The CEBPE rs2239633 genetic polymorphism on susceptibility to childhood acute lymphoblastic leukemia: An updated meta-analysis

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Abstract

Background: We performed an updated meta-analysis to clarify the relationship between the CEBPE rs2239633 polymorphism and the CALL susceptibility.

Methods: All the case-control studies updated on July 31, 2019 through Web of Science, Pubmed, Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI) electronic database. The heterogeneity in the study was tested by the Q-test and I^2 , and then the random ratio or fixed effect was utilized to merge the odds ratios (OR) and 95% confidence interval (CI). To estimate the impact of individual studies on aggregate estimates, we performed sensitivity analysis. Using funnel plot and Begger's regression test investigated the publication bias. All data Statistical analyses were performed using Stata 12.0.

Results: A total of 23442 participants (7014 patients; 16428 controls) were included in twenty case-control studies selected. There was no association of *CEBPE* rs2239633 polymorphism with CALL (CC vs CT + TT: OR = 1.08, 95% CI = 0.94 – 1.26; CC + CT vs TT: OR = 1.10, 95% CI = 0.94–1.30; C vs T: OR = 1.02, 95% CI = 0.92–1.13). In the subgroup analysis by ethnicity, no significant association of this polymorphism and CALL risks among Asia and Caucasian populations for the comparison of CC vs CT + TT, CC + CT vs TT and C vs T genetic models .

Conclusion: This meta-analysis did not find the CEBPE rs2239633 polymorphism can increase and decrease the risk of susceptibility to CALL.

Background

Acute lymphoblastic leukemia (ALL) was a malignant disease of the blood system. It occur mostly in children under 15 years of age, The peak age of onset was 2-5 years old [1, 2], accounting for about 1/3 of childhood malignant tumors [3]. Although the etiology and pathogenesis were not yet clear, previous studies had shown that ALL was the result of multiple factors such as genetic variation and exposure to carcinogens in the environment [4, 5]. In recent years, genome-wide association studies (GWAS) had shown that single nucleotide polymorphism (SNP) variation was an important risk factor for CALL [6-9].

The CEBPE gene was located on the human chromosome 14q11.2, which was a member of the CCAAT enhancer binding protein family, and its encoded protein belongs to the basic leucine transcription factor. The CEBPE gene-encoded protein was essential for terminal differentiation and functional maturation of myeloid committed progenitor cells, especially for the maturation of neutrophils and giant wah cells [10]. Mutations in CEBPE would cause loss of neutrophil granules [11]. Akasaka had reported that CEBPE mutations can cause translocation of immunoglobulin heavy chain chromosomes, which often occurred in children with B-precursor E-cell leukemia [12]. This indicated that the CEBPE gene played an important role in the occurrence and development of ALL.

Two meta-analytic studies in 2014 [13] and 2015 [14] found the association of *CEBPE* rs2239633 polymorphism with the risk of CALL, but the two conclusions were reversed. In addition, since 2015, many studies had reported *CEBPE* rs2239633 polymorphisms and the risk of CALL [11, 15-19]. Therefore, the purpose of this meta-analysis was to update previous meta-analyses to elucidate the relationship between *CEBPE* rs2239633 polymorphism and the risk of CALL.

Methods

Search strategies

We conducted a systematic online search of the literature in the Web of Science, Pubmed, Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI) electronic database, covering relevant studies published until June 5, 2020. The keywords for the search were as follows: ("rs2239633" OR "*CEBPE*") AND ("polymorphism" OR "variant" OR "mutation") AND ("acute lymphoblastic leukemia" or "ALL"). The literature on relevant data was searched in English and Chinese respectively. In addition, the retrieved articles and references were performed manual searches. Referring to the Preferred Reporting Project (PRISMA) Guide for Systematic Evaluation and Meta-Analysis [20], an information flow diagram related to the final eligibility data was constructed by screening all retrieved literatures.

Inclusion and Exclusion Criteria

Screening for the studies of the relationship between *CEBPE* rs2239633 polymorphism and the risk of ALL according to the following inclusion criteria: (1) the design of study was case-control; (2) The full text can be found; (3) the genotype information of the *CEBPE* rs2239633 polymorphism were available; (4) the relationship of the *CEBPE* rs2239633 polymorphism and the risk of ALL was evaluated; The major exclusion criteria were: (1) not a case-control study; (2) repeating early publications (studies used in different publications for the same sample data, including only the most complete samples after careful review); (3) Unpublished articles, conference papers, meta-analysis and systematic reviews; (4) family-based pedigree research. This meta-analysis strictly followed the requirements of the preferred reporting project for the systematic review and meta-analysis guidelines. [20].

Data Extraction

The analysis data of the selected studies were independently extracted by two researchers using standard data-collection forms. Studies related information extracted from each literature were as follows: First author, Year of publication, Country of origin, Mean age and Gender in cases and controls, Numbers of cases and controls, Hardy-Weinberg equilibrium, Genotyping method, Source of controls, and available genotype frequency information for *CEBPE* rs2239633. If the same sample data appeared in multiple publications, only the publication with the largest sample size was included in the study. The differences between the two investigators were resolved through discussion. If the discussion could not resolve the objection between the two, the objection would be judged by the third investigator. All data were obtained from the full text of the published research and the author was not contacted for further information.

Study Quality Assessment

Two evaluators evaluated the quality of the included studies according to the Newcastle-Ottawa Scale (NOS) [21], which was applicable to the quality assessment of observational studies. The difference between the two evaluators was reported and resolved by the third evaluator. The scores of research quality mainly included the following three aspects: (1) Selection of the case groups and control groups (4 stars); (2) Quality of confounding factors correction in case and control population (2 stars); and (3) determination of the exposure of interest in the studies (3 stars). For each item numbered in the selection and exposure categories, one study can be rated as up to one star, and comparability can be assigned up to two stars. Higher scores indicate an increase in the quality of the research method. Studies with scores equal to or higher than 6 are considered high quality studies.

Data Analysis

The heterogeneity in the study was tested by the Q-test and I^2 [22, 23], and then the random ratio or fixed effect was utilized to merge the odds ratios (OR) and 95% confidence interval (CI)[24]. The significance of the pooled OR was analyzed by Z-test ($P < 0.05$ Judged statistically significant). To estimate the impact of individual studies on aggregate estimates, we also performed Sensitivity analysis[25]. Using funnel plot and Begger's regression test investigated the publication bias [26, 27]. All data Statistical analyses were performed using Stata 12.0 (Stata Corp, College Station, TX, United States).

Results

Literature Search and Study Characteristics

The flow chart of the literature search was shown in Figure 1. 165 potentially relevant articles were selected in the preliminary online search. After verifying and deleting 80 duplicate articles, 85 articles entered the final review. Through the review of the title and abstract, 26 articles were included for full-text review. Finally, 16 articles were included in the final study. These studies were published between 2009 and 2017, and 20 studies included 7014 ALL patients and 16428 controls. The distribution of genotypes in controls in all studies followed HWE. In addition, the NOS scores for all studies ranged from 6 to 8 points, so that the selected articles were considered to be good in methodological quality. The relevant feature information of the included articles was in Tables 1 and Table 2.

Meta-analysis results

The heterogeneity of the three genetic models was determined by Q test and I squared statistics. As shown in Figure 2, there were serious heterogeneity in the three models (CC vs CT + TT: $P < 0.001$, $I^2 = 63.6\%$; CC + CT vs TT: $P = 0.002$, $I^2 = 70.2\%$; C vs T: $P < 0.001$, $I^2 = 79.2\%$), thus we used the random-effect model to analyze of the three models. Our results did not find significant associations between *CEBPE* rs2239633 polymorphism and the risk of ALL under the model of CC vs CT + TT (OR = 1.08, 95% CI = 0.94 – 1.26, $P = 0.280$), CC + CT vs TT (OR = 1.10, 95% CI = 0.94–1.30, $P = 0.228$), C vs T (OR = 1.02, 95% CI = 0.92–1.13, $P = 0.752$). In subgroup analysis by Ethnicity, no significant association was found in three models in both Caucasian and Asian populations (Table 3). Sensitivity analysis was used to assess the impact of each individual study on the pooled OR by sequentially removing each eligible study. Our results suggest that none of the studies affected the overall outcome of the pooled OR (Figure 3). Begg's funnel plot was used to assess publication bias, and the results showed that publication bias was not reflected in the three genetic models (CC vs CT + TT: $P = 0.742$; CC + CT vs TT: $P = 0.285$; C vs T: $P = 0.560$) (Figure 4).

Discussion

As a transcription factor specifically expressed in myeloid cells, CCAAT/ enhancer binding protein- ϵ (CEBPE) played an important role in the proliferation, growth, differentiation and apoptosis of myeloid cells, and participates in the transcriptional regulation of a series of myeloid-specific genes. Loss of activity was an important factor leading to the onset of bone marrow disease [28]. In recent years, A growing number of published studies had investigated the relationship between *CEBPE* rs2239633 polymorphism and ALL risk [29-37]. It also included some meta-analysis, but even the correlation results of meta-analysis were contradictory and conflicting. To further assess the relationship between *CEBPE* rs2239633 polymorphism and ALL risk, we performed an upgraded meta-analysis of the relationship between the two in conjunction with previous literature in the meta-analysis and the most recent published study.

Although GWAS study by Papaemmanuil et al [6] proved that the 5' SNP rs2239633 located in *CEBPE* has strong correlation with children's ALL in European population. However, this meta-analysis showed that no significant association was found in the three selected genetic models. In the subgroup analysis of ethnicity, no correlation was found between the three genetic models. On the one hand, this difference may be the linkage disequilibrium between these populations in different populations. There are also some differences between the population samples. On the other hand, the exact pathogenesis of *CEBPE* in the etiology of leukemia was still unclear. The CEBPE mutation may have different effects on the immune system of different children.

Previously, a meta-analysis was applied for 11 case-control studies with 5,639 cases and 10,036 controls by Wang et al [13], the results shown no association of the *CEBPE* rs2239633 polymorphism and childhood ALL risk, Subgroup analysis stratified by ethnicity found a significant association of this polymorphism with childhood ALL in the Caucasian subgroup and Hispanic subgroup, but not in the Asian subgroup. Sun et al [14] also conducted a meta-analysis of 22 published studies involving 6152 patients and 11739 healthy controls, the results also showed *CEBPE* rs2239633 variant was associated with decreased risk of childhood B-cell ALL in Europeans, but not among T-cell ALL, Asian and mixed populations. The results of the two meta-analyses are diametrically opposed, and this difference may be due to the difference in the number of samples included and the sample size. This study combines the latest research literature with the first two meta-analyses to more fully describe the relationship between *CEBPE* rs2239633 and CALL. In terms of statistical power, it is significantly better than the previous meta-analysis of Sun et al [14] and Wang et al [13].

However, there are certain limitations in our research. First, databases that include only published research in both Chinese and English are selected for analysis, and other language or unpublished potential research may be missed. Second, due to the lack of raw data, we were unable to assess potential interactions of gene-genes and genes-environments. Third, the meta-analysis includes data from Europeans and Asians, so the results of this item apply only to these two ethnic groups. Fourth, among the three models, heterogeneity may greatly influence the conclusion of the meta-analysis.

Conclusions

Our study showed that the *CEBPE* rs2239633 gene polymorphism did not increase or decrease the risk of susceptibility to CALL. Although the specific causes of childhood leukemia were still unclear, a large number of existing researches tended to suggest that the occurrence of childhood ALL was the result of a combination of factors, especially the genetic and environmental factors.

Therefore, in the future, when studying the relationship between *CEBPE* rs2239633 polymorphism and childhood ALL, the influence of environmental factors on the relationship between the two should be removed.

Abbreviations

CNKI: China National Knowledge Infrastructure; IARC: International Agency for Research on Cancer; WHO: World Health Organization; NOS: Newcastle-Ottawa Scale; OR: odds ratio; CI: confidence interval. ALL: Acute lymphoblastic leukemia; GWAS: genome-wide association studies; SNP: Single nucleotide polymorphism;

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable

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Authors' contributions: Manuscript writing, editing and review were conducted by JL; GW and LX participated in the articles search; WL and CZ performed data analysis and evaluation the quality of the selected studies. All authors have read and approved the manuscript

Availability of data and materials section: All data generated or analyzed during this study are included in this published article

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Tables

Table 1 Characteristic of studies included in the meta-analysis

Author	year	country	Ethnicity	Genotype Methods	Source of control	NOS score	HWE
Ellinghaus et al	2011	Germany	Caucasian	SNPlex and TaqMan	HB	7	Not Know
Ellinghaus et al	2011	Germany	Caucasian	SNPlex and TaqMan	HB	7	Not Know
Ellinghaus et al	2011	Italy	Caucasian	SNPlex and TaqMan	HB	7	Not Know
Papaemmanuil et al (GWAS-1)	2009	UK	Caucasian	Illumina arrays	PB	8	0.778
Papaemmanuil et al (GWAS-2)	2009	UK	Caucasian	Illumina arrays	HB	7	0.517
Prasad et al	2010	Germany	Caucasian	Kaspar allele-specific PCR	PB	8	0.233
Prasad et al	2010	UK	Caucasian	Kaspar allele-specific PCR	HB	7	0.310
Vijayakrishnan et al	2010	Thailand	Asian	Kaspar allele-specific PCR	PB	8	0.162
Pastorczyk et al	2011	Poland	Caucasian	PCR	HB	7	0.454
Lautner-Csorba et al	2012	Hungary	Caucasian	Sequenom iPLEX Gold MassARRAY technology	HB	7	0.508
Orsi et al	2012	France	Caucasian	Principal component analyses(PCA)	PB	8	0.472
Ross et al	2012	USA	Caucasian	Taqman	PB	6	0.091
Wang et al	2013	China	Asian	PCR	HB	7	0.147
Emerenciano et al	2014	Brazil	Mixed	Taqman	HB	7	0.135
Al-absi et al	2017	Yemen	Asian	Fluidigm 192.24 Dynamic Array	PB	6	0.149
Gharbi et al	2016	Tunisia	Caucasian	PCR	PB	7	0.700
Bekker-Mendez et al	2016	Mexico	Mexican	Taqman	HB	6	0.081
Bhandari et al	2016	India	Asian	Taqman Illumina	PB	7	0.085
Urayama et al	2017	Japan	Asian	HumanCoreExome BeadChip	HB	6	Not Know
Kreile et al	2016	Latvia	Caucasian	PCR-RFLP	PB	6	0.234

Table 2 The genotype distribution of *CEBPE* rs2239633

Author	Sample size (case/control)	Female (%) (case/control)	Case					Control				
			CC	CT	TT	C	T	CC	CT	TT	C	T
Ellinghaus et al	419/474	45.8/-	-	-	-	243	176	-	-	-	246	228
Ellinghaus et al	406/1682	45.3/-	-	-	-	240	166	-	-	-	841	841
Ellinghaus et al	287/579	49.5/-	-	-	-	178	109	-	-	-	330	249
Papaemmanuil et al (GWAS-1)	503/1435	-/-	78	244	181	400	606	332	722	381	1386	1484
Papaemmanuil et al (GWAS-2)	404/960	-/-	74	188	142	336	472	205	488	267	898	1022
Prasad et al	1193/1510	44.4/49.9	197	559	437	953	1433	307	773	430	1387	1633
Prasad et al	183/352	49.2/69.3	26	95	62	147	219	64	183	105	311	393
Vijayakrishnan et al	190/182	42.6/54.9	103	76	11	282	98	95	78	9	268	96
Pastorczyk et al	388/711	41.2/56.1	119	176	93	414	362	207	344	160	758	664
Lautner-Csorba et al	543/529	56.2/42.3	173	278	92	624	462	152	256	121	560	498
Orsi et al	441/1542	46.9/61.0	141	225	75	507	375	432	755	355	1619	1465
Ross et al	85/363	-/-	19	43	23	81	89	90	165	108	345	381
Wang et al	568/672	38.6/34.4	245	253	70	743	393	309	281	82	899	445
Emerenciano et al	160/505	-/48.1	21	68	71	110	210	62	201	220	325	641
Al-absi et al	136/153	63.2/53.6	10	46	80	66	206	9	70	74	88	218
Gharbi et al	58/150	44.8/-	15	33	10	63	53	78	59	13	215	85
Bekker-Mendez et al	285/476	-/52.7	122	128	35	372	198	167	245	64	579	373
Bhandari et al	162/150	32.7/40.7	21	65	76	107	217	17	69	64	103	197
Urayama et al	527/3882	-/-				578	476				4138	3626
Kreile et al	76/121	46.1/-	25	38	13	88	64	46	52	23	144	98

Table 3 Summary of pooled OR in different ethnicities

Genetic model	group	Pooled OR (95% CI)	Heterogeneity		Test for overall effect	
			P	I ²	Z	P
CC VS CT+TT	Caucasians	1.17(0.97-1.41)	<0.01	68.9%	1.68	0.092
	Asia	1.04(0.87-1.25)	0.701	0.0%	0.43	0.666
CC+CT VS TT	Caucasians	1.09(0.89-1.35)	<0.01	78.7%	0.85	0.393
	Asia	1.17(0.94-1.47)	0.583	0.0%	1.38	0.168
C VS T	Caucasians	1.03(0.89-1.18)	<0.01	84.3%	0.36	0.718
	Asia	1.00(0.92-1.10)	0.538	0.0%	0.10	0.917

Figures

Figure 1

The flow sheet of identification of eligible studies

Figure 2

Forest plots of the CEBPE rs2239633 polymorphism under different genetic models. a is the model of CC VS CT+TT; b is the model of CC+CT VS TT; c is the model of C VS T.

a

b

c

Figure 3

Sensitivity analysis examining the association between the CEBPE rs2239633 polymorphism and risk of childhood ALL under these model (CC VS CT+TT, CC+CT VS TT, C VS T).

Figure 4

Begg's funnel plot for publication bias analysis. a is the model of CC VS CT+TT; b is the model of CC+CT VS TT; c is the model of C VS T

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRISMA2009ChecklistMSWord.doc](#)