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Interferon-Gamma +874 (T/A) Polymorphism and Susceptibility to Aplastic Anemia: A Systematic Review and Meta-Analysis

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Abstract

Background: Many studies have assessed the relation between IFN-γ +874(T/A) polymorphism and risk of aplastic anemia. However, the results of these studies were inconclusive. In the current study, we performed a meta-analysis to evaluate the association between IFN-γ +874(T/A) polymorphism and susceptibility to aplastic anemia.

Methods: All publications were searched precisely to find eligible articles on IFN-γ polymorphism +874(T/A) and aplastic anemia. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated to evaluate the strength of association in the dominant model, recessive model, allelic model, homozygotes contrast, and heterozygotes contrast.

Results: A total of 4 case-control studies, including 210 cases and 537 healthy controls were elegble for this metta-analysis. Combined analysis of these studies showed no significant association between the IFN-γ polymorphism +874(T/A) and aplastic anemia risk in the overall population (dominant model: OR=1.52, 95% CI=0.57-2.46; recessive model: OR=1.27, 95% CI=0.47-2.08; allelic model: OR=0.98, 95% CI=0.63-1.34; TT vs. AA: OR=3.68, 95% CI=0.21-7.15, and AT vs. AA: OR=1.20, 95% CI=0.43-1.97). No heterogeneity or publication bias was observed in this study.

Conclusion: This meta-analysis showed that the IFN-γ +874(T/A) polymorphism was not associated with the risk of aplastic anemia.To confirm our results, further studies are needed.

Keywords: IFN- γ; Polymorphism; Aplastic anemia; Meta-analysis

Abriviations: IFN-γ: Interferon-Gamma; AA: Aplastic Anemia

Introduction

Aplastic anemia (AA) is a rare bone marrow failure syndrome characterized by hypocellularity of bone marrow and peripheral blood cytopenias [1]. Patients with AA frequently manifest with symptoms of purpura or hemorrhage, anemia and less often infection, leading to medical outcomes [2,3]. Most cases of AA are acquired and idiopathic [4]. Furthermore, in most cases, no agitating factor is known [1,4,5]. However, the principal etiology is thought to be immune-mediated damage of progenitor cells and hematopoietic stem cells [6,7]. Epidemiologic studies also suggest an influence of environmental exposures and genetic factors on AA pathogenesis [8]. The recent genome-wide transcriptional analysis of peripheral blood T cells from AA patients described various dysregulated genes in CD4 and CD8 T cells of the patients with AA [9]. In accordance with these findings, impaired functions of T cells has been reported in patients with aplastic anemia [10].

Interferon (IFN)-γ is one of the essential cytokines secreted by activated T cells and has immunomodulatory, antiviral and anti-proliferative activities [11,12]. The involvement of IFN-γ in the immunopathogenesis of AA has been well addressed and upregulation of IFN-γ in the bone marrow and peripheral blood of patients with AA is predominant [13,14]. The IFN-γ gene is located on chromosome 12q14.1, spanning approximately six kb and is considered as a conserved region with limited genetic polymorphisms [15]. Various single nucleotide polymorphisms (SNP) in the non-coding region of INF-γ has been reported in different diseases [16]. T to A single nucleotide polymorphism (SNP), which is located at position +874 of the first intron of the IFN-γ gene (IFN-γ +874), can obviously affect the expression of the IFN-γ gene [17].

The SNP +874 A>T of IFN-γ has been evaluated in several association studies with aplastic anemia and bone marrow hypocellularity [18,19]. But, the results were inconsistent and inconclusive, probably due to different study populations and limited sample sizes. Thus, we performed this meta-analysis on all eligible case-control studies to further elucidate the effect of IFN-γ +874 A/T polymorphisms on the risk of AA.

Materials and Methods

The current Meta-analysis carried out based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement including search strategy, inclusion and exclusion criteria, data extraction and statistical analysis [20].

Search strategy

A detailed literature search was carried out using Scopus, PubMed central and Web of Science databases. Our search was performed from database inception to last updated on January 7, 2017. The following keywords were applied for search: (interferon OR IFN OR interferon-gamma OR interferon-g OR IFN-g OR interferon-γ OR IFN-γ) AND

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(Aplastic Anemia OR Aplastic OR Anemia OR Pancytopenia) AND (polymorphism OR variant OR mutation OR allele OR genotype). Just English publications were included in searches, and all favorable articles were obtained and their references were evaluated for other relevant studies. Moreover, we applied the "Related Articles" function in PubMed database to search for other possible relevant articles.

Inclusion and exclusion criteria

All candidate articles, at the beginning, were scanned in titles and/or abstracts by two trained researchers independently. The main criteria for selection of studies to be considered in this meta-analysis were as following: 1) studies that had assessed the association between IFN-g polymorphism +874 (T/A) and risk of aplastic anemia; 2) case-control or nested case-control studies; and 3) reporting genotype frequency for the +874 (T/A) polymorphism in cases and controls. Animal studies, reviews, letters to the editor, summaries, book's chapters and duplicated articles were all excluded.

Data extraction and quality assessment

The following data were extracted from the qualified article: the first author, year of publication, ethnicity, country of origin, gender, mean or range of age, the number of cases and controls for each genotype, and the sample size of cases and controls. Data were collected independently by two investigators. The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality [21]. This quality assessment tool judges studies based on a star system. Studies awarded 0-3, 4-6 or 7-9 were considered as a low, moderate or high-quality study, respectively.

Statistical analysis

Deviation from Hardy-Weinberg equilibrium (HWE) was calculated by using the χ^2 test [22]. The association between IFN-γ polymorphism +874 (T/A) and aplastic anemia was assessed using ORs and their corresponding 95% (CIs). The allelic model (T vs. A), dominant model (TT+TA vs. AA), recessive model (TT vs. TA+AA), homozygote comparison (TT vs. AA) and heterozygote comparison (TA vs. AA) were examined. We used Cochran Q and the I^2 statistics to evaluated heterogeneity between included studies (I^2=(Q−df)/Q × 100%; I^2<25%, no heterogeneity; I^2=25-50%, moderate heterogeneity; I^2=50-75%, large heterogeneity, I^2>75%, extreme heterogeneity) [23]. Heterogeneity was considered to be significant if the Q statistic had p<0.1 or I^2>50%. In the presence of significant heterogeneity the random-effects model was applied, otherwise, the fixed - effect model was performed in the absence of significant heterogeneity (Q statistic p>0.1 or I^2<50%). Possible publication bias was assessed by Egger's and Begg's tests [24,25]. All statistical analysis for this meta-analysis were performed by STATA (version 14.0; Stata Corporation, College Station, TX) and SPSS (version 23.0; SPSS, Inc. Chicago, IL).

Results

Characteristics of eligible studies

Figure 1 shows the procedure of including/excluding potential studies selection. Based on the inclusion and exclusion criteria, 4 articles (210 cases and 537 healthy subjects) were included in the meta-analysis. The studies were performed in different countries; two studies were from Egypt [26,27], one from Italy [19] and the other one was from South Korea [18]. Based on the criteria of the NOS, all included studies had an overall good methodological quality with a total score ranging from 7 to 9. The general characteristics and the allele and genotype distributions of studies included in this meta-analysis are reported in Tables 1 and 2.

Meta-Analysis of the association between IFN-γ +874 A/T polymorphism and Aplastic anemia risk. The pooled results of meta-analysis in different models are shown in Table 3. when the eligible studies were pooled, there was no significant association between IFN-γ +874 A/T polymorphism and aplastic anemia risk in any genetic model tested (dominant model: OR=1.52, 95% CI=0.57-2.46; recessive model: OR=1.27, 95% CI=0.47-2.08; allelic model: OR=0.98, 95% CI=0.63-1.34; TT vs. AA: OR=3.68, 95% CI=0.21-7.15 and AT vs. AA:OR=1.20, 95% CI=0.43-1.97) (Table 3). Also, the results of

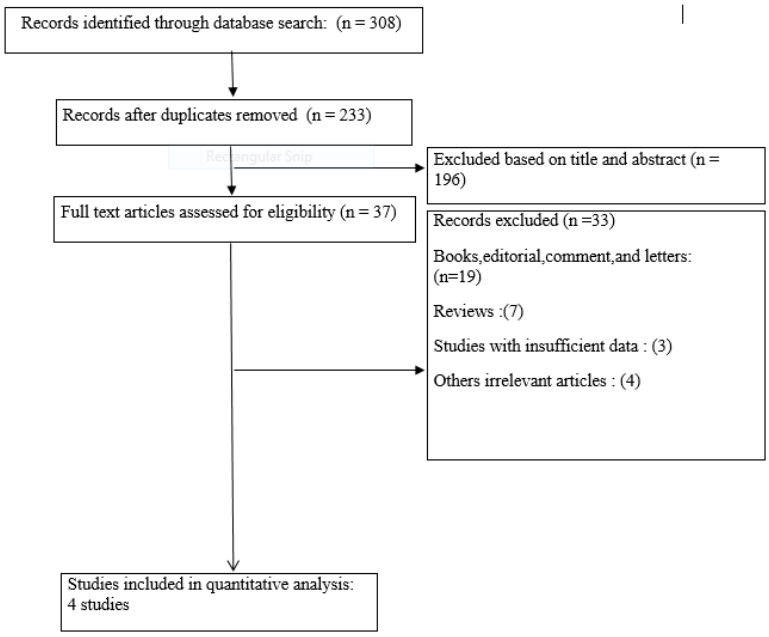

Figure 1: Flow diagram of study selection.

Study Author	Year	Country	Ethnicity	Sex	Total Cases/ Controls	Case Age/Control Age (mean ± SD)	Genotype Method	Quality Score
Roderick et al. [7]	2013	Egypt	Caucasian	M/F	50/50	11.2 ± 7.13/15.1 ± 7.25	PCR–RFLP	9
Lee et al. [18]	2011	S.korea	Caucasian	M/F	80/84	38/37	PCR–RFLP	7
Fermo et al. [19]	2004	Italy	Caucasian	M/F	40/363	NR/NR	PCR–RFLP	7
Zayed et al. [26]	2016	Egypt	Caucasian	M/F	40/40	11/12	PCR–RFLP	8

NR: Not Reported; M: Male; F: Female

Table 1: The characteristics of the studies included in the meta-analysis of the aplastic anemia.

Study Author	AA Cases					Healthy Control						
	AA	AT	TT	A	T	AA	AT	TT	A	T	P-HWE	MAF
Roderick et al. [7]	16	21	13	53	47	31	13	6	47	25	0.03	0.34
Lee et al. [18]	61	15	3	137	21	66	17	0	149	17	0.29	0.10
Fermo et al. [19]	6	19	15	49	31	116	170	77	402	324	0.31	0.44
Zayed et al. [26]	9	17	14	35	45	19	12	9	50	30	0.02	0.37

P-HWE: p-value for Hardy-Weinberg Equilibrium; MAF: Minor Allele Frequency of Control Group; NR: Not Reported; M: Male; F: Female

Table 2: Distribution of genotype and allele among AA patients and controls.

Genetic Models	Sample Size	Test of Association		Test of Heterogeneity		Test of publication bias			
						Begg's		Egger's	
	Case /Control	OR	95% CI	I^2 (%)	P	Z	P	t	P
Dominant model	210/537	1.52	0.57-2.46	0.0	0.45	0.49	0.68	0.29	1.39
Recessive model	210/537	1.27	0.47-2.08	0.0	0.92	0.60	-0.5	0.37	-1.50
Allelic model	210/537	0.98	0.63-1.34	0.35	0.20	0.49	0.68	0.15	2.22
TT vs. AA	210/537	3.68	0.21-7.15	0.0	0.98	0.60	-0.5	0.98	-0.11
AT vs. AA	210/537	1.20	0.43-1.97	0.0	0.63	1.00	0.0	0.33	1.26

Table 3: Main results of the pooled ORs in meta-analysis of the IFN-γ 874 A/T polymorphism.

heterogeneity tests in different analysis models are presented in Table 3. There was no significant heterogeneity among the studies in the dominant model (I2=0.0, P=0.45), recessive model (I2=0.0, P=0.92) allelic model (I2=0.35, P=0.20), TT vs. AA (I2=0.0, P=0.98) and AT vs. AA (I2=0.0, P=0.63).

Evolution of publication bias and sensitivity analysis

The sensitivity of this meta-analysis was assessed by removing non-HWE studies. However, the results remained unaltered, indicating the reliability of the results. Publication bias was calculated by using Egger's and Begg's tests (Table 3). For the IFN-γ 874 A/T polymorphism, Egger's test showed no evidence of publication bias for the dominant model (t=1.39, p=0.29), recessive model (t=-1.50, p=0.37), allelic model (t=2.22, p=0.15), TT vs. AA (t=-0.11, p=0.98) and AT vs. AA (t=1.26, p=0.33).

Discussion

The pathogenesis of aplastic anemia includes a change in the hematopoietic microenvironment, destruction and reduction of the hematopoietic stem cells, and altered cellular immunity, which finally culminate to bone marrow failure [28,29]. The immune mechanisms involved in AA consist of cell-mediated killing and cytokines secretion by Th1, which have an inhibitory activity on the hematopoietic progenitors, such as IFN-γ and TNF-α [30,31]. Moreover, it is known that many immunogenic factors may play a critical role in the increase and the decrease of predisposition to immune responses. Functional polymorphisms of cytokines are an interested group of immunogenic factors for the understanding of diseases risk [32-34]. These polymorphisms have been reported to be associated with specific clinical manifestations or susceptibility to some diseases [35]. Recently, several studies have focused on the association between the IFN-γ +874 (T/A) polymorphism and aplastic anemia, although the results of these studies were controversial. Therefore, this meta-analysis was performed to reveal the possible effect of the IFN-γ +874(T/A) polymorphism on susceptibility to AA.

To the best of the author's knowledge, this meta-analysis is the first quantitative assessment of the association between IFN-γ +874T/A polymorphism and risk of aplastic anemia. The results suggested that there was no significant association between the IFN-γ +874 (T/A) polymorphism and genetic susceptibility to aplastic anemia. Although the present meta-analysis did not find associations of IFN-γ +874 (T/A) polymorphism and the risk of AA, but results should be interpreted with cautions. For evaluation of the investigated polymorphism, there were limited published studies. Due to the relatively small sample size, the results are unable to come to a confirmed conclusion. Therefore, to conclude a reliable result, further studies are needed to assess the association between IFN-γ +874 (T/A) polymorphism and the risk of AA in different ethnicities.

The results of this meta-analysis are in agreement with some cross-sectional studies that have examined the risk of AA according to IFN-γ +874 (T/A) polymorphism. In the study that was carried out by Bestach et al. [31], no association was reported between polymorphisms in IFN-γ gene and susceptibility to AA, while, unlike to this study, Gidvani et al. [36] described a relationship between AA and IFN-γ polymorphisms. In consistent with Gidvani et al. [36], other studies [19,37] emphasize on the role of IFN-γ polymorphisms in clinical characteristics of AA. However, these studies did not evaluate the association between IFN-γ +874 (T/A) polymorphism and AA risk.

Limitations

The current study has some limitations. First, the number of studies

included in the analysis was limited and, for this reason, we could not perform subgroup analysis to evaluate the possible differences caused by age, sex and race of the participants. Second, this meta-analysis was restricted to English-language publications, therefor may result in the exclusion of some relevant article in other languages. Third, because of lack of sufficient data in the original studies, we could not evaluate the possible interactions between gene-environmental factors and gene-gene interactions, which this shortage might affect our results.

Conclusion

In conclusion, this gene-based meta-analysis found no significant association between IFN-γ +874 (T/A) polymorphism and genetic susceptibility to aplastic anemia. Because of the scarcity of data, additional large, well-designed studies are needed to assess the association between this polymorphism and risk of aplastic anemia.

Conflicts of Interests

The authors declared no conflicts of interests.

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