Published in final edited form as:
Nat Genet. ; 43(9): 825–827. doi:10.1038/ng.879.

Common variation at 10p12.31 near *MLLT10* influences meningioma risk

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Author Contributions

RSH and MS conceived the study. RSH designed the study and obtained financial support. RSH, MS and SED drafted the manuscript. SED, PB, FJH and YPM performed statistical and bioinformatic analyses; PB managed sample coordination and laboratory analyses; BO and AL performed genotyping. The German (Bonn) cases were collected by MS and JS. Funding was obtained by MS and JS. Sample preparation in Bonn was overseen by MS. In the UK, AS, MJS, KM, SJH and RSH developed patient recruitment, sample acquisition and performed sample collection of cases. SM and LE managed collection of HNR controls. PH and TWM performed genotyping of the HNR controls, MMN managed sample coordination and laboratory analyses. For the Swedish INTERPHONE Study, MF, SL and AA developed study design and conducted patient recruitment and control selection; MF, SL, AA, BM and RH organized sample acquisition and performed sample collection of case and controls; UA coordinated sample collection and complied information into data files of cases and controls for statistical analyses, and BM and RH performed laboratory management and oversaw DNA extraction. The NSHDS samples were collected by Umeå University (Principal Investigator Göran Hallmans), and the additional samples were collected at the neurosurgery department in Umeå from 2005 and onwards (TB and RH) and through the national GLIOGENE study (Principal Investigator BM). In Denmark CJ and MK conducted patient recruitment and sample collection. All authors contributed to the final paper.

Competing Interests Statement

The authors declare no competing financial interests.

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The R suite can be found at http://www.r-project.org/
Detailed information on the tag SNP panel can be found at http://www.illumina.com/
dbSNP: http://www.ncbi.nlm.nih.gov/projects/SNP/
HapMap: http://www.hapmap.org/
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WGAViewer: http://www.genome.duke.edu/centers/pg2/downloads/wgaviewer.php
SNAP http://www.broadinstitute.org/mpg/snap/
IMPUTE: https://mathgen.stats.ox.ac.uk/impute/impute.html
SNPTEST: http://www.stats.ox.ac.uk/~marchini/software/gwas/snptest.html
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Abstract

To identify predisposition loci for meningioma we conducted a genome-wide association study of 859 cases and 704 controls with validation in two independent sample sets totaling 774 cases and 1,764 controls. We identified a novel susceptibility locus for meningioma at 10p12.31 (*MLLT10*; rs11012732, OR=1.46, $P_{combined}=1.88x10^{-14}$). This finding advances our understanding of the genetic basis of meningioma development.

Meningioma are adult brain tumors originating from the meningeal coverings of the brain and spinal cord and account for ~30% of all primary brain tumors1,2. Excluding exposure to ionizing radiation no environmental factor has convincingly been shown to influence meningioma risk3. Evidence for an inherited predisposition to meningioma is provided by the elevated risk seen in neurofibromatosis type-2 (MIM101000), Cowden (MIM601728), Werner (MIM277700) and Gorlin (MIM109400) syndromes. While the risk of meningioma associated with these disorders is high all are rare and collectively contribute little to the 3-fold increased risk of meningioma in the relatives of meningioma patients4.

Predicated on the hypothesis that the co-inheritance of multiple low-risks variants contribute to meningioma risk we conducted a genome-wide association study (GWAS) of 961 cases ascertained through the Department of Neurosurgery, University of Bonn Medical Center, Germany. Genotyping was performed using Illumina 660w-Quad and OmniExpress BeadChips. There was no evidence of systematic bias between genotyping platforms (Supplementary Methods and Supplementary Figure 1). Genotype frequencies in the cases were compared with German genotype data generated by the Heinz-Nixdorf Recall study

(HNR) of 811 population based controls genotyped using Illumina HumanOmni-1 Quad BeadChips (Supplementary Methods). Data on 303,182 autosomal SNPs common to cases and controls were included in the analysis. After stringent quality control filtering (Supplementary Methods and Supplementary Table 1), we analyzed 270,875 SNPs in 859 meningioma cases and 704 controls. Principal component analysis showed that the cases and controls were genetically well matched (Supplementary Figure 2). We assessed the association between each SNP and meningioma risk using the Cochran-Armitage trend test. Quantile-quantile plots of the negative logarithm of genome-wide *P*-values showed there was minimal inflation of the test statistics rendering substantial cryptic population substructure or differential genotype calling between cases and controls unlikely (genomic control inflation factor5, λ_{gc}=1.08; Supplementary Figure 1). For completeness principal components analysis was performed using the Eigenstrat6 software to determine the effects of population substructure on our findings ($\lambda_{corrected}$=1.02, Table 1, Supplementary Methods and Supplementary Figure 1).

We carried out a fast-track replication of 10 SNP associations from the GWAS making use of two independent case-control series (Supplementary Methods) – UK replication series (412 cases; 760 controls), and Scandinavian replication series (362 cases; 1,004 controls). Selection of the 10 SNPs was based on statistical significance at each genomic locus and where support was provided by other SNPs mapping to the same region at $P<3x10^{-4}$ (Supplementary Table 2). rs12770228 validated (*i.e.* $P_{trend}\leq0.05$) in the UK replication series ($P_{trend}=2.06x10^{-6}$) and was further validated in the Scandinavian replication series (P_{trend}=0.015; Table 1). In a combined analysis of the three case-control series the rs12770228 association attained genome-wide significance ($P_{trend}=4.72\times10^{-11}$, OR=1.39, CI: 1.26-1.53, P_{het}=0.31; Table 1).

rs12770228 localises to 10p12.31 (21,823,640 bps) and is contained within a 500kb region of linkage disequilibrium (LD). This genomic region encompasses the genes *MLLT10* (ALL1-fused gene from chromosome 10, myeloid/lymphoid or mixed lineage leukemia translocated to 10; also known as *AF10*) and *DNAJC1* (DnaJ homolog, subfamily C, member 1; Figure 1 and Supplementary Figure 3). rs12770228 maps 40kb 5′ to *MLLT10* and is within the 3′ UTR of the predicted transcript *C10orf114*. To explore the region further we imputed unobserved genotypes in cases and controls using HapMap Phase III and 1000genomes data. This imputation indicated an extended region of association within the LD block encompassing *MLLT10* (Figure 1, Supplementary Methods) with the imputed SNP rs11012732 providing the best evidence for the association signal at the 10p12.31 locus (21,870,110 bps, $P=6.04x10^{-6}$). Direct genotyping of rs11012732 in each of the three case-control series showed that this SNP provided a stronger association signal with meningioma risk than rs12770228 ($P_{trend}=1.88x10^{-14}$, OR=1.46, CI:1.32-1.61, P_{het}=0.25; Table 1).

rs12770228 and rs11012732 are in strong LD (r^2=0.64, D'=0.83). The possibility of two independently acting loci annotated by rs12770228 and rs11012732 was not supported by logistic regression whereby the ORs for rs12770228 were 1.39 ($P=4.72\times10^{-11}$) and 1.06 (P=0.56) without and with adjustment for rs11012732. Similarly the ORs for rs11012732 were 1.46 ($P=1.88\times10^{-14}$) and 1.38 ($P=5.80x10^{-3}$) without and with adjustment for rs12770228.

MLLT10 participates in several chromosomal rearrangements that result in various leukemias. The leucine zipper domain of *MLLT10* interacts with *GAS41* and through interaction with integrase interactor-1 acts to remodel chromatin and modulate transcription. While *MLLT10* is ubiquitously expressed there is currently no evidence for a role in meningioma. However, loss of heterozygosity for markers from chromosome 10p (and therefore putatively including *MLLT10* and *DNAJC1*) have been described in >30% of meningioma7. *MLLT10* is an essential and dedicated activator of Wnt-dependent transcription8 and Wnt-pathway activation has been implicated in development of anaplastic meningioma1. Downregulation of microRNA-200a, which activates the Wnt pathway, has been shown to promote tumor growth in both meningioma cell cultures and in an athymic mouse model9.

Elucidation of the basis of the 10p12.31 association will require fine–mapping and functional analyses. However, to examine if any directly typed or imputed SNPs annotate a putative transcription factor (TF) binding/enhancer element, we conducted a bioinformatic search of the region of association using Transfac Matrix Database10 and PReMod11 software (Supplementary Table 3). Multiple transcript variants encoding different isoforms have been identified for *MLLT10*. While the most significant SNP, rs11012732, does not map to a known or predicted transcription factor binding module, it localizes within intron 2 of *MLLT10.* To explore whether the 10p12.31 association reflects *cis*-acting regulatory effects on a nearby gene, we searched for genotype-expression correlations in 90 EBV-transformed lymphoblastoid cell lines using previously described data12,13. There was no statistically significant association between either rs12770228 or rs11012732 genotype and *DNAJC1* or *MLLT10* expression after adjustment for multiple testing (Supplementary Figure 4). This finding does not however preclude the possibility that a causal variant at this locus may have subtle effects on expression. Furthermore, it is likely that a cumulative long-term imbalance in expression of target genes, and cell type specific expression differences, may not be well modeled by EBV-transformed lymphocytes.

Most meningioma (>80-90%) are slow growing (World Health Organization [WHO] grade I tumors), whilst rare subtype (clear cell, chordoid, papillary, rhabdoid), as well as brain invasive, atypical (all assigned to the WHO grade II) and particularly anaplastic (WHO grade III) meningioma are more aggressive1. All forms of meningioma are characterized by female predominance. We assessed the relationship between 10p12.31 genotype with WHO grade and sex by case-only analysis. To minimize diagnostic bias, analysis of the relationship between tumor grade and genotypes was restricted to the German cases which had all been treated by one clinical centre. These analyses provided no evidence for association between rs12770228 or rs11012732 with tumor grade or sex after adjusting for multiple testing, consistent with a generic effect of genotype on meningioma risk.

The identification of risk variants at 10p12.31 implicates an important role for networks involving *MLLT10* in the development of meningioma. Given the modest size of our study it is likely that further risk variants for meningioma will be identified through additional studies.

Online Methods

Subjects and samples

Genome-wide association study—The German case series was based on 961 patients (299 male; mean age at diagnosis 60 years, standard deviation [SD] 13) who underwent surgery for a meningioma (International Classification of Diseases, Tenth revision, codes D32/C70) at the Department of Neurosurgery, University of Bonn Medical Center, between 1996 and 2008. All histological diagnoses were made at the Institute for Neuropathology/ German Brain Tumor Reference Center, University of Bonn Medical Center. Control subjects were 811 healthy individuals with no past history of malignancy from the Heinz Nixdorf Recall study (HNR; 397 male, mean age at sampling 60 years, SD 8)14.

Replication series—Meningioma cases in the UK-replication (ICD10 codes D32/C70) and Scandinavian-replication series (ICD-O 9530-9537) were ascertained through the INTERPHONE Study15. Briefly, INTERPHONE was a multicenter epidemiologic case–control study coordinated by the International Agency for Research on Cancer to investigate whether mobile phone use is associated with the risk of primary brain tumors, acoustic neuroma and malignant parotid gland tumors.

The UK-replication series comprised 412 adult meningioma cases (91 male, age at diagnosis 50 years, SD 10) ascertained from the Southeast England and the Northern UK, including central Scotland. Controls were healthy population based individuals with no past history of any malignancy, ascertained through the National Study of Colorectal Cancer Genetics (381 male, average age at sampling 53 years, SD 12)16.

The Scandinavian-replication series comprised 362 adult meningioma cases (99 male, average age 55 years, SD 11) from Sweden (n=238) and Denmark (n=124). A subset of 71 meningioma cases in the Swedish-replication series were ascertained from the neurosurgery clinic at Umeå University Hospital. Controls were randomly selected from population registers within each country and frequency matched to case patients on age, sex, and region (468 male, average age at sampling 51 years, SD 12).

Ethics—Collection of blood samples and clinico-pathological information from subjects was undertaken with informed consent and relevant ethical review board approval in accordance with the tenets of the Declaration of Helsinki.

Genotyping—DNA was extracted from samples using conventional methodologies and quantified using PicoGreen (Invitrogen, Carlsbad, USA). Genotyping of cases in the GWAS was conducted using either Illumina Infinium HD Human660w-Quad or OmniExpress BeadChips according to the manufacturer's protocols (Illumina, San Diego, USA). DNA samples with GenCall scores <0.25 at any locus were considered “no calls”. A SNP was deemed to have failed if fewer than 95% of DNA samples generated a genotype at the locus. Cluster plots were manually inspected for all SNPs considered for replication. Validation and replication of associations were performed using competitive allele-specific PCR KASPar chemistry (KBiosciences Ltd, Hertfordshire, UK). All primers and probes used are

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available on request. Samples having SNP call rates of <95% were excluded from the analysis.

To ensure quality of genotyping in all assays, at least two negative controls and 1-2% duplicates (showing a concordance >99.99%) were genotyped. To exclude technical artifact in genotyping we performed cross-platform validation and sequenced a random series of 184 samples to confirm genotyping accuracy (concordance >99.99%).

Statistical and bioinformatic analysis—We applied pre-determined quality control metrics to the GWAS data (Supplementary Table 1). We restricted analyses to samples for whom >95% of SNPs were successfully genotyped, thus eliminating 21 cases. Controls from the HNR were excluded if they had a self-reported non-German Ancestry (n=32) or a personal history of cancer (n=71). We computed identity-by-state (IBS) probabilities for all pairs (cases and controls) to search for duplicates and closely related individuals amongst samples (defined as IBS ≥0.80, thereby excluding first-degree relatives). For all identical pairs the sample having the highest call rate was retained, eliminating 17 cases and 3 controls. To identify individuals who might have non-Western European ancestry, we merged our case and control data with phase II HapMap samples (60 western European [CEU], 60 Nigerian [YRI], 90 Japanese [JPT] and 90 Han Chinese [CHB]). For each pair of individuals we calculated genome-wide IBS distances on 11,768 randomly chosen markers shared between HapMap and our SNP panel, and used these as dissimilarity measures upon which to perform principal component analysis. The first two principal components for each individual were plotted and any individual not present in the main CEU cluster (*i.e.,* 5% furthest from cluster centroids) was excluded from analyses. We removed 64 cases with non-CEU ancestry. We filtered out SNPs having a minor allele frequency [MAF] <5%, and a call rate <95% in cases or controls. We also excluded SNPs showing departure from Hardy-Weinberg equilibrium (HWE) at $P>10^{-5}$ in either cases or controls. Cluster plots for SNPs genotyped in the replication phase were independently examined by two researchers.

Main analyses were undertaken using R (v2.6), Stata10 (State College, Texas, US) and PLINK17 (v1.06) software. The association between each SNP and risk of meningioma was assessed by the Cochran-Armitage trend test. The adequacy of the case-control matching and possibility of differential genotyping of cases and controls were formally evaluated using quantile-quantile (Q-Q) plots of test statistics. The inflation factor λ_{gc} was based on the 90% least significant SNPs. We undertook adjustment for possible population substructure using Eigenstrat software. Ten principal components (PC) were calculated from a pruned set of genome-wide sets ($r^2<0.2$) with outlier removal on and corrections applied along the first two PCs (which showed some evidence of correlation with case control status). Odds ratios (ORs) and associated 95% confidence intervals (CIs) were calculated by unconditional logistic regression. Meta-analysis was conducted using standard methods18. Cochran's Q statistic was calculated to test for heterogeneity and associated *P* value provide (P_{het})19. To conduct a pooled analysis incorporating the Eigenstrat adjusted *P*-values from the GWAS we used the weighted Z-method implemented in the program METAL. Associations by sex and tumor grade were examined by logistic regression in case-only analyses.

Prediction of the untyped SNPs was carried out using IMPUTEv2, based on HapMap Phase III haplotypes release 2 (HapMap Data Release 27/phase III Feb 2009 on NCBI B36 assembly, dbSNP26) and 1000genomes. Imputed data were analysed using SNPTEST v2 to account for uncertainties in SNP prediction. LD metrics between HapMap SNPs were based on Data Release 27/phase III (Feb 2009) on NCBI B36 assembly, dbSNP26, viewed using Haploview software (v4.2) and plotted using SNAP. LD blocks were defined on the basis of HapMap recombination rate (cM/Mb) as defined using the Oxford recombination hotspots20 and on the basis of distribution of confidence intervals defined by Gabriel *et al.*21

To annotate potential regulatory sequences within disease loci we implemented *in silico* searches using Transfac Matrix Database v7.29 and PReMod10 software.

Relationship between SNP genotypes and expression levels—To examine for a relationship between rs12770228 and rs11012732 SNP genotypes and expression levels of *MLLT10* and *DNAJC1* in lymphocytes, we made use of publicly available expression data generated from 90 Epstein-Barr virus-transformed lymphoblastoid cell lines, derived from individuals of European descent, using Sentrix Human-6 Expression BeadChips (Illumina)12,13. Online recovery of data was performed using WGAViewer version 1.25 Software and the HapMap HapMart tool. Differences in the distribution of levels of mRNA expression between SNP genotypes were compared using a Wilcoxon-type test for trend22.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Cancer Research UK (C1298/A8362 supported by the Bobby Moore Fund) provided principal funding for the study. Additional support for the UK study was provided by the DJ Fielding Medical Research Trust. We acknowledge National Health Service (NHS) funding to the National Institute for Health Research (NIHR) Biomedical Research Centre.

The UK, Swedish and Danish INTERPHONE studies were supported by the European Union Fifth Framework Program “Quality of life and Management of Living Resources” (contract number QLK4-CT-1999-01563), and the International Union against Cancer (UICC). The UICC received funds for this purpose from the Mobile Manufacturers' Forum and Global System for Mobile Communications Association. Provision of funds via the UICC was governed by agreements that guaranteed INTERPHONE's complete scientific independence. These agreements are publicly available at http://www.iarc.fr/ENG/Units/RCAd.html. The Swedish INTERPHONE centre was also supported by the Swedish Research Council, the Cancer Foundation of Northern Sweden, the Swedish Cancer Society, and the Nordic Cancer Union, and the Danish center by the Danish Cancer Society. The UK centres were also supported by the Mobile Telecommunications and Health Research (MTHR) Programme and the Northern UK centre was supported by the Health and Safety Executive, Department of Health and Safety Executive and the UK Network Operators (O_2, Orange, T-Mobile, Vodafone, and ‘3′). AA received support from the Emil Aaltonen Foundation. We acknowledge the participation of the clinicians and other hospital staff, cancer registries and study staff who contributed to the blood sample and data collection for this study detailed in the British Medical Journal 2006: 332:883.

In Germany funding was provided to MS and JS by the Deutsche Forschungsgemeinschaft (Si 552, Schr 285), the Deutsche Krebshilfe (70-2385-Wi2, 70-3163-Wi3, 10-6262) and BONFOR. We are indebted to R. Mahlberg (Bonn) who provided technical support.

The GWAS made use of genotyping data from the population based HNR study. The HNR study is supported by the Heinz Nixdorf Foundation (Germany). Additionally, the study is funded by the German Ministry of Education and Science and the German Research Council (DFG; Project SI 236/8-1, SI236/9-1, ER 155/6-1). Funding was provided to LE by the Medical Faculty of the University Hospital of Essen (IFORES). The genotyping of the

Illumina HumanOmni-1 Quad BeadChips of the HNR subjects was financed by the German Centre for Neurodegenerative Disorders (DZNE), Bonn. We are extremely grateful to all investigators who contributed to the generation of this dataset.

Finally, we are grateful to all patients and individuals for their participation and we would also like to thank the clinicians and other hospital staff, cancer registries and study staff in respective centers who contributed to the blood sample and data collection.

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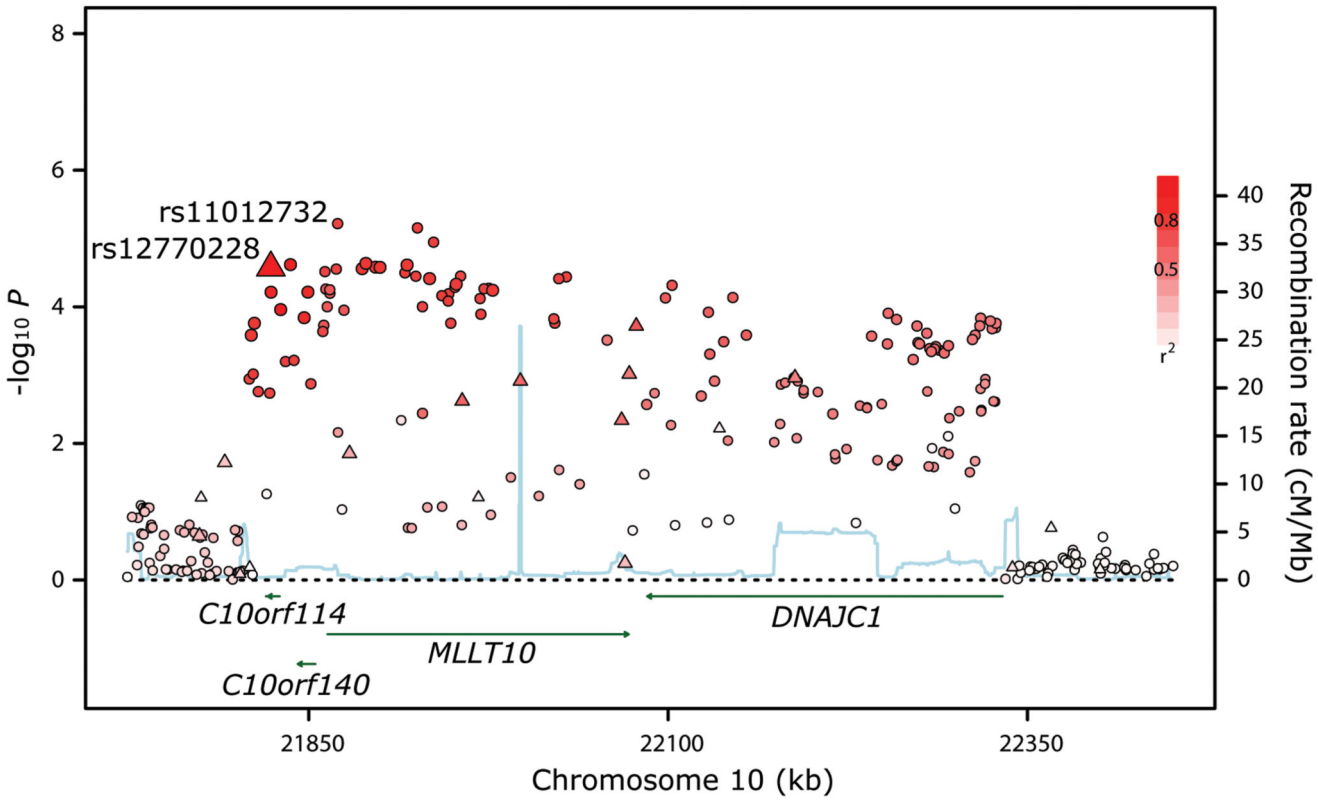

Figure 1. Regional plot of association results and recombination rates for the 10p12.31 susceptibility locus in the GWAS.

Association results of both genotyped (triangles) and imputed (circles) SNPs in the GWAS and recombination rates are plotted. $-\log_{10}P$ values (y-axis) of the SNPs are shown according to their chromosomal positions (x-axis). The top genotyped SNP in the combined analysis (rs12770228) and the most significant imputed SNP (rs11012732) are labeled. The color intensity of each symbol reflects the extent of LD with the top genotyped SNP – red (r^2>0.8) through to white (r^2<0.2). Genetic recombination rates (cM/Mb), estimated using HapMap CEU samples, are shown with a light blue line. Physical positions are based on build 36 (NCBI) of the human genome. Also shown are the relative positions of genes mapping to the region of association. Genes have been redrawn to show the relative positions; therefore, maps are not to physical scale.

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Table 1

Summary results for the 10p12.31 SNPs rs12770228 and rs11012732 associated with meningioma risk.

Results from the GWAS phase (German cases and HNR), replication series (UK and Scandinavian) and combined data are reported. [a]Minor allele frequency (MAF). [b]Odds ratio. [c]95% Confidence Interval.

SNP	Study	Cases				Controls						
		MAF[a]	AA	AG	GG	MAF	AA	AG	GG	OR[b]	95%CI[c]	*P*-value
rs12770228	German GWAS	0.39	123	426	309	0.32	74	302	328	1.37	1.18-1.59	2.67×10^{-5} *
	UK replication	0.41	73	187	144	0.31	76	321	361	1.54	1.30-1.85	2.06×10^{-6}
	Scandinavian replication	0.36	47	158	145	0.31	91	424	463	1.25	1.04-1.52	0.015
	Combined									**1.39**	**1.26-1.53**	**4.72×10^{-11}****
rs11012732	German	0.41	142	402	296	0.33	79	302	314	1.40	1.20-1.62	1.24×10^{-5}
	UK replication	0.45	80	198	118	0.33	87	316	338	1.70	1.40-2.00	2.02×10^{-8}
	Scandinavian replication	0.39	48	176	125	0.32	100	422	454	1.37	1.14-1.63	6.19×10^{-4}
	Combined									**1.46**	**1.32-1.61**	**1.88×10^{-14}**

*Eigenstrat corrected *P*-value = 4.53×10^{-4}

**Meta *P*-value with Eigenstrat corrected GWAS = 9.54×10^{-10}