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A Meta-analysis of the Association of *COX-1* Gene *rs3842788* and *rs1330344* Polymorphism with Aspirin Resistance in Chinese

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Abstract

The cyclooxygenase-1 (*COX-1*) gene *rs3842788* variant (128G>A) and rs1330344 variant (1676G>A) have been associated with aspirin resistance in patients with cardiovascular disease. However, there is not enough evidence to demonstrate whether the A or G allele of *COX-1* gene is indeed a genetic factor that can lead to aspirin resistance, with many of the studies coming to opposite conclusion. Here, we identified 10 articles on *COX-1* in a literature search, and conducted a meta-analysis on the *rs3842788* and *rs1330344* genotype difference between aspirin resistance and aspirin sensitive patients. We found that there is no significant difference between cases and controls on GA+AA and GG genotypes of rs3842788 (OR, 1.22; 95% CI, 0.85-1.75; P, 0.29). The results provide additional evidence that rs3842788 of *COX-1* gene maybe not a factor to cause aspirin resistance. However, we found that there is a significant difference between cases and controls on GA+GG and AA genotypes of *rs1330344* (OR, 1.48; 95% CI, 1.15-1.90; P, 0.002). The results provide evidence that *rs1330344* of *COX-1* gene may be a factor to cause aspirin resistance. Therefore, more researches are needed to show the relationship between *COX-1* gene and aspirin resistance.

Keywords: Aspirin resistance; *COX-1*; Allele; Genotype; Meta-analysis

Introduction

Acetylsalicylic acid (aspirin) is commonly used as an antiplatelet treatment for cardiovascular disease [1]. By inhibiting cyclooxygenase (COX) activity, a rostaglandins the formation of ht be and heln spirin impairs the formation of prostaglandin, and thromboxane A [2], which is critical to platelet aggregation. Long-term aspirin use therefore reduces the risks of heart attack and stroke [1]. A concept of "aspirin resistance (AR)" describes the inability of aspirin to thromboxane (TX) biosynthesis and produces an anticipated effect on one or more in vitro tests of platelet function [2]. Clinically, aspirin resistant patients still develop adverse vascular events despite aspirin intake [3].

This phenomenon indicates that aspirin may have unequal antiplatelet effects on individuals. While the causative factors of aspirin resistance have not been determined, speculations of possible influences are plentiful. Generally, there is agreement that the mechanisms for aspirin resistance are multifactorial, but genetic polymorphism is potentially one of the direct causes [4].

Abundant literature suggested that there exist genetic basis for aspirin resistance and evaluated whether polymorphisms on the candidate genes can be identified for antiplatelet resistance [5]. Specifically, single nucleotide polymorphisms (SNPs) on COX may be the most reported genetic determinants. Because of the heterogeneity of the population studied, the diverse methods used, and the inadequate sample size, current studies often provide inconsistent and irreproducible results [6-16].

Therefore, there remains a need to systematically analyze whether the *COX-1* genetic polymorphisms can be identified as biomarkers for aspirin resistance. In order to investigate the impact of *COX-1* polymorphisms on aspirin resistance, we present here a meta-analysis of individual participant data, evaluating the association of two *COX-1* polymorphisms (*rs3842788*: G128A, 128G>A *rs1330344*: A1676G, 1676AG) with the risk of having aspirin resistance. The result encompasses only patients with cardiovascular disease. The selection of *COX-1* enzyme is based on its critical role in platelet regulation, and the SNPs are selected for their relevance to studies concerning aspirin resistance. The polymorphism has more than 1000 subjects for sufficient data synthesis.

Materials and method

Data sources

PubMed, Web of Science, Wanfang (http://www.wanfangdata.com.cn), and CNKI (http://www.cnki.net) electronic databases were searched up until 1 August 2017 for all articles evaluating the association between the genetic polymorphism of *rs3842788* on *COX-1* with aspirin resistance. Search terms used for the primary search were "aspirin resistance" and "AR" in combination

with "*rs3842788*", "G128A", and "128G>A" or "*rs1330344*", "A1676G and "1676AG". Searches were limited to published English and Chinese language articles.

A secondary search was performed on all potentially relevant articles for any additional articles. Eligibility of the retrieved articles was evaluated by reading the titles and the abstracts if necessary. The search results were limited to human. Studies were required to have measured aspirin resistance using laboratory methods described previously.

Inclusion/exclusion criteria

Articles were included if (i) They evaluated the association of the genetic polymorphisms *rs3842788* or *rs1330344* with the risk of having aspirin resistance (ii) They were conducted on a case-control or nested case-control study design (iii) They provided the genotype and/or allele counts of examined polymorphisms between patients with aspirin resistance and controls in order to estimate odds ratio (OR) and 95% confidence interval (95% CI) (iv) The study contained a clear description of the method used to establish the effects of aspirin on platelet reactivity to compare patients with laboratory aspirin resistance with those without.

Articles were excluded if (i) They did not provide the genotype or allele counts of examined polymorphisms; (ii) They lacked either patient group or control group (iii) They were performed on nonhuman subjects (iv) They were meeting abstracts, case reports/series, editorials, review articles, or non-English and non-Chinese publications.

Data extraction

Data were extracted independently by different authors on a standardized Excel template and were verified with disagreements settled by consensus. For each article, information was extracted on the first author, publication year, age, aspirin dosages used, sample size of type of aspirin reactivity (aspirin resistance and aspirin sensitive), the genotypes/alleles of examined polymorphisms, study design, ethnicity as well as population characteristics.

Statistical analysis

Data were analyzed using Cochrane Review Manager, version 5.3 (Cochrane Collaboration, Syracuse, NY, USA). Risk estimate was expressed as a pooled odd ratio (OR) calculated using fixed and random effects model, along with the 95% CI to measure the strength of association. Fixed-effects summary ORs were calculated using the Mantel–Haenszel method. Test for heterogeneity were performed. For assessment of publication bias graphically, we used funnel plot on ORs.

Results

Qualified articles

The initial search identified 204 papers. When we refined the search by viewing the title, the number of papers was reduced to 97. We excluded 16 papers that are replicated. We reviewed 81 abstracts for evidence of data related to aspirin resistance and its relation to *rs3842788* or *rs1330344*. We further excluded papers that contain only nonhuman subjects, have no data, or associate only with other gene locus. Overall, 10 papers met the inclusion criteria.

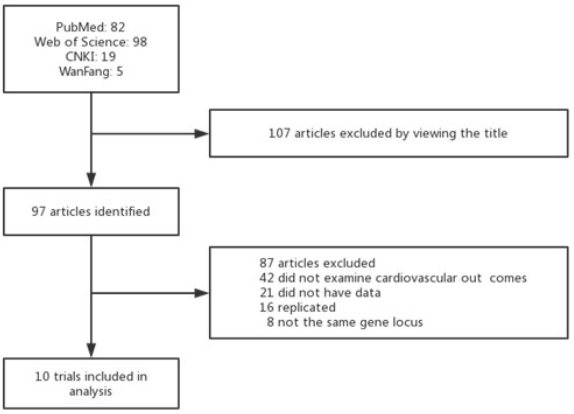

Figure 1: The process of incorporating the articles.

Figure 1 shows the selection process of identified articles with specific reasons, and the baseline characteristics of all qualified articles are presented in Table 1. The retrieved articles were published between 2009 and 2017, and four of them were written in Chinese and two in English. There were 330/1,610 cases/controls for *rs3842788*. There were 417/1,541 cases/controls for rs1330344.

Study characteristics

We included 10 full-text articles. Aspirin dosages used in included studies are between 75 and 100 mg daily. Different studies apply various criteria to distinguish whether the patients were aspirin resistant or sensitive. Various sequencing methods were used to examine the sample characteristics. Sequenom Mass ARRY iPLEX was used in three studies. (Peng Zhang LiXL). Three studies utilized Sequencing. PCR-RELP was used in three studies. And genechip were adopted in the other one study. All of the subjects in the meta-analysis are Chinese patients with cardiovascular disease. Five studies included Cerebral Ischemic Stroke patients. (Peng Zhang Cao). One study paid attention to Chronic Stable Angina patients. The other four studies involved patients with respectively Coronary Atherosclerotic Heart Disease and Ischemic Cerebrovascular. The aspirin resistance frequency of patients with genetic polymorphism *rs3842788* (AA+AG) was 14.88% in patients, and 17.76% in controls, and *rs1330344* (GG +AG) was 69.78% in patients, and 60.80% in controls. The 6 studies on the association between aspirin resistance and *rs382788* analyzed statistically included 1610 subjects sensitive, and 330 subjects resistant, to aspirin. An OR of 1.22 was observed for aspirin resistance in subjects carrying the *rs3842788* SNP (AG+AA). Interstudy OR heterogeneity was measured (χ^2=14.90, df=5(P=0.01) I2=66%). Moreover, The 5 studies on the association between aspirin resistance and *rs1330344* analyzed statistically included 1541 subjects' sensitive, and 417 subjects resistant, to aspirin. An OR of 1.48 (95% CI 0.83, 1.90; P=0.002) was observed for aspirin resistance in subjects carrying the *rs1330344* SNP (AG+GG). Interstudy OR heterogeneity was measured (χ^2=3.86, df=4 (P=0.43) I2=0%).

Meta-analysis

Figure 2 presents the OR and P values for the pooled analyses. The overall OR of the GA+AA genotypes compare to the GG genotype was

1.22 (95% CI 0.85-1.75, P=0.29). It indicates that there is no significant difference between AR and AS groups on *COX-1* gene *rs3842788*. There was no publication bias (not shown). Figure 3 presents the OR and P values for the pooled analyses. The overall OR of the AG+GG genotypes compare to the AA genotype was 1.48 (95% CI 0.83, 1.90; P=0.002). It indicates that there is significant difference between AR and AS groups on *COX-1* gene *rs1330344*. There was no publication bias (not shown).

Author (year)	Ethinicity	Average age ± (sd)		Drug dose	Sample size			Gene detection method	Sample characteristics
		AR	AS		Total	AR	AS		
Ping LL (2014)	Chinese	64.35 ± 11.88	61.13 ± 13.76	100 mg/d	192	18	174	Sequenom Mass ARRAY iPLEX	Cerebral Ischemic Stroke Patient
XU JJ (2017)	Chinese	58.59 ± 11.35	57.29 ± 9.86	100 mg/d	366	166	200	PCR-RFLP	Coronary Atherosclerotic Heart Disease Patients
XUE M (2016)	Chinese	61.80 ± 8.46	64.2 ± 8.20	100 mg/d	207	51	156	Sequencing	Chronic Stable Angina Patients
Wang B (2009)	Chinese	57.16 ± 9.59	58.81 ± 10.49	100 mg/d	220	19	201	genechip	Ischemic Cerebrovascular Patients
ZHANG SS (2015)	Chinese	64.35 ± 11.88	61.13 ± 13.76	100 mg/d	96	9	87	Sequenom Mass ARRAY iPLEX	Cerebral Ischemic Stroke Patient
CAO LP (2014)	Chinese	64.21 ± 12.71	59.45 ± 12.50	100 mg/d	859	67	792	Sequencing	Cerebral Ischemic Stroke Patient

Table 1: The general situation of the study.

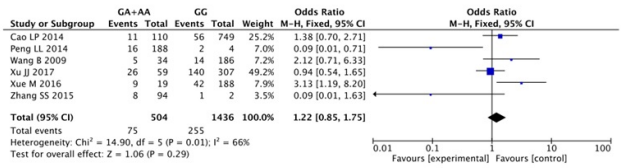

Figure 2: The forest plots in meta-analysis of the relationship between *COX-1* gene *ra3842788* polymorphism and aspirin resistance.

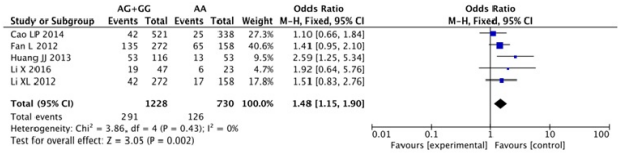

Figure 3: The forest plots in meta-analysis of the relationship between *COX-1* gene *ra1330344* polymorphism and aspirin resistance.

Discussion

Aspirin blocks the aggregation of platelet by inhibiting the acetylation of the 529 serine of cox-115. Therefore, we evaluate the association of two common polymorphisms (*rs3742788* and *rs1330344*) from *COX-1* with aspirin resistance via the meta-analysis.

RS3842788

In this systematical review and meta-analysis of six studies and 1940 subjects, there is no consistent association between a SNP (*rs3842788*) on *COX-1* and the resistance of aspirin.

One possible explanation for the negative association is that encoded Glutamine does not change because of the polymorphism. Since the mutant site is the third position of the codon, the mutation from G to A is synonymous.

Moreover, from the data shown in Table 2, we found that Homozygous mutation is rare, which might potentially reduce the effect of *rs3842788*. One of the reasons that some studies suggested positive correlation between this SNP and AR is the change of Motif structure [8].

Author (year)	AR		AS		P-value	Allelic frequency
	CG	GA+AA	GG	GA+AA		(G/A)
Ping LL (2014)	2	16	2	172	0.045	0.950/0.050
XU JJ (2017)	140	26	167	33	0.687	0.915/0.085
XUE M (2016)	42	9	146	10	0.016	0,954/0.046
Wang B (2009)	172	29	14	5	0.22	0.914/0.086
ZHANG SS (2015)	1	8	1	86	0.045	0.950/0.050
CAO LP (2014)	56	11	693	99	0.457	0.934/0.066

Table 2: Distribution of *rs3842788* genotype in *COX-1* gene in patients and controls.

RS1330344

In this systematical review and meta-analysis of five studies and 1958 subjects, there has a significant association between *rs1330344* and aspirin resistance. The possible reason is that *rs1330344* locate in the promoter region of the *COX-1* gene, and the GG type promotes the aggregation of platelets by increasing the expression of *COX-1* proteins and produces phenomenon of aspirin resistance [6]. The study shows that the average frequency of G alleles is 40%, and that the distribution frequencies of *rs1330344* in Japanese and Chinese are the same, so the *rs1330344* may be a marker SNP for aspirin resistance in Asians 14.

Author (year)	AR		AS		Allelic frequency
	CG	GA+AA	GG	GA+AA	(G/A)
Huang JJ (2013)	13	53	40	63	0.411/0.589
Fan L (2012)	65	135	93	137	0.399/0.601
Li XL (2012)	17	42	141	230	0.405/0.595
Cao LP (2014)	25	42	313	479	0.385/0.615
Li X (2016)	6	19	17	28	0.407/0.593

Table 3: Distribution of *rs1330344* genotype in *COX-1* gene in patients and controls.

Strengths and limitations of the study

Aspirin is a common drug in the treatment of cardiovascular and cerebrovascular diseases, but a phenomenon called "aspirin resistance" inhibits the therapeutic effect of aspirin. Previously, the association of aspirin resistance and genetic polymorphism was analyzed by a collection of clinical trials, but the results of these studies were sometimes inconsistent, and the sample size too small [12]. Therefore, we conducted a meta-analysis to combine results from different studies and did a comprehensive summary analysis. Despite the significance of our study, the meta-analysis has several potential limitations. First of all, although we have searched for all the published literature, the sample size is still relatively limited so that subgroup analyses cannot be taken into consideration. Second, since we only retrieved Chinese and English literatures, sample selection bias could not be excluded. At the same time, all the studied subjects are Chinese, while the occurrence of aspirin resistance may have diversity between Chinese and other ethnicities. Third, sometimes *COX-2* is also associated with AR. Therefore, the implication of the interaction between different genes that may lead to aspirin resistance cannot be assessed. These possible explanations indicated the need for further research.

Conclusions

In spite of these limitations, the study established that *rs1330344* in *COX-1* is associated with aspirin resistance directly while *rs3842788* isn't in Chinese populations. This meta-analysis offers contribution to the further study of genetic mutations to aspirin resistance. Along with the proposal of the Human Genome Project and the development of gene-sequencing technology, practitioners could find more effective therapy for individuals based on their genetic characteristics. This kind of method that connects individual's genes with disease treatment and prevention is defined as precision medicine. This meta-analysis provides a basis for the doctor's diagnose aspirin resistance.

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All authors (Zhu Wang, Yiyu Chen, Sihan Hu, Rui Liu, Wanxi Yang) contributed equally to the work and approved the final version of the manuscript submitted for publication.

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