Comprehensive Analysis of DNA Repair Gene Variants and Risk of Meningioma

Lara Bethke, Anne Murray, Emily Webb, Minouk Schoemaker, Kenneth Muir, Patricia McKinney, Sarah Hepworth, Polyxeni Dimitropoulou, Artitaya Lophatananon, Maria Feychting, Stefan Lönn, Anders Ahlbom, Beatrice Malmer, Roger Henriksson, Anssi Auvinen, Anne Kiuru, Tiina Salminen, Christoffer Johansen, Helle Collatz Christensen, Michael Kosteljanetz, Anthony Swerdlow, Richard Houlston

Background Meningiomas account for up to 37% of all primary brain tumors. Genetic susceptibility to meningioma is well established, with the risk among relatives of meningioma patients being approximately threefold higher than that in the general population. A relationship between risk of meningioma and exposure to ionizing radiation is also well known and led us to examine whether variants in DNA repair genes contribute to disease susceptibility.

Methods We analyzed 1127 tagging single-nucleotide polymorphisms (SNPs) that were selected to capture most of the common variation in 136 DNA repair genes in five case–control series (631 case patients and 637 control subjects) from four countries in Europe. We also analyzed 388 putative functional SNPs in these genes for their association with meningioma. All statistical tests were two-sided.

Results The SNP rs4968451, which maps to intron 4 of the gene that encodes breast cancer susceptibility gene 1–interacting protein 1, was consistently associated with an increased risk of developing meningioma. Across the five studies, the association was highly statistically significant (trend odds ratio = 1.57, 95% confidence interval = 1.28 to 1.93; $P_{trend} = 8.95 \times 10^{-6}$; P = .009 after adjusting for multiple testing).

Conclusions We have identified a novel association between rs4968451 and meningioma risk. Because approximately 28% of the European population are carriers of at-risk genotypes for rs4968451, the variant is likely to make a substantial contribution to the development of meningioma.

J Natl Cancer Inst 2008;100:270–276

Meningiomas account for up to 37% of all primary brain tumors (1–4). Direct evidence for an inherited predisposition to meningioma is provided by the elevated risk associated with neurofibromatosis type 2 (MIM #101000) and Werner (MIM #277700) and Gorlin (MIM #109400) syndromes (5). These disorders are rare and do not account for the threefold elevated risk of meningioma in relatives of patients (6). Therefore, much of the variation in genetic risk is likely to be explained by combinations of common lower penetrance variants. Because linkage studies lack power to detect alleles with moderate effects on risk, case–control association studies are required.

A relationship between meningioma risk and exposure to ionizing radiation has been established (7–10), as has evidence of an inherited predisposition to the development of radiation-associated meningioma (11). These findings provide a strong rationale to explore whether variants in DNA repair genes contribute to disease susceptibility. We examined the relationship between common variants in 136 DNA repair genes and meningioma risk using five case–control series that were established through the Interphone Study (12). In addition to assaying 1127 tagging single-nucleotide polymorphisms (SNPs) that were selected to capture most of the common variation in DNA repair genes, we also genotyped 388 putative functional SNPs in these genes, including 69 nonsynonymous coding SNPs that have the potential to directly affect the function of expressed proteins.

Affiliations of authors: Sections of Cancer Genetics (LB, AM, EW, RH) and Epidemiology (MS, AS), Institute of Cancer Research, Sutton, UK; Division of Epidemiology and Public Health, University of Nottingham Medical School Queen's Medical Centre, Nottingham, UK (KM, PD, AL); Centre for Epidemiology and Biostatistics, University of Leeds, UK (PM, SH); Division of Epidemiology, Institute of Environmental Medicine (MF, A. Ahlbom) and Department of Medical Epidemiology and Biostatistics (SL), Karolinska Institutet, Stockholm, Sweden; Department of Radiation Sciences, Oncology, Umeå University, Sweden (BM, RH); Department of Epidemiology, Tampere School of Public Health, University of Tampere, Finland (A. Auvinen, TS); Department of Research and Environmental Surveillance, Radiation and Nuclear Safety Authority, STUK, Helsinki, Finland (A. Auvinen, AK, TS); Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark (CJ, HCC); Neurosurgical Department, Rigshospitalet, Copenhagen, Denmark (MK).

Correspondence to: Richard Houlston, PhD, Section of Cancer Genetics, Institute of Cancer Research, 15 Cotswold Rd, Sutton, Surrey SM2 5NG, UK (e-mail: richard.houlston@icr.ac.uk).

See "Funding" and "Notes" following "References."

DOI: 10.1093/jnci/djn004

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Subjects and Methods

Study Subjects

The study was based on five case–control series that contributed to the Interphone Study (13) and have been previously used for candidate gene analyses (14,15). 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 five case–control series were assembled in the Thames regions of Southeast England (UK-Southeast); the Northern UK, including central Scotland, the West Midlands, West Yorkshire, and the Trent area (UK-North); the Stockholm, Lund, Göteborg, and Umeå regions of Sweden; throughout Denmark; and all regions of Finland, except Northern Lapland and Åland. All five centers followed the core protocol of the Interphone Study, with the following extensions to the study design: a wider age range of patients, an extended questionnaire, and collection of blood samples. Adult patients with primary brain tumors were identified through neurosurgery, neuropathology, oncology, and neurology centers and cancer registries. Eligible case patients were individuals diagnosed with primary brain tumors between September 1, 2000, and February 29, 2004 (the dates of case ascertainment within this period vary between centers). Control subjects were individuals of the same age and residence criteria as case patients and who had no history of a cerebral tumor. In Sweden, Denmark, and Finland, control subjects were randomly selected from population registers within each country and frequency matched to case patients on age, sex, and region. In the United Kingdom, control subjects were randomly selected from general practitioners' practice lists, individually matched in the UK-North, and frequency matched in the UK-Southeast. In Sweden, UK-Southeast, UK-North, and Denmark, a blood sample was sought from all case patients and control subjects who were interviewed. In Finland, investigators did not collect blood from all interviewed participants; rather, they collected blood from a convenience sample of predetermined size from patients (n = 177) who were registered in three hospitals and from control subjects (n = 110) who were living in the areas served by these hospitals.

Case patients eligible for this study were primary brain tumor patients with meningioma [*International Classification of Diseases, Tenth revision*, codes C70; *International Classification of Diseases for Oncology, Second Edition*, codes 9530–9539 (16)] who had provided a blood sample and were aged 20–69 years in Sweden, Denmark, and Finland, 18–69 in UK-North, and 18–59 years in UK-Southeast. To minimize population stratification, case patients and control subjects with ethnic origin other than that of the country of recruitment were excluded. All remaining case patients with sufficient DNA quantity and quality were included in the study. Control subjects who were genotyped met the same requirements for DNA quantity and quality as case patients and were randomly frequency matched by sex to eligible case patients for each study center. Samples from 639 meningioma case patients and 638 control subjects were submitted for genotyping, corresponding to 68% of meningioma case patients and 40% of control subjects who had participated in the Interphone Study. The number, sex, and age of case patients and control subjects in each of the five case–control series successfully genotyped in this study were as follows: UK-North, 174 case patients (37 males, 137 females; mean [SD] age at diagnosis = 52 [10] years) and 175 control subjects (41 males, 134 females; mean [SD] age at recruitment = 50 [11] years); UK-Southeast, 121 case patients (27 males, 94 females; mean [SD] age at diagnosis = 47 [8] years) and 123 control subjects (27 males, 96 females; mean [SD] age at recruitment = 46 [10] years); Sweden, 149 case patients (50 males, 99 females; mean [SD] age at diagnosis = 55 [9] years) and 149 control subjects (51 males, 98 females; mean [SD] age at recruitment = 52 [10] years); Denmark, 110 case patients (35 males, 75 females; mean [SD] age at diagnosis = 52 [11] years) and 113 control subjects (35 males, 78 females; mean [SD] age at recruitment = 50 [11] years); Finland, 77 case patients (14 males, 63 females; mean [SD] age at diagnosis = 52 [10] years) and 77 control subjects (14 males, 63 females; mean [SD] age at recruitment = 53 [11] years). Research protocols and informed consent were obtained according to each group's institutional review board in accordance with the tenets of the declaration of Helsinki.

CONTEXT AND CAVEATS

Prior knowledge

Meningioma is an uncommon tumor that occurs in the brain, and relatives of meningioma patients have an increased risk of developing the disease. Risk of meningioma is also associated with exposure to ionizing radiation.

Study design

Analysis of single-nucleotide polymorphisms (SNPs) in DNA repair genes and their associations with meningioma risk in populations from five case–control studies in northern Europe.

Contribution

A SNP that is located in the coding portion of the gene for the breast cancer susceptibility gene 1–interacting protein 1 was associated with increased risk for meningioma.

Implication

The SNP identified may contribute substantially to meningioma risk because almost 30% of the European population carry the genetic variation.

Limitations

The study was performed using participants from four countries in Europe who were chosen based on their ethnicity, so how these results may apply to other populations is still unclear. The functional consequence of the genetic variation and how it may contribute to the development of meningioma are unknown.

Selection of DNA Repair Genes and SNPs

A list of 141 candidate DNA repair genes was initially compiled from the inventory of human DNA repair genes published by Wood et al. (17). The gene symbols, chromosome position, and accession numbers for these genes were updated to the current genome build (RefSeq 36.1) using the University of California Santa Cruz Genome Browser (18–20) and the National Center for Biotechnology Information (NCBI) Entrez Gene database (21). SNPs mapping to these genes were extracted from NCBI dbSNP version 126 (22).

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Of more than 35 000 SNPs identified in these 141 autosomal genes, 2765 common tag SNPs were found in 136 genes (minor allele frequency [MAF] > 0.1, correlation coefficient $r^2 \geq .8$ in HapMap CEPH [CEU] Utah residents with ancestry from northern and western Europe) using an Illumina in-house algorithm (Illumina Inc., San Diego, CA) that is based on the algorithm LDselect by Carlson et al. (23) and data provided by the International HapMap Project (24,25). After eliminating SNPs that were not suitable for analysis on the Illumina GoldenGate genotyping platform, one or two tag SNPs were selected per bin (ie, set of markers in strong linkage disequilibrium [LD] with each other defined by $r^2 \geq .8$) and were prioritized by the ability to perform well on the genotyping platform and having a putative function. In total, 1127 tagging SNPs were selected across 136 genes. These SNPs tag a total of 863 bins, with between 1 and 59 bins tagged per gene (mean [SD] = 6 [7.6] bins per gene, median = 5 bins per gene). In addition to these 1127 tag SNPs, 388 putative functional SNPs with CEU MAF of 0.05 or greater, predicted using the Illumina in-house algorithm for SNP selection and PupaSuite Web-based software (26,27), were added to the array. These included 69 nonsynonymous coding SNPs, 53 synonymous coding SNPs, 79 SNPs in untranslated regions, 50 SNPs at or near putative splice sites, 124 SNPs with Phast conservation score greater than 15 [log odds conservation score based on the multiple alignment of human, chimp, mouse, rat, dog, chicken, fugu, and zebra fish (28)], and 13 putative transcription factor–binding SNPs.

SNP Genotyping and Data Manipulation

DNA was extracted from blood samples using a standard salt extraction procedure or using the Chemagic Separation Module I (Chemagen AG, Baesweiler, Germany) and quantified using PicoGreen (Invitrogen Corp., Carlsbad, CA). DNA samples were genotyped using customized GoldenGate Arrays (Illumina Inc.). DNA samples with GenCall scores of less than 0.25 at any locus were considered to be “no calls.” A DNA sample was deemed to have failed if it generated genotypes at fewer than 80% of loci. An SNP was deemed to have failed if fewer than 95% of DNA samples generated a genotype at the locus. To ensure high quality of genotyping, a series of duplicate samples were genotyped and case patients and control subjects were genotyped in the same batches.

Statistical Methods

Statistical analyses were performed using R (29) and STATA Software (StataCorp LP, College Station, TX). The possibility of differential genotyping of case patients and control subjects were formally evaluated using quantile–quantile (Q–Q) plots of test statistics. Genotypic frequencies in control subjects for each SNP were tested for departure from Hardy–Weinberg equilibrium (HWE) using an exact test. To detect possible population stratification, we used the genomic control approach with all SNPs to estimate the stratification parameter and its associated 95% confidence interval (CI). The possibility of sex differences as a source of population substructure was evaluated by a Cochran-Armitage trend test for each SNP in male and female control subjects, and the number of statistically significant results at the 5% level was compared with the number expected by the χ^2 test.

For each SNP, we tested the null hypothesis of no association with meningioma using the Cochran-Armitage trend test calculated by logistic regression. The risk of meningioma associated with each SNP was quantified by trend odds ratios (ORs) and their 95% confidence intervals. Because age and sex did not substantially affect the statistical significance of associations between risk of meningioma and SNP genotype, we restricted adjustment to study center. The exact logistic regression model was fitted using LogXact 7 software (Cytel, Cambridge, MA). Correction for multiple testing in association studies using a simple Bonferroni correction is conservative due to the assumption of independence between tests. We, therefore, adopted an empirical Monte Carlo simulation approach based on 100 000 permutations, thus allowing for correlations due to LD throughout the genome. At each iteration, case and control labels were permuted at random and the maximum likelihood ratio test statistic max(L) determined. The statistical significance level for each SNP was estimated as the proportion of permutation samples with max(L) larger than the observed value.

Meta-analysis was conducted using standard methods. We used Cochran’s Q statistic and associated P value to test for variation due to heterogeneity (30).

The sibling relative risk attributable to a given SNP was calculated using the formula (31)

$$\lambda^* = \frac{p(pr_2 + qr_1)^2 + q(pr_1 + q)^2}{[p^2 r_2 + 2pqr_1 + q^2]^2}$$

in which p is the population frequency of the minor allele, $q = 1-p$, and r_1 and r_2 are the relative risks (estimated as odds ratios) for heterozygotes and rare homozygotes, relative to common homozygotes. Assuming a multiplicative interaction, the proportion of the familial risk attributable to a SNP was calculated as $\log(\lambda)/\log(\lambda_0)$, for which λ_0 is the overall familial relative risk estimated from epidemiologic studies, assumed to be 3.0 (6). The population attributable fraction with a SNP was estimated by $(x - 1)/x$, for which $x = (1 - p)^2 + 2p(1 - p)\mathrm{OR}_1 + p^2\mathrm{OR}_2$, p is the population allele frequency, and OR_1 and OR_2 are the odds ratios associated with hetero- and homozygosity, respectively (32).

To investigate epistatic interactions, each pair of SNPs that displayed an association with meningioma risk at the 10% level was evaluated by fitting a saturated logistic regression model, and the log likelihood ratio statistic for comparison with the main effects model was computed as this procedure can yield greater power to detect statistically significant associations (33). This statistic was compared against a χ^2 distribution with 1 *df*. Statistics were then adjusted for multiple testing using a Bonferroni correction (34), with the number of independent tests based on the number of genes (49 genes and 1176 independent tests) rather than the total number of SNPs (151 SNPs and 11 325 tests).

All statistical analyses were two-sided. P values less than .05 were considered to be statistically significant.

Results

Of the 1277 DNA samples submitted for genotyping, 1271 were successfully processed, generating in excess of 1.8 million genotypes. Genotypes were obtained for 633 of 639 (99.1%) case

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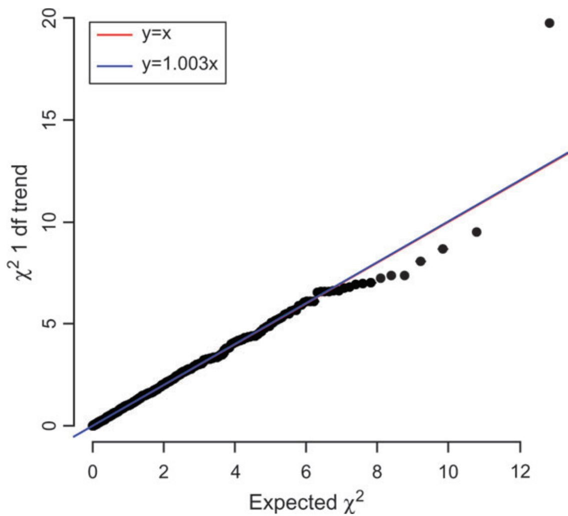

Fig. 1. Quantile–quantile plot of test statistics (1-*df* χ^2 trend test). **Black dots** represent the test statistics for the 1458 single-nucleotide polymorphisms tested in meningioma case patients and control subjects. The **blue line** (y = 1.003x) is fitted to the lower 90% of the distribution of observed test statistics and indicates no evidence of overinflation. The **red line** represents the global null hypothesis of no association at any locus.

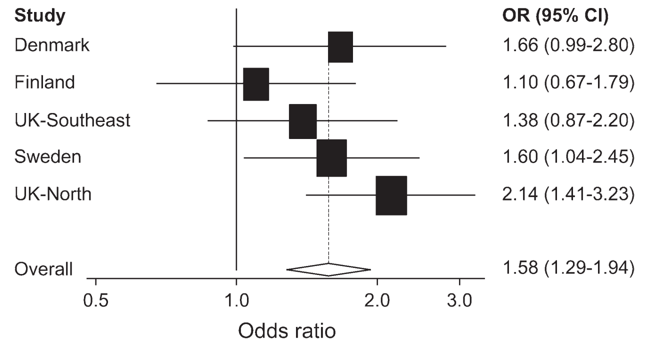

Fig. 2. Forest plot of the trend odds ratios (ORs) for rs4968451. The x-axis corresponds to the trend odds ratio. **Horizontal lines** represent 95% confidence intervals (CIs). Each **box** represents the odds ratio point estimate, and its area is proportional to the statistical weight of the study. The **diamond** (and **broken line**) represents the summary odds ratio adjusted by logistic regression for all five studies, with 95% confidence interval given by its width. The **unbroken vertical line** is at the null value (OR = 1.0). Genotype counts are (case patients; control subjects: AA, AC, CC): Denmark (73, 32, 5; 86, 26, 1); Finland (45, 27, 5; 51, 18, 8); UK-Southeast (73, 45, 3; 88, 30, 5); UK-North (106, 57, 11; 134, 40, 1); and Sweden (88, 54, 7; 102, 6, 1).

patients and 638 of 638 (100%) control subjects. Of the 1271 samples successfully genotyped, three were removed from the analysis due to unclear identity, leaving 1268 samples (631 case patients and 637 control subjects). Mean SNP call rates per sample were 99.8% for both the case patients and control subjects. Of the 1515 SNPs submitted for analysis, 1468 (96.9%) were satisfactorily genotyped. However, two of these were not polymorphic in control samples, one violated Hardy–Weinberg equilibrium in the control population from all five study centers, and seven had a genotype failure rate greater than 5%. Thus, these 10 SNPs were removed from further analysis, leaving 1458 SNPs for which genotype data were informative. These 1458 SNPs had mean individual sample call rates of 99.9% in both case patients and control subjects.

The observed number of SNPs with statistically significant deviation from Hardy–Weinberg equilibrium (exact test, $P < .05$) was not statistically significantly different from the expected number in the control subjects from any of the five study centers. Furthermore, the estimate of the stratification parameter ($\hat{\lambda}$) of the genomic control method was close to 1.0 in all five case–control datasets, with $\hat{\lambda}$ (95% CI) as follows: UK-North, 0.81 (0.71 to 0.92); UK-Southeast, 0.86 (0.74 to 0.96); Sweden, 1.09 (0.93 to 1.21); Finland, 0.90 (0.81 to 1.02); Denmark, 0.93 (0.84 to 1.07); overall, 0.99 (0.87 to 1.12), thereby providing additional evidence of no population substructure in any of the five study sample sets. No evidence of differential genotyping between case patients and control subjects was observed, as assessed by a Q–Q plot of the trend test statistics (Fig. 1). Similarly, there were no differences in genotype frequencies of SNPs between male and female control subjects as a source of potential confounding in analyses.

There was a statistically significant association ($P_{trend} < .01$) with meningioma for 12 SNPs. Of these, three mapped to breast cancer susceptibility gene 1 (BRCA1)–interacting protein 1 (*BRIP1*) and four to ataxia telangiectasia–mutated (Supplementary Table 1, available online). The most statistically significant was SNP rs4968451, which maps to intron 4 of *BRIP1* at 17q22 (OR = 1.57, 95% CI = 1.28 to 1.93; $P_{trend} = 8.95 \times 10^{-6}$; adjusted for study center); this SNP remained statistically significantly associated with risk after adjustment for multiple testing by permutation ($P_{adjusted}$ = .009) and by imposing a conservative Bonferroni correction (P = .01). We confirmed 96 genotyping results at this SNP by direct sequencing and obtained perfect concordance, thereby excluding a technical artifact. The association between rs4968451 and risk for meningioma was suggested in each of the five independent case–control datasets (Fig. 2), with no evidence of heterogeneity among studies (Q = 4.52, $P_{heterogeneity}$ = .34). Due to small cell counts for the rare homozygote genotype in individual studies, we fitted an exact logistic regression model. Results (OR = 1.58, 95% CI = 1.28 to 1.95; $P_{trend} = 9.62 \times 10^{-6}$) were similar to those found by asymptotic methods. Meningioma risks associated with hetero- and homozygosity for the minor allele of rs4968451 were 1.61 (95% CI = 1.26 to 2.06) and 2.33 (95% CI = 1.25 to 4.34), respectively, and were thus compatible with a multiplicative model of action.

Pairwise interactions among the 151 SNPs that showed some association with risk ($P < .1$) were examined by fitting full logistic regression models for each pair, generating 11 325 models. These models were then compared with the main effects model. A nominally statistically significant interaction at the 5% level was observed for 536 pairs of SNPs, but even the strongest interaction—between rs1776148 (nonsynonymous tagging SNP in *EXO1*) and rs966497 (tagging SNP in *ERCC8*) (P = .00018)—was not statistically significant after correction for multiple testing (P = .21).

A total of 18 SNPs mapped to *BRIP1*, of which two in addition to rs4968451 were associated with risk at the P = .01 level—rs9908659 and rs2048718, which map to introns 5 and 1 of *BRIP1*, respectively (Fig. 3). The risk allele for rs4968451 was found in only one of the five haplotypes predicted in the LD block defined by these three SNPs. Furthermore, previously published large-scale

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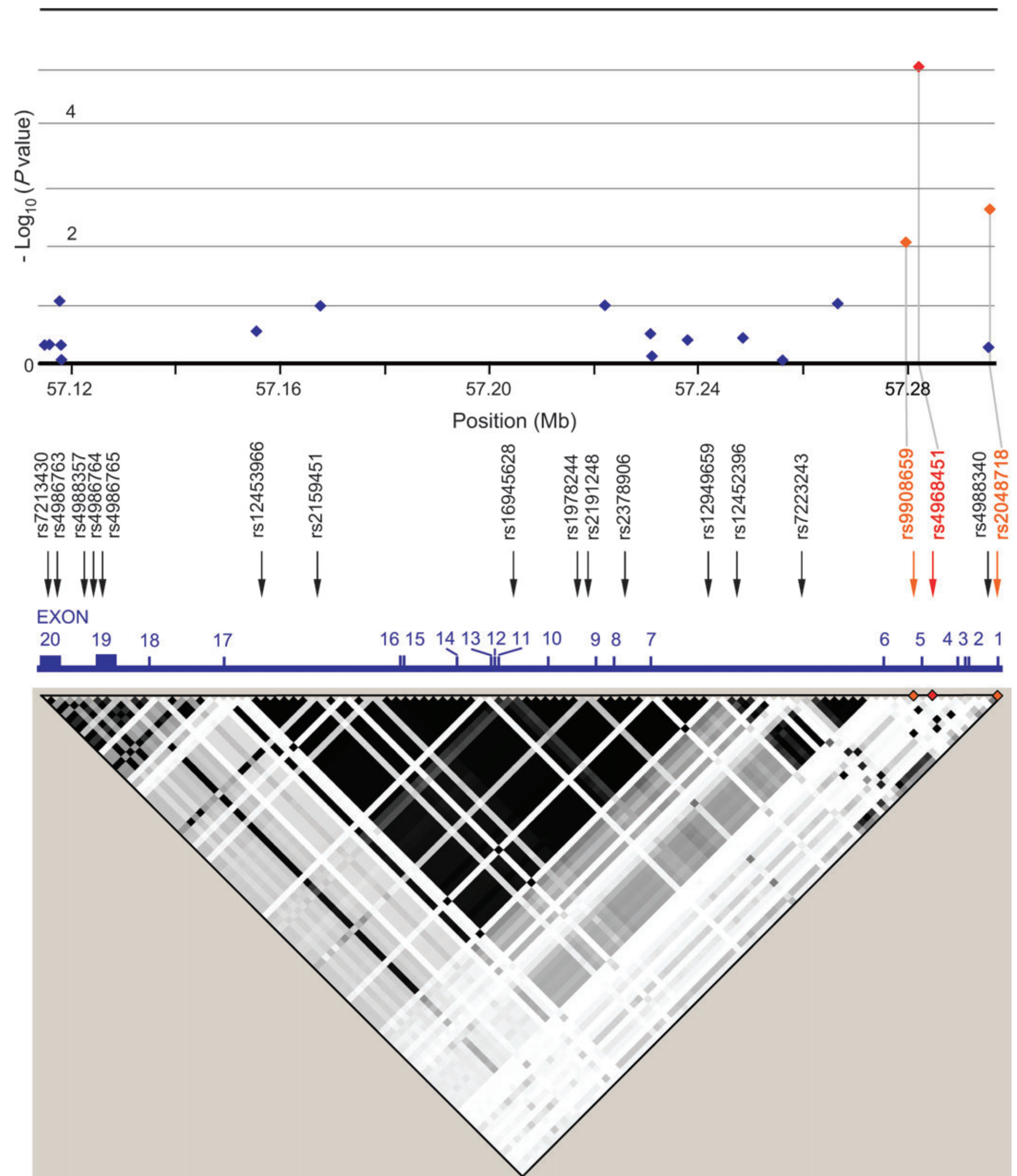

Fig. 3. Single-nucleotide polymorphisms (SNPs) tested across the breast cancer susceptibility gene 1–interacting protein 1 (*BRIP1*) locus. Map of the *BRIP1* gene, with schematic view of association analysis of the 18 SNPs mapping to the gene. The **upper panel** represents the negative log of the likelihood ratio *P* values (two-sided) adjusted by logistic regression for study center. The SNP statistically significantly associated with meningioma risk is shown in **red** ($P = 8.95 \times 10^{-6}$), and two other SNPs associated before correction for multiple testing are shown in **orange** (*P* = .008 and *P* = .002). The exon positions of the *BRIP1* gene are shown relative to 166 HapMap CEU SNPs, with minor allele frequency greater than 0.1% represented in the linkage disequilibrium heatmap (exon map is not to physical scale). The **lower panel** shows estimates of the square of the correlation coefficient (r^2) in gray scale (**black** = 1, **white** = 0), calculated for each pairwise comparison of SNPs derived by the Haploview (v.3.2) program.

resequencing data for *BRIP1* exclude the possibility that the variant associated with risk localizes within a coding region of the gene (35). Alternatively, because rs4968451 potentially tags the chromosome 17 region defined by 57,266,547–57,497,952 ($r^2 \geq 0.80$; HapMap database), there is the possibility that the variant is located 5′ to *BRIP1*.

Discussion

In this study, we have explored the role of polymorphic variation in DNA repair genes as a risk factor for meningioma on the basis of a priori evidence implicating such variation in disease risk. Our analysis has demonstrated that polymorphic variation within the *BRIP1* gene is associated with the risk of developing meningioma. The association was suggested in each of the case–control series and was statistically significant overall after adjusting for multiple testing, thereby providing robust evidence for the relationship between sequence variation in *BRIP1* and risk.

Because of the comparative rarity of meningiomas, previous searches for low-penetrance variants have, perhaps inevitably, been based on small numbers of case patients (36–38). A major strength of our study is that we have based our analysis on five independent case–control series, thereby providing data on a large sample set for a rare tumor.

A potential limitation of our study is that we analyzed a subset of subjects who were interviewed in the Interphone Study. We have, however, previously documented that there are no salient differences in the characteristics of those donating a blood sample from those who only responded to the study questionnaire (15). Population stratification is a concern in all association studies as a source of bias. Control subjects were, however, ascertained from population registries or general practitioners' lists, and we sought to further minimize this form of bias by excluding subjects with ethnicity other than that of the country of recruitment. Moreover, formal statistical analysis of the data provided no evidence that population substructure was a confounding

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factor in our study. Survivorship is another source of bias if a variant influences prognosis. However, this is unlikely to be a serious issue in this study because case patients were ascertained soon after diagnosis.

Our observation that variation in *BRIP1* is associated with risk of meningioma is biologically intriguing. *BRIP1* encodes a DEAH-box DNA helicase that interacts with the C-terminal domain of BRCA1 and has BRCA1-dependent DNA repair and checkpoint functions (39). The recent observation that truncating mutations in *BRIP1* can act as low-risk variants for breast cancer (35) provides biologic precedent for this finding. Breast cancer and meningioma are associated in that both occur most frequently in females aged 50–70 years, and women with meningioma have an approximately 1.5-fold increased risk for breast cancer and vice versa (40,41). Furthermore, both tumors express functional progesterone and estrogen receptors on their cell membranes (42), and there is increasing evidence implicating exogenous hormone use with risk of meningioma (43). Although there is currently no in vitro or in vivo evidence for estrogenic control of *BRIP1* expression, several canonical estrogen response elements have been identified within the gene, a major one being within 350 bp of rs4968451 (44). A change in estrogenically dependent *BRIP1* expression influencing meningioma risk rather than a direct functional consequence of sequence variation in the expressed protein is entirely plausible, given that the variant associated with risk is in an intron and, therefore, unlikely to effect an amino acid change.

In conclusion, we have identified a novel locus associated with meningioma risk. Because the MAF of rs4968451 is approximately 15% in the European populations we studied (and hence approximately 28% are carriers of risk alleles), the variant could be associated with the development of approximately 16% of meningioma. Although the locus may account for only approximately 1.1% of the excess familial risk of meningioma, under a multiplicative model of inherited susceptibility it has the potential to impact an individual's risk by acting in concert with other low-penetrance alleles. Further studies are required to characterize the genetic variation defined by rs4968451 and the functional consequences that lead to tumorigenesis. Specifically, examination of how *BRIP1* functions within the meninges and in meningioma may shed light on its relationship to tumor risk. Finally, our results provide evidence for a "common-disease common-variant" model of predisposition in the development of meningioma and justification for a continuing search for additional low-penetrance susceptibility alleles.

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Funding

Cancer Research UK (C1298/A6016 to R.S.H. and A.S.); European Commission Fifth Framework Program "Quality of Life and Management of Living Resources" (Contract QLK4-CT-1999-01563 to P.M., M.F., A. Auvinen., C.J., A.S., K.M.); the International Union against Cancer (UICC; RCA/01/08 to P.M., M.F., A. Auvinen., C.J., A.S., K.M.); Mobile Manufacturers' Forum and the Global System for Mobile Communications Association (to UICC); Danish Cancer Society (to C.J.); Emil Aaltonen Foundation (to A. Auvinen.); The Swedish Cancer Society, The Swedish Research Council, and the Cancer Foundation of Northern Sweden (to M.F.); Mobile Telecommunications and Health Research Program and the UK-North 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') (to P.M. and K.M.).

Notes

We are grateful to all the patients and individuals for their participation. We would also like to thank the clinicians and other hospital staff, cancer registries, and study staff and the funding bodies who contributed to the blood sample and data collection for this study and who are listed in our previous publications (14,45,46). The authors had full responsibility for the design of the study, the collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

Manuscript received August 30, 2007; revised December 7, 2007; accepted January 7, 2008.

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