

APPENDIX: Tables A – E and Figures A, B

**Association of Extreme Blood Lipid Profile Phenotypic Variation
with 11 Reverse Cholesterol Transport Genes and
10 Nongenetic Cardiovascular Disease Risk Factors**

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Appendix Table A. Type of sequence variants identified and frequency of the rare allele in 11 reverse cholesterol transport (RCT) genes of 95 subjects. (**Bold** : rare allele frequency $\geq 3\%$.)

| GENE | Exon | Base position [§] | Variant ^f | Rare allele frequency (%) |
|--------------|------|----------------------------|----------------------|---------------------------|
| ABCA1 | | | | |
| Promotor | | -1426 | C-T | 35 |
| | | -1283 | G-A | 9 |
| | | -1263 | T-C | 2 |
| | | -1248 | C-T | 8 |
| | | -1126 | G-T | 13 |
| | | -964 | T-G | 46 |
| | | -654 | G-A | 15 |
| | | | del-ins | 36 |
| | | -588 | C-T | 47 |
| | | -431 | G-C | 33 |
| | | -326 | C-T | 5 |
| | | -302 | G-C | 32 |
| | | -256 | ins ACCCC | 5 |
| | | -123 | G-C | 37 |
| | -107 | G-C | 1 | |
| | -38 | C-T 5' f | 38 | |
| 1 | | 11 | C-G 5' UTR | 1 |
| | | +92 | T-C 3' f | 37 |
| 2 | | 16 | G ins 5' UTR | 14 |
| | | 76 | G-C 5' UTR | 13 |
| | | +68 | G-A 3' f | 7 |
| 3 | | -50 | T-C 5' f | 13 |
| | | +26 | G-A 3' f | 2 |
| 4 | | | No variant | |
| 5 | | -83 | A-G 5' f | 1 |
| | | +76 | T-G 3' f | 3 |
| 6 | | 53 | G-A nc | 30 |
| 7 | | 113 | G-A nc | 29 |
| 8 | | | No variant | |
| 9 | | -14 | A ins 5' f | 5 |
| | | 123 | C-T nc | 14 |
| | | 135 | G-A nc | 9 |
| 10 | | | No variant | |
| 11 | | -105 | A-G 5' f | 9 |
| | | -62 | G ins 5' f | 34 |
| | | -39-(-37) | TCC del 5' f | 9 |
| | | -13 | C-T 5' f | 4 |
| 12-13 | | | No variant | |
| 14 | | +24 | T-A 3' f | 32 |
| 15 | | -59 | C-T 5' f | 3 |
| | | 148 | C-A nc | 14 |
| | | +32 | G-T 3' f | 2 |
| 16 | | 120 | G-T nc | 1 |
| | | 196 | G-A Val-Met | 7 |
| | | 210 | C-G nc | 1 |
| | | +55 | G-C 3' f | 1 |
| | | +95 | T-A 3' f | 17 |
| 17 | | 136 | G-A nc | 3 |
| 18 | | 107 | A-G Ile-Met | 11 |
| | | +75 | G-A 3' f | 1 |
| 19 | | -75 | G-A 3' f | 3 |
| | | -68 | G-C 5' f | 4 |
| 20 | | | No variant | |
| 21 | | -104 | C-T 5' f | 1 |

| | | | |
|--------------|-----------|---------------|----|
| 22 | +118 | T-G 3' f | 32 |
| 23 | +102 | A-G 3' f | 6 |
| 24 | -65 | G-A 5' f | 1 |
| | 54 | G-C nc | 5 |
| 25 | b.7 | C-T Ser-Phe | 1 |
| | b.98 | A-G nc | 1 |
| | +23 | G-A 3' f | 6 |
| 26 | | No variant | |
| 27 | +74 | C-A 3' f | 1 |
| 28 | 98 | G-A nc | 1 |
| 29 | -34 | C-T 5' f | 1 |
| 30 | | No variant | |
| 31 | 7 | G-A nc | 13 |
| 32 | 72 | G-T nc | 1 |
| | +30 | T-G 3' f | 7 |
| 34 | -144 | C-T 5' f | 1 |
| | -132 | CT ins 5' f | 22 |
| | -26 | G-C 5' f | 10 |
| 35 | 62 | G-A Arg-Lys | 23 |
| 36-37 | | No variant | |
| 38 | -61 | T-C 5' f | 1 |
| | -47 | T-C 5' f | 1 |
| 39 | 139 | C-T nc | 1 |
| 40 | | No variant | |
| 41 | -25 | C-T 5' f | 1 |
| 42 | -119 | C-T 5' f | 2 |
| 43 | | No variant | |
| 44 | +18 | T-C 3' f | 15 |
| 45 | +68 | T-C 3' f | 15 |
| 46 | -62 | ins-del 5' f | 1 |
| | 114 | C-T nc | 1 |
| 47 | -39 | T del 5' f | 1 |
| | -34 | C-T 5' f | 1 |
| 48 | +13 | A-G 3' f | 5 |
| 49 | +55 | G-C 3' f | 13 |
| 50 | 483 | G-T 3' UTR | 1 |
| | 834 | C-T 3' UTR | 28 |
| | 863 | T-C 3' UTR | 1 |
| | 1014-1015 | CG del 3' UTR | 1 |
| | 2037 | A-G 3' UTR | 14 |
| | 2064 | A-C 3' UTR | 2 |
| | 2452 | A-G 3' UTR | 21 |
| | 2658 | T-G 3' UTR | 6 |
| | 2691 | T-G 3' UTR | 1 |
| | 3038 | G-A 3' UTR | 5 |
| APOA1 | | | |
| 1 | +41 | C-T 3' f | 36 |
| 2 | -14 | C-T 5' f | 1 |
| | +33 | C-T 3' f | 14 |
| 3 | 75 | C-T Thr-Ile | 1 |
| APOE | | | |
| 1 | +69 | G-C 3' f | 32 |
| 2 | +64 | C-T 3' f | 1 |
| | +78 | G-A 3' f | 5 |
| 3 | -106 | G-T 5' f | 3 |
| 4 | 152 | T-C Cys-Arg | 8 |
| | 290 | C-T Arg-Cys | 15 |
| | 415 | C-T n.c. | 1 |
| CETP | | | |
| 1 | -11 | G-C 5' f | 36 |

| | | | |
|-------|------|-----------------------------------|-----------|
| | 66 | G-A 5' UTR | 1 |
| | 174 | C-G Ala-Gly | 1 |
| | +95 | C-A 3' f | 4 |
| 2 | | No variant | |
| 3 | -48 | C-A 5' f | 1 |
| 4 | | No variant | |
| 5 | +64 | C-T 3' f | 1 |
| 6 | -56 | G-A 5' f | 45 |
| | 7 | G-A n.c. | 1 |
| 7 | -70 | C-T 5' f | 1 |
| | +8 | C-T 3' f | 45 |
| 8 | +77 | G-A 3' f | 3 |
| 9 | -203 | C-T 5' f | 1 |
| | -51 | T-C 5' f | 5 |
| | 54 | G-T n.c. | 1 |
| | 111 | C-T n.c. | 6 |
| | +24 | T-G 3' f | 15 |
| | +29 | A-G 3' f | 17 |
| | +65 | C-T 3' f | 1 |
| 10-11 | | No variant | |
| 12 | 7 | G-A Val-Met | 1 |
| | 22 | G-C Ala-Pro | 2 |
| | +198 | 12bp INS 3' fl. (CTGCCAGGAAGA) | 13 |
| 13 | -14 | C-T 5' f | 31 |
| 14 | 16 | A-G Ile-Val | 31 |
| 15 | 82 | G-A Arg-Gln | 5 |
| 16 | -30 | A-G 5' f | 36 |
| | 159 | G-A 3' UTR | 22 |

EL

| | | | |
|----|------------|----------------------|-----------|
| 1 | 229 | T-G Trp-Gly (5' UTR) | 40 |
| | 315 | C-T n.c. | 1 |
| | +51 | C-T 3' f | 40 |
| | +55 | C-G 3' f | 40 |
| 2 | -44 | C-T 5' f | 2 |
| 3 | -22 | T-C 5' f | 17 |
| | 7 | G-A Gly-Ser | 1 |
| | 53 (T111I) | C-T Thr-Ile | 37 |
| 4 | +98 | G-A 3' f | 34 |
| 5 | -85 | C-T 5' f | 2 |
| | +42 | C-T 3' f | 40 |
| 6 | 142 | G-A Arg-His | 1 |
| 7 | -76 | T-G 5' f | 3 |
| 8 | -101 | T-C 5' f | 1 |
| | +120 | A-T 3' f | 2 |
| 9 | -108 | T-C 5' f | 43 |
| 10 | 304 | T-C 3' UTR | 3 |
| | 337 | A-G 3' UTR | 9 |
| | 470 | C-T 3' UTR | 1 |
| | 504 | A-G 3' UTR | 28 |
| | 506 | C-T 3' UTR | 2 |
| | 769 | G-A 3' UTR | 1 |
| | 1004 | C-T 3' UTR | 1 |
| | 1026 | T-C 3' UTR | 1 |
| | 1109 | T-A 3' UTR | 3 |
| | 1349 | T-C 3' UTR | 3 |
| | 1525 | T-G 3' UTR | 1 |
| | 1528 | T-C 3' UTR | 2 |
| | 1572 | G-A 3' UTR | 1 |
| | 2053 | T-G 3' UTR | 5 |

| | | | |
|-------------|-------------|--------------|-----------|
| | 2055 | T-G 3' UTR | 1 |
| HL | | | |
| Promotor | -544 | C-T | 30 |
| | -510 | C-T | 2 |
| | -280 | G-A | 32 |
| 1 | +52 | C-T 3' f | 10 |
| | +64 | A-G 3' f | 2 |
| | +111 | G-A 3' f | 1 |
| 2 | | No variant | |
| 3 | -279 | G-A 5' f | 39 |
| | -242 | T-C 5' f | 19 |
| | -46 | G-A 5' f | 20 |
| | 10 | G-A Val-Met | 4 |
| | 42 | C-T n.c. | 1 |
| | 67-70 | CCAG del | 1 |
| | 156 | G-A n.c. | 1 |
| | 159 | C-T n.c. | 1 |
| 4 | 9 | T-G n.c. | 42 |
| 5 | -95 | T-G 5' f | 1 |
| | -31 | C-T 5' f | 1 |
| | -8 | C-A 5' f | 5 |
| | 17 | A-G n.c. | 9 |
| | 70 | A-G Asp-Ser | 33 |
| | 98 | C-G n.c. | 44 |
| 6 | 58 | C-T Ser-Phe | 1 |
| | 173 | C-T n.c. | 1 |
| | 216 | G-A Val-Ile | 1 |
| 7 | 17 | A-C Leu-Phe | 1 |
| | 47 | G-A n.c. | 1 |
| | +31 | T-C 3' f | 8 |
| | +36 | CA ins 3' f | 1 |
| | +110 | G-A 3' f | 1 |
| | +111 | A-T 3' f | 1 |
| | +125 | G-C 3' f | 1 |
| 8 | 45 | C-T Thr-Met | 1 |
| | 57 | A-C Asp-Ala | 1 |
| | +28 | C-T 3' f | 1 |
| | +111 | T-C 3' f | 36 |
| 9 | 49 | C-A n.c. | 7 |
| | +124 | A-G 3' f | 1 |
| LCAT | | | |
| 1 | +123 | C-T 3' f | 2 |
| 2-3 | | No variant | |
| 4 | -23 | C-A 5' f | 1 |
| 5 | 171 | T-A n.c. | 3 |
| 6 | 429 | C-T n.c. | 7 |
| LPL | | | |
| 1 | | No variant | |
| 2 | -91 | G-A 5' flank | 1 |
| | 18 (D9N) | G-A Asp-Asn | 2 |
| 3 | 3 | A-C n.c. | 1 |
| | 156 | G-A n.c. | 3 |
| | +134 | T-C 3' f | 1 |
| 4 | b.6 | G-A n.c. | 6 |
| 5 | -108 | A-C 5' f | 1 |
| | +33 | C-G 3' f | 17 |
| | +37 | T-C 3' f | 17 |
| | +103 | C-T 3' f | 17 |
| 6 | -83 | C-G 5' f | 1 |
| | -34 | C-T 5' f | 1 |
| | 178 (N291S) | A-G Asn-Ser | 1 |

| | | | |
|--------------|------------|----------------|----|
| | +16 | T-C 3' f | 1 |
| | +73 | T-G 3' f | 22 |
| | +82 | C-A 3' f | 17 |
| | +108 | G-A 3' f | 16 |
| 7 | | No variant | |
| 8 | -102 | C-G 5' f | 1 |
| | 25 | C-A n.c. | 12 |
| 9 | -90 | T-G 5' f | 34 |
| | 99 (S447X) | C-G Ser-STP | 15 |
| 10 | -11 | C-T 5' f | 15 |
| | 10 | G-A 3' UTR | 16 |
| | 15 | T-A 3' UTR | 1 |
| PLTP | | | |
| Promotor | -405 | C-T | 1 |
| | -180 | G-GG | 11 |
| | -54-(-51) | GGA del. 5' f. | 1 |
| 1 | +26 | G-C 3' f | 11 |
| 2 | -76 | C-T 5' f | 45 |
| 3 | +56 | G-A 3' f | 1 |
| 4 | 106 | G-T n.c. | 1 |
| | +97 | A-C 3' f | 24 |
| 5-7 | | No variant | |
| 8 | -145 | G-A 5' f | 1 |
| 9 | 140 | G-A Arg-Gln | 1 |
| 10 | +70 | G-T 3' f | 6 |
| 11 | -34 | G-T 5' f | 1 |
| 12 | 8 | G-A Arg-His | 1 |
| | 31 | C-T Arg-Trp | 1 |
| | +68 | A-C 3' f | 34 |
| 13 | +19 | G-A 3' f | 1 |
| 14 | -64 | G-T 5' f | 1 |
| SR-BI | | | |
| 1 | 72 | G-A Gly-Ser | 6 |
| 2 | -88 | G-A 5' f | 1 |
| | +68 | G-A 3' f | 1 |
| 3 | 119 | G-A Val-Ile | 1 |
| 4 | 73 | G-A Gly-Ser | 1 |
| | 75 | C-T n.c. | 1 |
| | +60 | C-T 3' f | 1 |
| 5 | +54 | C-T 3' f | 10 |
| 6 | | No variant | |
| 7 | -202 | A-G 5' f | 1 |
| | 61 | C-T n.c. | 1 |
| 8 | 41 | C-T n.c. | 48 |
| | +73 | C-A 3' f | 1 |
| 9-10 | | No variant | |
| 11 | -41 | C-G 5' f | 4 |
| 12 | | No variant | |
| 13 | 49 | C-T 3' UTR | 1 |
| | 72 | G-A 3' UTR | 2 |
| | +37 | C-T poly A | 1 |
| | +72 | T-C poly A | 24 |

[§] Distance from the first/last exonic base on the 5' / 3' flanking regions.

[£] del : deletion ; f : flank ; ins : insertion ; n.c. : no amino acid change; UTR : untranslated region.

Appendix Table B. Tier 1 selected *Atherogenic*[‡], *Atheroprotective*[‡], and Gender-Dependent[‡] reverse cholesterol transport (RCT) gene SNPs assayed in all cases[§] and controls[§], with internal cross-validations in five 80%:20% subsamples. (→ : 37 SNPs retained for Tier 2, 3, 4 modeling in the total sample; **1b** : 14 Tier 1b SNPs excluded due to high correlation or rare variant ≤ 5%.)

| | | Internal Cross-Validations | | | | | → Total Sample Results | |
|----------------------------|--------------------|---|------------------|------------------|------------------|------------------|--|--|
| Gene | | Individual SNP Odds Ratio (OR (95% CI)) [‡] (<i>Atherogenic</i> [‡] or <i>Atheroprotective</i> [‡]), or SNP x Gender interaction p [‡] | | | | | Individual SNP OR (95% CI) [‡] <i>Atherogenic</i> [‡] or <i>Atheroprotective</i> [‡] | SNP x Gender interaction p (OR _m , OR _w) [‡] |
| Exon Position [#] | | Subsample | | | | | | |
| | | A | B | C | D | E | | |
| ABCA1 | | | | | | | | |
| 1 | → -1126 | | 0.059 | 0.035 | 0.030 | 0.093 | | 0.057 (0.42, 1.39) |
| | → -654 | 1.79 (0.91-3.52) | 1.63 (0.84-3.16) | 1.61 (0.80-3.24) | 1.67 (0.87-3.22) | 1.61 (0.84-3.09) | 1.66 (0.91-3.00) | |
| | -326 (1b) | NA | | 0.052 | NA | 0.047 | | 0.044 (7.25, 0.34) |
| | -38 | | | | | 0.097 | | |
| | +92 | | | | | 0.096 | | |
| 2 | → +68 | 0.43 (0.18-1.04) | | 0.60 (0.25-1.42) | 0.56 (0.24-1.30) | 0.59 (0.25-1.39) | 0.58 (0.27-1.25) | |
| 3 | -50 | | 1.74 (0.90-3.36) | | | 1.52 (0.80-2.88) | | |
| 5 | +76 (1b) | 1.83 (0.44-7.69) | 2.44 (0.52-11.4) | 2.61 (0.66-10.4) | 2.69 (0.65-11.0) | 2.49 (0.62-10.0) | 2.42 (0.69-8.52) | |
| 6 | 53 | | | | 0.064 | 0.087 | | |
| 7 | 113 | | | | 0.096 | | | |
| 9 | 123 | | 1.92 (0.91-4.04) | | 1.55 (0.75-3.22) | | | |
| | 135 | 0.64 (0.32-1.31) | | | | | | |
| 11 | -13 | | | | | 0.65 (0.28-1.52) | | |
| 16 | → 196 | 0.41 (0.12-1.36) | 0.65 (0.19-2.24) | | | 0.38 (0.11-1.33) | 0.59 (0.21-1.68) | |
| 17 | 136 | | | 0.64 (0.24-1.74) | | | | |
| 19 | -68 | 1.61 (0.64-4.06) | | | | | | |
| | -75 (1b) | 0.014 | NA | 0.39 (0.06-2.32) | 0.078 | 0.030 | | 0.031 (2.88, 0.092) |
| 22 | +118 | | | 0.58 (0.32-1.05) | 0.084 | | | |
| 23 | → +102 | 0.053 | 1.63 (0.60-4.38) | 0.058 | | 1.57 (0.62-3.96) | 1.51 (0.65-3.53) | |
| 24 | 54 | 0.54 (0.18-1.63) | | 0.028 | | | | |
| 32 | → +30 | 2.10 (0.97-4.54) | 1.98 (0.89-4.42) | 3.53 (1.62-7.72) | 0.057 | 2.69 (1.21-5.59) | 2.28 (1.16-4.52) | |
| 35 | → 62 | 0.069 | 1.74 (0.97-3.10) | 1.89 (1.05-3.44) | 1.80 (1.00-3.22) | | 1.59 (0.95-2.66) | |
| 45 | +68 | | 1.81 (0.98-3.34) | | | | | |
| 48 | +13 | | | 1.62 (0.68-3.85) | | | | |
| 49 | +55 | | | | 0.65 (0.33-1.28) | 0.60 (0.32-1.13) | | |
| 50 | → 834 | | | 0.60 (0.33-1.09) | 0.61 (0.34-1.10) | 0.52 (0.29-0.91) | 0.63 (0.38-1.06) | |
| | → 2037 | | | 0.072 | 0.062 | 0.046 | | 0.065 (0.73, 2.12) |
| | → 2452 | 0.059 | 0.079 | | | 0.063 | | 0.067 (1.25, 0.44) |
| | → 3038 | 0.25 (0.09-0.70) | 0.31 (0.11-0.84) | 0.30 (0.12-0.73) | 0.21 (0.08-0.55) | 0.21 (0.08-0.54) | 0.26 (0.11-0.61) | |
| APOA1 | | | | | | | | |

2 → +33 | 2.05 (0.94-4.45) | 2.48 (1.09-5.64) | 1.97 (0.90-4.30) | 2.45 (1.15-5.27) | 2.26 (1.04-4.89) | 2.21 (1.11-4.43) |

APOE

| | | | | | | | | |
|---|----------------------------|---|------------------|------------------|------------------|------------------|------------------|--|
| 1 | +69 | 1.50 (0.82-2.75) | | | | | | |
| 2 | +78 (1b) | 3.10 (1.32-7.29) | 3.22 (1.33-7.75) | 3.78 (1.50-9.50) | 3.88 (1.66-9.08) | 4.23 (1.82-9.85) | 3.54 (1.65-7.61) | |
| 4 | 152 (C128R) 290 (R175C) | <i>N.B.: 1 or 2 rare variants on exon 4b.290 (only) = APOE2 (E2/E3 or E2/E2)); on exon 4b.152 (only) = APOE4 (E3/4 or E4/E4); no rare variants on either 4b.152 or 4b.290 = APOE3 (E3/E3); excluded: 1 rare variant on APOE 4b.152 and APOE 4b.290 = E2/E4.</i> | | | | | | |
| | → APOE2 | 0.20 (0.08-0.46) | 0.13 (0.05-0.33) | 0.19 (0.08-0.44) | 0.15 (0.06-0.37) | 0.19 (0.08-0.42) | 0.17 (0.08-0.37) | |
| | APOE3 | 1.74 (0.96-3.18) | | | | | | |
| | → APOE4 | 1.82 (0.87-3.78) | 3.36 (1.55-7.29) | 2.22 (1.09-4.54) | 2.42 (1.19-4.93) | 2.69 (1.31-5.50) | 2.40 (1.26-4.56) | |

CETP

| | | | | | | | | |
|----|----------|------------------|------------------|------------------|------------------|------------------|------------------|--|
| 1 | → -629 | 2.38 (1.20-4.72) | 2.89 (1.49-5.61) | 2.45 (1.23-4.90) | 2.34 (1.21-4.53) | 2.85 (1.47-5.52) | 2.55 (1.41-4.63) | |
| | +95 | | 1.60 (0.64-4.01) | | | 0.065 | | |
| 6 | → -56 | 0.41 (0.22-0.79) | 0.49 (0.27-0.90) | 0.42 (0.22-0.79) | 0.46 (0.25-0.87) | 0.37 (0.20-0.70) | 0.43 (0.25-0.76) | |
| 7 | +8 (1b) | 0.41 (0.22-0.78) | 0.086 | 0.41 (0.22-0.76) | 0.46 (0.25-0.84) | 0.38 (0.21-0.70) | 0.42 (0.25-0.73) | |
| 8 | +77 (1b) | 2.26 (0.59-8.58) | | 1.70 (0.52-5.60) | 1.70 (0.51-5.70) | | 1.61 (0.54-4.81) | |
| 9 | -51 | | 0.098 | | | | | |
| | 111 | | | 1.56 (0.57-4.27) | 1.58 (0.59-4.23) | | | |
| | → +24 | | | | | 2.08 (1.13-3.85) | 1.51 (0.87-2.62) | |
| | +29 (1b) | 1.61 (0.86-3.01) | 1.54 (0.84-2.82) | | 1.56 (0.86-2.84) | 2.08 (1.14-3.82) | 1.63 (0.95-2.80) | |
| 13 | -14 | | 0.64 (0.35-1.16) | | | | | |
| 15 | 82 | 1.64 (0.46-5.86) | | | | | | |
| 16 | 159 | 1.66 (0.88-3.13) | 0.065 | | 1.53 (0.82-2.87) | | | |

EL

| | | | | | | | | |
|----|------------------|------------------|------------------|------------------|------------------|--------|---------------------|--------------------|
| 1 | +55 | 1.51 (0.82-2.77) | | | | | | |
| | 229 (1b) | | 0.012 | 0.063 | | 0.066 | | 0.033 (0.62, 2.01) |
| 3 | -22 | | | 0.57 (0.30-1.08) | 0.62 (0.33-1.16) | | | |
| | → & 53 (T111D) & | 0.56 & | 0.17 & | 0.28 & | 0.047 & | 0.54 & | 0.21 (0.70, 1.37) & | |
| 4 | +98 & | | 0.039 | 0.054 | 0.014 | | | 0.045 (0.60, 1.77) |
| 5 | +42 | | 0.079 | | 0.62 (0.34-1.13) | | | |
| 7 | -76 | | | | 0.61 (0.18-2.09) | | | |
| 9 | -108 | | 0.072 | | 0.039 | | | |
| 10 | 304 | | | 0.65 (0.23-1.87) | | | | |
| | → 337 | 1.64 (0.77-3.47) | 1.74 (0.85-3.57) | 2.27 (1.06-4.86) | 2.06 (0.95-4.49) | | 1.81 (0.93-3.50) | |
| | → 504 | | 0.058 | | 0.0085 | 0.066 | | 0.064 (1.28, 0.47) |
| | 1349 | | | 0.55 (0.20-1.56) | 0.56 (0.20-1.54) | | | |

HL

| | | | | | | | | |
|---|--------|------------------|------------------|-------|------------------|------------------|------------------|--------------------|
| 1 | -544 | 0.56 (0.30-1.04) | 0.67 (0.37-1.21) | | 0.66 (0.37-1.21) | 0.66 (0.37-1.19) | | |
| | → -280 | 0.51 (0.27-0.94) | 0.59 (0.33-1.07) | | | 0.63 (0.35-1.14) | 0.62 (0.36-1.05) | |
| 3 | → -279 | 0.0049 | | 0.011 | 0.038 | 0.071 | | 0.022 (0.59, 2.22) |
| | -242 | 0.093 | | | | | | |

| | | | | | | | |
|--------------------------|-----------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|--|
| → -46 10 (1b) | 0.0042 <i>1.59 (0.54-4.64)</i> | <i>1.87 (0.58-6.00)</i> | 0.0033 0.036 | 0.0075 0.015 | 0.66 (0.36-1.20) | | 0.017 (1.85, 0.47) 0.080 (4.16, 0.63) |
| 4 9 | | | 0.55 (0.30-1.01) | | 0.66 (0.37-1.19) | | |
| 5 -8 (1b) | 0.53 (0.20-1.38) | | 0.49 (0.19-1.26) | 0.55 (0.22-1.39) | 0.63 (0.27-1.47) | 0.56 (0.25-1.26) | |
| → 17 | 0.38 (0.13-1.09) | 0.65 (0.24-1.81) | 0.56 (0.22-1.46) | 0.46 (0.16-1.34) | | 0.46 (0.19-1.09) | |
| → 98 | 0.63 (0.32-1.23) | 0.025 | 0.61 (0.31-1.17) | 0.59 (0.30-1.15) | 0.085 | 0.65 (0.37-1.14) | |
| 7 +31 (1b) | 0.39 (0.12-1.28) | 0.048 | 0.50 (0.19-1.36) | 0.59 (0.22-1.61) | 0.53 (0.21-1.37) | 0.50 (0.21-1.21) | |
| 8 +111 | 0.099 | | | | 0.084 | | |
| LCAT | | | | | | | |
| 5 171 | 0.67 (0.15-3.03) | | | <i>1.54 (0.31-7.57)</i> | | | |
| 6 → 429 | | 0.067 | | 0.074 | 0.061 | | 0.079 (1.59, 0.41) |
| LDLR | | | | | | | |
| 2 → LDLR2 (rs2228671) | 0.64 (0.32-1.28) | 0.55 (0.28-1.12) | 0.44 (0.22-0.88) | 0.64 (0.33-1.26) | 0.52 (0.27-1.03) | 0.55 (0.30-1.02) | |
| Int 9 rs1003723 | | | 0.55 (0.29-1.05) | | | | |
| 11 → LDLR11 (rs5929) | 0.61 (0.20-1.84) | 0.52 (0.17-1.58) | 0.47 (0.16-1.41) | 0.36 (0.11-1.17) | 0.37 (0.12-1.13) | 0.46 (0.17-1.24) | |
| 12 rs5930 | | | 0.057 | | | | |
| UTR rs1433099 | | | | | 0.075 | | |
| LPL | | | | | | | |
| 3 156 | <i>1.90 (0.57-6.29)</i> | | 0.029 | | | | |
| 4 → 6 | 0.45 (0.18-1.17) | | | 0.46 (0.19-1.14) | | 0.61 (0.27-1.35) | |
| 5 +33 | | 0.62 (0.34-1.15) | | 0.65 (0.36-1.20) | 0.67 (0.36-1.22) | | |
| → +37 | | 0.59 (0.32-1.09) | | 0.63 (0.34-1.17) | 0.65 (0.35-1.20) | 0.66 (0.38-1.14) | |
| +103 | | 0.59 (0.32-1.09) | | | | | |
| 6 +73 (1b) | 0.63 (0.34-1.18) | 0.47 (0.26-0.84) | 0.64 (0.36-1.15) | 0.55 (0.31-0.99) | 0.50 (0.28-0.90) | 0.56 (0.33-0.94) | |
| → +82 | | <i>2.16 (1.07-4.38)</i> | <i>1.60 (0.79-3.26)</i> | | <i>1.74 (0.90-3.38)</i> | <i>1.55 (0.84-2.84)</i> | |
| +108 | | 0.60 (0.32-1.12) | | | | | |
| 8 25 | 0.55 (0.26-1.15) | | | | | | |
| → +481 (HindIII) | 0.54 (0.29-0.98) | 0.57 (0.31-1.03) | 0.59 (0.32-1.07) | 0.60 (0.33-1.08) | 0.68 (0.38-1.21) | 0.60 (0.36-1.01) | |
| 9 -90 (1b) | 0.56 (0.31-1.02) | 0.58 (0.32-1.03) | | 0.61 (0.34-1.08) | | 0.64 (0.38-1.07) | |
| → 99 (S447X) | 0.44 (0.21-0.90) | 0.30 (0.15-0.62) | 0.40 (0.16-0.81) | 0.45 (0.23-0.90) | 0.37 (0.19-0.75) | 0.39 (0.21-0.73) | |
| 10 -11 (1b) | 0.45 (0.22-0.90) | 0.34 (0.17-0.68) | 0.40 (0.20-0.80) | 0.43 (0.22-0.84) | 0.35 (0.18-0.68) | 0.39 (0.21-0.72) | |
| 10 10 | 0.61 (0.31-1.22) | | | | | | |
| PLTP | | | | | | | |
| 1 → -180 | 0.39 (0.15-1.04) | | 0.40 (0.16-1.02) | 0.63 (0.25-1.63) | 0.37 (0.13-1.02) | 0.50 (0.22-1.19) | |
| → +26 | 0.099 | 0.34 (0.16-0.76) | 0.29 (0.13-0.68) | 0.020 | 0.030 | | 0.023 (0.64, 0.15) |
| 2 -76 | | | | <i>1.57 (0.83-2.97)</i> | | | |
| 10 → +70 | 0.21 (0.07-0.61) | 0.19 (0.07-0.52) | 0.16 (0.06-0.46) | 0.053 | 0.18 (0.07-0.49) | 0.21 (0.09-0.51) | |
| 12 +68 | <i>1.69 (0.91-3.12)</i> | | <i>1.51 (0.83-2.74)</i> | | | | |

| SR-BI | | | | | | | | |
|-------|--------------|-------|------------------|------------------|-------|-------|--|--------------------|
| 1 | 72 (G2S) | | 0.064 | 1.67 (0.77-3.64) | | | | |
| 8 | → 41 (A350A) | 0.043 | 0.019 | 0.046 | 0.064 | 0.022 | | 0.020 (0.40, 1.74) |
| 11 | -41 | | 1.86 (0.65-5.30) | | | | | |

† Adjusted OR ≥ 1.50 (*Atherogenic* SNP), or OR $\leq 1/1.50=0.67$ (*Atheroprotective* SNP), or (SNP x gender) interaction (nominal) $p \leq .10$ and at least one gender-specific OR (men: OR_m; women: OR_w) satisfying *Atherogenic* or *Atheroprotective* criteria (Gender-Dependent SNP). (*N.B.* : Gender-Dependence overrides *Atherogenic* / *Atheroprotective* characterization)

§ Cases: atherogenic lipid profile (low HDL-C, high LDL-C) (186 subjects); controls: non-atherogenic lipid profile (high HDL_C, low LDL-C) (185 subjects).

Relative to first / last exonic base on the 5' / 3' flanking region.

£ Single SNP, case-control OR adjusted for nongenetic covariates [gender, age, BMI, education, country of birth, cigarette smoking, alcohol drinking, dietary fat (%), dietary fiber(g), physical inactivity].

§ Likelihood ratio test of model in £ vs. extended model including SNP x gender interaction.

& EL: exon 3 b.53 (T111I) was substituted for exon 4 b.+98 due to high correlation (total sample $r = 0.96$ (men/women: 0.99/0.93)) in modeling based on the total sample and modeling based on any subsample for which both SNPs were selected in Tier 1.

Appendix Table C. RCT gene Tier 2 (nominal) $p=.10$ stepdown selection final models within Tier 1 SNP groups, with internal cross-validations in five 80%:20% random subsamples.

| Atherogenic SNPs in final models | Entry Step [§] | | | | | |
|---|-------------------------|----------------------|---|----|---|---|
| <i>for total sample or subsamples:</i> | Total Sample | 80% random subsample | | | | |
| | | A | B | C | D | E |
| <i>APOE4</i> | 1 | 4 | 1 | 2 | 1 | 2 |
| CETP 1b.-629 | 2 | 1 | 3 | - | - | 1 |
| APOA1 2b.+33 | 3 | 3 | 4 | 4 | 2 | 6 |
| ABCA1 32b.+30 | 4 | 6 | - | 1 | - | 4 |
| LPL 6b.+82 | 5 | - | 2 | - | - | 3 |
| EL 10b.337 | 6 | - | - | 3 | 3 | - |
| <i>For subsamples only :</i> | | | | | | |
| ABCA1 45b.+68 | - | - | 5 | - | - | - |
| <i>APOE3</i> | - | 5 | - | - | - | - |
| CETP 9b.+29 | - | 2 | - | - | - | 5 |
| CETP 16b.159 | - | 2 | - | - | - | - |
| Atheroprotective SNPs in final models | Entry Step [§] | | | | | |
| <i>for total sample or subsamples:</i> | Total Sample | 80% random subsample | | | | |
| | | A | B | C | D | E |
| <i>APOE2</i> | 1 | 1 | 1 | 1 | 1 | 1 |
| PLTP 10b.+70 | 2 | 3 | - | - | - | 2 |
| LPL S447X | 3 | 9 | 3 | 2 | 3 | 5 |
| ABCA1 50b.3038 | 4 | 4 | 4 | 4 | 2 | 3 |
| CETP 6b.-56 | 5 | 5 | - | 5 | 4 | 4 |
| HL 5b.98 | 7 | 10 | - | 8 | - | - |
| HL 1b.-280 | 6 | 2 | - | - | - | - |
| LDLR2 (rs2228671) | 8 | - | - | 9 | - | 7 |
| <i>For subsamples only :</i> | | | | | | |
| ABCA1 2b.+68 | - | 6 | - | 10 | - | - |
| ABCA1 24b.54 | - | 8 | - | - | - | - |
| HL 1b.-544 | - | - | - | - | 6 | - |
| HL 4b.9 | - | - | - | 6 | - | - |
| HL 5b.17 | - | - | - | 7 | - | - |
| HL 5b.+42 | - | - | - | - | 5 | - |
| PLTP 1b.+26 | - | - | 2 | 3 | - | - |
| PLTP 1b.-180 | - | 7 | - | - | - | 6 |
| Gender-Dependent | | | | | | |

| SNPs in final models <i>for total sample or subsamples:</i> | Entry Step [§] | | | | | |
|--|-------------------------|----------------------|-----------------------|-----------------------|----|--------------|
| | Total Sample | 80% random subsample | | | | |
| | | A | B | C | D | E |
| PLTP 1b.+26 | 1 | 1 | | | 1 | 1 |
| + gender interaction | 2 | not retained | Athero- protective | Athero- protective | 2 | 2 |
| ABCA1 50b.2037 | 3 | - | - | - | 3 | |
| + gender interaction | 4 | - | - | - | 4 | |
| EL 10b.504 | 5 | - | - | - | 5 | 10 |
| + gender interaction | 6 | - | - | - | 6 | 11 |
| SR-BI A350A | 7 | 6 | 3 | 5 | 11 | 8 |
| + gender interaction | 8 | 7 | 4 | 6 | 12 | 9 |
| ABCA1 1b.-1126 | 9 | - | 7 | 3 | 13 | 12 |
| + gender interaction | 10 | - | 8 | 4 | 14 | 13 |
| HL 3b.-279 | 11 | 2 | - | 1 | 9 | 6 |
| + gender interaction | 12 | 3 | - | 2 | 10 | 7 |
| <i>For subsamples only :</i> | | | | | | |
| ABCA1 1b.-38 | - | - | - | - | - | 14 |
| + gender interaction | - | - | - | - | - | 15 |
| ABCA1 6b.53 | - | - | - | - | 7 | - |
| + gender interaction | - | - | - | - | 8 | - |
| ABCA1 23b.+102 | - | 4 | - | 7 | - | - |
| + gender interaction | - | 5 | - | 8 | - | - |
| ABCA1 24b.54 | - | - | - | 9 | - | - |
| + gender interaction | - | - | - | 10 | - | - |
| ABCA1 50b.2452 | - | 8 | - | - | - | - |
| + gender interaction | - | 9 | - | - | - | - |
| HL 5b.98 | - | - | 1 | - | - | 3 |
| + gender interaction | - | - | 2 | - | - | 4 |
| HL 7b.+31 | - | - | 5 | - | - | - |
| + gender interaction | - | - | - | - | - | - |
| LCAT 6b.429 | - | - | - | - | - | 5 |
| + gender interaction | - | - | - | - | - | not retained |

[§] Order of forced-forward entry of SNPs retained in model after stepdown selection.

Appendix Table D. RCT gene Tier 3 (nominal) $p=.05$ stepdown selection (SNPs only, nongenetic covariates forced into model) final models, with internal cross-validations in five 80%:20% random subsamples.

| SNPs in final models <i>for total sample or subsamples:</i> | Total Sample | Entry Step [§] 80% random subsample | | | | |
|--|-----------------|---|----|----|----|----|
| | | A | B | C | D | E |
| <i>APOE2</i> | 1 | 1 | 1 | 1 | 1 | 1 |
| PLTP 1b.+26 | 2 | 2 | 3 | 5 | 3 | 2 |
| LPL S447X | 3 | - | - | 2 | - | 3 |
| CETP 6b.-56 | 4 | - | - | - | 4 | - |
| ABCA1 50b.3038 | 5 | 3 | 2 | 8 | 2 | - |
| LDLR2 (rs2228671) | 6 | - | - | 3 | - | 4 |
| HL 1b.-280 | 7 | 5 | - | - | - | - |
| ABCA1 32b.+30 | 8 | 4 | - | 9 | - | - |
| PLTP 1b.+26 x Gender | 9 | - | - | - | 5 | - |
| SR-BI A350A | 10 | 8 | - | 17 | 11 | - |
| SR-BI A350A x Gender | 11 | 9 | - | 18 | 12 | - |
| HL 3b.-279 | 12 | 10 | - | 11 | 13 | - |
| HL 3b.-279 x Gender | 13 | 11 | - | 12 | 14 | - |
| <i>For subsamples only :</i> | | | | | | |
| ABCA1 1b.-1126 | - | - | 9 | 13 | 6 | 10 |
| ABCA1 1b.-1126 x Gender | - | - | 10 | 14 | 7 | 11 |
| ABCA1 1b.-38 | - | - | - | - | - | 8 |
| ABCA1 1b.-38 x Gender | - | - | - | - | - | 9 |
| ABCA1 23b.+102 | - | - | - | 15 | - | - |
| ABCA1 23b.+102 x Gender | - | - | - | 16 | - | - |
| ABCA1 45b.+68 | - | - | 5 | - | - | - |
| APOA1 2b.+33 | - | - | 8 | - | - | - |
| <i>APOE4</i> | - | - | 4 | 10 | - | - |
| CETP 1b.-629 | - | 6 | 7 | - | - | - |
| CETP 9b.+29 | - | - | - | - | - | 5 |
| HL 4b.9 | - | - | - | 4 | - | - |
| HL 5b.98 | - | 7 | - | - | - | - |
| HL 5b.17 | - | - | - | 6 | - | - |
| EL 5b.+42 | - | - | - | - | 8 | - |
| EL 10b.337 | - | - | - | 7 | - | - |
| EL 10b.504 | - | - | - | - | 9 | - |
| EL 10b.504 x Gender | - | - | - | - | 10 | - |
| LPL 6b.+82 | - | - | 6 | - | - | - |
| PLTP 1b.-180 | - | - | - | - | - | 7 |

[§] Order of forced-forward entry of SNPs retained in model after stepdown selection.

Appendix Table E. RCT gene Tier 4 (nominal) $p=.05$ stepdown selection (SNPs + nongenetic covariates) final models, with internal cross-validations in five 80%:20% random subsamples.

| Covariates/SNPs in final models <i>for total sample or subsamples:</i> | Total Sample | Entry Step [§] | | | | |
|--|-----------------|-------------------------|----|----------------------|----|----|
| | | A | B | 80% random subsample | | |
| | | | | C | D | E |
| BMI (kg/m ²) | 1 | 1 | 1 | 1 | 1 | 1 |
| <i>APOE2</i> | 2 | 2 | 2 | 5 | 3 | 2 |
| PLTP 1b.+26 | 3 | 5 | 4 | 2 | 5 | 5 |
| Alcohol: Medium+High | 4 | 6 | 3 | 4 | 4 | 10 |
| Alcohol: Low | 5 | 7 | 7 | 6 | 6 | 11 |
| Current Smoker | 6 | 4 | 5 | 3 | 2 | 3 |
| ABCA1 50b.3038 | 7 | 9 | 6 | 11 | 7 | - |
| LPL S447X | 8 | - | - | 7 | - | 4 |
| Age (yrs) | 9 | - | - | 12 | 8 | 9 |
| Gender | 10 | 3 | 12 | 15 | 10 | 12 |
| ABCA1 32b.+30 | 11 | 8 | - | 9 | - | - |
| LDLR2 (rs2228671) | 12 | - | - | 8 | - | 8 |
| HL 1b.-280 | 13 | 10 | - | - | - | - |
| HL 3b.-279 | 14 | 15 | - | 20 | 19 | - |
| HL 3b.-279 x Gender | 15 | 16 | - | 21 | 20 | - |
| SR-BI A350A | 16 | 13 | - | 24 | 17 | - |
| SR-BI A350A x Gender | 17 | 14 | - | 25 | 18 | - |
| <i>For subsamples only :</i> | | | | | | |
| Education (Low) | - | 12 | - | 19 | - | - |
| ABCA1 1b.-1126 | - | - | 11 | 17 | 13 | 14 |
| ABCA1 1b.-1126 x Gender | - | - | 13 | 18 | 14 | 15 |
| ABCA1 1b.-38 | - | - | - | - | - | 16 |
| ABCA1 1b.-38 x Gender | - | - | - | - | - | 17 |
| ABCA1 23b.+102 | - | - | - | 22 | - | - |
| ABCA1 23b.+102 x Gender | - | - | - | 23 | - | - |
| ABCA1 45b.+68 | - | - | 8 | - | - | - |
| APOA1 2b.+33 | - | - | - | 16 | - | - |
| <i>APOE4</i> | - | - | 10 | - | - | - |
| CETP 1b.-629 | - | 11 | - | - | - | - |
| CETP 6b.-56 | - | - | - | - | 9 | - |
| CETP 9b.+29 | - | - | - | - | - | 6 |
| HL 4b.9 | - | - | - | 10 | - | - |
| HL 5b.17 | - | - | - | 14 | - | - |
| EL 5b.+42 | - | - | - | - | 12 | - |

| | | | | | | |
|----------------------|---|---|---|----|----|----|
| EL 10b.337 | - | - | - | 13 | - | - |
| EL 10b.504 | - | - | - | - | 15 | - |
| EL 10b.504 x Gender | - | - | - | - | 16 | - |
| LPL 6b.+82 | - | - | 9 | - | - | - |
| PLTP 1b.-180 | - | - | - | - | - | 7 |
| PLTP 1b.+26 x Gender | - | - | - | - | 11 | 13 |

§ Order of forced-forward entry of SNPs retained in model after stepdown selection.

APPENDIX FIGURE LEGENDS

APPENDIX FIGURE A

Histogram of rare allele frequency (%) differences for 121 RCT gene common SNPs (rare allele frequency $\geq 3\%$) that were assayed in both the resequencing subsample (n=95) and in the remaining case-control sample (n=276). Median frequency difference = 0%, mean = -0.19%, SD = 3.9%.

APPENDIX FIGURE B

Minimum case (n=186) / control (n=185) single-SNP unadjusted odds ratio (OR) detectable with specified statistical power ($1-\beta$) = 60% (10%) 90%, 95%, 99% (2-tailed $\alpha = 5\%$) as a function of the control proportion with rare allele(s) (heterozygote/homozygote) for a given SNP. The power for the corresponding adjusted OR would be greater than for the unadjusted OR.