Table S2. Genetic variation identified in the core promoter, coding region and exon-intron boundaries of *APOA1* in the Copenhagen City Heart Study (n=10,330).

Gene Region	Nucleotide Substitution[a]	Amino Acid Residue	No. of individuals in CCHS, n=10,330 (minor allele frequency,%)	Functional Region/Function	Previous reports/ rs numbers
Promoter	g.-647A>G	-	106 (0.5)	192 bp 5' of regulatory region D (HRE)[b]	-
Promoter	g.-560A>C	-	718 (3.5)	105 bp 5' of regulatory region D (HRE)[b]	[1]/rs12718466
Promoter	g.-310G>A	-	3,043 (16.0)	2 bp 3' of regulatory region B (HRE)[b]	[1]/rs670
Intron 1	g.-151C>T	-	712 (3.5)	67 bp 3' of regulatory region A[b]	[1]/rs5069
Intron 1	g.-150G>A	-	143 (0.7)	68 bp 3' of regulatory region A[b]	rs1799837
Intron 1	g.-108_-106delCTC	-	3 (0.01)	111 bp 3' of regulatory region A[b]	rs61758321
Intron 1	g.-89G>A	-	7 (0.03)	130 bp 3' of regulatory region A[b]	-
Intron 1	g.-35_-33delCTT	-	1 (0.005)	184 bp 3' of regulatory region A[b]	-
Intron 1	g.-11G>A	-	12 (0.06)	208 bp 3' of regulatory region A[b]	-
Exon2	c. 9T>C	A(-22)A	1 (0.005)	Prepeptide[c]	-
Exon 2	c. 14T>C	V(-20)A	1 (0.005)	Prepeptide[c]	-
Intron 2	IVS2+41C>T		(30.0)[d]	-	[1]/rs5070
Exon 3	c. 83C>G	P4R	2 (0.01)	Amino-terminal end	[2,3]

Exon 3	c. 79delC	V11X	1 (0.005)	Helix 1	[4,5]
Exon 3	c. 108G>A	K12K	4 (0.02)	Helix 1	-
Exon 3	c. 147C>T	S25S	3 (0.01)	Between helix 1 and 2 – potential ESE	-
Exon 3	c. 176G>T	G35V	1 (0.005)	Between helix 1 and 2	-
Exon 3	c. 178T>G	S36A	5 (0.02)	Between helix 1 and 2	[6,7]
Exon 3	c. 181G>A	A37T	2 (0.01)	Between helix 1 and 2	[1,8,9] /rs12718465
Intron 3	IVS3+33C>T		(6.0)[d]	-	[1]/rs2070665
Exon 4	c.284T>A	F71Y	9 (0.04)	Induction of hypertriglyceridemia[e] and amyloidosis[f]	[7]
Exon 4	c. 294C>A	N74K	1 (0.005)	Induction of hypertriglyceridemia[e] and amyloidosis[f]	-
Exon 4	c. 298G>C	E76Q	2 (0.01)	Induction of hypertriglyceridemia[e] and amyloidosis[f]	-
Exon 4	c. 391delAAG	K107del	4 (0.02)	Induction of hypertriglyceridemia[e]	[10-14]
Exon 4	c.498C>A	S142R	1 (0.005)	Helix 5	-
Exon 4	c.503T>G	L144R	4 (0.02)	Activation of LCAT[e]	[4,15]
Exon 4	c.524G>A	R151H	1 (0.005)	Activation of LCAT[e]	-
Exon 4	c.526G>A	A152T	1 (0.005)	Activation of LCAT[e]	-
Exon 4	c.529C>T	R153C	1 (0.005)	Activation of LCAT[e]	-
Exon 4	c.562G>T	A164S	24 (0.1)	Activation of LCAT[e]	[4]
Exon 4	c.564G>G	A164A	2 (0.01)	Activation of LCAT[e] – potential ESE	-

Exon 4	[c.572G>A;c.753C>A]	S167L	2 (0.01)	Activation of LCAT[e]	-
Exon 4	c.642C>G	A190A	5 (0.02)	Helix 8 – potential ESE	-
Exon 4	c.669T>C	H199H	1 (0.005)	Helix 8 – potential ESE	-
Exon 4	c.732C>G	P220P	2 (0.01)	Interaction with ABCA1[e] – potential ESE	rs5080
3'UTR	*8G>A		4 (0.02)	Potential ESE	-
3'UTR	*17C>T		7 (0.03)	-	-
3'UTR	*141G>A		33 (0.2)	-	-
Intergenic	*178T>A		(1.6)[d]	-	[1]/rs5081
Intergenic	*181A>G		(3.5)[d]	-	[1]/rs12718463

In shaded grey, genetic variants identified by screening the regulatory and coding regions of *APOA1* in 95 individuals with extreme low apoA-I levels and 95 individuals with extreme high apoA-I levels in the Copenhagen City Heart Study followed by genotyping in the whole population [16]. [a]Nucleotide +1 denotes A in the start codon ATG (*translational* start site) in exon 2 (NM_000039.1), corresponding to base position 236 in *APOA1* consensus sequence NC_000011.9; to convert to nucleotide position relative to the *transcriptional* start site add 235 nucleotides. [b]Four regulatory regions, A-D, have been reported in the *APOA1* promoter, of which regions B and D are hormone responsive elements (HRE) that among others bind hepatic nuclear factor 4; element C binds CCAAT enhancer binding protein [17]. [c]Full-length apoA-I (267 amino acids) includes a preprotein (18 amino acids) and a proprotein (6 amino acids), which are consecutively cleaved to form the mature protein (243 amino acids). [d]Frequency of genetic variants determined based on screening the regulatory and coding regions of *APOA1* in 95 individuals with extreme low apoA-I levels and 95 individuals with extreme high apoA-I levels in the Copenhagen City Heart Study [16]. [e]Reference [18]. [f]Reference [19]. ABCA1 = ATP Binding Casette Transporter A1; ESE = exonic splicing enhancer region predicted by use of "Esefinder" (http://rulai.cshl.edu/cgi-bin/tools/ESE3/esefinder.cgi). LCAT = Lecithin:cholesterol acyltransferase.

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