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Candidate gene association studies and risk of Hodgkin Lymphoma: a systematic review and meta-analysis

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Abstract

To evaluate the contribution of association studies of candidate polymorphisms to inherited predisposition to Hodgkin lymphoma (HL), we conducted a systematic review and meta-analysis of published case-control studies. Of the variants examined more than once in candidate gene association studies, we identified 21 studies that reported on 12 polymorphic variants in 10 genes. Data were also extracted from a published genome wide-association study to allow analysis of an additional 47 variants in a further 30 genes. Promising associations were seen in nine of the variants ($p < 0.05$). Given that the estimated false positive report probabilities (FPRPs) for all associations are high (i.e. FPRP > 0.2), these findings should be interpreted with caution. While studies of candidate polymorphisms may be an attractive means of identifying risk factors for HL, future studies should employs ample sizes adequately powered to identify variants having only modest effects on HL risk. Furthermore, because of aetiological heterogeneity within HL, stratification of genotyping according to age, tumour Epstein-Barr virus status and histology is essential.

Keywords

Hodgkin Lymphoma; Genetic susceptibility; Meta-analysis; Systematic review; Candidate gene; Polymorphism

Introduction

Hodgkin Lymphoma (HL) is a B-cell malignancy affecting ~3 per 100,000 of the population each year in most Western countries(1). HL is typically classified based on histopathological appearances into classical HL (cHL) which accounts for 95% of cases and nodular lymphocyte predominant HL (NLPHL). The presence of EBV latent membrane protein

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and/or EBV-encoded small RNAs (EBERs) in Hodgkin Reed-Sternberg cells (HRS) defines EBV-positive disease(2).

Hodgkin lymphoma shows a bimodal age distribution in incidence, with geographic specific differences. In economically developed countries, the first peak of incidence typically occurs around 20 years of age with a second peak around 65 years of age(1). Evidence for the existence of inherited genetic predisposition to HL is derived from the high concordance rates in identical twins(3) and from case-control studies and cohort studies which have shown a 3-fold increased risk of HL in relatives of HL patients(4).

The failure to identify a major disease-causing locus has led to the proposal that a significant component of the inherited susceptibility is enshrined in the co-inheritance of multiple risk alleles, some of which are likely to be common. The most frequent method for identifying prevalent low risk variants is through association studies based on comparing the frequency of polymorphic genotypes in cases and controls. Alleles positively associated with the disease are analogous to risk factors in epidemiology and may be causally related to disease risk or be in linkage disequilibrium (LD) with disease-causing variants. There are a number of different methods of analysing the risk associated with a specific variant. For simple bi-allelic polymorphisms, the odds ratio (OR) of disease can be derived by comparing allele frequencies in cases and controls. Alternatively, a comparison of frequencies of the three genotypes among cases and controls can be made, using homozygosity of the “wild-type allele” as the reference group. Where homozygotes are rare, heterozygotes and homozygotes are grouped together, but this is only appropriate if a dominant model of disease susceptibility can be assumed. Similarly, combining heterozygotes with wild-type homozygotes is only appropriate if alleles act recessively.

The genetic candidates that have been evaluated as susceptibility genes for HL to date can be divided into the following groups: immune function/response, carcinogen metabolism enzymes, folate metabolism enzymes, DNA repair proteins, and others (table 1). We elected to exclude candidate gene association studies exploring the human leucocyte antigen (HLA) region and HL given the already established predisposition at the HLA region(5) and the complex LD structure making identification of the disease-causing variant problematic.

Although some polymorphic variants have only been examined once, most have been evaluated as risk factors in several studies but often with discordant findings. Furthermore, many of the studies have been based on small sample sizes with limited power to robustly demonstrate a relationship with HL risk. To gain better insight into the impact of polymorphic variants on risk of HL, we have undertaken a systematic review of published studies and used standard meta-analysis techniques according to Cochrane(6) In addition, we have used genotype data from a published Genome-Wide Association Study (GWAS) to perform a meta-analysis on variants that have only been examined once in the literature (7, 8).

Methods

Study identification

A literature search for studies reporting on the association between polymorphic variants and HL was conducted using the electronic database PubMed from May 1991 - December 2014. The search strategy included using the keywords 'Hodgkin Lymphoma', 'case', 'control', 'polymorphism', 'risk', 'genetic, association'. We searched for additional studies in the bibliographies of identified publications, including previous review articles and meta-analyses(9, 10).

Selection criteria

Studies were eligible if they were based on unrelated individuals and examined the association between HL and variants in candidate genes chosen based on *a priori* knowledge of HL/cancer biology. Variants were only carried forward for meta-analysis if full genotype data for both cases and controls were extractable from the article. Only studies published as full-length articles or letters in peer-reviewed journals in English were included in the analysis.

Data extraction

Data for analyses, including study design, sample size and ethnicity as well as allele and genotype frequencies, were extracted from the published articles and summarised in a consistent manner to aid comparison.

Data extraction from Genome Wide Association Studies

Where possible, genotype data from 1,465 cases and 6,417 controls were extracted from published GWAS to allow the inclusion of variants examined once in the literature (7, 8).

Statistical analysis

Raw data for genotype frequencies, without adjustment, were used for calculation of the study-specific estimates of odds ratio and 95% confidence limits (CIs). Cochran's Q-statistic was used to test for heterogeneity, and the percentage variability of the pooled OR attributable to heterogeneity between studies was quantified using the I^2 statistic (large heterogeneity typically defined by I^2>75%). A p-value>0.05 for the Q test was considered to indicate a lack of heterogeneity across studies, so the pooled estimation of the OR of each study was calculated by the fixed-effects model (11). Otherwise, the random effects model was employed(12). The significance of the pooled OR was determined by the Z-test and p<0.05 was considered as statistically significant. An estimate of the potential publication bias was conducted by the examination of funnel plots, in which the standard error (SE) of log(OR) of each study was plotted against its log(OR). An asymmetric plot is reflective of publication bias. The funnel plot symmetry was assessed by Egger's test based on inverse-variance weighted regression of the effect sizes on their precision (the inverse of standard error), to test whether the intercept deviated significantly from zero; a p<0.05 was considered indicative of statistically significant publication bias(13). To test for population stratification (*i.e.* deviation from Hardy-Weinberg equilibrium (HWE), the distribution of

genotypes in control subjects of each individual population was tested for departure by means of the χ^2 test(14). For each statistically significant association identified, we estimated the false positive reporting probability (FPRP) (15). The FPRP value is determined by the *p*-value, the prior probability for the association, and statistical power. We calculated FPRP assuming a prior probability of 0.001 proposed for candidate gene analyses(16). Statistical power was based on the ability to detect an OR of 1.2 and 1.5 (or reciprocal), with α equal to the observed *p*-value. To evaluate whether the association was noteworthy, we imposed a FPRP cut-off value of 0.2, advocated for summary analyses. Hence, FPRP values < 0.2 were considered to indicate robust associations (15).

Statistical analyses were undertaken using Stata version 10.0 (Stata Corporation, College Station, TX).

Results

Characteristics of published studies

Meta-analysis of variants studies more than once in the literature—We retrieved 84 published studies using our search criteria (Figure 1). Of variants examined more than once in the literature we identified a total of 21 publications detailing 12 variants in 10 genes (Table 1). Six of the variants were genotyped in the published GWAS. All of the published the studies were essentially of similar design, although different types of controls have been analysed (Table 2). In the final group, six studies included data on ethnicity of cases and controls (17–21), three studies included data on EBV-status (17, 22, 23), and eight studies included data on histopathological subtype of HL (17, 19, 20, 22, 24–27). Two studies stratified genotype by histology (23, 25), and two studies stratified genotypes by EBV-status (22, 23). ORs of HL associated with each polymorphism in individual studies are detailed in the Table 3.

Immune response genes—One of the two studies which examined the association between *IL-10* rs1800890 and HL demonstrated a lower risk of HL for those >40 years with homozygosity or carrier status of the T allele (24). The departure of genotype frequencies from HWE (p_{HWE} = 0.02) in the control group however suggests population stratification in this study. Pooling data from the both studies failed to demonstrate a significant association between the variant and HL risk (Table 4) (24, 28). In addition, there was no evidence of an association when pooling together three studies *IL10*, rs1800896 nor with the inclusion of data from the GWAS (Table 4) (7, 8, 24, 25, 29).

Two studies have evaluated rs1800795, a SNP located upstream of *IL-6* (21, 23). One study utilised monozygotic and dizygotic twins with at least one affected twin. When all cases were analysed, homozygosity of the C allele appeared to be protective for HL and this was identified in the NS subgroup (21). These findings were not however, supported by a larger analysis of unrelated patients with HL nor in the pooled analysis (23) (Table 4).

Carcinogen metabolism genes—Four studies have investigated the SNP rs1696 in *GSTP1* and risk of developing HL (18, 24, 30, 31). One study found a protective effect of the heterozygous (AG) genotype (24); while another study found the wild type genotype

(AA) was associated with an increased risk of HL (18) and a third study found the less prevalent genotype (GG) to be associated with an increased risk of HL (30) (Table 3). Two studies demonstrated evidence of population stratification with departure from HWE in the controls (p_{HWE} = 0.01). No evidence of association was found when these studies were pooled nor with the inclusion of data from the GWAS (Table 4).

Six studies have investigated deletion of the *GSTT1* gene and predisposition to HL. *GSTT1* deletion conferred an increased risk of HL in three studies (24, 27, 32) and no effect in three studies (18, 30, 31) (Table 3). Pooling data from the six studies revealed no evidence of association of *GSTT1* deletion with HL risk (Table 4).

Seven studies have examined *GSTM1* deletion and risk of developing HL (18, 24, 26, 30–33). Neither the studies nor a pooled analysis provides evidence for an association between *GSTM1* deletion and HL risk (Table 3, Table 4).

DNA repair genes—Two studies have examined the risk of HL and the SNP rs17655 in *XPG/ERCC5* (19, 34), neither demonstrating an association between genotype and HL risk (Table 3). However, in a pooled analysis, a significant association between *XPG/ERCC5,* rs17655 CC homozygosity and an increased risk of developing HL with an OR=2.03 (95% CI:1.01 - 4.06, p=0.046) (Figure 2). Furthermore with the addition of data from GWAS the association appeared promising 1.68 (95% CI:1.18 – 2.37, p=0.01) (Figure 2 and Table 4). There was no evidence of small study effect (Figure 3).

Folate metabolism genes—Four studies have evaluated the risk of HL with rs1801133, in *MTHFR* (17, 35–37). In isolation, none of the studies provided evidence for an association between the genotype and risk (Table 3). However, in a pooled analysis, heterozygosity conferred an OR of 0.74 (95% CI:0.578 - 0.95, p=0.018) and carrier status an OR of 0.75 (95% CI: 0.60 - 0.96, p=0.019). However, with the addition of GWAS data no association was demonstrated (Table 4).

Two studies have evaluated the risk of HL with rs1805087 in *MTR* (17, 34). Neither demonstrated an association (Table 3). Similarly no association was shown in a meta-analysis which included GWAS data (Table 4).

Other Genes—Three studies have investigated the role of rs20417 in *COX2* and HL risk (20, 22, 38). One study demonstrated an association with both carrier and homozygous minor genotype (20) (Table 3). However in a pooled analysis with the inclusion of data from GWAS no association was seen (Table 4). Two studies have also examined the risk of HL rs689466 in *COX2*, but no association is seen (Table 4) (22, 38).

Finally, two studies have investigated the tandem repeat in *UGT1A1* and HL risk. No significant association was seen in either study (Table 3). A pooled analysis did not provide evidence for a relationship between *UGT1A1* genotype and HL (Table 4) (24, 31).

Variants examined once in published studies—Using directly typed SNPs from the GWAS, we were able to include an additional 47 variants published in eight papers (39–46). There was evidence for association in eight of these variants (p<0.05).

False Positive Report Probability—To evaluate the robustness of the three significant findings from the pooled analyses, we calculated FPRP conditional on a prior probability of 0.001. None of the above results are not considered noteworthy on the basis of the pre-defined assumptions (Table 4 and Table 5). For example, although the summary OR from the pooled analysis of rs17655 indicated a statistically significant positive association with risk, the FPRP was 0.99 which is much higher than the conventionally accepted threshold cut off for noteworthiness of <0.2.

Discussion

It is clear that substantial research has been carried out examining polymorphic variants in a number of putative candidate genes as risk factors for HL. While our meta-analysis provides some support for a variation in XPG/*ERCC5* as a risk factors for HL, as well as 8 other variants, these data should be interpreted with caution as the identified associations are not robust on the basis of multiple testing correction and FPRP.

Even excluding this, a number of general conclusions can be constructed from the published studies. Few of the studies variants have been reported as statistically significant in more than one study. It is generally acknowledged that independent replication of study findings is a prerequisite to assess the robustness of findings. In some studies, the failure to demonstrate a relationship may simply be a consequence of poor power because of sample size. Genome-wide association studies (GWAS) of cancer have revealed that the relative risk associated with common variants is, typically between 1.1 and 1.3(47). Fewer than 40% of the studies we reviewed had 80% power to demonstrate even a 2-fold difference in risk at the 0.05 significance level. To overcome this lack of power, we have undertaken a meta-analysis pooling the data from the published studies. There are, however, caveats to this statistical procedure.

In any systematic review, publication bias is clearly of great concern. The most common scenario is that negative findings may go unreported. Furthermore, many studies excluded do not describe the ethnicity of cases or controls, and it is assumed that each polymorphism is functional with respect to risk in each study population. If, however, the polymorphism is a neutral marker for another variant, the assumption may well not apply, since LD is often population-dependent. Here we have relied on data extractable from published reports. Ideally, access to primary data is desirable; in the absence of this it would be advisable that in the future at least summary data be published to allow meta-analysis to be conducted.

An important lesson from the published studies is that greater attention should be paid to study design. Data from GWAS have demonstrated a differing allelic architecture of genetic susceptibility to HL with respect to histology and EBV status. Few studies have stratified genotype data according to histology and EBV status. This may explain the lack of consistency in candidate gene association studies and in our meta-analysis. Due to the lack of stratification in the majority of studies we were unable to include this in our meta-analysis. The issue of population stratification in case-control studies and resulting false positive results is also of concern. Such associations occur because of population subdivision and non-random mating, leading to variation in the marker frequency within the population

as a result of founder effects and/or genetic drift. The severity of spurious association becomes an increasing problem with increasing study size. To avoid this problem, potential confounding effect of population stratification should be allowed for in the design and analysis of the study. This requires the identification of sub-populations in terms of factors that can influence both disease and marker allele frequencies. Provided cases and controls are well matched, differences in the frequency of genotypes will only be seen at predisposition loci. Hence, stratification can be detected by typing a series of unlinked markers chosen from a panel known to exhibit differences in allele frequency between populations.

We have attempted to review published analyses of the relationship between polymorphic variation and risk of HL through several iterations of search criteria; it is possible, however, that we have missed some published studies. As the number of articles on genetic variation on risk of HL published in the past decade has increased considerably and continues to grow, we accept that this review provides a snapshot of progress to date in the field.

All of the studies we have reviewed have been based on a candidate gene approach. It is clear from studies of cancer that without a clear understanding of tumour causalities the definition of what constitutes a candidate gene is inherently problematic, making an unbiased approach through GWAS highly desirable. Moreover, the possibility of missing the identification of important variants in hitherto unstudied genes is avoided. Thus far GWAS of HL have provided evidence that variation in a number of genes including *REL, EOMES, ERAP1, IL13, PVT1, GATA3* and *TCF3* (7, 8, 48, 49) influence the risk of developing HL. In contrast to the candidate gene studies, the substantial evidence supporting these variants, including sizeable power and replication in large samples, indicate that the associations are highly robust. These data thus provide the first unambiguous evidence that common low penetrance susceptibility alleles contribute to the risk of HL.

Conclusions

The search for polymorphic variants influencing the risk of HL is a worthy enterprise. However, the studies that have been conducted to date have important lessons for the design and execution of future studies. Candidate gene analyses should be viewed as complementary to GWAS, as they theoretically offer advantages both in terms of statistical power and an ability to identify low frequency risk variants. Furthermore, many functional variants, such as the small scale insertion and deletions in carcinogen metabolism genes, are poorly captured by tagging SNPs used in GWAS. It is however, clear that in addition to conducting studies using adequate sample, attention should be paid to study design to avoid problems of aetiological heterogeneity, population stratification and other sources of potential bias in order to maximise the output of any future candidate gene study.

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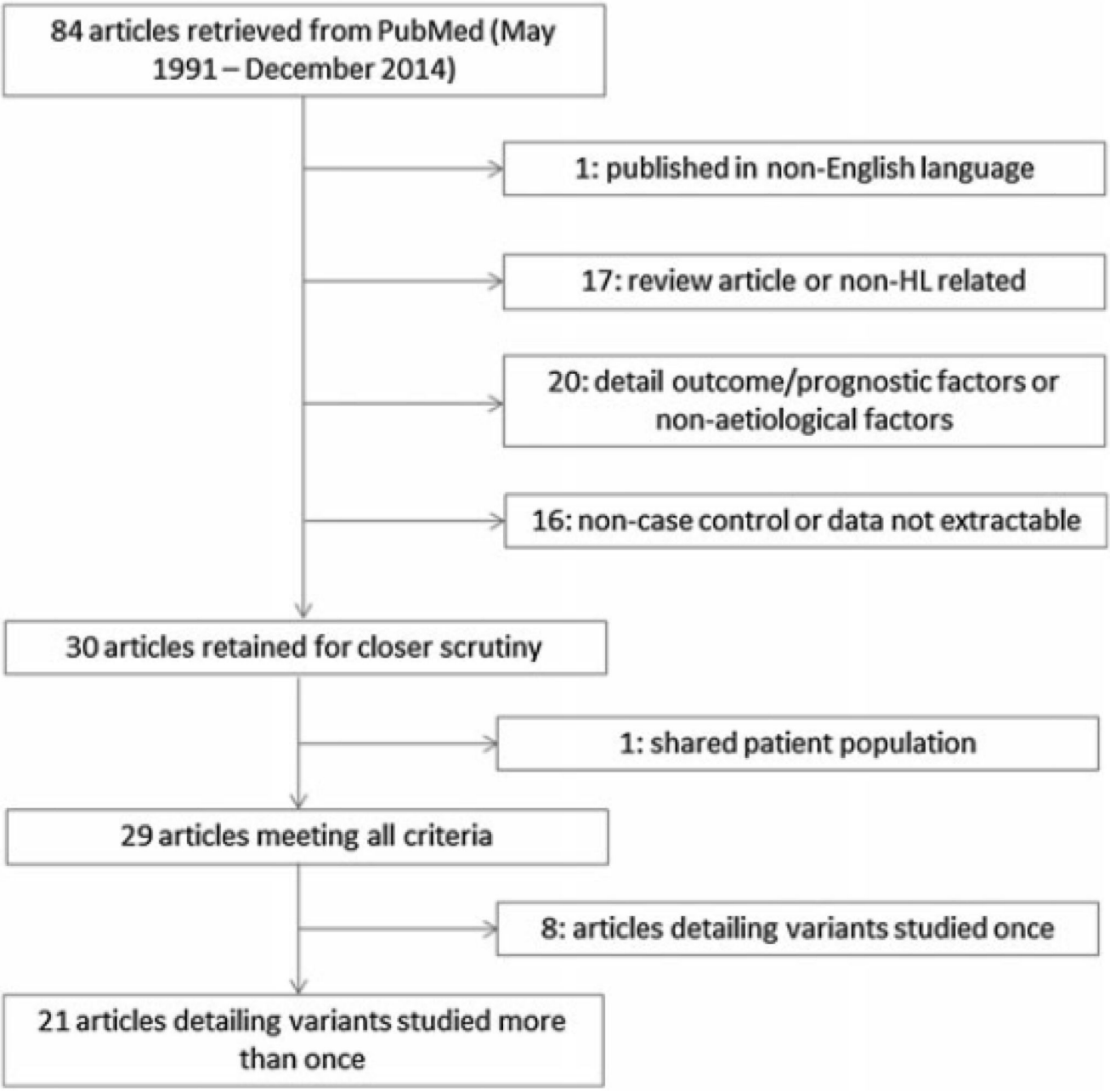

Figure 1.
Inclusion and exclusion criteria for studies

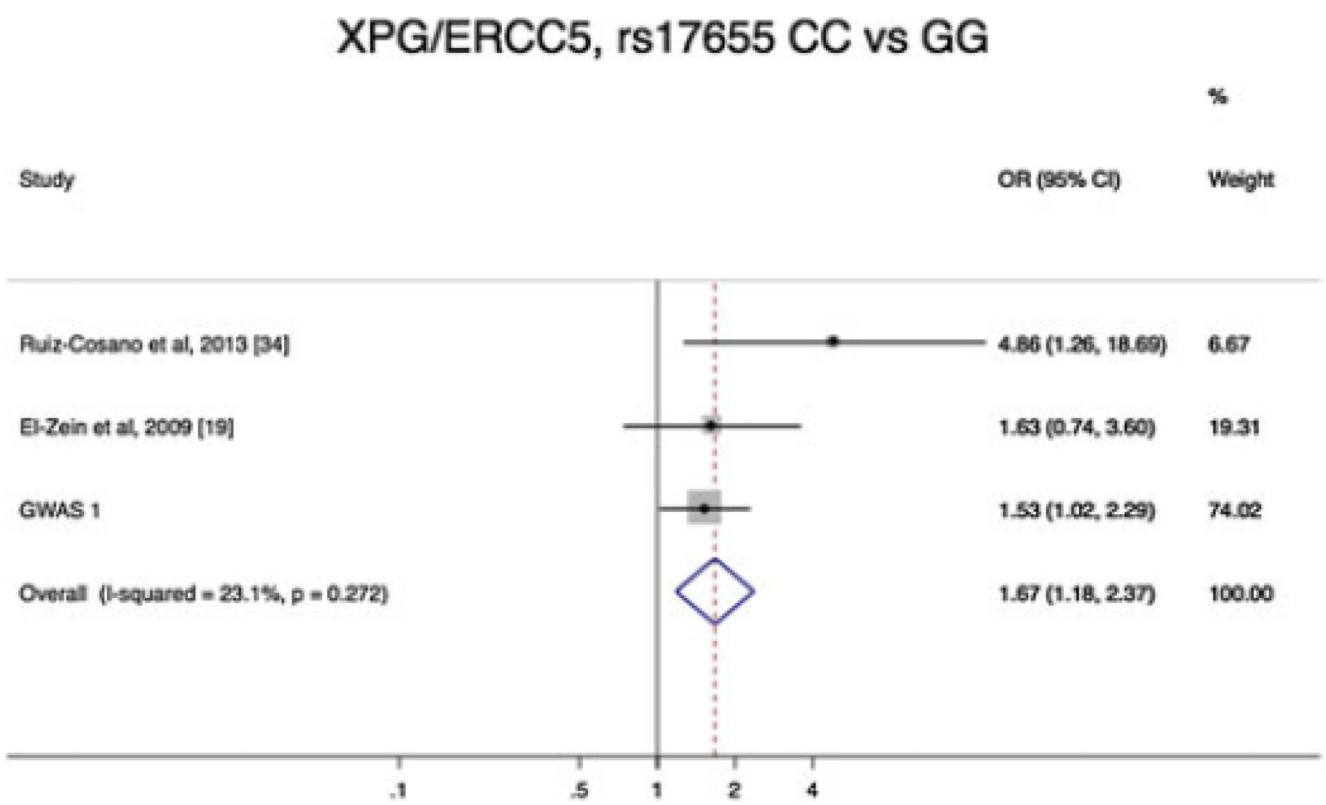

Figure 2.

Forest plot of odds ratios (ORs) of Hodgkin lymphoma associated with polymorphic variant XPG/ERCC5 rs17655 CC versus GG. Boxes denote allelic OR point estimates, their areas being proportional to the inverse variance weight of the estimate. Horizontal lines represent 95% confidence intervals (CI). The diamond (and broken line) represents the summary OR computed under a fixed effects model, with 95% CI given by its width. The unbroken vertical line is at the null value (OR = 1.0)

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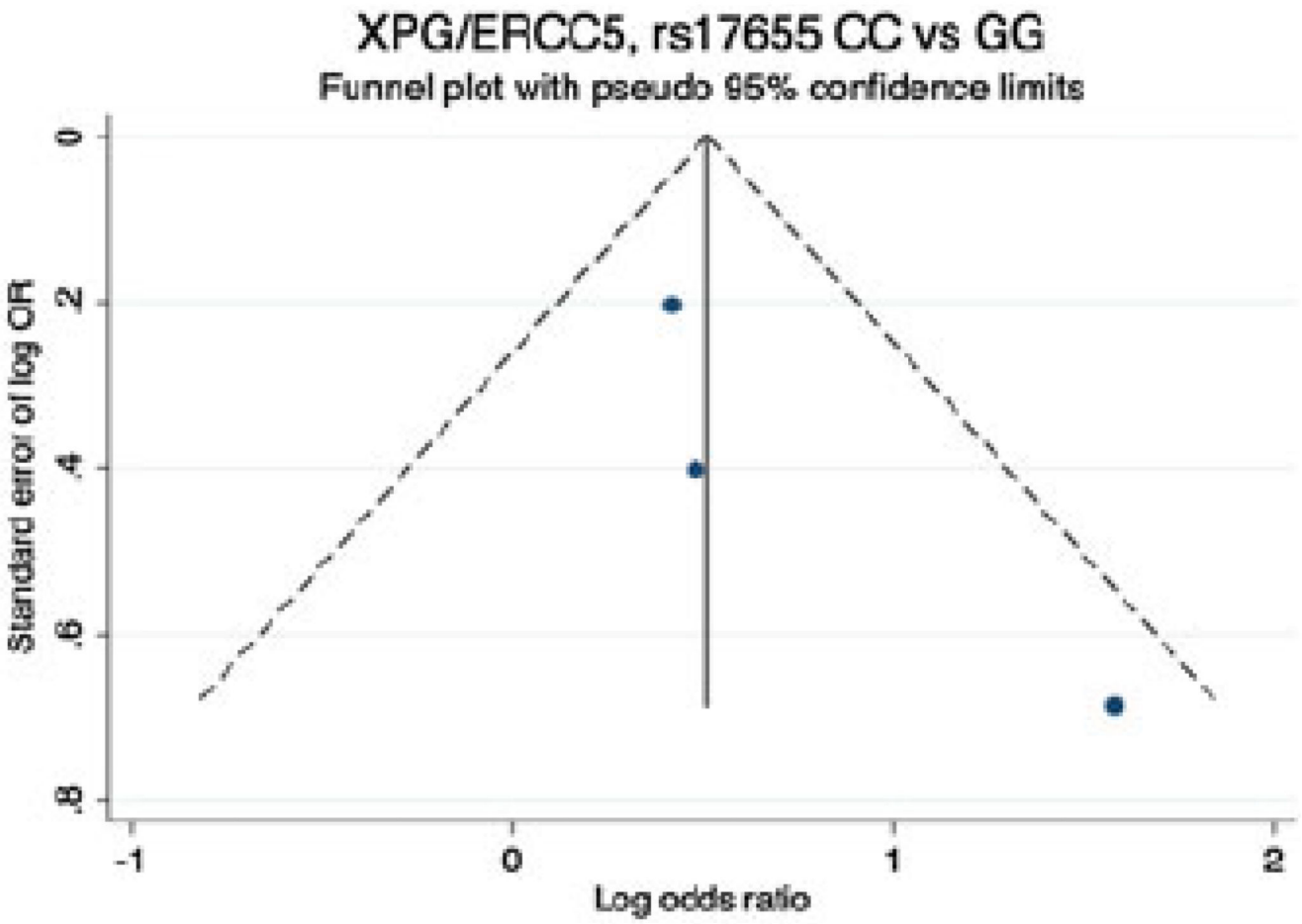

Figure 3.

Begg's funnel plot (using odds ratio (OR) of Hodgkin lymphoma risk associated with variant genotype rs17655 CC versus GG). The horizontal line represents the meta-analysis summary estimate, and the diagonal lines pseudo-95% CI limits about the effect estimate. In the absence of publication bias, studies will be distributed symmetrically above and below the horizontal line. Asymmetry on the top of the graph indicates evidence of publication bias towards studies reporting a positive logOR. LogOR, natural logarithm of the OR; s.e. of logOR, standard error of the logOR

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Table 1

Polymorphisms studied as risk factors for Hodgkin Lymphoma.

Class/Gene	Polymorphism	Type	AA change	Effect	Methods of detection
Immune response					
TNFα	rs1800629 A>G	Upstream	None	Reduced expression	Taqman
	rs1800750 G>A	Upstream	None	Reduced expression	Taqman
FCGR2	rs1801274 C>T	Missense	A519C, R131H	Altered activity	Pyrosequencing
IL1A	rs1800587 C>T	Upstream	None	Increased expression	Taqman
IL1B	rs16944 G>A	Upstream	None	Altered expression	Taqman
IL4	rs2243248 T>G	Upstream	None	Altered expression	Cycling temperature denaturing electrophoresis
	rs2243250C>T	Upstream	None	Altered expression	Sequenom MassARRAY iPLEX
IL4A	rs1801275 A>G	Missense	Q551R	Altered activity	Sequenom MassARRAY iPLEX
IL6	rs1800795 G>C	Upstream	None	Reduced expression	Taqman
IL10	rs1800890: T>A	Upstream	None	Lower expression?	Cycling temperature denaturing electrophoresis, PCR
	rs1800896 G>A	Upstream	None	Lower expression>	RFLP Taqman, SSCP
IL10RA	rs2229113: A>G	Missense	G330R	Altered activity	PCR-RFLP
	rs3135932 A>G	Missense	S159G	Altered activity	PCR-RFLP
IRF4A	rs872071 A>G	Upstream	None	Altered expression	Allele-Specific PCR
LTC4S	rs730012 A>C	Upstream	None	Altered expression	Taqman
CXCL12	rs1801157 G>A	Upstream	None	Altered expression	PCR-RFLP
TLR1	rs5743551 A>G	Upstream	None	Increased expression	PCR-RFLP
TLR2	rs4696480 T>A	Upstream	None	Altered expression	PCR-RFLP
TLR9	rs187084 T>C	Upstream	None	Altered expression	PCR-RFLP
	rs5743836 T>C	Upstream	None	Altered expression	PCR-RFLP
Carcinogen metabolism					
GSTM1	Deletion	NA	NA	Abolishes activity	PCR-RFLP
GSTT1	Deletion	NA	NA	Abolishes activity	PCR-RFLP
GSTP1	rs1695 A>G	Missense	I105V	Decreased activity	Cycling temperature denaturing electrophoresis, PCR-RFLP
GSTA1	rs3957357 C>T	Upstream	None	Altered expression	Cycling temperature denaturing electrophoresis
EPHX	rs1051740 T>C	Missense	T113C	Altered activity	PCR-RFLP
	rs2234922 A>G	Missense	H139G	Altered activity	PCR-RFLP

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Class/Gene	Polymorphism	Type	AA change	Effect	Methods of detection
CYP2C9	rs1057910 A>C	Missense	I359L	Altered activity	Taqman
	rs1799853 C>T	Missense	R144C	Altered activity	Taqman
DNA repair					
XPA	rs1800975 G>A	Missense	A23G	Altered activity	Taqman
XPC	rs2228000 A>G	Missense	A499V	Altered activity	Sequenom MassARRAY IPLEX
	rs2228001 A>G	Missense	K940Q	Altered activity	Taqman
XPF/ERCC1	rs3212986 C>A	Missense	Q504K	Altered activity	Taqman
XPG/ERCC5	rs17655 G>C	Missense	D1104H	Altered activity	Taqman
XRCC1	rs1799782 C>T	Missense	R194W	Altered activity	Sequenom MassARRAY iPLEX
XRCC3	rs861539 C>T	Missense	T241M	Altered activity	Taqman
Folate Metabolism					
MTHFR	rs1801133 C>T	Missense	A222V	Decreased activity	Taqman, Melting curve analysis, PCR-RFLP
MTR	rs1805087 A>G	Missense	D919G	Reduced activity	Taqman
Others					
COX2	rs5277 C>G	Missense	G102C	Altered activity	Taqman
	rs20417 G>C	Upstream	None	Decreased activity	Sequenom MassARRAY iPLEX, Taqman, Pyrosequencing
	rs689466 G>A	Upstream	None	Decreased activity	
ABCC2	rs17222723 T>A	Missense	V1188E	Altered activity	Cycling temperature denaturing electrophoresis
NBN	rs1801282 C>A	Missense	P12A	Altered activity	Sequenom MassARRAY iPLEX
TP53	rs1042522				
NFKB1	rs3774937				
NFKB1A	rs696				
	rs8904				
	rs1050851				
	rs19571006				
CHUK	rs2230804				
PTGES	rs10448290				
	rs2241270				
	rs4837404				

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Class/Gene	Polymorphism	Type	AA change	Effect	Methods of detection
HPSE	rs4693608				
	rs11099592				
	rs436425				
UGT1A1	NA	Tandem Repeats	None	Reduced promoter activity	PCR-RFLP, Sanger sequencing

AA, amino acid; NA, not applicable; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism;

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Table 2

Studies of polymorphisms and risk of Hodgkin lymphoma.

Reference	Place of study	Gene studied	Ethnicity	N	Cases	N	Controls
Ruiz-Cosano J et al, 2013	Spain	*XPG.ERCC5* *MTR*	Caucasian	20	HL a subset of lymphoma cases: no other information	214	Healthy blood donors matched for age, gender, ethnicity and geographical location
Yri O et al, 2012	Norway	*IL10* *GSTP1* *GSTT1* *GSTM1* *UGT1A1*	Unspecified	224	HL patients: 135 males, 89 males: mean age 38 (18-84).	1056	Healthy blood donors (age and gender unknown)
Ruiz-Cosano J et al, 2012	Spain	*GSTT1* *GSTM1*	Caucasian	20	HL a subset of lymphoma: no other information	214	Healthy blood donors matched for age, gender, ethnicity and geographical location
Monroy C et al, 2011	USA	*COX2*	Mixed	200	HL patients: mean age 47.2 years (SD 13.37 years). 107 males and 93 females. 80% NSHL.	220	Frequency matched to the age (within 5 years), sex, and race/ethnicity of the cases. Controls randomly selected random digit dialling. Mean age 49.27 years (SD 15.19 years). 123 males and 97 females.
Kasperzyk J et al, 2010	USA	*MTHFR* *MTR*	Mixed (predominantly Caucasian)	497	HL patients: mean age 38 years (SD 15 years). EBV positive 16.3% and EBV negative 57.6%. NLPHL excluded from the study.	638	Frequency matched to the age (within 5 year age groups), sex, and state of residency distribution of the cases. Controls randomly selected through “town books” in Boston or random digit dialling in Connecticut.
Ribrag V et al, 2009	France	*GSTT1* *GSTM1* *GSTP1* *UGT1A1*	Unspecified	313	HL patients: 180 males, 133 females. Median age 32 years (range 15-93 years).	226	Controls obtained from the French Blood Service.
Lourenco G et al, 2009	Brazil	*GSTP1* *GSTT1* *GSTM1*	Mixed	110	HL patients: median age 27 years (range 14-82 years), 57 males 53 females. Genotype data stratified by age, gender, ethnic origin and stage of disease.	226	Blood donors: median age 52 years (range 25-60 years), 151 males, 75 females.
El-Zein R et al, 2009	USA	*XPG/ERCC5*	Mixed	200	HL patients: mean age 47.2 years (SD 13.37 years). 107 males and 93 females.	220	Frequency matched to the age (within 5 years), sex, and race/ethnicity of the cases. Controls randomly selected random digit dialling. Mean age 49.27 years (SD 15.19 years). 123 males and 97 females.
Chang E et al, 2009	USA	*COX2*	Mixed	473	HL patients: 242 males, 231 females. NLPHL excluded from the study.	373	Frequency matched to the age (within 5 year age groups), sex, and state of residency distribution of the cases. Controls in Boston randomly selected through “town books”. Controls in Connecticut randomly selected through digit dialling (18-65 years of age) or Medicare files (66-79 years of age). 211 males and 162 females.
Hoeft K et al, 2008	Germany	*COX2*	Unspecified	116	HL a subset of lymphoma cases.	710	Randomly selected from the population registers of the study region. Matched for gender, age (1 year) and study region. 390 males and 320 females.

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Reference	Place of study	Gene studied	Ethnicity	N	Cases	N	Controls
Timuragaoglu A et al, 2006	Turkey	*MTHFR*	Unspecified	30	HL a subset of lymphoma cases.	82	Frequency matched to cases by age and gender.
Deligezer A et al, 2006	Turkey	*MTHFR*	Unspecified	51	HL a subset of lymphoma cases. 22 cases MCHL, 20 NSHL, 9 LRHL. Median age 35 years (range 19-70), 35 males, 31 females.	154	Frequency matched to cases by age and gender of similar ethnic background. Randomly selected.
Nieters A et al, 2006	Germany	*IL10*	Unspecified	115	HL a subset of lymphoma cases.	710	1:1 matched for gender, age (within 1 year) and study region.
Cordano et al, 1999	UK	*IL6*	Unspecified	584	HL patients: 61.3% NSHL and 21.4% cHL. 33% EBV positive.	513	Frequency matched to cases by age and gender, region of residence.
Cozen W et al, 2004	USA	*IL6*	Mixed (predominantly Caucasian)	27	HL patients: an affected twin of a monozygotic or dizygotic pair. Geneotype data stratified by zygosity and histology.	201	Spouses within 5 years of the twins' ages, non-blood relative/friend or a age (within 5 years) or ethnicity-matched control subject was chosen from employees within the institution.
Munro L et al, 2003	UK	*IL10*	Unspecified	125	HL patients: mean age 44.04 years, 52.7% NSHL, 17.7 MCHL, 6.8% NLPHL, 2% LRCHL, 19. UC. 69 males, 88 females. Geneotype data stratified by histopathology.	125	Mean age 58.3 years, 51 males, 60 females.
Hohaus S et al, 2003	Italy	*GSTT1* *GSTM1*	Unspecified	90	HL patients: median age 33 years, 54 males, 36 females. 67 NSHL, 7 MCHL, 6 NLPHL, 1 LDHL, 9 UC. Geneotype data stratified by age and gender.	176	Matched for sex and age (69 females, 107 males; median age 38 years, range 19–71 years)
Cunningham L et al, 2003	Australia	*IL10*	Mixed	44	HL a subset of lymphoma cases.	164	Geographically and ethnically similar metropolitan population.
Sarmanova J et al, 2001	Norway	*GSTP1* *GSTT1* *GSTM1*	Caucasian	143	HL a subset of lymphoma cases. Genotype data stratified by gender.	455	Similar gender and age distribution as overall lymphoma cohort. Staff from institute and nearby inhabitants of houses for elderly citizens.
Gonzalez Ordonez A et al, 2000	Spain	*MTHFR*	Unspecified	29	HL a subset of lymphoma cases. Mean age 24 years (SD 15 years).	200	Healthy Spanish volunteers.
Lemos M et al, 1999	Portugal	*GSTM1*	Portuguese	25	HL a subset of lymphoma cases.	128	Unrelated Portuguese Caucasian volunteers; 56 males, 72 females; no history of cancer or other chronic disease; no age-matching.

HL, Hodgkin Lymphoma; SD, standard deviation; EBV, Epstein-Barr Virus; cHL, Classical Hodgkin Lymphoma; NSHL, nodular sclerosis Hodgkin Lymphoma; MCHL, mixed cellularity Hodgkin Lymphoma; LRHL, lymphocyte-rich Hodgkin-Lymphoma; LDHL, lymphocyte-depleted Hodgkin-Lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin-Lymphoma; UC, unclassified

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Table 3

Summary of odds ratios of individual studies along with their confidence intervals.

		Heterozygous model				Homozygous model				Carrier status			
			95% CIs				95% CIs				95% CIs		
Study	**Polymorphism**	**OR**	**Upper**	**Lower**	***P***	**OR**	**Upper**	**Lower**	***P***	**OR**	**Upper**	**Lower**	***P***
Yri	*IL-10, rs1800890*	0.95	1.30	0.69	0.74	1.41	2.17	0.94	0.12	1.04	1.40	0.77	0.80
Nieters	*IL-10, rs1800890*	1.07	1.63	0.7	0.77	0.63	1.29	0.19	0.20	0.96	1.45	0.64	0.86
Nieters	*IL10*, rs1800896	0.96	1.51	0.61	0.86	0.62	1.14	0.15	0.12	0.85	1.30	0.55	0.45
Munro	*IL10*, rs1800896	0.84	1.48	0.47	0.54	0.83	1.68	0.44	0.61	0.84	1.43	0.49	0.51
Cunningham	*IL10*, rs1800896	0.92	2.00	0.43	0.84	0.54	1.49	0.18	0.23	0.79	1.66	0.38	0.54
Cordano	*IL6, rs1800795*	0.85	1.17	0.61	0.32	1.03	1.58	0.19	0.88	0.89	1.21	0.66	0.47
Cozen	*IL6, rs1800795*	0.58	1.13	0.30	0.11	0.35	0.95	0.14	0.04	0.52	0.98	0.27	0.04
Yri	*GSTP1*, rs1695	0.85	1.17	0.62	0.32	1.33	2.03	0.24	0.19	0.96	1.28	0.71	0.76
Lourenco	*GSTP1*, rs1695	0.34	0.57	0.20	0.00	0.58	1.13	0.04	0.11	0.39	0.63	0.25	0.00
Ribrag	*GSTP1, rs1695*	1.01	1.49	0.68	0.97	1.06	1.90	0.66	0.85	1.02	1.47	0.71	0.92
Sarmanova	*GSTP1*, rs1695	0.77	1.33	0.44	0.35	1.88	3.70	0.38	0.06	1.00	1.61	0.61	0.98
Yri	*GSTT1*, deletion	NA	NA	NA	NA	NA	NA	NA	NA	3.17	5.09	1.97	0.00
Ruiz-Cosano	*GSTT1*, deletion	NA	NA	NA	NA	NA	NA	NA	NA	2.95	7.96	1.10	0.03
Ribrag	*GSTT1*, deletion	NA	NA	NA	NA	NA	NA	NA	NA	0.90	1.47	0.55	0.67
Lourenco	*GSTT1*, deletion	NA	NA	NA	NA	NA	NA	NA	NA	0.92	1.65	0.51	0.78
Hohaus	*GSTT1*, deletion	NA	NA	NA	NA	NA	NA	NA	NA	1.90	3.46	1.04	0.03
Sarmanova	*GSTT1*, deletion	NA	NA	NA	NA	NA	NA	NA	NA	0.88	1.79	0.43	0.72
Yri	*GSTM1, deletion*	NA	NA	NA	NA	NA	NA	NA	NA	1.18	1.57	0.88	0.27
Ruiz-Cosano	*GSTM1, deletion*	NA	NA	NA	NA	NA	NA	NA	NA	0.53	1.34	0.21	0.18
Ribrag	*GSTM1, deletion*	NA	NA	NA	NA	NA	NA	NA	NA	0.83	1.2	0.58	0.33
Lourenco	*GSTM1, deletion*	NA	NA	NA	NA	NA	NA	NA	NA	1.35	2.14	0.86	0.19
Hohaus	*GSTM1, deletion*	NA	NA	NA	NA	NA	NA	NA	NA	0.75	1.25	0.45	0.26
Sarmanova	*GSTM1, deletion*	NA	NA	NA	NA	NA	NA	NA	NA	0.90	1.45	0.55	0.66

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		Heterozygous model				Homozygous model				Carrier status			
			95% CIs				95% CIs				95% CIs		
Study	**Polymorphism**	**OR**	**Upper**	**Lower**	***P***	**OR**	**Upper**	**Lower**	***P***	**OR**	**Upper**	**Lower**	***P***
Lemos	*GSTM1, deletion*	NA	NA	NA	NA	NA	NA	NA	NA	0.93	2.20	0.39	0.87
Ruiz-Cosano	*XPG/ERCC5, rs17655*	1.89	5.28	0.68	0.22	4.86	18.69	3.81	0.01	2.33	6.06	0.89	0.08
El-Zein	*XPG/ERCC5, rs17655*	1.19	1.79	0.79	0.40	1.63	3.60	0.58	0.22	1.25	1.84	0.85	0.26
Kasperzyk	*MTHFR, rs1801133*	0.76	1.03	0.56	0.08	0.96	1.52	0.16	0.87	0.80	1.06	0.60	0.13
Timuragaoglu	*MTHFR, rs1801133*	1.15	2.77	0.48	0.75	0.55	2.87	0.42	0.48	1.02	2.38	0.44	0.96
Deligezer	*MTHFR, rs1801133*	0.49	0.96	0.25	0.04	0.26	1.19	0.07	0.06	0.45	0.85	0.23	0.01
Gonzales Ordonez	*MTHFR, rs1801133*	0.77	1.76	0.33	0.53	0.92	3.48	0.34	0.9	0.8	1.73	0.36	0.56
Ruiz-Cosano	*MTR*, rs1805087	0.84	2.70	0.26	0.78	5.81	21.90	2.06	0.00	1.47	3.73	0.58	0.41
Kasperzyk	*MTR*, rs1805087	0.93	1.26	0.68	0.65	0.60	1.22	0.16	0.16	0.88	1.18	0.66	0.41
Monroy	*COX2*, rs20417	1.39	0.74	2.6	0.31	6.94	2.68	59.16	0.04	1.6	2.93	0.87	0.13
Chang	*COX2*, rs20417	1.11	1.49	0.82	0.51	1.99	4.24	0.65	0.07	1.18	1.57	0.88	0.27
Hoeft	*COX2*, rs20417	1.05	1.65	0.67	0.83	NA	NA	NA	NA	0.99	1.55	0.63	0.97
Chang	*COX2, rs689466*	0.99	1.36	0.73	0.97	1.16	2.39	0.33	0.69	1.01	1.36	0.75	0.93
Hoeft	*COX2, rs689466*	0.99	1.53	0.63	0.95	0.31	2.35	0.31	0.23	0.93	1.43	0.60	0.73
Yri	*UGT1A1*, tandem repeat	0.90	1.22	0.66	0.49	0.79	1.32	0.16	0.37	0.88	1.17	0.66	0.37
Ribrag	*UGT1A1*, tandem repeat	0.70	1.04	0.47	0.07	0.71	1.32	0.12	0.28	0.70	1.02	0.48	0.06

CI, confidence interval; OR, odds ratio

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Table 4

Pooled odds ratios of all polymorphisms examined more than once in the literature including data from GWAS together with the false positive report probabilities (FPRP).

								Power		FPRP at prior probability of 0.001	
Gene, variant	**Studies**	**Cases**	**Controls**	**OR**	**P**	**P_{het}**	**I^2**	**OR=1.2**	**OR=1.5**	**OR=1.2**	**OR=1.5**
IL-10 rs1800890	2	334	1709								
AT vs TT				0.99 (0.77 - 1.28)	0.93	0.67	0	0.91	1.00		
AA vs TT				0.99 (0.45 - 2.18)	0.98	0.06	72%	0.67	0.84		
Carrier				1.01 (0.79 - 1.29)	0.93	0.77	0	0.92	1.00		
IL10, rs1800896	5	1573	7026								
AG vs AA				1.01 (0.84 – 1.20)	0.95	0.89	0	0.98	1.00		
GG vs AA				0.88 (0.50 – 1.54)	0.65	0.01	73%	0.58	0.84		
Carrier				1.06 (0.89 – 1.25)	0.53	0.34	10%	1.00	1.00		
IL-6 rs1800795	2	435	374								
GC vs GG				0.79 (0.59 - 1.06)	0.11	0.316	1%	0.53	0.93		
CC vs GG				0.86 (0.59 - 1.29)	0.50	0.05	74%	0.78	0.97		
Carrier				0.92 (0.32 – 2.63)	0.17	<0.01	88.5%	0.63	0.96		
GSTP1, rs1695	6	2185	8287								
AG vs GG				0.82 (0.63 – 1.07)	0.15	<0.001	79%	0.45	0.94		
AA vs GG				1.08 (0.92 – 1.27)	0.35	0.06	52%	0.90	1.00		
Carrier				0.88 (0.69 – 1.13)	0.32	<0.001	78%	0.67	0.99		
GSTT1 deletion	6	796	2058								
Carrier				1.50 (0.90 - 2.50)	0.12	0	76%	0.20	0.50		
GSTM1 deletion	7	835	2205								
Carrier				0.99 (0.84-1.17)	0.90	0.32	15%	0.98	1		
XPG/ERCC5, rs17655	3	1094	1651								
GC vs GG				0.94 (0.80 – 1.12)	0.50	0.17	44%	0.91	1.00		
CC vs GG				1.68 (1.18 – 2.37)	0.01	0.27	23%	0.03	0.26	0.99	0.99

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Gene, variant	Studies	Cases	Controls	OR	P	P_{het}	I^2	Power OR=1.2	Power OR=1.5	FPRP at prior probability of 0.001 OR=1.2	FPRP at prior probability of 0.001 OR=1.5
Carrier				1.01 (0.86 – 1.19)	0.88	0.10	57%	0.65	0.82		
MTHFR rs1801133	4	2025	7202								
CT vs CC				0.96 (0.85 – 1.07)	0.47	0.19	33%	0.99	1.00		
TT vs CC				0.98 (0.82 – 1.17)	0.80	0.62	0	0.97	1.00		
Carrier				0.96 (0.86 – 1.07)	0.45	0.15	38%	1.00	1.00		
MTR rs1805087	4	1936	6991								
AG vs AA				0.97 (0.86 – 1.10)	0.63	0.99	0	0.99	1.00		
GG vs AA				1.18 (0.88 – 1.57)	0.27	0.05	67%	0.55	0.95		
Carrier				0.99 (0.88 – 1.11)	0.86	0.72	0	0.99	1.00		
COX2 rs20417	4	1538	2333								
GC vs GG				1.01 (0.92 – 1.24)	0.41	0.83	0	0.95	1.00		
CC vs GG				1.37 (0.88 – 2.13)	0.17	0.16	43%	0.28	0.67		
Carrier				1.01 (0.94 – 1.26)	0.27	0.50	0	0.94	1.00		
COX2 rs689466	2	567	1024								
AG vs AA				0.991 (0.77 - 1.28)	0.94	0.98	0	0.91	1		
GG vs AA				0.92 (0.48 - 1.76)	0.81	0.22	33%	0.62	0.84		
Carrier				0.98 (0.77 - 1.26)	0.90	0.74	0	0.91	1		
UGT1A1 TR	2	532	1208								
6/7 vs 6/6				0.82 (0.64 - 1.040)	0.10	0.33	0	0.44	0.95		
7/7 vs 6/6				0.76 (0.51 - 1.13)	0.17	0.79	0	0.32	0.74		
Carrier				0.81 (0.64 - 1.01)	0.06	0.36	0	0.38	0.95		

CI, confidence interval; OR, odds ratio

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Table 5

Pooled odds ratios of all the polymorphisms examined once in the literature and GWAS data with the false positive report probabilities (FPRP).

								Power		FPRP at prior probability of 0.001	
Gene, variant	**Studies**	**Cases**	**Controls**	**OR**	**P**	**P_{het}**	**I^2**	**OR=1.2**	**OR=1.5**	**OR=1.2**	**OR=1.5**
TNFα, rs1800750	2	928	1345								
GA vs GG				1.78 (0.34 – 9.19)	0.50	0.01	84%	0.32	0.42		
AA vs GG											
Carrier				1.78 (0.34 – 9.19)	0.50	0.01	84%	0.32	0.42		
TNFα, rs1800629	2	987	1893								
GA vs GG				1.14 (0.94 – 1.37)	0.19	0.66	0	0.71	1.00		
AA vs GG				1.17 (0.74 – 1.87)	0.50	0.43	0	0.54	0.85		
Carrier				1.14 (0.95 – 1.37)	0.15	0.81	0	0.71	1.00		
FCGR2, rs1801274	3	1704	7938								
CT vs CC				1.15 (1.00 - 1.31)	0.05	0.93	0	0.74	1.00		
TT vs CC				1.07 (0.91 - 1.26)	0.40	0.37	0	0.92	1.00		
Carrier				1.12 (0.99 - 1.27)	0.08	0.96	0	0.86	1.00		
IL1A, rs1800587	2	977	1877								
CT vs CC				0.85 (0.72 – 1.00)	0.05	0.87	0	0.59	1.00		
TT vs CC				0.72 (0.54 – 0.96)	0.02	0.10	63%	0.70	0.99	1.00	1.00
Carrier				1.00 (0.60 – 1.67)	0.99	0.03	80%	0.94	1.00		
IL1B, rs16944	2	981	1876								
GA cs GG				1.03 (0.87 – 1.22)	0.73	0.17	47%	0.96	1.00		
AA vs GG				1.36 (1.05 – 1.77)	0.02	0.329	9%	0.18	0.77	0.99	0.97
Carrier				1.09 (0.93 – 1.28)	0.30	0.41	0	0.88	1.00		
IL-4 rs2243248	3	1685	7465								
TG vs GG				0.97 (0.70 - 1.33)	0.83	0.04	70%	0.83	0.99		
GG vs TT				0.88 (0.42 - 1.86)	0.50	0.44	0	1.00	1.00		

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Gene, variant	Studies	Cases	Controls	OR	P	P_{het}	I^2	Power OR=1.2	Power OR=1.5	FPRP at prior probability of 0.001 OR=1.2	FPRP at prior probability of 0.001 OR=1.5
Carrier				1.02 (0.86 – 1.20)	0.84	0.08	61%	0.98	1.00		
IL-4 rs2243250	2	976	1318								
CT vs CC				1.06 (0.87 - 1.28)	0.58	0.91	0	0.90	1.00		
TT vs CC				1.17 (0.69 – 2.00)	0.57	0.08	68%	0.54	0.82		
Carrier				1.29 (0.77 – 2.16)	0.33	0.05	75%	0.39	0.72		
IL4A rs1801275	3	1565	6517								
AG vs AA				0.87 (0.76 – 0.99)	0.03	0.0	0	0.74	1.00	0.98	0.97
GG vs AA				1.07 (0.80 -1.43)	0.65	0.29	18%	0.78	0.99		
carrier				0.89 (0.79 – 1.01)	0.07	0.70	0	0.85	1.00		
IL10, rs1800872	2	987	1893								
CA vs CC				0.98 (0.82 – 1.16)	0.79	0.09	64%	0.97	1.00		
AA vs CC				1.26 (0.82 – 1.93)	0.30	0.65	0	0.41	0.79		
Carrier				1.00 (0.85 – 1.20)	0.96	0.16	49%	0.98	1..00		
IL10RA, rs2229113	3	986	1890								
CT vs CC				0.85 (0.72 – 1.01)	0.06	0.97	0	0.59	1.00		
TT vs CC				0.81 (0.62 – 1.06)	0.12	0.88	0	0.40	0.96		
Carrier				0.84 (0.72 – 0.99)	0.04	0.93	0	0.54	1.00	0.97	0.97
IL10RA, rs3135932	3	987	1893								
AG vs AA				0.98 (0.82 – 1.16)	0.76	0.09	64%	0.97	1.00		
GG vs AA				1.26 (0.82 – 1.93)	0.30	0.65	0	0.41	0.79		
Carrier				1.26 (0.46 – 3.48)	0.65	<0.001	94%	0.46	0.63		
IRF4, rs872071	3	1592	7442								
AG vs GG				0.92 (0.81 – 1.04)	0.19	0.41	0	0.94	1.00		
AA vs GG				0.88 (0.76 – 1.02)	0.09	0.39	0	0.77	1.00		
Carrier				0.90 (0.80 – 1.02)	0.09	0.52	0	0.89	1.00		
LTC4S, rs730012	3	1915	6778								

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Gene, variant	Studies	Cases	Controls	OR	P	P_{het}	I^2	Power OR=1.2	Power OR=1.5	FPRP at prior probability of 0.001 OR=1.2	FPRP at prior probability of 0.001 OR=1.5
CA vs AA				0.94 (0.84 – 1.06)	0.34	0.41	0	0.98	1.00		
CC vs AA				0.97 (0.79 – 1.19)	0.75	0.44	0	0.93	1.00		
CArrier				0.95 (0.85 – 1.06)	0.35	0.44	0	0.99	1.00		
CXCL12, rs1801157	2	912	1308								
GA vs GG				1.05 (0.87 – 1.23)	0.60	0.97	0	0.95	1.00		
AA vs GG				1.26 (0.78 – 2.02)	0.34	0.43	0	0.42	0.77		
Carrier				1.07 (0.89 – 1.28)	0.46	0.75	0	0.90	1.00		
TLR1, rs5743551	2	985	1881								
AG vs AA				0.90 (0.76 – 1.06)	0.21	0.12	59%	0.82	1.00		
GG vs AA				1.02 (0.72 – 1.45)	0.91	0.95	0	0.82	0.98		
Carrier				0.91 (0.77 – 1.07)	0.27	0.16	50%	0.57	0.74		
TLR2, rs4696480	2	986	1982								
TA vs TT				1.47 (0.89 – 2.45)	0.13	0.05	75%	0.22	0.53		
AA vs TT				1.09 (0.86 – 1.37)	0.48	0.20	40%	0.80	1.00		
Carrier				1.42 (0.85 – 2.37)	0.18	0.04	76%	0.26	0.59		
TLR9, rs187084	2	986	1982								
TC vs TT				0.97 (0.81 – 1.16)	0.71	0.63	0	0.95	1.00		
CC vs TT				0.83 (0.65 – 1.04)	0.11	0.99	0	0.49	0.97		
Carrier				0.93 (0.78 – 1.10)	0.72	0.34	0	0.90	1.00		
TLR9, rs5743836	2	986	1982								
TC vs TT				1.11 (0.91 – 1.34)	0.31	0.08	68%	0.79	1.00		
CC vs TT				1.02 (0.80 – 1.30)	0.89	0.99	0%	0.91	0.99		
Carrier				1.07 (0.89 – 1.23)	0.50	0.12	59%	0.95	1.00		
GSTA1, rs3957357	3	1688	7403								
CT vs CC				1.07 (0.91 – 1.25)	0.41	0.19	40%	0.93	1.00		
TT vsCC				0.81 (0.55 – 1.19)	0.28	0.67	0	0.44	0.84		
Carrier				1.04 (0.89 – 1.21)	0.62	0.23	33%	0.97	1.00		

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Gene, variant	Studies	Cases	Controls	OR	P	P_{het}	I^2	Power OR=1.2	Power OR=1.5	FPRP at prior probability of 0.001 OR=1.2	FPRP at prior probability of 0.001 OR=1.5
EPHX, rs1051740	2	953	1665								
TC vs TT				0.98 (0.83 – 1.17)	0.83	0.28	14%	0.96	1.00		
CC vs TT				2.76 (0.20 – 38.40)	0.45	<0.001	97%	0.27	0.33		
Carrier				1.14 (0.97 – 1.35)	0.11	0.06	72%	0.72	1.00		
EPHX, rs2234922	2	666	5652								
AG vs AA				0.87 (0.73 – 1.03)	0.11	0.78	0	0.70	1.00		
GG vs AA				0.93 (0.61 – 1.42)	0.73	0.34	0	0.70	0.94		
Carrier				0.87 (0.73 – 1.03)	0.11	0.58	0				
CYP2C9, rs1057910	2	1054	5570								
AC vs AA				1.26 (1.02 – 1.54)	0.03	0.97	0	0.70	1.00	0.99	0.96
CC vs AA				1.33 (0.49 – 3.67)	0.58	0.31	4%	0.42	0.59		
Carrier				1.30 (1.03 – 1.54)	0.03	0.87	0	0.18	0.95	0.93	0.72
CYP2C9, rs1799853	2	1059	5569								
CT vs CC				1.28 (1.07 – 1.51)	0.01	0.21	38%	0.22	0.97	0.94	0.78
TT vs CC				0.34 (0.02 – 6.89)	0.48	0.04	75%	0.28	0.33		
Carrier				1.24 (1.05 – 1.46)	0.01	0.41	0	0.35	0.99	1.00	0.99
XPA, rs1800975	2	896	1432								
GA vs GG				0.92 (0.76 – 1.10)	0.37	0.13	57%	0.86	1.00		
AA vs GG				3.60 (0.49 – 26.70)	0.21	0.01	86%	0.14	0.20		
Carrier				1.02 (0.86 – 1.22)	0.25	0.06	72%	0.96	1.00		
XPC, rs2228000	2	984	1878								
GA vs GG				0.84 (0.71 – 1.00)	0.05	0.53	0	0.52	0.89		
AA vs GG				0.89 (0.70 – 1.50)	0.47	0.14	46%	0.60	0.86		
Carrier				0.85 (0.71 – 1.00)	0.05	0.99	0	0.59	1.00		
XPC, rs2228001	2	1663	6637								

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Gene, variant	Studies	Cases	Controls	OR	P	P_{het}	I^2	Power OR=1.2	Power OR=1.5	FPRP at prior probability of 0.001 OR=1.2	FPRP at prior probability of 0.001 OR=1.5
GT vs TT				0.98 (0.86 – 1.12)	0.78	0.97	0	0.99	1.2		
GG vs TT				1.01 (0.85 – 1.20)	0.93	0.33	10%	0.98	1.00		
Carrier				0.99 (0.86 – 1.12)	0.84	0.88	0	0.91	1.00		
ERCC1, rs3212986	3	1633	6715								
CA vs CC				0.80 (0.69 – 0.91)	0.001	0.85	0	0.27	1.00	0.72	0.41
AA vs CC				0.87 (0.68 – 1.22)	0.28	0.22	35%	0.60	0.94		
Carrier				0.81 (0.72 – 0.91)	0.001	0.98	0	0.32	1.00	0.56	0.28
XRCC1, rs1799782	2	1072	1436								
CT vs CC				0.69 (0.28 – 1.71)	0.42	0.01	84%	0.35	0.53		
TT vs CC				0.73 (0.26 – 2.10)	0.56	0.38	0	0.40	0.57		
Carrier				0.66 (0.25 – 1.74)	0.42	0.01	86%	0.32	0.50		
XRCC3, rs861539	3	912	1308								
GA vs GG				0.97 (0.86 – 1.10)	0.68	0.30	17%	0.99	1.00		
AA vs GG				1.05 (0.88 – 1.26)	0.57	0.74	0	0.92	1.00		
Carrier				0.99 (0.88 – 1.12)	0.89	0.34	7%	1.00	1.00		
COX2 rs5277	2	1334	1577								
CG vs CC				1.07 (0.90 – 1.27)	0.45	0.36	0	0.91	1.00		
GG vs CC				0.79 (0.50 – 1.25)	0.31	0.73	0	0.41	0.77		
Carrier				1.01 (0.86 – 1.19)	0.92	0.69	0	0.98	1.00		
ABCC2, rs17222723	3	1688	6517								
AT vs TT				0.97 (0.79 – 1.20)	0.80	0.74	0	0.92	1.00		
AA vs TT				2.02 (0.85 – 4.77)	0.11	0.19	40%	0.12	0.25		
Carrier				1.01 (0.83 – 1.23)	0.94	0.95	0	0.96	1.00		
NBN, rs1801282	2	1044	1435								
CA vs CC				1.07 (0.89 – 1.29)	0.45	0.06	70%	0.95	1.00		
AA cs CC				0.99 (0.61 – 1.60)	0.95	0.21	37%	0.76	0.75		
Carrier				1.07 (0.89 – 1.27)	0.50	0.19	42%	0.71	0.95		

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Gene, variant	Studies	Cases	Controls	OR	P	P_{het}	I^2	Power OR=1.2	Power OR=1.5	FPRP at prior probability of 0.001 OR=1.2	FPRP at prior probability of 0.001 OR=1.5
TP53, rs104522	2	1174	1967								
GC vs CC				1.12 (0.96 – 1.30)	0.16	0.65	0	0.81	1.00		
GG vs CC				0.96 (0.71 – 1.29)	0.76	0.54	0	0.83	0.99		
Carrier				1.09 (0.94 – 1.26)	0.25	0.57	0				
NFKB1, rs3774937	2	1041	5565								
TC vs TT				1.02 (0.86 – 1.18)	0.92	0.65	0	0.90	1.00		
CC vs TT				1.13 (0.90 – 1.44)	0.29	0.46	0	0.69	0.99		
Carrier				0.85 (0.56 – 1.30)	0.45	0.01	86%	0.54	0.87		
NFKB1A, rs696	2	1052	5563								
AG vs GG				1.24 (1.06 – 1.45)	0.01	0.56	0	0.34	0.99	0.95	0.88
AA vs GG				1.40 (1.12 – 1.74)	0.003	0.25	23%	0.08	0.733	0.97	0.77
Carrier				1.27 (1.10 – 1.48)	0.002	0.35	0	0.23	0.98	0.90	0.70
NFKB1A, rs8904	2	1046	5566								
CT cs CC				1.13 (0.96 – 1.32)	0.14	0.20	40%	0.78	1.00		
TT vs CC				1.11 (0.89 – 1.39)	0.36	0.05	75%	0.77	1.00		
Carrier				1.12 (0.97 – 1.31)	0.13	0.08	67%	0.81	1.00		
NFKB1A, rs1050851	2	1331	1579								
CT vs CC				0.87 (0.50 – 1.48)	0.60	0.002	90%	0.56	0.84		
TT vs CC				0.88 (0.61 – 1.28)	0.51	0.52	0	0.61	0.93		
Carrier				0.87 (0.52 – 1.44)	0.58	0.002	89%	0.57	0.85		
NFKB1A, rs19571006											
AT vs AA				1.09 (0.93 – 1.27)	0.30	0.90	0	0.89	1.00		
TT vs AA				1.29 (0.67 – 2.48)	0.45	0.04	75%	0.41	0.67		
Carrier				1.09 (0.94 – 1.27)	0.24	0.61	0	0.89	1.00		
CHUK, rs2230804	2	1339	1577								
AG vs AA				0.81 (0.54 – 1.24)	0.33	0.03	78%	0.45	0.82		

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Gene, variant	Studies	Cases	Controls	OR	P	P_{het}	I^2	Power OR=1.2	Power OR=1.5	FPRP at prior probability of 0.001 OR=1.2	FPRP at prior probability of 0.001 OR=1.5
GG vs AA				0.75 (0.48 – 1.17)	0.21	0.04	75%	0.32	0.70		
Carrier				0.80 (0.52 – 1.22)	0.29	0.02	82%	0.43	0.80		
PTGES, rs10448290	2	986	1884								
AC vs AA				0.99 (0.80 – 1.23)	0.93	0.79	0	0.94	1.00		
CC vs AA				1.42 (0.61 – 3.31)	0.41	0.06	71%	0.35	0.55		
Carrier				1.01 (0.81 – 1.24)	0.96	0.48	0	0.95	1.00		
PTGES, rs2241270	2	700	5866								
AC vs AA				0.99 (0.82 – 1.20)	0.93	0.84	0	0.97	1.00		
CC vs AA				0.90 (0.48 – 1.68)	0.73	0.77	0	0.60	0.83		
Carrier				0.94 (0.82 – 1.18)	0.87	0.79	0	0.85	1.00		
PTGES, rs4837404	2	1326	1579								
AG vs AA				1.10 (0.94 – 1.29)	0.25	0.87	0	0.78	0.99		
GG vs AA				1.08 (0.85 – 1.34)	0.51	0.41	0	0.83	1.00		
Carrier				1.09 (0.94 – 1.27)	0.24	0.92	0	0.89	1.00		
HPSE, rs4693608	3	1481	6520								
GA vs GG				0.98 (0.84 – 1.14)	0.77	0.91	0	0.98	1.00		
AA vs GG				0.98 (0.82 – 1.15)	0.70	0.88	0	0.98	1.00		
Carrier				0.98 (0.85 – 1.13)	0.76	0.86	0	0.99	1.00		
HPSE, rs11099592	3	1483	6520								
GA vs GG				1.09 (0.96 – 1.24)	0.17	0.51	0	0.93	1.00		
AA vs GG				0.87 (0.66 – 1.16)	0.35	0.30	16%	0.62	0.97		
Carrier				1.06 (0.94 – 1.20)	0.34	0.39	0	0.98	1.00		
HPSE, rs436425	2	607	5302								
TC vs TT				1.00 (0.82 – 1.20)	0.97	0.60	0	0.98	1.00		
CC vs TT				0.90 (0.66 – 1.23)	0.51	0.26	21%	0.69	0.97		
Carrier				0.98 (0.83 – 1.16)	0.81	0.94	0	0.97	1.00		

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Gene, variant	Studies	Cases	Controls	OR	P	P_{het}	I^2	Power OR=1.2	Power OR=1.5	FPRP at prior probability of 0.001 OR=1.2	FPRP at prior probability of 0.001 OR=1.5
UGT1A6, rs1105879	3	1929	6774								
TC vs CC				0.96 (0.85 – 1.08)	0.46	0.40	0	0.99	1.00		
CC vs TT				1.02 (0.85 – 1.21)	0.87	0.74	0	0.97	1.00		
Carrier				0.97 (0.87 – 1.09)	0.58	0.60	0	1.00	1.00		
UGT1A6, rs2070959	3	1923	6785								
AG vs AA				0.97 (0.86 – 1.09)	0.61	0.54	0	1.00	1.00		
GG vs AA				1.07 (0.89 – 1.28)	0.49	0.66	0	0.86	1.00		
Carrier				1.77 (0.56 – 5.52)	0.33	<0.001	99%	0.25	0.39		

CI, confidence interval; OR, odds ratio