Table S1. Variation observed in *ABCA1* for phenotypic extreme samples and population-based samples.

Position is mapped to the human genome reference hg19, transcript NM_005502.3, codon changes are in reference to ENST00000374736.3 and protein changes are in reference to ENSP00000363868.3.

Position Chr9	DNA Change	Protein Change	rsID	N Extreme Carriers	HDL-C in Extremes	N RS Carriers	HDL-C in the RS	Observed in Extremes and RS	Previously Reported[12]
107546652	c.6730G>A	p.(Val2244Ile)	rs144588452	1	41				
107547734	c.6588G>C	p.(ln2196His)	rs564764153			1	68		
107547804	c.6518G>A	p.(Arg2173Gln)	rs375968445	1	96				
107548583	c.6397A>T	p.(Asn2133Tyr)				1	42		
107550221	c.6184G>A	p.(Gly2062Arg)				1	60		
107550823	c.5953C>T	p.(His1985Tyr)				1	23		
107554263	c.5774G>A	p.(Arg1925Gln)	rs142688906	3	30;115; 85	8	69;64;58;74; 49;47;40;53	✔	
107555536	c.5552G>A	p.(Arg1851Gln)				1	54		
107555551	c.5537G>T	p.(Trp1846Leu)				1	42		
107555570	c.5518T>C	p.(Phe1840Leu)				1	52		
107556776	c.5398A>C	p.(Asn1800His)	rs146292819			3	29;26;41		✔
107556782	c.5392A>G	p.(Asn1798Asp)		1	26				
107558450	c.5266G>A	p.(Ala1756Thr)	rs142382023			1	41		
107560784	c.5039G>A	p.(Arg1680Gln)	rs150125857			2	37;36		✔
107560803	c.5020G>A	p.(Val1674Ile)	rs138422574			2	46;43		
107560830	c.4993A>G	p.(Met1665Val)		1	33				
107566973	c.4493A>G	p.(Gln1498Arg)		1	41				
107568532	c.4454C>T	p.(Pro1485Leu)		1	31				
107574868	c.4037G>A	p.(Gly1346Glu)		1	41				
107574875	c.4030C>T	p.(Arg1344Trp)	rs193087674	1	40				
107576732	c.3763A>C	p.(Ser1255Arg)	rs41436749	1	41				
107576738	c.3757G>A	p.(Glu1253Lys)	rs138056193			1	63		
107578608	c.3554A>G	p.(Asn1185Ser)	rs148328750	1	82	1	85	✔	
107578618	c.3544G>A	p.(Ala1182Thr)	rs143180998			4	72;38;64;49		
107578620	c.3542C>T	p.(Ser1181Phe)	rs76881554			6	60;38;50;48; 53;44		✔
107579633	c.3515A>G	p.(Glu1172Gly)	rs142877738	1	25				
107579678	c.3470G>A	p.(Ser1157Asn)	rs200664068	1	36	1	37	✔	
107580963	c.3443C>T	p.(Thr1148Ile)		1	30				
107580991	c.3415C>G	p.(Leu1139Val)		1	126				
107582258	c.3053A>G	p.(Asp1018Gly)	rs140365800	1	103	1	30	✔	
107582316	c.2995C>T	p.(Arg999Cys)	rs138735406	1	42				
107584945	c.2669G>T	p.(Cys887Phe)	rs187652566	1	105				
107588062	c.2444A>G	p.(Glu815Gly)	rs145582736	1	26				✔
107588129	c.2377T>C	p.(Tyr793His)		1	120				

107589238	c.2328G>C	p.(Lys776Asn)	rs138880920	7	23;34;41;113;106;30;29	7	62;70;34;54;31;46;46	✔	
107589246	c.2320A>C	p.(Thr774Pro)	rs35819696	5	23;123;81;29;35	21	48;45;26;75;56;75;75;53;44;65;52;53;64;28;32;44;62;36;43;47;59	✔	
107591334	c.1978G>A	p.(Val660Met)		1	101				
107591390	c.1922C>T	p.(Pro641Leu)				1	53		
107593318	c.1780G>A	p.(Ala594Thr)	rs199655961			1	46		
107593329	c.1769G>T	p.(Trp590Leu)	rs137854496	1	41				
107593350	c.1748T>C	p.(Phe583Ser)				1	37		
107594878	c.1486C>T	p.(Arg496Trp)	rs147675550	2	30;26	3	86;36;37	✔	✔
107595026	c.1338C>G	p.(Asp446Glu)	rs148314522	1	40	2	40;95	✔	
107599281	c.1291C>G	p.(Gln431Glu)				1	46		
107599296	c.1276T>C	p.(Phe426Leu)	rs201586430			1	49		
107599376	c.1196T>C	p.(Val399Ala)	rs9282543	10	34;27;41;34;31;29;27;30;31;29	13	51;75;82;56;50;57;40;32;46;73;55;45;39	✔	
107599797	c.1106G>A	p.(Arg369His)	rs370223805			1	39		
107602586	c.1028C>T	p.(Ala343Val)	rs200030513			1	34		
107607822	c.749C>T	p.(Pro250Leu)	rs201134913	1	41	1	59	✔	
107607828	c.743C>T	p.(Pro248Leu)		1	30				
107624006	c.497A>G	p.(Lys106Arg)	rs377248142			1	55		
107624036	c.467G>T	p.(Gly156Val)	rs369793332			1	54		
107645341	c.400C>G	p.(Gln134Glu)				1	55		
107645379	c.92G>T	p.(Ser121Thr)		1	29				
107646756	c.254C>T	p.(Pro25Leu)	rs145183203			2	51;41		
107651451	c.92G>T	p.(Trp31Leu)		1	74				

Table S2. Power estimates from simulation mimicking real data. For common variants, a case/control and random sample give the same effect, but for rare variants, extremes are more powerful, even with a reduced sample size. This is more pronounced when with larger effects. Scenario A: Rare variants were simulated to have 1-SD effects, all same direction; Scenario B: rare variants were simulated to have ½-SD effects, all same direction; and Scenario C: ½ of the variant effects are simulated to have a ½-SD effect and ½ of the variant effects are simulated to have a 1.5-SD effect.

	N	**Common variant test**	**Rare variant test Scenario A**	**Rare variant test Scenario B**	**Rare variant test Scenario C**
Random Sample	3000	0.511	0.457	0.126	0.296
Case-Control	350/350	0.526	0.539	0.125	0.33
All	7000	0.877	0.640	0.193	0.442

Table S3. Type I error estimates from simulation comparing sampling strategies. Estimates of type I error based on 1,000 replicates. The 95% confidence interval around 0.05 is 0.036-0.063.

Sampling	Common variant test	Rare variant test
Random sample of 1100	0.053	0.033
Random sample of 2100	0.035	0.046
Random sample 5100	0.044	0.045
Random sample of 10100	0.044	0.045
c/c 100/100 from 5% tail	0.039	0.044
c/c 100/100 from 1% tail	0.062	0.040
c/c 100/100 from 0.1% tail	0.050	0.046
c/c 100/100 from 0.01% tail	0.046	0.046
c/c 100 from 5% tail and 1,000 random samples	0.054	0.052
c/c 100 from 1% tail and 1,000 random samples	0.051	0.049
c/c 100 from 0.1% tail and 1,000 random samples	0.046	0.046
c/c 100 from 0.01% tail and 1,000 random samples	0.044	0.040

Figure S1. Proportion of functional variants observed in extremes versus random sample design.

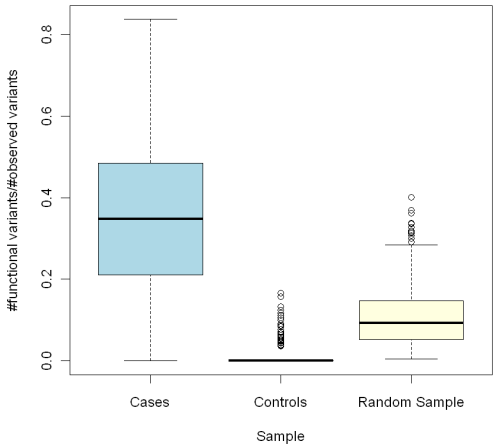

Figure S2. Power estimates from the fixed sample size simulation.
Samples were simulated with equal numbers for the population-based random sample (RS) and the extreme case-control (CC) sample. Threshold, the threshold for selecting the extreme samples; RV, rare variant test; CV, common variant test; sigma, the standard deviation effect of each of the functional rare variants. The probably that specific class of mutations are function was simulated as follows: Model 1 – prob=0.3, poss=0.05, benign=0.1; Model 2 – prob=0.5, poss=0.2, benign=0.05 (increases the amount of variation that is functional); Model 3 – prob=0.1, poss=0.01, benign=0.001 (decreases the amount of variation that is functional).