SUPPLEMENTAL MATERIAL

Top Heritable SNPs	**Protein Characteristics**		**FHS Discovery Cohort**		**Prior Chromosomal Position and Tissue Expression Data**				
SNP ID	**SOMAmer ID**	**SOMAmer Target Protein**	**P-Value**	**Estimated Heritability (h^2)**	**Predicted Location**	**eQTL Gene**	**eQTL P-Value**	**eQTL Tissue**	**eQTL Consortium**
rs740750	3459-49	Platelet derived growth factor receptor beta (PDGFRB)	**3.0E-300**	65.6%	PDGFRB intron.	**PDGFRB**	8.5E-29	Blood	MuTHER
rs6787861	2630-12	Interleukin 1 Receptor accessory protein (IL1RAP)	**1.8E-162**	46.8%	IL1RAP intron.	**IL1RAP**	6.9E-06	Transformed Fibroblasts	GTEx
rs11653614	4435-66	Ectonucleotide pyrophosphatase/phosphodiesterase family member 7 (ENPP7)	**1.8E-107**	38.4%	ENPP7 intron. rs8074547 ($r^2 = 0.94$) results in predicted pro:leu missense mutation in N-terminal signal sequence	**ENPP7**	7.3E-10	EBV transformed lymphocytes	GTEx
rs2519093	3470-1	E Selectin (SELE)	**1.6E-82**	31.7%	Different chromosome than SELE.	NA	NA	NA	NA
rs11582423	3366-51	Extracellular matrix protein 1 (ECM1)	**2.0E-76**	30.0%	ECM1 intron. rs3737240 ($r^2 = 0.95$) results in predicted thr:met missense mutation in ECM1. Rs13294 ($r^2 = 0.99$) also results in predicted gly:ser	NA	NA	NA	NA
rs704	3839-60	AH receptor interacting protein (AIP)	**6.3E-65**	27.0%	Different chromosome than AIP.	NA	NA	NA	NA
rs3869574	2687-2	Melanoma derived growth regulatory protein (MIA)	**5.2E-60**	25.9%	MIA intron. rs2230694 ($r^2 = 1.0$) results in predicted synonymous mutation in MIA.	**MIA**	5.0E-12	Nerve	GTEx
rs10445391	4913-78	C C motif chemokine 16 (CCL16)	**2.5E-67**	25.6%	CCL16 intron.	NA	NA	NA	NA
rs2041740	3446-7	Interleukin 18 receptor 1 (IL18R1)	**1.8E-57**	24.9%	IL18R1 intron.	**IL18R1**	9.6E-10	Burn exposed skin	GTEx
rs35647509	4559-64	Kynureninase (KYNU)	**2.8E-50**	22.4%	KYNU intron. rs9013 ($r^2 = 0.86$) results in predicted lys:glu missense mutation in KYNU.	NA	NA	NA	NA

Supplemental Table 1. Chromosomal position and tissue expression data for the top ten SNPs explaining heritability. Characteristics of the genomic location and selected prior expression data (if available) for the top ten SNPs with the highest estimated heritability (h^2). HaploReg v4.1 (Broad Institute, Boston, USA) was used to annotate genomic location prediction of each SNP and all variants in LD with $r^2 > 0.2$. GTEx Portal V6p (Broad Institute, Boston, MA) and Single Nucleotide Polymorphism Annotator SNIPA (HelmholtzZentrum, Munich, Germany) were used to annotate publicly-available expression data from GTEx and the Multiple Tissue Human Expression Resource Consortium (MuTHER).

Locus Characteristics				Protein Characteristics					FHS Discovery Cohort Correlations				MDCS Validation Cohort Correlations				Meta Analysis of FHS and MDCS			Prior Report in Literature				Annotation
Rank Order List	**Sentinel Variant**	**Variant Chromosomal Location**	**Variant Nearest Gene**	**SOMAmer Target Protein**	**SOMAmer Target UniProt ID**	**Context of Association (Chromosome)**	**Context of Association (<1Mb)**	**Context of Association (Closest Gene)**	**SOMAmer ID**	**P-Value**	**Beta**	**h^2**	**SOMAmer ID**	**N**	**P-Value**	**Beta**	**P-Value**	**Beta**	**N**	**Reported SNP**	**R^2**	**Reported Beta**	**Reported P-Value**	**pQTL Notes and Sentinel SNP Prior Associations**
1	rs2519093	chr9:136141870	ABO	- E Selectin	P16581		TRANS		- 3470 1	**1.6E-82**	1.10	31.7%	- 3470 1	1419	**8.5E-182**	1.01	**7.3E-262**	1.03	2178	rs651007	0.92	-0.94	1.2E-96	CAD (P=1.2E-11), MI (P=3.5E-17), DM2 (P=9.2E-5), Tot Chol (P=1.2E-26), LDL (P=1.2E-30)
2	rs8176672	chr9:136142185	ABO	Cadherin 5	P33151		TRANS		2819 23	**1.5E-35**	-1.13	16.6%	2819 23	1421	**1.3E-61**	-1.08	**2.6E-95**	-1.09	2180					LDL (P=3.2E-7)
3	rs112635299	chr14:94838142	SERPINA1	Alpha 1 antitrypsin	P01009	Same	CIS	Cognate Gene	3580 25	**7.0E-15**	1.41	7.2%	3580 25	1391	**4.0E-30**	1.33	**2.5E-43**	1.36	2150					CAD (P=3.9E-4)
4	rs217181	chr16:72114002	TXNL4B	Heparin cofactor 2	P05546		TRANS		3316 58	**4.6E-14**	-0.49	6.7%	3316 58	1421	**8.2E-19**	-0.41	**4.4E-31**	-0.44	2180	rs3852789	0.32	0.23	1.0E-04	Tot Chol (P=8.1E-31), Trigs (P=1.8E-4), LDL (P=1.1E-25)
5	rs41290120	chr19:45382675	NECTIN2	Apolipoprotein E	P02649	Same	CIS		2418 55	**2.2E-11**	1.50	5.5%	2418 55	1397	**4.9E-25**	1.01	**5.7E-34**	1.09	2156					CAD (P=1.4E-10), MI (P=2.6E-9)
6	*rs4846923*	*chr1:230307222*	*GALNT2*	*Neuropilin 1*	*O14786*		*TRANS*		*3214 3*	*2.4E-09*	*0.34*	*4.4%*	*5542-22*	*1318*	**4.6E-11**	*0.27*	**9.5E-19**	*0.30*	*2077*	*rs17315646*	*0.67*	*-0.22*	*8.4E-07*	Trigs (P=4.3E-14), HDL (P=8.3E-24)
7	*rs1320668*	*chr11:116967666*	*SIK3*	*Apolipoprotein E*	*P02649*		*TRANS*		*2418 55*	***4.3E-09***	*-0.50*	*4.3%*	*2418 55*	*1410*	*9.7E-04*	*-0.21*	*8.1E-10*	*-0.31*	*2169*					Tot Chol (P=2.5E-14), Trigs (P=1.6E-43), LDL (P=1.0E-5)
8	*rs635634*	*chr9:136155000*	*ABO*	*Hepatocyte growth factor receptor*	*P08581*		*TRANS*		*2837 3*	*3.0E-08 (1.1E-06)*	*0.38 (0.32)*	*3.8%*	*2837 3*	*1421*	**4.1E-20**	*0.39*	**7.7E-27**	*0.39*	*2180*	*rs651007*	*0.96*	*-0.44*	*3.3E-19*	DM2 (P=1.4E-4), Tot Chol (P=2.5E-35), LDL (P=1.8E-41)
9	*rs11682107*	*chr2:113835522*	*IL1F10*	*Interleukin 1 receptor type 1*	*P14778*	*Same*	*TRANS*		*2991 9*	*4.5E-08*	*0.29*	*3.8%*	*2991 9*	*1318*	*1.5E-03*	*0.12*	*7.4E-09*	*0.18*	*2077*	*rs6759676*	*0.90*	*-0.16*	*1.2E-04*	MI (P=3.4E-5)
10	rs740750	chr5:149515074	PDGFRB	Platelet derived growth factor receptor beta	P09619	Same	CIS	Cognate Gene	3459 49	**3.0E-308**	1.16	65.6%	3459 49	1421	**3.0E-308**	1.16	**3.0E-308**	1.16	2180	rs3776081	0.46	-0.96	3.3E-113	Evaluated by MR in Supplemental Figure 2
11	rs13469	chr17:26676135	POLDIP2	AH receptor interacting protein	O00170		TRANS		3839 60	**8.8E-53**	-0.73	23.0%	3839 60	1421	**1.2E-04**	-0.14	**4.1E-35**	-0.36	2180					Evaluated by MR in Supplemental Figure 2
12	rs72688441	chr1:46051053	NASP	Alcohol dehydrogenase [NADP(+)]	P14550	Same	CIS		4192 10	**5.5E-44**	1.65	20.0%	4192 10	1413	**1.9E-81**	1.19	**5.4E-121**	1.29	2172					Evaluated by MR in Supplemental Figure 2
13	rs6787861	chr3:190352527	IL1RAP	Interleukin 1 Receptor accessory protein	Q9NPH3	Same	CIS	Cognate Gene	2630 12	**1.8E-162**	-1.37	46.8%	2630 12	1153	**2.6E-200**	-1.37	**3.0E-308**	-1.37	1912	rs1024948	0.84	1.35	2.5E-165	
14	rs11653614	chr17:77703751	ENPP7	Ectonucleotide pyrophosphatase/phosphodiesterase family member 7	Q6UWV6	Same	CIS	Cognate Gene	4435 66	**1.8E-107**	-0.97	38.4%	4435 66	1356	**1.2E-262**	-0.99	**3.0E-308**	-0.98	2115					
15	rs11582423	chr1:150493925	FALEC	Extracellular matrix protein 1	Q16610	Same	CIS		3366 51	**2.1E-76**	0.89	30.0%	3366 51	1374	**8.3E-106**	0.72	**1.9E-178**	0.78	2133	rs13294	1.00	-0.85	7.7E-102	
16	rs3869574	chr19:41284915	RAB4B	Melanoma derived growth regulatory protein	Q16674	Same	CIS		2687 2	**5.2E-60**	-1.39	25.9%	2687 2	1418	**3.4E-120**	-1.31	**4.1E-178**	-1.33	2177					
17	rs10445391	chr17:34306106	CCL16	C C motif chemokine 16	O15467	Same	CIS	Cognate Gene	4913 78	**2.5E-67**	1.79	25.6%	4913 78	1368	**6.6E-222**	1.55	**2.8E-286**	1.59	2127	rs33995560	0.82	-1.39	1.9E-95	
18	rs2041740	chr2:102989734	IL18R1	Interleukin 18 receptor 1	Q13478	Same	CIS	Cognate Gene	3446 7	**1.8E-57**	-0.85	24.9%	3446 7	1330	**1.3E-136**	-0.89	**4.9E-192**	-0.88	2089	rs2058622	1.00	1.00	9.0E-108	
19	rs35647509	chr2:143808067	KYNU	Kynureninase	Q16719	Same	CIS	Cognate Gene	4559 64	**2.8E-50**	0.95	22.4%	4559 64	1351	**1.0E-111**	1.03	**7.3E-160**	1.00	2110	rs9013	1.00	-1.05	1.0E-81	
20	rs73707827	chr7:83039780	SEMA3E	Semaphorin 3E	O15041	Same	CIS	Cognate Gene	5363 51	**8.4E-40**	0.92	17.9%	5363 51	1421	**4.6E-124**	1.09	**4.6E-161**	1.04	2180	rs17284969	0.95	-1.07	2.4E-65	
21	rs10737680	chr1:196679455	CFH	Complement factor H	P08603	Same	CIS	Cognate Gene	4159 130	**2.33E-36 (8.6E-29)**	-0.61 (-0.59)	17.2%	4159 130	1421	**4.0E-48**	-0.50	**5.4E-82**	-0.54	2180	rs3753395	1.00	0.50	3.9E-36	
22	rs7024491	chr9:137775084	FCN2	Ficolin 2	Q15485	Same	CIS	Cognate Gene	3313 21	**7.4E-34**	0.59	16.1%	3313 21	1421	**2.4E-44**	0.51	**4.3E-76**	0.54	2180					
23	rs1102934	chr17:34389914	CCL18	C C motif chemokine 18	P55774	Same	CIS	Cognate Gene	3044 3	**1.9E-35**	-0.86	15.6%	3044 3	1421	**1.3E-89**	-0.97	**7.3E-123**	-0.93	2180	rs9904601	0.79	0.86	2.5E-43	
24	rs4549181	chr20:23728873	CST1	Cystatin SN	P01037	Same	CIS	Cognate Gene	5459 33	**1.6E-32**	0.63	15.3%	5459 33	1377	**2.0E-63**	0.67	**4.9E-94**	0.66	2136	rs2070856	0.31	-0.55	5.6E-19	
25	rs7207028	chr17:48916052	WFIKKN2	WAP, Kązal, immunoglobulin, Kunitz and NTR domain containing protein 2	Q8TEU8	Same	CIS	Cognate Gene	- 3235 50	**1.1E-29**	-0.58	14.0%	- 3235 50	1402	**5.6E-55**	-0.60	**7.1E-83**	-0.59	2161	rs3803884	0.94	0.56	1.4E-40	
26	rs9722289	chr9:136370287	TMEM8C	E Selectin	P16581		TRANS		3470 1	**2.0E-28**	4.51	13.4%	3470 1	1399	**1.1E-05**	0.47	**1.8E-12**	0.73	2158					
27	rs4549181	chr20:23728873	CST1	Cystatin SA	P09228	Same	CIS		4324 33	**7.7E-27**	0.57	12.6%	4324 33	1377	**1.2E-39**	0.54	**1.0E-64**	0.55	2136					
28	rs72702561	chr1:150685716	HORMAD1	Cathepsin S	P25774	Same	CIS		3181 50	**1.1E-25**	1.09	12.5%	3181 50	1385	**7.2E-42**	0.92	**2.0E-65**	0.97	2144	rs41271951	1.00	-0.96	4.1E-40	
29	rs73043837	chr6:169617889	THBS2	Thrombospondin 2	P35442	Same	CIS	Cognate Gene	3339 33	**9.1E-26**	-0.83	12.2%	3339 33	1421	**9.2E-47**	-0.80	**9.5E-71**	-0.81	2180					
30	rs151254127	chr1:150257775	C1orf54	Extracellular matrix protein 1	Q16610	Same	CIS		3366 51	**8.3E-25**	4.59	11.8%	3366 51	1299	**2.8E-08**	0.69	**4.9E-16**	0.97	2058					
31	rs6695321	chr1:196675861	CFH	Complement C1s subcomponent	P09871		TRANS		3590 8	**4.8E-24**	0.51	11.8%	3590 8	554	**2.7E-27**	0.60	**2.3E-49**	0.55	1313	rs10922096	0.60	-0.38	1.0E-21	
32	rs75776028	chr1:169653795	C1orf112	L Selectin	P14151	Same	CIS		4831 4	**5.7E-25**	0.55	10.9%	4831 4	1196	**1.0E-35**	0.55	**5.9E-59**	0.55	1955	rs12938	0.88	-0.49	4.5E-25	
33	1:46767127:TCTC_	chr1:46767127	LRRC41	Alcohol dehydrogenase [NADP(+)]	P14550	Same	CIS		4192 10	**2.3E-20**	-1.64	10.0%	4192 10	1267	**1.0E-23**	-0.90	**2.3E-39**	-1.05	2026					
34	rs2276109	chr11:102745791	MMP12	Macrophage metalloelastase	P39900	Same	CIS	Cognate Gene	4496 60	**1.4E-25**	0.68	9.9%	4496 60	1420	**5.8E-43**	0.67	**8.7E-67**	0.67	2179	rs17368582	1.00	-0.74	1.5E-37	
35	rs157594	chr19:45425175	APOC1P1	Apolipoprotein E (isoform E2)	P02649	Same	CIS		5312 49	**3.9E-20**	-0.99	9.9%	5312 49	744	**1.0E-09**	-0.28	**2.8E-20**	-0.39	1503					
36	rs11576766	chr1:9010984	CA6	Carbonic anhydrase 6	P23280	Same	CIS	Cognate Gene	3352 80	**1.1E-22**	0.45	9.5%	3352 80	1395	**1.1E-51**	0.50	**1.8E-72**	0.48	2154	rs6577541	0.49	0.24	3.7E-08	
37	1:27699670:AG_A	chr1:27699670	FCN3	Ficolin 3	O75636	Same	CIS	Cognate Gene	3811 1	**4.6E-19**	-1.89	9.2%	5462-62	1374	**1.1E-07**	-1.49	**6.1E-25**	-1.74	2133					
38	rs6445607	chr3:53877149	IL17RB	interleukin 17 receptor B	Q9NRM6	Same	CIS	Cognate Gene	5084 154	**1.3E-17**	-0.43	8.5%	5084 154	1418	**2.2E-31**	-0.45	**2.7E-47**	-0.44	2177	rs4453827	0.32	0.33	6.4E-11	
39	2:103221989:GTGCC	chr2:103221989		Interleukin 18 receptor 1	Q13478	Same	CIS		3446 7	**2.1E-16**	-0.68	8.1%	3446 7	883	**1.3E-18**	-0.53	**6.3E-33**	-0.58	1642	rs1016160	0.31	0.66	1.1E-29	
40	rs12134610	chr1:196422826	KCNT2	Complement factor H	P08603	Same	CIS		4159 130	**4.2E-16**	-1.50	8.0%	4159 130	1204	**7.1E-05**	-0.36	**1.1E-12**	-0.57	1963	rs10754196	0.30	0.32	5.4E-14	
41	rs72684498	chr1:45672811	ZSWIM5	Alcohol dehydrogenase [NADP(+)]	P14550	Same	CIS		4192 10	**3.2E-16**	3.07	8.0%	4192 10	1314	**2.1E-12**	1.29	**4.1E-23**	1.64	2073					
42	rs109467	chr7:83278893	SEMA3E	Semaphorin 3E	O15041	Same	CIS	Cognate Gene	5363 51	**2.7E-16**	-0.43	7.8%	5363 51	1389	**3.5E-22**	-0.36	**1.5E-36**	-0.38	2148	rs536299	0.90	0.47	2.2E-26	
43	rs77625270	chr19:8121189	CCL25	C C motif chemokine 25	O15444	Same	CIS	Cognate Gene	2705 5	**1.3E-15**	1.20	7.7%	2705 5	1402	**8.1E-64**	1.12	**1.1E-77**	1.14	2161	rs3848570	0.46	-0.92	7.6E-21	
44	rs9661107	chr1:150987886	PRUNE1	Cathepsin S	P25774	Same	CIS		3181 50	**1.1E-15**	0.76	7.7%	3181 50	1403	**2.7E-28**	0.75	**2.5E-42**	0.75	2162	rs12068365	0.77	-0.73	7.7E-23	
45	rs522162	chr6:31919917	CFB	Complement factor B	P00751	Same	CIS	Cognate Gene	4129 72	**8.6E-16**	-0.68	7.6%	4129 72	1421	**2.9E-28**	-0.75	**2.5E-42**	-0.72	2180					
46	rs72704686	chr1:150897800	SETDB1	Extracellular matrix protein 1	Q16610	Same	CIS		3366 51	**1.0E-14**	0.87	7.1%	3366 51	1395	**1.8E-14**	0.53	**3.7E-26**	0.62	2154					
47	rs10745925	chr12:102218899	GNPTAB	Cathepsin Z	Q9UBR2		TRANS		4971 1	**2.3E-14**	0.41	7.0%	4971 1	1412	**4.4E-20**	0.38	**8.4E-33**	0.39	2171	rs10860794	1.00	-0.35	1.4E-13	
48	rs17753556	chr14:95095434	SERPINA3	Alpha 1 antichymotrypsin	P01011	Same	CIS	Cognate Gene	2879 9	**3.1E-13**	0.50	6.5%	2879 9	1415	**1.1E-15**	0.37	**9.7E-27**	0.41	2174	rs6575449	1.00	-0.38	3.2E-12	
49	rs157594	chr19:45425175	APOC1P1	Apolipoprotein E (isoform E3)	P02649	Same	CIS		2937 10	**3.4E-13**	-0.80	6.5%	2937 10	744	**1.0E-09**	-0.28	**2.8E-20**	-0.39	1503					
50	rs141935877	chr1:150467096	TARS2	Cathepsin S	P25774	Same	CIS		3181 50	**3.2E-13**	0.84	6.4%	3181 50	1399	**5.0E-27**	0.73	**1.7E-38**	0.76	2158	rs11587606	0.48	-0.50	5.4E-15	
51	11:99047876:CT_C	chr11:99047876	CNTN5	Contactin 5	O94779	Same	CIS	Cognate Gene	3299 29	**5.5E-14**	-0.70	6.4%	3299 29	1421	**1.1E-23**	-0.63	**5.5E-36**	-0.65	2180	rs1893149	0.52	0.52	1.7E-10	
52	rs10006511	chr4:96558214	UNC5C	Netrin receptor UNC5C	O95185	Same	CIS	Cognate Gene	5139 32	**3.1E-14**	0.37	6.4%	5139 32	1402	**2.4E-08**	0.20	**2.1E-19**	0.26	2161	rs1485606	0.30	-0.19	4.1E-05	
53	rs3917256	chr2:102776855	IL1R1	Interleukin 18 receptor 1	Q13478	Same	CIS		3446 7	**6.9E-13**	-0.44	6.3%	3446 7	1342	**1.8E-19**	-0.40	**1.0E-30**	-0.41	2101	rs871659	0.90	0.34	3.9E-11	
54	rs10282458	chr7:150045302	LOC107986858	Retinoic acid receptor responder protein 2	Q99969	Same	CIS		3079 62	**4.0E-13**	-0.41	6.1%	3079 62	1421	**2.4E-30**	-0.46	**1.0E-41**	-0.45	2180	rs9640161	0.71	0.35	3.0E-16	

55	rs79427717	chr1:150203716	ANP32E	Cathepsin S	P25774	Same	CIS		3181 50	**2.2E-12**	1.07	6.0%	3181 50	1336	**8.4E-18**	0.75	**7.3E-28**	0.83	2095					
56	rs11679466	chr2:152142088	NMI	Tumor necrosis factor inducible gene 6 protein	P98066	Same	CIS		5036 50	**4.9E-12**	-0.35	5.7%	5036 50	1410	**1.8E-21**	-0.35	**6.4E-32**	-0.35	2169	rs289828	0.97	0.39	2.1E-21	
57	rs115204832	chr6:31704411	CLIC1	Complement C2	P06681	Same	CIS		3186 2	**9.7E-12**	1.56	5.7%	3186 2	1386	**4.6E-35**	1.69	**3.8E-45**	1.66	2145					
58	rs157594	chr19:45425175	APOC1P1	Apolipoprotein E (isoform E4)	P02649	Same	CIS		2938 55	**2.1E-11**	-0.74	5.5%	2938 55	744	**1.0E-09**	-0.28	**2.8E-20**	-0.39	1503					
59	rs2381409	chr9:35829390	FAM221B	Hemojuvelin	Q6ZVN8		TRANS		3332 57	**1.6E-11**	-0.35	5.4%	3332 57	1318	**5.9E-07**	-0.19	**1.1E-15**	-0.25	2077	rs2236293	0.40	-0.33	4.6E-14	
60	rs61765448	chr1:64611828	ROR1-AS1	Tyrosine protein kinase transmembrane receptor ROR1	Q01973	Same	CIS	Cognate Gene	2590 69	**2.4E-11**	0.43	5.4%	8474-6	1347	**7.9E-15**	0.38	**1.5E-24**	0.40	2106	rs1408416	0.91	-0.34	7.0E-09	
61	rs1864401	chr10:43605902	RET	Proto oncogene tyrosine protein kinase receptor Ret	P07949	Same	CIS	Cognate Gene	3220 40	1.8E-09	0.34	4.2%	3220 40	1406	**2.1E-24**	0.42	**5.0E-32**	0.39	2165	rs2505535	0.97	-0.43	2.8E-19	
62	17:26572852:T_TTT	chr17:26572852		WNT1 inducible signaling pathway protein 1	O95388		TRANS		3057 55	9.6E-09	-0.32	4.0%	3057 55	1324	**4.9E-21**	-0.34	**3.1E-28**	-0.34	2083	rs2239908	0.32	-0.29	1.1E-10	
63	rs10033900	chr4:110659067	CFI	Complement factor I	P05156	Same	CIS	Cognate Gene	2567 5	2.2E-09 (2.0E-09)	0.34 (0.30)	4.3%	2567 5	1421	**1.3E-16**	0.30	**2.1E-24**	0.31	2180	rs7439493	0.47	0.36	1.6E-17	
64	rs72676591	chr1:45436014	EIF2B3	Alcohol dehydrogenase [NADP(+)]	P14550	Same	CIS		4192 10	3.9E-10	1.48	4.8%	4192 10	1215	**5.9E-16**	0.81	**4.7E-23**	0.91	1974					
65	rs12983058	chr19:51642784	SIGLEC9	Sialic acid binding Ig like lectin 7	Q9Y286	Same	CIS		2742 68	3.7E-10	-0.39	4.9%	2742 68	1421	**4.5E-15**	-0.31	**1.9E-23**	-0.34	2180					
66	rs144769310	chr6:32133344	EGFL8	Advanced glycosylation end product specific receptor, soluble	Q15109	Same	CIS		4125 52	2.4E-09	0.71	4.4%	4125 52	1414	**1.3E-13**	0.65	**2.0E-21**	0.67	2173					
67	rs11640313	chr16:418462	MRPL28	Contactin 1	Q12860		TRANS		2974 61	**2.3E-11**	-0.36	5.3%	2974 61	1333	**2.0E-12**	-0.26	**1.1E-21**	-0.29	2092	rs12719801	0.41	-0.22	1.3E-06	
68	rs112211052	chr6:31397654	HCP5	Complement C2	P06681	Same	CIS		3186 2	4.1E-09	0.76	4.3%	3186 2	1386	**1.3E-11**	0.58	**6.4E-19**	0.63	2145					
69	rs8177107	chr7:142554145	EPHB6	Ephrin type B receptor 6	O15197	Same	CIS	Cognate Gene	5078 82	1.4E-08	0.40	3.9%	5078 82	1379	**2.2E-10**	0.30	**3.3E-17**	0.33	2138					
70	rs13132712	chr4:74345896	AFM	Afamin	P43652	Same	CIS	Cognate Gene	4763 31	5.4E-10	0.93	4.8%	4763 31	1381	**5.5E-10**	0.83	**1.9E-18**	0.87	2140					
71	20:60948294:ATC_A	chr20:60948294		Laminin	P25391		TRANS		2728 62	3.4E-10	-0.54	4.6%	2728 62	1146	**8.8E-10**	-0.28	**6.9E-17**	-0.34	1905					
72	rs1856746	chr1:207143422	FCAMR	Polymeric immunoglobulin receptor	P01833	Same	CIS		3216 2	**2.6E-10**	0.32	4.8%	3216 2	1421	**1.7E-09**	0.22	**1.0E-17**	0.25	2180	rs291083	0.85	-0.30	1.3E-11	
73	rs11623662	chr14:66021192	FUT8	Advanced glycosylation end product specific receptor, soluble	Q15109		TRANS		4125 52	4.3E-08	0.29	3.7%	4125 52	1412	**9.9E-09**	0.22	**3.5E-15**	0.25	2171	rs12882200	0.63	0.22	1.2E-07	
74	rs150845796	chr1:196884258	CFHR2	Complement factor H	P08603	Same	CIS		4159 130	3.7E-10	1.16	4.9%	4159 130	1205	**2.1E-08**	0.66	**5.8E-16**	0.81	1964					
75	11:126226554:GGAGT	chr11:126226554	ST3GAL4	Lymphatic vessel endothelial hyaluronic acid receptor 1	Q9Y5Y7	Same	TRANS		3206 4	1.2E-08	0.61	3.9%	3206 4	1412	**2.3E-08**	0.41	**4.6E-15**	0.47	2171					
76	rs805524	chr10:43384889		Proto oncogene tyrosine protein kinase receptor Ret	P07949	Same	CIS		3220 40	8.6E-09	0.36	3.9%	3220 40	1371	**3.7E-08**	0.27	**2.8E-15**	0.31	2130	rs2487917	0.50	-0.40	2.6E-10	
77	rs2506149	chr10:33480713	NRP1	Neuropilin 1	O14786	Same	CIS	Cognate Gene	3214 3	4.2E-08	0.29	3.7%	5542-22	1394	**6.6E-07**	0.19	**3.6E-13**	0.23	2153	rs2247383	0.78	-0.27	3.0E-10	
78	3:132391213:C_CAT	chr3:132391213	UBA5	C C motif chemokine 21	O00585		TRANS		2516 57	**3.3E-12**	-0.47	5.9%	2516 57	1391	8.7E-04	-0.18	**3.4E-12**	-0.29	2150					
79	rs11534419	chr9:136388223	TMEM8C	Cadherin 5	P33151		TRANS		2819 23	**8.1E-12**	-1.61	5.7%	2819 23	975	9.6E-04	-0.15	5.5E-06	-0.20	1734					
80	rs6679295	chr1:169522943	F5	Tissue factor pathway inhibitor	P10646		TRANS		3336 50	5.1E-10	-0.70	4.5%	3336 50	713	2.7E-03	-0.22	3.2E-09	-0.37	1472	rs4524	0.36	0.21	1.0E-05	
81	rs10816649	chr9:110981973	LOC105376214	Dickkopf like protein 1	Q9UK85		TRANS		3644 5	4.4E-08	-0.59	3.6%	3644 5	1416	6.2E-03	0.24	2.1E-01	-0.08	2175					
82	rs143618256	chr1:150031103	LOC105371427	Extracellular matrix protein 1	Q16610	Same	CIS		3366 51	**1.2E-14**	7.71	7.0%	3366 51	1327	1.3E-02	0.66	1.1E-05	1.13	2086					
83	12:7589946:ATATT	chr12:7589946	CD163L1	Glucose 6 phosphate isomerase	P06744		TRANS		4272 46	1.1E-08	-0.95	4.1%	4272 46	1408	1.4E-02	-0.24	5.5E-07	-0.42	2167	rs7485194	1.00	-0.72	5.4E-09	
84	rs79701073	chr9:116898329	COL27A1	Cystatin SN	P01037		TRANS		5459 33	3.2E-08	1.45	3.8%	5459 33	1387	2.8E-02	-0.30	5.5E-01	0.07	2146					
85	rs4733300	chr8:32016943	NRG1	Kynureninase	Q16719		TRANS		4559 64	2.9E-08	0.47	3.8%	4559 64	855	7.0E-02	-0.11	9.5E-02	0.08	1614					
86	rs150845796	chr1:196884258	CFHR2	Complement C1s subcomponent	P09871		TRANS		3590 8	2.3E-08	1.03	3.9%	3590 8	468	8.0E-02	0.28	7.2E-07	0.59	1227					
87	rs4403878	chr12:81985012	PPFIA2	Sonic hedgehog protein	Q15465		TRANS		2743 5	3.0E-08	-0.61	3.9%	2743 5	1359	1.1E-01	0.13	4.2E-02	-0.13	2118					
88	rs79701073	chr9:116898329	COL27A1	Cystatin SA	P09228		TRANS		4324 33	4.7E-08	1.42	3.6%	4324 33	1387	1.2E-01	-0.21	2.5E-01	0.14	2146					
89	rs8092427	chr18:42608214	SETBP1	Adiponectin	Q15848		TRANS		3554 24	2.2E-09	-0.58	4.0%	3554 24	954	1.4E-01	-0.09	1.2E-05	-0.22	1713					
90	rs9911014	chr17:26383960	NLK	AH receptor interacting protein	O00170		TRANS		3839 60	**7.2E-12**	0.45	5.7%	3839 60	1420	1.4E-01	0.07	2.3E-07	0.20	2179					
91	rs6076759	chr20:4947034	SLC23A2	Endothelial cell selective adhesion molecule	Q96AP7		TRANS		2981 9	2.0E-08	1.35	3.6%	2981 9	1164	1.6E-01	0.14	5.5E-04	0.32	1923					
92	rs73235337	chr13:77273301	KCTD12	Reticulon 4 receptor	Q9BZR6		TRANS		5105 2	2.1E-08	0.61	3.9%	5105 2	1415	1.7E-01	-0.10	4.4E-02	0.12	2174					
93	rs12285347	chr11:102396607	MMP7	Matrilysin	P09237	Same	CIS	Cognate Gene	2789 26	**3.1E-10**	0.32	4.4%	2789 26	1421	1.7E-01	0.05	1.9E-06	0.14	2180	rs7128808	0.32	-0.19	2.5E-05	
94	rs149923323	chr6:2711099	MYLK4	Wnt inhibitory factor 1	Q9Y5W5		TRANS		2848 2	4.7E-08	1.48	3.7%	2848 2	1320	1.9E-01	-0.20	1.1E-01	0.21	2079					
95	rs114805987	chr11:60200226	MS4A5	Ephrin A5	P52803		TRANS		2615 60	3.7E-08	1.92	3.8%	2615 60	1304	2.3E-01	-0.30	2.5E-02	0.46	2063					
96	rs12112554	chr7:135590210		Epidermal growth factor receptor	P00533	Same	TRANS		2677 1	3.4E-08	-2.32	3.2%	2677 1	1379	2.3E-01	0.19	3.9E-01	-0.13	2138					
97	rs390322	chr5:9390217	SEMA5A	Desmoglein 2	Q14126		TRANS		5071 3	3.9E-08	-0.29	3.8%	5071 3	554	2.4E-01	0.07	6.0E-04	-0.14	1313					
98	rs11733361	chr4:128672526	SLC25A31	Galectin 3 binding protein	Q08380		TRANS		5000 52	1.9E-08	-0.60	3.8%	5000 52	1390	2.5E-01	0.08	3.2E-02	-0.13	2149					
99	rs117955663	chr11:5786209	OR56B2P	Limbic system associated membrane protein	Q13449		TRANS		2999 6	4.0E-09	2.88	3.4%	2999 6	1388	2.5E-01	0.54	9.6E-07	1.66	2147					
100	rs11787241	chr8:19105847	LOC105379300	Alpha 1 antitrypsin	P01009		TRANS		3580 25	2.8E-08	-0.43	3.8%	3580 25	444	2.8E-01	-0.06	4.3E-05	-0.18	1203					
101	rs334516	chr7:47571488	TNS3	Antithrombin III	P01008		TRANS		3344 60	2.8E-08	-0.30	3.6%	3344 60	1263	3.4E-01	0.04	1.4E-02	-0.08	2022					
102	rs8042987	chr15:26179463	LOC100128714	Galectin 4	P56470		TRANS		2982 82	1.9E-08	0.39	3.8%	2982 82	1298	3.8E-01	-0.03	4.4E-02	0.07	2057					
103	rs75481816	chr5:114597748	PGGT1B	Coagulation Factor X	P00742		TRANS		4878 3	3.9E-09	1.66	4.2%	4878 3	1412	3.9E-01	0.41	3.6E-08	1.34	2171					
104	rs139504202	chr10:110097410		Insulin like growth factor binding protein 1	P08833		TRANS		2771 35	9.2E-09	-2.72	3.8%	2771 35	1382	4.1E-01	-0.21	5.0E-04	-0.79	2141					
105	7:57407593:TTCC_	chr7:57407593		Hemojuvelin	Q6ZVN8		TRANS		3332 57	2.6E-09	0.35	4.3%	3332 57	1362	4.5E-01	-0.03	4.6E-03	0.10	2121					
106	rs1439411	chr4:161340537		interleukin 17 receptor B	Q9NRM6		TRANS		5084 154	1.9E-08	-0.55	3.8%	5084 154	1416	4.5E-01	0.06	3.2E-03	-0.18	2175					
107	rs116932673	chr20:49328985	PARD6B	Dickkopf like protein 1	Q9UK85		TRANS		3644 5	4.0E-08	-2.13	3.6%	3644 5	1346	4.8E-01	-0.11	7.1E-03	-0.39	2105					
108	rs138414818	chr21:38962028	KCNJ6	Endothelial monocyte activating polypeptide 2	Q12904		TRANS		2714 78	3.5E-09	3.00	4.0%	2714 78	1374	5.3E-01	0.18	4.8E-04	0.88	2133					
109	8:79901168:A_AC	chr8:79901168		C C motif chemokine 18	P55774		TRANS		3044 3	3.3E-09	0.32	4.1%	3044 3	1353	5.4E-01	-0.02	3.9E-03	0.09	2112					
110	4:153885658:ATGGC	chr4:153885658	FHDC1	Vitamin K dependent protein S	P07225		TRANS		2700 56	1.5E-08	1.66	3.9%	2700 56	1331	5.5E-01	0.11	3.6E-04	0.56	2090					
111	rs11583804	chr1:2878366	ACTRT2	Complement C3	P01024		TRANS		2754 50	2.8E-08	0.53	3.8%	2754 50	1421	5.6E-01	0.02	9.5E-03	0.09	2180					
112	1:27450809:G_GA	chr1:27450809	SLC9A1	Ficolin 3	O75636	Same	CIS		3811 1	**1.5E-10**	-3.27	5.0%	5462-62	1319	5.9E-01	-0.09	9.2E-03	-0.44	2078					
113	rs75020762	chr13:49219796	CYSLTR2	Troponin I, cardiac muscle	P19429		TRANS		5441 67	3.0E-08	-0.65	3.9%	5441 67	1406	6.3E-01	0.05	1.2E-03	-0.25	2165					

114	*rs1558500*	*chr4:55482077*		*Cathepsin D*	*P07339*		*TRANS*		*3180 46*	*2.0E-08*	*-0.73*	*3.9%*	*5508-62*	*1421*	*8.5E-01*	*-0.02*	*5.1E-04*	*-0.27*	*2180*					
115	*rs71544591*	*chr7:158188449*	*PTPRN2*	*Serotransferrin*	*P02787*		*TRANS*		*4162 54*	*6.4E-09*	*1.34*	*4.0%*	*4162 54*	*1270*	*8.9E-01*	*0.02*	*6.1E-03*	*0.28*	*2029*					
116	*rs138015312*	*chr4:69512847*	*UGT2B15*	*Neurogenic locus notch homolog protein 1*	*P46531*		*TRANS*		*5107 7*	*3.9E-08*	*2.13*	*3.6%*	*5107 7*	*651*	*8.9E-01*	*-0.01*	*5.8E-01*	*0.03*	*1410*					
117	*rs10905367*	*chr10:8472876*		*Contactin 5*	*O94779*		*TRANS*		*3299 29*	*3.8E-08*	*-0.30*	*3.5%*	*3299 29*	*1394*	*9.0E-01*	*0.00*	*2.5E-03*	*-0.09*	*2153*					
118	*rs9516774*	*chr13:97518070*	*HS6ST3*	*Complement C2*	*P06681*		*TRANS*		*3186 2*	*4.7E-08*	*-0.30*	*3.7%*	*3186 2*	*1421*	*9.3E-01*	*0.00*	*2.4E-03*	*-0.09*	*2180*					
119	*rs56009545*	*chr13:106079978*		*Interleukin 1 Receptor accessory protein*	*Q9NPH3*		*TRANS*		*2630 12*	*4.3E-08*	*-0.43*	*3.6%*	*2630 12*	*1274*	*9.3E-01*	*0.00*	*1.2E-03*	*-0.15*	*2033*					
120	*8:38324424:ACC_A*	*chr8:38324424*	*FGFR1*	*Fibroblast growth factor receptor 1*	*P11362*	*Same*	*CIS*	*Cognate Gene*	*2424 69*	*1.1E-08*	*0.37*	*4.0%*	*5532-53*	*1037*	*9.5E-01*	*0.00*	*1.5E-03*	*0.12*	*1796*					

Supplemental Table 2. pQTLs identified through GWAS. Characteristics of the 120 pQTLs identified in the FHS discovery cohort and validated in the MDCS cohort are displayed. Chromosomal locations are based off of assembly GRCh37.p13. Bolded values denote Bonferroni-adjusted significance (FHS Offspring cohort and meta analysis P-value ≤ $5x10^{-8}$ / 156 tested proteins = 3.2 x 10^{-10}; MDCS validation P-value ≤ 0.05 / 120 = 4.1 x 10^{-4}). Variations in validation sample number in MDCS are due to missingness of genotypes. Values in parentheses reflect genotyping results when SNPs that were imputed from the Affymetrix array were available on the Illumina exome array. A rank order list of pQTLs of particular interest are presented in column A, based on annotations in Column Y, as well as association strength, validation, and heritability parameters. In columns U-X, reported sentinel SNPs (and variants in LD, r^2 ≥ 0.3) were queried against publicly-available data from three previous studies of human peripheral blood using a similar aptamer-based platform (Supplemental References 1-3). The reported SNP with the lowest P-value is shown. Although SNPs may have been detected in all three studies, all data from Columns U-X are from Supplemental Reference 3, since these had the lowest associated P-values, likely due to the comparatively large size of the study. Abbreviations: MAF: minor allele frequency; h^2: heritability; beta: estimated beta coefficient; MR: Mendelian Randomization.

pQTL		Target Protein Characteristics		FHS Discovery Cohort		MDCS Validation Cohort			CARDIoGRAMplusC4D Results	
									Coronary Artery Disease	Myocardial Infarction
Sentinel Variant	Variant Nearest Gene	SOMAmer Target Protein	Context of Association (<1Mb)	P-Value	Estimated Beta Coefficient	P-Value	Estimated Beta Coefficient	N	P-Value CAD	P-Value MI
rs2519093	ABO	E Selectin	TRANS	**1.6E-82**	1.10	**8.5E-182**	1.01	1419	**1.2E-11**	**3.5E-17**
rs41290120	NECTIN2	Apolipoprotein E	CIS	**2.2E-11**	1.50	**4.9E-25**	1.01	1397	**1.4E-10**	**2.6E-09**
rs112635299	SERPINA1	Alpha 1 antitrypsin	CIS	**7.0E-15**	1.41	**4.0E-30**	1.33	1391	**3.9E-04**	1.9E-03
rs11682107	IL1F10	Interleukin 1 receptor type 1	TRANS	**4.5E-08**	0.29	1.5E-03	0.12	*1318*	1.8E-03	**3.4E-05**

Supplemental Table 3. Overlap between pQTLs and CVD risk loci. Characteristics of pQTLs that overlap with risk loci for coronary artery disease (CAD) and myocardial infarction (MI) identified with Bonferroni-adjusted significance ($P \leq 0.05/120 = 4.2 \times 10^{-4}$) in the Coronary Artery Disease Genome-Wide Replication and Meta-Analysis plus the Coronary Artery Disease Genetics (CARDIoGRAMplusC4D) consortium data.

Exome Array Locus Characteristics									Protein Characteristics					FHS Discovery Cohort Correlations				MDCS Validation Cohort				
Exome ID	**SNP ID**	**Locus**	**Gene**	**Ref/Alt**	**Functional Consequence**	**Damaging**	**Loss of Function**	**MAF**	**SOMAmer Target Protein**	**SOMAmer UniProt ID**	**SNP/Gene Encoding Protein Relationship**			**SOMAmer ID**	**P-Value**	**Beta**	**h^2**	**SOMAmer ID**	**N**	**P-Value**	**Beta**	**h^2**
exm810762	rs61738953	Chr10:14862082	CDNF	C/G	Non-synonymous variant	TRUE	FALSE	4.9%	Cerebral dopamine neurotrophic factor	Q49AH0	Same Chr	CIS	Cognate	4962-52	**6.7E-20**	-1.06	21.8%	4962-52	1421	**8.9E-41**	-1.12	11.2%
exm533392	rs438999	Chr6:31928306	SKIV2L	A/G	Non-synonymous variant	FALSE	FALSE	9.6%	Complement factor B	P00751	Same Chr	CIS		4129-72	**8.6E-17**	0.74	11.1%	4129-72	1421	**1.5E-28**	0.78	8.0%
exm1313353	rs79254649	Chr17:34304605	CCL16	C/A	Non-synonymous variant	TRUE	FALSE	1.8%	C C motif chemokine 16	O15467	Same Chr	CIS	Cognate	4913-78	**9.2E-17**	-1.54	6.4%	4913-78	1421	**2.1E-45**	-1.58	12.1%
exm1553463	rs199825459	Chr20:57572709	CTSZ	A/G	Non-synonymous variant	TRUE	FALSE	0.5%	Cathepsin Z	Q9UBR2	Same Chr	CIS	Cognate	4971-1	**3.6E-12**	-2.48	17.4%	4971-1	1421	**1.0E-25**	-2.43	6.9%
exm683975	rs41341748	Chr8:16012594	MSR1	G/A	Stop site variant	TRUE	TRUE	0.9%	Galectin 3 binding protein	Q08380		TRANS		5000-52	**2.3E-11**	1.79	13.8%	5000-52	1421	**4.1E-20**	1.85	5.6%
exm533579	rs45531831	Chr6:31938120	DOM3Z	C/T	Splice Site variant	TRUE	TRUE	2.6%	Complement factor B	P00751	Same Chr	CIS		4129-72	**2.1E-09**	-0.94	6.1%	4129-72	1421	**1.9E-26**	-1.03	7.7%
exm687734	rs145284541	Chr8:22049596	BMP1	G/A	Non-synonymous variant	TRUE	FALSE	0.9%	Endothelial monocyte activating polypeptide 2	Q12904		TRANS		2714-78	**2.7E-08**	1.48	5.4%	2714-78	1421	6.1E-02	0.74	0.2%
exm793327	rs141547732	Chr9:136280025	REXO4	G/A	Non-synonymous variant	FALSE	FALSE	1.1%	Cadherin 5	P33151		TRANS		2819-23	**4.7E-08**	1.40	2.9%	2819-23	1421	2.1E-02	0.69	0.8%
exm533508	rs106287	Chr6:31935750	SKIV2L	G/A	Non-synonymous variant	TRUE	FALSE	3.6%	Complement factor B	P00751	Same Chr	CIS		4129-72	**5.1E-08**	0.76	3.1%	4129-72	1421	**5.4E-06**	0.61	1.4%
exm847175	rs143647630	Chr10:99531284	SFRP5	C/T	Non-synonymous variant	TRUE	FALSE	1.0%	C C motif chemokine 18	P55774		TRANS		3044-3	**5.8E-08**	1.43	11.8%	3044-3	1421	8.8E-01	-0.04	0.0%
exm534819	rs2070600	Chr6:32151443	AGER	C/T	Non-synonymous variant	TRUE	FALSE	4.9%	Advanced glycosylation end product specific receptor, soluble	Q15109	Same Chr	CIS	Cognate	4125-52	**1.3E-07**	-0.64	8.4%	4125-52	1421	**3.2E-14**	-0.66	4.1%
exm1403864	rs1128392	Chr19:2344022	SPPL2B	G/A	Non-synonymous variant	FALSE	FALSE	4.6%	Hepatocyte growth factor receptor	P08581		TRANS		2837-3	**2.4E-07**	0.64	8.8%	2837-3	1421	7.9E-01	-0.02	0.0%
exm1414617	rs2230199	Chr19:6718387	C3	G/C	Non-synonymous variant	FALSE	FALSE	20.5%	Complement C3b	P01024	Same Chr	CIS	Cognate	4480-59	**3.6E-07**	-0.32	5.2%	4480-59	1421	4.6E-03	-0.14	0.6%

Supplemental Table 4. pQTLs identified through exome array single variant analysis. Characteristics of the 13 pQTLs identified in the FHS discovery cohort that met a Bonferroni-adjusted level of significance (P-value ≤ 0.05/81,021 variants tested = 6.2 x 10^{-7}). Variants that validated with Bonferroni-adjusted levels of significance in MDCS are shown in bold (P ≤ 0.05 / 13 = 3.8 x 10^{-3}). Chromosomal locations are based off of assembly GRCh37.p13. Abbreviations: MAF: minor allele frequency; beta: estimated beta coefficient.

Exome Array Burden Analysis	**Protein Characteristics**					**FHS Discovery Cohort Results**			**MDCS Validation Cohort Results**			
Gene	**SOMAmer Target Protein**	**SOMAmer UniProt ID**	**Context of Association (Chromosome)**	**Context of Association (<1Mb))**	**Context of Association (Closest Gene)**	**SOMAmer ID**	**P-Value**	**Beta**	**SOMAmer ID**	**N**	**P-Value**	**Beta**
AKR1A1	Alcohol dehydrogenase [NADP(+)]	P14550	Same Chr	CIS	Cognate	4192-10	**3.4E-41**	-1.57	4192-10	1421	**1.8E-73**	-1.22
FCN2	Ficolin 2	Q15485	Same Chr	CIS	Cognate	3313-21	**3.2E-31**	-0.87	3313-21	1421	**1.0E-54**	-0.91
APOE	Apolipoprotein E (isoform E2)	P02649	Same Chr	CIS	Cognate	5312-49	**1.1E-28**	-1.12	5312-49	1421	**8.5E-31**	-0.85
APOE	Endothelial monocyte activating polypeptide 2	Q12904		TRANS		2714-78	**8.3E-21**	0.91	2714-78	1421	**2.9E-78**	1.38
APOE	Apolipoprotein E (isoform E3)	P02649	Same Chr	CIS	Cognate	2937-10	**1.7E-20**	-0.94	2937-10	1421	**1.6E-33**	-0.89
SERPINA1	Alpha 1 antitrypsin	P01009	Same Chr	CIS	Cognate	3580-25	**2.0E-20**	-1.53	3580-25	1421	**7.5E-11**	-0.62
CDNF	Cerebral dopamine neurotrophic factor	Q49AH0	Same Chr	CIS	Cognate	4962-52	**6.7E-20**	-1.06	4962-52	1421	**8.3E-36**	-1.11
APOE	Apolipoprotein E	P02649	Same Chr	CIS	Cognate	2418-55	**4.4E-19**	-0.91	2418-55	1421	**3.1E-36**	-0.93
APOE	Apolipoprotein E (isoform E4)	P02649	Same Chr	CIS	Cognate	2938-55	**6.8E-19**	-0.90	2938-55	1421	**8.3E-27**	-0.79
CCL16	C C motif chemokine 16	O15467	Same Chr	CIS	Cognate	4913-78	**9.2E-17**	-1.54	4913-78	1421	**5.8E-40**	-1.59
CTSZ	Cathepsin Z	Q9UBR2	Same Chr	CIS	Cognate	4971-1	**3.6E-12**	-2.48	4971-1	1421	**6.6E-20**	-1.84
CFB	Complement factor B	P00751	Same Chr	CIS	Cognate	4129-72	**5.4E-11**	-0.47	4129-72	1421	**3.1E-18**	-0.46
CERS2	Cathepsin S	P25774	Same Chr	CIS		3181-50	**7.9E-11**	-0.42	3181-50	1421	**6.9E-24**	-0.47
BNIPL	Cathepsin S	P25774	Same Chr	CIS		3181-50	**2.8E-10**	-0.41	3181-50	1421	**4.9E-11**	-0.29
DOM3Z	Complement factor B	P00751	Same Chr	CIS		4129-72	**6.6E-10**	-0.91	4129-72	1421	**7.0E-17**	-0.71
SURF6	Cadherin 5	P33151		TRANS		2819-23	**2.5E-09**	0.32	2819-23	1421	**6.8E-09**	0.23
GABPB2	Cathepsin S	P25774	Same Chr	CIS		3181-50	**2.0E-08**	-0.50	3181-50	1421	**3.8E-19**	-0.58
AGER	Advanced glycosylation end product specific receptor, soluble	Q15109	Same Chr	CIS	Cognate	4125-52	**2.9E-07**	-0.57	4125-52	1421	**2.3E-10**	-0.51
CAD	Glypican 3	P51654		TRANS		4842-62	**6.0E-07**	-0.83	4842-62	1421	8.9E-01	-0.02
SFRP5	C C motif chemokine 18	P55774		TRANS		3044-3	**8.6E-07**	1.25	3044-3	1421	3.8E-01	0.20
MYOM3	Netrin receptor UNC5D	Q6UXZ4		TRANS		5140-56	**1.3E-06**	-0.23	5140-56	1421	3.7E-01	-0.03
BMP1	Endothelial monocyte activating polypeptide 2	Q12904		TRANS		2714-78	**1.4E-06**	1.11	2714-78	1421	5.9E-01	0.13
SAT2	Tumor necrosis factor receptor superfamily member 17	Q02223		TRANS		2665-26	**1.4E-06**	-0.48	2665-26	1421	2.7E-01	0.07
AP2A2	Lymphocyte antigen 86	O95711		TRANS		3623-84	**1.5E-06**	2.30	3623-84	1421	6.5E-02	-0.82

FUT8	Advanced glycosylation end product specific receptor, soluble	Q15109		TRANS		4125-52	**2.2E-06**	-0.28	4125-52	1421	**1.5E-05**	-0.19
SLC39A2	Cystatin M	Q15828		TRANS		3303-23	**2.2E-06**	1.01	3303-23	1421	5.4E-01	-0.09
SEC24C	Iduronate 2 sulfatase	P22304		TRANS		3198-4	**2.2E-06**	-0.67	3198-4	1421	8.8E-01	-0.02
RRP36	Cystatin SA	P09228		TRANS		4324-33	**3.0E-06**	1.48	4324-33	1421	8.7E-01	0.06

Supplemental Table 5. pQTLs identified through exome array gene-based burden testing. Characteristics of the 28 pQTLs identified in the FHS discovery cohort using gene-based burden testing that reached a Bonferroni-adjusted level of statistical significance ($P \leq 0.05/13{,}008$ genes tested $= 3.8 \times 10^{-6}$). pQTLs that validated in MDCS with Bonferroni-adjusted significance are bolded ($P \leq 0.05 / 28 = 1.8 \times 10^{-3}$). Abbreviations: Beta: estimated beta coefficient.

Locus Characteristics							**FHS Discovery Cohort Results**			
Variant	**Variant Chromosomal Location**	**Ref/Alt**	**Variant Type**	**Closest Gene**	**Genes Within 60kb**	**SOMAmer Reagent**	**P-Value**	**Estimated Beta Coefficient**	**Estimated Heritability (h^2)**	**Observed Effect Allele Frequency**
rs740750	5:149515074	G/A	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	3.0e-316	1.16	65.6%	52.2%
rs2304058	5:149508544	C/G	SNP	PDGFRB	CDX1;CSF1R;PDGFRB	3459-49	7.2e-310	1.15	65.1%	52.1%
rs3816018	5:149508475	C/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB	3459-49	9.0e-310	1.15	65.0%	52.1%
rs2240781	5:149516480	C/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	1.8E-307	1.17	64.9%	52.3%
rs2240780	5:149513072	A/G	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	2.9E-278	1.12	62.6%	53.8%
rs4705415	5:149517235	A/G	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	5.3E-196	-1.06	54.0%	54.8%
rs11748255	5:149512042	A/G	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	2.0E-195	-1.06	54.0%	55.0%
rs1864972	5:149509270	A/G	SNP	PDGFRB	CDX1;CSF1R;PDGFRB	3459-49	2.2E-109	0.93	39.4%	61.1%
rs1864971	5:149509111	C/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB	3459-49	2.5E-109	0.93	39.4%	61.1%
NA	5:149519259	I/R	Insertion	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	9.1E-109	0.96	39.3%	66.6%
NA	5:149519261	I/R	Insertion	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	1.0E-108	0.96	39.3%	66.6%
NA	5:149519258	D/R	Deletion	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	9.9E-107	0.96	38.8%	67.2%
rs740751	5:149515888	T/C	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	3.0E-106	0.93	38.7%	62.1%
rs3776081	5:149532107	C/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	8.3E-97	0.93	36.5%	66.4%
rs3756312	5:149537194	G/A	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	4.0E-92	0.94	35.3%	66.7%
rs3776075	5:149518824	G/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	1.2E-74	0.83	30.6%	60.9%
rs3776078	5:149524179	G/C	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	3.2E-69	0.78	28.9%	61.4%
rs919751	5:149505489	G/A	SNP	PDGFRB	CDX1;CSF1R;PDGFRB	3459-49	1.7E-67	-0.79	28.4%	61.7%
rs10069910	5:149525169	C/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	4.9E-66	0.78	28.0%	61.5%
rs3756311	5:149537080	G/A	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	1.9E-65	0.82	27.8%	60.8%
rs9324641	5:149527844	C/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	1.9E-65	0.76	27.8%	61.3%
rs4583877	5:149531801	T/C	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	3.8E-65	0.78	27.7%	61.3%
rs3776079	5:149528319	A/G	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	6.4E-64	0.76	27.3%	61.7%
rs3828610	5:149535625	C/A	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	4.6E-62	0.78	26.7%	61.3%
rs2304061	5:149503670	A/G	SNP	PDGFRB	CDX1;CSF1R;PDGFRB	3459-49	2.0E-55	0.86	24.5%	75.3%
rs246391	5:149497177	C/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB	3459-49	2.2E-40	0.67	18.9%	56.0%
rs246396	5:149512678	C/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	4.8E-40	0.94	18.8%	82.3%
rs246388	5:149495395	C/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB	3459-49	4.8E-40	0.67	18.8%	56.1%
rs2229562	5:149495253	C/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB	3459-49	5.6E-40	0.67	18.8%	56.1%
rs246394	5:149498151	A/G	SNP	PDGFRB	CDX1;CSF1R;PDGFRB	3459-49	1.0E-39	0.72	18.6%	70.7%
rs246389	5:149496003	T/A	SNP	PDGFRB	CDX1;CSF1R;PDGFRB	3459-49	1.3E-38	0.67	18.2%	56.8%
rs11747083	5:149541826	C/T	SNP	CDX1	MK2A;CDX1;CSF1R;PDGFRB;SLC6	3459-49	5.0E-38	1.26	18.0%	78.2%
rs12515782	5:149519421	C/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	6.8E-38	0.75	17.9%	77.4%
rs11167495	5:149520580	C/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	8.4E-38	0.74	17.9%	77.4%
rs12523235	5:149519151	T/C	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	1.4E-37	0.74	17.8%	77.5%
rs11738390	5:149520206	T/G	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	2.7E-37	0.74	17.7%	77.5%
rs11738308	5:149520092	T/C	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	9.1E-37	0.74	17.5%	77.3%
rs2304060	5:149501751	C/A	SNP	PDGFRB	CDX1;CSF1R;PDGFRB	3459-49	3.0E-35	0.61	16.8%	54.2%
rs13171150	5:149523176	T/C	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	1.9E-34	0.71	16.5%	78.1%
rs7720799	5:149523777	T/C	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	2.2E-34	0.71	16.5%	78.1%
rs55915827	5:149521791	G/A	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	4.3E-34	0.98	16.3%	89.4%
rs10063714	5:149522627	A/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	4.5E-34	0.98	16.3%	89.4%
rs10066011	5:149523776	C/T	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	7.2E-34	0.97	16.2%	89.4%
rs72832182	5:149520435	T/C	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	7.7E-34	0.96	16.2%	89.3%
rs3776076	5:149520970	G/A	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	8.4E-34	0.96	16.2%	89.3%
rs67069374	5:149521256	C/G	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	8.5E-34	0.96	16.2%	89.3%
rs10062000	5:149525189	A/G	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	9.1E-34	0.97	16.2%	88.8%
rs6874642	5:149492296	T/C	SNP	CSF1R	CDX1;CSF1R;HMGXB3;PDGFRB	3459-49	2.4E-33	-0.83	16.0%	78.1%
rs4358508	5:149531832	G/A	SNP	PDGFRB	CDX1;CSF1R;PDGFRB;SLC6A7	3459-49	5.0E-33	0.93	15.9%	88.5%
rs7736526	5:149489242	T/C	SNP	CSF1R	CDX1;CSF1R;HMGXB3;PDGFRB	3459-49	8.5E-33	0.66	15.8%	68.7%

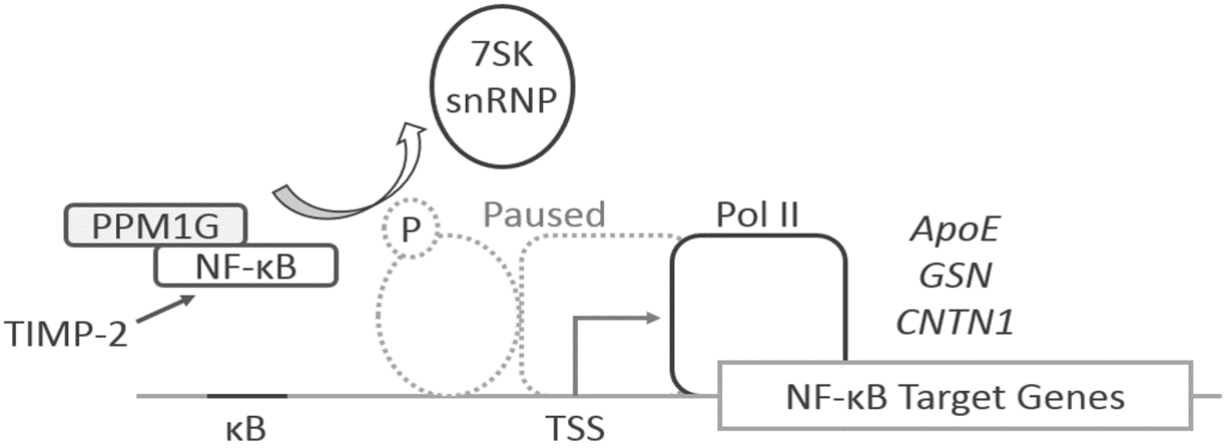
Supplemental Table 6. Representative GWAS data for PDGFRB. Characteristics of variant-protein associations for platelet derived growth factor receptor beta (SOMAmer 3459-49). This table has been abbreviated to include the top 50 variant-protein associations for ease of review. All associations with a P-value ≤ 1 x 10^{-3} are available on dbGaP.

Locus Characteristics							FHS Discovery Cohort Results			
Variant	Variant Chromosomal Location	Ref/Alt	Variant Type	Closest Gene	Genes Within 60kb	SOMAmer Reagent	P-Value	Estimated Beta Coefficient	Estimated Heritability (h^2)	Observed Effect Allele Frequency
rs6787861	3:190352527	A/C	SNP	IL1RAP	IL1RAP	2630-12	1.8E-162	-1.37	46.8%	83.1%
rs1024948	3:190347681	C/T	SNP	IL1RAP	IL1RAP	2630-12	4.3E-159	-1.34	46.3%	85.7%
NA	3:190348185	R/D	Deletion	IL1RAP	IL1RAP	2630-12	4.3E-159	-1.34	46.3%	85.7%
rs1058843	3:190347989	A/C	SNP	IL1RAP	IL1RAP	2630-12	4.3E-159	-1.34	46.3%	85.7%
rs7642607	3:190348298	G/A	SNP	IL1RAP	IL1RAP	2630-12	4.3E-159	-1.34	46.3%	85.7%
rs1024947	3:190347678	C/G	SNP	IL1RAP	IL1RAP	2630-12	4.3E-159	-1.34	46.3%	85.7%
rs7642797	3:190348515	G/A	SNP	IL1RAP	IL1RAP	2630-12	4.3E-159	-1.34	46.3%	85.7%
rs7611887	3:190347391	C/T	SNP	IL1RAP	IL1RAP	2630-12	4.4E-159	-1.34	46.3%	85.7%
rs1024944	3:190346723	G/A	SNP	IL1RAP	IL1RAP	2630-12	4.5E-159	-1.34	46.2%	85.7%
rs1024942	3:190346667	G/A	SNP	IL1RAP	IL1RAP	2630-12	4.5E-159	-1.34	46.2%	85.7%
rs1024941	3:190346658	T/A	SNP	IL1RAP	IL1RAP	2630-12	4.6E-159	-1.34	46.2%	85.7%
rs2361837	3:190346525	A/G	SNP	IL1RAP	IL1RAP	2630-12	4.6E-159	-1.34	46.2%	85.7%
rs2885373	3:190346468	T/C	SNP	IL1RAP	IL1RAP	2630-12	4.7E-159	-1.34	46.2%	85.7%
rs6444445	3:190346357	G/A	SNP	IL1RAP	IL1RAP	2630-12	4.7E-159	-1.34	46.2%	85.7%
rs6444444	3:190346231	A/G	SNP	IL1RAP	IL1RAP	2630-12	4.8E-159	-1.34	46.2%	85.7%
rs6444443	3:190346218	G/A	SNP	IL1RAP	IL1RAP	2630-12	4.8E-159	-1.34	46.2%	85.7%
rs6444442	3:190346060	A/G	SNP	IL1RAP	IL1RAP	2630-12	4.8E-159	-1.34	46.2%	85.7%
rs724609	3:190349078	G/A	SNP	IL1RAP	IL1RAP	2630-12	5.0E-159	-1.34	46.2%	85.7%
rs4686558	3:190349888	A/G	SNP	IL1RAP	IL1RAP	2630-12	5.9E-159	-1.34	46.2%	85.7%
rs1024943	3:190346702	T/C	SNP	IL1RAP	IL1RAP	2630-12	6.0E-159	-1.34	46.2%	85.6%
rs4543060	3:190354410	C/A	SNP	IL1RAP	IL1RAP	2630-12	1.0E-157	-1.36	46.0%	85.5%
rs724608	3:190348810	A/G	SNP	IL1RAP	IL1RAP	2630-12	3.3E-157	-1.34	46.0%	84.8%
rs11927365	3:190344128	G/A	SNP	IL1RAP	IL1RAP	2630-12	3.7E-155	-1.35	45.7%	85.6%
rs2361835	3:190344900	G/A	SNP	IL1RAP	IL1RAP	2630-12	8.4E-155	-1.33	45.6%	85.4%
rs2885372	3:190344871	C/T	SNP	IL1RAP	IL1RAP	2630-12	8.4E-155	-1.33	45.6%	85.4%
rs9813227	3:190340177	A/C	SNP	IL1RAP	IL1RAP	2630-12	1.2E-108	-1.15	37.2%	83.8%
rs2161060	3:190334615	C/T	SNP	IL1RAP	IL1RAP	2630-12	7.4E-105	-1.13	36.4%	83.8%
rs6793294	3:190328872	A/G	SNP	IL1RAP	IL1RAP	2630-12	1.9E-100	-1.11	35.4%	83.7%
rs6444438	3:190314871	C/T	SNP	IL1RAP	IL1RAP	2630-12	2.2E-93	-1.07	33.8%	83.6%
rs6444437	3:190314270	C/T	SNP	IL1RAP	IL1RAP	2630-12	2.7E-93	-1.07	33.8%	83.6%
rs6444436	3:190313582	C/T	SNP	IL1RAP	IL1RAP	2630-12	2.9E-93	-1.07	33.8%	83.6%
rs2193872	3:190313267	T/C	SNP	IL1RAP	IL1RAP	2630-12	1.9E-92	-1.06	33.6%	83.6%
rs6763761	3:190352514	G/T	SNP	IL1RAP	IL1RAP	2630-12	2.0E-90	-1.16	33.1%	74.4%
rs4624606	3:190354246	A/T	SNP	IL1RAP	IL1RAP	2630-12	2.3E-61	-0.81	25.1%	75.2%
rs7642899	3:190312715	C/G	SNP	IL1RAP	IL1RAP	2630-12	3.7E-59	-0.84	24.4%	78.3%
rs3773956	3:190311066	G/A	SNP	IL1RAP	IL1RAP	2630-12	7.6E-59	-0.84	24.3%	78.3%
rs6767500	3:190310701	A/C	SNP	IL1RAP	IL1RAP	2630-12	9.3E-59	-0.84	24.3%	78.2%
rs3773957	3:190310671	A/T	SNP	IL1RAP	IL1RAP	2630-12	1.0E-58	-0.84	24.3%	78.2%
NA	3:190350871	R/D	Deletion	IL1RAP	IL1RAP	2630-12	6.1E-58	-0.77	24.0%	72.3%
rs7628250	3:190308527	G/A	SNP	IL1RAP	IL1RAP	2630-12	1.6E-57	-0.83	23.9%	78.1%
rs2361836	3:190344922	T/C	SNP	IL1RAP	IL1RAP	2630-12	1.6E-56	-0.76	23.6%	72.2%
rs13071108	3:190355651	C/T	SNP	IL1RAP	IL1RAP	2630-12	8.4E-56	-1.20	23.3%	71.7%
rs10049319	3:190333699	T/C	SNP	IL1RAP	IL1RAP	2630-12	6.0E-48	-0.72	20.7%	70.7%
rs10049469	3:190333548	A/G	SNP	IL1RAP	IL1RAP	2630-12	6.1E-48	-0.72	20.7%	70.7%
rs16865696	3:190333462	G/C	SNP	IL1RAP	IL1RAP	2630-12	6.1E-48	-0.72	20.7%	70.7%
rs34581855	3:190333322	A/G	SNP	IL1RAP	IL1RAP	2630-12	6.1E-48	-0.72	20.7%	70.7%
NA	3:190333162	R/D	Deletion	IL1RAP	IL1RAP	2630-12	6.2E-48	-0.72	20.7%	70.7%
rs4140710	3:190332685	C/T	SNP	IL1RAP	IL1RAP	2630-12	6.4E-48	-0.72	20.7%	70.7%
rs4140711	3:190332654	C/T	SNP	IL1RAP	IL1RAP	2630-12	6.5E-48	-0.72	20.7%	70.7%
NA	3:190330977	R/D	Deletion	IL1RAP	IL1RAP	2630-12	7.8E-48	-0.72	20.6%	70.7%

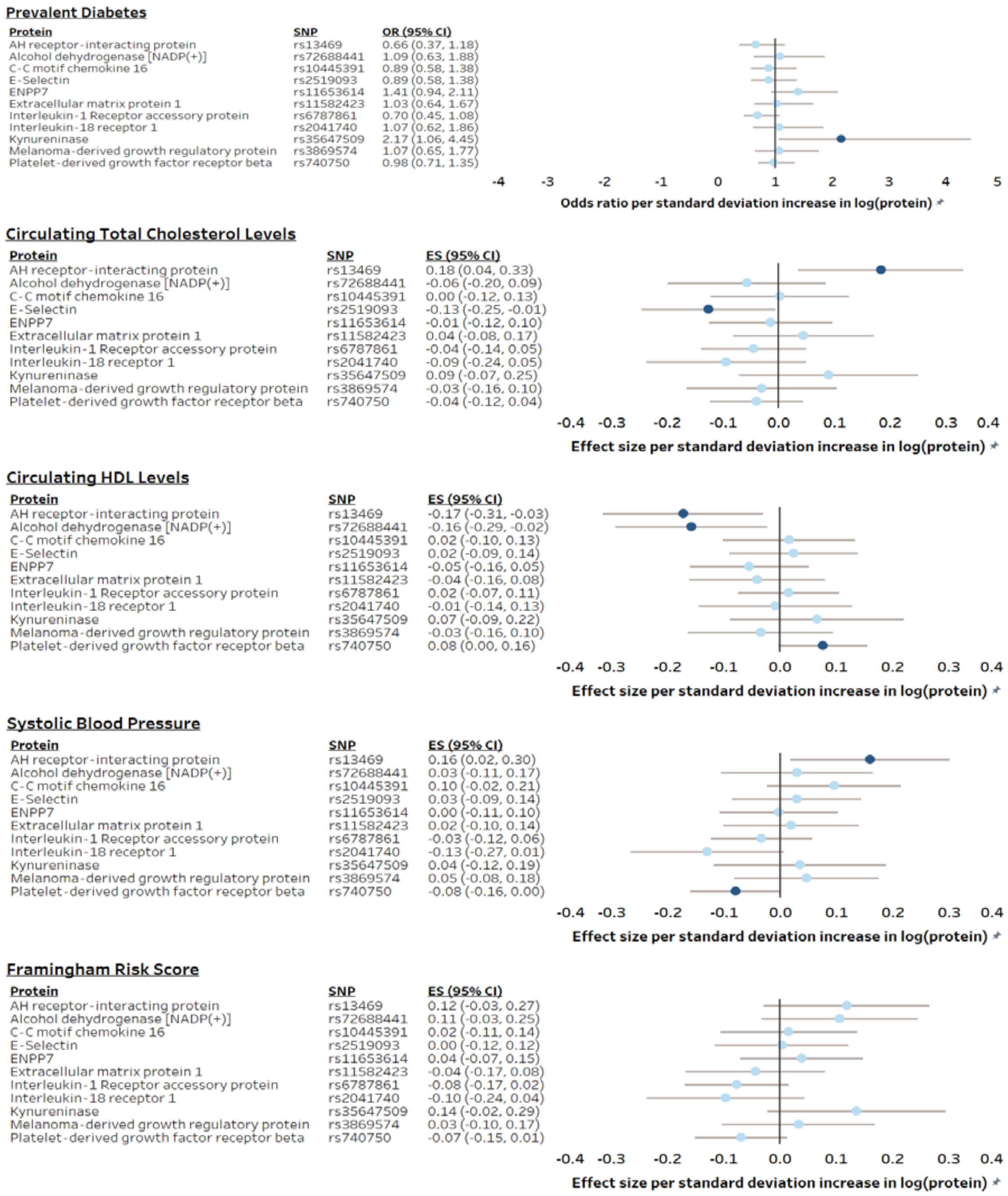
Supplemental Table 7. Representative GWAS data for IL1RAP. Characteristics of variant-protein associations for interleukin-1 receptor accessory protein (SOMAmer 2630-12). This table has been abbreviated to include the top 50 variant-protein associations for ease of review. All associations with a P-value ≤ 1 x 10^{-3} are available on dbGaP.

Locus Characteristics							FHS Discovery Cohort Results			
Variant	Variant Chromosomal Location	Ref/Alt	Variant Type	Closest Gene	Genes Within 60kb	SOMAmer Reagent	P-Value	Estimated Beta Coefficient	Estimated Heritability (h^2)	Observed Effect Allele Frequency
rs11653614	17:77703751	A/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	1.8E-107	-0.97	38.4%	64.6%
rs8072274	17:77701601	C/A	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	1.8E-107	-0.95	38.4%	64.3%
rs8072313	17:77699041	A/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.0E-107	-0.94	38.4%	64.1%
rs9908122	17:77699607	C/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.0E-107	-0.94	38.4%	64.1%
rs6565475	17:77702346	T/C	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.2E-107	-0.96	38.4%	64.3%
rs8064811	17:77701450	A/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.2E-107	-0.95	38.4%	64.3%
rs4383181	17:77698814	T/C	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.7E-107	-0.93	38.4%	64.3%
rs4497729	17:77698701	A/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.8E-107	-0.93	38.4%	64.3%
rs35759773	17:77698649	T/A	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.8E-107	-0.93	38.4%	64.3%
NA	17:77698638	I/R	Insertion	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.9E-107	-0.93	38.4%	64.3%
rs4313839	17:77698619	C/T	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	3.1E-107	-0.93	38.4%	64.3%
rs9910429	17:77703172	G/A	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	3.2E-107	-0.96	38.4%	64.4%
rs11653577	17:77703608	C/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	3.3E-107	-0.96	38.4%	64.4%
rs6565474	17:77702132	C/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	3.8E-107	-0.96	38.3%	64.4%
rs11657411	17:77703822	T/C	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.6E-107	-0.97	38.3%	64.1%
rs28682546	17:77704179	C/T	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.9E-107	-0.96	38.3%	64.4%
rs4627392	17:77698001	T/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	3.1E-106	-0.98	38.1%	64.3%
rs28689126	17:77704220	C/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	3.7E-106	-0.97	38.1%	64.7%
rs28502318	17:77704251	C/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	3.8E-106	-0.97	38.1%	64.7%
rs8074728	17:77705045	C/T	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	3.8E-106	-0.98	38.1%	63.8%
rs8076533	17:77704314	T/C	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.0E-106	-0.97	38.1%	64.7%
rs8074547	17:77704912	C/T	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.5E-106	-0.98	38.1%	64.1%
rs4442854	17:77698224	T/C	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.6E-106	-0.98	38.1%	64.3%
rs8067469	17:77698322	A/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.7E-106	-0.97	38.1%	64.4%
rs8071194	17:77698458	C/A	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.7E-106	-0.96	38.1%	64.2%
rs4474726	17:77698088	C/T	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.8E-106	-0.98	38.1%	64.3%
rs4496195	17:77698114	C/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.9E-106	-0.98	38.1%	64.3%
rs4313838	17:77698582	C/T	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	5.5E-106	-0.93	38.1%	64.5%
rs62077883	17:77705542	C/A	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	8.5E-106	-0.97	38.0%	64.8%
rs140493810	17:77705932	G/A	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.9E-104	-1.22	37.6%	70.7%
NA	17:77705953	D/R	Deletion	ENPP7	CBX2;ENPP7;MIR4739	4435-66	1.7E-103	-0.98	37.5%	64.8%
rs11868696	17:77706406	G/A	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	3.7E-103	-0.98	37.4%	64.6%
rs8077074	17:77697392	T/C	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.0E-103	-1.07	37.4%	67.3%
rs8065292	17:77697097	G/A	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.0E-103	-1.10	37.4%	67.3%
rs11871061	17:77706544	C/T	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	5.0E-103	-0.97	37.4%	64.8%
rs35948345	17:77697427	A/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.9E-101	5.41	37.0%	88.6%
rs4889994	17:77694616	C/T	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.3E-100	-2.13	36.8%	68.6%
rs11867997	17:77695676	T/C	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	1.8E-99	-1.62	36.6%	77.9%
rs146801384	17:77705921	C/T	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	9.3E-99	-1.56	36.4%	77.0%
NA	17:77696809	D/R	Deletion	ENPP7	CBX2;ENPP7;MIR4739	4435-66	1.7E-97	-1.85	36.1%	81.0%
rs35246623	17:77695987	T/C	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.1E-97	-1.84	36.0%	81.2%
rs35979434	17:77696836	A/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.2E-97	-1.82	36.0%	81.2%
rs3923265	17:77707120	G/A	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	4.7E-97	-0.97	36.0%	63.2%
rs34110129	17:77698142	T/C	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	1.0E-96	-1.70	35.9%	81.0%
NA	17:77702681	D/R	Deletion	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.7E-96	-1.63	35.8%	81.0%
rs62077882	17:77704482	T/C	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.2E-95	-1.63	35.6%	81.0%
rs9916601	17:77707018	T/C	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	3.2E-95	-1.01	35.6%	67.5%
NA	17:77705335	I/R	Insertion	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.1E-91	-1.03	34.6%	69.7%
rs34231971	17:77704697	A/G	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	8.7E-91	-1.02	34.5%	69.1%
rs112460278	17:77705742	T/C	SNP	ENPP7	CBX2;ENPP7;MIR4739	4435-66	2.5E-89	-2.34	34.1%	87.4%

Supplemental Table 8. Representative GWAS Data for ENPP7. Characteristics of variant-protein associations for ectonucleotide pyrophosphatase/phosphodiesterase family member 7 (SOMAmer 4435-66). This table has been abbreviated to include the top 50 variant-protein associations for ease of review. All associations with a P-value ≤ 1 x 10^{-3} are available on dbGaP.



Supplemental Figure 1. Pathway enrichment analysis suggests common mechanism underlying the pleiotropic effects of PPM1G. Bioinformatics observations may suggest a model by which PPM1G is recruited to nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) target gene promoters to release 7SK snRNP-mediated transcriptional inhibition of DNA polymerase II (Pol II) and allow for expression of NF-κB target genes such as apolipoprotein E (ApoE), gelsolin (GSN), and contactin-1 (CNTN1). Metalloproteinase inhibitor 2 (TIMP-2) is known to be a strong activator of NF-κB transcriptional activity.



Prevalent Diabetes

Protein	SNP	OR (95% CI)
AH receptor-interacting protein	rs13469	0.66 (0.37, 1.18)
Alcohol dehydrogenase [NADP(+)]	rs72688441	1.09 (0.63, 1.88)
C-C motif chemokine 16	rs10445391	0.89 (0.58, 1.38)
E-Selectin	rs2519093	0.89 (0.58, 1.38)
ENPP7	rs11653614	1.41 (0.94, 2.11)
Extracellular matrix protein 1	rs11582423	1.03 (0.64, 1.67)
Interleukin-1 Receptor accessory protein	rs6787861	0.70 (0.45, 1.08)
Interleukin-18 receptor 1	rs2041740	1.07 (0.62, 1.86)
Kynureninase	rs35647509	2.17 (1.06, 4.45)
Melanoma-derived growth regulatory protein	rs3869574	1.07 (0.65, 1.77)
Platelet-derived growth factor receptor beta	rs740750	0.98 (0.71, 1.35)

Circulating Total Cholesterol Levels

Protein	SNP	ES (95% CI)
AH receptor-interacting protein	rs13469	0.18 (0.04, 0.33)
Alcohol dehydrogenase [NADP(+)]	rs72688441	-0.06 (-0.20, 0.09)
C-C motif chemokine 16	rs10445391	0.00 (-0.12, 0.13)
E-Selectin	rs2519093	-0.13 (-0.25, -0.01)
ENPP7	rs11653614	-0.01 (-0.12, 0.10)
Extracellular matrix protein 1	rs11582423	0.04 (-0.08, 0.17)
Interleukin-1 Receptor accessory protein	rs6787861	-0.04 (-0.14, 0.05)
Interleukin-18 receptor 1	rs2041740	-0.09 (-0.24, 0.05)
Kynureninase	rs35647509	0.09 (-0.07, 0.25)
Melanoma-derived growth regulatory protein	rs3869574	-0.03 (-0.16, 0.10)
Platelet-derived growth factor receptor beta	rs740750	-0.04 (-0.12, 0.04)

Circulating HDL Levels

Protein	SNP	ES (95% CI)
AH receptor-interacting protein	rs13469	-0.17 (-0.31, -0.03)
Alcohol dehydrogenase [NADP(+)]	rs72688441	-0.16 (-0.29, -0.02)
C-C motif chemokine 16	rs10445391	0.02 (-0.10, 0.13)
E-Selectin	rs2519093	0.02 (-0.09, 0.14)
ENPP7	rs11653614	-0.05 (-0.16, 0.05)
Extracellular matrix protein 1	rs11582423	-0.04 (-0.16, 0.08)
Interleukin-1 Receptor accessory protein	rs6787861	0.02 (-0.07, 0.11)
Interleukin-18 receptor 1	rs2041740	-0.01 (-0.14, 0.13)
Kynureninase	rs35647509	0.07 (-0.09, 0.22)
Melanoma-derived growth regulatory protein	rs3869574	-0.03 (-0.16, 0.10)
Platelet-derived growth factor receptor beta	rs740750	0.08 (0.00, 0.16)

Systolic Blood Pressure

Protein	SNP	ES (95% CI)
AH receptor-interacting protein	rs13469	0.16 (0.02, 0.30)
Alcohol dehydrogenase [NADP(+)]	rs72688441	0.03 (-0.11, 0.17)
C-C motif chemokine 16	rs10445391	0.10 (-0.02, 0.21)
E-Selectin	rs2519093	0.03 (-0.09, 0.14)
ENPP7	rs11653614	0.00 (-0.11, 0.10)
Extracellular matrix protein 1	rs11582423	0.02 (-0.10, 0.14)
Interleukin-1 Receptor accessory protein	rs6787861	-0.03 (-0.12, 0.06)
Interleukin-18 receptor 1	rs2041740	-0.13 (-0.27, 0.01)
Kynureninase	rs35647509	0.04 (-0.12, 0.19)
Melanoma-derived growth regulatory protein	rs3869574	0.05 (-0.08, 0.18)
Platelet-derived growth factor receptor beta	rs740750	-0.08 (-0.16, 0.00)

Framingham Risk Score

Protein	SNP	ES (95% CI)
AH receptor-interacting protein	rs13469	0.12 (-0.03, 0.27)
Alcohol dehydrogenase [NADP(+)]	rs72688441	0.11 (-0.03, 0.25)
C-C motif chemokine 16	rs10445391	0.02 (-0.11, 0.14)
E-Selectin	rs2519093	0.00 (-0.12, 0.12)
ENPP7	rs11653614	0.04 (-0.07, 0.15)
Extracellular matrix protein 1	rs11582423	-0.04 (-0.17, 0.08)
Interleukin-1 Receptor accessory protein	rs6787861	-0.08 (-0.17, 0.02)
Interleukin-18 receptor 1	rs2041740	-0.10 (-0.24, 0.04)
Kynureninase	rs35647509	0.14 (-0.02, 0.29)
Melanoma-derived growth regulatory protein	rs3869574	0.03 (-0.10, 0.17)
Platelet-derived growth factor receptor beta	rs740750	-0.07 (-0.15, 0.01)

Supplemental Figure 2. Exploratory Mendelian randomization analyses. Mendelian randomization (MR) was used to test the causal association of circulating proteins (left column) to selected clinical phenotypes using the sentinel SNP of each pQTLs as an instrumental variable (second column). The effect size (ES, for continuous outcomes) or odds ratio (OR, for binary outcomes) per standard deviation increase in log(protein) with 95% confidence intervals (CI) are displayed as Forest plots. Analyses that suggest a causal association between protein and phenotype are highlighted in dark blue.

Supplemental References

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