

# Variation in DNA repair genes XRCC3, XRCC4, XRCC5 and susceptibility to myeloma

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**Cytogenetic analysis in myeloma reveals marked chromosomal instability. Both widespread genomic alterations and evidence of aberrant class switch recombination, the physiological process that regulates maturation of the antibody response, implicate the DNA repair pathway in disease pathogenesis. We therefore assessed 27 SNPs in three genes (XRCC3, XRCC4 and XRCC5) central to DNA repair in patients with myeloma and controls from the EpiLymph study and from an Irish hospital registry ( $n = 306$  cases, 263 controls). For the haplotype-tagging SNP (htSNP) rs963248 in XRCC4, Allele A was significantly more frequent in cases than in controls (86.4 versus 80.8%; odds ratio 1.51; 95% confidence interval 1.10–2.08;  $P = 0.0133$ ), as was the AA genotype (74 versus 65%) ( $P = 0.026$ ). Haplotype analysis was performed using Unphased for rs963248 in combination with additional SNPs in XRCC4. The strongest evidence of association came from the A–T haplotype from rs963248–rs2891980 ( $P = 0.008$ ). For XRCC5, the genotype GG from rs1051685 was detected in 10 cases from different national populations but in only one control ( $P = 0.015$ ). This SNP is located in the 3'-UTR of XRCC5. Overall, these data provide support for the hypothesis that common variation in the genes encoding DNA repair proteins contributes to susceptibility to myeloma.**

## INTRODUCTION

Severe inherited defects in DNA repair have long been known to confer an increased susceptibility to cancer. Interest in recent years has focused on the wide population variability in repair capacity phenotype, which appears to account for a several-fold variation in cancer risk (1,2). The completion of large-scale sequencing of population allelic variance in DNA repair genes has facilitated the investigation of their contri-

bution to disease susceptibility. Meta-analyses have shown correlations between polymorphisms in repair genes and the risk of various cancers (3,4). Defective DNA repair has also been implicated directly as an aetiological factor in haematological malignancy (5,6).

Myeloma is a largely incurable cancer of differentiated B-cells, which is characterised by anaemia, bone disease and renal impairment (7–9). Though associated with occupational exposure in the farming and petrochemical industries, the epi-

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demology remains largely conjectural (10). Two oncogenic pathways are considered central to disease pathogenesis; hyperdiploid myeloma involves multiple trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19 and 21, whereas in non-hyperdiploid myeloma, primary translocations involving the immunoglobulin heavy chain locus at 14q32 and a limited number of recurrent partner loci are present (11–13). These latter events are felt to represent aberrant class switch recombination (CSR), a process that normally functions to alter immunoglobulin isotype with the maturation of the immune response (14,15). Such translocations result in the placing of a number of proto-oncogenes under the control of the strong immunoglobulin heavy chain enhancer. Dysregulated CSR is believed to be central to the pathogenesis of myeloma.

CSR is a DNA deletion-recombination event that requires formation and repair of DNA double-strand breaks (DSB) (16,17). Once DNA damage sensor proteins such as p53, ATM, NBS1, BRCA1 and BRCA2 have sensed the DSB, ligation of the cleaved ends makes use of common DNA damage repair machinery. Both the non-homologous end joining (NHEJ) and the homologous recombination (HR) pathways are utilised (18,19). The primary proteins involved in NHEJ are Ku70, Ku80 (XRCC5), DNA-Protein Kinase (catalytic subunit), XRCC4 and DNA Ligase 4. Variant expression and function of Ku protein has been reported in human myeloma cells (20). HR utilises the RAD50 family (RAD50, 51, 52, 54, etc.) as well as BRCA1 and BRCA2. XRCC3 is a member of the RecA/Rad51-related protein family that participates in HR.

To date, the molecular epidemiology of myeloma has largely focused on the study of immune response genes. An initial report that haplotypes in the tumour necrosis factor region on chromosome 6 may have been associated with myeloma was not borne out on further analysis (21,22). Allelic variants of I $\kappa$ B- $\alpha$ , however, may be associated with an increased risk of disease (23,24). Equally, TNF- $\alpha$  promoter polymorphisms appear to predict for outcome after therapy with the immunomodulatory drug, thalidomide (25). More recently, IL-6 promoter genotypes may be associated with an increased risk of plasma cell neoplasms and common genetic variants in specific immune-mediated pathways could also influence the risk of myeloma (26,27). Finally, studies on DNA repair genes suggest that there is some evidence for a role for polymorphisms in DNA Ligase 4 in conferring susceptibility to myeloma and for defective DNA mismatch repair pathway in the evolution of the disease (28,29).

The first generation of genetic association studies in myeloma assessed 'candidate' single nucleotide polymorphisms (SNPs) chosen on the basis of a likely functional impact of the resulting nucleotide substitution. The increased density of SNP data provided by the HAPMAP project and high throughput genotyping technologies now allows for the selection of tagging SNPs, which allow for gene haplotypes to be compared in case-control studies (30–32).

Given both the widespread karyotypic abnormalities in this disease and the evidence that a process requiring DNA repair is central to the pathogenesis of myeloma, we selected three genes involved in DNA repair, XRCC3, XRCC4 and XRCC5 for analysis in a case control association study.

XRCC3 was chosen based on its role in the HR repair pathway and on previous data suggesting an association between polymorphic variation and follicular lymphoma (33). As both DNA ligase IV polymorphisms and Ku protein have also been tentatively implicated in myeloma pathogenesis, XRCC4 and XRCC5 were selected for assessment (20,28). A comprehensive haplotype-tagging approach was used to choose 31 SNPs across these genes for investigation. This allowed us to test a high proportion of common variation across these genes to determine if any particular SNP or haplotype confers susceptibility to myeloma.

## RESULTS

### Association analysis of SNPs with myeloma risk

We have successfully genotyped 27 htSNPs in three DSB repair genes: XRCC3, XRCC4 and XRCC5 in myeloma patients and controls from the EpiLymph Study and from an Irish hospital registry (306 cases, 263 controls in total). Thirty-one htSNPs were originally identified by tagger but four assays failed design. The 27 SNPs studied are shown in Table 1. Details of the results of single marker association tests for each SNP chosen for analysis in our full case-control study population are presented in Tables 2 and 3.

*XRCC3.* There was no significant difference in allele or genotype frequencies between cases and controls for any of the five SNPs tested across XRCC3.

*XRCC4.* Nine SNPs across XRCC4 were tested for evidence of association. The most significant result was for rs963248 where allele A was significantly more common in cases compared to controls (86.4 versus 80.8; odds ratio (OR) 1.51; 95% confidence interval (CI) 1.10–2.08;  $P = 0.0133$ ). Genotype analysis also showed evidence of association ( $P = 0.026$ ) with the AA genotype in excess in cases compared to controls (74 versus 65%). As single marker analysis suggested a trend towards association with rs963248, this SNP was combined in turn with each of the eight other SNPs to assess for haplotypic association. The strongest evidence of association came from the A–T haplotype from rs963248–rs2891980 (80.9 versus 74.5%;  $P = 0.008$ ).

*XRCC5.* No single marker at XRCC5 reached nominal significance levels. However, an interesting finding was noted for rs1051685 where the GG genotype was found in 10 cases from the different national populations but only in one control. This suggested a recessive model and was tested with Fisher's Exact Test and found to be significant ( $P = 0.015$ ). This SNP is located in the 3'-untranslated region (UTR) of XRCC5.

## DISCUSSION

This is the first study to report an analysis of common variants in the three DNA DSB repair genes, XRCC3, XRCC4 and XRCC5 and the risk of developing myeloma. A comprehensive SNP-tagging approach was employed, incorporating the HAPMAP CEU reference panel data, to

**Table 1.** Details of genes and SNPs

Gene	Chromosome	Db SNP ID	Location	Nucleotide change
XRCC3	14q32.3	rs861528	intron 1	A>G
		rs1799794	exon 2	A>G
		rs861530	intron 5	A>G
		rs 861531	intron 6	G>T
		rs1799796	intron 7	A>G
XRCC4	5q13–q14	rs1478486	intron 1	C>T
		rs1382376	intron 1	C>G
		rs1011980	intron 1	A>G
		rs1011981	intron 1	A>G
		rs1478483	intron 2	C>T
		rs963248	intron 6	A>G
		rs1193693	intron 6	A>G
		rs13178127	intron 7	A>G
		rs2891980	intron 7	C>T
		XRCC5	2q35	rs828704
rs2303400	intron 12			C>T
rs207906	exon 14			A>G
rs207908	intron 14			A>T
rs207916	intron 16			A>G
rs207922	intron 16			C>T
rs6753002	intron 16			C>T
rs207940	intron 16			C>T
rs3770500	intron 16			A>T
rs3770493	intron 16			A>G
rs1051677	3'-UTR			C>T
rs1051685	3'-UTR			A>G
rs2440	3'-UTR			C>T

select SNPs across these genes that effectively capture the majority of common variants at these loci. We report here that SNPs in XRCC4 and XRCC5 may alter the risk of developing myeloma. Although the risk estimates are modest, this nonetheless implicates the DNA repair pathway in disease susceptibility. Given the limited size of our study, these results need replication in larger independent samples to confirm and possibly elucidate their role in myelomagenesis.

The strength of our study is in the use of htSNPs. The recent availability of comprehensive SNP frequency data through the HAPMAP consortium allows for more robust assessment of genomic regions of interest rather than simply genotyping SNPs of theoretical a priori significance. At XRCC3, the five SNPs genotyped in this study effectively tagged 11 SNPs across the gene. For XRCC4, the nine SNPs analysed effectively tagged 116 SNPs and at XRCC5, the 13 tag SNPs selected effectively tagged 77 SNPs. Evidence is also accumulating that htSNPs selected using HAPMAP data efficiently tag for haplotypes in European populations (34,35).

There are some potential limitations to our study. Hospital as opposed to population controls were used in most participating EpiLymph centres. Although this is an important issue in the analysis of, for example, inflammatory gene polymorphisms, there is no a priori reason to assume that any given DNA repair gene alleles would be over-represented in hospital controls from which patients with cancer or systemic infection have been excluded. Nonetheless, we appreciate that in general, the use of hospital controls as opposed to population controls represents a potential confounding variable in genetic epidemiological studies. Equally, the choice of controls from

the EpiLymph study for the cases enrolled on the prospective Irish study should be noted. Though this is not methodologically ideal, they are derived from the same background population and are acceptable for an exploratory study aimed at producing a restricted set of hypotheses that can then be tested in studies employing more robust study designs.

XRCC3 is a member of the RecA/Rad51-related protein family that participates in HR. A recent meta-analysis suggests that XRCC3 might be associated with cancer susceptibility, especially for cancer of breast, bladder, head and neck, and non-melanoma skin cancer (36). However, a huGE review of XRCC3 variants in codon 241 found no definite associations between this commonly genotyped SNP and cancer (37). A Swedish study has suggested that rare homozygotes of three SNPs in the gene increase the risk of developing follicular lymphoma though evidence of differences in XRCC3 haplotype distributions between follicular lymphoma cases and controls was weak (33). Our study found no difference in genotype or haplotype distributions between cases with myeloma and controls.

The XRCC4 protein forms a complex with DNA Ligase 4 and DNA-dependent protein kinase in the repair of DNA DSBs by NHEJ. In our study, allele A of XRCC4 htSNP rs963248 was more frequent in cases than controls (86.4 versus 80.8%; OR 1.51; 95% CI 1.10–2.08;  $P = 0.0133$ ). FastSNP predicts that this SNP is an intronic enhancer, which may therefore be involved in affecting the stability of the XRCC4 mRNA transcript or altering its expression (38). Further analysis of this SNP by Transfac (<http://www.gene-regulation.com/index.htm>) suggests that the presence of the allele A instead of the G allele leads to loss of a GATA2 binding motif which may have potential pathological consequence. Additional work is required to characterise the functional aspects of this SNP and also to determine whether it is itself the high risk allele or in LD with a causal variant as on the basis of the HAPMAP dataset, rs963248 is in very high LD ( $r^2 > 0.8$ ) with 10 other SNPs (rs177297, rs35271, rs35270, rs35268, rs301279, rs301281, rs301286, rs301289, rs445403, rs369619) which merit further investigation.

A number of groups have examined the potential role of XRCC4 in cancer susceptibility. The SNP rs2075685 is located approximately 0.5 kb 5' of XRCC4 and was significantly associated ( $P = 0.02$ ) with the risk of breast cancer in a Taiwanese study (39). A recent evaluation of four XRCC4 htSNPs in breast cancer in Utah also found that two 2-locus haplotypes were nominally associated with breast cancer risk (40). Rs963248 was also one of their chosen htSNPs. In order to detect whether the Taiwanese and Utah findings were related, the Utah group assessed and found a high relative pair-wise LD ( $D' = 0.81$ ) between rs2075685 and rs963248. This raises the possibility that all three studies may be detecting the same haplotypic variant increasing the risk of cancer.

XRCC5 encodes the 80-kDa subunit of the Ku heterodimer protein, the DNA-binding component of the DNA-dependent protein kinase. In a search of both the Public Library of Medicine PubMed database (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed>) and the Genomics and Disease Prevention Information System database (<http://apps.nccd.cdc.gov/genomics/GDPQueryTool/default.asp>) in 2006,

**Table 2.** Genotype frequency and overall association with DNA repair genes for myeloma cases and controls

Gene polymorphism rs number	Genotype	Cases <i>n</i> (%)	Controls <i>n</i> (%)	OR <sup>a</sup>	95% CI	<i>P</i> -value	$\chi^2$ <i>P</i> -value
XRCC3 rs861528	GG	171 (56.6)	149 (58.2)	1.00	ref	–	0.615792
	AG	111 (36.8)	95 (37.1)	0.98	0.69–0.40	0.9916	
	AA	20 (6.2)	12 (4.7)	0.68	0.32–1.46	0.4266	
	AG/AA	131 (43.3)	107 (41.8)	0.94	0.67–1.31	0.7716	
XRCC3 rs1799794	AA	189 (62.6)	153 (59.5)	1.00	ref	–	0.74272
	AG	100 (33.1)	91 (35.4)	1.12	0.79–1.60	0.5787	
	GG	13 (43.0)	13 (5.1)	1.23	0.56–2.74	0.7524	
	AG/GG	113 (37.4)	104 (40.5)	1.14	0.80–1.60	0.5155	
XRCC3 rs861530	GG	144 (47.2)	119 (45.6)	1.00	ref	–	0.71225
	AG	130 (42.6)	108 (41.7)	1.00	0.71–1.43	0.9765	
	AA	31 (10.2)	32 (12.3)	1.25	0.72–2.17	0.5142	
	AG/AA	161 (52.8)	140 (54.0)	1.05	0.76–1.47	0.829	
XRCC3 rs861531	GG	118 (38.8)	109 (42.2)	1.00	ref	–	0.496803
	GT	140 (46.1)	118 (45.7)	0.91	0.64–1.30	0.6809	
	TT	46 (15.1)	31 (12.0)	0.73	0.43–1.23	0.2947	
	GT/TT	186 (61.2)	149 (42.8)	0.87	0.62–1.22	0.4592	
XRCC3 rs1799796	AA	150 (49.7)	113 (43.5)	1.00	ref	–	0.216477
	AG	123 (40.7)	125 (48.0)	1.35	0.95–1.91	0.1105	
	GG	29 (9.6)	22 (8.5)	1.00	0.55–1.84	0.9819	
	AG/GG	152 (50.3)	147 (56.5)	1.29	0.92–1.80	0.1658	
XRCC4 rs1478486	CC	104 (34.4)	94 (36.4)	1.00	ref	–	0.679814
	CT	148 (49.0)	117 (45.3)	0.88	0.60–1.27	0.5378	
	TT	50 (16.6)	47 (18.2)	1.04	0.64–1.69	0.9728	
	CT/TT	198 (65.6)	164 (63.6)	0.92	0.65–1.30	0.6862	
XRCC4 rs1382376	CC	103 (33.9)	88 (34.2)	1.00	ref	–	0.31567
	CG	143 (47.2)	109 (42.2)	0.89	0.61–1.30	0.6207	
	GG	57 (18.8)	61 (23.6)	1.25	0.79–1.98	0.3989	
	CG/GG	200 (66.0)	170 (65.9)	0.99	0.70–1.41	0.9771	
XRCC4 rs1011980	AA	151 (49.5)	136 (52.3)	1.00	ref	–	0.785573
	AG	129 (42.3)	105 (40.3)	0.90	0.64–1.28	0.6281	
	GG	25 (8.2)	19 (7.3)	0.84	0.44–1.60	0.7201	
	AG/GG	154 (50.5)	124 (47.7)	0.89	0.64–1.25	0.5626	
XRCC4 rs1011981	AA	107 (35.1)	100 (38.5)	1.00	ref	–	0.381548
	AG	142(46.5)	106 (40.8)	0.80	0.55–1.16	0.2742	
	GG	56(18.4)	54 (20.8)	1.03	0.65–1.63	0.9884	
	AG/GG	198 (64.9)	160 (61.5)	0.86	0.61–1.21	0.4572	
XRCC4 rs1478483	CC	245 (80.3)	200 (76.9)	1.00	ref	–	0.390792
	CT	56 (18.4)	53 (20.4)	1.16	0.76–1.76	0.5592	
	TT	4 (1.3)	7 (2.7)	2.14	0.62–7.43	0.3557	
	CT/TT	60 (19.7)	60 (23.0)	1.23	0.81–1.83	0.3772	
XRCC4 rs963248	AA	226 (73.9)	167 (64.7)	1.00	ref	–	<b>0.025692</b>
	AG	77 (25.1)	83 (32.2)	1.46	1.01–2.11	0.05	
	GG	3 (1.0)	8 (3.1)	3.61	0.94–13.8	0.0915	
	AG/GG	80 (26.1)	91 (35.3)	1.54	1.07–2.20	<b>0.024</b>	

XRCC4 rs13178127	AA	270 (89.4)	234 (90.3)	1.00	ref	–	0.895048
	AG	30 (9.9)	25 (9.7)	0.98	0.76–1.27	0.8906	
	GG	2 (0.7)	0 (0)	0.23	0.01–4.83	0.5460	
	AG/GG	32 (10.6)	25 (9.7)	0.9	0.52–1.57	0.8192	
XRCC4 rs11193693	AA	76 (25.2)	82 (31.7)	1.00	ref	–	0.056717
	AG	166 (55.0)	115 (44.4)	0.64	0.43–0.95	<b>0.0341</b>	
	GG	60 (19.8)	59 (22.8)	0.91	0.57–1.47	0.7943	
	AG/GG	226 (74.8)	174 (67.9)	0.71	0.49–1.03	0.0892	
XRCC4 rs2891980	TT	251 (83.1)	202 (78)	1.00	ref	–	<b>0.047871</b>
	CT	51 (16.9)	53 (20.5)	1.29	0.84–1.98	0.2861	
	CC	0 (0)	4 (1.5)	11.17	0.59–208.98	<b>0.0406</b>	
	CT/CC	51 (16.9)	57 (22.0)	1.39	0.91–2.12	0.1539	
XRCC5 rs828704	AA	192 (62.7)	163 (62.7)	1.00	ref	–	0.997813
	AC	96 (31.4)	82 (31.5)	1.00	0.70–1.44	0.9735	
	CC	18 (5.9)	15 (5.8)	0.98	0.48–2.01	0.9595	
	AC/CC	114 (37.3)	97 (37.3)	1.00	0.71–1.41	0.9897	
XRCC5 rs2303400	TT	97 (31.8)	91 (35.3)	1.00	ref	–	0.376677
	CT	153 (50.2)	131 (50.8)	0.91	0.63–1.32	0.6957	
	CC	55 (18.0)	36 (13.6)	0.70	0.42–1.16	0.2068	
	CT/CC	208 (68.2)	167 (64.7)	0.86	0.60–1.21	0.4356	
XRCC5 rs207906	GG	243 (79.4)	200 (76.9)	1.00	ref	–	0.299593
	AG	54 (17.6)	56 (21.5)	1.26	0.83–1.91	0.3281	
	AA	9 (2.9)	4 (1.5)	0.54	0.16–1.78	0.4565	
	AG/AA	63 (20.6)	60 (23.0)	1.16	0.78–1.72	0.5398	
XRCC5 rs207908	TT	81 (26.5)	70 (27.1)	1.00	ref	–	0.847781
	AT	157 (51.5)	127 (49.2)	0.94	0.63–1.39	0.8213	
	AA	67 (22.0)	61 (23.6)	1.05	0.66–1.69	0.9234	
	AT/AA	224 (73.4)	188 (72.9)	0.97	0.67–1.41	0.9539	
XRCC5 rs207916	AA	97 (31.8)	88 (34.4)	1.00	ref	–	0.11304
	AG	139 (45.6)	128 (50)	1.01	0.69–1.48	0.9379	
	GG	69 (22.6)	40 (15.6)	0.64	0.39–1.04	0.0903	
	AG/GG	208 (68.2)	168 (65.6)	0.89	0.63–1.27	0.5788	
XRCC5 rs207922	CC	132 (43.3)	95 (37)	1.00	ref	–	0.281351
	CT	134 (43.9)	127 (49.4)	1.32	0.92–1.89	0.1569	
	TT	39 (12.8)	37 (14.4)	1.32	0.78–2.22	0.3647	
	CT/TT	1739 (56.7)	164 (63.8)	1.31	0.94–1.85	0.132	
XRCC5 rs6753002	TT	201 (65.9)	159 (61.9)	1.00	ref	–	0.316159
	CT	85 (27.9)	88 (33.7)	1.31	0.91–1.88	<b>0.0173</b>	
	CC	19 (6.2)	14 (5.4)	0.93	0.45–1.91	0.9922	
	CT/CC	104 (34.1)	102 (39.7)	1.21	0.88–1.75	0.2541	
XRCC5 rs207940	CC	92 (30.2)	59 (22.9)	1.00	ref	–	0.11802
	CT	142 (46.6)	139 (53.9)	1.52	1.02–2.28	<b>0.0493</b>	
	TT	71 (23.2)	60 (23.2)	1.32	0.82–2.11	0.3076	
	CT/TT	213 (69.8)	199 (77.1)	1.46	0.99–2.13	0.0641	

Continued

Table 2. Continued

Gene polymorphism rs number	Genotype	Cases <i>n</i> (%)	Controls <i>n</i> (%)	OR <sup>a</sup>	95% CI	<i>P</i> -value	$\chi^2$ <i>P</i> -value
XRCC5 rs3770500	TT	259 (84.9)	215 (84.0)	1.00	ref	–	0.940862
	AT	42 (13.8)	37 (14.4)	1.06	0.66–1.71	0.9029	
	AA	4 (1.3)	4 (1.6)	1.21	0.29–4.88	0.7937	
	AT/AA	46 (15.1)	41 (16.0)	1.07	0.68–1.69	0.8515	
XRCC5 rs3770493	GG	244 (80.3)	205 (79.0)	1.00	ref	–	0.074405
	AG	50 (16.4)	52 (20.0)	1.24	0.80–1.90	0.3882	
	AA	10 (3.3)	2 (1.0)	0.24	0.05–1.09	0.0740	
	AG/AA	60 (19.7)	54 (20.8)	1.07	0.68–1.69	0.8242	
XRCC5 rs1051677	TT	260 (85.0)	218 (83.5)	1.00	ref	–	0.868561
	CT	41 (13.4)	39 (15.0)	1.13	0.71–1.82	0.6885	
	CC	5 (1.6)	4 (1.5)	0.95	0.25–3.60	0.9447	
	CT/CC	46 (15.0)	43 (16.5)	1.12	0.71–1.75	0.7227	
XRCC5 rs1051685	AA	246 (81)	204 (78.2)	1.00	ref	–	<b>0.015143</b>
	AG	49 (16)	56 (21.5)	0.73	0.47–1.11	0.1705	
	GG	10 (3)	1 (0.4)	8.3	1.05–65.35	<b>0.0269</b>	
	AG/GG	59 (19.4)	57 (21.8)	0.86	0.57–1.29	0.5297	
XRCC5 rs2440	CC	105 (34.3)	101 (39.0)	1.00	ref	–	0.098756
	CT	142 (46.4)	125 (48.3)	0.92	0.63–1.32	0.7004	
	TT	59 (19.3)	33 (12.7)	0.58	0.35–0.96	<b>0.0443</b>	
	CT/TT	201 (65.7)	158 (61.0)	0.82	0.58–1.15	0.2871	

<sup>a</sup>OR adjusted for age, sex and study centre.

**Table 3.** Allele frequency and overall association with DNA repair genes for myeloma cases and controls

Gene	db SNP ID	Alleles	Cases <i>n</i> (%)	Controls <i>n</i> (%)	OR (95% CI)	Allele <i>P</i> -value																																																																																																																																																																																																																																									
XRCC3	rs861528	G	453 (75)	393 (76.8)	0.91 (0.69–1.19)	0.5398																																																																																																																																																																																																																																									
		A	151 (25)	119 (23.2)			XRCC3	rs1799794	A	478 (79.10)	397 (77.3)	1.12 (0.84–1.5)	0.4867	G	126 (20.9)	117 (22.7)	XRCC3	rs861530	G	418 (68.5)	346 (66.8)	1.08 (0.84–1.40)	0.5788	A	192 (31.5)	172 (33.2)	XRCC3	rs861531	G	376 (61.8)	336 (65.1)	0.87 (0.68–1.10)	0.2832	T	232 (38.2)	180 (34.9)	XRCC3	rs1799796	A	423 (70)	351 (67.5)	1.13 (0.87–1.45)	0.3954	G	181 (30)	169 (32.5)	XRCC4	rs1478486	C	356 (58.9)	305 (59.1)	0.99 (0.78–1.26)	0.9545	T	248 (41.8)	211 (40.9)	XRCC4	rs1382376	C	349 (57.6)	285 (55.2)	1.10 (0.87–1.39)	0.4631	G	257 (42.4)	231 (44.8)	XRCC4	rs1011980	A	431 (70.7)	377 (72.5)	0.91 (0.70–1.18)	0.5363	G	179 (29.3)	143 (27.5)	XRCC4	rs1011981	A	356 (58.4)	306 (58.8)	0.98 (0.77–1.24)	0.9167	G	254 (41.6)	214 (41.2)	XRCC4	rs1478483	C	546 (89.5)	453 (87.1)	1.26 (0.87–1.82)	0.2464	T	64 (10.5)	67 (12.9)	XRCC4	rs963248	A	529 (86.4)	417 (80.8)	1.51 (1.10–2.08)	<b>0.0133</b>	G	83 (13.6)	99 (19.2)	XRCC4	rs1193693	A	318 (52.6)	279 (54.5)	0.93 (0.73–1.18)	0.5789	G	286 (47.4)	233 (45.5)	XRCC4	rs1317812	A	570 (94.4)	493 (95.2)	0.85 (0.50–1.45)	0.6408	G	34 (5.6)	25 (4.8)	XRCC4	rs2891980	T	553 (91.6)	457 (88.2)	1.45 (0.98–2.14)	0.079	C	51 (8.4)	61 (11.8)	XRCC5	rs828704	A	480 (78.4)	408 (78.5)	0.99 (0.75–1.33)	0.9902	C	132 (21.6)	112 (21.5)	XRCC5	rs2303400	T	347 (56.9)	313 (60.6)	0.85 (0.67–1.08)	0.2223	C	263 (43.1)	203 (39.3)	XRCC5	rs207906	G	538 (88.5)	456 (87.7)	1.08 (0.75–1.54)	0.7499	A	70 (11.5)	64 (12.3)	XRCC5	rs207908	A	319 (52.3)	249 (48.3)	1.17 (0.93–1.49)	0.1967	T	291 (47.7)	267 (51.7)	XRCC5	rs207916	A	333 (54.6)	304 (59.4)	0.82 (0.65–1.04)	0.1209	G	277 (45.4)	208 (40.6)	XRCC5	rs207922	C	398 (65.2)	317 (61.2)	1.19 (0.94–1.52)	0.1657	T	212 (34.8)	201 (38.8)	XRCC5	rs6753002	T	487 (79.8)	406 (77.8)	1.13 (0.85–1.50)	0.4396	C	123 (20.2)	116 (22.2)	XRCC5	rs207940	C	326 (53.4)	257 (49.8)	1.16 (0.91–1.46)	0.2473	T	284 (46.6)	259 (50.2)	XRCC5	rs3770500	T	560 (91.8)	467 (91.2)	1.08 (0.71–1.64)	0.8046	A	50 (8.2)	45 (8.8)	XRCC5	rs3770493	G	538 (88.5)	462 (89.2)	0.93 (0.64–1.35)	0.7812	A	70 (11.5)	56 (10.8)	XRCC5	rs1051677	T
XRCC3	rs1799794	A	478 (79.10)	397 (77.3)	1.12 (0.84–1.5)	0.4867																																																																																																																																																																																																																																									
		G	126 (20.9)	117 (22.7)			XRCC3	rs861530	G	418 (68.5)	346 (66.8)	1.08 (0.84–1.40)	0.5788	A	192 (31.5)	172 (33.2)	XRCC3	rs861531	G	376 (61.8)	336 (65.1)	0.87 (0.68–1.10)	0.2832	T	232 (38.2)	180 (34.9)	XRCC3	rs1799796	A	423 (70)	351 (67.5)	1.13 (0.87–1.45)	0.3954	G	181 (30)	169 (32.5)	XRCC4	rs1478486	C	356 (58.9)	305 (59.1)	0.99 (0.78–1.26)	0.9545	T	248 (41.8)	211 (40.9)	XRCC4	rs1382376	C	349 (57.6)	285 (55.2)	1.10 (0.87–1.39)	0.4631	G	257 (42.4)	231 (44.8)	XRCC4	rs1011980	A	431 (70.7)	377 (72.5)	0.91 (0.70–1.18)	0.5363	G	179 (29.3)	143 (27.5)	XRCC4	rs1011981	A	356 (58.4)	306 (58.8)	0.98 (0.77–1.24)	0.9167	G	254 (41.6)	214 (41.2)	XRCC4	rs1478483	C	546 (89.5)	453 (87.1)	1.26 (0.87–1.82)	0.2464	T	64 (10.5)	67 (12.9)	XRCC4	rs963248	A	529 (86.4)	417 (80.8)	1.51 (1.10–2.08)	<b>0.0133</b>	G	83 (13.6)	99 (19.2)	XRCC4	rs1193693	A	318 (52.6)	279 (54.5)	0.93 (0.73–1.18)	0.5789	G	286 (47.4)	233 (45.5)	XRCC4	rs1317812	A	570 (94.4)	493 (95.2)	0.85 (0.50–1.45)	0.6408	G	34 (5.6)	25 (4.8)	XRCC4	rs2891980	T	553 (91.6)	457 (88.2)	1.45 (0.98–2.14)	0.079	C	51 (8.4)	61 (11.8)	XRCC5	rs828704	A	480 (78.4)	408 (78.5)	0.99 (0.75–1.33)	0.9902	C	132 (21.6)	112 (21.5)	XRCC5	rs2303400	T	347 (56.9)	313 (60.6)	0.85 (0.67–1.08)	0.2223	C	263 (43.1)	203 (39.3)	XRCC5	rs207906	G	538 (88.5)	456 (87.7)	1.08 (0.75–1.54)	0.7499	A	70 (11.5)	64 (12.3)	XRCC5	rs207908	A	319 (52.3)	249 (48.3)	1.17 (0.93–1.49)	0.1967	T	291 (47.7)	267 (51.7)	XRCC5	rs207916	A	333 (54.6)	304 (59.4)	0.82 (0.65–1.04)	0.1209	G	277 (45.4)	208 (40.6)	XRCC5	rs207922	C	398 (65.2)	317 (61.2)	1.19 (0.94–1.52)	0.1657	T	212 (34.8)	201 (38.8)	XRCC5	rs6753002	T	487 (79.8)	406 (77.8)	1.13 (0.85–1.50)	0.4396	C	123 (20.2)	116 (22.2)	XRCC5	rs207940	C	326 (53.4)	257 (49.8)	1.16 (0.91–1.46)	0.2473	T	284 (46.6)	259 (50.2)	XRCC5	rs3770500	T	560 (91.8)	467 (91.2)	1.08 (0.71–1.64)	0.8046	A	50 (8.2)	45 (8.8)	XRCC5	rs3770493	G	538 (88.5)	462 (89.2)	0.93 (0.64–1.35)	0.7812	A	70 (11.5)	56 (10.8)	XRCC5	rs1051677	T	561 (91.7)	475 (91)	1.08 (0.72–1.64)	0.7684						
XRCC3	rs861530	G	418 (68.5)	346 (66.8)	1.08 (0.84–1.40)	0.5788																																																																																																																																																																																																																																									
		A	192 (31.5)	172 (33.2)			XRCC3	rs861531	G	376 (61.8)	336 (65.1)	0.87 (0.68–1.10)	0.2832	T	232 (38.2)	180 (34.9)	XRCC3	rs1799796	A	423 (70)	351 (67.5)	1.13 (0.87–1.45)	0.3954	G	181 (30)	169 (32.5)	XRCC4	rs1478486	C	356 (58.9)	305 (59.1)	0.99 (0.78–1.26)	0.9545	T	248 (41.8)	211 (40.9)	XRCC4	rs1382376	C	349 (57.6)	285 (55.2)	1.10 (0.87–1.39)	0.4631	G	257 (42.4)	231 (44.8)	XRCC4	rs1011980	A	431 (70.7)	377 (72.5)	0.91 (0.70–1.18)	0.5363	G	179 (29.3)	143 (27.5)	XRCC4	rs1011981	A	356 (58.4)	306 (58.8)	0.98 (0.77–1.24)	0.9167	G	254 (41.6)	214 (41.2)	XRCC4	rs1478483	C	546 (89.5)	453 (87.1)	1.26 (0.87–1.82)	0.2464	T	64 (10.5)	67 (12.9)	XRCC4	rs963248	A	529 (86.4)	417 (80.8)	1.51 (1.10–2.08)	<b>0.0133</b>	G	83 (13.6)	99 (19.2)	XRCC4	rs1193693	A	318 (52.6)	279 (54.5)	0.93 (0.73–1.18)	0.5789	G	286 (47.4)	233 (45.5)	XRCC4	rs1317812	A	570 (94.4)	493 (95.2)	0.85 (0.50–1.45)	0.6408	G	34 (5.6)	25 (4.8)	XRCC4	rs2891980	T	553 (91.6)	457 (88.2)	1.45 (0.98–2.14)	0.079	C	51 (8.4)	61 (11.8)	XRCC5	rs828704	A	480 (78.4)	408 (78.5)	0.99 (0.75–1.33)	0.9902	C	132 (21.6)	112 (21.5)	XRCC5	rs2303400	T	347 (56.9)	313 (60.6)	0.85 (0.67–1.08)	0.2223	C	263 (43.1)	203 (39.3)	XRCC5	rs207906	G	538 (88.5)	456 (87.7)	1.08 (0.75–1.54)	0.7499	A	70 (11.5)	64 (12.3)	XRCC5	rs207908	A	319 (52.3)	249 (48.3)	1.17 (0.93–1.49)	0.1967	T	291 (47.7)	267 (51.7)	XRCC5	rs207916	A	333 (54.6)	304 (59.4)	0.82 (0.65–1.04)	0.1209	G	277 (45.4)	208 (40.6)	XRCC5	rs207922	C	398 (65.2)	317 (61.2)	1.19 (0.94–1.52)	0.1657	T	212 (34.8)	201 (38.8)	XRCC5	rs6753002	T	487 (79.8)	406 (77.8)	1.13 (0.85–1.50)	0.4396	C	123 (20.2)	116 (22.2)	XRCC5	rs207940	C	326 (53.4)	257 (49.8)	1.16 (0.91–1.46)	0.2473	T	284 (46.6)	259 (50.2)	XRCC5	rs3770500	T	560 (91.8)	467 (91.2)	1.08 (0.71–1.64)	0.8046	A	50 (8.2)	45 (8.8)	XRCC5	rs3770493	G	538 (88.5)	462 (89.2)	0.93 (0.64–1.35)	0.7812	A	70 (11.5)	56 (10.8)	XRCC5	rs1051677	T	561 (91.7)	475 (91)	1.08 (0.72–1.64)	0.7684																
XRCC3	rs861531	G	376 (61.8)	336 (65.1)	0.87 (0.68–1.10)	0.2832																																																																																																																																																																																																																																									
		T	232 (38.2)	180 (34.9)			XRCC3	rs1799796	A	423 (70)	351 (67.5)	1.13 (0.87–1.45)	0.3954	G	181 (30)	169 (32.5)	XRCC4	rs1478486	C	356 (58.9)	305 (59.1)	0.99 (0.78–1.26)	0.9545	T	248 (41.8)	211 (40.9)	XRCC4	rs1382376	C	349 (57.6)	285 (55.2)	1.10 (0.87–1.39)	0.4631	G	257 (42.4)	231 (44.8)	XRCC4	rs1011980	A	431 (70.7)	377 (72.5)	0.91 (0.70–1.18)	0.5363	G	179 (29.3)	143 (27.5)	XRCC4	rs1011981	A	356 (58.4)	306 (58.8)	0.98 (0.77–1.24)	0.9167	G	254 (41.6)	214 (41.2)	XRCC4	rs1478483	C	546 (89.5)	453 (87.1)	1.26 (0.87–1.82)	0.2464	T	64 (10.5)	67 (12.9)	XRCC4	rs963248	A	529 (86.4)	417 (80.8)	1.51 (1.10–2.08)	<b>0.0133</b>	G	83 (13.6)	99 (19.2)	XRCC4	rs1193693	A	318 (52.6)	279 (54.5)	0.93 (0.73–1.18)	0.5789	G	286 (47.4)	233 (45.5)	XRCC4	rs1317812	A	570 (94.4)	493 (95.2)	0.85 (0.50–1.45)	0.6408	G	34 (5.6)	25 (4.8)	XRCC4	rs2891980	T	553 (91.6)	457 (88.2)	1.45 (0.98–2.14)	0.079	C	51 (8.4)	61 (11.8)	XRCC5	rs828704	A	480 (78.4)	408 (78.5)	0.99 (0.75–1.33)	0.9902	C	132 (21.6)	112 (21.5)	XRCC5	rs2303400	T	347 (56.9)	313 (60.6)	0.85 (0.67–1.08)	0.2223	C	263 (43.1)	203 (39.3)	XRCC5	rs207906	G	538 (88.5)	456 (87.7)	1.08 (0.75–1.54)	0.7499	A	70 (11.5)	64 (12.3)	XRCC5	rs207908	A	319 (52.3)	249 (48.3)	1.17 (0.93–1.49)	0.1967	T	291 (47.7)	267 (51.7)	XRCC5	rs207916	A	333 (54.6)	304 (59.4)	0.82 (0.65–1.04)	0.1209	G	277 (45.4)	208 (40.6)	XRCC5	rs207922	C	398 (65.2)	317 (61.2)	1.19 (0.94–1.52)	0.1657	T	212 (34.8)	201 (38.8)	XRCC5	rs6753002	T	487 (79.8)	406 (77.8)	1.13 (0.85–1.50)	0.4396	C	123 (20.2)	116 (22.2)	XRCC5	rs207940	C	326 (53.4)	257 (49.8)	1.16 (0.91–1.46)	0.2473	T	284 (46.6)	259 (50.2)	XRCC5	rs3770500	T	560 (91.8)	467 (91.2)	1.08 (0.71–1.64)	0.8046	A	50 (8.2)	45 (8.8)	XRCC5	rs3770493	G	538 (88.5)	462 (89.2)	0.93 (0.64–1.35)	0.7812	A	70 (11.5)	56 (10.8)	XRCC5	rs1051677	T	561 (91.7)	475 (91)	1.08 (0.72–1.64)	0.7684																										
XRCC3	rs1799796	A	423 (70)	351 (67.5)	1.13 (0.87–1.45)	0.3954																																																																																																																																																																																																																																									
		G	181 (30)	169 (32.5)			XRCC4	rs1478486	C	356 (58.9)	305 (59.1)	0.99 (0.78–1.26)	0.9545	T	248 (41.8)	211 (40.9)	XRCC4	rs1382376	C	349 (57.6)	285 (55.2)	1.10 (0.87–1.39)	0.4631	G	257 (42.4)	231 (44.8)	XRCC4	rs1011980	A	431 (70.7)	377 (72.5)	0.91 (0.70–1.18)	0.5363	G	179 (29.3)	143 (27.5)	XRCC4	rs1011981	A	356 (58.4)	306 (58.8)	0.98 (0.77–1.24)	0.9167	G	254 (41.6)	214 (41.2)	XRCC4	rs1478483	C	546 (89.5)	453 (87.1)	1.26 (0.87–1.82)	0.2464	T	64 (10.5)	67 (12.9)	XRCC4	rs963248	A	529 (86.4)	417 (80.8)	1.51 (1.10–2.08)	<b>0.0133</b>	G	83 (13.6)	99 (19.2)	XRCC4	rs1193693	A	318 (52.6)	279 (54.5)	0.93 (0.73–1.18)	0.5789	G	286 (47.4)	233 (45.5)	XRCC4	rs1317812	A	570 (94.4)	493 (95.2)	0.85 (0.50–1.45)	0.6408	G	34 (5.6)	25 (4.8)	XRCC4	rs2891980	T	553 (91.6)	457 (88.2)	1.45 (0.98–2.14)	0.079	C	51 (8.4)	61 (11.8)	XRCC5	rs828704	A	480 (78.4)	408 (78.5)	0.99 (0.75–1.33)	0.9902	C	132 (21.6)	112 (21.5)	XRCC5	rs2303400	T	347 (56.9)	313 (60.6)	0.85 (0.67–1.08)	0.2223	C	263 (43.1)	203 (39.3)	XRCC5	rs207906	G	538 (88.5)	456 (87.7)	1.08 (0.75–1.54)	0.7499	A	70 (11.5)	64 (12.3)	XRCC5	rs207908	A	319 (52.3)	249 (48.3)	1.17 (0.93–1.49)	0.1967	T	291 (47.7)	267 (51.7)	XRCC5	rs207916	A	333 (54.6)	304 (59.4)	0.82 (0.65–1.04)	0.1209	G	277 (45.4)	208 (40.6)	XRCC5	rs207922	C	398 (65.2)	317 (61.2)	1.19 (0.94–1.52)	0.1657	T	212 (34.8)	201 (38.8)	XRCC5	rs6753002	T	487 (79.8)	406 (77.8)	1.13 (0.85–1.50)	0.4396	C	123 (20.2)	116 (22.2)	XRCC5	rs207940	C	326 (53.4)	257 (49.8)	1.16 (0.91–1.46)	0.2473	T	284 (46.6)	259 (50.2)	XRCC5	rs3770500	T	560 (91.8)	467 (91.2)	1.08 (0.71–1.64)	0.8046	A	50 (8.2)	45 (8.8)	XRCC5	rs3770493	G	538 (88.5)	462 (89.2)	0.93 (0.64–1.35)	0.7812	A	70 (11.5)	56 (10.8)	XRCC5	rs1051677	T	561 (91.7)	475 (91)	1.08 (0.72–1.64)	0.7684																																				
XRCC4	rs1478486	C	356 (58.9)	305 (59.1)	0.99 (0.78–1.26)	0.9545																																																																																																																																																																																																																																									
		T	248 (41.8)	211 (40.9)			XRCC4	rs1382376	C	349 (57.6)	285 (55.2)	1.10 (0.87–1.39)	0.4631	G	257 (42.4)	231 (44.8)	XRCC4	rs1011980	A	431 (70.7)	377 (72.5)	0.91 (0.70–1.18)	0.5363	G	179 (29.3)	143 (27.5)	XRCC4	rs1011981	A	356 (58.4)	306 (58.8)	0.98 (0.77–1.24)	0.9167	G	254 (41.6)	214 (41.2)	XRCC4	rs1478483	C	546 (89.5)	453 (87.1)	1.26 (0.87–1.82)	0.2464	T	64 (10.5)	67 (12.9)	XRCC4	rs963248	A	529 (86.4)	417 (80.8)	1.51 (1.10–2.08)	<b>0.0133</b>	G	83 (13.6)	99 (19.2)	XRCC4	rs1193693	A	318 (52.6)	279 (54.5)	0.93 (0.73–1.18)	0.5789	G	286 (47.4)	233 (45.5)	XRCC4	rs1317812	A	570 (94.4)	493 (95.2)	0.85 (0.50–1.45)	0.6408	G	34 (5.6)	25 (4.8)	XRCC4	rs2891980	T	553 (91.6)	457 (88.2)	1.45 (0.98–2.14)	0.079	C	51 (8.4)	61 (11.8)	XRCC5	rs828704	A	480 (78.4)	408 (78.5)	0.99 (0.75–1.33)	0.9902	C	132 (21.6)	112 (21.5)	XRCC5	rs2303400	T	347 (56.9)	313 (60.6)	0.85 (0.67–1.08)	0.2223	C	263 (43.1)	203 (39.3)	XRCC5	rs207906	G	538 (88.5)	456 (87.7)	1.08 (0.75–1.54)	0.7499	A	70 (11.5)	64 (12.3)	XRCC5	rs207908	A	319 (52.3)	249 (48.3)	1.17 (0.93–1.49)	0.1967	T	291 (47.7)	267 (51.7)	XRCC5	rs207916	A	333 (54.6)	304 (59.4)	0.82 (0.65–1.04)	0.1209	G	277 (45.4)	208 (40.6)	XRCC5	rs207922	C	398 (65.2)	317 (61.2)	1.19 (0.94–1.52)	0.1657	T	212 (34.8)	201 (38.8)	XRCC5	rs6753002	T	487 (79.8)	406 (77.8)	1.13 (0.85–1.50)	0.4396	C	123 (20.2)	116 (22.2)	XRCC5	rs207940	C	326 (53.4)	257 (49.8)	1.16 (0.91–1.46)	0.2473	T	284 (46.6)	259 (50.2)	XRCC5	rs3770500	T	560 (91.8)	467 (91.2)	1.08 (0.71–1.64)	0.8046	A	50 (8.2)	45 (8.8)	XRCC5	rs3770493	G	538 (88.5)	462 (89.2)	0.93 (0.64–1.35)	0.7812	A	70 (11.5)	56 (10.8)	XRCC5	rs1051677	T	561 (91.7)	475 (91)	1.08 (0.72–1.64)	0.7684																																														
XRCC4	rs1382376	C	349 (57.6)	285 (55.2)	1.10 (0.87–1.39)	0.4631																																																																																																																																																																																																																																									
		G	257 (42.4)	231 (44.8)			XRCC4	rs1011980	A	431 (70.7)	377 (72.5)	0.91 (0.70–1.18)	0.5363	G	179 (29.3)	143 (27.5)	XRCC4	rs1011981	A	356 (58.4)	306 (58.8)	0.98 (0.77–1.24)	0.9167	G	254 (41.6)	214 (41.2)	XRCC4	rs1478483	C	546 (89.5)	453 (87.1)	1.26 (0.87–1.82)	0.2464	T	64 (10.5)	67 (12.9)	XRCC4	rs963248	A	529 (86.4)	417 (80.8)	1.51 (1.10–2.08)	<b>0.0133</b>	G	83 (13.6)	99 (19.2)	XRCC4	rs1193693	A	318 (52.6)	279 (54.5)	0.93 (0.73–1.18)	0.5789	G	286 (47.4)	233 (45.5)	XRCC4	rs1317812	A	570 (94.4)	493 (95.2)	0.85 (0.50–1.45)	0.6408	G	34 (5.6)	25 (4.8)	XRCC4	rs2891980	T	553 (91.6)	457 (88.2)	1.45 (0.98–2.14)	0.079	C	51 (8.4)	61 (11.8)	XRCC5	rs828704	A	480 (78.4)	408 (78.5)	0.99 (0.75–1.33)	0.9902	C	132 (21.6)	112 (21.5)	XRCC5	rs2303400	T	347 (56.9)	313 (60.6)	0.85 (0.67–1.08)	0.2223	C	263 (43.1)	203 (39.3)	XRCC5	rs207906	G	538 (88.5)	456 (87.7)	1.08 (0.75–1.54)	0.7499	A	70 (11.5)	64 (12.3)	XRCC5	rs207908	A	319 (52.3)	249 (48.3)	1.17 (0.93–1.49)	0.1967	T	291 (47.7)	267 (51.7)	XRCC5	rs207916	A	333 (54.6)	304 (59.4)	0.82 (0.65–1.04)	0.1209	G	277 (45.4)	208 (40.6)	XRCC5	rs207922	C	398 (65.2)	317 (61.2)	1.19 (0.94–1.52)	0.1657	T	212 (34.8)	201 (38.8)	XRCC5	rs6753002	T	487 (79.8)	406 (77.8)	1.13 (0.85–1.50)	0.4396	C	123 (20.2)	116 (22.2)	XRCC5	rs207940	C	326 (53.4)	257 (49.8)	1.16 (0.91–1.46)	0.2473	T	284 (46.6)	259 (50.2)	XRCC5	rs3770500	T	560 (91.8)	467 (91.2)	1.08 (0.71–1.64)	0.8046	A	50 (8.2)	45 (8.8)	XRCC5	rs3770493	G	538 (88.5)	462 (89.2)	0.93 (0.64–1.35)	0.7812	A	70 (11.5)	56 (10.8)	XRCC5	rs1051677	T	561 (91.7)	475 (91)	1.08 (0.72–1.64)	0.7684																																																								
XRCC4	rs1011980	A	431 (70.7)	377 (72.5)	0.91 (0.70–1.18)	0.5363																																																																																																																																																																																																																																									
		G	179 (29.3)	143 (27.5)			XRCC4	rs1011981	A	356 (58.4)	306 (58.8)	0.98 (0.77–1.24)	0.9167	G	254 (41.6)	214 (41.2)	XRCC4	rs1478483	C	546 (89.5)	453 (87.1)	1.26 (0.87–1.82)	0.2464	T	64 (10.5)	67 (12.9)	XRCC4	rs963248	A	529 (86.4)	417 (80.8)	1.51 (1.10–2.08)	<b>0.0133</b>	G	83 (13.6)	99 (19.2)	XRCC4	rs1193693	A	318 (52.6)	279 (54.5)	0.93 (0.73–1.18)	0.5789	G	286 (47.4)	233 (45.5)	XRCC4	rs1317812	A	570 (94.4)	493 (95.2)	0.85 (0.50–1.45)	0.6408	G	34 (5.6)	25 (4.8)	XRCC4	rs2891980	T	553 (91.6)	457 (88.2)	1.45 (0.98–2.14)	0.079	C	51 (8.4)	61 (11.8)	XRCC5	rs828704	A	480 (78.4)	408 (78.5)	0.99 (0.75–1.33)	0.9902	C	132 (21.6)	112 (21.5)	XRCC5	rs2303400	T	347 (56.9)	313 (60.6)	0.85 (0.67–1.08)	0.2223	C	263 (43.1)	203 (39.3)	XRCC5	rs207906	G	538 (88.5)	456 (87.7)	1.08 (0.75–1.54)	0.7499	A	70 (11.5)	64 (12.3)	XRCC5	rs207908	A	319 (52.3)	249 (48.3)	1.17 (0.93–1.49)	0.1967	T	291 (47.7)	267 (51.7)	XRCC5	rs207916	A	333 (54.6)	304 (59.4)	0.82 (0.65–1.04)	0.1209	G	277 (45.4)	208 (40.6)	XRCC5	rs207922	C	398 (65.2)	317 (61.2)	1.19 (0.94–1.52)	0.1657	T	212 (34.8)	201 (38.8)	XRCC5	rs6753002	T	487 (79.8)	406 (77.8)	1.13 (0.85–1.50)	0.4396	C	123 (20.2)	116 (22.2)	XRCC5	rs207940	C	326 (53.4)	257 (49.8)	1.16 (0.91–1.46)	0.2473	T	284 (46.6)	259 (50.2)	XRCC5	rs3770500	T	560 (91.8)	467 (91.2)	1.08 (0.71–1.64)	0.8046	A	50 (8.2)	45 (8.8)	XRCC5	rs3770493	G	538 (88.5)	462 (89.2)	0.93 (0.64–1.35)	0.7812	A	70 (11.5)	56 (10.8)	XRCC5	rs1051677	T	561 (91.7)	475 (91)	1.08 (0.72–1.64)	0.7684																																																																		
XRCC4	rs1011981	A	356 (58.4)	306 (58.8)	0.98 (0.77–1.24)	0.9167																																																																																																																																																																																																																																									
		G	254 (41.6)	214 (41.2)			XRCC4	rs1478483	C	546 (89.5)	453 (87.1)	1.26 (0.87–1.82)	0.2464	T	64 (10.5)	67 (12.9)	XRCC4	rs963248	A	529 (86.4)	417 (80.8)	1.51 (1.10–2.08)	<b>0.0133</b>	G	83 (13.6)	99 (19.2)	XRCC4	rs1193693	A	318 (52.6)	279 (54.5)	0.93 (0.73–1.18)	0.5789	G	286 (47.4)	233 (45.5)	XRCC4	rs1317812	A	570 (94.4)	493 (95.2)	0.85 (0.50–1.45)	0.6408	G	34 (5.6)	25 (4.8)	XRCC4	rs2891980	T	553 (91.6)	457 (88.2)	1.45 (0.98–2.14)	0.079	C	51 (8.4)	61 (11.8)	XRCC5	rs828704	A	480 (78.4)	408 (78.5)	0.99 (0.75–1.33)	0.9902	C	132 (21.6)	112 (21.5)	XRCC5	rs2303400	T	347 (56.9)	313 (60.6)	0.85 (0.67–1.08)	0.2223	C	263 (43.1)	203 (39.3)	XRCC5	rs207906	G	538 (88.5)	456 (87.7)	1.08 (0.75–1.54)	0.7499	A	70 (11.5)	64 (12.3)	XRCC5	rs207908	A	319 (52.3)	249 (48.3)	1.17 (0.93–1.49)	0.1967	T	291 (47.7)	267 (51.7)	XRCC5	rs207916	A	333 (54.6)	304 (59.4)	0.82 (0.65–1.04)	0.1209	G	277 (45.4)	208 (40.6)	XRCC5	rs207922	C	398 (65.2)	317 (61.2)	1.19 (0.94–1.52)	0.1657	T	212 (34.8)	201 (38.8)	XRCC5	rs6753002	T	487 (79.8)	406 (77.8)	1.13 (0.85–1.50)	0.4396	C	123 (20.2)	116 (22.2)	XRCC5	rs207940	C	326 (53.4)	257 (49.8)	1.16 (0.91–1.46)	0.2473	T	284 (46.6)	259 (50.2)	XRCC5	rs3770500	T	560 (91.8)	467 (91.2)	1.08 (0.71–1.64)	0.8046	A	50 (8.2)	45 (8.8)	XRCC5	rs3770493	G	538 (88.5)	462 (89.2)	0.93 (0.64–1.35)	0.7812	A	70 (11.5)	56 (10.8)	XRCC5	rs1051677	T	561 (91.7)	475 (91)	1.08 (0.72–1.64)	0.7684																																																																												
XRCC4	rs1478483	C	546 (89.5)	453 (87.1)	1.26 (0.87–1.82)	0.2464																																																																																																																																																																																																																																									
		T	64 (10.5)	67 (12.9)			XRCC4	rs963248	A	529 (86.4)	417 (80.8)	1.51 (1.10–2.08)	<b>0.0133</b>	G	83 (13.6)	99 (19.2)	XRCC4	rs1193693	A	318 (52.6)	279 (54.5)	0.93 (0.73–1.18)	0.5789	G	286 (47.4)	233 (45.5)	XRCC4	rs1317812	A	570 (94.4)	493 (95.2)	0.85 (0.50–1.45)	0.6408	G	34 (5.6)	25 (4.8)	XRCC4	rs2891980	T	553 (91.6)	457 (88.2)	1.45 (0.98–2.14)	0.079	C	51 (8.4)	61 (11.8)	XRCC5	rs828704	A	480 (78.4)	408 (78.5)	0.99 (0.75–1.33)	0.9902	C	132 (21.6)	112 (21.5)	XRCC5	rs2303400	T	347 (56.9)	313 (60.6)	0.85 (0.67–1.08)	0.2223	C	263 (43.1)	203 (39.3)	XRCC5	rs207906	G	538 (88.5)	456 (87.7)	1.08 (0.75–1.54)	0.7499	A	70 (11.5)	64 (12.3)	XRCC5	rs207908	A	319 (52.3)	249 (48.3)	1.17 (0.93–1.49)	0.1967	T	291 (47.7)	267 (51.7)	XRCC5	rs207916	A	333 (54.6)	304 (59.4)	0.82 (0.65–1.04)	0.1209	G	277 (45.4)	208 (40.6)	XRCC5	rs207922	C	398 (65.2)	317 (61.2)	1.19 (0.94–1.52)	0.1657	T	212 (34.8)	201 (38.8)	XRCC5	rs6753002	T	487 (79.8)	406 (77.8)	1.13 (0.85–1.50)	0.4396	C	123 (20.2)	116 (22.2)	XRCC5	rs207940	C	326 (53.4)	257 (49.8)	1.16 (0.91–1.46)	0.2473	T	284 (46.6)	259 (50.2)	XRCC5	rs3770500	T	560 (91.8)	467 (91.2)	1.08 (0.71–1.64)	0.8046	A	50 (8.2)	45 (8.8)	XRCC5	rs3770493	G	538 (88.5)	462 (89.2)	0.93 (0.64–1.35)	0.7812	A	70 (11.5)	56 (10.8)	XRCC5	rs1051677	T	561 (91.7)	475 (91)	1.08 (0.72–1.64)	0.7684																																																																																						
XRCC4	rs963248	A	529 (86.4)	417 (80.8)	1.51 (1.10–2.08)	<b>0.0133</b>																																																																																																																																																																																																																																									
		G	83 (13.6)	99 (19.2)			XRCC4	rs1193693	A	318 (52.6)	279 (54.5)	0.93 (0.73–1.18)	0.5789	G	286 (47.4)	233 (45.5)	XRCC4	rs1317812	A	570 (94.4)	493 (95.2)	0.85 (0.50–1.45)	0.6408	G	34 (5.6)	25 (4.8)	XRCC4	rs2891980	T	553 (91.6)	457 (88.2)	1.45 (0.98–2.14)	0.079	C	51 (8.4)	61 (11.8)	XRCC5	rs828704	A	480 (78.4)	408 (78.5)	0.99 (0.75–1.33)	0.9902	C	132 (21.6)	112 (21.5)	XRCC5	rs2303400	T	347 (56.9)	313 (60.6)	0.85 (0.67–1.08)	0.2223	C	263 (43.1)	203 (39.3)	XRCC5	rs207906	G	538 (88.5)	456 (87.7)	1.08 (0.75–1.54)	0.7499	A	70 (11.5)	64 (12.3)	XRCC5	rs207908	A	319 (52.3)	249 (48.3)	1.17 (0.93–1.49)	0.1967	T	291 (47.7)	267 (51.7)	XRCC5	rs207916	A	333 (54.6)	304 (59.4)	0.82 (0.65–1.04)	0.1209	G	277 (45.4)	208 (40.6)	XRCC5	rs207922	C	398 (65.2)	317 (61.2)	1.19 (0.94–1.52)	0.1657	T	212 (34.8)	201 (38.8)	XRCC5	rs6753002	T	487 (79.8)	406 (77.8)	1.13 (0.85–1.50)	0.4396	C	123 (20.2)	116 (22.2)	XRCC5	rs207940	C	326 (53.4)	257 (49.8)	1.16 (0.91–1.46)	0.2473	T	284 (46.6)	259 (50.2)	XRCC5	rs3770500	T	560 (91.8)	467 (91.2)	1.08 (0.71–1.64)	0.8046	A	50 (8.2)	45 (8.8)	XRCC5	rs3770493	G	538 (88.5)	462 (89.2)	0.93 (0.64–1.35)	0.7812	A	70 (11.5)	56 (10.8)	XRCC5	rs1051677	T	561 (91.7)	475 (91)	1.08 (0.72–1.64)	0.7684																																																																																																
XRCC4	rs1193693	A	318 (52.6)	279 (54.5)	0.93 (0.73–1.18)	0.5789																																																																																																																																																																																																																																									
		G	286 (47.4)	233 (45.5)			XRCC4	rs1317812	A	570 (94.4)	493 (95.2)	0.85 (0.50–1.45)	0.6408	G	34 (5.6)	25 (4.8)	XRCC4	rs2891980	T	553 (91.6)	457 (88.2)	1.45 (0.98–2.14)	0.079	C	51 (8.4)	61 (11.8)	XRCC5	rs828704	A	480 (78.4)	408 (78.5)	0.99 (0.75–1.33)	0.9902	C	132 (21.6)	112 (21.5)	XRCC5	rs2303400	T	347 (56.9)	313 (60.6)	0.85 (0.67–1.08)	0.2223	C	263 (43.1)	203 (39.3)	XRCC5	rs207906	G	538 (88.5)	456 (87.7)	1.08 (0.75–1.54)	0.7499	A	70 (11.5)	64 (12.3)	XRCC5	rs207908	A	319 (52.3)	249 (48.3)	1.17 (0.93–1.49)	0.1967	T	291 (47.7)	267 (51.7)	XRCC5	rs207916	A	333 (54.6)	304 (59.4)	0.82 (0.65–1.04)	0.1209	G	277 (45.4)	208 (40.6)	XRCC5	rs207922	C	398 (65.2)	317 (61.2)	1.19 (0.94–1.52)	0.1657	T	212 (34.8)	201 (38.8)	XRCC5	rs6753002	T	487 (79.8)	406 (77.8)	1.13 (0.85–1.50)	0.4396	C	123 (20.2)	116 (22.2)	XRCC5	rs207940	C	326 (53.4)	257 (49.8)	1.16 (0.91–1.46)	0.2473	T	284 (46.6)	259 (50.2)	XRCC5	rs3770500	T	560 (91.8)	467 (91.2)	1.08 (0.71–1.64)	0.8046	A	50 (8.2)	45 (8.8)	XRCC5	rs3770493	G	538 (88.5)	462 (89.2)	0.93 (0.64–1.35)	0.7812	A	70 (11.5)	56 (10.8)	XRCC5	rs1051677	T	561 (91.7)	475 (91)	1.08 (0.72–1.64)	0.7684																																																																																																										
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Continued

Table 3. Continued

Gene	db SNP ID	Alleles	Cases <i>n</i> (%)	Controls <i>n</i> (%)	OR (95% CI)	Allele <i>P</i> -value
XRCC5	rs1051685	C	51 (8.3)	47 (9)	0.98 (0.68–1.42)	0.9904
		A	541 (88.7)	464 (88.9)		
		G	69 (11.3)	58 (11.1)		
XRCC5	rs2440	C	352 (57.5)	327 (63.1)	0.79 (0.62–1.00)	0.0631
		T	260 (42.5)	191 (36.9)		

Table 4. FPRP values for an association between a variant in XRCC4 and myeloma

Gene/SNP rs	OR (95% CI)	Statistical power	Reported <i>P</i> -value	Prior probability				
				0.1	0.01	0.001	0.0001	0.00001
XRCC4 963248 A–G	1.50 (1.10–2.08)	0.484	0.0133 <sup>a</sup>	<b>0.192</b>	0.724	0.964	0.996	1.000
XRCC4 963248 A–G	1.54 (1.07–2.20)	0.488	0.024 <sup>b</sup>	0.307	0.829	0.980	0.998	1.000

<sup>a</sup> $\chi^2$  *P*-value for difference in allele frequencies between myeloma cases and controls.

<sup>b</sup> $\chi^2$  *P*-value for difference in genotype frequencies.

there were as yet no reported associations between SNPs in this gene and disease susceptibility. This may be related to both the size of the gene and the large number of SNPs with a high minor allele frequency (MAF) making it difficult to selectively choose a limited number of candidates for further study.

Rs1051685 is located in the 3' UTR of XRCC5 and may be of functional relevance since it is located in an exonic splice enhancer (ESE) sequence as determined by PupaSNP. SNPs in ESE sequences can result in exon skipping, lead to errors in alternative splicing patterns and affect mRNA stability and translation (41). In addition, rs1051685 tags 15 other SNPs at this locus ( $r^2 > 0.8$ ) (rs3770497, rs6729441, rs3770493, rs16855563, rs7581055, rs2241321, rs12466253, rs7583902, rs7587831, rs6747119, rs1438161, rs3835, rs3834, rs12616505, rs12617423, rs1051685) any of which can be in linkage disequilibrium with a causal variant.

In summary, we have genotyped 27 htSNPs in three DNA repair genes, XRCC3, XRCC4 and XRCC5. A number of SNPs show evidence of association with myeloma and are promising candidate SNPs for replication in larger studies. Even though the selected htSNPs efficiently tag variation within the available HAPMAP dataset, we cannot comment on the potential importance of as-yet unidentified variants at these genes or SNPs located in distant regulatory regions. The investigation of rare variants at these genes was beyond the scope of this study. The significant results for XRCC4 and XRCC5 have not been adjusted for multiple hypothesis testing. Since SNPs within the same gene may be in linkage disequilibrium, the standard methods for multiple testing, such as Bonferroni correction, may be too conservative. We therefore assessed the robustness of our significant findings by the FDR and FPRP methods. The FPRP value for XRCC4 rs963248 (allelic frequency) was notable with a <20% chance of being a false positive (Table 4). Adjustment

for FDR values did not yield significant associations. The other significant association for SNP rs1051685 was also not noteworthy. However, it should be noted that it is unlikely that any study of our sample size can generate positive results using these more stringent criteria under the common disease – common variant hypothesis. The observation that the SNP rs963248 has also been reported in two independent breast cancer studies suggests that it might be a true disease-causing variant or possibly tagging for the true causal variant.

To conclude, we report a significant association between two regulatory SNPs in DNA DSB repair genes XRCC4, XRCC5 and myeloma. Our findings should be considered in the context of both the strengths and limitations of the study and should be viewed as exploratory. The genetic epidemiology of rarer malignancies such as myeloma requires that promising SNPs such as those reported in the study are subjected to further analysis by large international disease-specific consortia. Multiple investigations should be pooled in order to assess the robustness of positive findings. Further evaluation of the functional relevance of identified variants and identification of the contribution of other genes involved in the DNA DSB repair pathways as well as potential interactions with other risk factors may eventually lead to a better understanding of myeloma pathogenesis.

## MATERIALS AND METHODS

### Study subjects

*EpiLymph study.* The EpiLymph study was carried out in six European countries (Germany, Italy, Spain, Ireland, France and the Czech Republic) from 1998 to 2003. A common core protocol and interview were used in all



countries (42,43). There were 2302 incident lymphoma cases and 2417 controls.

Cases were defined as all consecutive patients who were given an initial diagnosis of lymphoid malignancy during the study period. The diagnosis of lymphoma was verified by histological testing, and 99% of these tests were supplemented by immunohistochemistry tests and flow cytometry. Cases were categorised according to the World Health Organisation Classification of Neoplastic Diseases of the Haematopoietic and Lymphoid Tissue and included all B-cell, T-cell and natural killer-cell neoplasms, as well as Hodgkin's lymphoma (44). Subjects with a diagnosis of uncertain malignant potential or monoclonal gammopathies of uncertain significance were excluded.

In Italy and Germany, controls were identified at the same time as the cases and were sampled from the general population on the basis of census lists. In the other study populations, controls were recruited from the same hospitals as the cases. In all instances, controls were matched to the cases by age ( $\pm 5$  years), gender and study centre. Potential hospital controls were excluded if the main reason for the hospitalisation at the time of recruitment was cancer, organ transplant and/or systemic infection.

Informed consent was obtained from all subjects prior to enrolment, and the institutional review boards of participating centres approved the study. Cases and controls provided a blood sample for DNA extraction and serological testing and underwent a personal interview. Among cases, the participation rate was 87% (by study centre, refusal rates ranged from 7–18%). Among population controls, the participation rate was 75% (refusal rates by centre, 4–56%).

For subjects with myeloma and matched controls, there were 142 participants from Germany, 10 from Italy, 122 from Spain, 38 from Ireland, 62 from France and 64 from the Czech Republic, giving a total of 438. There were a total of 216 cases with myeloma and 222 controls in the EpiLymph study.

*The Irish myeloma study.* The Irish myeloma study is a prospective observational single-centre study on the biology and clinical course of myeloma in Ireland. Ninety patients with myeloma have been enrolled to date. Age and sex-matched controls for 41 of these patients were selected from the pool of controls for cases with diseases other than myeloma that had been enrolled in the Irish EpiLymph study from 1998 to 2003. These selected controls were, as per EpiLymph protocol, free from cancer, organ transplant, and/or systemic infection. This study was approved by the regional ethics committee. Informed consent was obtained from each participant before interview and blood sampling. The diagnoses for the Irish patients were confirmed at multi-disciplinary histopathology meetings at St James's Hospital in Dublin.

In total, therefore, the study population consisted of 306 cases of myeloma and 263 controls.

### Laboratory methods

DNA extraction – for all cases and controls in the EpiLymph study, a peripheral blood sample was collected after written informed consent was obtained. The blood was processed

using centrifugation and removal of buffy coat. In order to ensure sufficient material is available for future studies, whole genome amplification (WGA) was carried out on all of the EpiLymph samples using the REPLI-g Kit (QIAGEN, UK). WGA DNA was used for genotyping of the EpiLymph cases and controls. This product has been validated by the manufacturers for use in genotyping studies (45).

For the Irish subjects, a peripheral blood sample was collected after written informed consent was obtained. DNA was isolated using the QIAamp DNA blood MiniKit protocol (QIAGEN, UK) and was quantified by spectrofluorometry.

### Selection of genes and SNPs

SNPs from the chosen genes were identified from the International HapMap Project (HAPMAP) (<http://www.hapmap.org>), Public Release #20 on 26 January 2006. This release contains a remapping of the previous release (#19) on NCBI Build 35 coordinates. HAPMAP SNP genotyping data for the relevant genes was examined using Haploviewer Version 3.2 (<http://www.broad.mit.edu/mpg/haploviewer>) (46). Haplotype-tagging SNPs (htSNPs) were chosen using the *Tagger* (Paul de Bakker; <http://www.broad.mit.edu/mpg/tagger>) tag SNP selection algorithm available through Haploviewer. Selection of tags is based on  $r^2$  values between alleles of variable sites. *Tagger* employs both pairwise and effective haplotype predictors to capture alleles of interest. We used an  $r^2$  threshold of 0.8 and the 2- and 3- multimarker haplotype 'aggressive tagging' option for tag SNP selection. The criteria for htSNP selection included  $MAF > 10\%$ . Details of all variants genotyped at each gene in our reference panel are shown in Table 1.

### Genotyping and quality control

Genomic DNA was used for genotyping. Individual SNPs were genotyped using TaqMan® Validated SNP Genotyping Assays, TaqMan® Pre-Designed SNP Genotyping Assays or Custom TaqMan® SNP Genotyping Assays on an Applied Biosystems 7900HT Sequence Detection System. Each individual assay was carried out using 10 ng of DNA in a 5  $\mu$ l reaction using Taqman Universal Master Mix.

All assays were carried out in a 384 well format. For quality control purposes, duplicates of 10% of the samples were interspersed throughout the plates. The Allelic Discrimination Sequence Detection software (Applied Biosystems) was used to determine the genotypes, the genotyping was repeated if there was any discrepancy in the allele calls. For all the assays, there was >99% concordance between duplicate samples. The dropout rate for amplification or allele call was consistently <3%.

### Statistical analysis

The genotype frequencies were calculated for each SNP and comparisons between the observed and expected genotype frequencies in controls using the  $\chi^2$  test allowed assessment of departures from Hardy-Weinberg equilibrium (HWE). All the genotype frequencies were in accordance with HWE.

Genotype frequencies in cases and controls were compared by  $\chi^2$  tests. The homozygous wild-type genotype was used as the reference group to calculate the OR and 95% CI. The homozygous wild type genotype was also used as a referent for comparing with the heterozygote and homozygote variants (dominant model). The models were adjusted for age, gender and study centre.

SNPs were also tested for association with the phenotype using a  $2 \times 2$  (allele-wise) contingency table to calculate a  $\chi^2$  statistic.

We applied two methods – the false discovery rate (FDR) (47) and the false positive report probability (FPRP) (48) to address the issue of false positive SNP associations. Benjamini–Hochberg method was used to control for FDR. FDR is defined as the expected ratio of erroneous rejections of the null hypothesis to the total number of rejected hypotheses. The FDR values were computed using the  $\chi^2$  *P*-value for each genotype and allele frequency.

The FPRP method calculates the probability that a single SNP association is a false positive report for a range of prior probabilities, which were specified from 0.10 to 0.000001, we applied an FPRP cut-off value of 0.2 to identify which of the findings were noteworthy.

Haplotype association analysis was performed using UNPHASED (<http://www.mrc-bsu.cam.ac.uk/personal/frank/software/unphased/>) (49). This program calculates significance levels based on analysis of all haplotypes, described as an omnibus test. In addition, individual haplotypes can be tested for association. Given the non-independence of haplotype tests at a gene, UNPHASED also corrects for multiple testing using permutations.

*Conflict of Interest statement.* None declared.

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