

Supplemental Methods

Intimal Medial Thickness (IMT) analyses

Participants were from the Offspring Cohort of the Framingham Heart Study (FHS) who had IMT measurement data and were successfully genotyped for the Asn396Ser or Thr111Ile *LIPG* variant, with up to 1653 participants analyzed. We analyzed the mean and maximum common carotid artery IMT and internal carotid artery IMT measurements as previously described, creating ranked normalized deviates from the age-adjusted, sex-specific residuals obtained from a linear regression model (1). The additive genetic associations of the *LIPG* variants were evaluated.

Supplemental References

1. O'Donnell, C., Cupples, L.A., D'Agostino, R., Fox, C., Hoffmann, U., Hwang, S.-J., Ingelsson, E., Liu, C., Murabito, J., Polak, J., et al. 2007. Genome-wide association study for subclinical atherosclerosis in major arterial territories in the NHLBI's Framingham Heart Study. *BMC Medical Genetics* 8:S4.

Supplemental Table 1. Fasting lipid and lipoprotein measurements of high HDL subjects in whom *LIPG* was resequenced.

Variant	Sex	Age (y)	BMI (kg/m ²)	Alcohol (%)	Smoker (%)	HDL (mg/dl)	cLDL (mg/dl)	TC (mg/dl)	TG (mg/dl)	Apo A-I (mg/dl)	Apo B (mg/dl)	Lp(a) (mg/dl)
Fs114delA	F	57	24.6	0	0	121	160	298	85	207	93	13
Ala116Thr	F	57	-	-	-	124	115.4	253	68	299	66	54.1
Gly176Arg	F	66	22.9	1	0	129	152	292	57	230	117	46
Ile239Thr	F	57	21.0	0	0	113	212.4	340	73	214	122	100.2
Met342Val	F	48	21.3	1	1	141	78.6	245	127	301	54	46.8
Arg476Trp	F	59	24.2	1	0	129	169	313	74	230	107	82.8
Arg476Trp	F	35	21.3	1	1	101	130	251	98	254	129	>3
Arg476Trp	F	53	18.7	1	0	111	203	326	58	182	114	>3
Arg476Trp	F	40	24.2	0	0	98	209	345	190	187	160	17
X501Arg ^A	F	56	22.5	1	0	102	118.6	233	62	234	78	51.0

Asn396Ser (n = 23)	65.2	54.2 ± 13.8 (31 - 80)	23.0 ± 3.2 (18.8 - 32.0)	69.6	4.3	102.9 ± 20.8 (73 - 174)	125.1 ± 41.2 (52 - 199)	244.1 ± 43.1 (161 - 315)	80.7 ± 50.3 (27 - 290)	188.5 ± 27.0 (151 - 234)	111.0 ± 26.4 (78 - 151)	73.6 ± 66.9 (<3 - 176)
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WT (n = 340)	60.0	59.9 ± 11.5 (27 - 89)	23.5 ± 3.3 (15.8 - 37.4)	89.8	9.4	102.6 ± 20.0 (68 - 186)	124.6 ± 33.7 (36 - 248)	243.6 ± 38.9 (136 - 397)	75.5 ± 32.8 (27 - 260)	206.7 ± 40.8 (36 - 312)	81.9 ± 17.9 (52 - 149)	38.8 ± 37.3 (<3 - 135.9)
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^AThe subject carrying the X501Arg variant also carries the Asn396Ser variant. Values with '±' are means ± SD. -, data unavailable. Numbers in parentheses are ranges.

Supplemental Table 2. Additional lipoprotein measurement and NMR lipoprotein profile measurements.

Variant	ApoCIII mg/dl	Apo E mg/dl	Apo CII mg/dl	Apo AII mg/dl	VLDL & Chylomicron Particles (total) nmol/L	Large VLDL & Chylomicron Particles nmol/L	Medium VLDL Particles nmol/L	Small VLDL Particles nmol/L	LDL Particles (total) nmol/L	IDL Particles nmol/L	Large LDL Particles nmol/L	Small LDL Particles (total) nmol/L
Ala116Thr	21.3	6.3	5.6	45	17.7	0.1	17.2	0.4	804	0	741	63
Ile239Thr	17.9	6.6	6.4	38	42.3	0.1	3.8	38.4	1473	0	1374	99
Met342Val	24.3	4.2	5.5	70	31.7	6.3	17.9	7.6	571	32	468	72
Arg476Trp	20.2	5.7	6.1	38	40.8	0.2	15.1	25.4	1039	1	1037	0
X501Arg ^A	19.0	7.6	4.9	41	26.6	0.1	5.1	21.4	1215	0	403	812

WT (n = 25)	17.9 ± 3.0 (13.0 - 27.6)	5.6 ± 1.3 (3.1 - 8.5)	4.9 ± 1.3 (3.5 - 9.7)	45.0 ± 10.4 (30 - 69)	23.0 ± 16.1 (2.4 - 65.6)	0.3 ± 0.7 (0.0 - 3.2)	9.5 ± 7.2 (0.2 - 27.2)	13.2 ± 15.3 (0.0 - 58.2)	941.6 ± 294.9 (476.6 - 1719.3)	14.3 ± 38.51 (0.0 - 141.3)	676.5 ± 260.5 (265.8 - 1568.1)	250.8 ± 242.4 (0.0 - 831.3)
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Variant	Medium Small LDL Particles nmol/L	Very Small LDL Particles nmol/L	HDL Particles (total) µmol/L	Large HDL Particles µmol/L	Medium HDL Particles µmol/L	Small HDL Particles µmol/L	VLDL Size nm	LDL Size nm	HDL Size nm	Triglyceride (total) mg/dL	VLDL & Chylomicron Triglyceride (total) mg/dL	HDL Cholesterol (total) mg/dL
Ala116Thr	6	57	43.9	25	2.9	15.9	50.9	22.4	10.3	75	29	126
Ile239Thr	29	70	32.2	20.4	0	11.8	36.6	22.6	10.2	86	30	90
Met342Val	21	51	56.5	28.3	3.7	24.5	68.2	22.4	9.8	129	86	128
Arg476Trp	0	0	33.6	20.1	0	13.5	43.9	22.6	10.2	84	38	95
X501Arg ^A	338	474	35.4	19.9	1.4	14.1	43.3	21.4	10.1	65	21	96

WT (n = 25)	71.2 ± 80.5 (0.0 - 261.1)	179.6 ± 183.1 (0.0 - 700.1)	40.4 ± 9.1 (22.7 - 66.5)	21.3 ± 3.4 (13.3 - 26.1)	1.8 ± 4.3 (0.0 - 16.4)	17.3 ± 7.6 (0.7 - 40.6)	54.3 ± 15.6 (37.8 - 103.3)	22.2 ± 0.5 (21.2 - 22.7)	10.0 ± 0.3 (9.6-10.6)	69.0 ± 21.5 (43.6 - 141.8)	25.5 ± 13.6 (7.2 - 54.7)	101.3 ± 13.1 (79.3 - 134.2)
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^AThe subject carrying the X501Arg variant also carries the Asn396Ser variant. Values with '±' are means ± SD. -, data unavailable. Numbers in parentheses are ranges.

Supplemental Table 3. Mean lipid and lipoprotein values by genotype.

		Thr111Ile (rs2000813)			<i>P</i> ^D	Asn396Ser			<i>P</i> ^D
		C/C	C/T	T/T		A/A	A/G	G/G	
		n	n	n		n	n	n	
FHS	HDL-C ^A	50.49 ± 13.53	50.68 ± 13.20	51.19 ± 14.91	0.92	50.46 ± 13.47	58.76 ± 16.26	-	4 x 10 ⁻⁵
		798	672	139		1740	46	0	
	HDL ₂ ^B	7.49 ± 5.57	7.31 ± 5.20	7.70 ± 6.59	0.66	7.34 ± 5.42	9.88 ± 7.06	-	0.03
		718	616	124		1572	42	0	
	HDL ₃ ^B	42.60 ± 10.80	42.58 ± 10.91	43.25 ± 12.06	0.82	42.44 ± 10.84	49.03 ± 12.29	-	6 x 10 ⁻⁴
		673	584	114		1481	38	0	
	HDL Size ^B	9.18 ± 0.50	9.16 ± 0.46	9.20 ± 0.48	0.6	9.17 ± 0.48	9.43 ± 0.51	-	8 x 10 ⁻³
		624	527	110		1356	35	0	
	HDL small particle ^B	7.02 ± 4.95	7.07 ± 5.34	7.31 ± 4.78	0.45	7.16 ± 5.09	6.03 ± 4.91	-	0.59
		624	527	110		1356	35	0	
	HDL intermediate particle ^B	20.99 ± 6.40	21.22 ± 6.85	20.28 ± 6.80	0.63	21.00 ± 6.57	20.54 ± 7.70	-	0.74
624		527	110	1356		35	0		
HDL large particle ^B	23.18 ± 16.93	23.34 ± 17.03	23.93 ± 18.41	0.93	22.97 ± 16.97	34.31 ± 18.06	-	4 x 10 ⁻⁴	
	624	527	110		1356	35	0		
apoA-1 ^B	143.28 ± 29.10	144.33 ± 31.49	146.02 ± 30.29	0.62	143.17 ± 30.20	158.18 ± 40.67	-	7 x 10 ⁻³	
	677	579	118		1480	38	0		
Total Cholesterol ^A	204.15 ± 30.35	203.22 ± 30.05	205.64 ± 31.06	-	203.64 ± 29.99	209.60 ± 31.71	-	-	
	798	672	139		1740	46	0		
Triglycerides ^A	124.39 ± 72.90	124.51 ± 72.92	135.41 ± 129.30	0.18	124.51 ± 77.42	120.97 ± 76.22	-	0.79	
	798	672	139		1740	46	0		
LDL-C ^A	129.25 ± 27.33	128.17 ± 27.33	128.63 ± 27.98	0.72	128.81 ± 27.00	126.54 ± 30.83	-	0.37	
	796	672	139		1738	46	0		
NHS II/ HPFS^C	HDL-C	57.0 ± 16.87	56.5 ± 17.79	59.4 ± 19.33	0.18	55.4 ± 19.54	64.6 ± 21.61	-	0.03
		716	622	124		1780	28	0	
	Total Cholesterol	215.9 ± 45.43	214.8 ± 44.73	213.5 ± 44.38	0.74	212.3 ± 43.39	217.0 ± 45.40	-	0.14
		716	622	124		1780	28	0	
Triglycerides	117.8 ± 88.58	126.3 ± 98.42	118.3 ± 89.17	0.21	121.0 ± 89.15	91.9 ± 49.05	-	0.19	
	501	424	91		1146	20	0		
LDL-C	129.6 ± 36.00	127.9 ± 36.33	124.41 ± 36.30	0.37	127.6 ± 35.10	128.0 ± 36.22	-	0.36	
	716	622	124		1780	28	0		
PennCATH^C	HDL-C	-	-	-	-	43.70 ± 12.96	48.71 ± 12.38	-	0.02
		-	-	-		1267	41	0	
	Total Cholesterol	-	-	-	-	178.40 ± 41.41	184.70 ± 38.93	-	-
		-	-	-		1267	41	0	
Triglycerides	-	-	-	-	141.50 ± 103.2	128.40 ± 71.42	-	-	
	-	-	-		1267	41	0		
LDL-C	-	-	-	-	107.40 ± 35.55	110.3 ± 30.71	-	-	
	-	-	-		1240	41	0		

^AUnadjusted average of mean measurements across up to seven exams ± SD, ^BUnadjusted average of measurements from exam 4 ± SD, ^CUnadjusted average ± SD, ^D*P* from adjusted models as described in text, -, unavailable

Supplemental Table 4. IMT Analyses

Variant	Subclinical Atherosclerosis Measure	Phenotype Variable Name	β	n	P-value
Asn396Ser	Maximum common carotid artery IMT	RNKCARTOTCCAMAXAS6	0.16	1653	0.26
Asn396Ser	Mean common carotid artery IMT	RNKCARTOTCCAMEANAS6	0.16	1653	0.10
Asn396Ser	Maximum internal carotid artery IMT	RNKCARTOTICAMAXAS6	0.16	1548	0.19
Asn396Ser	Mean internal carotid artery IMT	RNKCARTOTICAMEANAS6	0.16	1548	0.24
Thr111Ile	Maximum common carotid artery IMT	RNKCARTOTCCAMAXAS6	0.04	1494	0.94
Thr111Ile	Mean common carotid artery IMT	RNKCARTOTCCAMEANAS6	0.04	1494	0.82
Thr111Ile	Maximum internal carotid artery IMT	RNKCARTOTICAMAXAS6	0.04	1394	0.44
Thr111Ile	Mean internal carotid artery IMT	RNKCARTOTICAMEANAS6	0.04	1394	0.22

Supplemental Figure 1. Evaluation of LD

Genotyping of downstream *LIPG* SNPs identified from reported GWAS analysis of HDL-C variants was performed in the HHDL (rs4939883), Penn HDL (rs4939883), and PennCATH (rs2156552) cohorts. HapMap (release 21) data and our genotyping data were used to estimate LD using the Haploview software. SNPs rs4939883 and rs2156552 are highly correlated with each other, but neither is well correlated with Thr111Ile (rs2000813) or Asn396Ser. Both D' and r^2 estimates of LD are displayed.

