



# Associations of single nucleotide polymorphisms of *PTPN22* and *Ctla4* genes with the risk of allergic rhinitis in a Chinese Han population



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## ABSTRACT

**Background:** Allergic rhinitis (AR) is an inflammatory disorder of the upper airway. Protein tyrosine phosphatase non-receptor 22 encoded by *PTPN22* gene and cytotoxic T-lymphocyte associated 4 encoded by *Ctla4* gene are associated with autoimmune diseases.

**Purpose:** This study was performed to evaluate the potential association of *PTPN22* and *Ctla4* single nucleotide polymorphisms (SNPs) with AR in a Chinese Han population.

**Methods:** A case-control study was performed in 783 Chinese AR patients and 811 healthy controls. Three SNPs in *PTPN22* gene (rs2488457, rs1310182, and rs3789604) and 6 SNPs in *Ctla4* gene (rs3087243, rs231779, rs11571302, rs11571315, rs231725, and rs35219727) were detected using a polymerase chain reaction–restriction fragment length polymorphism assay (PCR-RFLP).

**Results:** For *PTPN22* gene, a significantly decreased prevalence of the rs2488457 CC genotype and C allele was found in AR patients. The frequencies of the rs1310182 CC genotype, CT genotype, and C allele were significantly associated with the risk of AR. For *Ctla4* gene, a significantly increased prevalence of the rs11571302 AA genotype, CA genotype and A allele was noted in AR patients.

**Conclusion:** SNPs of *PTPN22* and *Ctla4* genes are significantly associated with the risk of AR in the Chinese Han population.

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## 1. Introduction

Allergic rhinitis (AR) is an IgE-mediated inflammation of the upper airway, which is induced by allergens. AR has an estimated global incidence of 10–20% [1]. Common symptoms include nasal obstruction, sneezing, and rhinorrhea. AR is known as a risk factor for comorbid conditions such as asthma, nasal polyp, sinusitis, and sleep disorders [2,3]. Genetic and environmental factors contribute to the pathogenesis of AR [4,5].

The *PTPN22* gene encodes a lymphoid-specific phosphatase (Lyp), which contains 4 proline-rich domains in the C-terminus and a catalytic N-terminal domain. By interacting with C-terminal Src kinase, zeta-associated protein-70 and Vav proteins, Lyp plays a suppressive role in T cell-mediated immune response [6,7]. This gene has been identified to be a susceptibility gene for various autoimmune diseases, such as Graves' disease, rheumatoid arthritis, type 1 diabetes, and systemic lupus erythematosus (SLE)

[8–12]. The *Ctla4* gene maps to chromosome 2q33 and encodes a glycoprotein receptor of the immunoglobulin family (CTLA-4), which is expressed on the surface of activated T cells [13]. CTLA-4 is also linked to autoimmune diseases such as Graves' disease and rheumatoid arthritis [14].

Single nucleotide polymorphisms (SNPs) in multiple immune-related genes such as *IL-4* [15], *IL-27* [16], *IL-23R* [17], and *FCRL3* [18] are associated with the susceptibility to AR. However, to date, no studies have examined the relationship between SNPs in *PTPN22* and *Ctla4* gene and AR risk.

In this study, we identified 3 possible variation sites in *PTPN22* and 6 potential variation sites in *Ctla4*, and checked whether these SNPs are associated with the susceptibility to AR in a Chinese Han population.

## 2. Materials and methods

### 2.1. Subjects

Overall, 783 patients (421 men and 362 women) aged between 7 and 72 years were enrolled in this study. The patients were

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treated at Department of Otolaryngology of the First Affiliated Hospital of Chongqing Medical University (Chongqing, China). The diagnosis of AR was based on patients' medical history, symptoms, and a positive response to a panel of common allergens in the skin prick tests (SPT, Allergopharma, Hamburg, Germany). A positive SPT result was defined in accordance with the recommendations of the Subcommittee on Allergen Standardization and Skin Tests of the European Academy of Allergy and Clinical Immunology [19]. Patients with any other systemic disease were excluded from the study. A total of 811 healthy volunteers who showed negative skin prick tests were recruited as the control subjects. All patients and controls were of the Chinese Han population.

2.2. Ethics statement

The study was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (approval number: 2011-201123) and performed in agreement with the Declaration of Helsinki. Written informed consent was obtained from the participants or their guardians.

2.3. DNA extraction

Genomic DNA was extracted from peripheral blood leukocytes using the Wizard Genomic DNA Purification Kit (Promega, Madison, WI, USA) following the manufacturer's instructions. Briefly, blood samples were mixed with cell lysis solution. Leucocytes were lysed with Nuclei Lysis Solution. The pellet was resuspended by Protein Precipitation Solution. Precipitated proteins were removed by centrifugation. Finally, DNA was extracted using methyl alcohol.

2.4. SNP genotyping

We selected 3 SNPs (i.e. rs2488457, rs1310182 and rs3789604) in the *PTPN22* gene and 6 SNPs (i.e. rs3087243, rs231779, rs11571302, rs11571315, rs231725 and rs335219727) in the *Ctla4* gene (Fig. 1). These SNPs were genotyped using the polymerase chain reaction-restriction fragment length polymorphism method (PCR-RFLP). The primer sequences and reaction conditions used in this study are shown in Tables 2 and 3. The PCR products were digested with restriction enzymes. Fragments were separated on a 4% agarose gel and stained with Gold View (SBS Genentech, Beijing, China). To confirm the genotyping results, purified PCR products were directly sequenced.

**Table 1**  
Demographic and clinical characteristics of the participants.

| Characteristic         | AR          | Control     |
|------------------------|-------------|-------------|
| Gender (male/female)   | 421/362     | 425/386     |
| Age, years (mean ± SD) | 34.5 ± 11.2 | 33.2 ± 12.1 |
| Allergen category (%)  |             |             |
| House dust mite        | 441 (57.1)  | 0           |
| Pollens                | 170 (21.7)  | 0           |
| Mixed allergens        | 172 (22.0)  | 0           |

2.5. Statistics analysis

Estimation of genotype frequencies was performed by direct counting. Odds ratios (OR) and 95% confidence intervals (CI) were calculated from logistic regression analysis to assess the associations between genotypes/alleles and AR risk. No corrections were used to adjust for type I error. All the statistical analyses were performed using the SPSS software (version 13.0; SPSS Inc., Chicago, Illinois, USA).

3. Results

3.1. Clinical characteristics of the study participants

Clinical characteristics of the participants at the time of diagnosis are summarized in Table 1. There were no significant differences between the cases and controls in terms of the mean age and gender distribution. Among the 783 AR patients, 441 (56.3%) were sensitive to house dust mite, 170 (21.7%) tree pollen, and 172 (22.0%) multiple allergens.

3.2. Genotype and allele frequencies of *PTPN22* polymorphisms

The 3 SNPs of *PTPN22* gene were in Hardy–Weinberg equilibrium in the AR patients and healthy controls ( $p > 0.05$ ; data not shown). The call rate for the SNPs was 100%. Notably, AR patients displayed a significantly decreased frequency of CC genotype ( $p = 1.7 \times 10^{-4}$ ; OR, 0.598, 95%CI, 0.457–0.782) and C allele ( $p = 0.9 \times 10^{-4}$ ; OR, 0.756, 95%CI, 0.658–0.869) of rs2488457 (Table 4). The results also showed obvious differences between the AR patients and control patients concerning the frequencies of rs1310182. Significantly higher frequencies of CC genotype ( $p = 2.6 \times 10^{-7}$ ; OR, 2.136; 95%CI, 1.600–2.852), CT genotype ( $p = 0.1 \times 10^{-3}$ ; OR, 1.563; 95%CI, 1.247–1.958), C allele ( $p = 6.7 \times 10^{-8}$ ; OR, 1.474; 95%CI, 1.280–1.696) were found in AR

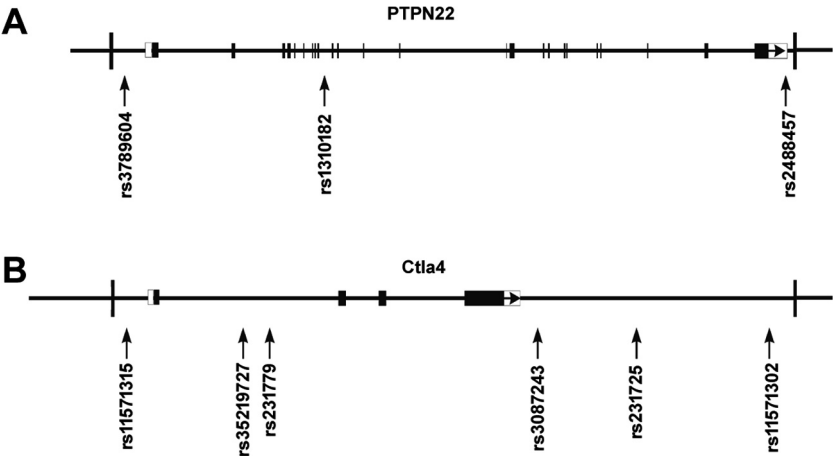


**Fig. 1.** Schematic diagrams showing the locations of *PTPN22* (A) and *Ctla4* (B) SNPs (arrow) examined in this study. Exons are depicted as black boxes.

**Table 2**

Primers and restriction enzymes used for RFLP analysis of the PTPN22 gene.

| SNP        | Primer sequence                                                         | Annealing temperature (°C) | Restriction enzyme |
|------------|-------------------------------------------------------------------------|----------------------------|--------------------|
| rs 248857  | F: 5' CCATTGAGAGGTTATGCGAGCT3'<br>R: 5' CGCCACCTTGCTGACAACAT3'          | 56                         | SacII              |
| rs 1310182 | F: 5' AAACCCAATGACCAATGACA3'<br>R: 5' AAGCATTAAATTATATGGTGCTGAG3'       | 58                         | Hsp92II            |
| rs 3789604 | F: 5' GCGAGAGGGGGCTCTGGCTCGGCCGC3'<br>R: 5' CGGCGGGGCGCGGGCGGAACACAGC3' | 60                         | PauI               |

**Table 3**

Primers and restriction enzymes used for RFLP analysis of the CTLA-4 gene.

| SNP         | Primer sequence                                                               | Annealing temperature (°C) | Restriction enzyme |
|-------------|-------------------------------------------------------------------------------|----------------------------|--------------------|
| rs 3087243  | F: 5' GGACAAATAATGCTTCATGAGTCAGC 3'<br>R: 5' GTTGCCATGACAACCTGTAATGCCT 3'     | 60                         | TaiI               |
| rs 231779   | F: 5' GAGAGAGGGGCTGGTTAGTT 3'<br>R: 5' AGGTCGCTTCCTCTCTAGGT 3'                | 56                         | Cac8I              |
| rs 11571302 | F: 5' CTTCCAGAGGACTTAGGAGAAGCATCTC 3'<br>R: 5' TTCTTACAATTCTCTCAGAGGAAGCTG 3' | 60                         | MspI               |
| rs11571315  | F: 5' TTAAGAGTGAAGAAACAAATGTTCTCTG3'<br>R: 5' AACCTTAGCCCATGTTATTCTCTGT3'     | 58                         | TasI               |
| rs231725    | F: 5' CGTCAGATTGCTGACACTTTAAG3'<br>R: 5' GATCAAATGGGAAAGAGATTAAGCT3'          | 60                         | BssSI              |
| rs35219727  | F: 5' GGGCTATAATCACTGCTCAGGA3'<br>R: 5' CAGAAGAGAAAACAGTTTGCCAGC3'            | 60                         | ForkI              |

**Table 4**

Frequencies of alleles and genotypes of PTPN22 polymorphisms in AR patients and controls.

| SNP       | Genotype | AR (n = 783) | Control (n = 811) | B         | S.E.  | Wald     | df        | P value               | OR (95%CI)         |
|-----------|----------|--------------|-------------------|-----------|-------|----------|-----------|-----------------------|--------------------|
| rs2488457 | CC       | 201          | 265               | −0.514    | 0.137 | 14.09693 | 1         | $1.70 \times 10^{-4}$ | 0.598(0.457–0.782) |
|           | CG       | 355          | 367               | −0.271    | 0.125 | 4.721    | 1         | 0.030                 | 0.763(0.597–0.974) |
|           | GG       | 227          | 179               | Reference |       |          | 2         | Reference             |                    |
|           | C        | 757          | 897               | −0.279    | 0.071 | 15.446   | 1         | $0.90 \times 10^{-4}$ | 0.756(0.658–0.869) |
|           | G        | 809          | 725               | Reference |       |          | Reference |                       |                    |
| rs1310182 | CC       | 178          | 124               | 0.759     | 0.148 | 26.466   | 1         | $2.60 \times 10^{-7}$ | 2.136(1.600–2.852) |
|           | CT       | 398          | 379               | 0.446     | 0.115 | 15.057   | 1         | $0.10 \times 10^{-3}$ | 1.563(1.247–1.958) |
|           | TT       | 207          | 308               | Reference |       |          | 2         | Reference             |                    |
|           | C        | 754          | 627               | 0.388     | 0.072 | 29.141   | 1         | $6.70 \times 10^{-8}$ | 1.474(1.280–1.696) |
|           | T        | 812          | 995               | Reference |       |          | Reference |                       |                    |
| rs3789604 | GG       | 50           | 53                | 0.231     | 0.208 | 1.225    | 1         | 0.268                 | 1.260(0.837–1.895) |
|           | GT       | 351          | 248               | 0.636     | 0.107 | 35.335   | 1         | $2.80 \times 10^{-9}$ | 1.890(1.532–2.331) |
|           | TT       | 382          | 510               | Reference |       |          | 2         | Reference             |                    |
|           | G        | 451          | 354               | 0.465     | 0.083 | 31.685   | 1         | $1.80 \times 10^{-8}$ | 1.592(1.354–1.871) |
|           | T        | 1015         | 1268              | Reference |       |          | Reference |                       |                    |

patients compared with the controls. Additionally, significantly increased frequencies of GT genotype ( $p = 2.8 \times 10^{-9}$ ; OR, 1.890; 95%CI, 1.532–2.331) and G allele ( $p = 1.8 \times 10^{-8}$ ; OR, 1.592; 95% CI, 1.354–1.871) of rs3789604 were observed in AR patients (Table 4).

### 3.3. Genotype and allele frequencies of *Ctla4* polymorphisms

As demonstrated in Table 5, the genotype and allele frequencies of rs11571302 were significantly different between AR patients and controls. The CA genotype ( $p = 4.6 \times 10^{-9}$ ; OR, 1.864; 95%CI, 1.514–2.296), AA genotype ( $p = 0.6 \times 10^{-3}$ ; OR, 1.902; 95%CI, 1.322–2.737) and A allele ( $p = 3.6 \times 10^{-8}$ ; OR, 1.528; 95%CI, 1.314–1.777) was more prevalent among AR patients than among healthy controls. However, no significant association was found for the other 5 SNPs tested with AR (Table 5).

## 4. Discussion

AR is the result of a complex interplay between genetic and environmental factors. In this study, we investigated the associations

of *PTPN22* and *Ctla4* gene polymorphisms with the risk of AR in the Chinese Han population. Our results showed that the 3 *PTPN22* SNPs (rs2488457, rs1310182, and rs3789604) and the *Ctla4* SNP rs11571302 were significantly correlated with the susceptibility to AR. The individuals carrying the favorable CC genotype or C allele of the *PTPN22* rs2488457 had a decreased risk of AR, while those with the CC genotype, CT genotype, or C allele of the *PTPN22* rs1310182 had an increased risk of AR. Additionally, the CA genotype, AA genotype, and A allele of the *Ctla4* rs11571302 were positively correlated with AR.

*PTPN22* is known to play key roles in lymphocyte differentiation and activation, immune tolerance, and immune cell-mediated host defense [20]. A genetic variant of the *PTPN22* gene C1858T encodes a more active Lyp R620W, which has the ability to interfere with T cell-mediated autoimmunity [21]. A previous study showed an association of *PTPN22* polymorphisms with the susceptibility to chronic urticaria [22]. There is evidence for the association of the gain-of-function variant rs2476601 (R620W) with the onset of type 1 diabetes [8], psoriatic arthritis [23], and rheumatoid arthritis [24]. A loss-of-function variant of *PTPN22* (rs33996649) was found to be significantly associated with

**Table 5**Frequencies of alleles and genotypes of *CTLA-4* polymorphisms in AR patients and controls.

| SNP        | Genotype | AR (n = 783) | Control (n = 811) | B         | S.E.  | Wald   | df        | P value                | OR (95%CI)         |
|------------|----------|--------------|-------------------|-----------|-------|--------|-----------|------------------------|--------------------|
| rs3087243  | AA       | 86           | 78                | 0.186     | 0.171 | 1.187  | 1         | 0.276                  | 1.205(0.862–1.685) |
|            | AG       | 298          | 297               | 0.092     | 0.107 | 0.735  | 1         | 0.391                  | 1.096(0.888–1.353) |
|            | GG       | 399          | 436               | Reference |       |        | 2         | Reference              |                    |
|            | A        | 470          | 453               | 0.101     | 0.078 | 1.682  | 1         | 0.195                  | 1.107(0.950–1.290) |
|            | G        | 1096         | 1169              | Reference |       |        | Reference |                        |                    |
| rs231779   | CC       | 82           | 100               | –0.226    | 0.165 | 1.879  | 1         | 0.170                  | 0.797(0.577–1.102) |
|            | CT       | 303          | 324               | –0.095    | 0.107 | 0.787  | 1         | 0.375                  | 0.909(0.737–1.112) |
|            | TT       | 398          | 387               | Reference |       |        | 2         | Reference              |                    |
|            | C        | 467          | 524               | 0.206     | 0.079 | 6.858  | 1         | $0.882 \times 10^{-2}$ | 0.229(1.053–1.435) |
|            | T        | 796          | 1098              | Reference |       |        | Reference |                        |                    |
| rs11571302 | AA       | 80           | 61                | 0.643     | 0.186 | 11.986 | 1         | $0.50 \times 10^{-3}$  | 1.902(1.322–2.737) |
|            | CA       | 401          | 312               | 0.623     | 0.106 | 34.341 | 1         | $0.50 \times 10^{-8}$  | 1.864(1.514–2.296) |
|            | CC       | 302          | 438               | Reference |       |        | 2         | Reference              |                    |
|            | A        | 561          | 434               | 0.424     | 0.077 | 30.344 | 1         | $3.60 \times 10^{-8}$  | 1.528(1.314–1.777) |
|            | C        | 1005         | 1188              | Reference |       |        | Reference |                        |                    |
| rs231725   | AA       | 302          | 319               | –0.033    | 0.145 | 0.051  | 1         | 0.821                  | 0.968(0.728–1.286) |
|            | AG       | 346          | 354               | –0.001    | 0.143 | 0.001  | 1         | 0.995                  | 0.999(0.755–1.322) |
|            | GG       | 135          | 138               | Reference |       |        | 2         | Reference              |                    |
|            | A        | 950          | 992               | –0.021    | 0.073 | 0.082  | 1         | 0.775                  | 0.979(0.850–1.129) |
|            | G        | 616          | 630               | Reference |       |        | Reference |                        |                    |
| rs35219727 | AG       | 102          | 97                | 0.098     | 0.152 | 0.414  | 1         | 0.520                  | 1.103(0.819–1.484) |
|            | GG       | 681          | 714               | Reference |       |        | Reference |                        |                    |
|            | A        | 102          | 97                | 0.091     | 0.146 | 0.387  | 1         | 0.534                  | 1.095(0.822–1.460) |
|            | G        | 1464         | 1525              | Reference |       |        | Reference |                        |                    |
| rs11571315 | AA       | 273          | 299               | –0.124    | 0.142 | 0.76   | 1         | 0.383                  | 0.883(0.668–1.168) |
|            | AG       | 357          | 364               | –0.053    | 0.137 | 0.147  | 1         | 0.701                  | 0.949(0.725–1.242) |
|            | GG       | 153          | 148               | Reference |       |        | 2         | Reference              |                    |
|            | A        | 903          | 962               | –0.068    | 0.072 | 0.89   | 1         | 0.346                  | 0.934(0.812–1.076) |
|            | G        | 663          | 660               | Reference |       |        | Reference |                        |                    |

ulcerative colitis [25]. In this study, we explored the impact of rs2488457, rs3789604 and rs1310182 SNPs in the non-coding regions of *PTPN22* on the onset of AR. Notably, we found a significant association between the non-coding variants of *PTPN22* and the susceptibility to AR. In contrast, the 3 SNPs in *PTPN22* gene were not significantly associated with the risk of ocular Behcet's disease [26]. Our data suggest that *PTPN22* may play an important role in the pathogenesis of AR. However, the molecular basis for the association between *PTPN22* SNPs and AR remains to be further determined.

The *CTLA-4* gene is another autoimmunity-related susceptibility gene. This gene acts as a negative regulator of self-reactive T cell proliferation and activation [27,28]. More than 100 single-nucleotide polymorphisms (SNPs) have been identified in the *Ctla4* region 2q34 [29], and some variants have been found to be associated with autoimmune disorders such as Sjögren's syndrome [30] and rheumatoid arthritis [31]. However, it has been reported that the SNPs in the *Ctla4* exon 1(+49) and promoter (–318) are not associated with susceptibility to rheumatoid arthritis [32]. No association of *Ctla4* A49G polymorphism with the risk of chronic spontaneous autoreactive urticaria is detected [33]. In this study, we evaluated the association between *Ctla4* SNPs and AR and identified the rs11571302 AA genotype, CA genotype, and A allele as potential risk factors.

However, it is worth mentioning that this study has a major limitation. We did not detect the protein levels of *PTPN22* and *CTLA-4* in the peripheral blood or perform functional validations. Therefore, it is still unclear about the influence of these polymorphisms on their expression.

In conclusion, this study provides evidence for the associations between *PTPN22* and *Ctla4* SNPs and risk of AR, suggesting their implication in the pathogenesis of AR. Further functional studies are warranted to determine how these genetic variants affect the susceptibility to AR.

## Disclosure statement

The authors declare no financial or other conflicts of interest regarding the content of this article.

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## References

- [1] A. Togias, Rhinitis and asthma: evidence for respiratory system integration, *J. Allergy Clin. Immunol.* 111 (6) (2003) 1171–1183, quiz 1184.
- [2] B. Leynaert, F. Neukirch, P. Demoly, J. Bousquet, Epidemiologic evidence for asthma and rhinitis comorbidity, *J. Allergy Clin. Immunol.* 106 (Suppl. 5) (2000) S201–S205.
- [3] M.C. Young, Rhinitis, sinusitis, and polyposis, *Allergy Asthma Proc.* 19 (4) (1998) 211–218.
- [4] G.H. Ibrahim, M.T. ElTabbakh, A.H. Gomaa, E.A. Mohamed, Interleukin-18 gene polymorphisms in Egyptian patients with allergic diseases, *Am. J. Rhinol. Allergy* 26 (5) (2012) 385–389.
- [5] S.L. Gaddam, V.H.S. Priya, B.M.V.S. Babu, L. Joshi, S. Venkatasubramanian, et al., Association of interleukin-10 gene promoter polymorphism in allergic patients, *Genet Test Mol. Biomarkers* 16 (2012) 632–635.
- [6] I. Rhee, A. Veillette, Protein tyrosine phosphatases in lymphocyte activation and autoimmunity, *Nat. Immunol.* 13 (2012) 439–447.
- [7] G. Fusteri, S.N. Liossis, M. Battaglia, Roles of the protein tyrosine phosphatase *PTPN22* in immunity and autoimmunity, *Clin. Immunol.* 149 (2013) 556–565.
- [8] G. Dultz, N. Matheis, M. Dittmar, B. Röhrig, K. Bender, G.J. Kahaly, The protein tyrosine phosphatase non-receptor type 22 C1858T polymorphism is a joint susceptibility locus for immunthyroiditis and autoimmune diabetes, *Thyroid* 19 (2) (2009) 143–148.
- [9] M. Ichimura, H. Kaku, T. Fukutani, H. Koga, T. Mukai, et al., Associations of protein tyrosine phosphatase nonreceptor 22 (*PTPN22*) gene polymorphisms with susceptibility to Graves' disease in a Japanese population, *Thyroid* 18 (2008) 625–630.

- [10] V. Orru, S.J. Tsai, B. Rueda, E. Fiorillo, S.M. Stanford, et al., A loss-of-function variant of PTPN22 is associated with reduced risk of systemic lupus erythematosus, *Hum. Mol. Genet.* 18 (2009) 569–579.
- [11] A.B. Begovich, V.E. Carlton, L.A. Honigberg, S.J. Schrodi, A.P. Chokkalingam, et al., A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (PTPN22) is associated with rheumatoid arthritis, *Am. J. Hum. Genet.* 75 (2004) 330–337.
- [12] C. Kyogoku, C.D. Langefeld, W.A. Ortmann, A. Lee, S. Selby, et al., Genetic association of the R620W polymorphism of protein tyrosine phosphatase PTPN22 with human SLE, *Am. J. Hum. Genet.* 75 (2004) 504–507.
- [13] T.L. Walunas, C.Y. Bakker, J.A. Bluestone, CTLA4 ligation blocks CD28-dependent T cell activation, *J. Exp. Med.* 183 (1996) 2541–2550.
- [14] M. Cutolo, A. Sulli, S. Paolino, C. Pizzorni, CTLA-4 blockade in the treatment of rheumatoid arthritis: an update, *Expert Rev. Clin. Immunol.* 12 (4) (2016) 417–425.
- [15] M. Movahedi, A.A. Amirzargar, R. Nasiri, A. Hirbod-Mobarakeh, E. Farhadi, M. Tavakol, et al., Gene polymorphisms of Interleukin-4 in allergic rhinitis and its association with clinical phenotypes, *Am. J. Otolaryngol.* 34 (6) (2013) 676–681.
- [16] Y. Shen, X.D. Yuan, D. Hu, X. Ke, X.Q. Wang, et al., Association between interleukin-27 gene polymorphisms and susceptibility to allergic rhinitis, *Hum. Immunol.* 75 (9) (2014) 991–995.
- [17] D. Hu, G. Hu, J. Zhu, Y. Shen, H. Kang, S. Hong, Association between polymorphisms of the IL-23R gene and allergic rhinitis in a Chinese Han population, *PLoS One* 8 (5) (2013) e63858.
- [18] Z. Gu, S.L. Hong, X. Ke, X.Q. Wang, Y. Shen, et al., FCRL3 gene polymorphisms confer autoimmunity risk for allergic rhinitis in a Chinese Han population, *PLoS One* 10 (1) (2015) e0116419.
- [19] Position paper, Allergen standardization and skin tests. The European Academy of Allergology and Clinical Immunology, *Allergy* 48 (Suppl. 14) (1993) 48–82.
- [20] N. Bottini, E.J. Peterson, Tyrosine phosphatase PTPN22: multifunctional regulator of immune signaling, development, and disease, *Annu. Rev. Immunol.* 32 (2014) 83–119.
- [21] E. Giancchetti, M. Palombi, A. Fierabracci, The putative role of the C1858T polymorphism of protein tyrosine phosphatase PTPN22 gene in autoimmunity, *Autoimmun. Rev.* 12 (7) (2013) 717–725.
- [22] Z. Brzoza, W. Grzeszczak, B. Rogala, W. Trautsolt, D. Moczulski, PTPN22 polymorphism presumably plays a role in the genetic background of chronic spontaneous autoreactive urticaria, *Dermatology* 224 (4) (2012) 340–345.
- [23] J. Bowes, S. Loehr, A. Budu-Aggrey, S. Uebe, I.N. Bruce, M. Feletar, H. Marzo-Ortega, P. Helliwell, A.W. Ryan, D. Kane, E. Korendowych, G.M. Alenius, E. Giardina, J. Packham, R. McManus, O. FitzGerald, M.A. Brown, F. Behrens, H. Burkhardt, N. McHugh, U. Huffmeier, P. Ho, A. Reis, A. Barton, PTPN22 is associated with susceptibility to psoriatic arthritis but not psoriasis: evidence for a further PsA-specific risk locus, *Ann. Rheum. Dis.* 74 (10) (2015) 1882–1885.
- [24] R. Bayley, K.A. Kite, H.M. McGettrick, J.P. Smith, G.D. Kitas, C.D. Buckley, S.P. Young, The autoimmune-associated genetic variant PTPN22 R620W enhances neutrophil activation and function in patients with rheumatoid arthritis and healthy individuals, *Ann. Rheum. Dis.* 74 (8) (2015) 1588–1595.
- [25] L.M. Diaz-Gallo, L. Espino-Paisán, K. Fransen, M. Gómez-García, S. van Sommeren, C. Cardena, L. Rodrigo, J.L. Mendoza, C. Taxonera, A. Nieto, G. Alcaín, I. Cueto, M.A. López-Nevot, N. Bottini, M.L. Barclay, J.B. Crusius, A.A. van Bodegraven, C. Wijmenga, C.Y. Ponsioen, R.B. Gearry, R.L. Roberts, R.K. Weersma, E. Urcelay, T.R. Merriman, B.Z. Alizadeh, J. Martin, Differential association of two PTPN22 coding variants with Crohn's disease and ulcerative colitis, *Inflamm. Bowel Dis.* 17 (11) (2011) 2287–2294.
- [26] Q. Zhang, S. Hou, Z. Jiang, L. Du, F. Li, X. Xiao, A. Kijlstra, P. Yang, No association of PTPN22 polymorphisms with susceptibility to ocular Behcet's disease in two Chinese Han populations, *PLoS One* 7 (3) (2012) e31230.
- [27] J.J. Engelhardt, T.J. Sullivan, J.P. Allison, CTLA-4 overexpression inhibits T cell responses through a CD28–B7-dependent mechanism, *J. Immunol.* 177 (2006) 1052–1061.
- [28] D.M. Sansom, L.S. Walker, The role of CD28 and cytotoxic T-lymphocyte antigen-4 (CTLA-4) in regulatory T-cell biology, *Immunol. Rev.* 212 (2006) 131–148.
- [29] H. Ueda, J.M. Howson, L. Esposito, J. Heward, H. Snook, G. Chamberlain, D.B. Rainbow, K.M. Hunter, A.N. Smith, G. Di Genova, M.H. Herr, I. Dahlman, F. Payne, D. Smyth, C. Lowe, R.C. Twells, S. Howlett, B. Healy, S. Nutland, H.E. Rance, V. Everett, L.J. Smink, A.C. Lam, H.J. Cordell, N.M. Walker, C. Bordin, J. Hulme, C. Motzo, F. Cucca, J.F. Hess, et al., Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease, *Nature* 423 (2003) 506–511.
- [30] S. Downie-Doyle, N. Bayat, M. Rischmueller, S. Lester, Influence of CTLA4 haplotypes on susceptibility and some extraglandular manifestations in primary Sjogren's syndrome, *Arthritis Rheum.* 54 (8) (2006) 2434–2440.
- [31] M.R. Rodríguez, A. Núñez-Roldán, F. Aguilar, A. Valenzuela, A. García, M.F. González-Escribano, Association of the CTLA4 3' untranslated region polymorphism with the susceptibility to rheumatoid arthritis, *Hum. Immunol.* 63 (1) (2002) 76–81.
- [32] Y.H. Lee, S.J. Choi, J.D. Ji, G.G. Song, No association of polymorphisms of the CTLA-4 exon 1(+49) and promoter(–318) genes with rheumatoid arthritis in the Korean population, *Scand. J. Rheumatol.* 31 (5) (2002) 266–270.
- [33] Z. Brzoza, W. Grzeszczak, B. Rogala, W. Trautsolt, D. Moczulski, CTLA-4 polymorphism in the pathogenesis of chronic spontaneous autoreactive urticaria, *Allergol Immunopathol. (Madr)* 42 (3) (2014) 241–244.