Umeå University

This is an accepted version of a paper published in *Acta Oncologica*. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the published paper:

Wibom, C., Sjöström, S., Henriksson, R., Brännström, T., Broholm, H. et al. (2012)

"DNA-repair gene variants are associated with glioblastoma survival"

Acta Oncologica, 51(3): 325-332

URL: <http://dx.doi.org/10.3109/0284186X.2011.616284>

Access to the published version may require subscription.

Permanent link to this version:

<http://urn.kb.se/resolve?urn=urn:nbn:se:umu:diva-48594>

<http://umu.diva-portal.org>

DNA-repair gene variants are associated with glioblastoma survival

Carl Wibom, Sara Sjöström, Roger Henriksson, Thomas Brännström, Helle Broholm, Patrik Rydén, Christoffer Johansen, Helle Collatz-Laier, Sara Hepworth, Patricia A McKinney, Lara Bethke, Richard S Houlston, Ulrika Andersson, Beatrice S Melin

Department of Radiation Sciences, Oncology, Umeå University Hospital, Umeå, Sweden (C.W., S.S., R.H., U.A., B.S.M.)

Computational Life Science Cluster (CLiC), Umeå University, Umeå, Sweden (C.W., P.R.)

Department of Medical Biosciences, Pathology, Umeå University, Sweden (T.B.)

Department of Pathology, The Centre of Diagnostic Investigations, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark (H.B.)

Department of Mathematics and Mathematical Statistics, Umeå University, Umeå, Sweden (P.R.)

Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark (C.J.)

Department of ENT Head and Neck Surgery, Slagelse Hospital, Slagelse, Denmark (H.C.-L.)

Centre for Epidemiology and Biostatistics, University of Leeds, Leeds, UK (S.H., P.A.M.)

Section of Cancer Genetics, Institute of Cancer Research, Sutton, UK (L.B., R.S.H.)

Address for correspondence: Carl Wibom, Computational Life Science Cluster (CLiC), Umeå University, 90187 Umeå, Sweden. Email: carl.wibom@onkologi.umu.se

Running Title

Gene variants associated with glioblastoma outcome

Conflict of interest

The authors have no conflict of interest to declare.

Funding

The Swedish centre was supported by the Swedish Research Council, the Cancer Foundation of Northern Sweden, the Swedish Cancer Society, and the Nordic Cancer Union and the Umeå University Hospital Excellence grant. The Danish centre was supported by the Danish Cancer Society. Beatrice Melin was supported from Acta Oncologica foundation through the Royal Swedish Academy of Science. The cases were identified through the INTERPHONE study and supported by the European Commission 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 GSM Association. Provision of funds to the INTERPHONE study investigators 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 Northern UK Study centre received funding from the Mobile Telecommunications and Health Programme, the Health and Safety Executive, the

Department of Health, the Scottish Executive, and the United Kingdom Network Operators (“O2”, Orange, T-Mobile, Vodafone, “3”).

Abstract

Patient outcome from glioma may be influenced by germline variation. Considering the importance of DNA repair in cancer biology as well as in response to treatment, we studied the relationship between 1,458 SNPs, which captured the majority of the common genetic variation in 136 DNA repair genes, in 138 glioblastoma samples from Sweden and Denmark. We confirmed our findings in an independent cohort of 121 glioblastoma patients from the UK. Our analysis revealed nine SNPs annotating *MSH2*, *RAD51L1* and *RECQL4* that were significantly ($p < 0.05$) associated with glioblastoma survival.

Key words: DNA-repair gene variants; Glioblastoma outcome; association study; survival

Introduction

Glioblastoma, the most aggressive type of primary brain tumour, is associated with a very poor prognosis. Well-established positive prognostic factors include young age at diagnosis, high performance status, O(6)-methylguanine methyltransferase (*MGMT*) promoter methylation, and concomitant chemo and radiation treatment. Although these prognostic factors are useful for predicting prognosis and treatment requirements, there is variability in clinical outcome for patients with apparently the same stage disease. Hence accurate assessment of prognosis would be beneficial when choosing specific therapeutic options, and an assessment of the likelihood of response and adverse reactions to chemotherapeutic treatments would allow patient-tailored decisions on drug selection. These assessments could improve survival. In addition to somatic differences, germline variation probably also plays a role in defining individual patient outcome.

Conventional glioblastoma treatment, with radio- and chemotherapy, aims to inhibit cancer cells by promoting DNA damage. In turn, the cancer cells' sensitivity to treatment partly depends on their ability to repair the sustained DNA damage¹. Therefore, DNA repair genes involved in restoring DNA after ionizing radiation and chemotherapy are central genes to study in association with glioblastoma outcome. Aside from homologous recombination (a key mechanism that repairs radiation-induced DNA double strand breaks), there are specific mechanisms for nucleotide excision repair (NER) as well as DNA mismatch repair. Mutations in the repair pathways typically sensitize cells towards radiotherapy. For example, inhibition of

RAD51 family members, key components in repairing double strand breaks through homologous recombination, enhances the radioresistance of glioma cells².

We have comprehensively investigated a set of 1127 tag SNPs and 388 putative functional SNPs, all mapped to DNA-repair genes, in association with glioblastoma outcome. Through a collaborative international study, we have collected and genotyped 172 glioblastoma samples from Sweden and Denmark and confirmed significant findings in an independent dataset of 295 glioblastoma cases from Northern UK.

MATERIALS AND METHODS

Patients

The cases studied were originally collected between September 2000 and February 2004 for three case-control studies that contributed to the INTERPHONE Study. Full details are provided in previously published literature^{3,4}. In this study, the datasets are referred to as the Swedish-Danish dataset (172 glioblastoma cases) and the UK-north dataset (295 glioblastoma cases). Parts of these datasets have previously been included in studies that looked at both risk for glioma and outcome of glioblastoma⁵⁻⁸. The Swedish-Danish dataset was supplemented with clinical data collected for surgery, chemotherapy, radiotherapy and survival. Survival data was also available for the UK-north dataset, but individual treatment data was not. The follow-up time for each patient was calculated as the time between date of diagnosis and date of death, or date of last follow-up in the medical record for living patients, or October 31, 2006, whichever occurred first. In the Swedish-Danish data, 21 cases were excluded from further analysis due to missing follow-up data, and an additional 13 cases were excluded due to poor

DNA quality. In total, 138 cases were chosen for further analyses. Another 17 patients were missing values for at least one of the clinical parameters used for adjusting the statistical tests (i.e., extent of surgery, radiotherapy, chemotherapy, sex, country, and age at diagnosis). Hence these tests were performed on a subset consisting of 121 cases (Figure 1). In the UK-north dataset, 97 cases were excluded from further analysis due to missing follow-up (all from the Trent region of northern UK) and an additional 77 cases were excluded due to poor DNA quality, leaving 121 cases for the final analyses (Figure 1). For the Swedish-Danish dataset, the median follow-up was 12.9 months (range: 1.0-71.8 months); for the UK-north dataset, the median follow-up was 11.3 months (range: 2.2-78.8 months). See Table 1 for descriptions and details of treatment.

Glioblastoma cases were identified through neurosurgery, neuropathology, oncology, and neurology centres and cancer registries. The following selection criteria were used: glioblastoma ICD 10th revision code 94403, aged 20 to 69 years in the Nordic countries or aged 18 to 69 years in the Northern UK, and resident in the study region at time of diagnosis. Samples and clinicopathological information from participants were obtained after informed consent and with ethical review board approval in accordance with the tenets of the Declaration of Helsinki.

Selection of DNA repair genes and SNPs

The selection of SNPs has been described in detail elsewhere⁹. Briefly, a list of over 35,000 candidate DNA repair polymorphisms was assembled through an inventory of 141 known DNA repair genes in current databases¹⁰⁻¹². Using an Illumina in house algorithm based on HapMap

and LD select^{13,14}, we shortened the list to 2765 tag SNPs found in 136 genes (MAF >0.1, r^2 >0.8 in HapMap CEPH (CEU) Utah residents with ancestry from northern and western Europe). After eliminating the SNPs unsuitable for the genotyping assay and further prioritizing, we selected 1127 tag SNPs across 136 genes. This set of SNPs was supplemented with an additional 388 putative functional SNPs using the Illumina in house algorithm and PupaSuite web-based software (<http://pupasuite.bioinfo.cipf.es/>)¹⁵.

SNP genotyping

Standard methods were used to extract DNA from the collected blood samples, and DNA quantity was measured using the PicoGreen assay (Invitrogen Corp., Carlsbad, CA, USA). Protocols were standardised across all study centres. Next, the samples were genotyped by customised Illumina GoldenGate Arrays (Illumina Inc., San Diego, CA, USA). Samples with a corresponding GenCall score < 0.25 at any locus were set to “no call”. Genotyping of a sample was considered to have failed if it returned genotypes from less than 80% of all loci. Genotyping of an SNP was considered to have failed if it returned genotypes from less than 95% of all samples.

Statistical methods

In previous studies, genotypic frequencies in control subjects for each SNP were tested for departure from Hardy-Weinberg equilibrium (HWE) using an exact test⁹. The hazard ratios for the heterozygous and rare homozygous variants were estimated in comparison with the common homozygous variant using Fisher’s exact test in the Swedish-Danish dataset. Polymorphisms with a significant ($p < 0.05$) association to survival were selected for further

validation in the UK-north dataset. The statistics for the SNPs displaying a significant ($p < 0.05$) association also in the UK-north dataset were subsequently adjusted for treatment – i.e., extent of surgery, radiotherapy, chemotherapy, sex, country, and age at diagnosis – with a Cox proportional hazard ratio and a 95% confidence interval. The adjustment was performed in a subset of the Swedish-Danish dataset (Figure 2). Polymorphisms found statistically significant ($p < 0.05$) after adjustment for treatment were considered final significant findings. Furthermore, p-values from the last test were adjusted by applying an empirical method based on permutations ($n = 10,000$), similar to the method described by Lystig¹⁶. These adjustments were performed in R 2.11.1.

Results

This dataset, including information regarding genotyping success rates and quality, has been described in detail in a previous study by Bethke et al.⁹. After eliminating SNPs that were not adequately genotyped and checking genotype failure rates as well as violations of the Hardy-Weinberg equilibrium, a total of 1,458 SNPs remained for further analysis. This was one variable less than in Bethke's report⁹, because we had to remove one additional variable (rs4647404) due to genotyping failure among the samples in the Swedish-Danish dataset.

Out of the 1,458 analysed SNPs, 142 were associated with outcome at the initial screening in the Swedish-Danish dataset as determined by Fisher's exact test at the 95% significance level (Supplementary Table 1, found online, at [http://www.informahealthcare.com/\(DOI number\)](http://www.informahealthcare.com/(DOI number))). Validation analyses were conducted using an independent dataset (UK-north). Fifteen polymorphisms were found significantly associated with survival when subjected to external

validation in the UK-north dataset with corresponding directions of increasing/decreasing odds ratios in both datasets. Subsequent adjustment of these 15 polymorphisms for country, sex, age, surgery (radical or not), radio- and chemotherapy using Cox regression in a subset of the Swedish-Danish dataset revealed nine SNPs with significant association to survival (Table 2 and Supplementary Table 1 – supplementary table to be found online, at [http://www.informahealthcare.com/\(DOI number\)](http://www.informahealthcare.com/(DOI number))). The subset consisted of the 121 patients where this complete set of information was available (Figure 1). Two of the nine SNPs displayed significant p-values also following adjustment by permutation (Table 2). Figure 2 illustrates the survival discrepancies between the different gene variants; their respective median survival times are listed in Table 2. For the *MSH2* SNP rs2042649, the median survival for patients who were homozygous for the common allele was 13.3 months, compared to 10.6 for patients with the heterozygous variant. The median survival for the *RECQL4* rs756627 common allele was 10.6 months, compared to 15.8 for the rare allele.

Five SNPs were found within the *RAD51L1* gene (Table 2), all in strong LD with each other. Four of these – rs17192586, rs6573805, rs2038565, and rs8022206 – were located within the same haplotype block as calculated by the Confidence interval algorithm in the Haploview 4.2 software¹⁷ (Figure 3). On the observational level, they consequently shared an almost identical distribution with the same 32 individuals displaying a heterozygous genotype (an additional three patients were heterozygous for rs6573805), and the same three individuals displaying the rare homozygous genotype. The distribution was somewhat different for the fifth SNP in *RAD51L1* (rs11626809), although the same three individuals were also homozygous for the rare allele.

In genes *RECQL4* and *MSH2*, two separate SNPs were found to be significantly associated with outcome. The two SNPs in each gene were in LD with each other ($r^2 = 1$) in all instances, and accordingly the observational distribution was almost identical between the SNPs within the same gene.

Discussion

We have comprehensively studied a set of 1,127 tag SNPs as well as 388 putative functional SNPs in DNA-repair genes to elucidate the potential association between genetic variation in these genes and glioblastoma outcome. Glioma patients' response to standard chemo- and radiotherapy may largely be determined by the tumour's ability to repair DNA-damage. Thus knowledge regarding polymorphic variants in DNA-repair genes associated with outcome may influence future treatment decisions.

The nine SNPs that were found associated with survival were located in three different DNA-repair genes – *RECQL4*, *MSH2*, and *RAD51L1*. The SNPs within the same gene were generally in strong LD with each other and displayed identical or almost identical observational distribution. In most instances, a clear gene dosage effect could be observed, where patients who were homozygous for the rare allele displayed a significantly different hazard ratio compared to patients who were homozygous for the common allele (Table 2). These three genes are all implicated in different aspects of the intricate machinery that upholds genome integrity. Hence, one plausible explanation for our findings may be a differential response to DNA damaging therapy in glioblastoma patients with different genetic variants. Naturally, defects in these three genes – *RECQL4*, *MSH2*, and *RAD51L1* – are typically linked to various cancers. *RECQL4*

belongs to the RecQ helicase family, which primarily functions to unwind double stranded DNA to allow for replication and DNA maintenance. *RECQL4* is known to partake in DNA repair following UV-irradiation induced damage and is suggested to interact with *RAD51*, a key regulator of p53, to repair DNA double strand breaks¹⁸. Mutations in this gene are known to be involved in the Rothmund-Thomson syndrome, characterized in part by elevated risk to develop osteosarcoma¹⁹. *MSH2* is part of the DNA mismatch repair mutS family. The protein initiates DNA repair through recognizing and binding directly to mismatched nucleotides²⁰. *MSH2* malfunction is known to be involved in both Lynch syndrome and Turcot syndrome, where some patients have an inherited predisposition for both glioma and colorectal cancer. Chemotherapy is shown to reduce the *MSH2* protein expression levels in glioma²¹. The *RAD51* protein family, of which *RAD51L1* is a member, is involved in repairing DNA double strand breaks through homologous recombination²². It has been shown in animal studies that radioresistance is reduced by *RAD51* inhibition².

The SNPs reported to be significantly associated with survival in glioblastoma are for the most part mapped to gene introns, whereas non-synonymous SNPs included in the analysis did not show significant associations. For instance, of all the analysed SNPs within the *RECQL4* gene, one was non-synonymous (rs2306386); however, it did not turn out to be significantly associated with survival in this study, whereas two polymorphisms in introns did (Table 2). Although SNPs mapped to introns most likely will not yield altered amino acid sequences, they may still alter gene regulation in terms of transcription, splicing, and transcript turnover rates. It is also possible that the polymorphisms presented here are not directly responsible for the observed effect on survival, but rather are in LD with causative gene variants.

Today information is limited regarding SNPs in the genes where we found potential correlations to cancer survival. Although previous studies have linked various SNPs in these genes to different cancers, the focus has largely been to find associations to cancer susceptibility. Recently, a genome-wide association study implicated a specific SNP in *RAD51L1* for the risk of developing breast cancer²³. Although allelic variants of the genes described in our study have not been found to be related to an increased propensity to develop glioma, studies show that there are a number of low penetrance genes with such properties^{6,8,24}, including genes in DNA repair pathways⁹. With respect to survival, certain SNPs in each of *RecQ1* and *RAD54L* – members of the same families as *RECQL4* and *RAD51L1*, respectively – may be linked to outcome in pancreatic cancer²⁵. A few polymorphisms in other genes have been linked to survival in malignant glioma, e.g., gene variants of *CX3CR1*²⁶, as well as specific SNPs in the genes for *IL4R* and epidermal growth factor^{7,27}. Moreover, minisatellites in the vicinity of the *hTERT* gene may be related to glioblastoma outcome, although no conclusive results exist^{5,28}. Few studies have been confirmed in independent datasets. To our knowledge, however, genotype variants of the three genes described here have not previously been associated with glioblastoma survival.

In this study, all tissue samples were subject for pathology review before inclusion in the analysis. We believe this step to be necessary in order to avoid the risk of including other diagnoses and thereby possibly reaching erroneous conclusions. To further minimise the risk of erroneous conclusions, we adjusted our initial findings in an external test set to reduce the risk

of false positive findings (type 1 errors). The concerns regarding false positive findings are particularly relevant for the allelic variants in *RAD51L1* (rs2038565, rs6573805, rs11626809, rs17192586, and rs8022206) that were particularly rare, where only three or four patients displayed homozygosity for the rare genotype. The risk of spurious associations is naturally elevated when analysing rare alleles. This is an important factor to consider when evaluating our findings. In addition, we adjusted all p-values based on 10,000 permutations, which rendered only two significant variants (rs756627 and rs3757966) (Table 2). This, however, is likely to be a too stringent test, generating much the same results as Bonferroni correction. Relying entirely on this could result in many false negatives (type 2 errors). Therefore, we present both adjusted and un-adjusted p-values.

In conclusion, we have revealed associations between SNPs in four separate genes within different DNA repair pathways and glioblastoma survival. Considering the importance of DNA-repair genes in the resistance to cancer treatment, we believe it is plausible that they are of functional importance and may constitute future drug targets, especially when it comes to enhancing the efficacy of radiotherapy.

Acknowledgements

The Northern UK Study thanks all study interviewers, administrators, computer programmers and the study Steering Group chaired by Professor David Coggon, along with the many neuropathologists, neuroradiologists, neurosurgeons, neurooncologists, clinical oncologists, neurologists, nurses, and administrators in Scotland, West Midlands and West Yorkshire.

References

1. Jeggo P, Lavin MF. Cellular radiosensitivity: how much better do we understand it? *International journal of radiation biology*. Dec 2009;85(12):1061-1081.
2. Ohnishi T, Taki T, Hiraga S, Arita N, Morita T. In vitro and in vivo potentiation of radiosensitivity of malignant gliomas by antisense inhibition of the RAD51 gene. *Biochemical and biophysical research communications*. Apr 17 1998;245(2):319-324.
3. Cardis E, Richardson L, Deltour I, et al. The INTERPHONE study: design, epidemiological methods, and description of the study population. *European journal of epidemiology*. 2007;22(9):647-664.
4. Hepworth SJ, Schoemaker MJ, Muir KR, Swerdlow AJ, van Tongeren MJ, McKinney PA. Mobile phone use and risk of glioma in adults: case-control study. *BMJ*. Apr 15 2006;332(7546):883-887.
5. Andersson U, Osterman P, Sjöström S, et al. MNS16A minisatellite genotypes in relation to risk of glioma and meningioma and to glioblastoma outcome. *International journal of cancer*. Aug 15 2009;125(4):968-972.
6. Shete S, Hosking FJ, Robertson LB, et al. Genome-wide association study identifies five susceptibility loci for glioma. *Nature genetics*. Aug 2009;41(8):899-904.
7. Sjöström S, Andersson U, Liu Y, et al. Genetic variations in EGF and EGFR and glioblastoma outcome. *Neuro-oncology*. Mar 2 2010.
8. Andersson U, Schwartzbaum J, Wiklund F, et al. A comprehensive study of the association between the EGFR and ERBB2 genes and glioma risk. *Acta oncologica (Stockholm, Sweden)*. May 7 2010.
9. Bethke L, Webb E, Murray A, et al. Comprehensive analysis of the role of DNA repair gene polymorphisms on risk of glioma. *Human molecular genetics*. Mar 15 2008;17(6):800-805.
10. Karolchik D, Baertsch R, Diekhans M, et al. The UCSC Genome Browser Database. *Nucleic acids research*. Jan 1 2003;31(1):51-54.
11. Kent WJ, Sugnet CW, Furey TS, et al. The human genome browser at UCSC. *Genome research*. Jun 2002;12(6):996-1006.
12. Wood RD, Mitchell M, Lindahl T. Human DNA repair genes, 2005. *Mutation research*. Sep 4 2005;577(1-2):275-283.
13. Carlson CS, Eberle MA, Rieder MJ, Yi Q, Kruglyak L, Nickerson DA. Selecting a maximally informative set of single-nucleotide polymorphisms for association analyses using linkage disequilibrium. *American journal of human genetics*. Jan 2004;74(1):106-120.
14. The International HapMap Project. *Nature*. Dec 18 2003;426(6968):789-796.
15. Conde L, Vaquerizas JM, Dopazo H, et al. PupaSuite: finding functional single nucleotide polymorphisms for large-scale genotyping purposes. *Nucleic acids research*. Jul 1 2006;34(Web Server issue):W621-625.
16. Lystig TC. Adjusted P values for genome-wide scans. *Genetics*. Aug 2003;164(4):1683-1687.
17. Gabriel SB, Schaffner SF, Nguyen H, et al. The structure of haplotype blocks in the human genome. *Science (New York, N.Y.)*. Jun 21 2002;296(5576):2225-2229.

18. Petkovic M, Dietschy T, Freire R, Jiao R, Stagljar I. The human Rothmund-Thomson syndrome gene product, RECQL4, localizes to distinct nuclear foci that coincide with proteins involved in the maintenance of genome stability. *Journal of cell science*. Sep 15 2005;118(Pt 18):4261-4269.
19. Kitao S, Lindor NM, Shiratori M, Furuichi Y, Shimamoto A. Rothmund-thomson syndrome responsible gene, RECQL4: genomic structure and products. *Genomics*. Nov 1 1999;61(3):268-276.
20. Fishel R, Ewel A, Lescoe MK. Purified human MSH2 protein binds to DNA containing mismatched nucleotides. *Cancer research*. Nov 1 1994;54(21):5539-5542.
21. Stark AM, Witzel P, Strege RJ, Hugo HH, Mehdorn HM. p53, mdm2, EGFR, and msh2 expression in paired initial and recurrent glioblastoma multiforme. *Journal of neurology, neurosurgery, and psychiatry*. Jun 2003;74(6):779-783.
22. Kawabata M, Kawabata T, Nishibori M. Role of recA/RAD51 family proteins in mammals. *Acta medica Okayama*. Feb 2005;59(1):1-9.
23. Thomas G, Jacobs KB, Kraft P, et al. A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). *Nature genetics*. May 2009;41(5):579-584.
24. Wrensch M, Jenkins RB, Chang JS, et al. Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. *Nature genetics*. Aug 2009;41(8):905-908.
25. Li D, Frazier M, Evans DB, et al. Single nucleotide polymorphisms of RecQ1, RAD54L, and ATM genes are associated with reduced survival of pancreatic cancer. *J Clin Oncol*. Apr 10 2006;24(11):1720-1728.
26. Rodero M, Marie Y, Coudert M, et al. Polymorphism in the microglial cell-mobilizing CX3CR1 gene is associated with survival in patients with glioblastoma. *J Clin Oncol*. Dec 20 2008;26(36):5957-5964.
27. Scheurer ME, Amirian E, Cao Y, et al. Polymorphisms in the interleukin-4 receptor gene are associated with better survival in patients with glioblastoma. *Clin Cancer Res*. Oct 15 2008;14(20):6640-6646.
28. Carpentier C, Lejeune J, Gros F, et al. Association of telomerase gene hTERT polymorphism and malignant gliomas. *Journal of neuro-oncology*. Sep 2007;84(3):249-253.

Fig. 1 Samples' exclusion schema. The use of each dataset is indicated in italics.

Fig. 2 Kaplan-Meier plots illustrating the survival times related to the different gene variants in the Swedish-Danish dataset. GT 0, GT 1, and GT 2 represent the common homozygote, the heterozygote, and the rare homozygote, respectively. The x-axes represent survival time measured in months.

Fig. 3 Linkage disequilibrium (LD) plot of the five SNPs found significantly associated with survival, mapping to the RAD51L1 gene. The shading of each box represents r^2 values, ranging from white ($r^2=0$) to black ($r^2=1$). The numeric r^2 value is given within each box.

References

1. Jeggo P and Lavin MF. Cellular radiosensitivity: how much better do we understand it? *International journal of radiation biology* 2009;85:1061-81.
2. Ohnishi T, Taki T, Hiraga S, Arita N and Morita T. In vitro and in vivo potentiation of radiosensitivity of malignant gliomas by antisense inhibition of the RAD51 gene. *Biochemical and biophysical research communications* 1998;245:319-24.
3. Cardis E, Richardson L, Deltour I, Armstrong B, Feychting M, Johansen C, et al. The INTERPHONE study: design, epidemiological methods, and description of the study population. *European journal of epidemiology* 2007;22:647-64.
4. Hepworth SJ, Schoemaker MJ, Muir KR, Swerdlow AJ, van Tongeren MJ and McKinney PA. Mobile phone use and risk of glioma in adults: case-control study. *BMJ* 2006;332:883-7.
5. Andersson U, Osterman P, Sjöström S, Johansen C, Henriksson R, Brannström T, et al. MNS16A minisatellite genotypes in relation to risk of glioma and meningioma and to glioblastoma outcome. *International journal of cancer* 2009;125:968-72.
6. Shete S, Hosking FJ, Robertson LB, Dobbins SE, Sanson M, Malmer B, et al. Genome-wide association study identifies five susceptibility loci for glioma. *Nature genetics* 2009;41:899-904.
7. Sjöström S, Andersson U, Liu Y, Brännström T, Broholm H, Johansen C, et al. Genetic variations in EGF and EGFR and glioblastoma outcome. *Neuro-oncology* 2010;
8. Andersson U, Schwartzbaum J, Wiklund F, Sjöström S, Liu Y, Tsavachidis S, et al. A comprehensive study of the association between the EGFR and ERBB2 genes and glioma risk. *Acta oncologica (Stockholm, Sweden)* 2010;
9. Bethke L, Webb E, Murray A, Schoemaker M, Johansen C, Christensen HC, et al. Comprehensive analysis of the role of DNA repair gene polymorphisms on risk of glioma. *Human molecular genetics* 2008;17:800-5.
10. Karolchik D, Baertsch R, Diekhans M, Furey TS, Hinrichs A, Lu YT, et al. The UCSC Genome Browser Database. *Nucleic acids research* 2003;31:51-4.
11. Kent WJ, Sugnet CW, Furey TS, Roskin KM, Pringle TH, Zahler AM, et al. The human genome browser at UCSC. *Genome research* 2002;12:996-1006.
12. Wood RD, Mitchell M and Lindahl T. Human DNA repair genes, 2005. *Mutation research* 2005;577:275-83.
13. Carlson CS, Eberle MA, Rieder MJ, Yi Q, Kruglyak L and Nickerson DA. Selecting a maximally informative set of single-nucleotide polymorphisms for association analyses using linkage disequilibrium. *American journal of human genetics* 2004;74:106-20.
14. The International HapMap Project. *Nature* 2003;426:789-96.
15. Conde L, Vaquerizas JM, Dopazo H, Arbiza L, Reumers J, Rousseau F, et al. PupaSuite: finding functional single nucleotide polymorphisms for large-scale genotyping purposes. *Nucleic acids research* 2006;34:W621-5.
16. Lystig TC. Adjusted P values for genome-wide scans. *Genetics* 2003;164:1683-7.

17. Gabriel SB, Schaffner SF, Nguyen H, Moore JM, Roy J, Blumenstiel B, et al. The structure of haplotype blocks in the human genome. *Science (New York, N.Y)* 2002;296:2225-9.
18. Petkovic M, Dietschy T, Freire R, Jiao R and Stagljar I. The human Rothmund-Thomson syndrome gene product, RECQL4, localizes to distinct nuclear foci that coincide with proteins involved in the maintenance of genome stability. *Journal of cell science* 2005;118:4261-9.
19. Kitao S, Lindor NM, Shiratori M, Furuichi Y and Shimamoto A. Rothmund-thomson syndrome responsible gene, RECQL4: genomic structure and products. *Genomics* 1999;61:268-76.
20. Fishel R, Ewel A and Lescoe MK. Purified human MSH2 protein binds to DNA containing mismatched nucleotides. *Cancer research* 1994;54:5539-42.
21. Stark AM, Witzel P, Strege RJ, Hugo HH and Mehdorn HM. p53, mdm2, EGFR, and msh2 expression in paired initial and recurrent glioblastoma multiforme. *Journal of neurology, neurosurgery, and psychiatry* 2003;74:779-83.
22. Kawabata M, Kawabata T and Nishibori M. Role of recA/RAD51 family proteins in mammals. *Acta medica Okayama* 2005;59:1-9.
23. Thomas G, Jacobs KB, Kraft P, Yeager M, Wacholder S, Cox DG, et al. A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 (RAD51L1). *Nature genetics* 2009;41:579-84.
24. Wrensch M, Jenkins RB, Chang JS, Yeh RF, Xiao Y, Decker PA, et al. Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. *Nature genetics* 2009;41:905-8.
25. Li D, Frazier M, Evans DB, Hess KR, Crane CH, Jiao L, et al. Single nucleotide polymorphisms of RecQ1, RAD54L, and ATM genes are associated with reduced survival of pancreatic cancer. *J Clin Oncol* 2006;24:1720-8.
26. Rodero M, Marie Y, Coudert M, Blondet E, Mokhtari K, Rousseau A, et al. Polymorphism in the microglial cell-mobilizing CX3CR1 gene is associated with survival in patients with glioblastoma. *J Clin Oncol* 2008;26:5957-64.
27. Scheurer ME, Amirian E, Cao Y, Gilbert MR, Aldape KD, Kornguth DG, et al. Polymorphisms in the interleukin-4 receptor gene are associated with better survival in patients with glioblastoma. *Clin Cancer Res* 2008;14:6640-6.
28. Carpentier C, Lejeune J, Gros F, Everhard S, Marie Y, Kaloshi G, et al. Association of telomerase gene hTERT polymorphism and malignant gliomas. *Journal of neuro-oncology* 2007;84:249-53.

Table 1. Distribution of clinical characteristics.

	UK-north n=121	Sweden n=75	Denmark n=63	Total^a n=138
Survival (months)				
Mean	14.8	16.5	15.2	15.9
Median	11.3	12.5	14.2	12.9
(range)	(2.2-78.8)	(2.1-71.8)	(1.0-51.9)	(1.0-71.8)
Gross total resection				
Yes		17 (22.7%)	21 (33.3%)	38 (27.6%)
No		53 (70.7%)	41 (65.1%)	94 (68.1%)
N/A	121 (100%)	5 (6.6%)	1 (1.6%)	6 (4.3%)
Chemotherapy				
Yes		53 (70.7%)	13 (20.6%)	66 (47.8%)
No		18 (24.0%)	43 (68.3%)	61 (44.2%)
N/A	121 (100%)	4 (5.3%)	7 (11.1%)	11 (8.0%)
Radiotherapy				
Yes		65 (86.7%)	53 (84.1%)	118 (85.5%)
No		9 (12.0%)	8 (12.7%)	17 (12.3%)
N/A	121 (100%)	1 (1.3%)	2 (3.2%)	3 (2.2%)
Number of deaths	116 (95.9%)	69 (92.0%)	61 (96.8%)	130 (94.2%)
Sex				
Male	78 (64.5%)	45 (60.0%)	38 (60.3%)	83 (61.1%)
Female	43 (35.5%)	30 (40.0%)	25 (39.7%)	55 (39.9%)
Age at diagnosis median (years)	55	56	55	56

a) Summary of datasets from Sweden and Denmark (i.e., the Swedish-Danish dataset)

Table 2. Allelic variants associated with survival, based on 121 patients in the Swedish-Danish dataset with complete data.

rs#	Chr#	Gene	Role	Major Allele	Genotype	n ^a	% ^b	Surv. ^c	HR ^d	CI95% ^e	P ^f	Adj. P ^g
rs2042649	chr2	MSH2	Intron	T	T/T	100	82.64%	13.32	1.66	(1.017-2.709)	0.043	0.547
					C/T	21	17.36%	10.65				
					C/C	0	0.00%					
rs2303428	chr2	MSH2	Intron (boundary)	T	T/T	100	82.64%	13.32	1.66	(1.017-2.709)	0.043	0.547
					C/T	21	17.36%	10.65				
					C/C	0	0.00%					
rs2038565	chr14	RAD51L1	Intron	G	G/G	86	71.07%	13.52	1.456	(0.921-2.303)	0.108	0.819
					G/T	32	26.45%	11.19				
					T/T	3	2.48%	2.73				
rs6573805	chr14	RAD51L1	Intron	A	A/A	83	68.60%	13.41	1.009	(0.649-1.569)	0.967	1
					A/G	35	28.93%	11.89				
					G/G	3	2.48%	2.73				
rs8022206	chr14	RAD51L1	Intron	G	G/G	86	71.07%	13.52	1.456	(0.921-2.303)	0.108	0.819
					A/G	32	26.45%	11.19				
					A/A	3	2.48%	2.73				
rs11626809	chr14	RAD51L1	Intron	G	G/G	93	76.86%	12.85	1.053	(0.640-1.732)	0.84	1
					G/T	24	19.83%	14.65				
					T/T	4	3.31%	3.89				
rs17192586	chr14	RAD51L1	Intron	G	G/G	86	71.07%	13.52	1.456	(0.921-2.303)	0.108	0.819
					A/G	32	26.45%	11.19				
					A/A	3	2.48%	2.73				
rs756627	chr8	RECQL4	Intron (boundary)	G	G/G	30	24.79%	10.56	0.671	(0.425-1.060)	0.087	0.758
					A/G	72	59.50%	12.81				
					A/A	19	15.70%	15.77				
rs3757966	chr8	RECQL4	Promotor	G	G/G	31	25.62%	10.65	0.692	(0.440-1.087)	0.11	0.822
					A/G	69	57.02%	12.85				
					A/A	21	17.36%	15.47				

a) Number of patients; b) Percent of patients; c) Median survival, measured in months; d) Hazard ratio (HR); e) 95% confidence interval for the hazard ratio; f) P-value, adjusted for country, sex, age, surgery (radical or not), radio- and chemotherapy; g) P-value, further adjusted by permutation.

Supplementary Table I

All analyzed SNPs

rs#	gene	P-value, Screen (SWE-DEN)	P-value, Valid (UK-north)	sign. ^a
rs243356	CHAF1A	-	-	-
rs12645561	NEIL3	-	-	-
rs243341	CHAF1A	-	-	-
rs105038	CHAF1A	0.025	0.234	*
rs3212986	ERCC1	-	-	-
rs2160138	RPA3	-	-	-
rs3761936	DCLRE1B	-	-	-
rs8079544	TP53	-	-	-
rs11920625	ATR	-	-	-
rs2992	CHAF1A	-	-	-
rs12022378	DCLRE1B	-	-	-
rs3212955	ERCC1	-	-	-
rs6947203	RPA3	-	-	-
rs4140805	RPA3	-	-	-
rs1673041	POLD1	-	-	-
rs707938	MSH5	-	-	-
rs17177522	ERCC6	-	-	-
rs7561771	FANCL	-	-	-
rs11680760	NHEJ1	-	-	-
rs4253211	ERCC6	-	-	-
rs1059262	ALKBH2	-	-	-
rs2158715	RPA3	-	-	-
rs7781054	RPA3	-	-	-
rs11813363	MGMT	-	-	-
rs10175081	NHEJ1	-	-	-
rs13242539	RPA3	-	-	-
rs6850861	NEIL3	-	-	-
rs10829615	MGMT	0.026	0.905	*
rs7223243	BRIP1	-	-	-
rs609261	ATM	-	-	-
rs600329	ATM	-	-	-
rs1981929	MSH2	-	-	-
rs4585	ATM	-	-	-
rs861530	XRCC3	-	-	-
rs13386793	NHEJ1	-	-	-
rs3213266	XRCC1	0.034	0.492	*
rs3771220	FANCL	-	-	-
rs8191649	NEIL2	-	-	-
rs207943	XRCC5	-	-	-
rs3212090	XRCC3	-	-	-
rs672655	ATM	-	-	-
rs11016884	MGMT	-	-	-
rs17714829	EME1	0.008	0.487	*
rs2546551	POLD1	-	-	-
rs17482047	RPA3	-	-	-
rs804292	NEIL2	-	-	-
rs1378641	NHEJ1	-	-	-
rs7080570	MGMT	-	-	-
rs207945	XRCC5	-	-	-
rs6982453	NEIL2	-	-	-
rs227075	ATM	-	-	-
rs12694447	NHEJ1	-	-	-

rs2030451	NHEJ1	-	-	-
rs17481971	RPA3	-	-	-
rs7585868	NHEJ1	-	-	-
rs897476	NHEJ1	-	-	-
rs6724465	NHEJ1	-	-	-
rs2228528	ERCC6	-	-	-
rs3131378	MSH5	-	-	-
rs3115672	MSH5	-	-	-
rs652541	ATM	-	-	-
rs664143	ATM	-	-	-
rs8191604	NEIL2	-	-	-
rs476630	POLI	-	-	-
rs804267	NEIL2	-	-	-
rs10505020	RRM2B	-	-	-
rs3117577	MSH5	-	-	-
rs1800067	ERCC4	-	-	-
rs580504	POLI	-	-	-
rs11615	ERCC1	-	-	-
rs2230931	RPA1	-	-	-
rs13168327	MSH3	-	-	-
rs5745433	MSH4	-	-	-
rs4253132	ERCC6	-	-	-
rs13249865	RRM2B	-	-	-
rs3136781	POLB	-	-	-
rs6683437	MSH4	-	-	-
rs1565717	MSH4	-	-	-
rs2293081	NHEJ1	-	-	-
rs2854496	XRCC1	-	-	-
rs3212948	ERCC1	-	-	-
rs2440	XRCC5	-	-	-
rs1314911	RAD51L1	-	-	-
rs4838524	ERCC6	0.041	0.939	*
rs1274638	RAD51L1	-	-	-
rs9352	CHAF1A	0.000	0.908	*
rs2242478	HUS1	-	-	-
rs1314913	RAD51L1	-	-	-
rs3176595	HUS1	0.032	0.190	*
rs1274652	RAD51L1	-	-	-
rs12769288	MGMT	-	-	-
rs10802996	EXO1	-	-	-
rs7095819	MGMT	-	-	-
rs1056663	HUS1	-	-	-
rs3019280	RAD54B	-	-	-
rs5745022	POLE	-	-	-
rs904009	NEIL2	-	-	-
rs3740526	MMS19L	-	-	-
rs7080949	MGMT	-	-	-
rs2113950	WRN	-	-	-
rs3770496	XRCC5	-	-	-
rs1274656	RAD51L1	-	-	-
rs4883614	POLE	-	-	-
rs1650697	MSH3	-	-	-
rs12515548	MSH3	-	-	-
rs2291439	RAD54B	-	-	-
rs5745323	MSH4	-	-	-
rs1980418	WRN	-	-	-
rs2930964	RAD54B	-	-	-
rs8191542	NEIL2	-	-	-
rs12917	MGMT	-	-	-
rs6900341	REV3L	-	-	-
rs10804682	ATR	-	-	-
rs861544	XRCC3	-	-	-
rs12432907	XRCC3	-	-	-
rs2303400	XRCC5	-	-	-
rs3136790	POLB	-	-	-
rs2227869	ERCC5	-	-	-
rs172814	TDG	-	-	-

rs2925790	RRM2B	-	-	-
rs966497	ERCC8	-	-	-
rs587118	FANCG	-	-	-
rs9649886	WRN	-	-	-
rs17675654	NEIL3	-	-	-
rs8191534	NEIL2	-	-	-
rs4840583	NEIL2	-	-	-
rs12452396	BRIP1	0.001	0.845	*
rs799917	BRCA1	-	-	-
rs9082	RPA1	-	-	-
rs7626117	FANCD2	0.023	0.455	*
rs611646	ATM	-	-	-
rs10870483	POLE	-	-	-
rs538394	MUS81	-	-	-
rs633877	MUS81	-	-	-
rs558114	MUS81	-	-	-
rs1316118	RAD51L1	-	-	-
rs4149867	EXO1	-	-	-
rs4733224	WRN	-	-	-
rs16948981	EME1	0.000	0.084	*
rs2306371	MSH3	-	-	-
rs630303	MUS81	-	-	-
rs9914073	RPA1	0.003	0.927	*
rs2808676	XPA	-	-	-
rs648732	MUS81	0.047	0.871	*
rs12902	EME1	0.013	0.150	*
rs1800734	MLH1	-	-	-
rs2281793	ERCC6	-	-	-
rs5744738	POLE	-	-	-
rs2191248	BRIP1	-	-	-
rs11656253	RPA1	0.039	0.664	*
rs12164500	MSH4	-	-	-
rs2272125	FANCD2	-	-	-
rs799905	BRCA1	-	-	-
rs2919662	RAD54B	-	-	-
rs1265116	RRM2B	-	-	-
rs16945628	BRIP1	0.042	0.375	*
rs16941	BRCA1	-	-	-
rs25487	XRCC1	-	-	-
rs3176683	XPA	-	-	-
rs17545935	RPA3	-	-	-
rs1264308	GTF2H4	-	-	-
rs1561648	RAD54B	-	-	-
rs16940	BRCA1	-	-	-
rs3834	XRCC5	-	-	-
rs7602535	REV1L	-	-	-
rs1364726	XRCC5	-	-	-
rs2072267	POLG	-	-	-
rs3756399	RAD17	-	-	-
rs3135967	LIG3	-	-	-
rs8176265	BRCA1	-	-	-
rs8075760	RAD51L3	-	-	-
rs1799794	XRCC3	-	-	-
rs1146644	MSH4	-	-	-
rs1045580	RPA3	-	-	-
rs243372	CHAF1A	0.001	0.929	*
rs1051685	XRCC5	-	-	-
rs1876268	NEIL3	-	-	-
rs3730787	POLI	-	-	-
rs2104075	MNAT1	-	-	-
rs3744767	RPA1	-	-	-
rs5743185	PMS1	-	-	-
rs7151235	RAD51L1	-	-	-
rs1060915	BRCA1	-	-	-
rs1799966	BRCA1	-	-	-
rs3092994	BRCA1	-	-	-
rs8176318	BRCA1	-	-	-

rs10188090	MSH2	-	-	-
rs2152092	MMS19L	-	-	-
rs16942	BRCA1	-	-	-
rs1552244	FANCD2	0.021	0.425	*
rs6070067	SPO11	-	-	-
rs1800392	WRN	-	-	-
rs1011314	FANCL	-	-	-
rs560852	POLI	-	-	-
rs8305	POLI	-	-	-
rs458017	REV3L	-	-	-
rs1978244	BRIP1	0.027	0.350	*
rs1326188	FANCC	-	-	-
rs7689099	NEIL3	-	-	-
rs12516	BRCA1	-	-	-
rs1052536	LIG3	-	-	-
rs8176257	BRCA1	-	-	-
rs3087374	POLG	-	-	-
rs10808311	WRN	-	-	-
rs3756400	RAD17	-	-	-
rs7610821	FANCD2	-	-	-
rs9879080	FANCD2	0.019	0.395	*
rs799923	BRCA1	-	-	-
rs2015230	WRN	-	-	-
rs1316014	RAD51L1	-	-	-
rs1080321	RAD51L1	-	-	-
rs3737574	MSH4	-	-	-
rs7525919	MSH4	-	-	-
rs6951443	PMS2L4	-	-	-
rs3730758	POLI	-	-	-
rs7583902	XRCC5	-	-	-
rs6968090	SHFM1	-	-	-
rs12611088	XRCC1	-	-	-
rs240972	REV3L	-	-	-
rs867612	NEIL3	-	-	-
rs1003918	LIG3	-	-	-
rs11903456	FANCL	-	-	-
rs17105586	RAD51L1	-	-	-
rs12949659	BRIP1	0.007	0.350	*
rs7830743	PRKDC	-	-	-
rs17332991	ERCC8	-	-	-
rs17064661	NEIL3	-	-	-
rs2378906	BRIP1	0.003	0.350	*
rs6734662	XRCC5	-	-	-
rs12513549	MSH3	-	-	-
rs1744947	RAD51L1	-	-	-
rs8176199	BRCA1	-	-	-
rs246079	UNG	0.016	0.359	*
rs2075685	XRCC4	-	-	-
rs431649	RAD51L1	0.011	0.189	*
rs1001581	XRCC1	-	-	-
rs483959	MGMT	-	-	-
rs3176582	HUS1	-	-	-
rs2025009	RAD51L1	-	-	-
rs12407107	MSH4	-	-	-
rs4547519	NHEJ1	-	-	-
rs2725362	WRN	-	-	-
rs1859604	RPA3	-	-	-
rs4721505	NUDT1	-	-	-
rs1138465	POLG	-	-	-
rs7916722	DCLRE1C	-	-	-
rs2302084	POLG	-	-	-
rs5762746	CHEK2	-	-	-
rs206118	BRCA2	-	-	-
rs1061316	POLG	-	-	-
rs4253077	ERCC6	0.047	0.718	*
rs2229032	ATR	-	-	-
rs1054875	POLG	-	-	-

rs1314917	RAD51L1	-	-	-
rs207932	XRCC5	-	-	-
rs17829281	RAD51L1	-	-	-
rs10488836	POLN	-	-	-
rs207927	XRCC5	-	-	-
rs1050244	DDB2	-	-	-
rs504082	FANCG	-	-	-
rs1537257	MGMT	-	-	-
rs207936	XRCC5	0.046	0.258	*
rs1012997	RPA3	-	-	-
rs8077346	RPA1	-	-	-
rs1871892	RAD51L3	-	-	-
rs2275583	MMS19L	-	-	-
rs12453966	BRIP1	0.029	0.280	*
rs4135063	TDG	-	-	-
rs6791810	FANCD2	0.034	0.425	*
rs4253164	ERCC6	-	-	-
rs17032278	FANCD2	0.029	0.425	*
rs4408133	EXO1	-	-	-
rs10950066	PMS2L4	-	-	-
rs11158733	RAD51L1	0.043	0.975	*
rs9625533	CHEK2	-	-	-
rs14302	POLE	-	-	-
rs10829619	MGMT	-	-	-
rs3821104	XRCC5	-	-	-
rs3805169	NEIL3	-	-	-
rs3890995	UNG	-	-	-
rs12470316	FANCL	-	-	-
rs17032283	FANCD2	0.014	0.425	*
rs4968451	BRIP1	0.037	0.614	*
rs125701	OGG1	-	-	-
rs4151289	MNAT1	-	-	-
rs3735461	RPA3	-	-	-
rs2686843	HUS1	-	-	-
rs3784095	RAD51L1	-	-	-
rs2061783	XRCC4	-	-	-
rs12409592	MSH4	-	-	-
rs17169194	RPA3	-	-	-
rs12763287	MGMT	-	-	-
rs2247233	POLG	-	-	-
rs3786133	RPA1	-	-	-
rs4720750	RPA3	-	-	-
rs10861152	TDG	0.044	0.917	*
rs2607659	RRM2B	-	-	-
rs26279	MSH3	-	-	-
rs4135054	TDG	-	-	-
rs7916804	MGMT	-	-	-
rs7565513	MSH2	-	-	-
rs10786351	MMS19L	-	-	-
rs2237060	RAD50	0.007	0.777	*
rs758130	POLG	-	-	-
rs2854510	XRCC1	-	-	-
rs3756558	POLK	-	-	-
rs3736772	FANCM	-	-	-
rs2607658	RRM2B	-	-	-
rs13178127	XRCC4	-	-	-
rs206079	BRCA2	-	-	-
rs10882939	MMS19L	-	-	-
rs1805327	RAD1	-	-	-
rs10764896	MGMT	-	-	-
rs1713413	PARP2	-	-	-
rs4750761	MGMT	-	-	-
rs3738948	ERCC3	-	-	-
rs4150506	ERCC3	-	-	-
rs4986764	BRIP1	-	-	-
rs28059	MSH3	-	-	-
rs4491586	FLJ35220	-	-	-

rs1265154	RRM2B	-	-	-
rs4917772	MMS19L	-	-	-
rs1800359	FANCA	-	-	-
rs4986763	BRIP1	-	-	-
rs7720588	XRCC4	-	-	-
rs6950845	RPA3	-	-	-
rs32960	MSH3	-	-	-
rs2767379	RAD51L1	0.046	0.091	*
rs4150018	EXO1	-	-	-
rs7071825	MGMT	-	-	-
rs2700	PARP2	-	-	-
rs9282681	FANCA	-	-	-
rs7213430	BRIP1	-	-	-
rs5744983	POLE	-	-	-
rs326222	DDB2	-	-	-
rs17105585	RAD51L1	-	-	-
rs2075310	FANCD2	-	-	-
rs11592922	MGMT	-	-	-
rs151886	MSH3	-	-	-
rs5744934	POLE	-	-	-
rs245340	MSH3	-	-	-
rs721204	MSH4	-	-	-
rs4750760	MGMT	-	-	-
rs4150530	GTF2H1	-	-	-
rs12639363	ATR	-	-	-
rs1800286	FANCA	-	-	-
rs17132321	POLM	-	-	-
rs1802904	ATR	-	-	-
rs2266690	CCNH	-	-	-
rs11646374	FANCA	-	-	-
rs2048073	NEIL3	-	-	-
rs11762961	POLM	-	-	-
rs11016816	MGMT	-	-	-
rs3219211	UNG	-	-	-
rs4952887	MSH2	-	-	-
rs2130756	CDK7	-	-	-
rs6955679	POLM	-	-	-
rs17132330	POLM	-	-	-
rs11668886	CHAF1A	0.038	0.443	*
rs1011980	XRCC4	-	-	-
rs4930737	GTF2H3	-	-	-
rs6851446	POLN	-	-	-
rs4424945	FLJ35220	-	-	-
rs144848	BRCA2	-	-	-
rs3218660	POLM	-	-	-
rs1952246	RAD51L1	0.027	0.072	*
rs1958115	RAD51L1	-	-	-
rs17185052	RPA2	-	-	-
rs10146321	RAD51L1	-	-	-
rs6974232	RPA3	-	-	-
rs2229760	ERCC6	-	-	-
rs7083508	MGMT	-	-	-
rs4790830	RPA1	-	-	-
rs13180356	XRCC4	-	-	-
rs240993	REV3L	-	-	-
rs820190	RECQL5	-	-	-
rs11078671	RPA1	-	-	-
rs4342522	SHFM1	-	-	-
rs3821367	POLQ	-	-	-
rs3218655	POLM	-	-	-
rs1061438	MPG	-	-	-
rs3087403	REV1L	-	-	-
rs4751100	MGMT	-	-	-
rs2271818	ALKBH3	-	-	-
rs13269094	WRN	-	-	-
rs458486	REV3L	-	-	-
rs7799948	PMS2L4	-	-	-

Wibom et al

rs207924	XRCC5	-	-	-
rs2767383	RAD51L1	0.027	0.080	*
rs901746	DDB2	-	-	-
rs4986765	BRIP1	-	-	-
rs1685404	DDB2	-	-	-
rs17466737	RPA3	-	-	-
rs7778745	POLM	-	-	-
rs487848	POLQ	-	-	-
rs4751108	MGMT	-	-	-
rs12479064	REV1L	-	-	-
rs4883545	POLE	-	-	-
rs494140	POLQ	-	-	-
rs2877985	NEIL3	-	-	-
rs240968	REV3L	-	-	-
rs240966	REV3L	-	-	-
rs8022206	RAD51L1	0.009	0.011	***
rs2039374	MGMT	-	-	-
rs10128350	DCLRE1C	0.043	0.447	*
rs4150667	GTF2H1	-	-	-
rs16855552	XRCC5	-	-	-
rs430781	RAD18	-	-	-
rs1950764	RAD51L1	0.006	0.014	**
rs11016879	MGMT	-	-	-
rs7068306	MGMT	-	-	-
rs8065937	RPA1	-	-	-
rs2020911	MSH6	-	-	-
rs17829311	RAD51L1	0.033	0.505	*
rs3218647	POLQ	-	-	-
rs1799801	ERCC4	-	-	-
rs1100188	FANCL	-	-	-
rs8065843	FLJ35220	0.024	0.733	*
rs2074512	GTF2H4	-	-	-
rs2303428	MSH2	0.012	0.035	***
rs4150386	ERCC5	-	-	-
rs3136176	ERCC4	-	-	-
rs11037703	ALKBH3	-	-	-
rs4640970	POLM	-	-	-
rs707939	MSH5	-	-	-
rs3786136	RPA1	-	-	-
rs110732	REV3L	-	-	-
rs455732	REV3L	-	-	-
rs9896073	RECQL5	-	-	-
rs1654891	ALKBH2	-	-	-
rs820157	RECQL5	-	-	-
rs10249092	SHFM1	-	-	-
rs3740615	FANCF	-	-	-
rs3801293	SHFM1	-	-	-
rs11571789	BRCA2	0.007	0.644	*
rs16855534	XRCC5	-	-	-
rs3218815	GTF2H4	-	-	-
rs916920	GTF2H4	-	-	-
rs532411	POLQ	-	-	-
rs3752451	BRCA2	0.021	0.856	*
rs4253234	ERCC6	-	-	-
rs917029	EME1	-	-	-
rs588701	MRE11A	-	-	-
rs2725385	WRN	-	-	-
rs3793784	ERCC6	-	-	-
rs3218634	POLQ	-	-	-
rs669277	POLQ	-	-	-
rs17547731	RPA3	0.047	0.790	*
rs7968453	UBE2N	-	-	-
rs5762763	CHEK2	-	-	-
rs1483003	UBE2N	0.024	0.494	*
rs1124303	XPC	-	-	-
rs9868609	POLQ	-	-	-
rs456871	REV3L	-	-	-

rs12046289	DCLRE1B	-	-	-
rs11756643	REV3L	-	-	-
rs11626809	RAD51L1	0.008	0.004	***
rs3093930	PARP2	-	-	-
rs2257111	RAD51L1	-	-	-
rs4899246	RAD51L1	-	-	-
rs3950069	RAD51L1	-	-	-
rs3784115	RAD51L1	0.010	0.024	**
rs11517377	DCLRE1C	-	-	-
rs11623593	RAD51L1	0.018	0.528	*
rs615967	RAD18	-	-	-
rs412334	FEN1	-	-	-
rs3783819	MNAT1	-	-	-
rs4838518	ERCC6	-	-	-
rs13002401	XRCC5	-	-	-
rs10764899	MGMT	-	-	-
rs1805330	RAD23B	-	-	-
rs2038565	RAD51L1	0.002	0.011	***
rs2569987	UNG	0.001	0.297	*
rs1367580	FANCM	-	-	-
rs5752773	CHEK2	0.035	0.237	*
rs963917	RAD51L1	-	-	-
rs3138326	MBD4	-	-	-
rs1805355	MSH3	-	-	-
rs4423955	CDK7	-	-	-
rs5744990	POLE	-	-	-
rs617914	POLN	-	-	-
rs13065800	ATR	-	-	-
rs2078555	CHEK2	-	-	-
rs158937	ERCC8	-	-	-
rs989095	MGMT	-	-	-
rs7659386	POLN	-	-	-
rs2022302	POLN	-	-	-
rs10946136	GTF2H5	0.030	0.899	*
rs9941566	REV1L	-	-	-
rs5745515	MSH4	-	-	-
rs929780	ERCC8	-	-	-
rs1038144	ERCC8	-	-	-
rs4235484	ERCC8	-	-	-
rs9567552	BRCA2	0.038	0.852	*
rs11064607	RAD52	-	-	-
rs7773620	GTF2H5	-	-	-
rs17772583	RAD50	-	-	-
rs132788	XRCC6	-	-	-
rs2026975	MGMT	-	-	-
rs6830513	POLN	-	-	-
rs9328764	POLN	-	-	-
rs13180316	XRCC4	-	-	-
rs4647151	ERCC8	-	-	-
rs8031341	BLM	-	-	-
rs250408	RAD18	-	-	-
rs3731422	CHEK1	-	-	-
rs245346	MSH3	-	-	-
rs2805835	XPA	-	-	-
rs9459620	GTF2H5	-	-	-
rs11581448	EXO1	-	-	-
rs11511217	MGMT	-	-	-
rs4150471	ERCC3	-	-	-
rs976080	ERCC8	-	-	-
rs11845507	FANCM	-	-	-
rs12380720	FANCC	-	-	-
rs1061626	RECQL	-	-	-
rs640603	H2AFX	-	-	-
rs387833	BLM	-	-	-
rs167715	TDG	-	-	-
rs971173	DCLRE1B	-	-	-
rs3218499	XRCC2	-	-	-

rs4150622	GTF2H1	-	-	-
rs6496724	BLM	-	-	-
rs2257103	PNKP	-	-	-
rs10132294	RAD51L1	-	-	-
rs3730476	POLL	-	-	-
rs17466949	RPA3	-	-	-
rs2445837	POLD1	-	-	-
rs2040639	XRCC2	-	-	-
rs1874546	NEIL2	-	-	-
rs2110159	RECQL	-	-	-
rs11574227	WRN	-	-	-
rs3087409	WRN	-	-	-
rs10217136	RAD23B	-	-	-
rs10829605	MGMT	-	-	-
rs2854509	XRCC1	-	-	-
rs3730465	POLL	-	-	-
rs4150561	GTF2H1	-	-	-
rs32952	MSH3	-	-	-
rs12450550	EME1	-	-	-
rs3730484	POLL	-	-	-
rs743725	MPG	-	-	-
rs12771882	MGMT	-	-	-
rs12243174	MGMT	-	-	-
rs4150393	ERCC5	-	-	-
rs7845909	PRKDC	-	-	-
rs17192586	RAD51L1	0.001	0.009	***
rs1978759	MGMT	-	-	-
rs3136245	MSH6	-	-	-
rs848279	FANCL	-	-	-
rs17064668	NEIL3	-	-	-
rs10011549	POLN	-	-	-
rs2353552	POLN	-	-	-
rs1233284	PMS1	-	-	-
rs2189712	EME1	-	-	-
rs7913426	DCLRE1C	-	-	-
rs7489112	POLE	-	-	-
rs11571686	BRCA2	0.014	0.347	*
rs7325708	ERCC5	-	-	-
rs1130409	APEX1	-	-	-
rs1800389	WRN	-	-	-
rs1011019	ERCC3	-	-	-
rs6463709	RPA3	-	-	-
rs2032765	XRCC5	-	-	-
rs4676677	POLQ	-	-	-
rs3218408	XRCC2	-	-	-
rs3821211	FANCL	-	-	-
rs140695	MBD4	-	-	-
rs4150276	ERCC5	-	-	-
rs2725351	WRN	-	-	-
rs1801516	ATM	-	-	-
rs10018786	POLN	-	-	-
rs4150351	ERCC5	-	-	-
rs1555944	RAD51L1	-	-	-
rs301276	XRCC4	-	-	-
rs3136166	ERCC4	-	-	-
rs1381057	POLQ	-	-	-
rs4150027	EXO1	0.016	0.390	*
rs2230009	WRN	-	-	-
rs2270052	NUDT1	-	-	-
rs207933	XRCC5	0.017	0.093	*
rs3784116	RAD51L1	-	-	-
rs861528	XRCC3	-	-	-
rs5742981	PMS1	0.002	0.913	*
rs5744857	POLE	-	-	-
rs12816436	UBE2N	-	-	-
rs5744944	POLE	-	-	-
rs2725363	WRN	-	-	-

rs2005618	MBD4	-	-	-
rs10768994	ALKBH3	-	-	-
rs13266	RECQL	-	-	-
rs6573805	RAD51L1	0.033	0.009	***
rs3111471	XRCC2	-	-	-
rs1956533	RAD51L1	-	-	-
rs17627102	RECQL	-	-	-
rs4988023	ATM	-	-	-
rs12112667	RPA3	-	-	-
rs3828488	NEIL3	-	-	-
rs3768347	PARP1	-	-	-
rs7962050	RAD52	-	-	-
rs12412853	MGMT	-	-	-
rs897477	NHEJ1	-	-	-
rs654718	MRE11A	0.046	0.752	*
rs3136329	MSH6	0.004	0.537	*
rs1956538	RAD51L1	-	-	-
rs3793786	ERCC6	-	-	-
rs3026271	NBN	0.030	0.278	*
rs3784782	BLM	-	-	-
rs17763718	REV1L	-	-	-
rs2029298	DDB2	-	-	-
rs11064598	RAD52	-	-	-
rs12880237	RAD51L1	-	-	-
rs2257022	RAD51L1	0.002	0.206	*
rs1230	FANCA	-	-	-
rs2072447	MSH6	0.019	0.789	*
rs2974755	RAD23A	-	-	-
rs878156	PARP2	-	-	-
rs1047768	ERCC5	-	-	-
rs1800391	WRN	-	-	-
rs3219053	PARP1	-	-	-
rs9647886	PMS2L4	-	-	-
rs3792136	REV1L	-	-	-
rs10133262	RAD51L1	-	-	-
rs3219489	MUTYH	-	-	-
rs730566	TREX1	-	-	-
rs7893335	MMS19L	-	-	-
rs356686	FANCC	-	-	-
rs4796030	LIG3	0.009	0.813	*
rs7709909	MSH3	0.030	0.349	*
rs3792151	REV1L	-	-	-
rs11623751	RAD51L1	-	-	-
rs4102401	RRM2B	-	-	-
rs1869802	NHEJ1	-	-	-
rs10846537	GTF2H3	-	-	-
rs17806132	PMS1	-	-	-
rs3092991	ATM	-	-	-
rs1805405	PARP1	-	-	-
rs5744941	POLE	-	-	-
rs2042649	MSH2	0.003	0.035	***
rs1131636	RPA1	-	-	-
rs33013	MSH3	-	-	-
rs10870482	POLE	-	-	-
rs686425	RAD51C	-	-	-
rs10838202	ALKBH3	-	-	-
rs341781	RAD18	-	-	-
rs9943888	BRCA2	-	-	-
rs7309933	UBE2N	-	-	-
rs4150274	ERCC5	-	-	-
rs12137934	RAD54L	-	-	-
rs8178071	PRKDC	-	-	-
rs1264302	GTF2H4	-	-	-
rs10768995	ALKBH3	-	-	-
rs304270	RAD51C	-	-	-
rs1060499	RAD52	-	-	-
rs2270132	BLM	-	-	-

rs4240506	ERCC6	-	-	-
rs9634161	RAD52	-	-	-
rs1776148	EXO1	-	-	-
rs7915501	MMS19L	-	-	-
rs17608747	NHEJ1	-	-	-
rs7319	RECQL	-	-	-
rs6732562	NHEJ1	-	-	-
rs1540354	MLH1	0.018	0.669	*
rs565416	CHEK1	-	-	-
rs17104889	RAD51L1	-	-	-
rs3024239	WRN	-	-	-
rs2251660	RDM1	-	-	-
rs1051669	RAD52	-	-	-
rs820206	RECQL5	-	-	-
rs1233288	PMS1	-	-	-
rs1264303	GTF2H4	-	-	-
rs304269	RAD51C	-	-	-
rs12727	RPA1	-	-	-
rs2075801	MSH5	-	-	-
rs5030740	RPA1	-	-	-
rs389480	BLM	-	-	-
rs1460817	BRCA2	-	-	-
rs3172417	FANCD2	-	-	-
rs848291	FANCL	-	-	-
rs729138	RAD51L1	-	-	-
rs3218536	XRCC2	-	-	-
rs13447623	MRE11A	-	-	-
rs16918482	RRM2B	-	-	-
rs12668835	RPA3	-	-	-
rs10858022	DCLRE1B	-	-	-
rs10742797	DDB2	-	-	-
rs7184015	BLM	-	-	-
rs2957873	DDB2	-	-	-
rs663530	MRE11A	0.034	0.550	*
rs7152152	RAD51L1	-	-	-
rs7757405	FANCE	-	-	-
rs6661817	DCLRE1B	-	-	-
rs2233004	MAD2L2	-	-	-
rs3087404	SMUG1	-	-	-
rs5751129	XRCC6	-	-	-
rs11573628	RAD23B	-	-	-
rs2331701	RAD51L1	-	-	-
rs2619681	RAD51	-	-	-
rs3735460	RPA3	-	-	-
rs8178017	PRKDC	-	-	-
rs356684	FANCC	-	-	-
rs11016831	MGMT	-	-	-
rs1993947	XRCC4	-	-	-
rs1776139	EXO1	-	-	-
rs6800901	POLQ	-	-	-
rs17783388	RAD51L1	-	-	-
rs2735475	RDM1	-	-	-
rs6789845	RAD18	-	-	-
rs886950	FANCA	-	-	-
rs4134851	XAB2	-	-	-
rs330792	MSH6	-	-	-
rs4647038	ERCC8	-	-	-
rs8058895	FANCA	-	-	-
rs4278157	PRKDC	-	-	-
rs7458260	PMS2L4	-	-	-
rs9908659	BRIP1	-	-	-
rs8081162	FLJ35220	0.018	0.206	*
rs465646	REV3L	-	-	-
rs6482747	MGMT	-	-	-
rs2279400	SMUG1	-	-	-
rs206115	BRCA2	-	-	-
rs4150650	GTF2H1	-	-	-

rs4796136	RDM1	-	-	-
rs3218455	XRCC2	-	-	-
rs3784621	DUT	-	-	-
rs2710163	MSH6	0.025	0.921	*
rs491528	CHEK1	-	-	-
rs16869269	RRM2B	-	-	-
rs7805658	SHFM1	-	-	-
rs936656	RAD51L3	-	-	-
rs2642666	XRCC4	-	-	-
rs2238526	FANCA	-	-	-
rs9323505	RAD51L1	-	-	-
rs12924101	FANCA	-	-	-
rs13112390	NEIL3	-	-	-
rs6846091	NEIL3	-	-	-
rs1062492	NUDT1	-	-	-
rs2308321	MGMT	-	-	-
rs1062372	PMS2	-	-	-
rs12146051	RAD54L	-	-	-
rs9350	EXO1	-	-	-
rs11212570	ATM	-	-	-
rs1776179	EXO1	-	-	-
rs10829624	MGMT	-	-	-
rs12704873	SHFM1	-	-	-
rs3176208	POLG	-	-	-
rs2292891	ALKBH3	-	-	-
rs3093872	PARP2	-	-	-
rs380691	MSH3	-	-	-
rs11868055	EME1	-	-	-
rs1776177	EXO1	-	-	-
rs3764959	MSH2	-	-	-
rs4751113	MGMT	-	-	-
rs10764900	MGMT	-	-	-
rs10567	DCLRE1A	-	-	-
rs251692	LIG1	0.015	0.691	*
rs2074885	POLG	-	-	-
rs4462560	NEIL1	-	-	-
rs12441867	DUT	-	-	-
rs301281	XRCC4	-	-	-
rs2386523	LIG1	-	-	-
rs3204953	REV3L	-	-	-
rs11593133	DCLRE1C	-	-	-
rs1800337	FANCA	-	-	-
rs7406953	RPA1	-	-	-
rs907187	PARP1	-	-	-
rs3730477	POLL	-	-	-
rs2053138	MGMT	-	-	-
rs820196	RECQL5	-	-	-
rs7187436	FANCA	-	-	-
rs12435914	RAD51L1	0.036	0.815	*
rs2351000	POLG	-	-	-
rs1805329	RAD23B	-	-	-
rs2239359	FANCA	-	-	-
rs1801320	RAD51	-	-	-
rs13141136	HEL308	-	-	-
rs884716	SHFM1	-	-	-
rs4075784	FLJ35220	-	-	-
rs4521758	PRKDC	-	-	-
rs927221	RAD51L1	-	-	-
rs1061388	REV3L	-	-	-
rs3219065	PARP1	-	-	-
rs2348244	MSH6	-	-	-
rs132774	XRCC6	-	-	-
rs6463524	PMS2	-	-	-
rs12477242	FANCL	-	-	-
rs2047435	MSH4	-	-	-
rs2562182	MPG	-	-	-
rs10495944	MSH2	-	-	-

rs521102	CHEK1	-	-	-
rs1478483	XRCC4	-	-	-
rs1054753	NEIL3	-	-	-
rs356689	FANCC	-	-	-
rs2304579	RAD51	-	-	-
rs8067574	FLJ35220	-	-	-
rs9971190	MGMT	-	-	-
rs11158743	RAD51L1	-	-	-
rs175071	MLH3	-	-	-
rs6465533	SHFM1	-	-	-
rs17652297	WRN	0.023	0.252	*
rs3092989	BRCA2	-	-	-
rs13091637	ATR	-	-	-
rs3730913	LIG1	0.045	0.434	*
rs10466114	MGMT	-	-	-
rs2267437	XRCC6	-	-	-
rs3748522	RAD52	-	-	-
rs884546	APTX	-	-	-
rs1051672	RAD52	-	-	-
rs12889770	RAD51L1	-	-	-
rs16943186	RAD51C	0.044	0.867	*
rs11721073	RAD18	-	-	-
rs4135061	TDG	-	-	-
rs4693626	HEL308	-	-	-
rs1762429	MGMT	-	-	-
rs156639	LIG1	0.000	0.673	*
rs17169553	RPA3	-	-	-
rs20580	LIG1	-	-	-
rs4902579	RAD51L1	-	-	-
rs7791642	PMS2L4	-	-	-
rs707937	MSH5	-	-	-
rs506504	CHEK1	-	-	-
rs9303556	EME1	-	-	-
rs10161263	SMUG1	-	-	-
rs2292889	ALKBH3	-	-	-
rs10764901	MGMT	-	-	-
rs3757966	RECQL4	0.040	0.008	***
rs2236330	SPO11	-	-	-
rs2072668	OGG1	-	-	-
rs2345060	PMS2	-	-	-
rs1052555	ERCC2	-	-	-
rs3749953	MSH5	-	-	-
rs9793263	RAD54L	-	-	-
rs4150642	GTF2H1	-	-	-
rs11076626	FANCA	-	-	-
rs7075748	MGMT	-	-	-
rs2295464	RAD54L	0.039	0.379	*
rs2295465	RAD54L	0.014	0.379	*
rs7682807	NEIL3	-	-	-
rs2020892	MNAT1	-	-	-
rs2227999	XPC	-	-	-
rs1047840	EXO1	-	-	-
rs2434470	ALKBH3	-	-	-
rs4151351	MNAT1	-	-	-
rs10852623	FANCA	-	-	-
rs1136410	PARP1	-	-	-
rs1805415	PARP1	-	-	-
rs1805404	PARP1	0.039	0.310	*
rs907190	PARP1	-	-	-
rs26784	MSH3	-	-	-
rs5750616	DMC1	-	-	-
rs971	SMUG1	-	-	-
rs12888301	RAD51L1	-	-	-
rs1494961	HEL308	-	-	-
rs6905572	MSH5	-	-	-
rs3828486	NEIL3	-	-	-
rs17755752	RAD51L1	0.046	0.093	*

rs1800889	ATM	-	-	-
rs4135050	TDG	-	-	-
rs11573709	RAD23B	-	-	-
rs3093933	PARP2	-	-	-
rs12771521	MGMT	-	-	-
rs3793910	MGMT	-	-	-
rs4253231	ERCC6	-	-	-
rs7003908	PRKDC	-	-	-
rs4899243	RAD51L1	-	-	-
rs7143663	RAD51L1	-	-	-
rs7190823	FANCA	-	-	-
rs8016488	RAD51L1	0.012	0.373	*
rs2297616	PARP2	-	-	-
rs3136711	POLB	-	-	-
rs10954778	WRN	-	-	-
rs11846526	RAD51L1	-	-	-
rs226981	FANCM	-	-	-
rs12112229	PMS2	-	-	-
rs2518968	BLM	-	-	-
rs863221	MSH3	-	-	-
rs794078	XAB2	-	-	-
rs7665103	HEL308	-	-	-
rs9323512	RAD51L1	-	-	-
rs2518967	BLM	-	-	-
rs1193693	XRCC4	-	-	-
rs4150563	GTF2H1	-	-	-
rs8551	H2AFX	0.046	0.550	*
rs12829302	RECQL	-	-	-
rs643788	H2AFX	-	-	-
rs1799787	ERCC2	-	-	-
rs10013040	NEIL3	-	-	-
rs2228529	ERCC6	-	-	-
rs17755734	RAD51L1	-	-	-
rs11846360	RAD51L1	0.003	0.093	*
rs915927	XRCC1	-	-	-
rs12589872	RAD51L1	-	-	-
rs7087131	MGMT	-	-	-
rs3829300	TDG	-	-	-
rs4135087	TDG	-	-	-
rs4790838	RPA1	-	-	-
rs4596	GTF2H1	0.038	0.429	*
rs4988340	BRIP1	0.050	0.858	*
rs6872787	XRCC4	-	-	-
rs175076	MLH3	-	-	-
rs4253042	ERCC6	-	-	-
rs848287	FANCL	-	-	-
rs1760944	APEX1	-	-	-
rs794083	XAB2	-	-	-
rs301279	XRCC4	-	-	-
rs10971260	APTX	-	-	-
rs10813919	APTX	-	-	-
rs10971262	APTX	-	-	-
rs10971263	APTX	-	-	-
rs4149965	EXO1	0.028	0.601	*
rs16966142	FANCA	-	-	-
rs108622	MLH3	-	-	-
rs11852361	BLM	-	-	-
rs2733537	XPC	-	-	-
rs2607737	XPC	0.021	0.049	*
rs8009813	RAD51L1	-	-	-
rs7759	H2AFX	-	-	-
rs16855489	XRCC5	-	-	-
rs7141945	RAD51L1	-	-	-
rs2525507	RAD51L1	-	-	-
rs6998169	NBN	-	-	-
rs1805794	NBN	-	-	-
rs587553	POLQ	-	-	-

Wibom et al

rs4150581	GTF2H1	-	-	-
rs3767300	MAD2L2	-	-	-
rs2048718	BRIP1	-	-	-
rs7195066	FANCA	0.028	0.000	**
rs3093921	PARP2	-	-	-
rs1549066	POLL	-	-	-
rs735943	EXO1	-	-	-
rs1799793	ERCC2	-	-	-
rs11813056	MGMT	-	-	-
rs2721173	RECQL4	-	-	-
rs12231436	RECQL	-	-	-
rs828704	XRCC5	-	-	-
rs5757140	DMC1	-	-	-
rs4840584	NEIL2	-	-	-
rs175057	MLH3	-	-	-
rs4549504	POLK	-	-	-
rs1106087	XPC	-	-	-
rs1983130	NEIL3	-	-	-
rs4253106	ERCC6	-	-	-
rs4150355	ERCC5	-	-	-
rs10230651	RPA3	-	-	-
rs2300211	RECQL	-	-	-
rs5744707	POLK	-	-	-
rs12894381	MNAT1	-	-	-
rs1886134	RAD23B	-	-	-
rs865644	MSH3	-	-	-
rs2299851	MSH5	0.018	0.573	*
rs4253101	ERCC6	-	-	-
rs10813916	APTX	-	-	-
rs529126	MRE11A	0.031	0.302	*
rs3825663	TDP1	-	-	-
rs1053544	REV1L	-	-	-
rs2753403	RAD51L1	-	-	-
rs2296147	ERCC5	-	-	-
rs13181	ERCC2	-	-	-
rs1799943	BRCA2	-	-	-
rs10796227	DCLRE1C	-	-	-
rs10474078	XRCC4	-	-	-
rs702019	POLQ	-	-	-
rs2048076	NEIL3	-	-	-
rs3852507	MGMT	-	-	-
rs7307680	RAD52	-	-	-
rs17783214	RAD51L1	0.029	0.168	*
rs1045064	PMS2L4	-	-	-
rs2287498	TP53	-	-	-
rs932554	RAD51L1	-	-	-
rs2228006	PMS2	-	-	-
rs3212964	ERCC1	-	-	-
rs7109087	FANCF	-	-	-
rs794084	XAB2	-	-	-
rs414634	BLM	0.027	0.375	*
rs2293775	NBN	-	-	-
rs1650649	MSH3	-	-	-
rs7758978	FANCE	-	-	-
rs2078486	TP53	-	-	-
rs3742780	MLH3	-	-	-
rs610611	MRE11A	0.012	0.324	*
rs6776700	TREX1	-	-	-
rs37433	RAD1	0.031	0.630	*
rs5750621	DMC1	-	-	-
rs3793907	MGMT	-	-	-
rs10138140	RAD51L1	0.044	0.108	*
rs12256667	MGMT	-	-	-
rs11571475	RAD52	-	-	-
rs13712	MLH3	-	-	-
rs1233255	PMS1	-	-	-
rs4873772	PRKDC	0.039	0.163	*

rs4143456	NEIL2	-	-	-
rs11593181	MGMT	-	-	-
rs2287499	TP53	-	-	-
rs1042522	TP53	-	-	-
rs1063045	NBN	-	-	-
rs3829195	MGMT	-	-	-
rs668844	XRCC5	0.016	0.188	*
rs3218649	POLQ	-	-	-
rs11713643	POLQ	-	-	-
rs8679	PARP1	-	-	-
rs17655211	UBE2B	-	-	-
rs516037	MRE11A	0.021	0.291	*
rs6099553	SPO11	-	-	-
rs12522154	ERCC8	-	-	-
rs158938	ERCC8	-	-	-
rs517118	BRCA2	-	-	-
rs717454	REV1L	-	-	-
rs10131	LIG4	-	-	-
rs4447177	FANCF	-	-	-
rs10851465	DUT	-	-	-
rs1061302	NBN	-	-	-
rs12951053	TP53	-	-	-
rs7900814	DCLRE1C	-	-	-
rs373572	RAD18	-	-	-
rs12572872	DCLRE1C	-	-	-
rs2155209	MRE11A	0.005	0.291	*
rs377012	RAD18	-	-	-
rs1805388	LIG4	-	-	-
rs4902562	RAD51L1	-	-	-
rs50871	ERCC2	-	-	-
rs9567578	BRCA2	0.011	0.921	*
rs12827646	RAD52	-	-	-
rs7777879	RPA3	-	-	-
rs10253681	PMS2L4	-	-	-
rs741777	NBN	-	-	-
rs3785754	RAD51L3	0.019	0.759	*
rs477692	MGMT	-	-	-
rs2145423	RAD51L1	-	-	-
rs2531213	NTHL1	-	-	-
rs11876	NTHL1	-	-	-
rs3731014	LIG1	-	-	-
rs17105443	RAD51L1	-	-	-
rs3821107	XRCC5	-	-	-
rs751402	ERCC5	-	-	-
rs6999227	NBN	-	-	-
rs4639	NEIL2	-	-	-
rs174541	FEN1	0.017	0.397	*
rs12486046	TREX1	-	-	-
rs181747	MSH3	-	-	-
rs2241031	MLH1	-	-	-
rs2242150	TREX1	-	-	-
rs7301931	RAD52	-	-	-
rs4151330	MNAT1	-	-	-
rs3219337	POLD1	-	-	-
rs1805833	NBN	-	-	-
rs12593359	RAD51	-	-	-
rs3805173	NEIL3	-	-	-
rs2308962	NBN	-	-	-
rs17257252	RPA2	-	-	-
rs7023656	RAD23B	-	-	-
rs3729558	PCNA	-	-	-
rs5744680	POLK	-	-	-
rs709816	NBN	-	-	-
rs3792149	REV1L	-	-	-
rs11988	DDB2	-	-	-
rs3815611	RPA1	-	-	-
rs11592973	MMS19L	-	-	-

rs8019592	RAD51L1	-	-	-
rs4942486	BRCA2	-	-	-
rs2532105	BLM	-	-	-
rs1168405	RAD17	-	-	-
rs299080	RAD17	-	-	-
rs8009876	RAD51L1	-	-	-
rs4899244	RAD51L1	-	-	-
rs500558	MRE11A	0.005	0.320	*
rs1956345	RAD51L1	-	-	-
rs1016674	APTX	-	-	-
rs7029997	RAD23B	-	-	-
rs2853228	RRM2B	-	-	-
rs2048074	NEIL3	-	-	-
rs963248	XRCC4	-	-	-
rs4035540	CHEK2	-	-	-
rs4246215	FEN1	0.016	0.381	*
rs156640	LIG1	-	-	-
rs401549	BLM	-	-	-
rs2286939	MLH1	-	-	-
rs16951698	RPA1	-	-	-
rs6413436	RAD52	-	-	-
rs872106	MMS19L	-	-	-
rs3731081	XPC	-	-	-
rs17162868	RPA2	-	-	-
rs226984	FANCM	-	-	-
rs1061627	RECQL	-	-	-
rs4986850	BRCA1	-	-	-
rs1888869	APTX	-	-	-
rs8065290	FLJ35220	-	-	-
rs537046	CHEK1	-	-	-
rs7682729	HEL308	-	-	-
rs1799950	BRCA1	-	-	-
rs1800975	XPA	-	-	-
rs2017309	CHEK2	-	-	-
rs4647554	FANCC	-	-	-
rs3730783	POLI	-	-	-
rs3135998	LIG3	0.016	0.998	*
rs3093816	CCNH	0.038	0.855	*
rs207908	XRCC5	0.030	0.886	*
rs7898934	MGMT	-	-	-
rs9323508	RAD51L1	-	-	-
rs932555	RAD51L1	-	-	-
rs6470522	NBN	-	-	-
rs206081	BRCA2	-	-	-
rs10104756	RAD54B	-	-	-
rs6805118	ATR	0.040	0.800	*
rs6151640	MSH3	-	-	-
rs4135060	TDG	-	-	-
rs9651726	DDB1	-	-	-
rs3093819	CCNH	-	-	-
rs2236141	CHEK2	-	-	-
rs1566823	ERCC3	-	-	-
rs511361	MGMT	-	-	-
rs3800377	FANCE	-	-	-
rs2233921	SMUG1	-	-	-
rs6482752	MGMT	-	-	-
rs4796033	RAD51L3	0.004	0.975	*
rs1805334	RAD23B	-	-	-
rs11855560	RAD51	-	-	-
rs304272	RAD51C	-	-	-
rs7594702	FANCL	-	-	-
rs13436	LIG1	-	-	-
rs9608698	CHEK2	-	-	-
rs2737342	WRN	0.025	0.304	*
rs2276182	POLI	-	-	-
rs2063060	NEIL3	-	-	-
rs6817959	NEIL3	-	-	-

Wibom et al

rs12822733	RAD52	-	-	-
rs2735383	NBN	-	-	-
rs9995	NBN	-	-	-
rs1063054	NBN	-	-	-
rs569235	MGMT	-	-	-
rs12946522	RAD51C	-	-	-
rs3093772	LIG4	-	-	-
rs1800935	MSH6	-	-	-
rs2110554	RPA3	-	-	-
rs17676249	NEIL3	-	-	-
rs963918	RAD51L1	0.048	0.150	*
rs10278521	SHFM1	-	-	-
rs17822908	RAD51C	-	-	-
rs7503173	RPA1	-	-	-
rs1726801	POLD1	-	-	-
rs12680687	NBN	-	-	-
rs4020454	UBE2N	-	-	-
rs50872	ERCC2	-	-	-
rs2241721	LIG1	-	-	-
rs356659	FANCC	-	-	-
rs3815003	BLM	-	-	-
rs2306386	RECQL4	-	-	-
rs17726200	NEIL3	-	-	-
rs10515159	RAD51C	-	-	-
rs3786764	LIG1	-	-	-
rs3213263	XRCC1	-	-	-
rs9488	TDP1	-	-	-
rs4750768	MGMT	-	-	-
rs4771436	ERCC5	-	-	-
rs3219484	MUTYH	-	-	-
rs32984	MSH3	0.004	0.523	*
rs238406	ERCC2	-	-	-
rs9534262	BRCA2	-	-	-
rs3759500	ERCC5	-	-	-
rs3213255	XRCC1	-	-	-
rs1956346	RAD51L1	-	-	-
rs238415	ERCC2	-	-	-
rs4150360	ERCC5	-	-	-
rs756627	RECQL4	0.037	0.011	***
rs6151735	MSH3	-	-	-
rs2228001	XPC	-	-	-
rs16869282	RRM2B	-	-	-
rs9808943	ATR	-	-	-
rs369032	RAD18	-	-	-
rs509017	MGMT	-	-	-
rs1784304	H2AFX	0.045	0.106	*
rs3744524	EME1	-	-	-
rs6674384	DCLRE1B	-	-	-
rs240962	REV3L	-	-	-
rs7916932	MGMT	-	-	-
rs9459639	GTF2H5	-	-	-
rs464822	BLM	-	-	-
rs1956532	RAD51L1	-	-	-
rs174538	FEN1	-	-	-
rs735482	ERCC1	-	-	-
rs2073327	CHEK2	-	-	-
rs10007075	NEIL3	-	-	-
rs17675452	NEIL3	-	-	-
rs2291120	DDB2	-	-	-
rs10138997	FANCM	-	-	-
rs11797	TREX1	-	-	-
rs1043180	NEIL2	0.046	0.393	*
rs6830266	NEIL3	-	-	-
rs2213178	PRKDC	-	-	-
rs2072352	BLM	-	-	-
rs1800932	MSH6	-	-	-
rs7916726	DCLRE1C	-	-	-

rs3218651	POLQ	-	-	-
rs9634672	BRCA2	0.030	0.355	*
rs1350344	XPC	0.012	0.047	*
rs2797604	EXO1	-	-	-
rs1061646	FANCA	-	-	-
rs942190	TDP1	-	-	-
rs12318289	RECQL	-	-	-
rs2287497	TP53	-	-	-
rs4150454	ERCC3	-	-	-
rs13245945	RPA3	-	-	-
rs10136055	RAD51L1	-	-	-
rs13156510	XRCC4	-	-	-
rs2607734	XPC	-	-	-
rs2019726	WRN	-	-	-
rs1805414	PARP1	-	-	-
rs10890386	RAD54L	-	-	-
rs7041137	RAD23B	-	-	-
rs16944863	BLM	-	-	-
rs17169361	RPA3	-	-	-
rs2183869	APTX	-	-	-
rs11016866	MGMT	-	-	-
rs3750898	DCLRE1A	-	-	-
rs4647558	FANCC	-	-	-
rs3219095	PARP1	-	-	-
rs184967	MSH3	0.046	0.427	*
rs1217390	DCLRE1B	-	-	-
rs3814176	DCLRE1C	-	-	-
rs828705	XRCC5	0.008	0.750	*
rs5030755	RPA1	-	-	-
rs1151403	LIG4	-	-	-
rs4150383	ERCC5	-	-	-
rs828701	XRCC5	0.014	0.452	*
rs10868	RAD23B	-	-	-
rs1564379	XRCC4	-	-	-
rs7149482	RAD51L1	-	-	-
rs17655	ERCC5	-	-	-
rs5744712	POLK	-	-	-
rs513736	MGMT	-	-	-
rs2048424	PARP1	-	-	-
rs3219142	PARP1	-	-	-
rs3797887	MSH3	-	-	-
rs2320236	BRCA2	-	-	-
rs1803541	ERCC3	-	-	-
rs3942589	SHFM1	-	-	-
rs7923750	MGMT	-	-	-
rs7165790	BLM	-	-	-
rs1800936	MSH6	-	-	-
rs7910123	MGMT	-	-	-
rs3784099	RAD51L1	-	-	-
rs356665	FANCC	-	-	-
rs11016887	MGMT	-	-	-
rs9913559	RDM1	-	-	-
rs10514249	XRCC4	-	-	-
rs4151374	MNAT1	-	-	-
rs2793380	PARP1	-	-	-
rs1956523	RAD51L1	-	-	-
rs8516	XPC	-	-	-
rs2026976	MGMT	-	-	-
rs3757527	RPA3	-	-	-
rs249633	MSH3	-	-	-
rs3907099	RRM2B	-	-	-
rs6477569	RAD23B	-	-	-
rs3784104	RAD51L1	-	-	-
rs1805410	PARP1	-	-	-
rs12125573	RAD54L	-	-	-
rs3730447	PCNA	-	-	-
rs2236142	CHEK2	-	-	-

rs17102086	RAD54L	-	-	-
rs3731108	XPC	-	-	-
rs7182283	NEIL1	-	-	-
rs13088787	RAD18	-	-	-
rs499952	MRE11A	0.037	0.123	*
rs3817364	ALKBH3	-	-	-
rs3916874	ERCC2	0.047	0.590	*
rs2279017	XPC	-	-	-
rs11574214	WRN	-	-	-
rs11574221	WRN	-	-	-
rs1054754	NEIL3	-	-	-
rs2284392	RECQL	-	-	-
rs4647167	ERCC8	-	-	-
rs7726671	ERCC8	-	-	-
rs1801406	BRCA2	0.039	0.832	*
rs4660917	RAD54L	-	-	-
rs12255679	MGMT	-	-	-
rs4151316	MNAT1	-	-	-
rs10744729	RAD52	-	-	-
rs3829213	DCLRE1A	-	-	-
rs1618536	ERCC2	-	-	-
rs873601	ERCC5	-	-	-
rs765899	RAD51L1	-	-	-
rs10841832	RECQL	-	-	-
rs1805377	XRCC4	-	-	-
rs462779	REV3L	-	-	-
rs3176757	XPA	-	-	-
rs1518818	ALKBH3	-	-	-
rs1346044	WRN	-	-	-
rs17284218	XRCC4	-	-	-
rs373759	ATM	-	-	-
rs2233006	MAD2L2	-	-	-
rs10906778	DCLRE1C	-	-	-
rs861534	XRCC3	-	-	-
rs10971259	APTX	0.016	0.654	*
rs7311263	RAD52	-	-	-
rs1233258	PMS1	0.033	0.221	*
rs33003	MSH3	-	-	-
rs7078706	MGMT	-	-	-
rs976631	ERCC8	-	-	-
rs17102087	RAD54L	-	-	-
rs3087386	REV1L	-	-	-
rs2309585	REV1L	-	-	-
rs2434474	ALKBH3	0.040	0.816	*
rs6679432	RPA2	0.043	0.908	*
rs3176639	XPA	-	-	-
rs13447720	MRE11A	-	-	-
rs10816492	RAD23B	-	-	-
rs3136249	MSH6	-	-	-
rs4942448	BRCA2	-	-	-
rs543304	BRCA2	-	-	-
rs7310449	RAD52	-	-	-
rs769105	REV1L	-	-	-
rs2331648	RAD51L1	-	-	-
rs2286680	PMS2	-	-	-
rs3213212	RECQL	-	-	-
rs12880109	RAD51L1	-	-	-
rs4978849	RAD23B	-	-	-
rs9625534	CHEK2	-	-	-
rs3824948	ALKBH3	-	-	-
rs16855458	XRCC5	-	-	-
rs227060	ATM	-	-	-
rs876430	ERCC5	-	-	-
rs2159943	RECQL	-	-	-
rs1650737	MSH3	-	-	-
rs3219110	PARP1	-	-	-
rs2244012	RAD50	-	-	-

rs911263	RAD51L1	-	-	-
rs4718479	PMS2L4	-	-	-
rs3213801	POLK	-	-	-
rs911254	RAD51L1	-	-	-
rs455645	REV3L	-	-	-
rs1063053	NBN	-	-	-
rs11157432	FANCM	0.001	0.465	*
rs17507066	CHEK2	-	-	-
rs963774	FANCC	-	-	-
rs11037720	ALKBH3	-	-	-
rs1988728	POLK	-	-	-
rs3754093	EXO1	-	-	-
rs2183878	MGMT	-	-	-
rs2808668	XPA	-	-	-
rs3824457	APTX	0.033	0.713	*
rs5744545	POLK	-	-	-
rs10813913	APTX	-	-	-
rs1800058	ATM	-	-	-
rs11158730	RAD51L1	-	-	-
rs132770	XRCC6	-	-	-
rs7311151	RAD52	-	-	-
rs1923775	POLN	-	-	-
rs803335	FANCD2	-	-	-
rs861531	XRCC3	0.012	0.196	*
rs1055677	NEIL3	-	-	-
rs3176748	XPA	-	-	-
rs6596087	RAD50	-	-	-
rs7905095	MGMT	-	-	-
rs10741199	MGMT	-	-	-
rs12219606	MGMT	-	-	-
rs11037710	ALKBH3	-	-	-
rs2401863	TDP1	-	-	-
rs6599418	POLN	-	-	-
rs1805386	LIG4	-	-	-
rs459809	REV3L	-	-	-
rs462832	REV3L	-	-	-
rs3117813	POLN	-	-	-
rs7356	RPA2	0.012	0.908	*
rs6565686	FLJ35220	-	-	-
rs1021005	ERCC8	-	-	-
rs206147	BRCA2	-	-	-
rs4253079	ERCC6	-	-	-
rs1950769	RAD51L1	-	-	-
rs11107018	UBE2N	-	-	-
rs3117	ERCC8	0.024	0.866	*
rs4235483	ERCC8	0.011	0.866	*
rs1382367	XRCC4	-	-	-
rs2353005	PNKP	-	-	-
rs2029682	MSH4	-	-	-
rs5745543	MSH4	-	-	-
rs5745553	MSH4	-	-	-
rs1805812	NBN	-	-	-
rs6151616	MSH3	-	-	-
rs1382543	MSH3	-	-	-
rs979182	POLK	-	-	-
rs17349	PCNA	-	-	-
rs2227928	ATR	-	-	-
rs2304136	LIG1	-	-	-
rs10739234	RAD23B	-	-	-
rs11950902	MSH3	-	-	-
rs1677652	MSH3	-	-	-
rs461646	REV3L	-	-	-
rs240969	REV3L	-	-	-
rs10829622	MGMT	-	-	-
rs7535816	RPA2	0.017	0.908	*
rs9862879	POLQ	-	-	-
rs17574343	NHEJ1	-	-	-

rs1001160	MSH4	-	-	-
rs2159451	BRIP1	-	-	-
rs5744564	POLK	-	-	-
rs11637235	DUT	-	-	-
rs2662241	XRCC4	-	-	-
rs4988357	BRIP1	-	-	-
rs2336030	MAD2L2	-	-	-
rs10030779	HEL308	-	-	-
rs10841833	RECQL	-	-	-
rs3136337	MSH6	-	-	-
rs5744636	POLK	-	-	-
rs588341	POLN	-	-	-
rs4608577	MSH2	-	-	-
rs1217398	DCLRE1B	-	-	-
rs2522414	RAD50	-	-	-
rs1799977	MLH1	-	-	-
rs7764543	REV3L	-	-	-
rs158920	ERCC8	0.019	0.004	**
rs747863	MAD2L2	-	-	-
rs15869	BRCA2	-	-	-
rs4151223	MNAT1	-	-	-
rs2270412	RPA1	-	-	-
rs7897876	MGMT	-	-	-
rs171140	ERCC2	-	-	-
rs6782400	ATR	-	-	-
rs1494962	HEL308	-	-	-
rs4902586	RAD51L1	-	-	-
rs158931	ERCC8	-	-	-
rs1866074	TDG	-	-	-
rs1805335	RAD23B	-	-	-
rs10805813	XRCC4	-	-	-
rs11147005	POLE	-	-	-
rs17755657	RAD51L1	0.036	0.057	*
rs12587397	RAD51L1	-	-	-
rs942292	RAD23B	-	-	-
rs3798134	RAD50	-	-	-
rs2972381	CDK7	-	-	-
rs158928	ERCC8	0.016	0.004	**
rs2706338	RAD50	-	-	-
rs3093748	LIG4	-	-	-
rs10858024	DCLRE1B	-	-	-
rs2292890	ALKBH3	-	-	-
rs9831613	RAD18	-	-	-
rs1800937	MSH6	-	-	-
rs4693623	HEL308	-	-	-
rs245400	MSH3	0.019	0.043	**
rs4840581	NEIL2	-	-	-
rs10741191	MGMT	-	-	-
rs2972388	CDK7	-	-	-
rs32959	MSH3	-	-	-
rs301275	XRCC4	-	-	-
rs3730849	LIG1	-	-	-
rs4841593	NEIL2	-	-	-
rs3176658	XPA	-	-	-
rs5744533	POLK	-	-	-
rs3087399	REV1L	-	-	-
rs2227930	ATR	-	-	-
rs16878166	MSH3	-	-	-
rs7920514	DCLRE1C	-	-	-
rs2733532	XPC	-	-	-
rs10940210	CDK7	-	-	-
rs2974448	XRCC4	-	-	-
rs10474079	XRCC4	-	-	-
rs2395626	FANCE	-	-	-
rs4647404	FANCC	-	-	-
rs11851266	TDP1	-	-	-

a) The asterisks denote significance ($P < 0.05$) in different tests, according to:

* sign in the screening test

** sign in the external validation

*** sign after adjusting for country, sex, age, surgery (radical or not), radio- and chemotherapy

Samples removed:

- 21 missing follow-up data
- 13 poor DNA quality

Samples removed:

- 17 missing clinical parameters

Samples removed:

- 97 missing follow-up data
- 77 poor DNA quality

RS2042649

RS2303428

RS2038565

RS6573805

RS8022206

RS11626809

RS17192586

RS756627

RS3757966

Block 1 (66 kb)