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Genetic Variant rs1800795 (G>C) in the Interleukin 6 (*IL6*) Gene and Susceptibility to Coronary Artery Diseases, Type 2 Diabetes, Acute Pancreatitis, Rheumatoid Arthritis, and Bronchial Asthma in Asians: A Comprehensive Meta-Analysis Based on 30154 Subjects

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Abstract: Numerous studies conducted globally have explored the possible connection between the *IL6* gene variant rs1800795 (G>C) and the risk of several diseases. Nonetheless, the correlation specifically within the Asian population remains inconclusive. Hence, this extensive meta-analysis aims to establish a conclusive correlation between the rs1800795 variant and susceptibility to various diseases among Asians. Fifty eligible articles were chosen from Google Scholar, PubMed, Web of Science, and PMC based on specific inclusion criteria. Odds ratios alongside 95% confidence intervals (CI) were utilized. Additionally, subgroup analysis, publication bias, and sensitivity evaluation were conducted. The analysis, of 14,737 cases and 15,417 controls, showed a notable correlation between the rs1800795 (G>C) single-nucleotide polymorphism and the overall disease susceptibility to all models (p-value <2.5E-05). The ethnicity-specific stratified findings indicated that the C-allele of (C vs. G) model of −174G/C polymorphism expressively elevated the overall disease susceptibility in both East and South Asian populations. The disease-based stratified analyses suggested that the C variant of rs1800795 was related to coronary artery diseases and bronchial asthma (under all models), type 2 diabetes (CG vs. GG), acute pancreatitis (AP) (C vs. G; and CC vs. GG), rheumatoid arthritis (CC+CG vs. GG; CC vs. CG+GG; and C vs. G), and AP (C or CC vs. G or GG respectively). *IL6* rs1800795 polymorphism is a highly significant disease risk factor in Asians and can potentially serve as a prognostic biomarker for future disease screening and evaluation.

Keywords: rs1800795, meta-analysis, Asian, CAD, rheumatoid arthritis

1. Introduction

Multiple factors, including genetic, behavioral, physiological, demographic, and environmental components, collectively influence the emergence of human illnesses. The likelihood of having a specific disease is influenced partially or entirely by genetic variations, which can lead to developing genetic disorders. Therefore, understanding the functioning of genes with genetic disorders is of utmost importance. Interleukin 6 (*IL6*) gene codes a cytokine playing essential roles in the cells' immunity and tissue regeneration, while also possessing the capacity to trigger diverse innate and acquired immune reactions [1]. The molecular characteristics of the *IL6* gene have been recognized as a potential clinical target for neoplastic, autoimmune, infectious, and viral disorders, including the emerging COVID-19 [2, 3]. The *IL6* in humans, on chromosome 7p15.3, at the –174 of the promoter region, contains a single-nucleotide polymorphism (SNP) rs1800795 (G>C), which has a significant impact on the levels of expression of this important cytokine [4, 5]. *IL6* is a key player in activating immunological pathways and maintaining inflammatory processes, among the pro-inflammatory cytokines [5, 6].

Globally, in different populations, the *IL6* gene rs1800795 G/ C variation has been widely explored as a biomarker linked with increasing disease risks through genetic studies [3, 7, 8]. Also, some earlier studies explored the link between the rs1800795 (G>C) SNP and the probability of various disorders in Asians. However, these studies reported conflicting findings, leading to ambiguities in the results [3, 9–30]. For coronary artery diseases

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(CADs), several studies reported that the rs1800795 SNP was significantly associated [9, 12, 13, 15, 17, 19–22, 24, 25, 27, 29, 30], while others did not find any such association [10, 11, 14–16, 18, 22, 23, 26, 28]. Similarly, for Asians, ischemic stroke (IS): a study by Chakraborty et al. [31] indicated a notable correlation, while subsequent research did not find any link [32–34]; for rheumatoid arthritis (RA), some researchers reported a significant association [35–37] and others reported not [38, 39]. Also, type 2 diabetes (T2D) was significantly associated with the Asian population [40–43], whereas others claimed no association [44, 45]. The *IL6* gene rs1800795 polymorphism was significantly associated with bronchial asthma (BA) [46, 47] and showed no significant association with acute lung injury (ALI) [48], acute pancreatitis (AP) [49–51], and bronchopulmonary dysplasia (BPD) in Asians [52]. The ambiguity in results might be due to diversity in research design, variations in the sample size, and overall operational quality. Furthermore, earlier investigations included single-case meta-analyses on a global scale, examining the correlation between the *IL6* rs1800795 SNP and individual diseases such as CADs [53–56], type 1 diabetes [57], T2D [58, 59], BA [60], AP [61], inflammatory conditions [62], RA [63], and IS [7]. Nonetheless, the link between the rs1800795 SNP and various diseases, and an overall assessment of disease risk in Asians, remains inconclusive.

IL6 is one of the significant contributing mediators for obesity and related inflammatory disorders and cancer [64]. In this research, we aimed to conduct a thorough assessment of the overall disease risk linked with the *IL6* gene rs1800795 (−174G/C) polymorphism, as well as its correlation with inflammatory disorders related to obesity in the Asian population. Here, we conducted an enhanced and extensive meta-analysis using multi-statistical methods. We analyzed the genetic variant data from 14,737 cases and 15,417 controls to quantitatively assess the possible correlation between the −174G>C SNP of *IL6* and the likelihood of different diseases among the Asian population.

2. Methods

2.1. Literature searching strategy

The online literature resources, such as Google Scholar, PubMed, PMC, and Web of Science were mined for suitable research papers that were available till March 2023 on the Asian populations only. The dataset was compiled using the following search terms: "−174G/C," "−174G>C, rs1800795," "diseases," "−174G>C, disorders," "*IL6*, Acute pancreatitis," "*IL6*, coronary artery disease," "*IL6*, Bronchial asthma," "*IL6*, T2D," "*IL6*, Inflammatory diseases," "*IL6*, T1D," "*IL6*, Ischemic stroke," "*IL6*, Rheumatoid arthritis," and "association, *IL6*, disease" and additionally reviewed the bibliography of the pertinent publications that examined the same goals.

2.2. Exclusion–inclusion criteria

In this meta-analysis, the primary criteria for inclusion were: (i) the research engaged a case–control design, (ii) it provided genotyping distributions, and (iii) it was conducted in the English language. Only studies meeting these core inclusion criteria were incorporated into the analysis. All other studies including reviews, studies using animal models, meta-analyses, and articles not in English were excluded from further analysis.

2.3. Data mining

The information gathered during the research encompassed several key variables, including the publication year, author's identity, disease category, and country of origin, sample sizes for the case and control groups, along with the genotypic frequencies for both sets. This study was particularly centered on datasets related to Asian populations and further stratified into East Asian and South Asian subgroups. The authors individually conducted data extraction and verification procedures.

2.4. Quality assessment

Each of the studies comprised in this work underwent quality evaluation by the Newcastle–Ottawa scale (NOS) [65]. An accumulative score of nine points was assigned by NOS to evaluate the quality of individual studies. Scores can range from 0 to 9, with studies scoring between 0 and 3 considered poor, those scoring between 4 and 6 categorized as fair, and those scoring between 7 and 9 classified as excellent in terms of quality. In this meta-analysis, we identified 10 studies with fair quality assessments, while the remaining 40 studies were deemed to be of excellent quality (Supplementary file, Table S1).

2.5. Statistical evaluation

To reach a unanimous decision regarding the correlation of the *IL6* gene −174 (G>C) SNP and various disease possibilities, an extensive statistical meta-analysis was performed that integrated all the individual genetic studies encompassed in this research. The precision of all individual studies included was measured by the test for Hardy–Weinberg equilibrium (HWE). The Chi-square value was employed to conduct a HWE assessment, aimed to check the congruence of genotypic ratios between the control groups. An eligible meta-analysis was determined when the p-value was 0.05 or higher. To enhance the impact, we employed the combined odds ratio (OR) along with a 95% confidence interval (CI). The combined outcomes were predicted utilizing either the random effect (RE) or fixed effect (FE) models, as described by Harun-Or-Roshid et al. [8], depending on the assessment of heterogeneity. Heterogeneity among the chosen individual studies was quantified via Cochran's Q-test and the enhanced Higgins and Thompson I^2 metric [8, 66, 67]. Significant variability was characterized by the Q-test p-value < 0.10 and an I^2 value exceeding 50%. In cases of substantial heterogeneity, the RE model was employed to determine the combined effect. For cases of smaller heterogeneity, the FE model was applied. Furthermore, a goodness-of-fit (GoF) examination was led to evaluate the appropriateness of both the RE and FE models when the number of studies exceeded 7. This GoF test involved three normality assessments: Cramer–von Mises (CvM), Shapiro–Wilk (SW), and Anderson–Darling (AD), as suggested by Chen et al. [68]. The combined ORs for the RE and FE models were assessed using the Mantel–Haenszel and inverse variance methods [69]. We evaluated the connection between the datasets by employing a set of five distinct genetic prototypes: (a) Dominant (CC + CG *vs.* GG); (b) Recessive (CC *vs.* CG + GG); (c) Allelic (C *vs.* G); (d) Homozygote (CC vs. GG); and (e) the Heterozygote (CG vs. GG) models. Forest plots illustrated the link between polymorphisms and susceptibility to diseases. Forest plots were used to depict the connection between genetic variations and vulnerability to diseases. Moreover, we investigated the association through subgroup analyses, classifying them according to type of

disease and ethnic background. To examine the presence of publication bias, we utilized a combination of qualitative evaluation, employing the funnel plot, and quantitative analysis through Begg's and/or Egger's linear regression tests. If the *p*-values from these tests exceeded 0.05, we considered no trace of publication bias. Furthermore, we ensured the reliability of the meta-analysis by excluding datasets that did not adhere to the criteria for HWE. A brief overview of the statistical discourse needed for performing a meta-analysis was provided by Harun-Or-Roshid et al. [70]. All mathematical calculations were performed employing the "meta" package in R (version R64 3.5.2) software [71].

3. Results

3.1. The attributes of studies encompassed

From the initial literature search, 987 articles on the *IL6* gene rs1800795 polymorphism were retrieved. After applying exclusion and inclusion criteria and eliminating duplicates identified through reading titles and abstracts, a total of 73 studies, presented in full text, were chosen for additional assessment. Subsequently, 24 studies were excluded due to limitations in the full-text articles or incomplete information. Ultimately, 50 full-text papers containing case–control datasets, which included 14,737 cases and 15,417 controls, were selected for data extraction to perform this meta-analysis. The complete process of study selection adhered to the PRISMA statement [72] and is depicted in Figure 1. The combined analysis of the 50 included datasets [9–45, 48–52, 62] was pooled together including 3 studies of AP [49–51], 2 for BA [44, 45], 27 for CAD [9–30], 5 for RA [35–37], 6 for T2D [38–43], 4 for IS [31–34], and 3 for 'Other' diseases [48, 52, 62] (incorporating one study for each of the following: BPD, ALI, and inflammatory bowel diseases). The dataset comprised 29 East Asian populations and 21 South Asian populations in terms of ethnicity. The genomic allele distribution of the group serving as the controls was examined by the HWE equilibrium test where 41 studies were found HWE positive and 9 studies failed HWE. Despite some studies demonstrating a negative response to the HWE test, we examined the effects of all the studies on the polled estimate. Table 1 provides the specific details and attributes of incorporated studies.

3.2. Quantitative assessments

The collective findings of this research were presented in Table 2. The meta-analysis summary results on the correlation between SNP variant and diseases were customized with ORs, 95% CI, and Z-test probability scores, and the significant p-value < 0.05 was highlighted in bold. The outcomes of the association of *IL6* rs1800795 G/C polymorphism were stratified based on the overall disease, subgroup disease, subpopulation, and HWE test-satisfied groups. The findings of this research illustrated a robust correlation between the *IL6* rs1800795 (G>C) variant and the susceptibility to disease or disorder in all genetic prototypes [(CG *vs.* GG) (OR 1.33, 95% CI: 1.17–1.52, *p*-value 2.5E-05), (CC + CG *vs.* GG) (OR 1.40, 95% CI: 1.23–1.61, *p*-value 7.4E-07), (CC *vs.* GG) (OR 1.75, 95% CI: 1.44–2.12, *p*-value 1.4E-08), (CC *vs.* CG + GG) (OR 1.57, 95% CI: 1.30–1.90, *p*-value 3.8E-06), and (C *vs.* G) (OR 1.37, 95% CI: 1.20–1.56, *p*-value 3.9E-06)] (Figure 2, Supplementary Figures S1–S4) (Table 2). The disease-specific stratified data revealed a statistically significant link with: AP (CC *vs.* GG) (OR 1.69, 95% CI: 1.03–2.78, *p*-value 0.0389); (C *vs.* G) (OR 1.22, 95% CI: 1.01–1.48, *p*-value 0.0405) and BA (CG *vs.* GG) (OR 1.78, 95% CI: 1.41–2.25, *p*-value 1.1E-06); (CC *vs.* GG) (OR 2.79, 95% CI: 1.77–4.38, *p*-value 8.5E-06); (CC + CG *vs.* GG) (OR 1.91, 95% CI: 1.53–2.38, *p*-value 1.1E-08); (CC *vs.* CG + GG) (OR 2.25, 95% CI: 1.45–3.49; *p*-value 3.0E-04); (C *vs.* G) (OR 1.76, 95% CI: 1.47–2.10, *p*-value 6.2E-10), CAD (C *vs.* G) (OR 1.40, 95% CI: 1.29–1.53, *p*-value 8.3E-16); (CC *vs.* GG) (OR 2.04, 95% CI: 1.78–2.35, *p*-value 2.1E-24); (CG *vs.* GG) (OR 1.28, 95% CI: 1.13–1.46, *p*-value 2.0E-04); (CC + CG *vs.* GG) (OR 1.41, 95% CI: 1.25–1.58, *p*-value 8.5E-09); (CC *vs.* CG + GG) (OR 1.83, 95% CI: 1.61–2.08, *p*-value 2.3E-20), and RA (CC + CG *vs.* GG) (OR 3.05, 95% CI: 1.09–8.54, *p*-value 0.0343); (CC *vs.* CG + GG) (OR 4.62, 95% CI: 2.01–10.6, *p*-value 0.0003); and (C *vs.* G) (OR 3.0, 95% CI: 1.14–7.95, *p*-value 0.0263). However, other diseases did not show any statistical correlation with rs1800795 SNP. The ethnicity-based stratified data of −174G/C SNP exhibited an elevated risk of overall disorders in East Asians across all genetic models [(CC *vs.* GG) (OR 2.03, 95% CI: 1.75–2.37, *p*-value 1.1E-15), (CG *vs.* GG) (OR 1.35, 95% CI: 1.08–1.70, *p*-value 0.0088), (CC + CG *vs.* GG) (OR 1.46, 95% CI:1.17–1.82, *p*-value 9.0E-04), (CC *vs.* CG + GG) (OR 1.77, 95% CI: 1.47–2.12, *p*-value 1.6E-09), and (C *vs.* G) (OR 1.44, 95% CI: 1.17–1.77, *p*-value 5.0E-04)] and for three genetic models in South Asians [(CG *vs.* GG) (OR 1.30, 95% CI: 1.11–2.52, *p*-value 0.001), (CC + CG *vs.* GG) (OR 1.33, 95% CI: 1.14–1.55, *p*-value 3.0E-04), and (C *vs.* G) (OR 1.26, 95% CI: 1.08–1.48, *p*-value 3.1E-04)] (Table 2).

3.3. Sources of heterogeneity

Studies encompassing the *IL6* variant rs1800795 (G>C) showed notable heterogeneity in disease risk when considering different allelic model comparisons [(C *vs.* G model Q 170.93, df = 48, *p*-value 1.1E-15, $\tau 2 = 0.14$, $I^2 = 71.92\%$); (CC *vs.*GG: Q 83.07, df = 48, *p*-value 0.0013, $\tau 2 = 0.14$, $I^2 = 42.21\%$; CC *vs.* CG + GG: Q 130.45, df = 48, *p*-value 1.5E-09, $\tau^2 = 0.13$, $I^2 = 63.2\%$); (CC + CG *vs.* GG: Q 139.95, df = 48, *p*-value 6.3E-11, $\tau^2 = 0.14$, $I^2 = 65.7\%$); and (CG *vs.* CC + GG: Q 97.97, df = 48, *p*-value 2.8E-05, $\tau^2 = 0.15$, $I^2 = 51.0\%$)] (Supplementary file, Table S2). Here, we performed a stratified inquiry, by categorizing the data according to disease types and diverse Asian ethnic groups, to pinpoint the major roots of heterogeneity. The findings revealed that the primary sources of heterogeneity were CAD, RA, T2D, as well as the East Asian and South Asian populations (Supplementary file, Table S2).

3.4. Sensitivity test

This analysis was conducted after excluding the study that failed the HWE test. The exclusion of nine studies did not produce any significant impact on the overall association. Thus, the data obtained from this meta-analysis are deemed to be stable and resilient (Table 2).

3.5. Publication bias study

Asymmetric distribution of ORs in relation to standard error was observed for the *IL6* gene rs1800795 variant in Begg's funnel plot (Figure 3). Furthermore, both the rank correlation analysis (CC *vs.*GG model: z value −1.12, *p*-value 0.2625; C *vs.* G model: z value −0.76, *p*-value 0.4481) and Egger's linear regression analysis (CC *vs.*GG: $t = -1.38$, df = 47, *p*-value 0.1727; C vs. G: $t = -0.35$, df = 47, *p*-value 0.7314) presented proof indicating the lack of publication bias (Supplementary file, Table S3).

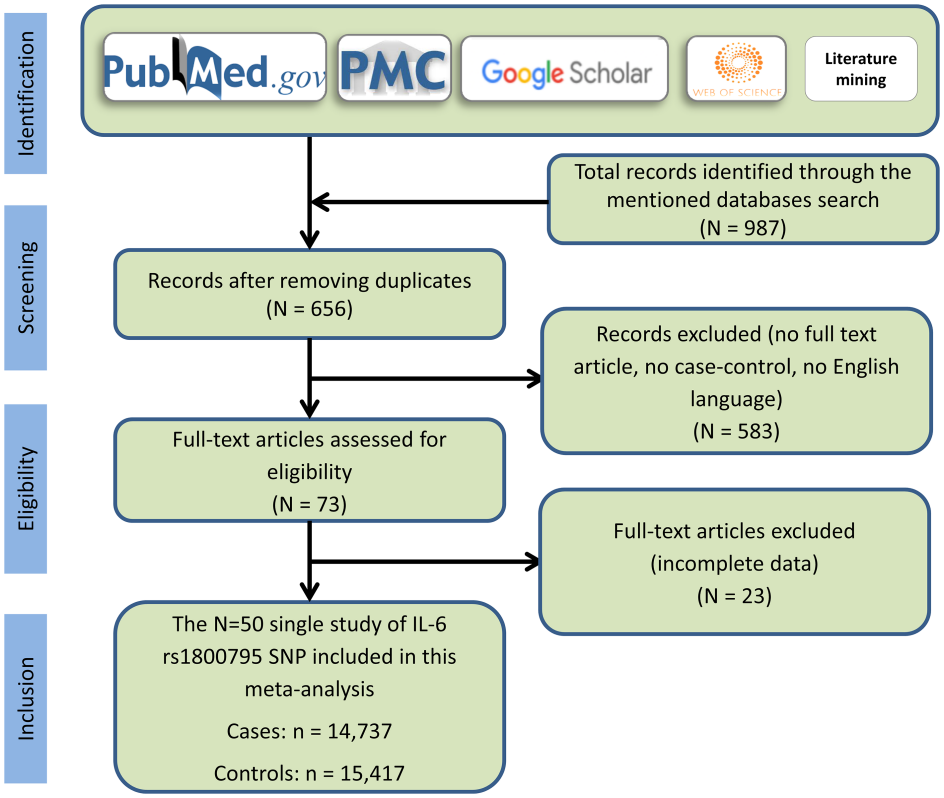

Figure 1. PRISMA flowchart depicting the comprehensive study selection procedure for *IL6* gene rs1800795 SNP in the Asian population, with "N" denoting the corresponding study number and "n" the sample sizes

4. Discussion

Interleukin-6 (*IL6*) is one of the most vital cytokines that are produced wherever there is inflammation in the body, either acute or chronic. *IL6* plays important roles in inflammation, immunity, and diseases. It has both pro- and anti-inflammatory actions [12]. Increased *IL6* levels have been linked to a range of conditions, including diabetes, RA, heart diseases, and cancer [3, 12, 28]. Recent genetic investigations have explored the potential link between the *IL6* rs1800795 polymorphism and susceptibility to various diseases, including cancer, across diverse populations [3, 8, 12, 28]. In this work, an extensive statistical meta-analysis was carried out to establish a unified link between the *IL6* gene variant rs1800795 (G>C) and the susceptibility to various inflammatory diseases in Asian populations. The collective findings from examining 50 distinct research investigations indicate a notable link among the C allele of the rs1800795 (G>C) variant and an increased vulnerability to these conditions in all five genetic models. Additionally, categorized by disease type, it became evident that the incidence of the C variant of the rs1800795 SNP significantly elevated the possibility of AP, BA, CAD, RA, and T2D. Furthermore, in the context of a subgroup analysis focusing on ethnic populations, it was observed that the rs1800795 variant C allele substantially raised the overall disease vulnerability in East Asians across all five genetic models and in South Asians for three genetic models (CC+CG *vs*. GG, CG *vs*. GG, and C *vs*. G). Hence, all findings from this study offered strong evidence supporting the link between the *IL6* gene rs1800795 SNP and an elevated risk of multiple diseases in Asian populations. Nevertheless, this meta-analysis had constraints, including (i) not accounting for all heterogeneous factors, (ii) reliance solely on studies published in English, and (iii) forming subgroups with a restricted number of studies due to the accessibility of data.

To gain a deeper comprehension of the link between C alleles and various disorders among Asians, we conducted a comparative analysis of the allelic variation of the *IL6* gene rs1800795 (−174G>C) polymorphism among the East, South, and overall Asian populations using datasets from the 1000 Genome Project Phase 3 [73] (Figure 4). Within the *IL6* gene promoter region at −174 G>C of the rs1800795 variant, the major allele is G, while C is the minor allele [74]. In genotypic interactions, when the wild-type dominant allele is missing or not expressed, then the altered/mutant allele might lead to produce some abnormal functions. The analyzed data indicated a C allele frequency of 6.9% compared to the major G allele in the overall Asian population (Figure 4, Supplementary file, Table S4). However, the subgroup stratified data indicated statistically significant variation in minor C allele frequency between East Asians (0.1%) and South Asians (13.9%) (p-value <0.0001) (Figure 4, Supplementary file, Table S5). The minor C allele frequency indicated a significant difference between East Asians and South Asians compared to the overall Asian population (p-value 0.00002 and 0.0081, respectively) (Figure 4, Supplementary file Table S5). The varied minor C allele frequency might be a risk factor for the Asian populations in association with different inflammation-related disorders. In future, further availability of different Asian case–control experimental datasets of *IL6* gene rs1800795 polymorphism in association with diseases could confirm our findings. Nonetheless, *IL6* rs1800795 G/C could serve as a valuable prognostic biomarker for early disease screening, diagnosis, and detection in the Asian population.

Table 1. Attributes of individual studies of the *IL6* rs1800795 (G>C) variant

Authors	Yr.	Country	Ethnicity	SC	Disease	Case/control	Case GG/GC/CC	Control GG/GC/CC	*p*-Value (HWE)
Du et al. [46]	2021	China	EA	HB	BA	430/862	210/176/44	554/267/41	0.231(Y)
Kamdee et al. [33]	2021	Thailand	EA	PB	IS	200/200	190/10/0	188/12/0	0.662(Y)
Zhao et al. [48]	2019	China	EA	PB	ALI	1075/1382	1045/29/1	1349/32/1	0.080(Y)
Indumathi et al. [17]	2019	India	SA	HB	CAD	265/205	163/99/3	145/57/3	0.323(Y)
Chen and Zheng [52]	2018	China	EA	PB	BPD	1022/1039	33/352/637	41/371/627	0.127(Y)
Shabana et al. [25]	2018	Pakistan	SA	PB	CAD	426/219	194/133/99	96/90/33	0.124(Y)
Chen et al. [13]	2018	China	EA	PB	CAD	429/350	155/218/56	190/133/27	0.581(Y)
Hameed et al. [40]	2018	India	SA	HB	T2D	414/477	213/156/45	280/152/45	0.001(N)
Mastana et al. [22]	2017	India	SA	HB	CAD	138/131	105/32/1	91/39/1	0.144(Y)
Ansari et al. [9]	2017	Pakistan	SA	HB	CAD	340/310	242/85/13	236/71/3	0.352(Y)
Dar et al. [38]	2017	India	SA	HB	RA	34/80	20/8/6	64/16/0	0.320(Y)
Neelofar et al. [42]	2017	India	SA	HB	T2D	50/50	28/19/3	27/20/3	0.780(Y)
Kavitha et al. [41]	2017	India	SA	HB	T2D	30/30	30/0/0	29/1/0	0.926(Y)
Lv et al. [16]	2016	China	EA	HB	CAD	275/296	256/19/0	282/14/0	0.677(Y)
Mao et al. [21]	2016	China	EA	HB	CAD	224/360	142/45/37	267/63/30	0.000(N)
Bao et al. [49]	2015	China	EA	PB	AP	335/335	202/109/24	213/106/16	0.550(Y)
Chi et al. [51]	2015	China	EA	PB	AP	272/272	159/94/19	173/88/11	0.964(Y)
Yang et al. [30]	2015	China	EA	HB	CAD	410/410	198/163/49	239/146/25	0.669(Y)
Wang et al. [29]	2015	China	EA	PB	CAD	402/402	153/171/78	182/169/51	0.234(Y)
Li et al. [19]	2015	China	EA	HB	CAD	365/365	213/113/39	245/105/15	0.382(Y)
Lu et al. [53]	2015	China	EA	HB	CAD	402/402	153/171/78	176/187/39	0.292(Y)
Sun et al. [27]	2014	China	EA	PB	CAD	296/327	191/61/44	236/63/28	0.000(N)
Galimudi et al. [15]	2014	India	SA	PB	CAD	200/200	72/102/26	113/69/18	0.123(Y)
Biswas et al. [12]	2014	India	SA	HB	CAD	500/500	348/139/13	407/92/1	0.073(Y)
Galimudi et al. [15]	2014	India	SA	HB	CAD	180/200	72/102/6	113/69/18	0.123(Y)
Li et al. [35]	2014	China	EA	HB	RA	752/798	613/124/15	786/10/2	0.000(N)
Li et al. [36]	2014	China	EA	HB	RA	256/331	247/7/2	329/1/1	0.000(N)
Shafia et al. [37]	2014	India	SA	HB	RA	150/200	122/27/1	167/30/3	0.233(Y)
Saxena et al. [43]	2014	India	SA	HB	T2D	213/145	163/46/4	105/21/19	0.000(N)
Tong et al. [28]	2013	China	EA	PB	CAD	326/341	201/87/38	220/98/23	0.011(N)
Bhanushali and Das [11]	2013	India	SA	HB	CAD	100/150	77/20/3	121/25/4	0.068(Y)
Satti et al. [24]	2013	Pakistan	SA	PB	CAD	36/52	18/11/7	38/14/0	0.262(Y)
Lu et al.[53]	2013	China	EA	HB	CAD	231/275	221/10/0	264/11/0	0.735(Y)
Mishra et al. [23]	2013	India	SA	HB	CAD	310/230	218/83/9	172/54/4	0.92(Y)
Chakraborty et al. [31]	2013	India	SA	HB	IS	100/120	57/35/8	73/39/8	0.38(Y)
You et al. [39]	2013	China	EA	HB	RA	452/373	431/21/0	357/16/0	0.672(Y)
Srikanth Babu et al. [26]	2012	India	SA	HB	CAD	651/432	134/294/223	135/206/91	0.451(Y)
Fan et al. [14]	2011	China	EA	HB	CAD	84/130	84/0/0	129/1/0	0.965(Y)
Lu et al. [53]	2011	China	EA	HB	CAD	126/150	123/3/0	148/2/0	0.934(Y)
Zhang et al. [45]	2011	China	EA	HB	T2D	512/483	510/2/0	482/1/0	0.982(Y)
Banerjee et al. [10]	2009	India	SA	HB	CAD	210/232	159/43/8	171/57/4	0.763(Y)
Liu et al. [62]	2009	China	EA	HB	IBD	60/60	46/10/4	42/16/2	0.757(Y)
Tong et al. [34]	2009	China	EA	HB	IS	748/748	747/1/0	743/5/0	0.927(Y)
Xiao et al. [44]	2009	China	EA	PB	T2D	132/85	132/0/0	85/0/0	0.000(N)
Liu et al. [47]	2008	China	EA	HB	BA	108/88	72/36/0	71/17/0	0.316(Y)
Maitra et al. [20]	2008	India	SA	PB	CAD	46/40	36/10/0	30/7/3	0.024(N)
Kuo et al. [18]	2008	China	EA	HB	CAD	58/77	27/27/4	32/32/13	0.313(Y)
Banerjee et al. [32]	2008	India	SA	HB	IS	176/212	123/53/0	156/52/4	0.89(Y)
Chen et al. [50]	2007	China	EA	PB	AP	74/78	72/2/0	77/1/0	0.955(Y)
Lu et al. [53]	2004	China	EA	HB	CAD	112/183	110/2/0	179/4/0	0.881(Y)

SC: sources of control; EA: East Asians; SA: South Asians; PB: population-based; HB: hospital-based; T2D: type 2 diabetes; IS: ischemic stroke; CAD: coronary artery diseases; BA: bronchial asthma; T1D: type 1 diabetes; BPD: bronchopulmonary dysplasia, IBD: inflammatory bowel disease; AP: acute pancreatitis; RA: rheumatoid arthritis; ALI: acute lung injury; HWE: Hardy–Weinberg equilibrium; yes (Y): passed HWE test; no (N): failed HWAE test.

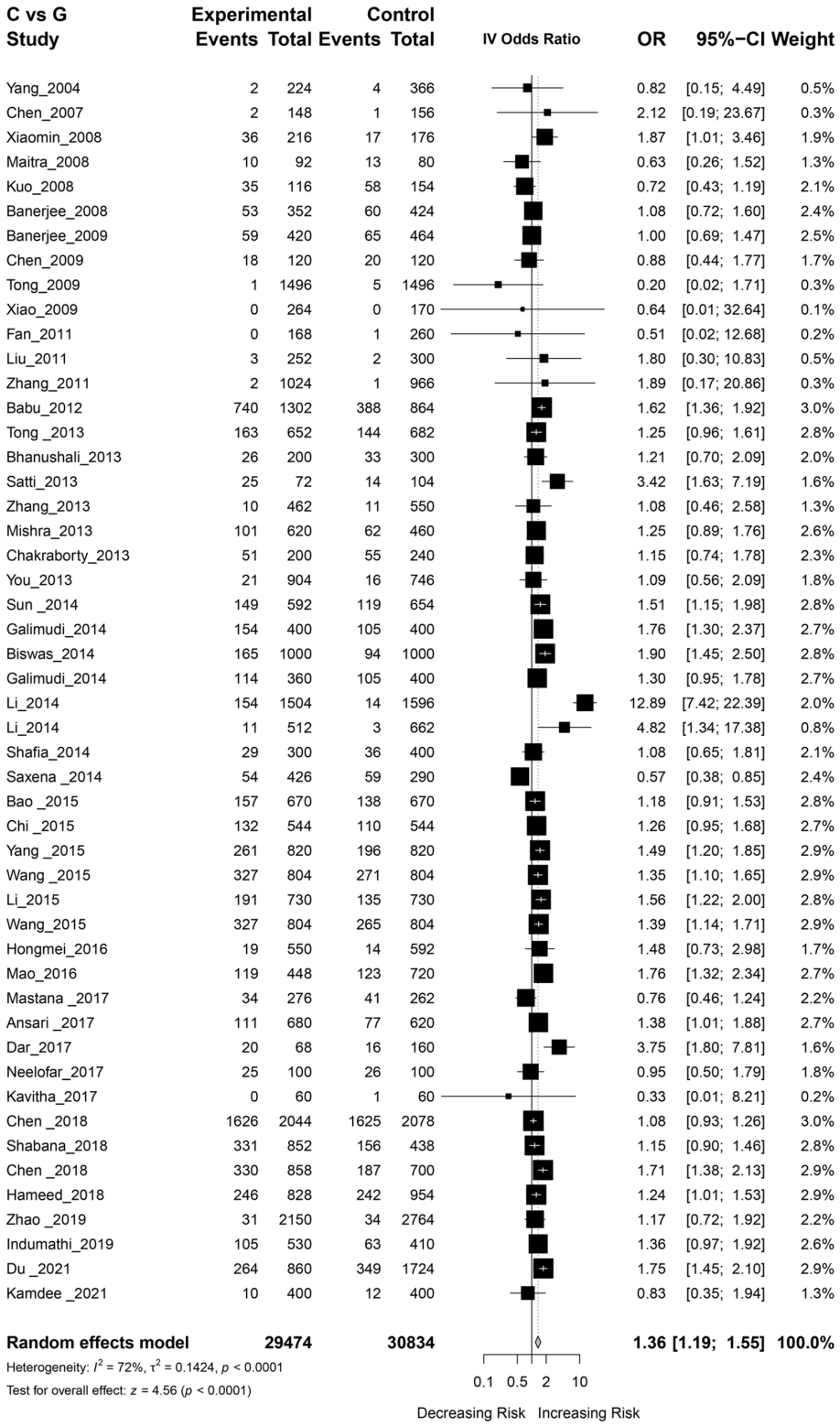

Figure 2. The link between the *IL6* gene rs1800795 variant and the overall predisposition to disease is illustrated by the allelic C *vs*. G model in a forest plot

In an earlier study, we investigated the correlation between three genetic variants (rs1800795, rs1800796, and rs1800797) within the *IL6* gene and various types of cancers. Currently, in a new study, we are examining the connection between the rs1800796 and rs1800797 SNPs and diverse neurological disorders. Therefore, it will be essential in future research to investigate the remaining two SNPs (rs1800796 and rs1800797) to obtain a comprehensive understanding of *IL6* gene variants and their relationship with disease risks among Asian populations.

Table 2. Summary results on the statistical correlation between rs1800795 (G>C) variant and its association with various diseases

Subgroups	Study No.	Sample size	CC vs. GG		CC vs. CG + GG		CC + CG vs. GG		CG vs. GG		C vs. G	
			OR (95% CI)	***p*-Value**	OR (95% CI)	***p*-Value**	OR (95% CI)	***p*-value**	OR (95% CI)	***p*-Value**	OR (95% CI)	***p*-Value**
Overall	50	30154	1.75 [1.44–2.12]	1.4E-08	1.57 [1.30–1.90]	3.6E-06	1.39 [1.22–1.59]	1.1E-06	1.32 [1.16–1.51]	3.1E-05	1.36 [1.19–1.55]	5.1E-06
Acute pancreatitis (AP)	3	1366	**1.69 [1.03–2.78]**	**0.0389**	1.63 [1.00–2.66]	0.0521	1.20 [0.95–1.51]	0.1260	1.13 [0.88–1.44]	0.3341	**1.22 [1.01–1.48]**	**0.0405**
Bronchial asthma (BA)	2	1488	**2.79 [1.77–4.38]**	**8.5E-06**	**2.25 [1.45–3.49]**	**0.0003**	**1.91 [1.53–2.38]**	**1.1E-08**	**1.78 [1.41–2.25]**	**1.1E-06**	**1.76 [1.47–2.10]**	**6.2E-10**
Coronary artery diseases (CAD)	27	14111	**2.04 [1.78–2.35]**	**2.1E-24**	**1.83 [1.61–2.08]**	**2.3E-20**	**1.41 [1.25–1.58]**	**8.5E-09**	**1.28 [1.13–1.46]**	**0.0002**	**1.40 [1.29–1.53]**	**8.3E-16**
Ischemic stroke (IS)	4	2504	0.86 [0.36–2.04]	0.7254	0.82 [0.35–1.93]	0.6544	1.07 [0.78–1.46]	0.6731	1.10 [0.80–1.51]	0.5664	1.03 [0.78–1.36]	0.8267
Rheumatoid arthritis (RA)	5	3426	3.68 [0.79–17.13]	0.0964	**4.62 [2.01–10.6]**	**0.0003**	**3.05 [1.09–8.54]**	**0.0343**	2.90 [0.94–8.97]	0.0647	**3.01 [1.14–7.96]**	**0.0263**
Type 2 diabetes (T2D)	6	2621	0.62 [0.21–1.86]	0.3932	0.59 [0.20–1.76]	0.3449	1.16 [0.93–1.45]	0.1823	**1.30 [1.02–1.66]**	**0.0310**	0.89 [0.57–1.41]	0.6292
Other	3	4638	1.30 [0.83–2.03]	0.2578	1.10 [0.92–1.31]	0.3089	1.11 [0.81–1.52]	0.5080	1.06 [0.77–1.47]	0.7050	1.08 [0.94–1.25]	0.2688
Ethnicity												
East Asians	29	21370	**2.03 [1.75–2.37]**	**1.1E-15**	**1.77 [1.47–2.12]**	**1.6E-09**	**1.46 [1.17–1.82]**	**0.0009**	**1.35 [1.08–1.70]**	**0.0088**	**1.44 [1.17–1.77]**	**0.0005**
South Asians	21	8784	1.40 [0.88–2.24]	0.1608	1.26 [0.79–2.03]	0.3360	**1.33 [1.14–1.55]**	**0.0003**	**1.30 [1.11–1.52]**	**0.0011**	**1.26 [1.08–1.48]**	**0.0031**
HWE tested data												
Overall	41	24591	**1.99 [1.75–2.26]**	**1.0E-25**	**1.64 [1.37–1.95]**	**4.2E-08**	**1.37 [1.23–1.51]**	**1.7E-09**	**1.28 [1.15–1.42]**	**9.4E-06**	**1.34 [1.23–1.46]**	**3.8E-12**

OR: odds ratio; CI: confidence intervals; 1.1E-10: 1.1×10^{-10}; bold indicated the statistical significance; 'Other' group included (acute lung injury, inflammatory bowel diseases, and bronchopulmonary dysplasia). *p*-Value below 0.05 is deemed as significant.

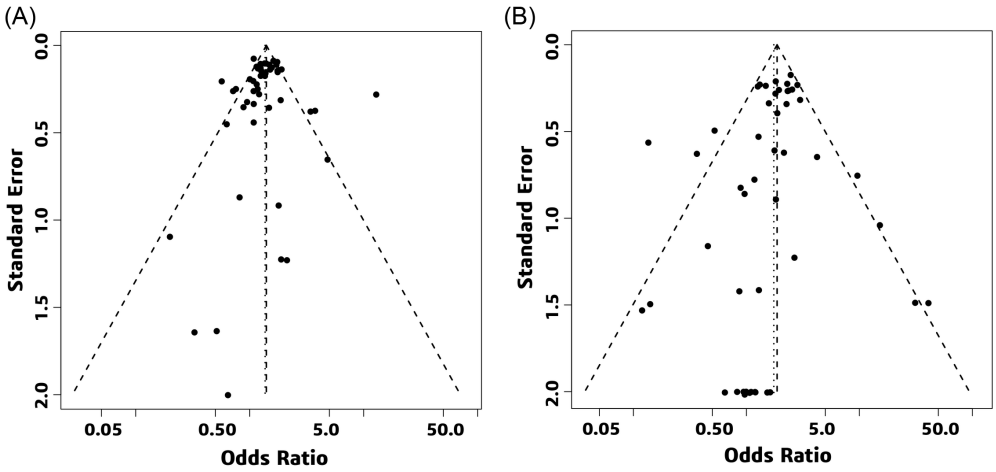

Figure 3. Publication bias analysis employing Begg's funnel plots. Assessing the correlation among the *IL6* rs1800795 (G>C) variant and several disorders in Asians using two distinct models: (A) the C *vs.* G and (B) CC *vs.* GG models, along with their respective meta-datasets.

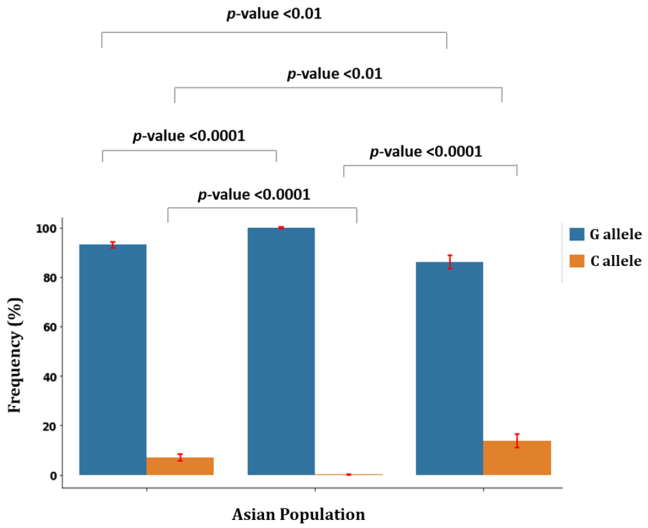

Figure 4. The allelic frequency distribution of the *IL6* gene rs1800795G/C polymorphisms in Asian populations using Phase 3 of the 1000 Genome Project datasets

5. Conclusion

The outcomes of this meta-analysis revealed a notable connection between the *IL6* rs1800795 (G>C) variant and overall susceptibility to various inflammatory diseases in Asian populations. This particular variant rs1800795 (G>C) demonstrated a robust connection with increased susceptibility to conditions such as AP, RA, CADs, BA, and T2D among Asians. Hence, the *IL6* gene variant rs1800795 presents further support as a promising biomarker for disease diagnosis and research in the Asian population. To substantiate this claim, it would be necessary to access more comprehensive genomic data from various Asian populations in the future.

Ethical Statement

This study does not contain any studies with human or animal subjects performed by any of the authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

The data that support this work are available upon reasonable request to the corresponding author.

Supplementary Information

The supplementary figures and tables are available at: https://doi.org/10.47852/bonviewMEDIN42021996

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Appendix

List of Abbreviations

IL6	interleukin-6
OR	odds ratio
CI	confidence intervals
RE	random effects model
FE	fixed effects model
HWE	Hardy-Weinberg equilibrium
NOS	Newcastle-Ottawa scale
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
SNP	singlenucleotide polymorphism
CAD	coronary artery diseases
RA	rheumatoid arthritis
IS	ischemic stroke
T2D	type 2 diabetes
BA	bronchial asthma
ALI	acute lung injury
AP	acute pancreatitis
BPD	bronchopulmonary dysplasia