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Common variation at 10p12.31(AF10/MLLT10) influences meningioma risk

AUTHOR ORDER TO BE CONFIRMED (HENCE PROVISIONAL)

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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 1,763 controls. We identified a novel susceptibility locus for meningioma at 10p12.31 (AF10/MLLT10; rs12770228, OR=1.39, $P_{\text{combined}}=4.7 \times 10^{-11}$). This finding advances our understanding of the genetic basis of meningioma development.

Meningiomas are adult brain tumors originating from the meningeal coverings of the brain and spinal cord and account for ~30% of all primary brain tumors. Excluding exposure to ionizing radiation no environmental risk factor for meningioma has convincingly been shown to influence meningioma risk. 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 substantive all are rare and collectively they do not make a significant contribution to the ~3-fold increased risk of meningioma seen in the relatives of meningioma patients.

Predicated on the hypothesis that the co-inheritance of multiple low-risks variants contribute to disease risk we conducted a genome-wide association study (GWAS) of 961 meningioma cases using Illumina 660w-Quad and OmniExpress BeadChips. The cases were ascertained through the Department of Neurosurgery, University of Bonn Medical Center, Germany. There was no evidence of systematic bias between genotyping platforms (Supplementary Methods and Supplementary Figure 1). Genotype frequencies in the cases were compared with publicly accessible German genotype data generated by the Heinz-Nixdorf Recall study (HNR) of 811 healthy individuals that had been genotyped using Illumina HumanOmni-1 Quad BeadChips (Supplementary Methods). Data on 303,182 autosomal SNPs common to cases and controls were included in this 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 these 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 significant cryptic population substructure or differential genotype calling between cases and controls unlikely (genomic control inflation factor, $\lambda_{gc}=1.08$; Supplementary Figure 1). For completeness principal components analysis was performed using the Eigenstrat software to determine the effects of population substructure on our findings (Table 1, Supplementary Methods and Supplementary Figure 1).

We carried out a fast-track replication of 10 associations from the GWAS. These SNPs were selected on the basis of statistical significance at each genomic locus and where support was provided by other SNPs mapping to the same region at $P<3\times 10^{-4}$. We performed additional genotyping in two independent case-control series (Supplementary Methods, Supplementary Table 1) – UK replication series (412 cases; 760 controls), and Scandanavian replication series (362 cases; 1,003 controls). A combined analysis of all case-control series revealed a genome-wide significant association (i.e. $P<5.0\times 10^{-8}$) at 10p12.31 (Table 1).

The SNP showing an association with meningioma, rs12770228 (combined $P=4.66\times 10^{-11}$, OR=1.39, CI: 1.25-1.51), localises to 10p12.31 (21,823,640 bp) and is contained within a 500kb region of linkage disequilibrium (LD). This genomic region encompasses the genes $AF10/MLLT10$ (ALL1-fused gene from chromosome 10, myeloid/lymphoid or mixed lineage leukemia translocated to 10) and $DNAJC1$ (DnaJ homolog, subfamily C, member 1; Figure 1 and Supplementary Figure 3). rs12770228 maps 40kb 5’ to $AF10/MLLT10$ 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 $AF10/MLLT10$ (Figure 1, Supplementary Methods).

$AF10/MLLT10$ participates in several chromosomal rearrangements which result in various leukemias. The leucine zipper domain of $AF10/MLL10$ interacts with $GAS41$ and through interaction with integrase interactor-1 act to remodel chromatin and modulate transcription. While $AF10/MML10$ 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 $AF10/MLL10$ and $DNAJC1$) have been described in >30% of meningiomas. It is intriguing that $AF10/MLLT10$ is an essential and dedicated activator of Wnt-dependent
transcription\(^8\) as Wnt pathway activation is implicated in development of anaplastic meningioma\(^1\). Downregulation of microRNA-200a promotes tumor growth in a meningioma cell cultures and in an athymic mouse model via activation of the Wnt pathway\(^9\).

Elucidation of the basis of the 10p12.31 association will require fine-mapping and functional analyses. 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 Database\(^10\), and PReMod\(^11\) software. The imputed SNP rs11012732 provided the best evidence for the association signal (\(P=6.04\times10^{-5}\)). Multiple transcript variants encoding different isoforms have been identified for \textit{AF10/MLLT10}. While rs11012732 SNP does not map to a known or predicted transcription factor binding module it localizes within the intron 2 of \textit{AF10/MLLT10}, thereby potentially having a direct effect on transcription (Supplementary Table 3, Supplementary Figure 3).

To explore whether the 10p12.31 association reflects \textit{cis}-acting regulatory effects on a nearby gene, we searched for genotype-expression correlations in 90 EBV-transformed lymphoblastoid cell lines using previously described data\(^12,13\). No association between rs11012732 genotype and \textit{DNAJC1} or \textit{MLLT10} expression was shown (Supplementary Figure 4). This does not preclude the possibility that a causal variant at this locus has subtle effects on expression. Furthermore, it is likely that only a cumulative long-term imbalance in expression of target genes, and expression differences may only be cell type specific, which may not be well modeled by EBV-transformed lymphocytes.

Most meningiomas (>80-90\%) are slow growing (World Health Organization [WHO] grade I tumors), rare subtypes (clear cell, chordoid, papillary, rhabdoid), as well as brain invasive, atypical (all assigned to the WHO grade II), and particularly anaplastic (WHO grade III) meningiomas are more aggressive\(^1\). Also, meningioma is characterized by female predominance. We therefore assessed the relationship between 10p12.31 genotype with WHO grade and sex by case-only analysis. Analysis of the relationship between tumour grade and genotypes was restricted to the German cases which had all been under the clinical care of one centre (Supplementary Table 4). There was no association between rs12770228 with
tumour grade or sex, consistent with a generic effect of genotype on meningioma risk (Supplementary Table 4).

The identification of risk variants at 10p12 implicates an important role for networks involving \textit{AF10/MLL10} 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.

\textit{Note: Supplementary information is available on the Nature Genetics website}

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**AUTHOR CONTRIBUTIONS**

RSH and MS conceived the study. RSH designed the study and obtained financial support. RSH, SED and MS drafted the manuscript. SED 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. XXXXXXX. All authors contributed to the final paper.

**PLEASE ADD**

**COMPETING INTERESTS STATEMENT**

The authors declare no competing financial interests (PLEASE SPECIFY IF ANY)
METHODS

Subjects and samples

Genome-wide association study

The German series was based on 961 patients 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)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. Full details of the Interphone Study have been previously published15. Briefly, the Interphone Study was a multicenter epidemiologic case–control study that was coordinated by the International Agency for Research on Cancer to investigate whether mobile phone use is associated with the risk of primary brain tumors and malignant parotid gland tumors.

The UK-replication series comprised 412 adult meningioma cases ascertained from the Southeast England and the Northern UK, including central Scotland (age at diagnosis 50 years, standard deviation [SD] 10). Controls were healthy population based individuals with no past history of any malignancy, ascertained through the National Study of Colorectal Cancer (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). 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 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 available on request. Samples having SNP call rates of <90% 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 96 samples to confirm genotyping accuracy (concordance >99.9%).

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. Samples self-reporting origin outside of the country of recruitment (n=32) or history of cancer (n=71) were excluded. 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 PLINK$^{17}$ (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 $\lambda_{gc}$ 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 methods$^{18}$. Cochran’s Q statistic to test for heterogeneity and the $I^2$ statistic to quantify the proportion of the total variation due to heterogeneity were calculated$^{19}$. Large heterogeneity is typically defined as $I^2 \geq 75\%$. 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, age and tumour 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 hotspots\textsuperscript{20} and on the basis of distribution of confidence intervals defined by Gabriel \textit{et al.}\textsuperscript{21}

To annotate potential regulatory sequences within disease loci we implemented \textit{in silico} searches using Transfac Matrix Database v7.29, PReMod10 and EEL software.

**Relationship between SNP genotypes and expression levels**

To examine for a relationship between SNP genotype and expression levels of rs12770228 in lymphocytes, we made use of publicly available expression data generated from analysis of 90 Caucasian-derived Epstein-Barr virus-transformed lymphoblastoid cell lines using Sentrix Human-6 Expression BeadChips (Illumina)\textsuperscript{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 trend\textsuperscript{22}.

**URLS**

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/


HapMap: http://www.hapmap.org/

1000Genomes: http://www.1000genomes.org/

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

EEL: http://www.cs.helsinki.fi/research/algodan/EEL/

PReMod: http://genomequebec.mcgill.ca/PReMod/welcome.do


JASPAR2 database: http://jaspar.cgb.ki.se/
EIGENSTRAT: http://genepath.med.harvard.edu/~reich/Software.htm
METAL: www.sph.umich.edu/csg/abecasis/metal
KBioscience: http://kbioscience.co.uk/
TABLE AND FIGURE LEGENDS

Table 1: Summary results for SNP rs12770228 associated with meningioma risk. Results from the GWAS phase (German cases and HNR controls), replication series (UK and Scandinavian) and combined data are reported. \(^{a}\)Odds ratio with 95% Confidence Interval. \(^{b}\)Eigenstrat adjusted \(P\)-values.

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 samples 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 is labeled by rs ID. 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.

SUPPLEMENTARY FIGURES AND TABLES

Supplementary Figure 1: Q-Q plots of the observed genome wide association \(P\)-values \((-\log_{10}P\) for (a) the meningioma cases typed on the Illumina 660w-Quad and OmniExpress beadchips \((\lambda=1.00)\); (b) meningioma cases and the HNR controls \((\lambda=1.08)\); (c) Eigenstrat corrected plot \((\lambda=1.02)\).

Supplementary Figure 2: Identification of individuals in the GWAS of non-European ancestry in cases and controls. The first two principal components of the analysis were plotted. HapMap CEU individuals are plotted in blue; CHB+JPT individuals are plotted in green; YRI individuals are plotted in red; GWAS cases after exclusions \((n=64)\) are plotted in orange and GWAS controls are plotted in purple.
Supplementary Figure 3: Plots of linkage disequilibrium and transcription factor binding sites at 10p12.31 locus. Upper panel shows: the positions of genes and transcripts encoded by the region and positions of relevant SNPs; regions with high densities of TFBSs, modules predicted by PReMod are shown in orange and groups predicted by EEL and the Transfac Matrix Database are shown in blue; sequence conservation across the region in mammals. Middle and lower panels show $r^2$ and $D'$ LD statistics from HapMap phase II data. The darker shading indicates strong LD between SNPs.

Supplementary Figure 4: Relationship between rs12770228 genotype and normalized lymphocyte MLLT10 mRNA expression. Expression of genes (normalized –log2 levels) is based on data from analysis of 90 Epstein-Barr virus–transformed lymphoblastoid cell lines using Sentrix Human-6 Expression BeadChip (Illumina, San Diego, USA). Data was recovered using WGAViewer Version 1.25 and the HapMap HapMart tool. Differences in the distribution of expression by SNP genotype were compared using a Wilcoxon-type test for trend.

Supplementary Table 1: a) Basic characteristics and b) quality control in each of the case-control series.

Supplementary Table 2: SNPs chosen for replication from GWAS phase. G1 and G2 refer to the german case data typed on the Illumina 660w-quad and OmniExpress chips respectively. a Chromosome location based on NCBI Human Genome Build 36 coordinates. b Minor Allele Frequency. c Hardy Weinberg Equilibrium P-values. d Eigenstrat adjusted P-values.

Supplementary Table 3: Details of transcription factor binding sites (TFBSs) as predicted by EEL (using binding profiles from the JASPAR2 database), the Transfac Matrix Database and PReMod. "Score" refers to the confidence value assigned to each predicted binding region by the three different programs. For comparison, the observed and imputed SNPs and associated P-values are shown.

Supplementary Table 4: Relationship between rs12770228 genotype and a) WHO grade and b) tumour grade. RAF, risk allele frequency.
REFERENCES


### Table 1: Summary results for SNP rs12770228 associated with meningioma risk.

Results from the GWAS phase (German cases and HN1), replication series (UK and Scandinavian) and combined data are reported. aOdds ratio with 95% Confidence Interval. bEigenstrat adjusted P-values.

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