Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The SEARCH Collaborative Group. *SLCO1B1* variants and statin-induced myopathy — a genomewide study. N Engl J Med 2008;359. DOI: 10.1056/NEJMoa0801936.

Supplementary Appendix for: "*SLCO1B1* Variants and Statin-Induced Myopathy – A Genomewide Study"

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Supplementary Tables

Baseline characteristics	*Number (%) or mean (SD)* Cases (85)	Controls (90)
Matched characteristics		
Male	61 (72%)	67 (74%)
Amiodarone use	10 (12%)	12 (13%)
Age (years)	67 (9)	67 (10)
eGFR (ml/min/1.73m^2)	69.4 (17.3)	70.1 (17.5)
Other characteristics		
Current smoker	2 (2%)	11 (12%)
Body-mass Index (kg/m^2)	27.7 (3.8)	27.4 (3.5)
Diabetes mellitus	13 (15%)	8 (9%)
Treated hypertension	39 (46%)	34 (38%)
Cerebrovascular disease	7 (8%)	10 (11%)
Other arterial disease*	2 (2%)	3 (3%)
Total cholesterol (mmol/l)	4.03 (0.68)	4.28 (0.76)
LDL-cholesterol (mmol/l)	2.34 (0.54)	2.51 (0.68)
HDL-cholesterol (mmol/l)	1.06 (0.32)	1.11 (0.37)
Triglycerides (mmol/l)	1.71 (1.03)	1.86 (1.42)
Apolipoprotein-A_1 (g/l)	1.36 (0.20)	1.37 (0.22)
Apolipoprotein B (g/l)	0.87 (0.16)	0.90 (0.17)
Creatine kinase (IU/L)	135 (75)	139 (87)
Alanine transaminase (IU/L)	23.6 (8.5)	24.8 (9.7)

Supplementary Table 1: Baseline characteristics of 85 myopathy cases and 90 matched controls in SEARCH

All of these cases and controls had been allocated 80mg simvastatin daily and classified themselves as with European ancestry, with matching of controls for sex, age (3 groups), estimated glomerular filtration rate (eGFR; 3 groups) and amiodarone use at baseline. Blood factors were measured after participants had received 20mg simvastatin daily for 2 months prior to randomisation. *Other arterial disease = history of non-coronary arterial bypass surgery or angioplasty.

Supplementary Table 2a

Variant name	Position	Alleles		Minor allele frequency		Trend p-value	OR (95% CI) per minor allele	Genotyped (G)/imputed (I)*
		Minor	Major	Case	Control			
5' Upstream sequence								
rs17387842	21165584	C	T	0.13	0.22	2×10^{-2}	0.5 (0.3-0.9)	I
rs327544	21165757	T	C	0.04	0.02	3×10^{-1}	2.2 (0.5-9.1)	I
rs12368786	21165942	A	T	0.13	0.22	2×10^{-2}	0.5 (0.3-0.9)	I
rs327543	21166718	A	C	0.14	0.07	4×10^{-2}	2.1 (1.0-4.3)	I
rs11045775	21167081	A	G	0.15	0.25	2×10^{-2}	0.5 (0.3-0.9)	I
rs10841751	21167328	C	T	0.15	0.25	2×10^{-2}	0.5 (0.3-0.9)	I
rs11045776	21169459	G	A	0.15	0.25	2×10^{-2}	0.5 (0.3-0.9)	I
rs16923481	21169585	G	A	0.02	0.03	8×10^{-1}	0.8 (0.2-3.2)	I
rs11045777	21170848	A	G	0.13	0.22	2×10^{-2}	0.5 (0.3-0.9)	I
rs704166	21171109	A	G	0.14	0.07	6×10^{-2}	1.9 (1.0-3.9)	I
rs4149012	21172826	G	A	0.02	0.07	3×10^{-2}	0.3 (0.1-0.9)	I
rs852550	21173034	C	T	0.14	0.07	4×10^{-2}	2.1 (1.0-4.3)	G*
rs852549	21173156	T	G	0.14	0.07	4×10^{-2}	2.1 (1.0-4.3)	G*
rs4149013	21173677	G	A	0.02	0.07	3×10^{-2}	0.3 (0.1-0.9)	I
rs17328763	21173837	C	T	0.13	0.22	2×10^{-2}	0.5 (0.3-0.9)	I
CNG40001729	21175214	G	C	0.00	0.01	3×10^{-1}	-	G
CNG40001730	21175277	C	A	0.14	0.03	5×10^{-4}	5.1 (1.9-14.0)	G
CNG40001731	21175387	T	A	0.01	0.00	3×10^{-1}	-	G
Intron 1								
CNG40001732	21175502	C	G	0.00	0.01	3×10^{-1}	-	G
rs4149089	21175894	A	-	0.15	0.30	1×10^{-3}	0.4 (0.2-0.7)	G
rs12816706	21183278	G	A	0.04	0.02	5×10^{-1}	1.6 (0.4-6.0)	I
rs3829310	21183323	G	A	0.14	0.07	4×10^{-2}	2.1 (1.0-4.3)	I
rs3829307	21183473	T	A	0.15	0.29	1×10^{-3}	0.4 (0.2-0.7)	I
rs3829306	21183547	T	C	0.02	0.07	3×10^{-2}	0.3 (0.1-0.9)	G*
rs2010668	21185560	T	G	0.14	0.07	4×10^{-2}	2.1 (1.0-4.3)	I
Intron 2								
rs4149021	21186052	A	G	0.02	0.01	3×10^{-1}	3.3 (0.3-31.9)	I
rs12812795	21186062	T	A	0.04	0.02	5×10^{-1}	1.6 (0.4-6.0)	I
rs4149022	21186879	A	G	0.15	0.29	1×10^{-3}	0.4 (0.2-0.7)	I
rs11045785	21187494	A	T	0.13	0.22	2×10^{-2}	0.5 (0.3-0.9)	I
rs11045786	21187538	T	C	0.12	0.21	2×10^{-2}	0.5 (0.3-0.9)	I
rs2417954	21187611	A	G	0.32	0.38	2×10^{-1}	0.8 (0.5-1.2)	I
rs2417955	21187742	T	A	0.32	0.38	2×10^{-1}	0.8 (0.5-1.2)	I
rs10743408	21187974	C	G	0.14	0.07	4×10^{-2}	2.1 (1.0-4.3)	I
rs2061903	21189969	A	G	0.12	0.21	4×10^{-2}	0.5 (0.3-0.9)	I
rs7977197	21190855	C	A	0.12	0.21	2×10^{-2}	0.5 (0.3-0.9)	I
rs11045787	21191269	G	T	0.12	0.21	2×10^{-2}	0.5 (0.3-0.9)	I
rs11513411	21194706	A	G	0.02	0.07	2×10^{-2}	0.3 (0.1-0.9)	I
rs11045790	21195636	G	A	0.04	0.04	3×10^{-2}	0.8 (0.3-2.3)	I
rs7489119	21196565	A	C	0.12	0.22	7×10^{-1}	0.5 (0.3-0.9)	I
rs12372124	21199483	C	A	0.12	0.22	2×10^{-2}	0.5 (0.3-0.9)	I
rs11045796	21199890	G	A	0.02	0.07	2×10^{-2}	0.3 (0.1-0.9)	I
rs4149023	21200724	T	G	0.02	0.07	3×10^{-2}	0.3 (0.1-0.9)	I
rs4149024	21200790	T	A	0.02	0.01	3×10^{-2}	3.3 (0.3-31.9)	I

Supplementary Table 2a (continued)

rs11045797	21200981	C	T	0.12	0.22	2×10^{-2}	0.5 (0.3-0.9)	I
rs11045799	21202292	C	T	0.12	0.22	2×10^{-2}	0.3 (0.1-0.8)	I
rs11045800	21202515	C	T	0.04	0.11	1×10^{-2}	1.2 (0.7-2.0)	I
rs16923519	21202985	G	A	0.21	0.18	6×10^{-1}	0.3 (0.1-0.8)	I
rs11045802	21203587	G	T	0.04	0.11	1×10^{-2}	0.7 (0.5-1.1)	I
rs981262	21203777	A	G	0.32	0.40	1×10^{-1}	2.7 (1.3-5.4)	I
rs7138177	21204191	G	A	0.18	0.08	5×10^{-3}	0.7 (0.5-1.1)	I
rs7962588	21204643	G	C	0.33	0.40	2×10^{-1}	0.5 (0.3-0.9)	I
rs11045805	21205463	G	A	0.12	0.22	2×10^{-2}	0.5 (0.3-0.9)	I
rs4149026	21206682	C	A	0.22	0.35	1×10^{-2}	0.2 (0.0-0.6)	G*
rs976754	21206789	G	A	0.02	0.10	1×10^{-3}	0.2 (0.1-1.2)	I
rs4149028	21207219	C	T	0.01	0.04	6×10^{-2}	0.9 (0.6-1.3)	I
rs4149030	21207480	A	G	0.45	0.49	5×10^{-1}	0.4 (0.2-0.8)	G*
rs10444413	21208935	C	T	0.08	0.18	7×10^{-3}	0.3 (0.2-0.6)	I
rs4149032	21209058	T	C	0.14	0.34	3×10^{-5}	2.3 (1.4-3.7)	I
rs4149033	21209077	A	G	0.36	0.19	8×10^{-4}	0.3 (0.2-0.6)	I
rs4149034	21209189	A	G	0.14	0.34	3×10^{-5}	1.3 (0.8-1.9)	I
rs4149035	21209532	T	C	0.44	0.37	2×10^{-1}	0.7 (0.2-2.0)	I
rs11045808	21209956	C	G	0.03	0.04	5×10^{-1}	0.7 (0.2-2.0)	I
rs2219828	21210580	A	G	0.03	0.04	5×10^{-1}	0.8 (0.3-2.3)	I
rs7296796	21211953	G	A	0.04	0.04	7×10^{-1}	1.1 (0.7-1.6)	I
rs7973095	21212537	T	C	0.45	0.43	8×10^{-1}	0.4 (0.2-0.7)	I
rs10841753	21212637	C	T	0.08	0.21	1×10^{-3}	1.0 (0.5-2.2)	I
rs7139376	21212696	T	C	0.09	0.09	1×10^{-0}	0.9 (0.6-1.4)	I
rs11045812	21212749	T	C	0.44	0.47	6×10^{-1}	0.2 (0.0-1.8)	I
rs12311454	21212774	T	G	0.01	0.03	1×10^{-1}	0.4 (0.2-0.8)	I
rs11045813	21213323	A	G	0.09	0.19	9×10^{-3}	0.3 (0.1-1.4)	I
rs11045814	21213479	A	T	0.01	0.04	9×10^{-2}	1.1 (0.7-1.6)	I
rs10841754	21213502	T	A	0.48	0.46	6×10^{-1}	0.3 (0.1-1.4)	I
rs12313639	21214239	C	G	0.01	0.04	9×10^{-2}	0.4 (0.2-0.8)	I
rs11045816	21214539	G	A	0.09	0.19	9×10^{-3}	0.9 (0.6-1.4)	I
rs17388851	21214823	T	C	0.44	0.47	6×10^{-1}	0.3 (0.1-1.4)	I
rs2417957	21214878	T	C	0.01	0.04	9×10^{-2}	1.2 (0.8-1.9)	I
rs7136445	21216015	G	A	0.46	0.40	3×10^{-1}	0.5 (0.3-0.9)	I
rs7295464	21216614	G	A	0.07	0.09	5×10^{-1}	0.8 (0.3-1.7)	G
CNG40001743	21216745	C	T	0.04	0.01	4×10^{-2}	6.9 (0.8-58.3)	G
Intron 3								
CNG40001744	21217040	A	-	0.00	0.01	3×10^{-1}	-	G
rs2291073	21217081	G	T	0.02	0.11	5×10^{-4}	0.1 (0.0-0.5)	G*
rs2291074	21217216	G	A	0.01	0.04	9×10^{-2}	0.3 (0.1-1.4)	I
Exon 4								
CNG40001739 (Ser85Ser)	21218806	C	T	0.01	0.00	3×10^{-1}	-	G
Intron 4								
rs4149036	21219007	A	C	0.38	0.22	2×10^{-3}	2.1 (1.3-3.3)	I
rs4149037	21219478	G	A	0.01	0.04	9×10^{-2}	0.3 (0.1-1.4)	I
rs4149038	21219509	G	A	0.38	0.22	2×10^{-3}	2.1 (1.3-3.3)	G*
rs4149040	21219691	C	G	0.47	0.44	6×10^{-1}	1.1 (0.7-1.6)	I
rs17329885	21219832	C	T	0.08	0.18	7×10^{-3}	0.4 (0.2-0.8)	G*
rs4149041	21220106	T	G	0.01	0.04	9×10^{-2}	0.3 (0.1-1.4)	I
rs964614	21220657	C	T	0.09	0.09	1×10^{-0}	1.0 (0.5-2.2)	I
rs964615	21220691	T	C	0.09	0.09	1×10^{-0}	1.0 (0.5-2.2)	G*

Supplementary Table 2a (continued)

Exon 5								
rs2306283 (Asn130Asp)	21221005	G	A	0.48	0.44	5×10^{-1}	1.2 (0.8-1.7)	G*
rs11045818 (Ser137Ser)	21221028	A	G	0.08	0.18	7×10^{-3}	0.4 (0.2-0.8)	G
rs11045819 (Pro155Thr)	21221080	A	C	0.08	0.18	7×10^{-3}	0.4 (0.2-0.8)	G
Intron 5								
rs11045820	21221258	T	C	0.08	0.18	7×10^{-3}	0.4 (0.2-0.8)	G
rs4149044	21221263	T	A	0.39	0.23	2×10^{-3}	2.1 (1.3-3.3)	G
rs4149045	21221287	A	G	0.39	0.23	2×10^{-3}	2.1 (1.3-3.4)	G
rs4149046	21221289	A	G	0.43	0.47	6×10^{-1}	0.9 (0.6-1.3)	G
rs4149048	21221618	G	A	0.38	0.22	2×10^{-3}	2.1 (1.3-3.3)	I
rs4149050	21222255	C	T	0.47	0.24	3×10^{-5}	2.6 (1.6-4.0)	I
rs4149054	21222446	A	G	0.47	0.24	3×10^{-5}	2.6 (1.6-4.0)	I
Exon 6								
rs4149056 (Val174Ala)	**21222816**	**C**	**T**	**0.46**	**0.13**	**3×10^{-9}**	**4.4 (2.6-7.6)**	**G**
rs4149056 (Val174Ala)	**21222816**	**C**	**T**	**0.45**	**0.13**	**2×10^{-9}**	**4.5 (2.6-7.7)**	**G + I**
rs2291075 (Phe199Phe)	21222892	T	C	0.55	0.42	3×10^{-4}	2.2 (1.4-3.5)	I
rs2291075 (Phe199Phe)	21222892	T	C	0.55	0.42	2×10^{-2}	1.6 (1.1-2.5)	I
Intron 7								
rs2291076	21223254	T	C	0.34	0.46	3×10^{-2}	0.6 (0.4-1.0)	G
rs2291077	21223488	T	A	0.42	0.55	3×10^{-2}	0.6 (0.4-1.0)	G
rs11045821	21223690	A	G	0.08	0.18	8×10^{-3}	0.4 (0.2-0.8)	I
rs4762698	21224110	A	G	0.09	0.09	1×10^{-0}	1.0 (0.5-2.2)	I
rs12812279	21224307	G	A	0.08	0.18	8×10^{-3}	0.4 (0.2-0.8)	I
rs4149058	21224481	G	A	0.47	0.23	2×10^{-5}	2.6 (1.7-4.1)	I
rs6487213	21224533	C	T	0.44	0.54	7×10^{-2}	0.7 (0.5-1.0)	I
rs1000691	21224693	A	G	0.01	0.04	6×10^{-2}	0.2 (0.0-1.5)	I
rs999278	21224918	A	C	0.35	0.46	5×10^{-2}	0.7 (0.4-1.0)	I
rs11045823	21225012	A	G	0.08	0.19	5×10^{-3}	0.4 (0.2-0.8)	I
rs11045824	21225179	T	G	0.08	0.19	5×10^{-3}	0.4 (0.2-0.8)	I
rs11045825	21225277	C	T	0.08	0.19	5×10^{-3}	0.4 (0.2-0.8)	I
rs991262	21225481	A	G	0.06	0.08	5×10^{-1}	0.7 (0.3-1.7)	I
rs1564370	21226457	G	C	0.38	0.49	4×10^{-2}	0.6 (0.4-1.0)	I
rs1463565	21226648	C	G	0.47	0.46	5×10^{-2}	2.7 (1.7-4.3)	I
rs2900476	21227330	C	T	0.38	0.23	9×10^{-6}	0.6 (0.4-1.0)	I
rs2100996	21229464	G	A	0.01	0.49	4×10^{-2}	0.2 (0.0-1.5)	G*
rs1120964	21230957	T	C	0.15	0.04	6×10^{-2}	0.4 (0.3-0.8)	I
rs11045834	21232363	T	C	0.34	0.28	3×10^{-3}	0.4 (0.2-0.8)	G*
Intron 8								
rs7957274	21241663	C	T	0.09	0.20	5×10^{-3}	0.4 (0.2-0.8)	G
rs4149061	21241935	T	C	0.40	0.51	5×10^{-2}	0.7 (0.4-1.0)	I
rs4149063	21242057	T	G	0.05	0.07	4×10^{-1}	0.7 (0.3-1.6)	I
rs4149064	21242128	G	A	0.05	0.07	5×10^{-1}	0.7 (0.3-1.7)	G*
rs12302293	21243214	A	G	0.02	0.01	2×10^{-1}	4.4 (0.5-40.1)	I
rs12424765	21243244	C	T	0.01	0.03	1×10^{-1}	0.2 (0.0-1.8)	I
rs1871395	**21243582**	**G**	**A**	**0.45**	**0.13**	**4×10^{-9}**	**4.3 (2.5-7.4)**	**I**
rs12317268	**21243808**	**G**	**A**	**0.45**	**0.13**	**4×10^{-9}**	**4.3 (2.5-7.4)**	**I**
rs12310977	21243822	C	T	0.02	0.04	3×10^{-1}	0.5 (0.1-1.8)	I
rs11045858	21243938	G	A	0.09	0.20	5×10^{-3}	0.4 (0.2-0.8)	I

Supplementary Table 2a (continued)

Intron 9								
rs1564365	21245737	G	A	0.06	0.05	7×10^{-1}	1.2 (0.5-3.1)	I
Intron 10								
rs12427008	21249215	C	T	0.05	0.08	4×10^{-1}	0.7 (0.3-1.6)	I
CNG40001759	21249941	-	A	0.01	0.07	3×10^{-3}	0.1 (0.0-0.6)	G
rs4149099	21249964	-	CTT	0.44	0.54	8×10^{-2}	0.7 (0.5-1.0)	G
CNG40001761	21249994	T	C	0.00	0.02	9×10^{-2}	-	G
CNG40001762	21250055	C	T	0.02	0.00	2×10^{-1}	-	G
Intron 11								
rs2417967	21252002	A	G	0.01	0.04	9×10^{-2}	0.3 (0.1-1.4)	I
rs11045863	21253135	T	C	0.09	0.20	5×10^{-3}	0.4 (0.2-0.8)	I
rs4363657	**21259989**	**C**	**T**	**0.46**	**0.13**	**4×10^{-9}**	**4.3 (2.5-7.2)**	**G***
rs2900478	**21260064**	**A**	**T**	**0.46**	**0.13**	**3×10^{-9}**	**4.3 (2.5-7.3)**	**I**
rs4149068	21260458	C	T	0.01	0.03	1×10^{-1}	0.2 (0.0-1.8)	I
rs4149069	21260593	G	C	0.42	0.53	5×10^{-2}	0.7 (0.5-1.0)	I
rs4149070	21261150	G	C	0.03	0.13	1×10^{-3}	0.2 (0.1-0.6)	G
rs4149071	21261231	C	T	0.03	0.13	2×10^{-3}	0.2 (0.1-0.6)	G
rs4149100	**21261245**	**-**	**A**	**0.47**	**0.14**	**4×10^{-9}**	**4.3 (2.5-7.4)**	**G**
rs4149072	21261252	A	G	0.02	0.05	2×10^{-1}	0.5 (0.2-1.6)	G
Exon 12								
CNG40001756 (Pro525Ser)	21261395	T	C	0.00	0.01	3×10^{-1}	-	G
CNG40001757 (Gln541Leu)	21261444	T	A	0.01	0.00	3×10^{-1}	-	G
Intron 12								
rs4149076	21262411	C	T	0.55	0.33	2×10^{-4}	2.2 (1.4-3.4)	I
rs2417968	21263396	C	G	0.42	0.53	5×10^{-2}	0.7 (0.5-1.0)	I
rs11045872	21263611	G	A	0.09	0.20	5×10^{-3}	0.4 (0.2-0.8)	I
rs987839	21266105	A	G	0.42	0.53	5×10^{-2}	0.7 (0.5-1.0)	G*
Intron 14								
rs4149081	**21269288**	**A**	**G**	**0.46**	**0.13**	**3×10^{-9}**	**4.3 (2.5-7.3)**	**I**
rs7966613	21270899	G	A	0.55	0.33	2×10^{-4}	2.2 (1.4-3.4)	G*
rs11045878	21273489	G	A	0.55	0.36	1×10^{-3}	2.0 (1.3-3.1)	I
rs10841763	21273609	C	T	0.55	0.33	2×10^{-4}	2.2 (1.4-3.4)	G*
rs11045879	**21273886**	**C**	**T**	**0.46**	**0.13**	**3×10^{-9}**	**4.3 (2.5-7.3)**	**I**
rs717958	21273997	G	T	0.02	0.05	1×10^{-1}	0.4 (0.1-1.4)	I
rs7137060	21274097	T	C	0.12	0.22	2×10^{-2}	0.5 (0.3-0.9)	I
rs11045880	21274167	C	T	0.55	0.33	2×10^{-4}	2.2 (1.4-3.4)	I
rs11045884	21275649	C	G	0.09	0.20	5×10^{-3}	0.4 (0.2-0.8)	I
rs7969341	**21276871**	**G**	**A**	**0.46**	**0.13**	**3×10^{-9}**	**4.3 (2.5-7.3)**	**I**
rs11045885	**21277285**	**G**	**A**	**0.46**	**0.13**	**3×10^{-9}**	**4.3 (2.5-7.3)**	**I**
rs10841767	21277328	G	A	0.09	0.20	5×10^{-3}	0.4 (0.2-0.8)	G*
rs12371792	21278110	C	T	0.55	0.33	2×10^{-4}	2.2 (1.4-3.4)	I
rs11045887	21278745	G	C	0.09	0.19	7×10^{-3}	0.4 (0.2-0.8)	I
rs12829704	21279888	A	G	0.09	0.20	5×10^{-3}	0.4 (0.2-0.8)	I
rs12830367	21280172	T	G	0.55	0.33	2×10^{-4}	2.2 (1.4-3.4)	I
rs11045889	21280304	T	A	0.55	0.33	2×10^{-4}	2.2 (1.4-3.4)	I
rs2199763	21280975	G	A	0.58	0.41	3×10^{-3}	1.9 (1.2-2.8)	I
rs12578392	21281237	C	T	0.58	0.41	3×10^{-3}	1.9 (1.2-2.8)	I
rs12371604	21282603	C	T	0.49	0.21	7×10^{-7}	3.0 (1.9-4.7)	I
rs12369881	**21282619**	**A**	**G**	**0.46**	**0.13**	**3×10^{-9}**	**4.3 (2.5-7.3)**	**I**
rs12366582	**21282875**	**G**	**A**	**0.46**	**0.13**	**3×10^{-9}**	**4.3 (2.5-7.3)**	**I**

Supplementary Table 2a (continued)

Exon 15								
rs34671512 (Leu643Phe)	21283243	C	A	0.01	0.08	1 x10^{-3}	0.1 (0.0-0.6)	G
Exon 15: 3' untranslated region								
CNG40001747	21283436	G	T	0.03	0.01	3 x10^{-1}	2.3 (0.4-12.8)	G
rs4149085	21283557	C	T	0.00	0.01	3 x10^{-1}	-	G
rs4149087	21283829	T	G	0.40	0.59	1 x10^{-3}	0.5 (0.3-0.8)	G
rs11045891	21283839	C	A	0.09	0.20	1 x10^{-2}	0.5 (0.2-0.9)	G
rs4149088	21283853	A	G	0.40	0.59	1 x10^{-3}	0.5 (0.3-0.8)	G
CNG40001749	21283871	C	T	0.01	0.00	3 x10^{-1}	-	G
CNG40001750	21283965	A	G	0.01	0.01	6 x10^{-1}	0.5 (0.0-6.0)	G
3' downstream sequence								
rs11045892	21284061	G	A	0.09	0.19	1 x10^{-2}	0.4 (0.2-0.9)	G
rs11045893	21284086	C	T	0.09	0.20	5 x10^{-3}	0.4 (0.2-0.8)	I
rs12372157	21284285	G	T	0.58	0.40	2 x10^{-3}	1.9 (1.2-2.8)	I
rs12370842	21284853	A	G	0.09	0.19	1 x10^{-2}	0.4 (0.2-0.8)	I
rs10841769	21286286	G	A	0.41	0.52	7 x10^{-2}	0.7 (0.5-1.0)	I
rs7960688	21287136	C	G	0.09	0.19	7 x10^{-3}	0.4 (0.2-0.8)	I
rs7960384	21287175	G	A	0.09	0.19	7 x10^{-3}	0.4 (0.2-0.8)	I
rs11045900	21290186	G	A	0.58	0.40	2 x10^{-3}	1.9 (1.2-2.8)	I
rs11045901	21290488	C	T	0.58	0.40	2 x10^{-3}	1.9 (1.2-2.8)	I
rs12372067	21292800	A	C	0.58	0.40	2 x10^{-3}	1.9 (1.2-2.8)	I
rs12372111	21292943	T	G	0.58	0.40	2 x10^{-3}	1.9 (1.2-2.8)	I
rs12372162	21293291	G	A	0.41	0.52	7 x10^{-2}	0.7 (0.5-1.0)	I

Supplementary Table 2a: Associations with myopathy for SNPs within *SLCO1B1* (+/- 10kb) from the genome-wide association study, candidate genotyping and imputation in SEARCH

Based on the 85 cases and 90 controls in Supplementary Table 1. SNPs in Supplementary Tables 2a and 2b are ordered by position and labelled by their region status (according to Ensembl!; November 2007: http://www.ensembl.org/Homo_sapiens/exonview?db=core;transcript=ENST00000256958). Single SNP p-values smaller than 5 x10^{-7} are highlighted in bold. For exonic variants, the protein change is listed with the name of the variant. Allele codings are in the forward orientation (positive strand). *Asterisks indicate genotyped variants in the Illumina panel.

Variant name	Position	Alleles		Minor allele frequency		Trend p-value	OR (95% CI) per minor allele	Genotyped (G)/imputed (I)*
		Minor	Major	Case	Control			
3' Untranslated region								
rs2005548	99184309	A	G	0.00	0.01	3×10^{-1}	-	I
rs6945984	99186264	G	A	0.06	0.08	5×10^{-1}	0.8 (0.4-1.7)	I
rs2404955	99191215	T	C	0.06	0.08	7×10^{-1}	0.9 (0.4-1.8)	I
rs12333983	99192050	T	A	0.06	0.08	7×10^{-1}	0.9 (0.4-1.8)	I
CNG40001939	99192883	C	T	0.04	0.02	3×10^{-1}	2.4 (0.4-13.7)	G
CNG40001938	99192925	-	T	0.00	0.01	3×10^{-1}	-	G
CNG40001777	99193009	T	C	0.07	0.11	3×10^{-1}	0.7 (0.3-1.6)	G
rs12721631	99193363	T	C	0.04	0.02	3×10^{-1}	2.4 (0.4-13.4)	G
CNG40001775	99193585	C	T	0.00	0.01	3×10^{-1}	-	G
Exon 13								
CNG40001774 (Pro488Thr)	99193741	A	-	0.00	0.01	3×10^{-1}	-	G
Intron 12								
CNG29950523	99193843	C	T	0.01	0.00	3×10^{-1}	-	G
CNG29950522	99193911	G	A	0.08	0.10	5×10^{-1}	0.8 (0.3-1.9)	G
Exon 12								
rs4986910 (Met445Thr)	99196460	C	T	0.00	0.01	3×10^{-1}	-	I
Intron 11								
CNG40001773	99197591	T	C	0.00	0.01	3×10^{-1}	-	G
Exon 11								
CNG40001772 (Thr363Met)	99197765	T	C	0.01	0.00	3×10^{-1}	-	G
CNG40001771 (Val359Glu)	99197777	A	T	0.00	0.01	4×10^{-1}	-	G
Intron 10								
rs12721617	99197847	C	A	0.00	0.03	6×10^{-2}	-	G
rs4646440	99198806	T	C	0.00	0.01	3×10^{-1}	-	I
rs2242480	99199402	A	G	0.04	0.10	1×10^{-1}	0.4 (0.1-1.3)	G
Intron 7								
rs4646437	99203019	T	C	0.07	0.10	4×10^{-1}	0.7 (0.3-1.7)	G
CNG40001765	99203108	C	T	0.01	0.00	3×10^{-1}	-	G
rs2246709	99203655	C	T	0.30	0.31	9×10^{-1}	1.0 (0.6-1.5)	I
rs2687116	99203879	G	T	0.00	0.06	1×10^{-2}	-	G
Exon 7								
CNG40001763 (Lys209Lys)	99203956	A	G	0.00	0.01	3×10^{-1}	-	G
Intron 6								
CNG29950512	99204252	T	C	0.05	0.10	2×10^{-1}	0.5 (0.2-1.4)	G
Intron 2								
rs2687105	99214882	T	A	0.00	0.04	2×10^{-2}	-	I
Intron 1								
CNG40001764	99215762	-	ATT	0.00	0.01	4×10^{-1}	-	G
rs6957392	99219399	A	G	0.00	0.01	3×10^{-1}	-	G
5' downstream sequence								
rs2740574	99220032	G	A	0.00	0.04	2×10^{-2}	-	I
rs11773597	99220387	G	C	0.04	0.03	5×10^{-1}	1.5 (0.5-5.0)	I
rs1851426	99220872	T	C	0.00	0.04	2×10^{-2}	-	I

Supplementary Table 2b: Associations with myopathy for SNPs within *CYP3A4* (+/- 10kb) from candidate genotyping and imputation in SEARCH

Genotyping based on 54 cases and 62 controls with sufficient DNA and imputation based on the 85 cases and 90 controls in Supplementary Table 1. Alleles codings are in reverse orientation (negative strand).

rs4149056 genotype	*rs2306283 genotype*	*No. of participants*	*LDL-cholesterol (mg/dL)*				
			Mean (SD) at screening	**Mean (SD) at randomisation**	**Mean (SE) reduction**	**Percent (SE) reduction**	**Joint test for trend by genotype in % reduction (SE)**
TT	AA	5630	130.0 (31.7)	76.6 (25.2)	53.4 (0.4)	40.6% (0.20)	
TT	AG	5211	130.0 (31.0)	76.2 (24.8)	53.8 (0.4)	40.9% (0.21)	
TT	GG	1231	131.2 (31.0)	75.5 (24.0)	55.7 (0.8)	42.0% (0.42)	
CT	AA	620	129.6 (30.6)	78.6 (25.5)	51.1 (0.8)	38.8% (0.62)	-1.28% (0.25) per rs4149056 C allele [p<0.0001] 0.62% (0.18) per rs2306283 G allele [p=0.0005]
CT	AG	2516	131.2 (31.0)	78.2 (23.6)	53.0 (0.4)	39.6% (0.30)	
CT	GG	1092	130.4 (32.1)	76.2 (24.8)	54.2 (0.8)	40.8% (0.46)	
CC	AA	24	130.0 (24.4)	77.0 (19.4)	53.0 (4.6)	40.3% (2.73)	
CC	AG	122	127.3 (31.0)	77.4 (26.3)	49.9 (1.9)	39.1% (1.28)	
CC	GG	214	130.8 (32.1)	78.9 (23.6)	51.9 (1.5)	39.1% (0.91)	

Supplementary Table 3*:* LDL-cholesterol concentrations and reductions with 40mg simvastatin daily in HPS, subdivided by rs4149056 and rs2306283 *SLCO1B1* genotypes

Supplementary Table 4

Previously reported studies of myopathy, myalgia and intolerance									*Findings in SEARCH case-control study*		
Author	**Hypotheses investigated**	**Gene**	**Candidate gene SNP or haplotype**	**SNP frequency**	**Statin therapy**	**Cases/ Controls**	**Endpoint**	**Lowest p-value†**	**SNP (r^2 to reported SNP)**	**Trend p-value**	**Genotypic p-value**
Genes with p<0.05 associations (including other studies of the same gene with p>0.05 results)											
Morimoto[1,2]	152 SNPs in 8 genes	*SLCO1B1*	*15 haplotype: rs4149056 rs2306283	 0.13 0.39	pravastatin/ atorvastatin	<10/26	Myopathy	<0.01	 rs4149056 rs2306283	 2×10^{-9} 5×10^{-1}	 1×10^{-8} 5×10^{-1}
Hermann[3]	9 SNPs in 3 genes	*SLCO1B1*	rs4149056 rs2306283 rs11045819	0.13 0.39 0.23	atorvastatin	13/15	Myalgia	>0.05 >0.05 >0.05	rs4149056 rs2306283 rs11045819	2×10^{-9} 5×10^{-1} 7×10^{-3}	1×10^{-8} 5×10^{-1} 2×10^{-2}
Morimoto[2]	152 SNPs in 8 genes	*ABCB1/ MDR1*	rs2032582	0.39	simvastatin/ atorvastatin	<10/26	Myopathy	<0.05	rs6949448 (0.93)	4×10^{-1}	6×10^{-1}
Fiegenbaum[4]	5 SNPs in 3 genes	*ABCB1/ MDR1*	Haplotype : rs1128503 [1236T] rs2032582 [2677 non-G] rs1045642 [3435T]	 0.46 0.49 0.56	simvastatin	15/99	Myalgia	<0.03	 rs1202169 (1.00) rs6949448 (0.93) rs6949448 (0.52)	 5×10^{-1} 4×10^{-1} 4×10^{-1}	 6×10^{-1} 6×10^{-1} 6×10^{-1}
Hermann[3]	9 SNPs in 3 genes	*ABCB1/ MDR1*	rs2229109 [1199A] rs1128503 [1236T] rs2032582 [2677 non-G] rs1045642 [3435T]	0.00 0.37 0.63 0.57	atorvastatin	13/15	Myalgia	>0.05 >0.05 >0.05 >0.05	rs4148732 (0.38) rs1202169 (1.00) rs6949448 (0.93) rs6949448 (0.52)	$1 \times 10^{+0}$ 5×10^{-1} 4×10^{-1} 4×10^{-1}	8×10^{-1} 6×10^{-1} 6×10^{-1} 6×10^{-1}
Frudakis[5]	388 SNPs in 23 genes	*ABCB1/ MDR1*	rs1045642 [3435T]	0.46	atorvastatin	51/55	Muscle events	>0.05	rs6949448 (0.52)	4×10^{-1}	6×10^{-1}
Frudakis[5]	388 SNPs in 23 genes	*CYP2D6*	*4 haplotype : rs1065852 [100T] rs3892097 [1846A]	 0.10 0.18	atorvastatin simvastatin	136/296	Muscle events	0.001	rs764481 (NA)	6×10^{-1}	7×10^{-1}
Zuccaro[6]	8 SNPs in 3 genes	*CYP2D6*	*4 haplotype : rs1065852[100T] rs3892097 [1846A]	 0.10 0.18	simvastatin/ fluvastatin	17/12	Myalgia	>0.05	rs764481 (NA)	6×10^{-1}	7×10^{-1}
Mulder[7]	4 mutations in 1 gene	*CYP2D6*	*4 haplotype : rs1065852 [100T] rs3892097 [1846A]	 0.10 0.18	simvastatin	26/61	Statin intolerance	0.0008	rs764481 (NA)	6×10^{-1}	7×10^{-1}
Oh[8]	2 SNPs in 1 gene	*COQ2*	Haplotype: rs4693075 rs6535454	 0.34 0.23	atorvastatin/ rosuvastatin/ other statin	133/158	Statin intolerance (myopathy)	0.007	 rs4693596 (1.00) rs6535450 (0.70)	 6×10^{-1} 2×10^{-1}	 4×10^{-1} 5×10^{-1}

Supplementary Table 4 (continued)

Vladutiu[9]	*11 SNPs in 3 genes*	CPT2 PYGM AMPD1	CPT2: *P50H* *S113L* *Q413fs* *R503C* *G549D* *R631C* PYGM: *R49X* *G240S* AMPD1: *rs17602729 [Q12X]* *P48L* *rs34526199 [K287I]*	*0.00* *0.01* *0.02*	*atorvastatin/ simvastatin/ cerivastatin/ pravastatin/ lovastatin/ gemfibrozil/ fenofibrate*	*110/248*	*Statin-induced myalgia*	*<0.0001 (for any variant allele in* CPT2, PYGM *or* AMPD1*)*	*rs17108140 (NA)* *rs477549 (NA)* *rs2268697 (NA)*	*1 x10^{-1}* *5 x10^{-1}* *5 x10^{-1}*	*2 x10^{-1}* - *4 x10^{-1}*
Ruano[10]	14 SNPs in 9 genes	*HTR3B*	rs2276307	0.17	atorvastatin/ simvastatin/ pravastatin	51/144	Myalgia	0.007	rs2276307 (1.00)	3 x10^{-1}	6 x10^{-1}
Ruano[10]	14 SNPs in 9 genes	*HTR7*	rs1935349	0.12	atorvastatin/ simvastatin/ pravastatin	51/144	Myalgia	0.026	No SNPs in this gene in Illumina 318K panel		
Genes with p>0.05 association only											
Morimoto[2]	152 SNPs in 8 genes	*VLCAD/ ACADVL*	rs2230178 [128A]	rare	pravastatin/ atorvastatin/ simvastatin	<10/26	Myopathy	>0.05	rs222853 (NA)	4 x10^{-1}	-
Morimoto[2]	152 SNPs in 8 genes	3 Other inherited myopathy genes considered, not reported			pravastatin/ atorvastatin/ simvastatin	<10/26	Myopathy	>0.05			
Morimoto[2]	152 SNPs in 8 genes	*ABCC2/ MRP2*	2 SNPs (not specified)	?	pravastatin/ atorvastatin/ simvastatin	<10/26	Myopathy	>0.05	rs2002042 (NA)	2 x10^{-1}	3 x10^{-2}
Morimoto[2]	152 SNPs in 8 genes	*CYP3A4*	1 SNP (not specified)	?	pravastatin/ atorvastatin/ simvastatin	<10/26	Myopathy	>0.05	rs2740574 (NA) imputed	2 x10^{-2}	5 x10^{-2}
Fiegenbaum[4]	5 SNPs in 3 genes	*CYP3A4*	*1b haplotype: rs2740574 [-392G]	0.03	simvastatin	15/99	Myalgia	>0.05	rs2740574 (1.00) imputed	2 x10^{-2}	5 x10^{-2}
Fiegenbaum[4]	5 SNPs in 3 genes	*CYP3A5*	* 3 haplotype: rs776746 [6986G]	0.91	simvastatin	15/99	Myalgia	>0.05	rs776746 (1.00)	4 x10^{-2}	1 x10^{-1}
Zuccaro[6]	8 SNPs in 3 genes	*CYP3A5*	* 3 haplotype: rs776746 [6986G]	0.87	simvastatin/ atorvastatin	34/39	Myalgia	>0.05	rs776746 (1.00)	4 x10^{-2}	1 x10^{-1}
Hermann[3]	9 SNPs in 3 genes	*CYP3A5*	*2: rs28365083 [27289A] *3: rs776746 [6986G]	0.00 0.93	atorvastatin	13/15	Myalgia	>0.05	rs4646458 (NA) rs776746 (1.00)	4 x10^{-1} 4 x10^{-2}	- 1 x10^{-1}

Supplementary table 4 (continued)

Zuccaro[6]	*8 SNPs in 3 genes*	CYP2C9	**2: rs1799853 [C430T]* **3: rs1057910 [1075C]*	*0.11* *0.07*	*simvastatin/ fluvastatin/ rosuvastatin*	*18/14*	*Myalgia*	*>0.05*	*rs2185570 (0.83)* *rs1057910 (1.00)*	*1 x10^{-1}* *5 x10^{-3}*	*2 x10^{-1}* *2 x10^{-2}*
Frudakis[5]	388 SNPs in 23 genes: *CYP3A4, CYP3A7, CYP3A5, CYP2C9, CYP2E1, CYP1A1, CYP1A2, PON1, AHR, CYP2C8, CYP1B1, GSTM1, GSTP1, PON3, CYP2B6, CYP4B1, CYP2A6, HMGCR, OCA2, MVK, CYP2C19, NAT2*				atorvastatin	51/55	Muscle events	>0.006 (Bonferroni-corrected)	All SNPs in these genes associated p>10^{-5}		
Ruano[10]	14 SNPs in 9 genes: *HTR1D, HTR2A, HTR2C, HTR3A, HTR5A, HTR6, SLC6A4.*				atorvastatin/ simvastatin/ pravastatin	51/144	Myalgia	>0.05	All SNPs in these genes associated p>10^{-5}		

Supplementary Table 4: Previous candidate gene studies of statin-induced myopathy, myalgia or intolerance (also included in Supplementary Table 5); and findings for associations of these genes with myopathy in SEARCH

SNP frequency from reference where provided, otherwise from HapMap CEU panel. NA = not ascertained. †No allowance for multiple hypothesis testing (unless stated). SEARCH finding given for SNP within gene with lowest p-value.

Supplementary Table 5

Gene	Chr	Findings in SEARCH study			Previously reported findings related to statin-induced myopathy, statin intolerance or statin pharmacokinetics
		SNPs genotyped	Lowest p-value (trend)	OR for lowest p-value	
Transport of statins into liver from intestinal cell					
SLCO1B1 / SLC21A6 (Liver specific transporter-1)	12	18 [38]	4 x 10^{-9} [3 x 10^{-9}]	4.3 [4.4]	The 521T>C polymorphism that exists commonly in SLCO1B1 haplotypes of *5, *15 and *15+C1007G is the key SNP that determines functional properties of these allelic proteins.[11] The SLCO1B1*15 haplotype is associated with abnormal increase in plasma creatine kinase or severe muscle complaints in up to 10 Japanese patients taking pravastatin or atorvastatin compared to 26 control patients also receiving statins (p<0.01), with an OR of 11.3 (95% CI: 1.6-80.3; p<0.05) for possession of 1 or more *15 haplotypes.[2] 2 cases did not have this mutation, but 1 did have 1628T>G novel mutation.[1] SLCO1B1*5 (521T>C) not associated with myalgia in 13 cases and 15 controls taking atorvastatin.[3] SLCO1B1*15/*15 (n=1) reduced non-renal clearance of pravastatin in Japanese subjects compared to SLCO1B1*15/*1b (n=9) and SLCO1B1*1b/*1b(n=4).[12] Similar results *in vivo* for pravastatin (for *1b/*15 genotype)[13] and *in vitro* for pravastatin, atorvastatin and cerivastation, but not simvastatin.[11] 521CC genotype (n=4) had 144% (p<0.001) and 61% (p=0.049) greater mean area under the plasma atorvastatin concentration-time curve from 0 to 48h than those with 521TT (n=16) and 521TC (n=12) genotype respectively.[14] Significant differences for rosuvastatin,[14,15] pitavastatin[16] and pravastatin[12,13,17-19] but not for fluvastatin.[18] Mean area under the curve from 0 hours to infinity for simvastatin acid concentration was 162% and 221% higher, and C_{max} was 120% and 200% higher, for CC genotype than for TC and TT genotypes respectively (P<0.001). C_{max} of simvastatin acid occurred earlier in CC and TC genotypes than TT genotypes.[20] 521 CT genotype (n=20) showed smaller reduction in total cholesterol compared to TT genotype (n=44): reduction of 16.5% for CT vs 22.3% for TT (p<0.05).[21] Pharmacokinetic interaction between simvastatin and amiodarone was not influenced by the T521C genetic polymorphism (CT n=5; TT n=7).[22]
SLCO2B1	11	10	0.08	5.6	
SLCO1B3	12	7	0.008	2.5	

Supplementary Table 5 (continued)

Transport of statins out of liver via bile for elimination					
ABCB1/ MDR1	7	18	0.1	1.7	2677G>A associated with abnormal increase in plasma creatine kinase or severe muscle complaints in up to 10 Japanese patients taking simvastatin or atorvastatin ($p<0.05$) with compared to 26 control patients also receiving statins.[2] 2677non-G, 1236T and 3435T alleles less frequent in 17 adverse drug reaction cases compared to 99 controls after treatment with 20mg/d simvastatin for 6 months ($p<0.05$).[4] G1199A, C1236T, G2677A or T and C3435T allele frequencies were not different in 13 cases with "atorvastatin-related myopathy" and 15 healthy controls (who had taken 10mg atorvastatin for 1 week without muscle symptoms). The cases had muscular side-effects related to statin therapy reported (case subjects were termed atorvastatin-induced as there was severe muscular pain on atorvastatin, rapid improvement with withdrawal of atorvastatin and repeated symptoms on rechallenge with atorvastatin).[3] C3435T no evidence of association with muscle events (myalgia; statin mypathy; other muscle-related symptoms such as weakness, cramps, spasms, soreness and twitching; CK elevation; myositis with CK elevations; and rhabdomyolysis with CK levels >10xULN) in 51 cases (where the condition was attributed specifically to atorvastatin or other statin therapy by a physician) and 55 controls taking atorvastatin.[5]
ABCC2/ MRP2	10	7	0.2	1.4	No difference in frequencies of 2 SNPs in 10 Japanese patients with abnormal increase in plasma creatine kinase or severe muscle complaints compared to 26 control patients also receiving statins.[2]
Metabolism of statins within liver to active and inactive metabolites					
UGT1A1	2	10	0.05	1.9	Association tests for 12 SNPs and 1 insertion/deletion in 33 myopathy cases and 101 controls from SEARCH found no association (2003; unpublished).
UGT1A3	2	13	0.05	1.9	
UGT2B7	4	3	0.9	1.0	
CYP2C9 (Cytochrome P450 2D6)	10	13	0.005	3.7	Amiodarone is a moderate inhibitor. No differences in genotype frequencies between 18 cases with muscular symptoms and 14 controls taking simvastatin, fluvastatin or rosuvastatin.[6]
CYP2C19	10	7	0.01	2.9	
CYP2C8 (Cytochrome P450 2C8)	10	7	0.02	1.8	Involved with amiodarone N-deethylation in the human liver.[23]
CYP2D6 (Cytochrome P450 2D6)	22	2	0.6	1.1	No differences in allele frequencies of *1, *4 or 2xN alleles between 18 cases of muscle pain recorded on standardised medical record review form after treatment with simvastatin or fluvastatin compared to 12 controls taking simvastatin or fluvastatin, but reduced CYP2D6 metabolism (such as with *1/*4 alleles) was associated with larger LDL cholesterol reductions with simvastatin and fluvastatin.[6] *4 allele (captured by rs1058174, rs2267446) associated ($p<0.001$) with muscle events (myalgia, myopathy, rhabdomyolysis) in 136 cases and 296 controls previously taking simvastatin or atorvastatin.[5] *4 allele associated ($p=0.0008$) with statin intolerance on simvastatin in 26 cases and 61 controls.[7]

Supplementary Table 5 (continued)

Metabolism of statins within intestinal and liver cells to active and inactive metabolites					
CYP3A4 (Cytochrome P450 3A4)	7	0 [20]	[0.01]	[not estimated]	No association in 17 adverse drug reaction cases compared to 99 controls after treatment with 20mg/d simvastatin for 6 months.[4] No difference in frequencies of 1 SNP in 10 Japanese patients with abnormal increase in plasma creatine kinase or severe muscle complaints taking simvastatin or atorvastatin compared to 26 control patients also receiving statins.[2] The A-290G variant was associated with higher LDL cholesterol compared to non-variant carriers after treatment with 10mg/d atorvastatin (AA+AG vs GG p=0.04).The percentage change in LDL cholesterol after treatment was not significantly different in genotype groups (AA+AG n=332; GG n=8, p=0.113).[24]
CYP3A5 (Cytochrome P450 3A5)	7	5	0.04	3.3	No association in 17 adverse drug reaction cases compared to 99 controls after treatment with 20mg/d simvastatin for 6 months.[4] No evidence of higher incidence of toxicity with *3 compared to *1 in 34 cases with muscular symptoms and 39 controls taking simvastatin or atorvastatin.[6] *2 allele (27289C>A) and *3 allele (6986G>A) not associated with myalgia in 13 cases and 15 controls taking atorvastatin.[3] 1 year of atorvastatin/simvastatin/lovastatin associated with smaller percentage reduction (p=0.03) in total cholesterol from baseline in those with the CYP3A5*1 allele (n=7) than those with the CYP3A5*3 allele (n=39).[25]
Vascular genes associated with creatine kinase activity during statin therapy					
NOS3 (Nitric oxide synthase 3)	7	4	0.2	1.3	Produces nitric oxide (NO) from L-arginine in endothelial cells. NO inhibits smooth muscle contraction and platelet aggregation. rs1799983 (D298E) associated (p=0.005) with log creatine kinase levels in 102 patients taking atorvastatin (10mg-80mg/d) or simvastatin (5mg-80mg/d).[26]
AGTR1 (Angiotensin II receptor, Type 1)	3	7	0.02	1.9	Encodes the type I receptor for angiotensin II and mediates the cardiovascular effects of angiotensin II. rs12695902 associated (p=0.002) with log creatine kinase levels in 102 patients taking atorvastatin (10mg-80mg/d) or simvastatin (5mg-80mg/d).[26]
Serotonergenic neurotransmission; pain perception and transduction of nociceptive stimuli					
HTR3B	11	9	0.1	1.4	Encodes homologous ligand-gated ion channels that may be involved in psychiatric disorders. Risk allele in rs2276307 associated (p=0.007) with 14% higher risk of myalgia in 195 patients (39 definite myalgia, 12 probable myalgia and 144 no myalgia) taking atorvastatin (10mg-80mg/d) or simvastatin (5mg-80mg/d).[10]
HTR7	10	0			Encodes a serotonin receptor that is a possible schizophrenia susceptibility factor, with additional roles in pain. Risk allele in rs1935349 associated (p=0.026) with 13% higher risk of myalgia in 195 patients (39 definite myalgia, 12 probable myalgia and 144 no myalgia) taking atorvastatin (10mg-80mg/d) or simvastatin (5mg-80mg/d).[10]

Supplementary Table 5 (continued)

Inherited metabolic myopathies					
CPT2 (carnitine palmitoyltransferase 2)	1	5	0.1	1.8	Associated with carnitine palmitoyltransferase II deficiency. 3.6% of 110 cases with muscle symptoms while taking statins were CPTII deficiency carriers compared to 0% of the statin-treated control group.[9]
PYGM	11	2	0.5	1.3	Associated with myophosphorylase deficiency (McArdle disease; glycogen storage disease type V). 12.3% of 110 patients with muscle symptoms while taking statins were carriers of McArdle disease R49X mutation, 0.9% had McArdle disease compared to 0.9% in the treated controls.[9]
AMPD1	1	4	0.5	1.2	Associated with myoadenylate deaminase defiency. Homozygosity for mutations in this gene was found in 7 of 110 (6.5%) drug-induced myopathies, compared to 2 of 116 (1.7%) asymptomatic statin treated subjects.[9]
RYR1 (ryanodine receptor 1)	19	20	0.06	1.5	Primary gene responsible for central core disease, which is a congenital myopathy predisposing to susceptibility for malignant hyperthermia (pharmacogenetic disorder of skeletal muscle after exposure to anesthetics).[27]
COQ2	4	3	0.1	1.6	CoQ10 deficiency is the most common defect found in muscle. CoQ10 is essential in mitochondria for the transport of electrons through the respiratory chain. In a study of 133 myopathy cases compared to 158 matched controls taking statin, the OR for rs4693075 was 2.3 (1.1 to 4.8) in a recessive model (p=0.019) and 2.6 (1.3 to 5.3) for a haplotype with rs6535454 (recessive; p=0.007).[8]
ACADVL/ VLCAD	17	2	0.4	1.5	Inherited rhabdomyolysis gene. No difference in genotype frequencies in 10 Japanese patients with abnormal increases in plasma creatine kinase or severe muscle complaints taking simvastatin or atorvastatin compared to 26 control patients also receiving statins.[2]

Supplementary Table 5: Genes previously reported to be associated with statin-induced myopathy, statin intolerance or statin pharmacokinetics; and associations with SNPs in these genes (+/- 10kb) with myopathy in SEARCH

Supplementary Table 6

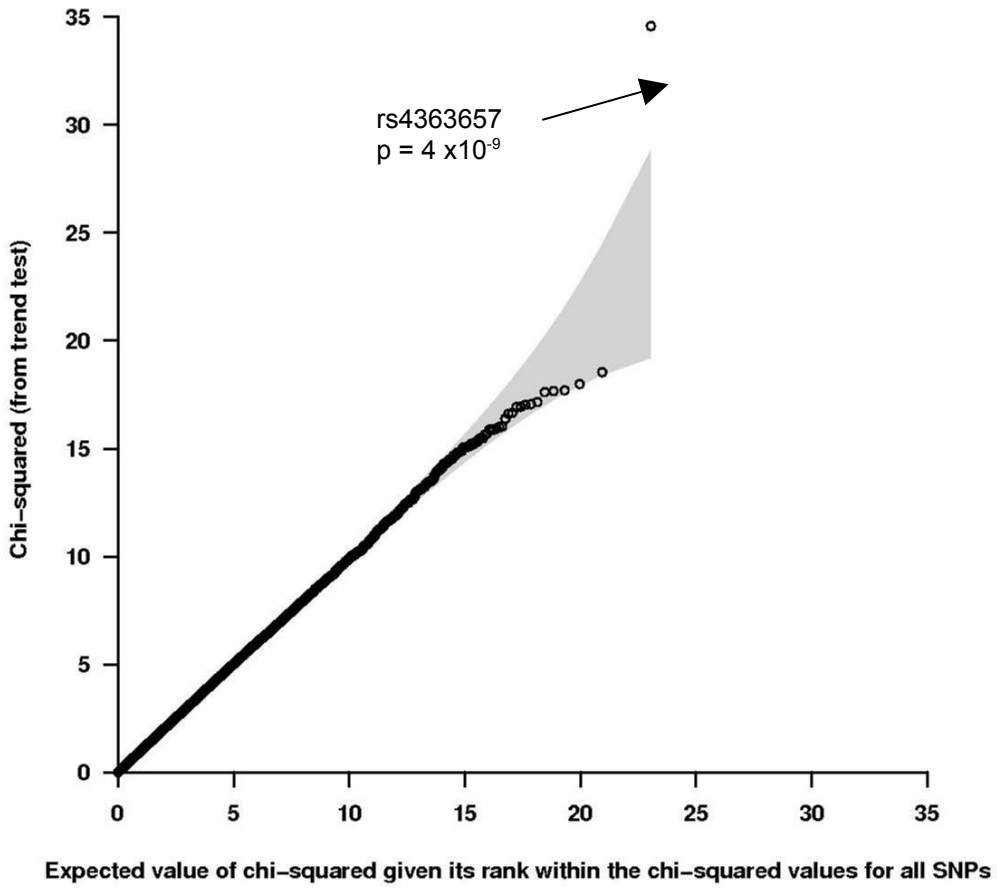
Study (population)	*Statin and dose*	*Number of subjects*	*Pharmacokinetic variable*	*Mean (SD) of pharmacokinetic variable by rs4149056 genotype*			*P-value for trend or for TT vs CT or CC*	*% increase (95% CI) per C allele*
				TT	**CT**	**CC**		
Area under the plasma concentration-time curve (ng.h/ml)††								
Lee 2005** [15] (white)	Rosuvastatin 40mg	25+ 6+5	Rosuvastatin AUC (0-time last obs. conc.)	192 (75)	204 (113)	416 (228)	>0.05, <0.05	39 (14, 69)
Lee 2005** [15] (Malay)	Rosuvastatin 40mg	26+ 9+0	Rosuvastatin AUC (0-time last obs. conc.)	400 (238)	454 (251)		Not reported	14 (-27, 77)
Lee 2005** [15] (Chinese)	Rosuvastatin 40mg	29+ 6+0	Rosuvastatin AUC (0-time last obs. conc.)	485 (181)	579 (229)		Not reported	19 (-14, 66)
Lee 2005** [15] (Asian-Indian)	Rosuvastatin 40mg	30+ 5+0	Rosuvastatin AUC (0-time last obs. conc.)	348 (185)	378 (187)		Not reported	9 (-34, 79)
Pasanen 2006 [20] (Caucasian)	Simvastatin 40mg	16+11+4	Simvastatin (lactone) AUC(0-∞)	26.4 (10.5)	31.9 (17.6)	37.9 (14.7)	Not incl as same study as next row.	
Pasanen 2006 [20] (Caucasian)	Simvastatin 40mg	16+11+4	Simvastatin acid AUC(0-∞)	16.4 (6.4)	20.1 (10.3)	52.7 (12.5)	<0.001 for CC vs TT or TC	61 (30,100)
Pasanen 2007 [14] (white)	Atorvastatin 20mg	16+12+4	Atorvastatin AUC(0-∞)	24.2 (8.6)	36.2 (20.3)	59.3 (17.4)	0.046, <0.001	54 (24 , 92)
Pasanen 2007 [14] (white)	Rosuvastatin 10mg	16+12+4	Rosuvastatin AUC (0-∞)	35.0 (18.1)	55.0 (22.7)	56.7 (5.1)	>0.05, 0.002	35 (8, 69)
Niemi 2006 [18] (white)	Fluvastatin 40mg	16+12+4	Fluvastatin AUC(0-∞)	422.7 (132.1)	479.5 (215.0)	503.4 (251.2)	>0.05, p>0.05	10 (-9, 34)
Niemi 2006 [18] (white)	Pravastatin 40mg	16+12+4	Pravastatin AUC (0-∞)	150.3 (78.1)	164.8 (85.7)	287.4 (102.9)	0.04: CT vs CC 0.02: TT vs CC	29 (1, 66)
Niemi 2004 [17] (white)	Pravastatin 40mg	28+11+2	Pravastatin AUC(0-12)	89.5(64.0)	184.7(105.0)	140.1 (39.3)	0.003, 0.64	62 (13, 132)
Mwinyi 2004† [19] (white)	Pravastatin 40mg	20+10+0	Pravastatin AUC(0-6)	94.7 (54.6)	163.0 (64.6)	-	0.006	72 (16, 157)
Nishizato 2003† [12] (Japanese)	Pravastatin 10mg	12+10+1	Pravastatin AUC(0-∞)	50.6 (19.9)	66.9 (21.8)	111.8 (0)	Not reported	38 (5, 82)
Maeda 2006† [13] (Japanese)	Pravastatin 10mg	12+11+0	Pravastatin AUC(0-24)	58.2 (21.4)	55.1 (20.4)	-	Not reported	-5 (-30, 28)
Chung 2005† [16] (Korean)	Pitavastatin 1-8mg	13+11+0	Dose-normalised AUC (0-∞) (ng.h/ml/mg)	49.6 (12.7)	68.1(16.3)		0.004	37 (13, 68)
Overall*			**% increase (95% CI)**	**vs TT group:**	**28 (17, 40)**	**97 (64, 137)**	**Per C allele:**	**34 (25, 44)**

Elimination of statin: renal or non-renal clearance ($L.kg^{-1}h^{-1}$; unless stated)								
Nishizato 2003† [12] (Japanese)	Pravastatin 10mg	12+10+1	Pravastatin non-renal	1.88 (0.59)	1.08 (0.34)	0.28 (0)	Not reported	-51 (-61, -38)
Nishizato 2003† [12] (Japanese)	Pravastatin 10mg	12+10+1	Pravastatin renal clearance	0.44 (0.09)	0.46 (0.13)	0.51 (0)	Not reported	5 (-12, 24)
Maeda 2006† [13] (Japanese)	Pravastatin 10mg	12+11+0	Pravastatin renal clearance (L/h)	17.1 (6.1)	14.6 (3.0)	-	Not reported	-15 (-33, 8)

Supplementary Table 6: *In vivo* studies of the association between statin elimination and *SLCO1B1* rs4149056 SNP

* For the overall result, there was no evidence of heterogeneity between studies in log mean AUC by genotype (p=0.7 for interaction term for study and number of C alleles).
** SD for AUC estimated from geometric mean and confidence intervals.
† Results reported only for multi-marker haplotypes (4 of the 5 studies mentioned in Discussion of main paper). Genotype mean and SD estimated by combining the relevant haplotypes.
†† Area under the plasma concentration-time curve between $time_1$ and $time_2$ (in hours) denoted by AUC ($time_1$-$time_2$)

Supplementary Figure



Supplementary Figure: Trend test chi-squared values for each measured SNP versus expected values given rank (quantile-quantile plot)

The shaded area shows the 95% confidence limits of the expected distribution under the null hypothesis of no association at any locus. A small number of points outside the bounds of the shaded area may indicate a true disease association, while inflation of the observed chi-squared statistics within the tail-end of the distribution may indicate SNP allele frequency differences between case and control groups due either to true disease association or to population substructure and artificial associations.

Supplementary Methods

Resequencing of SLCO1B1 and CYP3A4 genes: This was performed using PCR amplicons generated by PRIMER3 to cover the whole set of exons and parts of the introns (15 fragments for *SLCO1B1*; 18 fragments for *CYP3A4*). PCR was undertaken in 8-uL reaction volumes using 1 unit of Taq DNA polymerase (Abgene, Epsom, UK) and 20ng of genomic DNA (primer sequences in Supplementary Methods Tables 1a & b). PCR products were purified using Bio-gel P100 Gel (Bio-Rad Inc, Hercules, CA, USA) and sequenced using the Bigdye Terminator cycle sequencing chemistry method (Applied Biosystems, Palo Alto, CA, USA). Reactions were purified using Sephadex G-50 Superfine (Amersham Biosciences, Uppsala, Sweden) before applying the products to ABI 3730 DNA analysers. Detection of genetic variants was performed with the Genalys program (http://www.cng.fr).

Quantile-quantile plots: In a quantile-quantile plot, a set of independent observations $Y=\{y_1, y_2, \ldots, y_n\}$ sampled from a distribution with cumulative distribution function $F(y)$ ($_1^2$ in the present context) is first ordered ($y_{(1)} \leq y_{(2)} \leq \ldots \leq y_{(n)}$) and then $y_{(i)}$ is plotted against the expected value of $y_{(i)}$, which is approximated by $F^{-1}([i-0.5]/n)$. $F(y_{(i)})$ follows a beta distribution, with shape parameters i and $(n-i+1)$.[28] Expected values and 95% confidence limits were calculated point by point using standard statistical functions. (This follows the approach used by the Wellcome Trust Case Control Consortium which noted that these point by point estimates may slightly underestimate the confidence limits.[29]) In the present genome-wide association study, comparison of the chi-squared value for each SNP versus its expected value given rank order followed the expected distribution under the null hypothesis of no association at any locus, and the median of the 316,184 chi-squared values was not statistically different from the expected value for null SNPs. Hence, it was not considered necessary to adjust the associations for genomic control by attributing extra variance in the test statistics to population substructure.[30]

Cumulative and attributable myopathy risk by rs4149056 genotype: Simple life-table analysis of genotyped cases and controls does not suffice to estimate the cumulative myopathy risk because the controls were selected for not having developed myopathy. Instead, it was estimated as follows among the 5761 participants with European ancestry not on amiodarone at baseline who had been allocated 80mg simvastatin daily. First, the cumulative probability of still being exposed at time t was estimated from a standard Kaplan-Meier life-table analysis,[31] with death or stopping study 80mg simvastatin daily (defined as when supply permanently ceased) as endpoints and with censoring when any myopathy occurred (which was regarded as being prior to stopping treatment if both occurred on the same day). Denote this probability by $e(t)$, and define:

p_g = initial proportion with each genotype (g), taken to be in Hardy-Weinberg equilibrium, with C allele frequency of 0.146;

$n_g(t_i)$ = number of myopathy cases occurring in subjects of each genotype at each time (t_i) that any myopathy cases occurred; and

$S_g(t)$ = probability of being free of myopathy at time t, given genotype.

Among the 5761 participants with European ancestry, 75/85 (0.882) of the myopathy cases were successfully genotyped. The cumulative myopathy risk was calculated by a life-table analysis in which the genotyped myopathy cases were the endpoints and the number of participants of genotype *g* at risk at time t_i were:

$$5761 \times 0.882 \times p_g \times e(t_i) \times S_g(t_{i-1})$$

Risk attributable to the genotypes CT and CC was calculated as the excess cumulative myopathy risk in these genotypes over that for the TT genotype.

Coverage of the genome-wide screen: Genomic coverage of the Illumina HumanHap300 panel for common SNPs (at $r^2 \geq 0.8$) in people with European ancestry has been estimated in HapMap CEU samples to be 75%.[32] Application of this approach to the similar HumanHap300-Duo panel with allowance for the genotyping failure rate in the present study yields an estimated coverage of 74%.

Supplementary Methods Table 1a

Exon number	*Name*	*Sequence*	*Usage*
Exon1	SLCO1B1_P001_PF	AATGGTCTTGCAGTTAATTGGG	PCR
	SLCO1B1_P001_PR	TCCCTTCACCCTGTATCAAACT	PCR
	SLCO1B1_P001_SF	TGGCAACTGGAGTGAACTCTT	sequencing
	SLCO1B1_P001_SR	TTCCCTCTACTCCCACCCTT	sequencing
Exon2	SLCO1B1_P002_PF	TCTACTCTGTGCAAGGGGCT	PCR
	SLCO1B1_P002_SF	TCCAGCATTGACCTAGCAGA	sequencing
	SLCO1B1_P002_SR	TCGTGATCAATCCAAAACCA	PCR and sequencing
Exon3	SLCO1B1_P003_PF	TGTTTTTCAGCTGGCTTCCT	PCR
	SLCO1B1_P003_PR	GGTCTAACGTAGGTTGCTCTGAA	PCR
	SLCO1B1_P003_SF	AGAATGTACTGCCACTCCCCT	sequencing
	SLCO1B1_P003_SR	TATTGCCAAATTGCCTGTGA	sequencing
Exon4	SLCO1B1_P004_PF	ATGCCATGGTTTATTCTTTTTCA	PCR
	SLCO1B1_P004_PR	TAAGTTTCTCCCCCATGTGC	PCR
	SLCO1B1_P004_SF	TGTCTTTGAGGGAAGGCACT	sequencing
	SLCO1B1_P004_SR	GCTTCAGTGAAATGATGGGAA	sequencing
Exon5	SLCO1B1_P005_PF	ATAACCCACTTAGCCTGGGG	PCR
	SLCO1B1_P005_PR	GCTGCCTGTGTGTTCTCAAA	PCR
	SLCO1B1_P005_SF	GGGGAAGATAATGGTGCAAA	sequencing
	SLCO1B1_P005_SR	CGGCAGGTTTATCATCCAGT	sequencing
Exon6	SLCO1B1_ex6_PF	TTGTCAAAGTTTGCAAAGTG	PCR and sequencing
	SLCO1B1_ex6_PR	GCCAAGAATGCATGGTTCTT	PCR and sequencing
Exon7	SCLO1B1_P127_PF	TTGTATGATCACTTTCCCTTTGTC	PCR and sequencing
	SCLO1B1_P127_PR	CACATCAACATCCAAGCCAC	PCR and sequencing
Exon8	SLCO1B1_P007_PF	TTCATTGCTGACCCTTTCTTG	PCR
	SLCO1B1_P007_PR	GCATCACCCACTAGGTTCTTG	PCR
	SLCO1B1_P007_SF	AGCCATCAAGTGCACACAAG	sequencing
	SLCO1B1_P007_SR	TTTTGTTGGTTTCTCCCTGC	sequencing
Exon9	SLCO1B1_P008_PF	AAAACAGCACTTACGTATGACCC	PCR and sequencing
	SLCO1B1_P008_PR	TGCAACTTCAAATGCAGAGC	PCR and sequencing
Exon10	SLCO1B1_P009_PF	CAAACACTGCATGTTCCCAC	PCR
	SLCO1B1_P009_PR	TCCATCCAAGATTACAGTGGTG	PCR
	SLCO1B1_P009_SF	AGCAAGGGGAGGAAGAACAT	sequencing
	SLCO1B1_P009_SR	TTTCTCTAAGCCTTACTTTTCCCA	sequencing
Exon11	SLCO1B1_P010_PF	CAGTGAGCTGAAAGGAATGTCA	PCR
	SLCO1B1_P010_PR	AGGAAGTGCTGACAATGGGT	PCR
	SLCO1B1_P010_SF	GGCAAAGATGGAGAGCGTAA	sequencing
	SLCO1B1_P010_SR	AGAAAAACCTGATTGTGCCCT	sequencing
Exon12	SLCO1B1_P011_PF	GGATAATTCCTCCTCAGGGC	PCR
	SLCO1B1_P011_PR	TGGAATGTTATCAAATGGAGCA	PCR
	SLCO1B1_P011_SF	TCTGCAGAGGGTAAAAGGGA	sequencing
	SLCO1B1_P011_SR	TACCCTGAGAGATGCAAGGC	sequencing
Exon13	SCLO1B1_P151_PF	GGCCATTCAACTGTGAGCTT	PCR and sequencing
	SCLO1B1_P151_PR	TAGGCCCTTCACTCTGCCTA	PCR and sequencing
Exon14	SLCO1B1_25	TTGGGTAGATGCAGAACAAA	PCR and sequencing
	SLCO1B1_26	TGACATGAGGAGAGTTTTGG	PCR
Exon15	SLCO1B1_P014_PF	GAAGGCCAGAGGCAACTAGA	PCR
	SLCO1B1_P014_PR	GTGGGAAAGCTGCAAAAGAA	PCR

Supplementary Methods Table 1a (continued)

SLCO1B1_P014_SF1	*CGTTATGCCCCAATAAAAAGAA*	*sequencing*
SLCO1B1_P014_SR1	AGCTCCTCCTTTTTAACCTCTACC	sequencing
SLCO1B1_P014_SF2	GCTGGGGCAGATAGTGAAAC	sequencing
SLCO1B1_P014_SR2	GCGGCAAATGATCTAGGAAA	sequencing

Supplementary Methods Table 1a: Oligonucleotides used for resequencing *SLCO1B1* gene

Exon number	*Name*	*Sequence*	*Usage*
Exon1	CYP3A4ex1_PF	CCTTGGACTCCCCAGTAACA	PCR
	CYP3A4ex1_PR	TCCCACCAGTGAGAGGATTC	PCR
	CYP3A4ex1_SF	CCAACTTCCAAGGTGGAGAA	sequencing
	CYP3A4ex1_SR	CACCATGCCCAGCTAATTTT	sequencing
Exon2	CYP3A4ex2_PF	ACTGAGTGGCTGCAGTGATG	PCR
	CYP3A4ex2_SF	TTTTGGTGTCTCATGGTGGA	sequencing
	CYP3A4ex2_SR	TGTACCTTCCTGGGAACCTG	PCR and sequencing
Exon3	JF_51548DA05_F	AACACTGTGCATTCTCTTCTGATG	PCR and sequencing
	JF_51548DA05_R	GGCTGAGACTGTCCTCTGTGC	PCR and sequencing
Exon4	CYP3A4_P04_PF3	CTACTGTCATTTCTAACCATGG	PCR and sequencing
	CYP3A4_P04_PR3	GGACAGGATGAAGTGGACG	PCR and sequencing
Exon5	CYP3A4_P250_PF	CAGTGGACTACCCCTTGGAA	PCR and sequencing
	CYP3A4_P250_PR	CACCTGCTTGTCTGTCTCCA	PCR and sequencing
Exon6	CYP3A4_P501_PF	AAGTTGCATTACCACAGCCC	PCR and sequencing
	CYP3A4_P501_PR	CCAAGGGGTAGTCCACTGAA	PCR and sequencing
Exon7	CYP3A4ex7_SF	TTCCTATGATGGGCTCCTTG	PCR and sequencing
	CYP3A4ex7_SR	TTGTGACAGGGGGCTGATAG	PCR and sequencing
Exon8	CYP3A4ex8_PF	CCCTCTGAGCACTTCCTTTG	PCR
	CYP3A4ex8_PR	AGGTGGCCTGATAGGGACTT	PCR
	CYP3A4ex8_SF	AAGGCAAAGAGATTAGGGCA	sequencing
	CYP3A4ex8_SR	CAAACCCCACTTTCTGCATT	sequencing
Exon9	CYP3A4ex9_PF	AATGCAGAAAGTGGGGTTTG	PCR
	CYP3A4ex9_PR	TCAGAGGTTTTCCCCACAAG	PCR
	CYP3A4ex9_SF	AAGTCCCTATCAGGCCACCT	sequencing
	CYP3A4ex9_SR	AGGCTGAGAATTGGCATTTG	sequencing
Exon10	CYP3A4ex10_SF	GACCTTGGGGAAAACTGGAT	PCR and sequencing
	CYP3A4ex10_SR	CAGAGCCAGCACGTTTTACA	PCR and sequencing
Exon11	JF_50694BF05_F	CTTCCCGAATGCTTCCCAC	PCR
	JF_50694BF05_R	GGCAGAATATGCTTGAACCAGG	PCR
	JF_50694BF05_I_F	GCTTCCCACCTTCATAACT	sequencing
	JF_50694BF05_I_R	GCTTGAACCAGGCTGGTTCAGG	sequencing
Exon12	JF_50928BC05_F	GTGGACACATCACCACCCTG	PCR and sequencing
	JF_50928BC05_R	GCCTAATTGATTCTTTGGCCC	PCR and sequencing
Exon13	JF_50694BG05_F	TGCTCTCACTGTCCAATCTTCAC	PCR
	JF_50694BG05_R	TCACACTGATTTGGTCACCTCC	PCR
	JF_50694BG05_I_F	GTCCAATCTTCACACATCTTATA	sequencing
	JF_50694BG05_I_R	TTGGTCACCTCCTTTATATTCC	sequencing
	1576_P010_SF1	GTCCCCTCAACACTGAAGGA	PCR and sequencing
	1576_P010_PR	GCCAGGCTTGTCTTGAACTC	PCR
	1576_P010_SR1	TAGGATTACAGGCGTGAGCC	sequencing
	1576_P010_SF2	CTGTGCCTGAGAACACCAGA	sequencing
	1576_P010_SR2	TAGGATTACAGGCGTGAGCC	sequencing
	CYP3A4_P204_PF	ATGAAAGGAGATGGGCTGAA	PCR and sequencing
	CYP3A4_P204_PR	CACGGGACTATTTCCACCAC	PCR and sequencing
	CYP3A4_ex13fin_PF	AATCCACTGTGACTTTGCCC	PCR and sequencing
	CYP3A4_ex13fin_PR	CATGTGGGTTCTCCATACCC	PCR and sequencing

Supplementary Methods Table 1b: Oligonucleotides used for resequencing *CYP3A4* gene

Supplementary Appendix References

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