http://dx.doi.org/10.2106/JBJS.19.01335

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SNV, Gene, candidate gene approach and GWAS

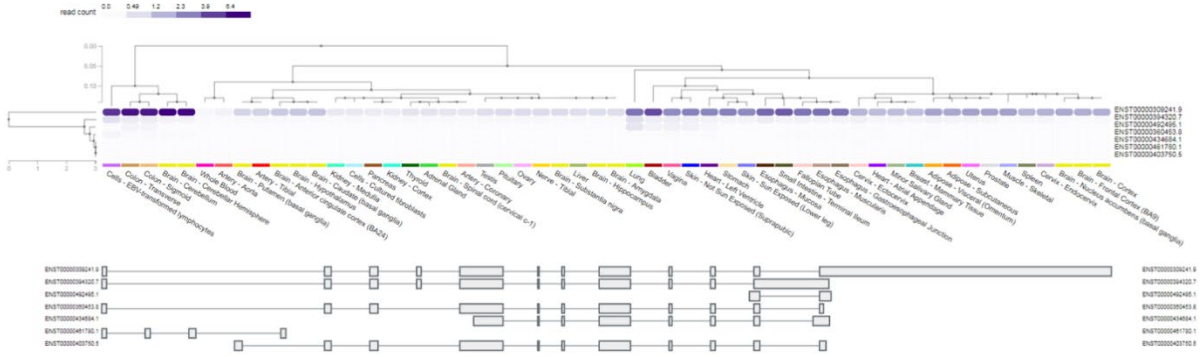
A single-nucleotide variant (SNV) is defined as variation in a single nucleotide without any limitations of frequency in a population. An SNV may fall within the coding sequences of genes (exons), non-coding regions of genes (introns), or in the intergenic regions (regions between genes).

Two strategies are used to detect the association between a variant and a disease: the candidate gene approach and the Genome-wide association study (GWAS). In the candidate gene approach, certain variant(s) that fall within a gene (both exons and introns) are examined. In GWAS, all the variants or SNVs (usually minor allele frequency >1%) across the genome are examined. Because of the large numbers of variants tested in GWAS, a much stricter significance level than the candidate gene approach is adopted to reduce the chance of false positive. Conventionally, genome-wide significance level is defined at p<5e-8 and a suggestive significance level is defined at p<1e-5.

Genotyping, imputation and data processing

Genotyping was performed on the Illumina Infinium OmniExpress Exome array and GSA-24v1-0 array for two phases. Imputation to HRC.r1-1 EUR reference genome (GRCh37 build) was performed on the Michigan Imputation Server separately for samples genotyped using different chips. **Samples with genetically informed European ancestry were imputed. The** two imputed datasets were then merged to only include the overlapped variants. Subsequent data processing only included biallelic SNPs with an info score > 0.7, call rate > 99%, minor allele frequency (MAF) > 1% and followed the Hardy-Weinberg Equilibrium (HWE, $p > 10^{-5}$) for GWAS. Relatedness and principal components were calculated using the built-in functions in PLINK1.9 [1] on a set of pruned-in high-quality SNPs. One individual from each related pair was then removed from association tests.

Supplementary figure 1: Isoform expression of *PPARGC1B* in various tissues



Supplementary figure 1: isoform expression of the *PPARGC1B* in various tissues. GTEx portal and data of GTEx V8 release were used in this figure. Isoform of ENST00000309241.9 is widely expressed than other isoforms.

http://dx.doi.org/10.2106/JBJS.19.01335

Supplementary table 1: List of the ICD and CPT codes of risk diseases and procedures for ONFH

Code	Description	Code system
733.4	Aseptic necrosis of bone	ICD9
733.40	Aseptic necrosis of bone, site unspecified convert	ICD9
733.41	Aseptic necrosis of head of humerus	ICD9
733.42	Aseptic necrosis of head and neck of femur	ICD9
733.43	Aseptic necrosis of medial femoral condyle	ICD9
733.44	Aseptic necrosis of talus	ICD9
733.45	Aseptic necrosis of bone, jaw	ICD9
733.49	Aseptic necrosis of bone, other	ICD9
M87	Osteonecrosis	ICD10
M87.0	Idiopathic aseptic necrosis of bone	ICD10
M87.00	Idiopathic aseptic necrosis of unspecified bone	ICD10
M87.01	Idiopathic aseptic necrosis of shoulder	ICD10
M87.011	Idiopathic aseptic necrosis of right shoulder	ICD10
M87.012	Idiopathic aseptic necrosis of left shoulder	ICD10
M87.019	Idiopathic aseptic necrosis of unspecified shoulder	ICD10
M87.02	Idiopathic aseptic necrosis of humerus	ICD10
M87.021	Idiopathic aseptic necrosis of right humerus	ICD10
M87.022	Idiopathic aseptic necrosis of left humerus	ICD10
M87.029	Idiopathic aseptic necrosis of unspecified humerus	ICD10
M87.03	Idiopathic aseptic necrosis of radius, ulna and carpus	ICD10
M87.031	Idiopathic aseptic necrosis of right radius	ICD10
M87.032	Idiopathic aseptic necrosis of left radius	ICD10
M87.033	Idiopathic aseptic necrosis of unspecified radius	ICD10
M87.034	Idiopathic aseptic necrosis of right ulna	ICD10
M87.035	Idiopathic aseptic necrosis of left ulna	ICD10
M87.036	Idiopathic aseptic necrosis of unspecified ulna	ICD10
M87.037	Idiopathic aseptic necrosis of right carpus	ICD10
M87.038	Idiopathic aseptic necrosis of left carpus	ICD10
M87.039	Idiopathic aseptic necrosis of unspecified carpus	ICD10
M87.04	Idiopathic aseptic necrosis of hand and fingers	ICD10
M87.041	Idiopathic aseptic necrosis of right hand	ICD10
M87.042	Idiopathic aseptic necrosis of left hand	ICD10
M87.043	Idiopathic aseptic necrosis of unspecified hand	ICD10
M87.044	Idiopathic aseptic necrosis of right finger(s)	ICD10
M87.045	Idiopathic aseptic necrosis of left finger(s)	ICD10
M87.046	Idiopathic aseptic necrosis of unspecified finger(s)	ICD10
M87.05	Idiopathic aseptic necrosis of pelvis and femur	ICD10
M87.050	Idiopathic aseptic necrosis of pelvis	ICD10
M87.051	Idiopathic aseptic necrosis of right femur	ICD10
M87.052	Idiopathic aseptic necrosis of left femur	ICD10
M87.059	Idiopathic aseptic necrosis of unspecified femur	ICD10
M87.06	Idiopathic aseptic necrosis of tibia and fibula	ICD10
M87.061	Idiopathic aseptic necrosis of right tibia	ICD10
M87.062	Idiopathic aseptic necrosis of left tibia	ICD10
M87.063	Idiopathic aseptic necrosis of unspecified tibia	ICD10
M87.064	Idiopathic aseptic necrosis of right fibula	ICD10
M87.065	Idiopathic aseptic necrosis of left fibula	ICD10
M87.066	Idiopathic aseptic necrosis of unspecified fibula	ICD10
M87.07	Idiopathic aseptic necrosis of ankle, foot and toes	ICD10

M87.071	Idiopathic aseptic necrosis of right ankle	ICD10
M87.072	Idiopathic aseptic necrosis of left ankle	ICD10
M87.073	Idiopathic aseptic necrosis of unspecified ankle	ICD10
M87.074	Idiopathic aseptic necrosis of right foot	ICD10
M87.075	Idiopathic aseptic necrosis of left foot	ICD10
M87.076	Idiopathic aseptic necrosis of unspecified foot	ICD10
M87.077	Idiopathic aseptic necrosis of right toe(s)	ICD10
M87.078	Idiopathic aseptic necrosis of left toe(s)	ICD10
M87.079	Idiopathic aseptic necrosis of unspecified toe(s)	ICD10
M87.08	other site	ICD10
M87.09	multiple sites	ICD10
291.*	ALCOHOL INDUCED MENTAL DISORDERS	ICD9
303.*	ALCOHOL DEPENDENCE	ICD9
305	ALCOHOL ABUSE	ICD9
305.00	ALCOHOL ABUSE-UNSPEC	ICD9
305.01	ALCOHOL ABUSE-CONTINUOUS	ICD9
425.5	Alcoholic Cardiomyopathy	ICD9
571	Alcoholic Liver Diseases	ICD9
571.1	Alcoholic Liver Diseases	ICD9
V11.3	Personal History of Alcoholism	ICD9
282.41	SICKLE-CELL W/O CRISIS	ICD9
282.42	SICKLE-CELL WITH CRISIS	ICD9
282.6	SICKLE-CELL DISEASE	ICD9
282.60	SICKLE-CELL DISEASE NOS	ICD9
282.63	SICKLE-CELL/HB-C W/O CRI	ICD9
282.68	OTHR SICKLE-CEL W/O CRIS	ICD9
282.69	OTHER SICKLE-CELL W/CRIS	ICD9
282.64	SICKLE-CEL/HB-C W/CRISIS	ICD9
272.7	LIPIDOSES	ICD9
330.1	CEREBRAL LIPIDOSES	ICD9
732.1	JUV OSTEOCHONDROS PELVIS	ICD9
042	HIV DISEASE	ICD9
043	HIV CAUSING CONDITN NEC	ICD9
044	OTHER HIV INFECTION	ICD9
079.53	HIV 2	ICD9
795.71	NONSPEC SEROL FIND-HIV	ICD9
V08	ASYMPTOMATIC HIV STATUS	ICD9
577.0	Acute pancreatitis	ICD9
577.1	chronic pancreatitis	ICD9
710.0	Systemic lupus erythematosus	ICD9
P012	eMERGE_T2DM alogrihtm	eMERGE alogrithm
203	Myeloma	ICD9
204-208	Leukemia	ICD9
201	Lymphoma	ICD9
909.2, 905	Pelvic Radiation	ICD9
D57.*	Sickle Cell Disorders	ICD10
E75.22	Gaucher	ICD10
M91.1*	Legg-Calve-Perthes	ICD10
B20	HIV	ICD10
K86.0	Alcohol-induced chronic pancreatitis	ICD10
K86.1	Other chronic pancreatitis	ICD10
K85.0*	Idiopathic acute pancreatitis	ICD10

K85.1*	Biliary acute pancreatitis	ICD10
M32.1*	Systemic lupus erythematosus with organ or system involvement	ICD10
M32.8	Other forms of systemic lupus erythematosus	ICD10
M32.9	Systemic lupus erythematosus, unspecified	ICD10
F10*	alcohol abuse	ICD10
P012	Diabetes	ICD10
C90.	Myeloma	ICD10
C91-C95	Leukemia	ICD10
C81-C88	Lymphoma	ICD10
32851	LUNG TRANSPLANT, SINGLE; WITHOUT CARDIOPULMONARY BYPASS	CPT code
32852	LUNG TRANSPLANT, SINGLE; WITH CARDIOPULMONARY BYPASS	CPT code
32853	LUNG TRANSPLANT, DOUBLE (BILATERAL SEQUENTIAL OR EN BLOC); WITHOUT	CPT code
32854	LUNG TRANSPLANT, DOUBLE (BILATERAL SEQUENTIAL OR EN BLOC); WITH	CPT code
33935	HEART-LUNG TRANSPLANT WITH RECIPIENT CARDIECTOMY-PNEUMONECTOMY	CPT code
33945	HEART TRANSPLANT, WITH OR WITHOUT RECIPIENT CARDIECTOMY	CPT code
38240	BONE MARROW OR BLOOD-DERIVED PERIPHERAL STEM CELL TRANSPLANTATION;	CPT code
00580	ANESTHESIA FOR HEART TRANSPLANT OR HEART/LUNG TRANSPLANT	CPT code
38241	BONE MARROW OR BLOOD-DERIVED PERIPHERAL STEM CELL TRANSPLANTATION;	CPT code
38242	BONE MARROW OR BLOOD-DERIVED PERIPHERAL STEM CELL TRANSPLANTATION;	CPT code
0085T	BREATH TEST FOR HEART TRANSPLANT REJECTION	CPT code
50360	RENAL ALLOTRANSPLANTATION, IMPLANTATION OF GRAFT; WITHOUT RECIPIENT	CPT code
50365	RENAL ALLOTRANSPLANTATION, IMPLANTATION OF GRAFT; WITH RECIPIENT	CPT code
50370	REMOVAL OF TRANSPLANTED RENAL ALLOGRAFT	CPT code
50380	RENAL AUTOTRANSPLANTATION, REIMPLANTATION OF KIDNEY	CPT code
44135	INTESTINAL ALLOTRANSPLANTATION; FROM CADAVER DONOR	CPT code
44136	INTESTINAL ALLOTRANSPLANTATION; FROM LIVING DONOR	CPT code
44137	REMOVAL OF TRANSPLANTED INTESTINAL ALLOGRAFT, COMPLETE	CPT code
76776	ULTRASOUND, TRANSPLANTED KIDNEY, REAL TIME AND DUPLEX DOPPLER WITH IMAGE	CPT code
47135	LIVER ALLOTRANSPLANTATION; ORTHOTOPIC, PARTIAL OR WHOLE, FROM CADAVER OR	CPT code
47136	LIVER ALLOTRANSPLANTATION; HETEROTOPIC, PARTIAL OR WHOLE, FROM CADAVER	CPT code
48160	PANCREATECTOMY, TOTAL OR SUBTOTAL, WITH AUTOLOGOUS TRANSPLANTATION OF	CPT code
48554	TRANSPLANTATION OF PANCREATIC ALLOGRAFT	CPT code
48556	REMOVAL OF TRANSPLANTED PANCREATIC ALLOGRAFT	CPT code
32851P	LUNG TRANSPLANT, SINGLE;	CPT code
32852P	LUNG TRANSPLANT, SINGLE;	CPT code
33635-50	HEART-LUNG TRANSPLANT W	CPT code
33945P	HEART TRANSPLANT, W/WO RE	CPT code
S2054	TRANSPLANTATION MULTIVISC	CPT code
S2060	LOBAR LUNG TRANSPLANTATIO	CPT code
S2103	ADRENAL TISSUE TRANSPLANT	CPT code

Supplementary table 2: Replication of prior reported GWAS loci in MyCode Cohort

SNP	CHR:BP	Published GWAS					Replication in MyCode		
		A1	GENE	OR	P	Study	A1	OR	P
rs10849004	12:4292862	C	*CCND2*	1.39-3.45	5.75×10^{-6}	Steroid-induced ONFH in children with ALL [2]	-	-	-
rs1536407	13:75095567	A	*KLF12*	1.59-2.13	4.43×10^{-6}		C	1.18	0.232
rs4789693	17:80421870	C	*NARF*	1.86-1.95	5.73×10^{-6}		C	0.89	0.454
rs2154490	21:30915962	G	*GRIK1*	1.8-2.1	1.28×10^{-6}		A	0.95	0.74
rs6797178	3:137253713	A	*SOX14*	1.63-2	5.74×10^{-6}		A	0.90	0.429
rs72733993	5:18408908	A	/	1.3-2.89	2.67×10^{-6}		A	0.80	0.322
rs11594258	10:79218030	A	*KCNMA1*	1.52-2.44	8.61×10^{-6}		-	-	-
rs10989692	9:104674555	A	*GRIN3A*	1.87-2.26	2.68×10^{-8}		A	0.42	0.008
rs11144550	9:78261548	A	*PCSK5*	1.71-2.0	3.08×10^{-6}		-	-	-
rs17021408	1:213943238	C	*PROX1-AS1*	5.89	1.01×10^{-6}	Steroid-induced ONFH in children with ALL under 10 [3]	-	-	-
rs61818937	1:213943334	A		5.89	1.01×10^{-6}		-	-	-
rs80223967	1:213943679	G		6.1	6.63×10^{-7}		-	-	-
rs1891059	1:213946009	A		6.48	2.28×10^{-7}		-	-	-
rs115602884	1:213949408	T		6.48	2.28×10^{-7}		T	0.60	0.181
rs74533616	1:213949611	T		6.48	2.28×10^{-7}		-	-	-
rs117532069	20:53301068	A	*DOK5*	21	1.7×10^{-6}		A	0.37	0.322
rs79085477	20:55701215	T	*BMP7*	15	5.34×10^{-8}		-	-	-
rs75161997	20:55701691	T		15	5.34×10^{-8}		-	-	-
rs141059755	8:66107605	G	*LINC00251*	23.3	8.48×10^{-7}		-	-	-
rs3858704	12:111705893	G	*12q24.11-12*	1.33-2.73	$10^{-12,-21}$	ONFH, Alcohol [4]	G	0.87	0.380
rs4766566	12:111706877	T	*12q24.11-13*	1.33-2.73	$10^{-12,-21}$		T	0.85	0.311
rs13426947	2:191933254	A	*2q32.3*	1.33	1.63×10^{-9}	Steroids-ONFH [4]	-	-	-
rs9268978	6:32434978	A	*6p21.32*	1.52-1.88	$10^{-8,-9}$		A	0.93	0.707
rs6028718	20:38548977	T	*20q12 LINC01370*	1.32-1.61	$10^{-14,-7}$	ONFH, steroids, alcohol [4]	C	1.22	0.139
rs12032616	1:65703484	G	*DNAJC6*	0.47	8.32×10^{-6}	ONFH, Korean [5]	G	0.84	0.284
rs6679032	1:65764742	G		0.47	7.94×10^{-6}		G	0.85	0.621
rs10493374	1:65783231	T		0.46	6.05×10^{-6}		T	0.85	0.624
rs17127529	1:65799440	C		0.52	3.27×10^{-6}		-	-	-
rs220324	21:43586699	C	*UMODL1, ABCG1*	0.35	2.35×10^{-7}		-	-	-
rs709159	3:12481203	C	*PPARG*	0.49	6.76×10^{-5}	Mayo, Atraumatic ONFH [6]	-	-	-
rs13090265	3:12484985	G		1.64	1.28×10^{-2}		G	0.93	0.730
rs13088214	3:12487827	C		1.43	1.58×10^{-2}		C	1.02	0.875
rs7618046	3:12488027	T		0.53	2.27×10^{-5}		T	1.15	0.296
rs9855622	3:12493347	T		1.92	8.09×10^{-4}		-	-	-
rs1185784	3:12494278	T		0.5	1.32×10^{-2}		T	1.02	0.943
rs9809905	3:12500651	G		1.94	5.5×10^{-6}		-	-	-

Supplementary table 3: Replication of variants reported in candidate gene study in MyCode Cohort

SNP	GENE	CHR:BP	A1	OR	L95	U95	P
rs1801131	*MTHFR*	1:11854476	G	0.9534	0.7191	1.264	0.7404
rs1801133	*MTHFR*	1:11856378	A	1.084	0.827	1.42	0.5596
rs4655686	*ANXA2*	1:67638004	A	1.09	0.8272	1.436	0.5408
rs7539625	*IL23R*	1:67672765	A	0.9414	0.7079	1.252	0.6777
rs2269091	*NRP1*	10:33529028	T	0.9089	0.6513	1.268	0.5742
rs12573218	*KDR*	10:33587733	T	1.082	0.7495	1.561	0.6753
rs2012390	*MMP8*	11:102590777	G	1.037	0.771	1.394	0.8105
rs11225394	*MMP8*	11:102595413	T	1.126	0.8437	1.502	0.4208
rs650108	*MMP3*	11:102708787	A	0.9571	0.7149	1.281	0.7683
rs7943316	*CAT*	11:34460472	A	1.05	0.8018	1.376	0.7219
rs1049982	*CAT*	11:34460541	T	1.053	0.8037	1.379	0.7082
rs525938	*CAT*	11:34463593	C	1.063	0.8041	1.405	0.6678
rs3758730	*CAT*	11:34475099	T	1.178	0.7871	1.764	0.4253
rs769217	*CAT*	11:34482908	T	0.93	0.6825	1.267	0.646
rs2284365	*CAT*	11:34484973	C	0.9263	0.6798	1.262	0.6278
rs2200287	*RANKL*	13:43168660	A	1.144	0.8813	1.485	0.3122
rs12601420	*NRP1/SREBF1*	17:17721736	T	1.025	0.3792	2.769	0.9615
rs4309	*IGFBP3*	17:61559923	T	0.9497	0.7295	1.236	0.7013
rs4344	*ACE*	17:61566724	A	1.012	0.7818	1.31	0.9274
rs2274755	*MMP9*	20:44639692	T	0.8692	0.5943	1.271	0.4698
rs1880669	*PLAT*	3:133483696	T	1.219	0.9423	1.578	0.1315
rs2692695	*TF*	3:133485454	A	1.219	0.9422	1.578	0.1318
rs2718806	*TF*	3:133486093	A	0.9063	0.6712	1.224	0.5208
rs6837735	*ACE*	4:55985815	T	0.961	0.6864	1.345	0.8167
rs1570360	*VEGF*	6:43737830	A	1.055	0.8039	1.385	0.6982
rs2010963	*VEGF*	6:43738350	C	0.9837	0.7485	1.293	0.9059
rs7242	*PAI-1*	7:100781445	G	0.8674	0.6684	1.126	0.2846
rs1045642	*ABCB1*	7:87138645	G	1.181	0.9105	1.532	0.2099
rs2032582	*ABCB1*	7:94937446	C	0.8286	0.6135	1.119	0.2203
rs1032128	*OPG*	8:119951773	A	1.093	0.8191	1.457	0.5467
rs11573828	*OPG*	8:119959813	T	0.6634	0.2109	2.087	0.4829

Supplementary Table 4: Variants associated with ONFH at the *PPARGC1B* locus with p<1e-5

rsID	CHR:BP	A1/A2	P_GWAS	OR	SE	Impact	* R^2
rs75548653	5:149190248	G/C	4.06E-06	2.773	0.2213	intronic	1
rs79694606	5:149190799	A/G	3.68E-06	2.785	0.2213	intronic	1
rs79489540	5:149190810	T/C	4.14E-06	2.769	0.2212	intronic	1
rs78814834	**5:149191547**	**T/C**	**1.40E-06**	**2.86**	**0.2178**	**intronic**	**1**
rs4705384	5:149192166	C/T	1.59E-06	2.846	0.2179	intronic	1
rs77655035	5:149193133	T/C	4.29E-06	2.765	0.2213	intronic	0.972
rs80069564	5:149194785	A/G	1.56E-06	2.848	0.2179	intronic	0.972
rs17110463	5:149195726	T/C	1.56E-06	2.848	0.2179	intronic	0.972
rs4705385	5:149196638	T/C	1.61E-06	2.844	0.2179	intronic	0.972
rs112183859	5:149196916	G/A	1.61E-06	2.844	0.2179	intronic	0.972
rs76390604	5:149197609	C/T	1.79E-06	2.832	0.2179	intronic	0.972
rs17600568	5:149197747	G/C	4.18E-06	2.77	0.2214	intronic	0.972
rs10491360	5:149197815	C/T	1.79E-06	2.832	0.2179	intronic	0.972
rs79435714	5:149199467	T/C	4.17E-06	2.77	0.2214	intronic	0.972
rs2003602	5:149200932	A/G	4.21E-06	2.769	0.2214	intronic	0.972
rs17653577	5:149203782	G/A	3.80E-06	2.783	0.2214	intronic	0.972
rs741582	5:149205992	A/G	3.73E-06	2.785	0.2214	intronic	0.945
rs45560442	5:149206531	A/G	3.61E-06	2.789	0.2214	intronic	0.945
rs76994147	5:149208516	T/G	7.68E-06	2.338	0.1898	intronic, CTCF binding	0.660
rs45520937	**5:149212430**	**A/G**	**3.70E-06**	**2.787**	**0.2215**	**exonic, missense variant**	**0.945**
rs45588534	5:149216256	T/C	3.86E-06	2.78	0.2214	exonic, CTCF binding	0.945
rs45543631	5:149216304	T/C	3.76E-06	2.783	0.2213	exonic, CTCF binding	0.945
rs113346136	5:149223091	C/T	2.49E-06	2.841	0.2217	intronic	0.945
rs75739000	5:149226633	A/G	3.57E-06	2.789	0.2213	UTR3	0.945
rs76174857	5:149227540	C/T	3.47E-06	2.793	0.2213	UTR3	0.945
rs6579761	5:149229822	T/G	7.77E-06	2.338	0.19	UTR3, CTCF binding	0.660
rs1549186	5:149230745	C/T	7.81E-06	2.338	0.19	UTR3	0.660
rs1549187	5:149230787	T/C	7.81E-06	2.338	0.19	UTR3	0.685
rs1549188	5:149230952	G/A	7.48E-06	2.342	0.19	UTR3	0.674
rs1107344	5:149231786	A/G	7.93E-06	2.337	0.19	UTR3	0.674
rs888853	5:149232525	G/A	8.31E-06	2.332	0.1899	UTR3, CTCF binding	0.674
rs7712296	5:149233110	A/C	7.16E-06	2.347	0.1901	UTR3, CTCF binding	0.674
rs17653703	5:149233186	T/C	5.00E-06	2.381	0.1901	UTR3, CTCF binding	0.674
rs4705386	5:149234701	A/G	6.12E-06	2.387	0.1924	downstream	0.674

* R^2 with the lead SNV rs78814843. OR: odds ratio; SE: standard error

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