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Original Article

Factor XIII-A Val34Leu polymorphism might be associated with myocardial infarction risk: an updated meta-analysis

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Abstract: Although many epidemiologic studies have investigated the *FXIII-A* Val34Leu polymorphism and their associations with myocardial infarction (MI), definite conclusions can't be drawn. To clarify the effects of *FXIII-A* Val34Leu polymorphism on the risk of MI, a meta-analysis was performed. Related studies were identified from PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) till 10 August 2014. Pooled ORs and 95% CIs were used to assess the strength of the associations. A total of 12 studies including 3139 MI cases and 6343 healthy controls were involved in this meta-analysis. A significantly decreased MI risk was found (adjusted OR = 0.70, 95% CI 0.60-0.82, $P < 0.00001$). In the subgroup analysis by age, significantly decreased risks were found in the young population (OR = 0.70, 95% CI 0.54-0.91, $P = 0.008$) and old population (OR = 0.63, 95% CI 0.50-0.80, $P = 0.0001$). In the subgroup analysis by gender, significantly decreased risks were found in male (OR = 0.55, 95% CI 0.34-0.88, $P = 0.01$) and female (OR = 0.72, 95% CI 0.55-0.95, $P = 0.02$). When we limited the meta-analysis to studies that controlled for confounders such as age, sex, BMI, smoking, diabetes, hypertension, dyslipidemia, and fibrinogen, a significant association between *FXIII-A* Val34Leu polymorphism and MI risk remained. This meta-analysis provides the evidence that *FXIII-A* Val34Leu polymorphism may significant associated with the MI risk.

Keywords: Meta-analysis, FXIII-A, polymorphism, myocardial infarction

Introduction

Myocardial infarction (MI), one of the most serious cardiovascular diseases, remains a leading cause of morbidity and mortality worldwide [1]. Rapid and precise diagnosis provides opportunity to immediate therapy and to dramatically decrease the mortality. However, it is straightforward, difficult, or somewhere in between to recognize if the patient is suffering from MI.

Circulating FXIII consists of two identical proenzyme (A_2) and carrier-protein (B_2) subunits. The A subunit contains the active center, the activation peptide, a calcium-binding site, and free sulfhydryl groups. A depression of FXIII activities with a nadir on day 4 after the onset of MI was demonstrated [2]. It was also shown on postmortem material that the local FXIII-A level in the myocardium was significantly lower in MI patients with infarct rupture when compared with the myocardium of MI patients who died without rupture [3]. The gene for subunit A is on chromosome 6 (p24-p25), consists of 160 kilobases and has 15 exons. The FXIII Leu34 genetic variant, present in 40% of the caucasian population, is one ofthe most relevant functional polymorphisms described in the haemostatic system, as it increases and accelerates fibrin stabilization. A series of studies have investigated the association between the *FXIII-A* Val34Leu polymorphism and MI susceptibility, but provided controversial or inconclusive results [4-15]. Thus, we performed this meta-analysis to assess the relationship of *FXIII-A* Val34Leu polymorphism with risk of MI.

Materials and methods

Materials

We searched databases containing PubMed, Springer Link, Ovid, Chinese Wanfang Data

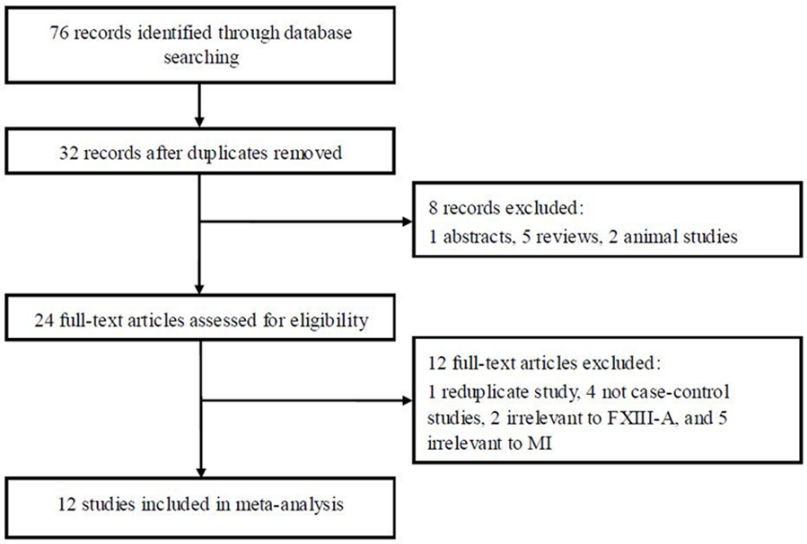

Figure 1. Flow of study identification, inclusion, and exclusion.

Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM) up to 10 August 2014, using the following Mesh terms: ("myocardial infarction" [MeSH] or "myocardial infarct" or "MI") and ("Factor XIII" or "F13A1"). We limited the languages to English and Chinese. Besides, the references from retrieved articles were also searched.

Inclusion/exclusion criteria

Studies included in this meta-analysis have to meet the following criteria: (1) case-control study or cohort study studying on associations between *FXIII-A* Val34Leu polymorphism and the risk of MI; (2) all patients with the diagnosis of MI confirmed by coronary angiography; (3) all studies should provided adjusted odds ratios (ORs), and their 95% confidence intervals (CIs); (4) published in English or Chinese language; (5) the distribution of the genotypes in control groups was in the Hardy-Weinberg equilibrium (HWE). Studies were excluded when they were: (1) duplicate of previous publication; (2) based on incomplete data; (3) meta-analyses, letters, reviews, or editorial articles.

Data extraction

Data were independently extracted by two reviewers using a standardized data extraction form. Discrepancies were resolved by discussion and if consensus was not achieved the decision was made by all the reviewers. The title and abstract of all potentially relevant articles were screened to determine their relevance. Full articles were also scrutinized if the title and abstract were ambiguous. The following information was collected from each study: author, year of publication, race, sample size, age, gender, numbers of cases and controls, covariates.

Methodological quality assessment

Two authors assessed the study quality. The Newcastle-Ottawa Scale (NOS) was used to evaluate the methodological quality [16].

Statistical analysis

Statistical analysis was conducted by using STATA statistical package (version 11, STATA, College Station, TX). The distributions of genotypes in controls were tested by HWE using the Chi-square test. The association of *FXIII-A* Val34Leu polymorphism and MI risk was estimated by ORs with 95% CIs. The heterogeneity was tested by the Q-statistics with *P*-values < 0.1, and its possible sources of heterogeneity were assessed by subgroup analysis. The random effect model (DerSimonian and Laird) was selected to summarize the combined OR and their 95% CI. The significance of the pooled OR was determined by the z test. Publication bias was investigated by the method of Egger's linear regression test [17]. All the *P* values were two sided. *P* value less than 0.05 was considered statistically significant.

Results

Eligible studies

The flow chart in **Figure 1** summarizes this literature review process. According to the inclusion criteria, 12 case-control studies were included. The publication year of involved studies ranged from 1999 to 2011. In total, 3139 MI cases and 6343 healthy controls were

Table 1. Characteristics of the included studies

Study	Year	Race	Age	Gender	No. of participants	Adjustment for covariates	Quality score
Wartiovaara 1	1999	Caucasian	58.3	Male	68/219	Age, body mass index	7
Wartiovaara 2	1999	Caucasian	56.3	Male	58/126	Age, body mass index, smoking, total cholesterol, HDL, cholesterol, triglycerides	7
Kakko	2002	Caucasian	52.8	Mixed	142/142	Plasma HDL cholesterol levels, body mass index, smoking, Gpla polymorphism	8
Reiner	2002	Caucasian	23-44	Female	68/345	Smoking, obesity, hypertension, diabetes, hypercholesterolaemia, menopausal status, Factor V Leiden, Prothrombin G20210A polymorphism, Glycoprotein Iib polymorphism	7
ATVB	2003	Caucasian	39	Mixed	1210/1210	Smoking, diabetes, hypertension, family history, body mass index, hypercholesterolemia, alcohol, cocaine, physical exercise	9
Reiner	2003	Caucasian	67.3	Female	234/721	Age, race	8
Martini	2005	Caucasian	20-47	Mixed	54/1210	Gender, age, geographical origin	9
Roldan	2005	Caucasian	44	Mixed	281/530	Gender, smoking habit, diabetes, hypertension, hypercholesterolemia	7
Hancer	2006	Caucasian	27-60	Mixed	130/130	Body mass index, smoking, diabetes mellitus, hypertension, hyperlipidemia, positive family history	8
Salazar-Sánchez	2006	Caucasian	16-77	Mixed	186/201	Gender, smoking, obesity, hypertension, diabetes, hypercholesterolaemia, fibrinogen, family history	7
Bereczky	2007	Caucasian	47.9-69.3	Mixed	307/1146	Gender, age	8
Rallidis	2008	Caucasian	32.1	Mixed	159/121	Smoking, hypertension, hypercholesterolaemia, fibrinogen	9
Silvain	2011	Caucasian	39.1	Mixed	242/242	Heredity, smoking status, overweight, dyslipidemia, diabetes, fibrinogen	7

Table 2. Results of this meta-analysis

	OR (95% CI)	*P* Value	I^2 (%)
Overall	0.70 (0.60-0.82)	<0.00001	38
Age <50	0.70 (0.54-0.91)	0.008	53
Age >50	0.63 (0.50-0.80)	0.0001	0
Male	0.55 (0.34-0.88)	0.01	0
Female	0.72 (0.55-0.95)	0.02	0
Adjust for			
Gender	0.70 (0.51-0.97)	0.03	60
Age	0.76 (0.63-0.90)	0.002	0
BMI	0.73 (0.56-0.94)	0.02	37
Hypertension	0.65 (0.48-0.89)	0.007	64
Diabetes	0.70 (0.53-0.93)	0.01	60
Fibrinogen	0.72 (0.53-0.99)	0.04	0
Dyslipidemia	0.66 (0.53-0.83)	0.0003	49

involved in this meta-analysis, which evaluated the relationship between *FXIII-A* Val34Leu polymorphism and MI risk. All the MI cases and controls were Caucasians. The characteristics of the included studies are summarized in **Table 1**.

Quantitative synthesis

The main results of this meta-analysis and the heterogeneity test were shown in **Table 2**. A significantly decreased MI risk was found (adjusted OR = 0.70, 95% CI 0.60-0.82, *P* < 0.00001, **Figure 2**). In the subgroup analysis by age, significantly decreased risks were found in the young population (OR = 0.70, 95% CI 0.54-0.91, *P* = 0.008) and old population (OR = 0.63, 95% CI 0.50-0.80, *P* = 0.0001). In the subgroup analysis by gender, significantly decreased risks were found in male (OR = 0.55, 95% CI 0.34-0.88, *P* = 0.01) and female (OR = 0.72, 95% CI 0.55-0.95, *P* = 0.02). When we limited the meta-analysis to studies that controlled for confounders such as age, sex, BMI, smoking, diabetes, hypertension, dyslipidemia, and fibrinogen, a significant association between *FXIII-A* Val34Leu polymorphism and MI risk remained (**Table 2**).

Sensitive analysis and bias diagnosis

To evaluate the stability of the results of the meta-analysis, sensitivity analysis was performed through sequentially omitted individual studies. None of the results were materially changed, which suggested the robustness of our results (data not shown).

The Egger's test was performed to assess the publication bias of literatures. The Egger's test indicated that there was no obvious publication bias (P = 0.441).

Discussion

Although many studies analyzing the research results about the *FXIII-A* Val34Leu polymorphism and MI risk, definite conclusions cannot be drawn. Therefore, we did this meta-analysis to estimate the relationships between *FXIII-A* Val34Leu polymorphism and susceptibility to MI. The meta-analysis involved 12 articles. The results from this meta-analysis showed that the *FXIII-A* Val34Leu polymorphism had a significant protective effect against MI.

To our knowledge, there are two published meta-analyses regarding *FXIII-A* Val34Leu polymorphism and MI risk [18, 19]. Shafey et al. [18] found that there was an association between the *FXIII-A* Leu allele and a modest protective effect against MI. Chen et al. [19] found that *FXIII-A* Val34Leu polymorphism was a protective factor for MI in Caucasians. These results were consistent with our results in over all analysis. However, Chen et al. [19] suggested that *FXIII-A* Val34Leu polymorphism was not significantly associated with MI risk in males, which was not in line with our result. It was possible that there was significant heterogeneity in their meta-analysis, and no significant heterogeneity was found in our meta-analysis.

Our meta-analysis has several strengths. First, it was the first meta-analysis which reported the adjusted ORs between *FXIII-A* Val34Leu polymorphism and MI risk. Second, when we limited the meta-analysis to studies that controlled for age, sex, BMI, smoking, diabetes, hypertension, dyslipidemia, and fibrinogen, the significant positive association was only marginally altered. Third, we have followed the inclusion and exclusion criteria strictly to reduce possible selection bias. Fourth, Egger's linear regression test was used to assess publication bias. Fifth, the sensitivity analysis had been performed to confirm the reliability and stability of this meta-analysis. Last but not least, impact of different genetic background was minimized, because all included studies were performed with Caucasians.

The limitations to this meta-analysis should be acknowledged. First, the number of studies

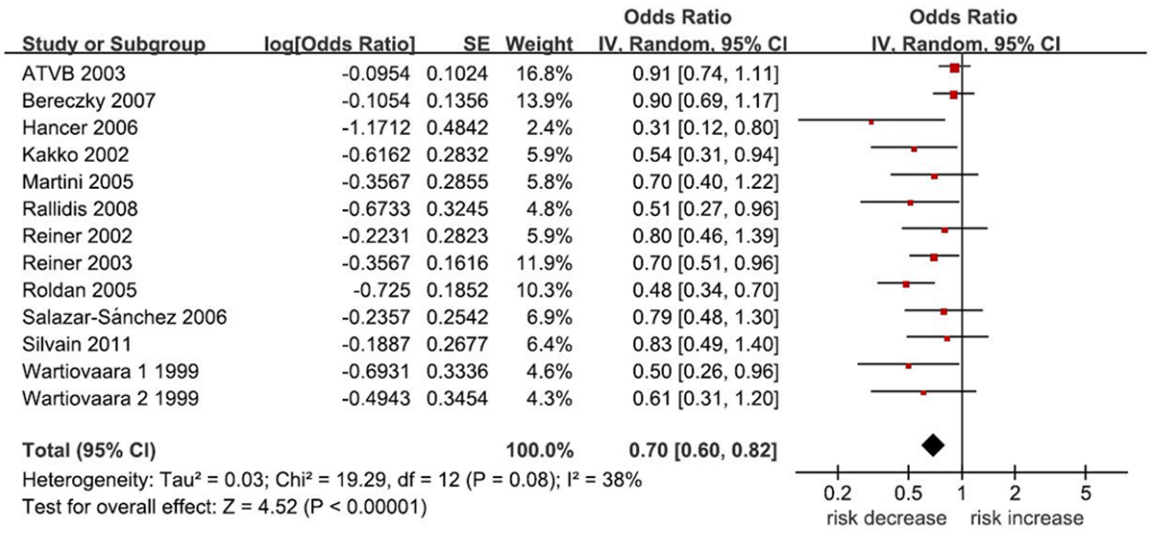

Figure 2. Forest plot for the association between *FXIII-A* Val34Leu polymorphism and MI risk.

included in our meta-analysis remained small. Thus, publication bias may exist, although Egger's linear regression tests indicated no remarkable publication bias. Second, lacking of the original data of the eligible studies limited the evaluation of the effects of the gene-environment interactions in MI development. Third, no prospective studies have addressed this association between *FXIII-A* Val34Leu polymorphism and MI risk, and all included studies followed a retrospective case-control design. Thus, owing to the limitations of case-control design, we can't exclude the possibility of undetected bias.

In conclusion, our meta-analysis supports that *FXIII-A* Val34Leu polymorphism might be associated with the susceptibility to MI.

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Disclosure of conflict of interest

None.

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