Association of tyrosine kinase 2 polymorphisms with Susceptibility to Microscopic polyangiitis in a Guangxi Population (#104289)

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Association of tyrosine kinase 2 polymorphisms with Susceptibility to Microscopic polyangiitis in a Guangxi Population

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Background. Heredity and epigenetics affect the pathogenesis of microscopic polyangiitis (MPA). Tyrosine kinase 2 (TYK2) polymorphisms (rs2304256C>A, rs280519A>G, and rs12720270G>A) may be potential protective factors against anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Current research suggests that TYK2 is associated with various autoimmune diseases; however, no study has examined the relationship between TYK2 polymorphisms and AAV. This study assesses the effect of TYK2 polymorphisms on susceptibility to MPA. **Methods.** A total of 562 Chinese participants (265 MPA patients and 297 healthy volunteers) were recruited. Polymerase chain reactions combined with high-throughput sequencing were used to analyze polymorphic loci, and logistic regression analysis was used to analyze the relationship between polymorphism of TYK2 gene and MPA susceptibility. **Results.** In males, individuals with the CA genotype (rs2304256) in the overdominant model showed a significantly reduced risk of MPA (OR = 0.52; 95% CI = 0.29–0.93; p = 0.025). In the dominant model, the rs280519, carriers of the AG genotype in the codominant model (OR = 0.51; 95% CI: 0.28–0.93; p = 0.039) and overdominant model (OR = 0.48; 95% CI: 0.27–0.86; p = 0.013) showed a significantly lower risk of MPA. For the rs12720270, the GA genotype was associated with a low susceptibility to MPA (OR = 0.52; 95% CI: 0.29–0.93; p = 0.027). **Conclusions.** This study indicates that mutations in the TYK2 gene (rs2304256, rs280519, and rs12720270) may be associated with a reduced risk of MPA in the male Chinese population in Guangxi. The A allele of single nucleotide polymorphism (SNP) rs2304256 may be a protective factor against MPA, while the G alleles of SNPs rs280519 and rs12720270 are protective factors against MPA.

Association of Tyrosine kinase 2 Polymorphisms with Susceptibility to Microscopic Polyangiitis in a Guangxi Population

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Abstract

Background. Heredity and epigenetics affect the pathogenesis of microscopic polyangiitis (MPA). Tyrosine kinase 2 (TYK2) polymorphisms (rs2304256C>A, rs280519A>G, and rs12720270G>A) may be potential protective factors against anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Current research suggests that TYK2 is associated with various autoimmune diseases; however, no study has examined the relationship between TYK2 polymorphisms and AAV. This study assesses the effect of TYK2 polymorphisms on susceptibility to MPA.

Methods. A total of 562 Chinese participants (265 MPA patients and 297 healthy volunteers) were recruited. Polymerase chain reactions combined with high-throughput sequencing were used to analyze polymorphic loci, and logistic regression analysis was used to analyze the relationship between polymorphism of TYK2 gene and MPA susceptibility.

Results. In males, individuals with the CA genotype (rs2304256) in the overdominant model showed a significantly reduced risk of MPA (OR = 0.52; 95% CI = 0.29–0.93; $p = 0.025$). In the dominant model, the rs280519, carriers of the AG genotype in the codominant model (OR = 0.51; 95% CI: 0.28–0.93; $p = 0.039$) and overdominant model (OR = 0.48; 95% CI: 0.27–0.86; $p = 0.013$) showed a significantly lower risk of MPA. For the rs12720270, the GA genotype was associated with a low susceptibility to MPA (OR = 0.52; 95% CI: 0.29–0.93; $p = 0.027$).

Conclusions. This study indicates that mutations in the TYK2 gene (rs2304256, rs280519, and rs12720270) may be associated with a reduced risk of MPA in the male Chinese population in Guangxi. The A allele of single nucleotide polymorphism (SNP) rs2304256 may be a protective

factor against MPA, while the G alleles of SNPs rs280519 and rs12720270 are protective factors against MPA.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a heterogeneous group of small vasculitis of unknown etiology, characterized by the presence of proteinase 3 (PR3) and myeloperoxidase (MPO) in the serum (Kitching et al. 2020). This condition often involves inflammation and necrosis of the vessel wall. There are several types of this systemic vasculitis, including granulomatosis with polyangiitis (GPA) (Puechal 2020) , microscopic polyangiitis (MPA) (Aiyegbusi et al. 2021; Hunter et al. 2020), and eosinophilic granulomatosis with polyangiitis (EGPA) (Treccani et al. 2024). The distribution of AAV subtypes varies by region. GPA is prevalent in Northern Europe (Berti et al. 2017), while MPA is more common in China and Japan (Fujimoto et al. 2011; Watts & Scott 2012).

The incidence of MPA ranges from 0.5 to 24.0 cases per million person-years, and its prevalence ranges from 9.0 to 94.0 cases per million person-years, with onset ages ranging from 55 to 75 years (Kitching et al. 2020). In Asia, the reported prevalence of AAV is between 46 and 421 per million population (Kawasaki & Tsuchiya 2021). Kidney damage occurs in nearly all patients with MPA, characterized by necrotizing and crescentic pauci-immune glomerulonephritis. Deterioration of renal function can lead to end-stage renal disease and increased mortality (Binda et al. 2018).

The human leukocyte antigen (Genotyping and data quality control) region is a significant genetic risk factors for AAV (Trivioli et al. 2022). Genome-wide studies have identified a unique association between MPA and HLA-DQ (Li et al. 2021). In Chinese populations, the alleles HLA DQA1*03:02 and DQB1*03:03 are associated with MPO-AAV susceptibility (Wang et al. 2019). Similarly, in Japanese populations, these alleles are associated with both MPO-AAV susceptibility and recurrence risk (Kawasaki et al. 2023). The genetic studies enhance our understanding of the genetic susceptibility factors contributing to AVV, thereby improving patient management and treatment strategies.

Tyrosine kinase 2 (TYK2) is a vital signal transduction kinase in Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway (Gonciarz et al. 2021), which is crucial in the differentiation of T helper 1 (Th1) and T helper type 17 (Th17) cells. Dysfunction of TYK2 can contribute to the development of autoimmune and inflammatory diseases (Muromoto et al. 2021). The necessity of TYK2 activity for interleukin (IL)-12, IL-23 and type I interferon (IFN1) signaling has been demonstrated experimentally in mice with TYK2 deficiency (Gorman et al. 2019). Moreover, inhibiting TYK2 activity has been reported to block the downstream signal transduction of IL-12 and other cytokines (Elyoussfi et al. 2023). TYK2 gene mutations are genetically linked to ankylosing spondylitis, psoriasis, Crohn's disease, ulcerative colitis, type 1 diabetes (T1DM), multiple sclerosis (MS), lupus erythematosus (SLE), and rheumatoid arthritis (RA) (Parkes et al. 2013). Currently, research indicates that multiple selective inhibitors of TYK2 have been approved for the treatment of autoimmune

diseases, such as plaque psoriasis (Rusinol & Puig 2023; Yuan et al. 2023). Novel TYK2 inhibitors are expected to have significant clinical impacts (Muromoto et al. 2021). Previous research has reported a close association between TYK2 variants and AAV in European individuals; however, there are currently no reports on the association between TYK2 gene rs2304256, rs280519, rs1272027 variants and MPA in the Chinese population in Guangxi.

Materials & Methods

Ethics approval

This study was approved by the Medical Ethics Committee of The Second Affiliated Hospital of Guangxi Medical University (2018 KY-0100) and was carried out in compliance with the Declaration of Helsinki. We have obtained written consent from all subjects.

Study subjects

The MPA cohort was comprised of 265 patients with microscopic polyangiitis from the Second Affiliated Hospital of Guangxi Medical University during January 2005 and January 2019, whose diagnosis criteria met the International Chapel Hill Consensus Conference Nomenclature of Vasculitides criteria (Jennette et al. 2013). Patients with secondary vasculitis caused by other factors (external infections, tumors, drugs) and with other autoimmune disease (rheumatoid arthritis, systemic lupus erythematosus, Henoch-Schonlein purpura) were excluded. In addition, 297 healthy subjects were included in the normal control group who were confirmed to be free of MPA, other autoimmune diseases and malignancies.

Genotyping and data quality control

Genotyping was performed using multiplex polymerase chain reaction (PCR) and high-throughput sequencing (Sangon Biotech, Shanghai, China). **Data quality control**: First, any part of the sequence containing the sequenced splitter sequence was excised using cutadapt (v 1.2.1)(Martin 2011) software, then the remaining sequence was quality-controlled using PRINSEQ-lite (v 0.20.3) software(Huang et al. 2018), and bases with a quality threshold <20 were removed from the 3' end to the 5' end of the sequence. The remaining sequences were considered to be qualified for quality control. **Genotyping**: The mapping program BWA-MEM (v 0.7.13-r1126)(Alganmi & Abusamra 2023) was used to align the qualified sequences to the reference genome(Genome Reference Consortium Human Build 37). According to the comparison results(Zheng-Bradley et al. 2017), the genotypic results of the target locus were calculated by samtools software (version 0.1.18)(Li et al. 2009a). Finally, Annovar(version 2018-04-16) software(Wang et al. 2010) was used to annotate the mutation sites. Genomic DNA was extracted using the corresponding kit (cat. no. DP319-02; Beijing Tiangen Biotech (Beijing) Co., Ltd.). Nanodrop 2000 spectrophotometer (Thermo Fisher Scientific, Inc.) was used to measure the concentration of DNA.

Statistical analysis

The SPSS 26.0 software (IBM, Armonk, NY, USA) (Liang et al. 2019)was used for statistical analysis. We used the two-sample T-test and Chi-square test (x2) to analyze the demographic features of subjects. The Chi-square test (x2) and Fisher's exact tests were used to evaluate Hardy-Weinberg equilibrium, genotype, and allele frequencies. SNPstats (https://www.snpstats.net/start.htm) (Sole et al. 2006), a web tool used for SNP analysis, was used to examine the link between TYK2 gene polymorphism and MPA susceptibility with an unmatched case-control design and unconditional logistic regression. Indeed, to assess the association between TYK2 gene polymorphisms and MPA susceptibility, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated after adjustment for age, race, and gender. In addition, haplotypes analysis(Li et al. 2009b) were estimated by SHEsis online software (http://analysis.bio-x.cn)(Shi & He 2005). Bonferroni correction was performed for multiple analyses with more than two groups. The p-value<0.05 was considered significant.

Results

Characteristics of the Study Subjects

The case group consisted of 265 cases, including 96 males and 169 females; 163 were Han Chinese and 102 were non-Han Chinese. The participant's ages ranged from 18 and 86 years, with a median age of 59. The control group consisted of 297 healthy volunteers who underwent physical examinations during the same period, including 124 males and 173 females; 220 were Han Chinese and 77 were non-Han Chinese. The age range was between 18 and 81 years old, with a median age of 48. While there was no statistically significant difference in the gender distribution between the two groups ($p = 0.18$), there were statistically significant differences in the ethnicity and age distribution ($p < 0.001$). Further stratification analysis using 60 years as the cutoff point showed no statistically significant difference between the two groups (Age < 60, $p = 0.099$; Age>=60, $p = 0.621$). Theoretically, the control group's age and gender should match those of the patients with MPA group; however, only partial matching was observed between the case and control groups. Consequently, in the subsequent genetic model analysis and subgroup analysis, adjustment was made for confounding factors such as age and ethnicity (Table 1).

Information for selected single nucleotide polymorphisms (SNPs)

Table 2 lists the basic information of 4 TYK2 SNP loci and the preliminary analysis of susceptibility to MPA. The four SNPs selected in this study were located in different regions of the TYK2 gene on chromosome 19, including exon (rs2304256 and rs2304255) and intron (rs280519 and rs12720270). The genotype frequency distributions of all SNPs were in Hardy-Weinberg equilibrium (HWE) ($p > 0.05$), and minor allele frequency (MAF) were also calculated for patients with MPA and healthy controls. Previous studies have demonstrated that rare genotypes may produce spurious findings (Tabangin et al. 2009). Therefore, we prioritized SNPs with MAF>0.05 as the primary research targets (International HapMap 2003). However,

rs2304255 did not meet the MAF threshold (MAF ⩽5%), showing no statistical significance, and was thus excluded from subsequent correlation analyses.

Association between the selected SNPs and MPA susceptibility

We conducted a further analysis across different layers utilizing various genetic models to assess the impact of TYK2 variant polymorphisms (rs2304256, rs280519, and rs12720270) on the risk of MPA. However, no statistically significant differences were observed (see Table 3). Consequently, we performed a subgroup analysis of the sample based on gender (male and female), age (<60 years and ⩾60 years), and ethnicity (Han and non-Han).The results showed that the association between SNPs and MPA risk was influenced by sex, particularly in male subgroup ($p < 0.05$). Specifically, rs2304256 reduced the risk of MPA with the CA genotype in the overdominant model (odds ratio (OR) = 0.52; 95% confidence interval (CI): 0.29–0.93; p = 0.025). In rs280519, carriers of the AG genotype in the codominant (OR = 0.51; 95% CI: 0.28-0.93; p = 0.039) and overdominant models (OR = 0.48; 95% CI: 0.27–0.86; p = 0.013) showed a significantly lower risk of MPA. For rs12720270, the GA genotype in the overdominant model was associated with a low susceptibility to MPA (OR = 0.52; 95% CI: 0.29–0.93; p = 0.027) (Table 4). However, no positive results were observed in the female subgroup (Table 5). Similarly, we performed a subgroup analysis based on age (< 60 years and ⩾ 60 years) and ethnicity (Han and non-Han) within the sample; however, no statistically significant differences were observed (p > 0.05) (Supplementary Table 1-2).

Correlation of the haplotypes of TYK2 gene with MPA susceptibility

The analysis of haplotypes of the TYK2 gene in relation to MPA susceptibility is presented in Table 6. Four haplotypes, formed by the alleles of rs2304256, rs280519, and rs12720270, were identified. However, these haplotypes did not demonstrate any significant association with susceptibility to MPA.

Discussion

Current research indicates that MPA is closely associated with genetic, environmental, and patient age (Hunter et al. 2020), In this case-control study, we examine the relationships between three potential effect SNPs of TYK2 gene and MPA risk in a Guangxi population in China.TYK2 is the first member of the JAK family, a 27.9-kb gene with 25 exons located on chromosome 19p13.2 (Lindqvist et al. 2000). This gene moderates immune responses to IL-12, IL-23, IFNα, and Th17 (Gonzalez Lopez de Turiso & Guckian 2022). The research shows that IL-12, IL-23, IFNα, Th1, and Th17 are closely associated with PMA (Ortiz-Fernandez et al. 2020; Yuan et al. 2023). For example, in an ANCA-mediated mouse model of experimental vasculitis, Hoshino et al. found that activated neutrophils produced IL-17A and IL-23 via the classical complement pathway in response to MPO-ANCA. This pathway provides a local environment that promotes IL-17 production and Th17-mediated autoimmunity, becoming the first step in the initiation of chronic autoimmune inflammation (Hoshino et al. 2008).

Rs2304256 is one of the most common SNPs of TYK2, located in exon 8, and its genetic association has been widely investigated (Gonciarz et al. 2021; Morand et al. 2024). Although rs2304256 is associated with SLE in Finnish, Swedish, British (Cunninghame Graham et al. 2007; Hellquist et al. 2009; Sigurdsson et al. 2005; Suarez-Gestal et al. 2009), and Chinese Han populations (Tang et al. 2015), it shows reversed association in Hong Kong (Li et al. 2011) and Japanese (Kyogoku et al. 2009) populations. TYK2 rs2304256 was verified to be closely related to systemic sclerosis susceptibility (SSc) in the European population (Lopez-Isac et al. 2016), while the results were negative in the Chinese Han SSc population (Liu et al. 2021). These inconsistencies appear to arise from differences in geography and ethnicity (Liu et al. 2021). Pellenz et al. (2021b) pooled data from 34 articles for a meta-analysis assessing the impact of multiple TYK2 variants on susceptibility to autoimmune diseases. Their data suggested that rs2304256 is a susceptibility factor for several autoimmune diseases, including SLE, MS, and rheumatoid RA, with the A allele acting as a protective factor (Pellenz et al. 2021). Our study illustrated that the rs2304256 (A>C) variant in the overdominant model potentially decreases susceptibility to MPA in males. This effect is because the A allele contributes to the substitution of valine 362 with phenylalanine in the JAK homologous 4 (JH4) region. This domain is crucial for the interaction between TYK2 and IFNAR1, essential for maintaining IFNAR1 expression on the cell membrane. The amino acid substitution affects the processing of precursor mRNA (Li et al. 2020), leading to downregulation of IFN-α signaling and subsequent reduction in proinflammatory cytokines and inflammation (Marroqui et al. 2015). Additionally, both the PolyPhen-2 and sorting intolerant from tolerant (SIFT) tools indicate that rs2304256 is a benign variant (Adzhubei et al. 2010; Kumar et al. 2009), aligning with our research findings.

The rs280519 and rs12720270 variants are located in the TYK2 intron region. An earlier meta-analysis, including 16,335 SLE patients and 30,065 controls, revealed that the rs280519 polymorphism was significantly associated with SLE risk in Caucasians and Asians (Lee & Bae 2016). A Turkish study involving 60 patients with Crohn's disease and 151 patients with ulcerative colitis found that the rs280519 AA genotype was a risk factor for ulcerative colitis, while the AG genotype was a protective factor for ulcerative colitis and Crohn's disease (Can et al. 2015). Affected by the interferon (IFN) signaling pathway, the rs280519 G (A>G) allele may influence the severe National Institute on Aging classification in patients with chronic hepatitis C (Lopez-Rodriguez et al. 2017). Moreover**,** both the rs280519 and rs12720270 variants reduced the risk of juvenile idiopathic arthritis in a Chinese Han population (Qian et al. 2022), Additionally, rs12720270 may downregulate COVID-19 severity by decreasing TYK2 expression (Zabihi Rizi et al. 2023). Our study results show that rs280519A>G may be related to autoimmune diseases and chronic inflammatory diseases, which is consistent with our research findings. Similarly, in the codominant and overdominant models, the AG genotype of rs280519 can reduce male susceptibility to PMA. In the overdominant model, the GA genotype of rs12720270 can also reduce male susceptibility to PMA. We hypothesize that the intronic variants rs280519 and rs12720270 may cause splicing abnormalities, intronic mutations, protein coding disruption, altering of residues positions, and loss or insertion of the internal coding

frame (Bryen et al. 2019). This may lead to abnormal expression of TYK2, thus affecting the cytokine signaling pathway (Zabihi Rizi et al. 2023) and ultimately reducing susceptibility to MPA. However, no significant effects were found in females across the three loci (Table 4). Overall, this study explored the relationship between TYK2 gene polymorphisms in the Guangxi population and susceptibility to MPA. It revealed that TYK2 gene polymorphisms rs2304256, rs280519, and rs12720270 in the male population of Guangxi may be associated with susceptibility to MPA. The strength of this study include the subgroup analysis across various genetic models and multiple SNP interactions. However, as a single-center retrospective study with limited cases, these conclusions require validation through larger, multi-center, prospective clinical studies.

Conclusions

This study found that mutations in the TYK2 gene—rs2304256, rs280519, and rs12720270—may be associated with a reduced risk of MPA in the male Chinese population in Guangxi. The A allele of SNP rs2304256 may be a protective factor against MPA, while the G alleles of SNPs rs280519 and rs12720270 are protective factors against MPA. However, the potential molecular mechanisms need further investigation.

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References

Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, Kondrashov AS, and Sunyaev SR. 2010. A method and server for predicting damaging missense mutations. *Nat Methods* 7:248-249. 10.1038/nmeth0410-248

Aiyegbusi O, Frleta-Gilchrist M, Traynor JP, Mackinnon B, Bell S, Hunter RW, Dhaun N, Kidder D, Stewart G, Joss N, Kelly M, Shah S, Dey V, Buck K, Stevens KI, Geddes CC, McQuarrie EP, and Scottish Renal Biopsy R. 2021. ANCA-associated renal vasculitis is associated with rurality but not seasonality or deprivation in a complete national cohort study. *RMD Open* 7. 10.1136/rmdopen-2020-001555

Alganmi N, and Abusamra H. 2023. Evaluation of an optimized germline exomes pipeline using BWA-MEM2 and Dragen-GATK tools. *PLoS One* 18:e0288371. 10.1371/journal.pone.0288371

Berti A, Cornec D, Crowson CS, Specks U, and Matteson EL. 2017. The Epidemiology of Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis in Olmsted County, Minnesota: A Twenty-Year US Population-Based Study. *Arthritis Rheumatol* 69:2338-2350. 10.1002/art.40313

Binda V, Moroni G, and Messa P. 2018. ANCA-associated vasculitis with renal involvement. *J Nephrol* 31:197-208. 10.1007/s40620-017-0412-z

Bryen SJ, Joshi H, Evesson FJ, Girard C, Ghaoui R, Waddell LB, Testa AC, Cummings B, Arbuckle S, Graf N, Webster R, MacArthur DG, Laing NG, Davis MR, Luhrmann R, and Cooper ST. 2019. Pathogenic Abnormal Splicing Due to Intronic Deletions that Induce Biophysical Space Constraint for Spliceosome Assembly. *Am J Hum Genet* 105:573-587. 10.1016/j.ajhg.2019.07.013

Can G, Tezel A, Gurkan H, Can H, Yilmaz B, Unsal G, Soylu AR, and Umit HC. 2015. Tyrosine kinase-2 gene polymorphisms are associated with ulcerative colitis and Crohn's disease in Turkish Population. *Clin Res Hepatol Gastroenterol* 39:489-498. 10.1016/j.clinre.2015.01.005

Cunninghame Graham DS, Manku H, Wagner S, Reid J, Timms K, Gutin A, Lanchbury JS, and Vyse TJ. 2007. Association of IRF5 in UK SLE families identifies a variant involved in polyadenylation. *Hum Mol Genet* 16:579-591. 10.1093/hmg/ddl469

Elyoussfi S, Rane SS, Eyre S, and Warren RB. 2023. TYK2 as a novel therapeutic target in psoriasis. *Expert Rev Clin Pharmacol* 16:549-558. 10.1080/17512433.2023.2219054

Fujimoto S, Watts RA, Kobayashi S, Suzuki K, Jayne DR, Scott DG, Hashimoto H, and Nunoi H. 2011. Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the U.K. *Rheumatology (Oxford)* 50:1916-1920. 10.1093/rheumatology/ker205

Gonciarz M, Pawlak-Bus K, Leszczynski P, and Owczarek W. 2021. TYK2 as a therapeutic target in the treatment of autoimmune and inflammatory diseases. *Immunotherapy* 13:1135-1150. 10.2217/imt-2021-0096

Gonzalez Lopez de Turiso F, and Guckian K. 2022. Selective TYK2 inhibitors as potential therapeutic agents: a patent review (2019-2021). *Expert Opin Ther Pat* 32:365-379. 10.1080/13543776.2022.2026927

Gorman JA, Hundhausen C, Kinsman M, Arkatkar T, Allenspach EJ, Clough C, West SE, Thomas K, Eken A, Khim S, Hale M, Oukka M, Jackson SW, Cerosaletti K, Buckner JH, and Rawlings DJ. 2019. The TYK2-P1104A Autoimmune Protective Variant Limits Coordinate Signals Required to Generate Specialized T Cell Subsets. *Front Immunol* 10:44. 10.3389/fimmu.2019.00044

Hellquist A, Jarvinen TM, Koskenmies S, Zucchelli M, Orsmark-Pietras C, Berglind L, Panelius J, Hasan T, Julkunen H, D'Amato M, Saarialho-Kere U, and Kere J. 2009. Evidence for genetic association and interaction between the TYK2 and IRF5 genes in systemic lupus erythematosus. *J Rheumatol* 36:1631-1638. 10.3899/jrheum.081160

Hoshino A, Nagao T, Nagi-Miura N, Ohno N, Yasuhara M, Yamamoto K, Nakayama T, and Suzuki K. 2008. MPO-ANCA induces IL-17 production by activated neutrophils in vitro via classical complement pathway-dependent manner. *J Autoimmun* 31:79-89. 10.1016/j.jaut.2008.03.006

Huang G, Zhao G, Xia J, Wei Y, Chen F, Chen J, and Shi J. 2018. FGF2 and FAM201A affect the development of osteonecrosis of the femoral head after femoral neck fracture. *Gene*:S0378111918301112.

Hunter RW, Welsh N, Farrah TE, Gallacher PJ, and Dhaun N. 2020. ANCA associated vasculitis. *BMJ* 369:m1070. 10.1136/bmj.m1070

International HapMap C. 2003. The International HapMap Project. *Nature* 426:789-796. 10.1038/nature02168

Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, and Watts RA. 2013. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 65:1-11. 10.1002/art.37715

Kawasaki A, Sada KE, Kusumawati PA, Hirano F, Kobayashi S, Nagasaka K, Sugihara T, Ono N, Fujimoto T, Kusaoi M, Tamura N, Kusanagi Y, Itoh K, Sumida T, Yamagata K, Hashimoto H, Makino H, Arimura Y, Harigai M, and Tsuchiya N. 2023. Association of HLA-class II alleles with risk of relapse in myeloperoxidase-antineutrophil cytoplasmic antibody positive vasculitis in the Japanese population. *Front Immunol* 14:1119064. 10.3389/fimmu.2023.1119064

Kawasaki A, and Tsuchiya N. 2021. Advances in the genomics of ANCA-associated vasculitis-a view from East Asia. *Genes Immun* 22:1-11. 10.1038/s41435-021-00123-x

Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, Kullman J, Lyons PA, Merkel PA, Savage COS, Specks U, and Kain R. 2020. ANCA-associated vasculitis. *Nat Rev Dis Primers* 6:71. 10.1038/s41572-020-0204-y

Kumar P, Henikoff S, and Ng PC. 2009. Predicting the effects of coding non-synonymous variants on protein function using the SIFT algorithm. *Nat Protoc* 4:1073-1081. 10.1038/nprot.2009.86

Kyogoku C, Morinobu A, Nishimura K, Sugiyama D, Hashimoto H, Tokano Y, Mimori T, Terao C, Matsuda F, Kuno T, and Kumagai S. 2009. Lack of association between tyrosine kinase 2 (TYK2) gene polymorphisms and susceptibility to SLE in a Japanese population. *Mod Rheumatol* 19:401-406. 10.1007/s10165-009-0173-1

Lee YH, and Bae SC. 2016. Association between TYK2 polymorphisms and susceptibility to autoimmune rheumatic diseases: a meta-analysis. *Lupus* 25:1307-1314. 10.1177/0961203316638933

Li H, Handsaker B, Wysoker A, Fennell T, Ruan J, Homer N, Marth G, Abecasis G, Durbin R, and Genome Project Data Processing S. 2009a. The Sequence Alignment/Map format and SAMtools. *Bioinformatics* 25:2078-2079. 10.1093/bioinformatics/btp352

Li P, Chang YK, Shek KW, and Lau YL. 2011. Lack of association of TYK2 gene polymorphisms in Chinese patients with systemic lupus erythematosus. *J Rheumatol* 38:177-178. 10.3899/jrheum.100424

Li W, Huang H, Cai M, Yuan T, and Sheng Y. 2021. Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Update: Genetic Pathogenesis. *Front Immunol* 12:624848. 10.3389/fimmu.2021.624848

Li Z, Rotival M, Patin E, Michel F, and Pellegrini S. 2020. Two common disease-associated TYK2 variants impact exon splicing and TYK2 dosage. *PLoS One* 15:e0225289. 10.1371/journal.pone.0225289

Li Z, Zhang Z, He Z, Tang W, Li T, Zeng Z, He L, and Shi Y. 2009b. A partition-ligation-combination-subdivision EM algorithm for haplotype inference with multiallelic markers: update of the SHEsis (http://analysis.bio-x.cn). *Cell Res* 19:519-523. 10.1038/cr.2009.33

Liang G, Fu W, and Wang K. 2019. Analysis of t-test misuses and SPSS operations in medical research papers. *Burns Trauma* 7:31. 10.1186/s41038-019-0170-3

Lindqvist AK, Steinsson K, Johanneson B, Kristjansdottir H, Arnasson A, Grondal G, Jonasson I, Magnusson V, Sturfelt G, Truedsson L, Svenungsson E, Lundberg I, Terwilliger JD, Gyllensten UB, and Alarcon-Riquelme ME. 2000. A susceptibility locus for human systemic lupus erythematosus (hSLE1) on chromosome 2q. *J Autoimmun* 14:169-178. 10.1006/jaut.1999.0357

Liu C, Yan S, Chen H, Wu Z, Li L, Cheng L, Li H, and Li Y. 2021. Association of GTF2I, NFKB1, and TYK2 Regional Polymorphisms With Systemic Sclerosis in a Chinese Han Population. *Front Immunol* 12:640083. 10.3389/fimmu.2021.640083

Lopez-Isac E, Campillo-Davo D, Bossini-Castillo L, Guerra SG, Assassi S, Simeon CP, Carreira P, Ortego-Centeno N, Garcia de la Pena P, Spanish Scleroderma G, Beretta L, Santaniello A, Bellocchi C, Lunardi C, Moroncini G, Gabrielli A, Riemekasten G, Witte T, Hunzelmann N, Kreuter A, Distler JH, Voskuyl AE, de Vries-Bouwstra J, Herrick A, Worthington J, Denton CP, Fonseca C, Radstake TR, Mayes MD, and Martin J. 2016. Influence of TYK2 in systemic sclerosis susceptibility: a new locus in the IL-12 pathway. *Ann Rheum Dis* 75:1521-1526. 10.1136/annrheumdis-2015-208154

Lopez-Rodriguez R, Hernandez-Bartolome A, Borque MJ, Rodriguez-Munoz Y, Martin-Vilchez S, Garcia-Buey L, Gonzalez-Moreno L, Real-Martinez Y, Munoz de Rueda P, Salmeron J, Vidal-Castineira JR, Lopez-Larrea C, Rodrigo L, Moreno-Otero R, and Sanz-Cameno

P. 2017. Interferon-related genetic markers of necroinflammatory activity in chronic hepatitis C. *PLoS One* 12:e0180927. 10.1371/journal.pone.0180927

Marroqui L, Dos Santos RS, Floyel T, Grieco FA, Santin I, Op de Beeck A, Marselli L, Marchetti P, Pociot F, and Eizirik DL. 2015. TYK2, a Candidate Gene for Type 1 Diabetes, Modulates Apoptosis and the Innate Immune Response in Human Pancreatic beta-Cells. *Diabetes* 64:3808-3817. 10.2337/db15-0362

Martin M. 2011. Cutadapt removes adapter sequences from high-throughput sequencing reads. *Embnet Journal* 17.

Morand E, Merola JF, Tanaka Y, Gladman D, and Fleischmann R. 2024. TYK2: an emerging therapeutic target in rheumatic disease. *Nat Rev Rheumatol* 20:232-240. 10.1038/s41584-024-01093-w

Muromoto R, Shimoda K, Oritani K, and Matsuda T. 2021. Therapeutic Advantage of Tyk2 Inhibition for Treating Autoimmune and Chronic Inflammatory Diseases. *Biol Pharm Bull* 44:1585-1592. 10.1248/bpb.b21-00609

Ortiz-Fernandez L, Lopez-Mejias R, Carmona FD, Castano-Nunez AL, Lyons PA, Caruz A, Gonzalez-Escribano MF, Smith KGC, Gonzalez-Gay MA, Martin J, Spanish Gca Study Group ISGAAVSG, and Group HIVS. 2020. The role of a functional variant of TYK2 in vasculitides and infections. *Clin Exp Rheumatol* 38:949-955.

Parkes M, Cortes A, van Heel DA, and Brown MA. 2013. Genetic insights into common pathways and complex relationships among immune-mediated diseases. *Nat Rev Genet* 14:661-673. 10.1038/nrg3502

Pellenz FM, Dieter C, Lemos NE, Bauer AC, Souza BM, and Crispim D. 2021. Association of TYK2 polymorphisms with autoimmune diseases: A comprehensive and updated systematic review with meta-analysis. *Genet Mol Biol* 44:e20200425. 10.1590/1678-4685-GMB-2020-0425

Puechal X. 2020. Granulomatosis with polyangiitis (Wegener's). *Joint Bone Spine* 87:572-578. 10.1016/j.jbspin.2020.06.005

Qian Y, Chen B, Wang Z, and Peng Y. 2022. Genetic association between the PTPN22, IRF5 and TYK2 gene variants and susceptibility to juvenile idiopathic arthritis. *Exp Ther Med* 24:756. 10.3892/etm.2022.11692

Rusinol L, and Puig L. 2023. Tyk2 Targeting in Immune-Mediated Inflammatory Diseases. *Int J Mol Sci* 24. 10.3390/ijms24043391

Shi YY, and He L. 2005. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. *Cell Res* 15:97-98. 10.1038/sj.cr.7290272

Sigurdsson S, Nordmark G, Goring HH, Lindroos K, Wiman AC, Sturfelt G, Jonsen A, Rantapaa-Dahlqvist S, Moller B, Kere J, Koskenmies S, Widen E, Eloranta ML, Julkunen H, Kristjansdottir H, Steinsson K, Alm G, Ronnblom L, and Syvanen AC. 2005. Polymorphisms in the tyrosine kinase 2 and interferon regulatory factor 5 genes are associated with systemic lupus erythematosus. *Am J Hum Genet* 76:528-537. 10.1086/428480

Sole X, Guino E, Valls J, Iniesta R, and Moreno V. 2006. SNPStats: a web tool for the analysis of association studies. *Bioinformatics* 22:1928-1929. 10.1093/bioinformatics/btl268

Suarez-Gestal M, Calaza M, Endreffy E, Pullmann R, Ordi-Ros J, Sebastiani GD, Ruzickova S, Jose Santos M, Papasteriades C, Marchini M, Skopouli FN, Suarez A, Blanco FJ, D'Alfonso S, Bijl M, Carreira P, Witte T, Migliaresi S, Gomez-Reino JJ, Gonzalez A, and European Consortium of SLEDNAC. 2009. Replication of recently identified systemic lupus erythematosus genetic associations: a case-control study. *Arthritis Res Ther* 11:R69. 10.1186/ar2698

Tabangin ME, Woo JG, and Martin LJ. 2009. The effect of minor allele frequency on the likelihood of obtaining false positives. *BMC Proc* 3 Suppl 7:S41. 10.1186/1753-6561-3-S7-S41

Tang L, Wan P, Wang Y, Pan J, Wang Y, and Chen B. 2015. Genetic association and interaction between the IRF5 and TYK2 genes and systemic lupus erythematosus in the Han Chinese population. *Inflamm Res* 64:817-824. 10.1007/s00011-015-0865-2

Treccani M, Veschetti L, Patuzzo C, Malerba G, Vaglio A, and Martorana D. 2024. Genetic and Non-Genetic Contributions to Eosinophilic Granulomatosis with Polyangiitis: Current Knowledge and Future Perspectives. *Curr Issues Mol Biol* 46:7516-7529. 10.3390/cimb46070446

Trivioli G, Marquez A, Martorana D, Tesi M, Kronbichler A, Lyons PA, and Vaglio A. 2022. Genetics of ANCA-associated vasculitis: role in pathogenesis, classification and management. *Nat Rev Rheumatol* 18:559-574. 10.1038/s41584-022-00819-y

Wang HY, Cui Z, Pei ZY, Fang SB, Chen SF, Zhu L, Chen M, Chen N, and Zhao MH. 2019. Risk HLA class II alleles and amino acid residues in myeloperoxidase-ANCA-associated vasculitis. *Kidney Int* 96:1010-1019. 10.1016/j.kint.2019.06.015

Wang K, Li M, and Hakonarson H. 2010. ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data. *Nucleic Acids Res* 38:e164. 10.1093/nar/gkq603

Watts RA, and Scott DG. 2012. ANCA vasculitis: to lump or split? Why we should study MPA and GPA separately. *Rheumatology (Oxford)* 51:2115-2117. 10.1093/rheumatology/kes230

Yuan S, Wang L, Zhang H, Xu F, Zhou X, Yu L, Sun J, Chen J, Ying H, Xu X, Yu Y, Spiliopoulou A, Shen X, Wilson J, Gill D, Theodoratou E, Larsson SC, and Li X. 2023. Mendelian randomization and clinical trial evidence supports TYK2 inhibition as a therapeutic target for autoimmune diseases. *EBioMedicine* 89:104488. 10.1016/j.ebiom.2023.104488

Zabihi Rizi F, Ghorbani A, Zahtab P, Darbaghshahi NN, Ataee N, Pourhamzeh P, Hamzei B, Dolatabadi NF, Zamani A, and Hooshmand M. 2023. TYK2 single-nucleotide variants associated with the severity of COVID-19 disease. *Arch Virol* 168:119. 10.1007/s00705-023-05729-2

Zheng-Bradley X, Streeter I, Fairley S, Richardson D, Clarke L, Flicek P, and Genomes Project C. 2017. Alignment of 1000 Genomes Project reads to reference assembly GRCh38. *Gigascience* 6:1-8. 10.1093/gigascience/gix038

Table 1(on next page)

Demographic features of MPA cases and control group

Table 1: Demographic features of MPA cases and control group

Variable	Case (n=265)	Control (n=297)	*p*
Gender (male/female)	96/169	124/173	0.18
Ethnicity (Han/ non-Han)	163/102	220/77	<0.01*
Age (years)	59(47,67) [a]	48(38,55.5) [a]	<0.01*
Age<60 (years)	136	244	0.099
Age≥60 (years)	129	53	0.621

NOTE: MPA: microscopic polyangiitis; n: number of people; a: The description of skewed distribution data statistics uses median (lower quartile, upper quartile) representation; *p*-value: The Student's t-test or the Chi-square test (x2) was used to compare variables in groups; * denotes statistical significance($p<0.05$)

Table 2(on next page)

Basic information of the selected SNPs

Table 2: Basic information of the selected SNPs

SNP	Chromosome	Position	Alleles	Gene	Role	MAF		HWE-*p*	Allele-*p*	Genotype-*p*
						Control	Case			
rs2304256	chr19	10475652	C>A	TYK2	Exon	0.40	0.38	0.46	0.55	0.83
rs280519	chr19	10472933	A>G	TYK2	Intron	0.33	0.33	0.19	0.91	0.65
rs2304255	chr19	10475649	C>T	TYK2	Exon	**0.03**	**0.03**	0.61	--	--
rs12720270	chr19	10475760	G>A	TYK2	Intron	0.43	0.42	0.34	0.74	0.89

NOTE:MPA: microscopic polyangiitis; SNP: single nucleotide polymorphism; MAF: minor allele frequency; HWE: Hardy-Weinberg equilibrium; chr: chromosome; The *p*-value was calculated using Chi-square test (x2) and Fisher's exact tests; Bonferroni correction was used for multiple comparison.

Table 3(on next page)

The relationship between the SNPs and the risk of MPA in Guangxi population in different genetic models

Table 3: The relationship between the SNPs and the risk of MPA in Guangxi population in different genetic models

SNP	Models	Genotype/Allele	Control	Case	OR (95% CI)	*p* -value
rs2304256	Allele	A	355(59.8%)	326(61.5%)	1.08(0.85-1.37)	0.55
		C	239(40.2%)	204(38.5%)		
	Codominant	AA	103 (34.7%)	98 (37%)	1.00	0.79
		CA	149 (50.2%)	130 (49.1%)	0.87 (0.60-1.29)	
		CC	45 (15.2%)	37 (14%)	0.95 (0.55-1.65	
	Dominant	AA	103 (34.7%)	98 (37%)	1.00	0.54
		CA-CC	194 (65.3%)	167 (63%)	0.89 (0.62-1.28)	
	Recessive	AA-CA	252 (84.8%)	228 (86%)	1.00	0.92
		CC	45 (15.2%)	37(14%)	1.03 (0.62-1.70)	
	Overdominant	AA-CC	148 (49.8%)	135 (50.9%)	1.00	0.51
		CA	149 (50.2%)	130 (49.1%)	0.89 (0.62-1.26)	
rs280519	Allele	G	396(66.7%)	355(67.0%)	0.99(0.77-1.26)	0.91
		A	198(33.3%)	175(33.0%)		
	Codominant	GG	127 (42.8%)	119 (44.9%)	1.00	0.37
		AG	142 (47.8%)	117 (44.1%)	0.82 (0.57-1.20)	
		AA	28 (9.4%)	29 (10.9%)	1.22 (0.66-2.28)	
	Dominant	GG	127 (42.8%)	119 (44.9%)	1.00	0.5
		AG-AA	170 (57.2%)	146 (55.1%)	0.88 (0.62-1.26)	
	Recessive	GG-AG	269 (90.6%)	236 (89.1%)	1.00	0.32
		AA	28 (9.4%)	29 (10.9%)	1.35 (0.74-2.44)	
	Overdominant	GG-AA	155 (52.2%)	148 (55.9%)	1.00	0.2
		AG	142 (47.8%)	117 (44.1%)	0.79 (0.56-1.13)	
rs12720270	Allele	A	336(56.6%)	305(57.5%)	1.04(0.82-1.32)	0.74
		G	258(43.4%)	225(42.5%)		
	Codominant	AA	91 (30.6%)	86 (32.5%)	1.00	0.63
		GA	154 (51.9%)	133 (50.2%)	0.83 (0.56-1.24)	
		GG	52 (17.5%)	46 (17.4%)	0.97 (0.57-1.66)	
	Dominant	AA	91 (30.6%)	86 (32.5%)	1.00	0.46
		GA-GG	206 (69.4%)	179 (67.5%)	0.87 (0.59-1.26)	
	Recessive	AA-GA	245 (82.5%)	219 (82.6%)	1.00	0.73
		GG	52 (17.5%)	46 (17.4%)	1.09 (0.68-1.74)	
	Overdominant	AA-GG	143 (48.1%)	132 (49.8%)	1.00	0.34
		GA	154 (51.9%)	133 (50.2%)	0.84 (0.59-1.20)	

NOTE:MPA: microscopic polyangiitis; SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval; The *p*-value, OR, and 95% CI were derived from a logistic regression model adjusted for age, ethnicity, and gender.; * denotes statistical significance($p<0.05$).

Table 4(on next page)

The relationship between the SNPs and the risk of MPA in male of Guangxi population in different genetic models

Table 4: The relationship between the SNPs and the risk of MPA in male of Guangxi population in different genetic models

SNP	Models	Genotype/Allele	Control	Case	OR (95% CI)	*p*-value
rs2304256	Allele	A	140(56.4%)	124(64.6%)	0.711(0.48-1.05)	0.085
		C	108(43.5%)	68(35.4%)		
	Codominant	AA	36 (29%)	43 (44.8%)	1.00	0.082
		CA	68 (54.8%)	38 (39.6%)	0.53 (0.28-0.99)	
		CC	20 (16.1%)	15 (15.6%)	1.05 (0.43-2.54)	
	Dominant	AA	36 (29%)	43 (44.8%)	1.00	0.11
		CA-CC	88 (71%)	53 (55.2%)	0.62 (0.34-1.12)	
	Recessive	AA-CA	104 (83.9%)	81 (84.4%)	1.00	0.31
		CC	20 (16.1%)	15 (15.6%)	1.52 (0.67-3.42)	
	Overdominant	AA-CC	56 (45.2%)	58 (60.4%)	1.00	**0.025***
		CA	68 (54.8%)	38 (39.6%)	**0.52 (0.29-0.93)**	
rs280519	Allele	G	155(62.5%)	134(69.8%)	1.59(1.06-2.39)	0.11
		A	93(37.5%)	58(31.2%)		
	Codominant	GG	43 (34.7%)	49 (51%)	1.00	**0.039***
		AG	69 (55.6%)	36 (37.5%)	**0.51 (0.28-0.93)**	
		AA	12 (9.7%)	11 (11.5%)	1.30 (0.47-3.57)	
	Dominant	GG	43 (34.7%)	49 (51%)	1.00	0.078
		AG-AA	81 (65.3%)	47 (49%)	0.60 (0.33-1.06)	
	Recessive	GG-AG	112 (90.3%)	85 (88.5%)	1.00	0.2
		AA	12 (9.7%)	11 (11.5%)	1.88 (0.72-4.91)	
	Overdominant	GG-AA	55 (44.4%)	60 (62.5%)	1.00	**0.013***
		AG	69 (55.6%)	36 (37.5%)	**0.48 (0.27-0.86)**	
rs12720270	Allele	A	135(54.4%)	115(59.9%)	0.80(0.55-1.17)	0.25
		G	113(45.6%)	77(40.1%)		
	Codominant	AA	33 (26.6%)	37 (38.5%)	1.00	0.071
		GA	69 (55.6%)	41 (42.7%)	0.57 (0.30-1.09)	
		GG	22 (17.7%)	18 (18.8%)	1.32 (0.55-3.14)	
	Dominant	AA	33 (26.6%)	37 (38.5%)	1.00	0.25
		GA-GG	91 (73.4%)	59 (61.5%)	0.70 (0.38-1.28)	
	Recessive	AA-GA	102 (82.3%)	78 (81.2%)	1.00	0.12
		GG	22 (17.7%)	18 (18.8%)	1.85 (0.85-4.03)	
	Overdominant	AA-GG	55 (44.4%)	55 (57.3%)	1.00	**0.027***
		GA	69 (55.6%)	41 (42.7%)	**0.52 (0.29-0.93)**	

NOTE:MPA: microscopic polyangiitis; SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval; The *p*-value, OR, and 95% CI were derived from a logistic regression model adjusted for age and ethnicity; * denotes statistical significance($p<0.05$).

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Table 5(on next page)

The relationship between the SNPs and the risk of MPA in female of Guangxi population in different genetic models

Table 5: The relationship between the SNPs and the risk of MPA in female of Guangxi population in different genetic models

SNP	Models	Genotype/Allele	Control	Case	OR (95% CI)	*p* -value
rs2304256	Allele	A	215(62.1%)	201(59.6%)	1.11(0.82-1.51)	0.50
		C	131(37.9%)	136(40.4%)		
	Codominant	AA	67 (38.7%)	55 (32.5%)	1.00	0.6
		CA	81 (46.8%)	92 (54.4%)	1.22 (0.74-1.99)	
		CC	25 (14.4%)	22 (13%)	0.91 (0.44-1.86)	
	Dominant	AA	67 (38.7%)	55 (32.5%)	1.00	0.58
		CA-CC	106 (61.3%)	114 (67.5%)	1.14 (0.71-1.83)	
	Recessive	AA-CA	148 (85.5%)	147 (87%)	1.00	0.53
		CC	25 (14.4%)	22 (13%)	0.81 (0.42-1.56)	
	Overdominant	AA-CC	92 (53.2%)	77 (45.6%)	1.00	0.33
		CA	81 (46.8%)	92 (54.4%)	1.25 (0.80-1.96)	
rs280519	Allele	G	241(69.7%)	221(65.4%)	1.22(0.88-1.67)	0.23
		A	105(30.3%)	117(34.6%)		
	Codominant	GG	84 (48.5%)	70 (41.4%)	1.00	0.83
		AG	73 (42.2%)	81 (47.9%)	1.14 (0.71-1.83)	
		AA	16 (9.3%)	18 (10.7%)	1.20 (0.54-2.65)	
	Dominant	GG	84 (48.5%)	70 (41.4%)	1.00	0.56
		AG-AA	89 (51.5%)	99 (58.6%)	1.15 (0.73-1.81)	
	Recessive	GG-AG	157 (90.8%)	151 (89.3%)	1.00	0.76
		AA	16 (9.2%)	18 (10.7%)	1.12 (0.53-2.40)	
	Overdominant	GG-AA	100 (57.8%)	88 (52.1%)	1.00	0.68
		AG	73 (42.2%)	81 (47.9%)	1.10 (0.70-1.73)	
rs12720270	Allele	A	201(58.1%)	190(56.2%)	1.08(0.80-1.46)	0.62
		G	145(41.9%)	148(43.8%)		
	Codominant	AA	58 (33.5%)	49 (29%)	1.00	0.76
		GA	85 (49.1%)	92 (54.4%)	1.08 (0.64-1.79)	
		GG	30 (17.3%)	28 (16.6%)	0.85 (0.43-1.69)	
	Dominant	AA	58 (33.5%)	49 (29%)	1.00	0.95
		GA-GG	115 (66.5%)	120 (71%)	1.02 (0.62-1.65)	
	Recessive	AA-GA	143 (82.7%)	141 (83.4%)	1.00	0.5
		GG	30 (17.3%)	28 (16.6%)	0.81 (0.44-1.49)	
	Overdominant	AA-GG	88 (50.9%)	77 (45.6%)	1.00	0.57
		GA	85 (49.1%)	92 (54.4%)	1.14 (0.72-1.79)	

NOTE:MPA: microscopic polyangiitis; SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval; The *p*-value, OR, and 95% CI were derived from a logistic regression model adjusted for age and ethnicity; * denotes statistical significance($p<0.05$).

Table 6(on next page)

Correlations between the haplotypes of TYK2 gene and MPA susceptibility

Table 6: Correlations between the haplotypes of TYK2 gene and MPA susceptibility

Geng	SNP	Haplotypes	Control	Case	χ 2	*p*	OR (95% CI)
TYK2	rs2304256/ rs280519/ rs12720270	AGA	336.00(0.566)	303.94(0.573)	0.092	0.762	1.037 (0.819~1.314)
		AGG	19.00(0.032)	21.00(0.040)	0.485	0.486	1.251 (0.665~2.354)
		CAG	198.00(0.333)	173.94(0.328)	0.025	0.873	0.980 (0.764~1.257)
		CGG	41.00(0.069)	30.06(0.057)	0.701	0.402	0.813 (0.500~1.321)

SNP: single nucleotide polymorphism; OR: odds ratio; CI: confidence interval; The *p*-value was calculated using Chi-square(x2) and Fisher's exact tests; Bonferroni correction was used for multiple comparison.