G	0.28	0.32	0.8 (0.09)	**1.27E-02**	8.17E-02	4.97E-01	-0.04 (0.03)	2.66E-01	5.84E-01	7.86E-01	-0.03 (0.03)	3.97E-01	6.81E-01	7.44E-01	rs2327951	0.7
rs2076017	16238538	i	A/G	0.17	0.21	0.78	**2.72E-02**	1.87E-01	6.48E-01	-0.03	4.40E-01	9.01E-01	6.84E-01	-0.02	5.78E-01	9.45E-01	6.32E-01	rs2327951	0.4

						(0.12)				(0.04)				(0.04)					
rs1011616	16240388	i	C/T	0.27	0.31	0.81 (0.09)	**1.98E-02**	1.03E-01	6.36E-01	-0.04 (0.03)	2.60E-01	5.86E-01	8.02E-01	-0.03 (0.03)	3.44E-01	6.10E-01	8.17E-01	rs2327951	0.6
rs2237106	16241965	i	C/T	0.17	0.2	0.78 (0.12)	**2.86E-02**	2.02E-01	6.78E-01	-0.03 (0.04)	4.52E-01	9.22E-01	6.68E-01	-0.02 (0.04)	5.74E-01	9.44E-01	6.33E-01	rs2327951	0.4
rs4515393	16249207	i	A/G	0.01	0.01	0.59 (0.67)	3.79E-01	4.47E-01	3.93E-01	0.13 (0.17)	4.80E-01	4.50E-01	4.56E-01	0.15 (0.17)	4.29E-01	4.08E-01	4.09E-01		
rs7763395	16250338	i	A/G	0.4	0.43	0.9 (0.08)	1.86E-01	2.78E-01	2.41E-01	-0.05 (0.03)	1.24E-01	1.87E-01	8.22E-01	-0.03 (0.03)	2.55E-01	3.28E-01	7.31E-01	rs3757354	0.8
rs2205796	16250976	g	T/G	0.35	0.37	0.92 (0.09)	3.57E-01	6.22E-01	1.92E-01	-0.03 (0.03)	3.08E-01	5.05E-01	5.43E-01	-0.01 (0.03)	6.40E-01	8.45E-01	3.41E-01	rs3757354	0.7
rs2072783	16251876	i	A/G	0.27	0.33	0.76 (0.09)	**2.08E-03**	**1.47E-02**	2.16E-01	-0.05 (0.03)	9.94E-02	2.51E-01	8.39E-01	-0.04 (0.03)	1.57E-01	2.98E-01	8.36E-01	rs2327951	0.7
rs2056937	16252593	g	T/C	0.4	0.43	0.89 (0.08)	1.39E-01	2.10E-01	3.06E-01	-0.05 (0.03)	8.71E-02	1.34E-01	9.20E-01	-0.04 (0.03)	1.73E-01	2.30E-01	8.56E-01	rs3757354	0.8
rs9370867	16253304	g	G/A	0.31	0.23	1.52 (0.09)	**1.51E-06**	**8.81E-05**	NA	0.12 (0.03)	**2.26E-04**	**2.34E-03**	NA	0.11 (0.03)	**1.81E-03**	**8.51E-03**	NA	rs9370867	1
rs1060901	16253452	i	C/T	0.04	0.05	0.78 (0.21)	2.24E-01	1.16E-01	5.45E-01	-0.11 (0.07)	1.19E-01	6.81E-02	2.62E-01	-0.13 (0.07)	7.57E-02	**4.86E-02**	1.59E-01		
rs2072781	16255328	g	T/C	0.05	0.06	0.87 (0.18)	4.41E-01	2.64E-01	9.15E-01	-0.07 (0.06)	2.75E-01	1.72E-01	5.57E-01	-0.08 (0.06)	1.87E-01	1.25E-01	3.69E-01		
rs2205795	16256037	i	G/T	0.36	0.39	0.87 (0.09)	1.36E-01	3.49E-01	3.20E-01	-0.05 (0.03)	1.08E-01	2.47E-01	8.49E-01	-0.02 (0.03)	4.51E-01	6.72E-01	4.84E-01	rs3757354	0.7
rs16877675	16259227	i	G/T	0.06	0.09	0.61 (0.19)	**4.95E-03**	**2.85E-02**	6.06E-02	-0.05 (0.05)	4.27E-01	7.36E-01	9.43E-01	-0.03 (0.05)	6.27E-01	8.92E-01	9.10E-01		
rs2072779	16261724	g	G/T	0.38	0.39	0.97 (0.08)	7.50E-01	9.79E-01	7.55E-02	-0.02 (0.03)	5.46E-01	7.49E-01	3.33E-01	0 (0.03)	9.14E-01	7.44E-01	1.34E-01	rs3757354	0.7
rs17580572	16261941	g	G/A	0.33	0.35	0.92 (0.09)	3.55E-01	6.76E-01	2.53E-01	-0.03 (0.03)	3.95E-01	6.59E-01	4.85E-01	0 (0.03)	8.87E-01	8.60E-01	2.20E-01	rs3757354	0.7
rs7742617	16264783	g	T/C	0.3	0.37	0.71 (0.09)	**1.07E-04**	**1.02E-03**	**2.42E-02**	-0.08 (0.03)	**7.36E-03**	**2.43E-02**	1.64E-01	-0.09 (0.03)	**3.48E-03**	**9.33E-03**	5.93E-02	rs2327951	0.9
rs17641827	16265098	i	C/G	0.26	0.29	0.85 (0.1)	9.04E-02	4.04E-01	8.83E-01	-0.05 (0.03)	1.22E-01	3.64E-01	9.20E-01	-0.03 (0.03)	3.96E-01	7.06E-01	6.98E-01	rs3757354	0.8
rs6921316	16265240	i	C/T	0.3	0.37	0.71 (0.09)	**8.16E-05**	**8.52E-04**	**2.39E-02**	-0.08 (0.03)	**8.23E-03**	**3.03E-02**	2.16E-01	-0.09 (0.03)	**3.99E-03**	**1.18E-02**	9.08E-02	rs2327951	0.9
rs9367897	16266253	g	G/A	0.3	0.37	0.71 (0.09)	**7.94E-05**	**7.80E-04**	**2.00E-02**	-0.08 (0.03)	**6.87E-03**	**2.29E-02**	1.57E-01	-0.09 (0.03)	**3.38E-03**	**9.11E-03**	5.78E-02	rs2327951	0.9
rs9349997	16266842	i	A/G	0.3	0.37	0.71 (0.09)	**6.06E-05**	**6.67E-04**	**1.96E-02**	-0.08 (0.03)	**8.28E-03**	**2.98E-02**	2.13E-01	-0.09 (0.03)	**4.39E-03**	**1.26E-02**	9.46E-02	rs2327951	0.9
rs7770341	16276393	g	A/C	0.14	0.19	0.73 (0.11)	**5.38E-03**	**1.87E-02**	8.87E-02	-0.07 (0.04)	5.65E-02	1.15E-01	3.11E-01	-0.07 (0.04)	8.61E-02	1.44E-01	3.35E-01	rs2327951	0.4
rs2235214	16280949	i	G/C	0.13	0.18	0.71	**2.43E-03**	**1.01E-02**	**4.71E-02**	-0.07	7.83E-02	1.64E-01	3.71E-01	-0.06	1.25E-01	2.09E-01	4.15E-01	rs2327951	0.4

						(0.12)				(0.04)				(0.04)				
rs2038037	16283274	g	G/A	0.32	0.25	1.47 (0.09)	**8.95E-06**	**5.46E-04**	4.36E-01	0.11 (0.03)	**8.37E-04**	**8.79E-03**	6.26E-01	0.09 (0.03)	**7.26E-03**	**3.29E-02**	8.73E-01	rs9370867	0.8
rs11963956	16286779	i	A/G	0.12	0.17	0.71 (0.12)	**3.36E-03**	**1.41E-02**	6.53E-02	-0.07 (0.04)	6.59E-02	1.45E-01	3.40E-01	-0.06 (0.04)	1.19E-01	2.04E-01	4.18E-01	rs2327951	0.4
rs11966292	16287092	g	G/A	0.12	0.17	0.71 (0.12)	**4.30E-03**	**1.65E-02**	7.37E-02	-0.08 (0.04)	5.60E-02	1.21E-01	3.21E-01	-0.07 (0.04)	9.36E-02	1.65E-01	3.73E-01	rs2327951	0.4
rs9370869	16290223	i	C/G	0.04	0.04	0.93 (0.27)	7.52E-01	8.52E-01	6.23E-01	-0.03 (0.08)	7.33E-01	9.47E-01	9.08E-01	-0.05 (0.08)	5.91E-01	7.38E-01	8.98E-01		
rs7773751	16290900	i	C/A	0.12	0.17	0.71 (0.12)	**3.71E-03**	**1.56E-02**	7.16E-02	-0.07 (0.04)	6.55E-02	1.47E-01	3.43E-01	-0.06 (0.04)	1.17E-01	2.03E-01	4.17E-01	rs2327951	0.4
rs11965222	16294263	i	A/G	0.01	0.01	1.58 (0.55)	3.97E-01	4.17E-01	3.35E-01	-0.18 (0.15)	3.81E-01	3.58E-01	4.54E-01	-0.29 (0.15)	1.73E-01	1.65E-01	2.08E-01		
rs6459451	16295314	i	A/C	0.24	0.24	0.96 (0.1)	6.69E-01	6.74E-01	5.06E-01	-0.02 (0.04)	5.48E-01	5.35E-01	8.54E-01	-0.04 (0.04)	2.38E-01	2.32E-01	5.91E-01	rs2327951	0.5
rs7760540	16301395	i	G/T	0.35	0.4	0.8 (0.09)	**1.09E-02**	**2.77E-02**	3.88E-01	-0.05 (0.03)	1.37E-01	2.21E-01	8.59E-01	-0.05 (0.03)	8.17E-02	1.23E-01	5.28E-01	rs2327951	1
rs2327951	16303287	g	T/C	0.35	0.4	0.81 (0.09)	**1.23E-02**	**3.08E-02**	4.01E-01	-0.05 (0.03)	1.33E-01	2.12E-01	8.18E-01	-0.05 (0.03)	7.75E-02	1.17E-01	4.68E-01	rs2327951	1
rs9370870	16304738	i	G/A	0.35	0.4	0.81 (0.09)	**1.11E-02**	**2.81E-02**	3.88E-01	-0.05 (0.03)	1.38E-01	2.22E-01	8.58E-01	-0.05 (0.03)	8.28E-02	1.24E-01	5.28E-01	rs2327951	1
rs2142672	16305173	g	G/A	0.35	0.4	0.81 (0.09)	**1.14E-02**	**2.78E-02**	3.86E-01	-0.05 (0.03)	1.42E-01	2.21E-01	8.49E-01	-0.05 (0.03)	8.10E-02	1.20E-01	4.85E-01	rs2327951	1

SNPs surpassing the multiple-testing correction threshold (P<7.2x10-04) are designated in red and results at P≤ 0.05 are in boldface.

[A]The genotyped SNPs are indicated by 'g' and imputed SNPs by 'i'.

[B]Major/minor alleles are in + strand relative to the human reference sequence (Build 36.1).

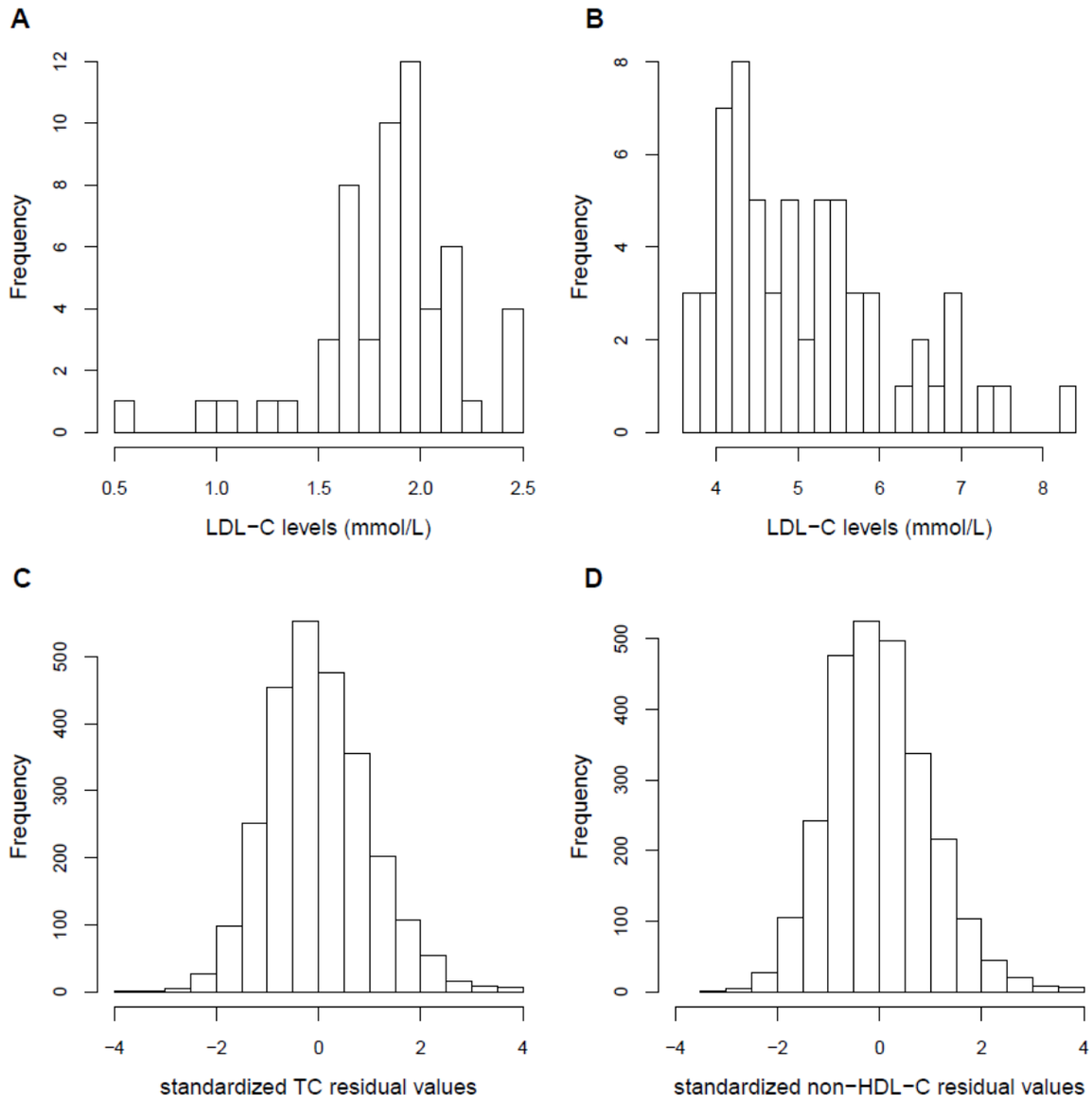
[C]The effect size represents the odds-ratio of each copy of the risk allele for the TC affection status and the proportion of 1 SD change in standardized residual values for each copy of the risk allele for the continuous TC and non-HDL-C levels.

[D]P-value adjusted for admixture ancestry using the individual ancestry estimates as a covariate in the regression analysis.

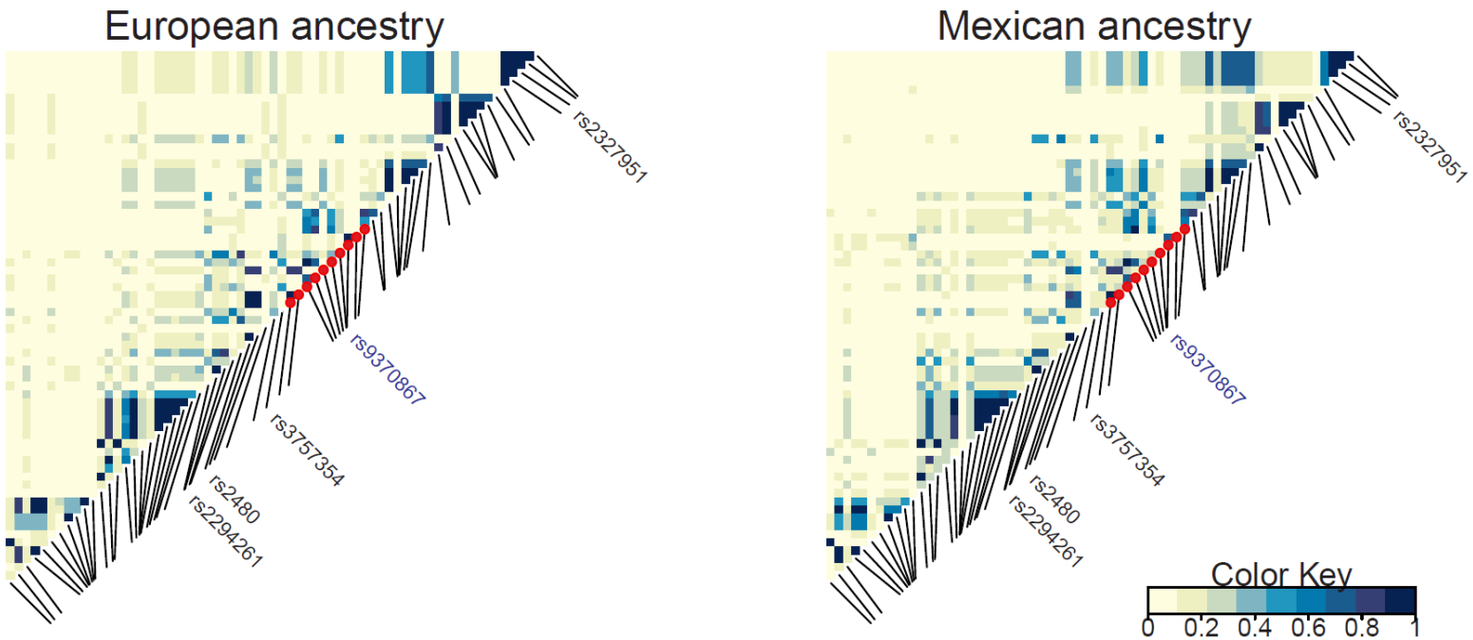
[E]P-value for conditional analysis including rs9370867genotypes as a covariate in the regression analysis.

[F]The GWA signal (rs3757354, rs9370867, or rs2327951) that captures best this allele with r^2 threshold ≥0.3.

Supplementary Figure S1.



Supplementary Figure S2.



Supplementary Figure S3