## **Associations between TYK2 polymorphism and susceptibility to multiple** **autoimmune diseases: rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis**

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Tables: xxx

Figures: xx

Run title: TYK2 polymorphism and multiple autoimmune diseases

## **Abstract**

TYK2 gene play important roles in RET signaling and interferon gamma signaling and has been reported to be associated with multiple autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis. However, the quantitative evaluation to the association have never been conducted yet. In this study, we applied meta-analysis to provide accurate assessment to the association between polymorphism in TYK2 with multiple autoimmune diseases in different population. We retrieved nine studies from different database including Pubmed, xx and xxx and finally genotyping distribution in 33,345 cases and 57,642 controls was collected.

Keywords Tyrosine kinase 2 ·polymorphism · autoimmune diseases

## **Introduction**

Autoimmune diseases are known as immune system disorders, the immune cells are unable to distinguish self-antigens from foreign ones 1.The clear pathogenesis of these diseases is complicated and it is a combination of many factors, such as genetic and environmental factors 2.The etiologic pathways or mechanism of autoimmune diseases have something in common.

Tyrosine kinase 2 (TYK2) is a member of the Janus kinase (JAK) family, its situation is on the chromosome 19p13.2. The function of TYK2 is regulating the signaling of proinflammatory cytokines, including type 1 interferons (IFNα) and IL12, IL233. TYK2 binds to the interferon-α receptor (IFNAR) on the cell surface of IFN-producing cells. TYK2 is bound to IFNAR in its inactive state. When IFN-α binds to IFNAR, TYK2 can be phosphorylated and further activated4. If the TYK2 is activated, then the IFNAR is phosphorylated subsequently allowing binding of signal transducer and activator of transcription 3 (STAT3) and signal transducer and activator of transcription 5 (STAT5)5. We have reason to believe that TYK2 is related to autoimmune diseases. So far, many case-control studies was done to verify this conclusion6–14. Limited by sample size, clinical heterogeneity, ethnic background or other conditions, the conclusions are inconsistent. Therefore, we perform a meta-analysis to overcome these limitations. Our meta-analysis was aim to investigate associations between TYK2 polymorphism and susceptibility to autoimmune diseases: rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc).

## **Method**

#### Study Oversight

The study was conducted at two hospitals including Shanghai Guanghua Hospital, Shanghai, China. The research protocol were approved by the institute review board at Guanghua Hospital with the approve No. 09DZ1906500. The entire author participated manuscript draft and made the decision to submit the manuscript. In addition, all the authors vouch for the completeness and accuracy of the data and corresponding analysis.

#### Identification of eligible studies

Autoimmune diseases include a lot of diseases, our study focus on RA, SLE and SSc. We use the keywords (“tyrosine kinase 2” or “TYK2”) and (‘‘polymorphism’’ or ‘‘variation’’) and (‘‘rheumatoid arthritis” or “systemic” or “lupus erythematosus” or “systemic sclerosis” or “autoimmune diseases”) searching the relevant publications in the Pubmed database. We also investigated the references to these articles, in case of missing relevant literature.

#### Inclusion and exclusion criteria

A study was included in our meta-analysis if (1) it was published up to October 2019; (2) it was a case–control study; (3) provided sufficient genotype or allele data. Studies were excluded if (1) it contained overlapping data; (2) its number of genotypes or alleles could not be ascertained; (3) it included the family member; (4) reviews, conference or meeting abstracts.

#### Data extraction

Two investigators (Zhang and xx) screened titles, abstracts and full texts independently blind to journal names, countries, institutions, supporting organizations and funds. The differences between the two investigators were resolved by discussion. The following data from each study were extracted: first author's name, publication year, country, continent, ethnicity, HWE, number of cases and controls, the gender ratios in cases and controls, mean ages in cases and controls, minor allele frequencies (MAFs) in cases and controls, the source of controls, quality score, genotyping methods, gout type and other descriptions. The result was reviewed by the another two independent investigator (xxx and xxx).

#### Statistical analysis

Pooled ORs and 95% confidence intervals (CIs) were used to evaluate the strength of association between polymorphism and RA, SLE, SSc risk for every study. Hardy–Weinberg equilibrium (HWE) was tested in control using Chi square test 15. When P <0.05, it was considered as HWE deviation.

## **Results**

#### Studies involved in our meta-analysis

The information of every studies including author, year, number of genotypes, diseases, countries are presented in Table16–14.A total of 85 studies were identified according to searching items (**Fig. 1)** .72 studies were excluded for review, meta-analysis and repetition, 13 studies were included for full articles reading. 4 studies16–19were excluded for unavailable data, then 9 studies6–14 were included in our meta-analysis finally. ………………………………………………………………………………………………………………………………………………………………………………………………………………………….………

Kinases or transcription regulatory factors often have an abnormal expression in the autoimmune cells that participate in the pathogenesis of autoimmune disease, the Janus kinase family is a kind of these20. TYK2, a member of the JAK family, is associated with some autoimmune disease, such as RA, SLE, SSc and multiple sclerosis(MS)9,14,21. In other studies, the conclusions are reversed7,10. It is necessary to perform a comprehensive meta-analysis to assess the association between TYK2 gene polymorphisms and autoimmune diseases susceptibility. Autoimmune diseases are caused by complex genetic and environmental interactions which comprise at least 80 disorders20. And there is hypothesis that autoimmune and inflammatory diseases shared a common genetic basis2. We chose RA, SLE, SSc as our research target.

9 studies were retrieved in our meta-analysis, including 33345 cases and 57642 controls…………………………………………………..

Table1 Characteristics of the individual studies included in the meta-analysis

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SNP | Auther/year | population | Diseases | Genotype  (case/ctrl) | | | | | |  | |
|  |  |  |  | TT |  | CT |  | CC |  | |  |
| rs12720270 | Contreras, 201913 | Mexicans | SLE | 9 | 16 | 97 | 150 | 262 | 350 | |
|  | Hellquist,20096 | Finland | SLE | 21 | 28 | 37 | 94 | 200 | 217 | |
|  | Kyogoku,20097 | Japanese | SLE | 13 | 10 | 31 | 50 | 25 | 34 | |
|  | Li P, 201110 | Chinese | SLE | 207 | 760 | 331 | 1257 | 131 | 521 | |
|  | Tang L, 201511 | Chinese | SLE | 545 | 539 | 95 | 101 | 2 | 2 | |
|  |  |  |  | AA |  | AC |  | CC |  | |
| rs12720356 | Contreras, 2019 | Mexicans | SLE | 363 | 493 | 5 | 23 | 0 | 0 | |
|  | Hellquist, 2009 | Finland | SLE | 240 | 295 | 36 | 58 | 1 | 3 | |
|  | Lo, 201512 | Mixed | SSc | 6183 | 10388 | 888 | 1758 | 32 | 74 | |
|  |  |  |  | AA |  | AC |  | CC |  | |
| rs2304256 | Contreras, 2019 | Mexicans | SLE | 11 | 21 | 103 | 167 | 254 | 328 | |
|  | Hellquist, 2009 | Finland | SLE | 12 | 34 | 92 | 153 | 173 | 169 | |
|  | Kyogoku, 2009 | Japanese | SLE | 13 | 11 | 31 | 50 | 25 | 33 | |
|  | Li P, 2011 | Chinese | SLE | 230 | 842 | 325 | 1240 | 114 | 456 | |
|  | Lo, 2015 | Mixed | SSc | 430 | 951 | 2635 | 4916 | 4038 | 6353 | |
|  | Suarez, 20098 | Spanish | RA | 109 | 138 | 626 | 750 | 900 | 1018 | |
|  | Suarez, 20099 | Mixed | SLE | 84 | 126 | 559 | 680 | 936 | 920 | |
|  | Tang L, 2015 | Chinese | SLE | 367 | 465 | 248 | 160 | 27 | 17 | |
|  |  |  |  | GG |  | GA |  | AA |  | |
| rs280500 | Contreras, 2019 | Mexicans | SLE | 1 | 1 | 42 | 51 | 325 | 464 | |
|  | Li P, 2011 | Chinese | SLE | 1 | 5 | 59 | 214 | 609 | 2319 | |
|  | Tang L, 2015 | Chinese | SLE | 352 | 408 | 228 | 229 | 62 | 35 | |
|  |  |  |  | GG |  | GA |  | AA |  | |
| rs280519 | Kyogoku, 2009 | Japanese | SLE | 18 | 21 | 33 | 49 | 17 | 24 | |
|  | Li P, 2011 | Chinese | SLE | 283 | 1049 | 305 | 1166 | 81 | 323 | |
|  | Tang L, 2015 | Chinese | SLE | 183 | 150 | 270 | 256 | 189 | 206 | |
|  |  |  |  | CC |  | CG |  | GG |  | |
| rs34536443 | Contreras, 2019 | Mexicans | SLE | 0 | 0 | 9 | 21 | 359 | 495 | |
|  | Lo, 2015 | Mixed | SSc | 4 | 8 | 319 | 619 | 6780 | 11593 | |
|  | Mohamad, 201914 | Iranian | RA | 1 | 0 | 8 | 7 | 691 | 693 | |

Response:

1. Author/Year can reduced to year only to make the table much concise.
2. We do not need HWE in the last column.
3. Think about how make this table looks better and we hope we can put them in one page, not two page.
4. Find another collaborator to check your reference collection steps, he/she will be co-first author.
5. I will help you to prepare all the remaining figures and tables for you after you are sure the table 1 is accurate and perfect. I want you make sure no paper was left in reference collection step.
6. I hope we can complete it and submit before spring festival
7. Check more previous meta-analysis, and find a best way to check this table within in one page.



Figure 1.

## **Availability of data and materials**

All the data were available upon the reader’s request.

## **Authors’ contributions**

SG and DH designed and coordinated the study. RZ and xx collected the literature. RZ, xx and xx extract the genotype and clinical information from the manuscript. SG, RZ, xx, xx, and xx analyzed the data. SG and RZ prepared the draft and all authors were involved in critical review, editing, revision, and approval of the final manuscript.

## **Disclosure of Conflicts of Interest**

The authors declare no conflict of interest.

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