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# Meta-analysis of genetic polymorphisms and gastric cancer risk: Variability in associations according to race

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ABSTRACT

The goal of this study was to consolidate information on genetic risk factors for gastric cancer. An additional aim was to investigate the influence of race on these genetic risk associations. Relevant studies were identified from PubMed and references of retrieved articles. Meta-analysis techniques were used to summarise associations between genetic polymorphisms and gastric cancer. A total of 203 relevant studies were identified, assessing 225 polymorphisms across 95 genes. Subgroup analysis indicated that Chinese, Japanese and Korean data were consistent and could be pooled. However, 6 of 13 polymorphisms (*ACE I/D*, *CCND1 870G > A*, *CDH1 −160C > A*, *IL1B −511C > T*, *IL4 −590C > T*, *IL10 −592A > C*) displayed conflicting effects between Asian and Caucasian populations, three of which (*ACE I/D*, *CCND1 870G > A*, *IL1B −511C > T*) had significantly different odds ratios between the two racial groups. In total, 37 polymorphisms across 27 genes were found to be significantly associated with gastric cancer in Asians, and 12 polymorphisms across 11 genes in Caucasians. Consolidated panels of polymorphisms associated with gastric cancer risk were identified in Asians and Caucasians. The results caution against the assumption that genetic risk factors are consistent between races.



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## 1. Introduction

Gastric cancer remains a major public health issue as the fourth most common cancer type and as the second leading cause of cancer death worldwide.[1,2] The incidence of gastric cancer varies greatly between regions, with rates much higher in Asian and South American countries than for example in the United States. *Helicobacter pylori* (*H. pylori*) strains have been proposed as one major factor in this disparity, based on their geographical prevalence.[3] However, they do not provide a complete explanation.

The possibility that genetic polymorphisms could influence gastric cancer risk was first proposed by Ishizaki and colleagues.[4] The authors reported the correlation of *L-myc* genotypes with respect to both gastric and breast cancers. This was developed further by El-Omar and colleagues who found that pro-inflammatory genotypes of interleukin-1 polymorphisms were predictive of increased risk of gastric cancer, possibly through an exacerbation of mucosal damage.[5]

The number of association studies between genetic polymorphisms and gastric cancer has increased exponentially over the last two decades in parallel with major advances in sequencing and genotyping technology. These polymorphisms, either alone or in panels, could be useful indicators for assessing gastric cancer risk. However, the volume and diversity of studies have made it difficult to assess the accuracy and reliability of the published results. The aim of this study was therefore to consolidate the data on associations between genetic polymorphisms and gastric cancer risk, while concurrently examining the potential influence of race on these genetic risk associations.

## 2. Materials and methods

### 2.1. Identification and eligibility of relevant studies

A systematic literature search in PubMed was carried out in September 2008 using 'gastric cancer and polymorphism' with restriction to 'Human'. Additional articles were identified through references cited in retrieved articles. To ensure that all information was considered, no language restriction was applied. Publications containing the same or overlapping data from the same authors were excluded. Studies were considered as eligible for the meta-analysis if the frequency of relevant genotypes was reported in both gastric cancer cases and healthy controls. Data from review/meta-analyses were not included, as the component studies would have been included as individual studies.

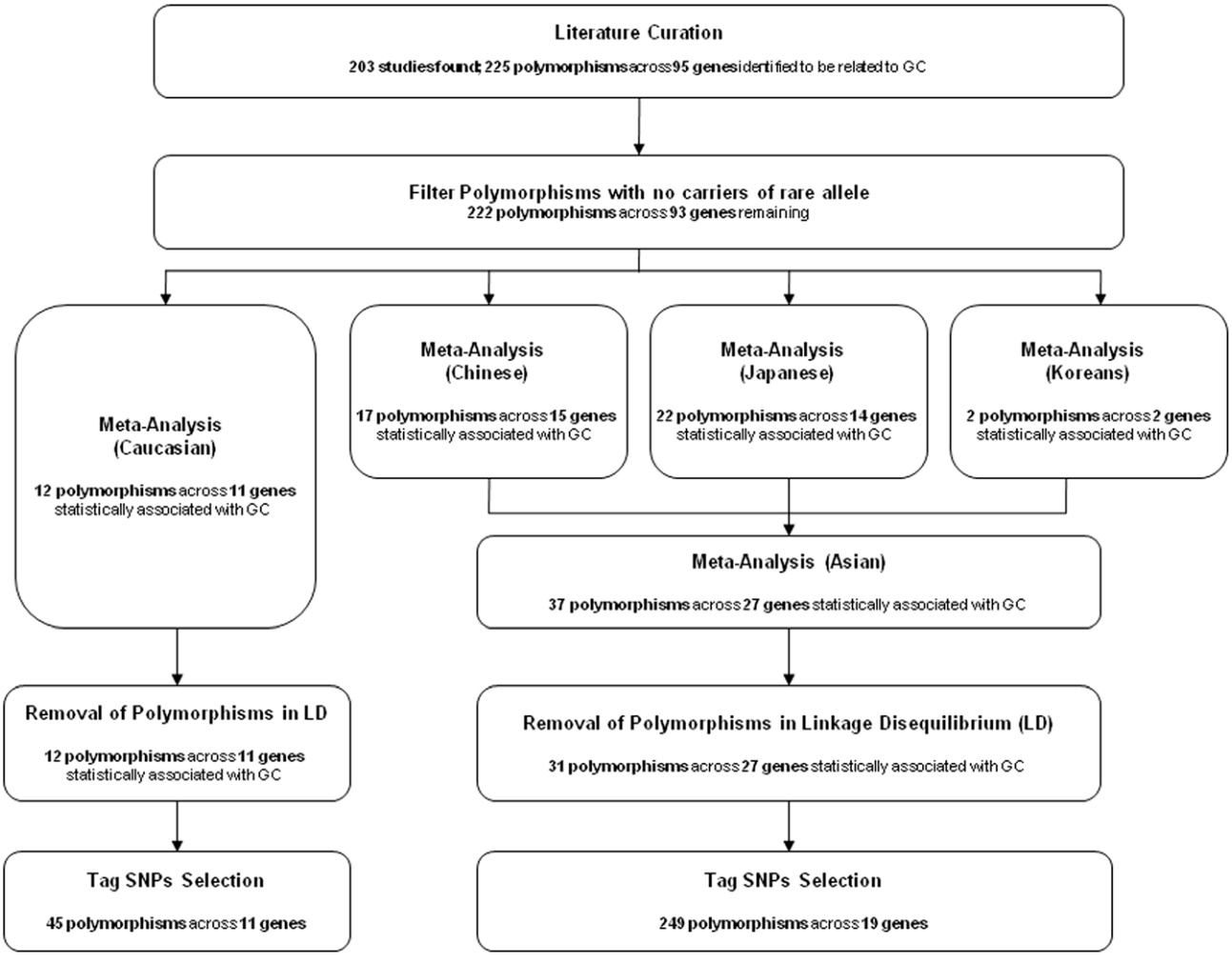


**Fig. 1 – Flowchart summarising the number of polymorphisms/genes selected at each stage of analysis.**

### 2.2. Meta-analysis

For each study, information on the first author, year of publication, race of the study population and the number of genotyped cases and controls was recorded (Supplementary Table S1). Polymorphisms were recorded in their most commonly used notation for easy cross-referencing. These were analysed separately in Chinese, Japanese, Korean and Caucasian populations, as well as across all races. In view of its diverse racial makeup, studies from the United States which did not specify racial composition were not considered in the subgroup analysis by race. These are labelled as 'US' in Supplementary Table S1. For other races such as Arab, Hispanic and African-Americans, no subgroup analysis was done as there were too few studies. However, data from these studies were still included in the analysis across all races. Analyses were performed using Review Manager 5 (The Cochrane Collaboration, Copenhagen, Denmark). Homogeneity amongst studies for the same polymorphism was assessed on the basis of the $\chi 2$ test using the *Cochran* Q statistic. The $I^2$ statistic, which measures the extent of inconsistency between studies, was also assessed. Mantel–Haenszel odds ratios (ORs) were calculated by applying the fixed effect model. In the case of between-study heterogeneity, the random effect model was applied instead. ORs were computed for each polymorphism by combining subjects with the heterozygous and the homozygous rare genotype, using the homozygous common genotype as the reference group. To check for significant

**Table 1 – Odd ratios, 95% confidence interval and the number of studies (S#) of genotypes associated with gastric cancer in Asians, and its components of Chinese, Japanese and Koreans.**

| Polymorphism | Asian | S# | Chinese | S# | Japanese | S# | Korean | S# |
|---|---|---|---|---|---|---|---|---|
| *CDH1 –160C > A* | 0.85 (0.73, 0.99)* | 8 | 0.88 (0.72, 1.08) | 4 | 0.77 (0.56, 1.06) | 2 | 0.84 (0.58, 1.22) | 2 |
| *TNF –1031T > C* | 0.99 (0.79, 1.25) | 3 | 0.87 (0.57, 1.32) | 1 | 2.17 (1.32, 3.57)* | 1 | 0.77 (0.55, 1.08) | 1 |
| *TNF –863C > A* | 0.96 (0.76, 1.22) | 3 | 0.88 (0.58, 1.35) | 1 | 1.92 (1.15, 3.23)* | 1 | 0.73 (0.51, 1.04) | 1 |
| *EGF +61A > G* | 0.78 (0.66, 0.91)* | 3 | 0.78 (0.62, 0.96)* | 1 | 0.78 (0.60, 0.99)* | 2 | | |
| *IL1B +3954C > T* | 2.08 (1.52, 2.86)* | 5 | 2.04 (1.45, 2.86)* | 4 | 2.22 (1.02, 4.76)* | 1 | | |
| *IL8 –251T > A* | 1.20 (1.04, 1.37)* | 5 | 0.88 (0.70, 1.10) | 2 | 1.45 (1.22, 1.75)* | 3 | | |
| *PPAR Pro12Ala* | 2.56 (1.42, 4.64)* | 2 | 2.51 (1.09, 5.82)* | 1 | 2.61 (1.13, 6.04)* | 1 | | |
| *CDH1 –347G > GA* | 1.52 (1.10, 2.04)* | 2 | 1.45 (1.03, 2.00)* | 1 | | | 2.00 (0.86, 4.55) | 1 |
| *IL10 –592A > C* | 1.47 (1.11, 1.96)* | 3 | 1.69 (1.20, 2.38)* | 2 | | | 1.06 (0.64, 1.79) | 1 |
| *IL10 –1082A > G* | 1.56 (1.23, 1.96)* | 6 | 1.67 (1.30, 2.13)* | 5 | | | 0.92 (0.46, 1.85) | 1 |
| *MTHFR 667C > T* | 1.11 (0.98, 1.27) | 10 | 1.23 (1.06, 1.43)* | 9 | | | 0.65 (0.39, 1.06) | 1 |
| *XRCC1 26304C > T* | 0.76 (0.59, 0.97)* | 3 | 0.81 (0.60, 1.11) | 2 | | | 0.66 (0.44, 1.00)* | 1 |
| *ECE1b –338C > A* | 1.60 (1.13, 2.27)* | 1 | 1.60 (1.13, 2.27)* | 1 | | | | |
| *FOLR1 1314A > G* | 1.54 (1.10, 2.17)* | 1 | 1.54 (1.10, 2.17)* | 1 | | | | |
| *IL4 –590C > T* | 2.50 (1.03, 5.88)* | 1 | 2.50 (1.03, 5.88)* | 2 | | | | |
| *JWA –76G > C* | 1.67 (1.19, 2.33)* | 1 | 1.67 (1.19, 2.33)* | 1 | | | | |
| *LTBP1 –509C > T* | 2.28 (1.40, 3.72)* | 1 | 2.28 (1.40, 3.72)* | 1 | | | | |
| *LTBP1 +869T > C* | 3.18 (1.87, 5.41)* | 1 | 3.18 (1.87, 5.41)** | 1 | | | | |
| *MMP2 –1306T > C* | 0.42 (0.33, 0.54)* | 2 | 0.42 (0.33, 0.54)* | 2 | | | | |
| *PARP1 Val762Ala* | 1.41 (1.16, 1.69)* | 2 | 1.41 (1.16, 1.69)* | 2 | | | | |
| *RAGE Gly82Ser* | 1.49 (1.07, 2.08)* | 1 | 1.49 (1.07, 2.08)* | 1 | | | | |
| *SHMT 1420C > T* | 1.82 (1.23, 2.63)* | 1 | 1.82 (1.23, 2.63)* | 1 | | | | |
| *TIMP2 –418G/C* | 1.52 (1.02, 2.28)* | 1 | 1.52 (1.02, 2.28)* | 1 | | | | |
| *ALDH2 MboII* | 2.50 (1.04, 6.25)* | 1 | | | 2.50 (1.04, 6.25)* | 1 | | |
| *CMA –1903G > A* | 2.63 (1.54, 4.55)* | 1 | | | 2.63 (1.54, 4.55)* | 1 | | |
| *CYP19A1 rs4646* | 0.66 (0.44, 1.00)* | 1 | | | 0.66 (0.44, 1.00)* | 1 | | |
| *DRD2 rs6277* | 1.82 (1.01, 3.27)* | 1 | | | 1.82 (1.01, 3.27)* | 1 | | |
| *ERBB2 Ile/Val* | 2.00 (1.32, 3.03)* | 1 | | | 2.00 (1.32, 3.03)* | 1 | | |
| *IL1A 1264C > T* | 0.55 (0.31, 0.98)* | 1 | | | 0.55 (0.31, 0.98)* | 1 | | |
| *IL1A 5953C > A* | 0.54 (0.30, 0.97)* | 1 | | | 0.54 (0.30, 0.97)* | 1 | | |
| *IL1RN –9876G > A* | 0.44 (0.24, 0.78)* | 1 | | | 0.44 (0.24, 0.78)* | 1 | | |
| *IL1RN –9739ins/del* | 0.49 (0.27, 0.88)* | 1 | | | 0.49 (0.27, 0.88)* | 1 | | |
| *IL1RN –9091A > C* | 0.44 (0.24, 0.79)* | 1 | | | 0.44 (0.24, 0.79)* | 1 | | |
| *NQO1 rs2965757* | 1.76 (1.17, 2.66)* | 1 | | | 1.76 (1.17, 2.66)* | 1 | | |
| *NQO1 rs689456* | 1.54 (1.02, 2.31)* | 1 | | | 1.54 (1.02, 2.31)* | 1 | | |
| *STCH rs12479* | 0.66 (0.47, 0.93)* | 1 | | | 0.66 (0.47, 0.93)* | 1 | | |
| *STCH rs1882881* | 1.54 (1.06, 2.22)* | 1 | | | 1.54 (1.06, 2.22)* | 1 | | |
| *STCH rs2242661* | 1.52 (1.05, 2.17)* | 1 | | | 1.52 (1.05, 2.17)* | 1 | | |
| *STCH rs9982492* | 0.65 (0.46, 0.93)* | 1 | | | 0.65 (0.46, 0.93)* | 1 | | |
| *GTF2A1 rs1864169* | 0.72 (0.52,1.00)* | 1 | | | | | 0.72 (0.52, 1.00)* | 1 |

Odds ratio describes risk of AA versus AB + BB, where A is the most frequent and B is the less frequent allele. Only studies in which respective genotypes that were significantly associated with gastric cancer in at least one ethnic population are displayed. Genotypes that were not significant in Asians or any one of Chinese, Japanese or Korean populations are displayed in Supplementary Tables S2–S4.

* *p*-Value < 0.05.

differences between races, the 95% confidence intervals of the odds ratio were compared. If the confidence intervals did not overlap, the two odds ratio were significantly different at the 10% level (since $1 - (0.95 * 0.95) \approx 0.9$).

Funnel plots as well as Begg's tests[6] were used to check for publication bias in the case of polymorphisms that were reported in 20 or more studies, as these methods typically do not work well with sample sizes of less than 20.[7] Publication bias was considered significant when the *p*-value was less than 0.1.[8]

In cases where two or more polymorphisms in the same gene were found to be significantly associated with gastric cancer, linkage disequilibrium (*D'*) was assessed.[9] In the calculation of a polymorphism panel, only the variant with the

**Table 2 – Odd ratios, 95% confidence interval and the number of studies (S#) of all genotypes significantly associated with gastric cancer in all studies, and its components of studies on Asians and Caucasian.**

| Polymorphism | All | S# | Caucasian | S# | Asian | S# |
|---|---|---|---|---|---|---|
| *ACE I/D* | 1.19 (0.79, 1.82) | 2 | 4.03 (1.61, 10.06)* | 1 | 0.74 (0.44, 1.22) | 1 |
| *CCND1 870G > A* | 1.05 (0.79, 1.39) | 2 | 1.85 (1.14, 3.03)* | 1 | 0.77 (0.54, 1.10) | 1 |
| *CDH1 –160C > A* | 0.98 (0.87, 1.11) | 14 | 1.18 (0.98, 1.43) | 5 | 0.85 (0.73, 0.99)* | 8 |
| *IL1B –511C > T* | 1.10 (1.02, 1.18)* | 38 | 1.29 (1.15, 1.46)* | 13 | 0.97 (0.88, 1.07) | 21 |
| *IL1B +3954C > T* | 1.22 (1.08, 1.39)* | 13 | 1.06 (0.91, 1.23) | 5 | 2.08 (1.52, 2.86)* | 5 |
| *IL1RN 86-bp VNTR* | 1.19 (1.09, 1.30)* | 34 | 1.33 (1.17, 1.52)* | 9 | 1.00 (0.86, 1.18) | 15 |
| *IL4 –590C > T* | 1.06 (0.84, 1.35) | 4 | 0.83 (0.62, 1.12) | 1 | 2.50 (1.03, 5.88)* | 2 |
| *IL10 –592A > C* | 1.12 (0.95, 1.31) | 8 | 0.97 (0.76, 1.23) | 2 | 1.47 (1.11, 1.96)* | 3 |
| *IL10 –1082A > G* | 1.16 (1.00, 1.35)* | 12 | 1.05 (0.82, 1.36) | 3 | 1.56 (1.23, 1.96)* | 6 |
| *MMP2 –1306T > C* | 0.47 (0.38, 0.59)* | 3 | 0.88 (0.51, 1.54) | 1 | 0.42 (0.33, 0.54)* | 2 |
| *MTHFR 667C > T* | 1.20 (1.08, 1.33)* | 19 | 1.45 (1.16, 1.79)* | 5 | 1.11 (0.98, 1.27) | 11 |
| *TIMP2 –418G > C* | 1.53 (1.03, 2.29)* | 2 | 2.17 (0.13, 33.33) | 1 | 1.52 (1.02, 2.28)* | 1 |
| *TNF –308G > A* | 1.19 (1.06, 1.32)* | 22 | 1.28 (1.09, 1.52)* | 7 | 1.08 (0.90, 1.27) | 11 |
| *ADH1C Ile349Val* | 0.37 (0.20, 0.68)* | 1 | 0.37 (0.20, 0.68)* | 1 | | |
| *EPHX1 –28T > C* | 1.23 (0.97, 1.59) | 2 | 1.89 (1.47, 2.38)* | 2 | | |
| *IFNGR2 –128T > C* | 1.56 (1.09, 2.27) | 1 | 1.56 (1.09, 2.27)* | 1 | | |
| *IL6 –174G > C* | 1.14 (0.80, 1.61) | 2 | 1.96 (1.09, 3.45)* | 1 | | |
| *SULT1A1 638G > A* | 1.41 (1.01, 2.00)* | 2 | 1.41 (1.01, 2.00)* | 2 | | |
| *TNF –1210T > C* | 0.71 (0.51, 0.99)* | 1 | 0.71 (0.51, 0.99)* | 1 | | |
| *ALDH2 MboII* | 2.50 (1.04, 6.25)* | 1 | | | 2.50 (1.04, 6.25)* | 1 |
| *CDH1 –347G > GA* | 1.52 (1.10, 2.04)* | 2 | | | 1.52 (1.10, 2.04)* | 2 |
| *CMA –1903G > A* | 2.63 (1.54, 4.55)* | 1 | | | 2.63 (1.54, 4.55)* | 1 |
| *CYP19A1 rs4646* | 0.66 (0.44, 1.00)* | 1 | | | 0.66 (0.44, 1.00)* | 1 |
| *DRD2 rs6277* | 1.82 (1.01, 3.27)* | 1 | | | 1.82 (1.01, 3.27)* | 1 |
| *ECE1b –338C > A* | 1.60 (1.13, 2.27)* | 1 | | | 1.60 (1.13, 2.27)* | 1 |
| *EGF +61A > G* | 0.78 (0.66, 0.91)* | 3 | | | 0.78 (0.66, 0.91)* | 3 |
| *ERBB2 Ile/Val* | 2.00 (1.32, 3.03)* | 1 | | | 2.00 (1.32, 3.03)* | 1 |
| *FOLR1 1314A > G* | 1.54 (1.10, 2.17)* | 1 | | | 1.54 (1.10, 2.17)* | 1 |
| *GTF2A1 rs1864169* | 0.72 (0.52, 1.00)* | 1 | | | 0.72 (0.52, 1.00)* | 1 |
| *IL1A 1264C > T* | 0.55 (0.31, 0.98)* | 1 | | | 0.55 (0.31, 0.98)* | 1 |
| *IL1A 5953C > A* | 0.54 (0.30, 0.97)* | 1 | | | 0.54 (0.30, 0.97)* | 1 |
| *IL1RN –9876G > A* | 0.44 (0.24, 0.78)* | 1 | | | 0.44 (0.24, 0.78)* | 1 |
| *IL1RN –9739ins/del* | 0.49 (0.27, 0.88)* | 1 | | | 0.49 (0.27, 0.88)* | 1 |
| *IL1RN –9091A > C* | 0.44 (0.24, 0.79)* | 1 | | | 0.44 (0.24, 0.79)* | 1 |
| *IL8 –251T > A* | 1.15 (1.01, 1.33)* | 7 | | | 1.20 (1.04, 1.37)* | 5 |
| *JWA –76G > C* | 1.67 (1.19, 2.33)* | 1 | | | 1.67 (1.19, 2.33)* | 1 |
| *LTBP1 –509C > T* | 2.28 (1.40, 3.72)* | 1 | | | 2.28 (1.40, 3.72)* | 1 |
| *LTBP1 +869T > C* | 3.18 (1.87, 5.41)* | 1 | | | 3.18 (1.87, 5.41)* | 1 |
| *NQO1 rs2965757* | 1.76 (1.17, 2.66)* | 1 | | | 1.76 (1.17, 2.66)* | 1 |
| *NQO1 rs689456* | 1.54 (1.02, 2.31)* | 1 | | | 1.54 (1.02, 2.31)* | 1 |
| *PARP1 Val762Ala* | 1.41 (1.16, 1.69)* | 2 | | | 1.41 (1.16, 1.69)* | 2 |
| *RAGE Gly82Ser* | 1.49 (1.07, 2.08)* | 1 | | | 1.49 (1.07, 2.08)* | 1 |
| *SHMT 1420C > T* | 1.82 (1.23, 2.63)* | 1 | | | 1.82 (1.23, 2.63)* | 1 |
| *STCH rs12479* | 0.66 (0.47, 0.93)* | 1 | | | 0.66 (0.47, 0.93)* | 1 |
| *STCH rs1882881* | 1.54 (1.06, 2.22)* | 1 | | | 1.54 (1.06, 2.22)* | 1 |
| *STCH rs2242661* | 1.52 (1.05, 2.17)* | 1 | | | 1.52 (1.05, 2.17)* | 1 |
| *STCH rs9982492* | 0.65 (0.46, 0.93)* | 1 | | | 0.65 (0.46, 0.93)* | 1 |
| *XRCC1 26304C > T* | 0.78 (0.61, 0.98)* | 4 | | | 0.76 (0.59, 0.97)* | 3 |
| *PPAR Pro12Ala* | 2.56 (1.42, 4.64)* | 2 | | | 2.56 (1.42, 4.64)* | 2 |

Odds ratio describes risk of AA versus AB + BB, where A is the most frequent allele and B is the less frequent. Only studies in which respective genotypes were significantly associated with gastric cancer in at least one ethnic population are displayed. Genotypes that were not significant in either Asians or Caucasians are displayed in Supplementary Tables S5 and S6.

* *p*-Value < 0.05.

higher OR amongst those in linkage disequilibrium was listed. All statistical tests were conducted at the 5% significance level unless otherwise stated.

## 3. Results

A total of 610 studies were found using PubMed, of which 203 independent studies describing 225 polymorphisms across 95 genes were considered relevant. A genome-wide association study[10] was excluded from subsequent analysis as it was inconsistent with the candidate gene approach of the other case–control association studies. The odds ratio for three polymorphisms (*NAT2 191G > A*, *TLR4 Asp299Gly*, *TLR4 Thr399Ile*) could not be computed as there were no subjects with the homozygous rare or heterozygous genotypes. Four polymorphisms (*IL1B –31T>C*, *IL1B –511C/T*, *IL1RN 86-bp VNTR* and *TNF –308G > A*) were each reported in more than 20 studies and were thus eligible for analysis of publication bias. Although funnel plots showed no obvious indication of publication bias (result not shown), Begg's test showed statistically significant bias for the *IL1B –511C/T*, *IL1RN 86-bp VNTR* and *TNF –308G > A* polymorphisms.

Fig. 1 displays the workflow and the number of polymorphisms and genes selected at each stage of the study. Table 1 shows polymorphisms that were significantly associated with gastric cancer in Chinese, Japanese or Korean populations. Supplementary Tables S2–S4 show the odds ratios for polymorphisms that were not significant in any of these three Asian subpopulations, respectively. For the 12 polymorphisms that were investigated in more than one Asian subpopulation, 5 (*TNF –1031T > C*, *TNF –863C > A*, *IL8 –251T > A*, *IL10 –1082A > G* and *MTHFR 667C > T*) presented some degree of conflict between the subpopulations. However, this difference was only significant for *IL8 –251T > A*, indicating that in general it was reasonable to pool studies from Chinese, Japanese and Koreans to form an Asian group providing more statistical power.

Table 2 lists polymorphisms that were significantly linked to gastric cancer in Asians and Caucasians, as well as the combined ORs from all series. For polymorphisms that were not significant in Asians or Caucasians, the ORs are shown in Supplementary Tables S5 and S6, respectively. Amongst the 13 polymorphisms that were investigated in both Asians and Caucasians, six (*ACE I/D*, *CCND1 870G > A*, *IL1B –511C > T*, *CDH1 –160C > A*, *IL4 –590C > T* and *IL10 –592A > C*) appeared to have different effects in the two populations, of which the first three had significantly different ORs between the two races. Fig. 2 presents the forest plot of the studies on Asians and Caucasians for one of these polymorphisms, *IL1B –511C > T*, demonstrating non-overlapping overall ORs.

No polymorphisms were found to be in linkage disequilibrium for the Caucasian list. For the Asian list, polymorphisms within *CDH1*, *LTBP1* and *STCH* were in nearly complete linkage disequilibrium. Therefore, only the most significant polymorphisms (*CDH1 –160C > A*, *LTBP1 +869T > C*, *STCH rs9982492*) were chosen for subsequent analyses. We were unable to determine whether polymorphisms within *IL1A*, *IL1RN* and *NQO1* were in linkage disequilibrium as there was only one study on these. No haplotype data were provided in the publications and attempts to contact authors for details were unsuccessful. Therefore, these polymorphisms remained in the list.

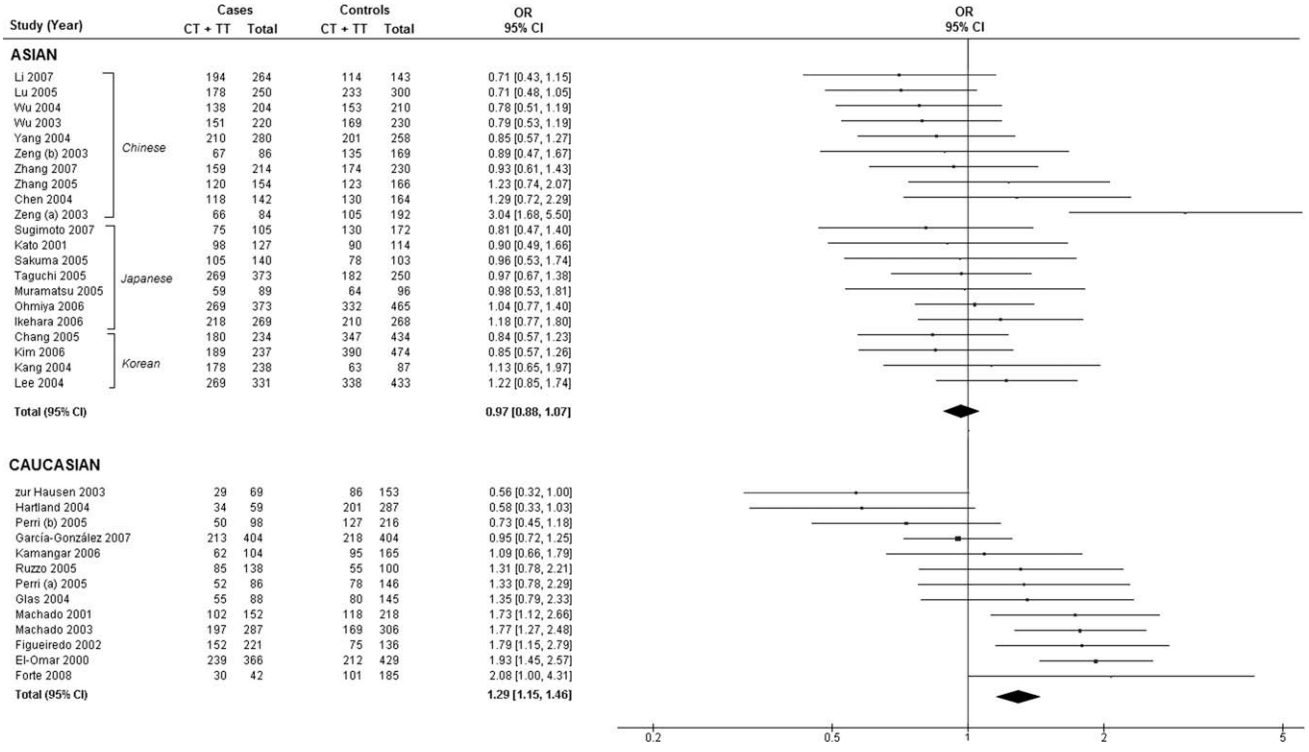


**Fig. 2 – Forest plot of *IL1B –511C > T* and gastric cancer risk. The component studies are sorted according to ascending sample size for each race.**

## 4. Discussion

The contribution of a single genetic polymorphism to the risk of a complex disease such as cancer is unlikely to be significant. A multigenic approach has proven effective in the preliminary studies for breast and prostate cancers where genotype combinations were able to predict risk with greater sensitivity than any single genotype.[11,12] For gastric cancer, there have been 15 meta-analyses on risk and polymorphisms to date, all confined to single gene or pathway polymorphisms. Recently, a meta-analysis of published meta-analyses on the contribution of gene polymorphisms to the cancer risk across all cancer types was also reported.[13]

The focus of the current work was to comprehensively summarise the results of published case–control association studies on all polymorphisms investigated to date in gastric cancer. In total, 203 studies describing 255 polymorphisms across 95 genes were reviewed. By not applying English language restriction in the search, three additional studies published in Chinese with a total of 514 cases and 1531 controls were retrieved. Two panels of polymorphisms that were significantly associated with gastric cancer were identified, one comprising 37 polymorphisms in 27 genes for Asians and the other 12 polymorphisms in 11 genes for Caucasians. This should be a useful reference for future candidate studies into genetic polymorphisms and gastric cancer risk.

A major finding of our study was the differing associations of certain polymorphisms with the risk of gastric cancer according to race. Almost half the polymorphisms investigated in both Asian and Caucasian populations showed differences in risk associations, whereas the associations within the three Asian subpopulations (Chinese, Japanese and Koreans) were generally found to be consistent. Indeed, many polymorphisms that were significant in Asian or Caucasian cohorts were no longer significant following analysis of the combined populations (Table 2). There have been reports of similar conflicting risk associations according to race for other health conditions, although these reports are rare. In a family-based study, three polymorphisms in neuropeptide S receptor 1 (*NPSR1*) were associated with under-transmission of minor asthma-linked alleles in Hispanics, but with over-transmission in Caucasians.[14] Similarly, a tumour necrosis factor superfamily member 15 (*TNFSF15*) haplotype was associated with lower risk of inflammatory bowel disease in non-Jewish, but not in Jewish, individuals.[15] These findings, together with the results from the current meta-analysis, provide accumulating evidence cautioning against the combination of results from different races. Some of the conflicting risk associations could also potentially provide an explanation for the variability in gastric cancer incidence between races.

A total of 34 studies investigated the *IL1B* –*511C* > *T* polymorphism in Asian and Caucasian populations. Strong evidence was obtained for an ethnic difference in risk for gastric cancer associated with this polymorphism (Fig. 2), as well as another in *IL1B* (*+3954C* > *T*). An earlier meta-analysis that included fewer studies reported similar results for the -*511C* > *T* polymorphism, but found no difference for *+3954C* > *T*.[16] One possible biological explanation for the ethnic difference in gastric cancer risk associated with the *IL1B* polymorphisms could be the varying *H. pylori* infection rates between Asians and Caucasians.[17]

Apart from race, the influence of factors such as *H. pylori* infection status, *tumour* location and histopathological subtypes (intestinal and diffuse) would also have been interesting to investigate. Conflicting results had been reported on the possible effect of *H. pylori* status in modifying the contribution of polymorphisms to gastric cancer risk.[18–20] Similarly, several studies found no significant differences in genotype distribution according to diffuse and intestinal histological subtypes,[21–24] while others reported significant association in one but not in the other subtype.[25,26] However, insufficient studies reported on genotype distribution according to *H. pylori* status, tumour location or histological subtype to allow us to investigate this further. These limitations were reported previously in the past studies that have attempted to determine the interaction of *H. pylori* with genetic risk factors.[27]

It is important to note that this study encountered difficulties that are common to most meta-analyses. Begg's test indicated that there was publication bias for 3 of 4 polymorphisms eligible for analysis. Nevertheless, this may not be a major issue as it has been shown that publication bias did not affect the conclusions in more than 90% of meta-analyses.[28] Also, due to the lack of homozygotes for rare alleles for some of the polymorphisms investigated, only the odds ratios comparing wild-type homozygotes with carriers of the minor allele were calculated. A further limitation of our study is the possibility of Type I and Type II errors. These could arise due to small sample sizes and limited number of component studies for some polymorphisms.

In conclusion, we have summarised here the significance of all the previously reported polymorphisms for their association with gastric cancer, with specific consideration towards race. Our results provide evidence that race can have a significant influence on the risk of gastric cancer associated with some polymorphisms. The integration of race-specific genetic risk markers into strategies for the early detection of gastric cancer holds great promise. It has been estimated that early detection could contribute up to 76% of improvements in survival compared to other advances in the management of this disease.[29] Future prospective studies testing the value of genetic risk panels such as those identified in this study will reveal the potential of these approaches.

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## Conflict of interest statement

None declared.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2009.03.017.

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