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PTPN22 R620W Polymorphism is Associated with Myasthenia Gravis Risk: A Systematic Review and Meta-Analysis





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Statistical Analysis C
Data Interpretation D
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- Background:** The association between PTPN22 R620W polymorphism and risk of myasthenia gravis (MG) remains controversial. Therefore, we did this meta-analysis to investigate this association.
- Material/Methods:** We did a comprehensive search in PubMed, Medline, Embase, CNKI (China National Knowledge Infrastructure), and Wanfang electronic databases to retrieve relevant articles. The overall effect was measured by odds ratios (ORs) with its 95% confidence intervals (CIs). Statistical analyses were conducted with STATA software.
- Results:** Overall, a total of 7 case-control studies with 2802 cases and 3730 controls were finally included in this review. PTPN22 R620W polymorphism was significantly associated with an increased risk of MG (OR=1.57; 95% CI, 1.34–1.82; $I^2=31\%$). In the subgroup analysis, thymoma patients were significantly associated with risk of MG (OR=1.59; 95% CI, 1.28–1.98; $I^2=0\%$). However, non-thymoma patients with this polymorphism did not have increased MG risk (OR=1.36; 95% CI, 0.86–2.15; $I^2=77\%$). In addition, PTPN22 R620W polymorphism showed increased early-onset myasthenia gravis (EOMG) risk (OR=2.38; 95% CI, 1.52–3.71; $I^2=0\%$).
- Conclusions:** This meta-analysis shows a significant association between PTPN22 R620W polymorphism and MG risk.
- MeSH Keywords:** **Genetic Association Studies • Meta-Analysis • Myasthenia Gravis**
- Full-text PDF:** <http://www.medscimonit.com/abstract/index/idArt/894307>

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Background

The annual incidence of myasthenia gravis (MG) is reported to be 0.25–4 patients per 100 000 population, with the first peak of onset around the second and third decades of life and the second peak around the fifth and sixth decades [1]. In most cases, it is caused by pathogenic autoantibodies directed toward the skeletal muscle acetylcholine receptor (AChR), but in others, non-AChR components of the postsynaptic muscle endplate, such as the muscle-specific receptor tyrosine kinase (MUSK), might serve as targets of autoimmune attack [2]. The exact mechanism of the autoimmune response in MG is unknown [3–5]. However, genetic factors might play an important role in the development of MG [6,7].

Human leukocyte antigen (HLA) *loci* are associated with all autoimmune diseases and are the strongest genetic factors for individual predisposition [8]. Of the non-HLA susceptibility genes, variants of protein tyrosine phosphatase non-receptor type (PTPN22) show the strongest associations with autoimmune diseases. A SNP in PTPN22 has been reported to be associated with type 1 diabetes (T1DM) [9], rheumatoid arthritis (RA) [10], systemic lupus erythematosus (SLE) [11], Hashimoto's thyroiditis [12].

In addition, some studies also suggested that PTPN22 R620W polymorphism was associated with MG risk [13–19]. However, the association between this polymorphism and the risk of MG was controversial and inconclusive. Thus, we did a meta-analysis to determine if this polymorphism could influence MG risk.

Material and Methods

Publication search

We did a comprehensive search in PubMed, Medline, Embase, CNKI (China National Knowledge Infrastructure) and Wanfang to retrieve relevant articles. We retrieved the relevant articles using the following terms: “myasthenia gravis”, “PTPN22”, and “polymorphism or variant or mutation” as well as their combinations. We searched the references of retrieved articles with no language restriction.

Inclusion and exclusion criteria

The studies must meet the following criteria: 1) the paper should be case-control studies; 2) evaluating the contribution of PTPN22 R620W polymorphism with MG risk; 3) genotype distributions in the cases and controls were available to extract, and the results presented in odds ratio (ORs) with its 95% confidence interval (CI); and 4) for a certain polymorphism, genotype distribution in the controls must be in Hardy-Weinberg equilibrium (HWE).

Data extraction

Two investigators independently estimated the extracted data of the included studies to reach a consensus. The following information was extracted from each article: first author, year of publication, country, ethnicity, age, gender, type of MG, sample size.

Quality assessment

The Newcastle-Ottawa scale (NOS) for case-control studies was used to assess the methodological quality of every included study. Three parameters were examined in the NOS: selection, comparability, and exposure. The highest study quality was nine stars with a maximum of four stars for selection, two stars for comparability, and three stars for exposure in the NOS. The ultimate score of 6 stars or more was regarded as high-quality.

Statistical analysis

The overall effect was measured by ORs with its 95% CI. The significance of the pooled ORs was determined by the Z test with a *P* value less than 0.05 considering statistically significant. The per-allele model was examined to assess this association. Between-studies heterogeneity was assessed by the I^2 test and the Q-statistic test. The random-effect model was used. The publication bias was estimated by funnel plot. We did a sensitivity analysis. Statistical analyses were conducted in STATA version 11.0 (Stata Corporation, College station, TX, USA). All the tests were two-sided. Bonferroni correction was applied.

Results

Study characteristics

Of the 46 references, 3 records excluded for duplication and 43 articles were judged potentially relevant. Following titles and abstracts screened for relevance, 36 full-text articles comprehensively assessed against inclusion criteria. A total of 7 case-control studies with 2802 cases and 3730 controls were finally included in this review. Figure 1 showed the study flow. All of the studies were performed using Caucasians. Table 1 shows the main characteristics of studies for meta-analysis. All the included studies were high quality studies.

Results of meta-analysis

The results are summarized in Table 2. PTPN22 R620W polymorphism was significantly associated with the risk of MG (OR=1.57; 95% CI, 1.34–1.82; $I^2=31%$; Figure 2). In addition, thymoma patients was significantly associated with risk of MG (OR=1.59; 95% CI, 1.28–1.98; $I^2=0%$). However, non-thymoma

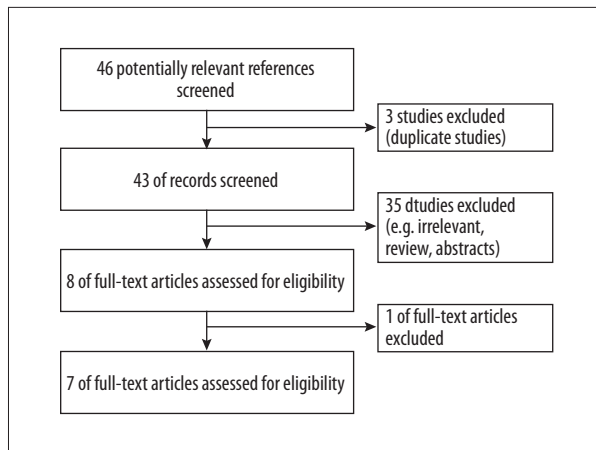


Figure 1. Flow chat of study selection process.

patients with this polymorphism did not have increased MG risk (OR=1.36; 95% CI, 0.86-2.15; $I^2=77\%$). Furthermore, PTPN22 R620W polymorphism showed increased early-onset myasthenia gravis (EOMG) risk (OR=2.38; 95% CI, 1.52-3.71; $I^2=0\%$). The sensitivity analysis suggested that the corresponding pooled ORs were not materially altered (data not shown).

Table 1. Characteristics of the included studies.

First author	Year	Country	Ethnicity	Age	Gender	Type of MG	Total cases (n)	Total controls (n)	Hardy-Weinberg equilibrium	Quality Score
Vandiedonck	2006	France	Caucasian	33	Mixed	Mixed	470	296	Yes	7
Lefvert	2008	Sweden	Caucasian	NA	Mixed	Mixed	409	1557	Yes	9
Chuang	2009	Germany	Caucasian	27	Mixed	EOMG	129	172	Yes	7
Greve 1	2009	Germany	Caucasian	NA	Mixed	Mixed	134	199	Yes	8
Greve 2	2009	Hungary	Caucasian	NA	Mixed	Mixed	148	180	Yes	8
Gregersen	2012	France	Caucasian	45	Mixed	EOMG	740	649	Yes	9
Provenzano	2012	Italy	Caucasian	40	Mixed	Mixed	356	384	Yes	8
Kaya	2014	Turkey	Caucasian	50	Mixed	Mixed	416	293	Yes	8

EOMG – early-onset myasthenia gravis.

Table 2. Results of meta-analysis and subgroup analyses.

	Test of association			Model	Heterogeneity		
	OR (95% CI)	Z	P value		χ^2	P value	I^2 (%)
Overall	1.57 (1.34–1.82)	5.74	<0.00001	R	10.08	0.18	31
Thymoma	1.59 (1.28–1.98)	4.15	<0.0001	R	4.80	0.44	0
Nonthymoma	1.36 (0.86–2.15)	1.31	0.19	R	8.51	0.01	77
EOMG	2.38 (1.52–3.71)	3.82	0.001	R	0.01	0.93	0

R – random-effects model; EOMG – early-onset myasthenia gravis.

The shape of the funnel plot showed symmetry (Figure 3). Egger's test also found no evidence of publication bias ($P=0.865$).

Discussion

MG is an acquired organ-specific autoimmune disease, characterized by fluctuating weakness and fatigability of voluntary muscles due to the impairment of the neuromuscular transmission caused by autoantibodies. There is an urgent need to look for biomarkers evaluating the severity of the disease, predicting the prognosis of patients, and targeting the pathogenic genes. The present meta-analysis including 7 studies evaluated the association between PTPN22 R620W polymorphism and MG risk. We found that individuals with the PTPN22 R620W polymorphism showed an increased risk of MG in the overall population. This result suggested that PTPN22 R620W polymorphism may be a risk factor of MG. Furthermore, we found that PTPN22 R620W polymorphism might also be a risk factor of EOMG. In the subgroup analysis, thymoma patients with PTPN22 R620W polymorphism were significantly associated with risk of MG.

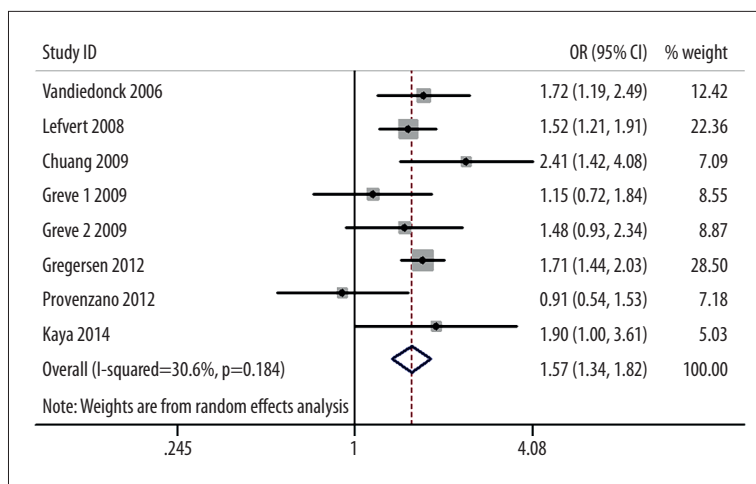


Figure 2. Meta-analysis for the association between PTPN22 R620W polymorphism and MG risk.

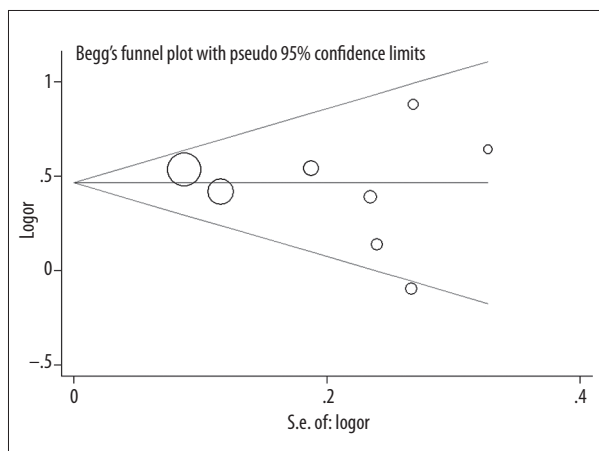


Figure 3. Funnel plot for the association between PTPN22 R620W polymorphism and MG risk.

Previous study has reported the function of PTPN22 R620W polymorphism in Jurkat cell transfectants [20]. Vang and co-workers investigated effects of R620 versus W620 in cell stimulation with anti-CD3 and anti-CD28 [21]. They found that mutant phosphatase inhibited NFAT/AP1 more efficient with

W620 variant than R620 variant. Thus, they suggested that W620 variant predisposed to MG because W620 variant may suppress T cell antigen receptor (TCR) signaling more potentially during thymic development.

Several limitations should be addressed. Firstly, the subgroups may have a relatively lower power based on a small number of studies. Secondly, a more precise analysis should be conducted if individual information including other covariates such as age, sex and smoking condition becomes available. Thirdly, the gene-gene interaction is important for the development of complex diseases including MG.

Conclusions

This meta-analysis suggested a significant association between PTPN22 R620W polymorphism and MG risk.

Disclosure of conflict of interest

None.

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