Published in final edited form as:
Nat Genet. 2009 September ; 41(9): 986–990. doi:10.1038/ng.429.

Genome-wide association study identifies variants in the *ABO* locus associated with susceptibility to pancreatic cancer

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Abstract

We conducted a two-stage genome-wide association study (GWAS) of pancreatic cancer, a cancer with one of the poorest survival rates worldwide. Initially, we genotyped 558,542 single nucleotide polymorphisms in 1,896 incident cases and 1,939 controls drawn from twelve prospective cohorts plus one hospital-based case-control study. In a combined analysis adjusted for study, sex, ancestry and five principal components that included an additional 2,457 cases and 2,654 controls from eight case-control studies, we identified an association between a locus on 9q34 and pancreatic cancer marked by the single nucleotide polymorphism, rs505922 (combined P=5.37 × 10-8; multiplicative per-allele odds ratio (OR) 1.20; 95% CI 1.12-1.28). This SNP maps to the first intron of the *ABO* blood group gene. Our results are consistent with earlier epidemiologic evidence suggesting that people with blood group O may have a lower risk of pancreatic cancer than those with groups A or B.

Pancreatic cancer shows amongst the highest mortality rates of any cancer, with a five year relative survival rate of less than 5%[1,2]. There is currently no effective screening test for the malignancy, and by the time of initial diagnosis, metastatic disease is commonly present. Established risk factors include a family history of pancreatic cancer, a medical history of diabetes type II and cigarette smoking3. Studies have also suggested an increased risk of pancreatic cancer within families with hereditary pancreatitis4,5. It has also been estimated that a small proportion of pancreatic cancers are due to highly penetrant germ-line mutations[6]. These studies suggested genetic contribution to pancreatic cancer, although there has been limited success in resolving common variants associated to this disease. We report here a genome-wide association study (GWAS) to resolve common variants associated to pancreatic cancer.

We conducted a GWAS in 1,896 cases and 1,939 controls of incident pancreatic cancer cases drawn from twelve prospective cohorts plus one hospital-based case-control study (American Cancer Society Cancer Prevention Study-II (CPS II)7 Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC)8 European Prospective Investigation into Cancer and Nutrition Study (EPIC)9 CLUE II10 Health Professionals Follow-up Study (HPFS)11 New York University Women's Health Study (NYUWHS)12 Nurses' Health Study (NHS)11 Physicians' Health Study I (PHS)11 Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)13 Shanghai Men's and Women's Health Study (SMWHS)14,15 Women's Health Initiative (WHI)16 the Women's Health Study (WHS)17 and the Mayo Clinic Molecular Epidemiology of Pancreatic Cancer Study18; Supplemental Table 1). Eight case-control studies participated in the independent 'Fast-Track' replication phase of 2,457 cases and 2,654 controls (the University of Toronto[19] University of California San Francisco20 Johns Hopkins University, MD Anderson Cancer Center21 PACIFIC Study of Group Health and Northern California Kaiser Permanente, Memorial Sloan-Kettering Cancer Center22 Yale University[23] and the Mayo Clinic Molecular Epidemiology of Pancreatic Cancer Study[18]; Supplemental Table 2).

After quality control assessment of genotypes assayed using the HumanHap500 chip (Illumina, San Diego, CA), 558,542 SNPs were available for analysis. A logistic regression model was fit for genotype trend effects (1 d.f.) adjusting for study, age, sex, ancestry and the top five principal components of population stratification (Online Methods). The quantile-quantile plot (QQ plot) does not demonstrate a systematic deviation from the expected distribution, minimizing the likelihood of systematic genotype error or bias due to underlying population substructure (Supplemental Figure 1). The results of the GWAS are shown in Figure 1a. Because of the potential for survivor bias in case-control studies due to rapid mortality, we also analyzed the GWAS for cohort studies only as shown in Figure 1b (i.e., excluding Mayo subjects).

We conducted a rapid follow-up scan, or "Fast Track", of SNPs from three regions in eight case-control studies (four hospital based and four population based). At least two SNPs per region were ranked among the lowest 25 p-values in the initial GWAS; 1.) chromosome 9q34, which includes the *ABO* gene (rs505922, rs495828, rs657152 and rs630014; ranked 2, 3, 8 and 17); 2.) chromosome 7q36, which includes Sonic Hedgehog (*SHH*), (rs167020, rs172310, and rs288746; ranked 6, 10 and 89); and 3.) a gene desert on chromosome 15q14 (rs8028529, rs4130461 and rs4459505, ranked 1, 18 and 26) (Table 1).

In a combined analysis of individuals of European background[24] the strongest association with pancreatic cancer below the threshold for genome-wide significance[25] was observed for a locus on chromosome 9q34, located within the first intron of *ABO*, a well-described blood group gene, marked by rs505922 (P=5.37 × 10^{-8}; trend model; heterozygous odds ratio [OR_{Het}] of 1.20; 95% CI 1.12-1.28 and homozygous odds ratio [OR_{Hom}] of 1.44; 95% CI 1.26-1.63). A comparable result was observed when all ethnic groups were included in the first stage (P=2.61 × 10^{-8}; Supplemental Table 3). In the case-control replication set, we genotyped a second SNP, rs687621 (r^2=1 with rs505922 in HapMap CEU and r^2=0.91 in Stage 2 control individuals), located 12 kb centromeric in intron 2; the results provided confirmation of the locus (P=1.57×10^{-4} in the second-stage case-control studies only). In the combined analysis, a comparably strong signal was observed for rs630014 (P=1.58×10^{-7}; OR_{Het} 0.85, OR_{Hom} 0.71), which resides within 500 bp of rs505922 and is in linkage disequilibrium (r^2=0.52 in HapMap CEU and 0.40 in PanScan GWAS European control individuals). After adjusting for rs505922, none of the remaining SNPs in *ABO* were significant at the P<0.01 level. The SNPs reside in a haplotype block that encompasses the proximal promoter and introns 1 and 2 (Figure 2).

Blood groups were first described by Karl Landsteiner in 1900 but the structure of the ABO antigens and their biosynthesis remained elusive until after 1950. The *ABO* gene encodes a glycosyltransferase that catalyzes the transfer of carbohydrates to the H antigen, forming the antigenic structure of the ABO blood groups. The proteins encoded by the A and B alleles of the *ABO* gene differ minimally in amino acid sequence but catalyze the transfer of different carbohydrates (N-acetylgalactosamine or galactose) onto the H antigen to form the A or B antigens. Individuals with the O blood group do not produce either the A or B antigens due to a single base deletion.

Our findings are notable because multiple studies, mainly from the 1950s and 1960s reported an association between ABO blood type and gastrointestinal cancers, strongest for gastric cancer but also for pancreatic cancer[26,27]. The protective allele (T) for rs505922 is in complete linkage disequilibrium (LD) (r^2=1.0) with the O allele of the ABO locus, consistent with earlier reports showing increased risk of gastric and pancreatic cancer for individuals of the A and B blood groups. It is plausible that the single base deletion that generates the O blood group underlies the association signal but further mapping and laboratory work is required to determine which variant(s) account for the observed association.

Genetic variation in the first intron of the *ABO* gene has also been associated with circulating levels of serum tumor necrosis factor alpha (TNF-alpha) levels[28] circulating soluble intracellular adhesion molecule 1 (sICAM-1)[29] and plasma levels of alkaline phosphatase[30]. Although higher TNF-alpha levels are associated with the common allele of rs505922, protective for pancreatic cancer in our study, the data concerning the relationship between blood groups and TNF-alpha levels are inconsistent[28]. Furthermore, this region could be important for regulating circulating sICAM-1 levels as rs507666 and rs505922 (located 170 bps apart) were recently reported to be associated with circulating ICAM-1 levels[29]. Also, SNPs in the *ABO* locus, including rs657152, have been associated with plasma levels of liver derived alkaline phosphatase[30]. Lastly, altered ABO antigen expression has been observed in primary and metastatic pancreatic cancer as compared to normal pancreatic tissues[31].

For rapidly fatal conditions, case-control studies are prone to distortion because they disproportionately include survivors. For variants unrelated to survival, case-control data are suitable for discovery and replication of risk-related markers. However, for variants related to survival, case-control studies yield biased estimates of the association with pancreatic cancer risk. *ABO* variants appear unrelated to survival and show strong and similar signals in both cohort and case-control data.

We observed an association at the genome-wide level ($P=1.76 \times 10^{-7}$) with *SHH* among cohorts that was not replicated in follow-up in case-control studies ($P=0.12$), raising three possibilities: the cohort finding is due to chance, *SHH* is related to both survival and to risk or that the SNPs failed to replicate because of chance (Table 1). Because there is substantial evidence that *SHH* plays a role in pancreatic carcinogenesis, further work is required to investigate this region[32].

Pancreatic cancer is among the deadliest cancers with mortality rates approaching incidence rates[1]. Given there are few known risk factors, improved diagnostics and a finer understanding of the molecular pathogenesis are urgently needed. Our findings have identified the contribution of genetic variation in the *ABO* locus of 9q34 to pancreatic carcinogenesis, a finding that supports an epidemiologic observation first made half a century ago and recently confirmed[33]. We are currently conducting a GWAS in the eight studies of stage 2 in this study and anticipate that this will bring the identification of additional loci associated to pancreatic cancer. The discovery of additional genetic risk variants for this highly lethal cancer could contribute to novel risk stratification and improvements in prevention, early detection and therapeutic approaches to pancreatic cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors gratefully acknowledge the energy and contribution of our late colleague, Robert Welch. Additional acknowledgements are in the Supplemental Note.

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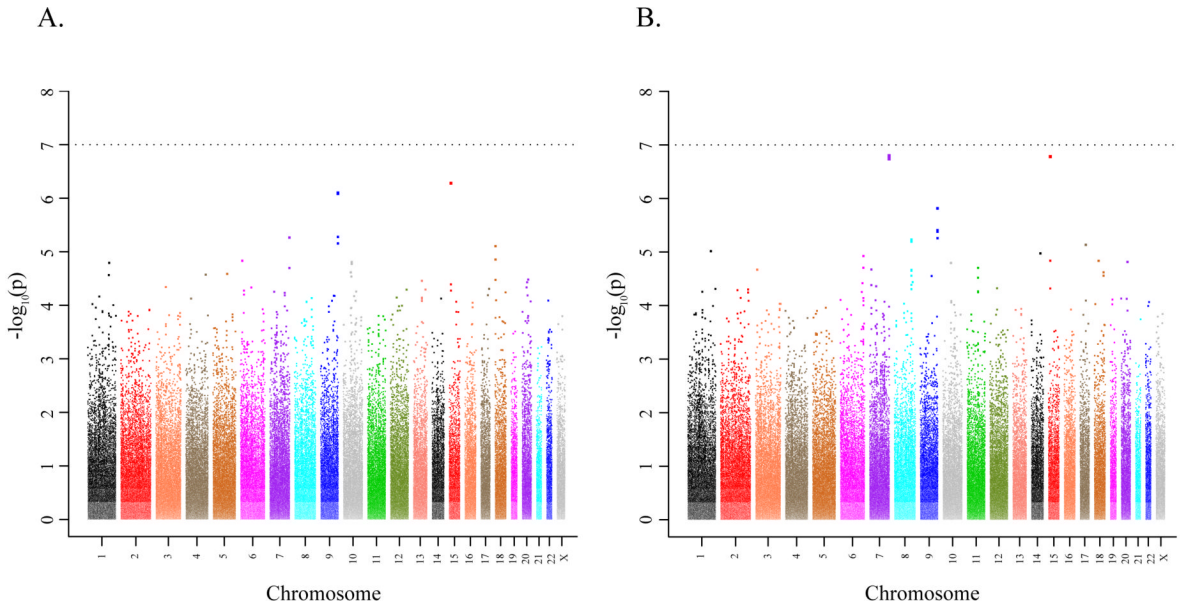

Figure 1. Manhattan plot of the *P* values in the pancreatic cancer GWAS

The association with pancreatic cancer is shown for the entire GWAS (12 cohort studies, and the Mayo case-control study, see Online Methods) (A), and the results of the GWAS including only the 12 cohorts studies (B). Association was assessed using unconditional logistic regression adjusted for study, arm, age, sex, ancestry and the top five principal components of the population stratification analysis. The x axis represents chromosomal locations and the y axis shows *P* values on a logarithmic scale.

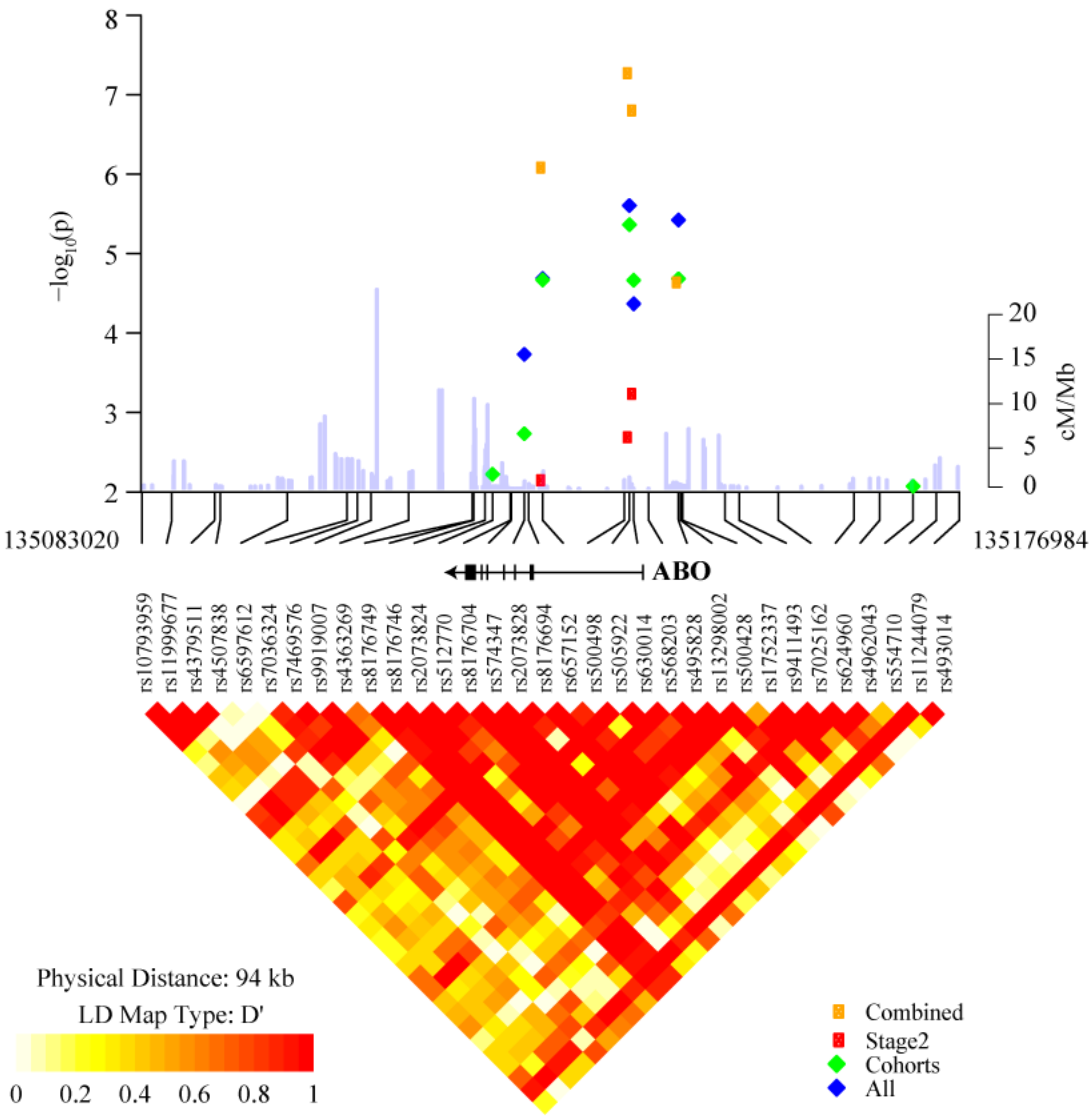

Figure 2. Association and linkage disequilibrium plot of the 9q34 locus

Association results are shown for all GWAS studies (blue diamonds), GWAS cohorts (green diamonds), replication studies (red circles) and all studies combined (yellow circles). Overlaid on the association panel is a plot of estimated recombination rates (cM/Mb) across the region from HapMap Phase II. The LD plot shows a region of chromosome 9 marked by SNPs, rs505922 and rs630014 (r^2=0.52 in HapMap CEU and 0.40 in PanScan European control individuals) and bounded by SNPs between chr9; 135,083,020-135,176,984 (NCBI Genome build 36). LD is depicted for SNPs with MAF > 5% within PanScan. Controls of European background (n=1,799 unrelated individuals). Note that rs505922 and rs630014 are located in the first intron of the *ABO* gene, shown above the LD plot. Only SNPs genotyped in both the GWAS and "Fast Track" replication are shown.

Table 1

Association of SNPs on chromosomes 9q34, 7q36 and 15q14 to risk of pancreatic cancer

The results from the unconditional logistic regression of the genotypes generated in the initial GWAS and the follow-up studies in a total of 3,891 pancreatic cancer cases and 4,001 controls. The analysis was adjusted for age in ten-year categories, sex, study, arm, ancestry and five principal components of population stratification.

Marker[a], Alleles[b], Chr[c], Location[c] and Gene[d]	Subset[e]	MAF[f]	Subjects[g]	χ^2[h]	*P* value[h]	OR_{Het} (95% CI)	OR_{Hom} (95% CI)[i]
rs505922 (T, C)	Stage 1 Cohorts	0.357|0.417	1462|1406	21.11	4.33E-06	1.29 (1.16-1.43)	1.66 (1.33-2.05)
9q34	Stage 1 All	0.357|0.411	1805|1771	22.18	2.48E-06	1.26 (1.14-1.39)	1.59 (1.31-1.92)
135139050	Stage 2	0.343|0.375	2127|2120	9.50	2.06E-03	1.15 (1.05-1.26)	1.32 (1.11-1.58)
ABO	Stage 1 + 2	0.349|0.392	3932|3891	29.58	5.37E-08	1.20 (1.12-1.28)	1.44 (1.26-1.63)
rs495828 (G, T)	Stage 1 Cohorts	0.192|0.236	1423|1362	18.11	2.08E-05	1.35 (1.18-1.55)	1.82 (1.38-2.41)
9q34	Stage 1 All	0.194|0.236	1755|1717	21.37	3.78E-06	1.34 (1.18-1.51)	1.79 (1.40-2.29)
135144688	Stage 2	0.223|0.238	1786|1718	2.10	1.47E-01	1.09 (0.97-1.21)	1.18 (0.94-1.47)
ABO	Stage 1 + 2	0.209|0.237	3541|3435	17.93	2.30E-05	1.19 (1.10-1.30)	1.43 (1.21-1.68)
rs657152 (G, T)	Stage 1 Cohorts	0.380|0.437	1463|1408	18.05	2.15E-05	1.26 (1.13-1.40)	1.59 (1.28-1.97)
9q34	Stage 1 All	0.380|0.430	1806|1773	18.13	2.06E-05	1.23 (1.12-1.35)	1.51 (1.25-1.83)
135129086	Stage 2	0.374|0.404	1791|1729	7.24	7.13E-03	1.14 (1.04-1.26)	1.30 (1.07-1.58)
ABO	Stage 1 + 2	0.377|0.417	3597|3502	24.29	8.28E-07	1.19 (1.11-1.27)	1.41 (1.23-1.61)
rs630014 (C, T)	Stage 1 Cohorts	0.475|0.421	1463|1408	18.04	2.16E-05	0.80 (0.72-0.88)	0.63 (0.51-0.78)
9q34	Stage 1 All	0.473|0.427	1805|1773	16.74	4.28E-05	0.82 (0.75-0.90)	0.67 (0.56-0.81)
135139543	Stage 2	0.479|0.441	2196|2118	11.83	5.84E-04	0.86 (0.79-0.94)	0.74 (0.63-0.88)
ABO	Stage 1 + 2	0.477|0.435	4001|3891	27.49	1.58E-07	0.85 (0.79-0.90)	0.71 (0.63-0.81)
rs167020 (G, A)	Stage 1 Cohorts	0.250|0.313	1462|1408	27.28	1.76E-07	1.37 (1.22-1.54)	1.88 (1.48-2.38)
7q36	Stage 1 All	0.259|0.307	1805|1773	20.06	7.52E-06	1.27 (1.15-1.41)	1.62 (1.31-2.00)
155312494	Stage 2	0.278|0.294	1802|1 734	2.39	1.22E-01	1.09 (0.98-1.20)	1.18 (0.96-1.45)
SHH	Stage 1 + 2	0.269|0.301	3607|3507	18.12	2.07E-05	1.17 (1.09-1.26)	1.38 (1.19-1.60)
rs172310 (C, A)	Stage 1 Cohorts	0.272|0.336	1454|1399	27.02	2.01E-07	1.36 (1.21-1.53)	1.85 (1.47-2.34)
7q36	Stage 1 All	0.282|0.329	1796|1763	17.43	2.98E-05	1.25 (1.12-1.38)	1.56 (1.26-1.92)
155308388	Stage 2	0.305|0.323	1768|1699	2.80	9.45E-02	1.09 (0.99-1.21)	1.19 (0.97-1.46)
SHH	Stage 1 + 2	0.293|0.326	3564|3462	17.04	3.66E-05	1.17 (1.08-1.25)	1.36 (1.17-1.57)
rs288746 (T, C)	Stage 1 Cohorts	0.109|0.144	1458|1403	14.57	1.35E-04	1.37 (1.16-1.61)	1.87 (1.36-2.59)

Marker[a], Alleles[b], Chr[c], Location[c] and Gene[d]	Subset[e]	MAF[f]	Subjects[g]	χ^2[h]	*P* value[h]	OR_{Het} (95% CI)	OR_{Hom} (95% CI)[i]
7q36	Stage 1 All	0.114|0.138	1800|1768	8.08	4.48E-03	1.23 (1.07-1.42)	1.52 (1.14-2.02)
155299433	Stage 2	0.116|0.128	1805|1735	2.59	1.08E-01	1.12 (0.97-1.30)	1.26 (0.95-1.68)
SHH	Stage 1 + 2	0.115|0.133	3605|3503	10.14	1.45E-03	1.18 (1.07-1.30)	1.39 (1.13-1.70)
rs8028529 (T, C)	Stage 1 Cohorts	0.198|0.255	1457|1404	25.92	3.55E-07	1.38 (1.22-1.56)	1.91 (1.49-2.45)
15q14	Stage 1 All	0.202|0.249	1800|1768	23.13	1.51E-06	1.31 (1.17-1.47)	1.72 (1.38-2.15)
34441889	Stage 2	0.231|0.229	1800|1736	0.02	8.92E-01	0.99 (0.89-1.11)	0.98 (0.79-1.23)
none	Stage 1 + 2	0.217|0.239	3600|3504	11.12	8.53E-04	1.14 (1.06-1.24)	1.31 (1.12-1.53)
rs4130461 (G, T)	Stage 1 Cohorts	0.224|0.273	1463|1408	18.71	1.53E-05	1.31 (1.16-1.47)	1.70 (1.34-2.17)
15q14	Stage 1 All	0.231|0.272	1806|1773	16.64	4.52E-05	1.25 (1.12-1.39)	1.56 (1.26-1.94)
34439130	Stage 2	0.256|0.250	1802|1736	0.39	5.32E-01	0.97 (0.87-1.08)	0.93 (0.75-1.16)
none	Stage 1 + 2	0.243|0.261	3608|3509	6.15	1.32E-02	1.10 (1.02-1.19)	1.21 (1.04-1.41)
rs4459505 (G, A)	Stage 1 Cohorts	0.177|0.218	1455|1402	15.51	8.21E-05	1.30 (1.14-1.49)	1.70 (1.30-2.21)
15q14	Stage 1 All	0.178|0.214	1796|1765	14.92	1.12E-04	1.26 (1.12-1.42)	1.59 (1.26-2.01)
34443314	Stage 2	0.196|0.198	1803|1737	0.08	7.81E-01	1.02 (0.90-1.14)	1.03 (0.82-1.31)
none	Stage 1 + 2	0.187|0.206	3599|3502	8.52	3.51E-03	1.13 (1.04-1.23)	1.28 (1.08-1.51)

[a] NCBI dbSNP identifier.

[b] Major allele, minor allele.

[c] Chromosome and NCBI Human genome Build 36 location.

[d] Gene neighborhood within 20 kb upstream and 10 kb downstream of SNP.

[e] Stage 1 is the initial GWAS and stage 2 the replication.

[f] Minor allele frequency in control and case participants.

[g] Controls, cases.

[h] 1 d.f. score test.

[i] Estimate assuming multiplicative odds model OR, odds ratio; Het, heterozygous; Hom, homozygous for minor allele. CI, 95% confidence interval.