Review
Genetic Polymorphism of PTPN22 in Autoimmune Diseases: A Comprehensive Review

Kalthoum Tizaoui 1,†, Jae Il Shin 2,†, Gwang Hun Jeong 3,†, Jae Won Yang 4,†, Seoyeon Park 5, Ji Hong Kim 2,*,©, Soo Young Hwang 5, Se Jin Park 6,©, Ai Koyanagi 7,8,© and Lee Smith 9,©

1 Department of Basic Sciences, Division of Histology and Immunology, Faculty of Medicine Tunis, Tunis El Manar University, Tunis 2092, Tunisia; kalttizaoui@gmail.com
2 Department of Pediatrics, Yonsei University College of Medicine, Seoul 03722, Korea; shinji@yuhs.ac
3 College of Medicine, Gyeongsang National University, Jinju 52727, Korea; pearlmed15@gmail.com
4 Department of Nephrology, Yonsei University Wonju College of Medicine, Wonju 26426, Korea; kidney74@yonsei.ac.kr
5 Yonsei University College of Medicine, Seoul 06273, Korea; harryme1713@yonsei.ac.kr (S.P.); sooyoungsarah@yonsei.ac.kr (S.Y.H.)
6 Department of Pediatrics, Eulji University School of Medicine, Daejeon 35233, Korea; fil018@hanmail.net
7 Research and Development Unit, Parc Sanitari Sant Joan de Déu, CIBERSAM, Dr. Antoni Pujadas, 42, Sant Boi de Llobregat, 08830 Barcelona, Spain; ai.koyanagi@sjd.es
8 ICREA, Pg. Lluis Companys 23, 08010 Barcelona, Spain
9 Centre for Health Performance and Wellbeing, Anglia Ruskin University, Cambridge CB1 1PT, UK; lee.smith@aru.ac.uk
* Correspondence: kkkjhjyd@yuhs.ac; Tel.: +82-2-2019-3352; Fax: +82-2-3461-9473
† These authors contributed equally to this work.

Abstract: It is known that the etiology and clinical outcomes of autoimmune diseases are associated with a combination of genetic and environmental factors. In the case of the genetic factor, the SNPs of the PTPN22 gene have shown strong associations with several diseases. The recent exploding numbers of genetic studies have made it possible to find these associations rapidly, and a variety of autoimmune diseases were found to be associated with PTPN22 polymorphisms. Proteins encoded by PTPN22 play a key role in the adaptive and immune systems by regulating both T and B cells. Gene variants, particularly SNPs, have been shown to significantly disrupt several immune functions. In this review, we summarize the mechanism of how PTPN22 and its genetic variants are involved in the pathophysiology of autoimmune diseases. In addition, we sum up the findings of studies reporting the genetic association of PTPN22 with different types of diseases, including type 1 diabetes mellitus, systemic lupus erythematosus, juvenile idiopathic arthritis, and several other diseases. By understanding these findings comprehensively, we can explain the complex etiology of autoimmunity and help to determine the criteria of disease diagnosis and prognosis, as well as medication developments.

Keywords: PTPN22; single nucleotide polymorphisms (SNPs); autoimmune diseases; genetic association; Lyp protein

1. Introduction
An autoimmune disease refers to the condition of activating an abnormal immune response in our body, causing damage to the tissues or organs through continuous inflammation. The estimated prevalence of autoimmune diseases accounts for 4.5% of the general population and the number of new cases and mortality rates has increased over the past decades, which has increased the burden on society in spite of the development of immunosuppressants [1–3]. The phenotype of autoimmune diseases is heterogeneous, with over eighty autoimmune diseases such as rheumatoid arthritis, Grave’s disease, Hashimoto’s thyroiditis, Sjogren’s syndrome, and less common diseases identified [4]. The cause of
autoimmune diseases is not well understood, and physicians have suggested that both environmental and genetic factors, as well as other factors such as infection, are accountable for the diseases. Recent advancements in the field of genetic epidemiology and genome-wide association (GWA) studies have made it possible to discover the genetic variants and genes associated with the diseases [5]. Since most autoimmune disorders present similar clinical features, some of the common genes are known to be strongly correlated with the autoimmunity [5,6]. Investigating the characteristics of these common genes can give clues in identifying the diseases with unknown etiology.

The protein tyrosine phosphatase non-receptor 22 gene (PTPN22) is one of the candidate susceptibility genes for autoimmune diseases. It is located on chromosome 1p13.3-13.1 and encodes the protein called lysine tyrosine phosphatase (Lyp) [7,8]. The single nucleotide polymorphism (SNP) PTPN22 C1858T (rs2476601) in exon 14 is mainly associated with the onset of autoimmune diseases. A change in cytosine to thymidine at nucleotide 1858 resulted in a change in amino acids from arginine to tryptophan at codon 620 (R620W), and a change in the Lyp protein interrupts the cell signaling by disrupting the function of the T cell antigen receptor, mostly found in various types of lymphoid tissues. The Lyp protein is important in the prevention of spontaneous T cell activation, development, and inactivating of T-cell-receptor-associated kinases and their substrates [9]. Since Botinetti et al. first reported the association between PTPN22 gene variants and type 1 diabetes mellitus (T1DM), studies on other diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), autoimmune thyroid diseases, and vitiligo have been published successively. This strongly reflects the association of PTPN22 SNPs with autoimmunity.

Previously, our team systematically analyzed the association between the PTPN22 polymorphism and autoimmune diseases using the Bayesian approach, then reviewed the immunologic functions of the PTPN22 polymorphism [6,10]. To broaden the perspective of this association, in this review, we aim to summarize how the PTPN22 gene and its variants are associated with the onset and progress of a large set of autoimmune diseases (Table 1).

2. PTPN22 C1858T Associations with Autoimmune Diseases

2.1. Association of PTPN22 C1858T with Type 1 Diabetes

Bottini et al. first confirmed the association between PTPN22 R620W polymorphism and T1DM [8]. Afterward, Heneberg et al. confirmed that the 1858T allele serves as a risk allele for latent autoimmune diabetes in adults (LADA) [11]. They also confirmed gender-related differences in the frequency of some PTPN22 polymorphisms (but not c.1858C>T) in LADA. Re-analysis of the genetic association between the R620W variant and the risk of T1DM under Bayesian approaches false-positive report probability (FPRP) or Bayesian false discovery probability (BFDP) come in support of these findings. Out of 22 comparisons from observational studies, 19 (86.4%) comparisons had noteworthy findings [6].

At the cellular level, in addition to its impact on T cells, the PTPN22 variant conferred a risk for T1DM by influencing B cell activation. The Lyp R620W variant increases the number of autoreactive B cells, promoting the onset of autoimmune pathologies through the internalization and the presentation of autoantigens to T lymphocytes [12,13]. The group of Habib reported that the presence of the Lyp R620W variant has an effect on the peripheral B cell homeostasis in heterozygous healthy controls, promoting a specific expansion of the transitional and anergic IgD+, IgM−, CD27−, and B cell populations [14]. They also reported reduced B cell receptor signaling and resistance to apoptosis in both the transitional and naive B cell compartments in T1DM patients, irrespective of the presence of the PTPN22 genotype [14]. PTPN22 C1858T influences innate and adaptive immunity by perturbing the homeostasis of B cells and Toll-like receptor (TLR)-9-mediated response in T1DM patients [15]. In addition, the Lyp variant may influence cytokine production [16]. Meta-analysis investigations showed that in the Caucasian population, T cells of some patients with T1DM are characterized by a defect in IL-2 production [17–20].

Interestingly, PTPN22 acts in T1DM through the modulation of Treg cells. Both in vivo and in vitro experiments using PTPN22 knock-out mice showed that PTPN22 plays
a key role in Treg induction and acts mainly through modulating the threshold of the T cell activation [21]. Unexpectedly, some experiments on animal models suggested a protective role of PTPN22 in T1DM. Overexpression of PTPN22 resulted in attenuated Th1 differentiation at low strength T cell receptor (TCR) stimulation and protected mice from a model of diabetes [22]. NOD mice where PTPN22 expression was targeted by a knock-down genetic approach were protected from autoimmune diabetes. Surprisingly, Yeh et al. found that PTPN22 transgenic NOD mice that overexpressed PTPN22 were also protected from T1DM [22]. Experiments by Lin et al. confirmed previous findings showing that in contrast to PTPN22 knocked-down mice, PTPN22 R619W NOD mice showed accelerated T1DM and increased prevalence and elevated titer of insulin [23]. Thus, either downregulation or overexpression of PTPN22 had a protective effect from T1DM in NOD mice. PTPN22 knock-down in NOD mice resulted in T1DM prevention possibly because of a dominant effect of PTPN22 on the Treg cells [24]. As it was shown in several mouse models of diverse genetic backgrounds, the number and functionality of Treg cells increase when PTPN22 levels reduce [24–26]. Studies in humans found that the PTPN22 variant conferred significant risk to T1DM; however, one meta-analysis showed a protective effect [27]. Re-analysis of previous results by using Bayesian approaches did not confirm this exception, thus this meta-analysis may meet one of several meta-analysis limitations [6]. Overall, results suggested a significant risk conferred by the PTPN22 620W variant in T1DM.

2.2. Association of PTPN22 C1858T with Rheumatoid Arthritis

PTPN22 is the strongest non-HLA genetic predisposition factor in RA. The first report on the significant association between the PTPN22 1858T allele and RA was published by Begovich and co-workers in 2004 [28]. The homozygous PTPN22 1858C variant is shown to increase the risk of RA by twice that of the 1858T variant, from which it can be interpreted that this variant is a co-dominant allele [28–32]. The data in RA show a dosage effect of the PTPN22 risk allele [33]. Several studies focused on the association of the PTPN22 variant with RA risk and its clinical features. The PTPN22R620W allele is associated with seropositive diseases [30,33], anti-citrullinated protein antibodies (ACPA) [34,35], erosive diseases [36], and earlier disease onset [37]. In a stratified meta-analysis, PTPN22C1858T was more common in RF-positive than in RF-negative patients and was also more common in patients with anti-CCP antibodies than those without [38]. Although PTPN22 1858T is associated with both autoantibody seropositive and seronegative RA, most studies have reported stronger associations of PTPN22 with RF-positive or ACPA-positive RA [28,35,37]. A GWAS confirmed that PTPN22 1858T is only of genome-wide significance in ACPA-positive RA patients [39]. Although some studies have detected an effect of PTPN22 on the presence of radiographic erosions or the rate of joint destruction in RA, a meta-analysis indicated no such association in either anti-CCP antibody seropositive or seronegative individuals [36,40,41]. Most studies showed an earlier (2–7.5 years) age at onset of RA in carriers of the PTPN22 1858T allele, but not all studies showed the same effect [36,42,43]. Several limitations related to experiment design and methods raise discrepancies between results. Re-analysis of previous findings using Bayesian approaches showed that 32 (82.1%) of the 39 comparisons from observational studies and one meta-analysis of GWAS had noteworthy findings by FPRP or BFDP [6].

At the molecular level, genetic polymorphism in PTPN22 may contribute to RA disease through a number of distinct mechanisms. The deficiency of PTPN22 function could contribute to the chronic activation of antigen-specific, class-II-restricted CD4+ T cells and other types of effector T cells which contribute to driving the inflammatory process within the synovium [44,45]. In a mouse model, PTPN22 could regulate vimentin-dectin-1 driven uptake and presentation of autoantigens, in addition to cytokine secretion [44]. Serum autoantibodies against citrullinated vimentin, common in RA patients, have been shown to promote osteoclastogenesis and bone resorption [44]. Human cells expressing PTPN22 Trp620 have deficient TLR-induced IFN production, and PTPN22 dysfunction
results in lowering thresholds for TCR signaling [46,47]. In a model of IL-1β-dependent synovial inflammation, overexpression of transgenic human PTPN22 Trp620 in mice impaired amelioration of inflammatory arthritis by treatment with an IFN-inducing TLR agonist [47]. Autoimmune pathogenesis promoted by PTPN22 1858T probably involves concerted anomalies in the differentiation of T cell subsets, B cell repertoire, and the balance between immunoregulatory and proinflammatory cytokine production.

In addition to the C1858T polymorphism, PTPN22 variants have been found in RA association, particularly in populations with low frequencies of the 1858T allele. A meta-analysis reports that the PTPN22 gene C1858T (rs2476601) SNP increases RA risk, especially in Caucasians and Africans [48].

2.3. Association of PTPN22 C1858T with Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis, the common type of autoimmune arthritis in children under 16, is also known to be associated with the PTPN22 1858T allele [49]. Several meta-analyses and SNP replication studies proved the significant contributions of PTPN22 1858T to the risk of JIA onset [50–53]. The PTPN22 1858T conferred risk for oligoarticular and RF-negative polyarticular JIA in white European, American, and Australian individuals [50,52]. A meta-analysis by Kaalla et al. reported that the 1858T allele was associated with RF-positive polyarticular JIA, but not with systemic-onset or enthesitis-related JIA [53]. Re-analysis of previous results including five studies with 15 genotype and allele comparisons showed that 9 (60%) and 1 comparison from a GWAS meta-analysis had noteworthy findings by FPRP or BFDP Bayesian approaches [6].

2.4. Association of PTPN22 C1858T with Systemic Lupus Erythematosus

In 2004, Kyogoku and colleagues first reported that the PTPN22 1858T allele is associated with SLE [54]. GWAS found an association of PTPN22 1858T with seropositive SLE in a case-only analysis and another study found a positive association with anti-cardiolipin IgG and a trend towards an increased frequency of PTPN22 1858T in patients with lupus nephritis or in individuals seropositive for anti-dsDNA autoantibodies [55,56]. In the case of SLE, both immune complex deposition and the direct effects of antibodies can contribute to this disease. Re-analysis of previous associations including seven observational studies with 15 genotypes and allelic comparisons reported that 13 (86.7%) of the 15 comparisons had noteworthy findings by FPRP or BFDP [6].

SLE is a systemic inflammatory disorder characterized by the production of autoantibodies, immune complex formation, and immune complex deposition in end-organs. The PTPN22 1858T allele has been demonstrated to be associated with lower IFN-γ and higher IFN-α levels in SLE [57]. As a consequence of dysregulated IFN-γ expression in SLE, patients carrying the 1858T risk variant may have enhanced IFN-α-mediated JAK-STAT signaling [58]. Pep and IFN-γ might cooperate to give rise to dysfunctional hematopoiesis. Animal models showed that the PTPN22*W polymorphism may also influence TCR signaling, augmenting the mediators implicated in the early events of the TCR-initiated response such as protein tyrosine phosphorylation and calcium mobilization [59]. It has been shown previously that TCR signaling was increased in SLE upon anti-CD3 monoclonal antibody (mAb) stimulation [60]. In addition, high PTPN22 transcript numbers in CD8+ T cells correlated with poor prognosis of SLE and AAV [61].

2.5. Association of PTPN22 C1858T with Vasculitides

The PTPN22 polymorphism is positively associated with microscopic polyangiitis (MPA) and granulomatosis with polyangiitis (GPA), formerly known as Wegener’s granulomatosis, but has not been reported in eosinophilic granulomatosis with polyangiitis (eGPA), formerly known as Churg–Strauss syndrome [62,63]. The association with GPA is stronger in patients with organ pathology (lung, kidney, eye, or peripheral nervous system) [63]. Several studies have documented and replicated a significant association of the 1858T allele with biopsy-proven giant cell arteritis (GCA) [64]. Intriguingly, two
studies reported that PTPN22 1858T can protect against Behçet’s disease (BD) [65]. In Bayesian re-analysis, a total of four studies with 11 genotypic and allelic comparisons were included for ANCA-associated vasculitis. Out of 11 comparisons, 6 (54.5%) had noteworthy findings by FPRP or BFDP [6]. For the studies including subjects with GCA, re-analysis of observational studies and GWAS by Bayesian approaches revealed that among three comparisons, two were noteworthy [6].

2.6. PTPN22 C1858T in Autoimmune Thyroid Disease

In addition to T1DM, RA, SLE, JIA, and vasculitis, other autoimmune disorders such as autoimmune thyroid diseases (AITD), including Grave’s disease and Hashimoto’s disease, Addison’s disease, autoimmune thrombocytopenia, inflammatory bowel disease, vitiligo, etc., had a significant correlation with the PTPN22 1858T allele [38,66]. A meta-analysis showed that PTPN22 C1858T is associated with the risk of Grave’s disease and Hashimoto’s thyroiditis in the overall study population. In addition, this polymorphism is associated with elevated AITD risk in Caucasians, but not in Asians [67]. A total of 212 Korean AITD patients were studied; interestingly, a minor allele of an SNP (rs12730735) and a haplotype (GGCTT) showed significant association with the susceptibility of AITD, especially with that of Hashimoto’s thyroiditis [68]. In Chinese AITD patients, Gong et al. reported rare missense mutation in PTPN22 (NM_015967.5; c.77A > G; p.Asn26Ser) using whole-exome sequencing in Hashimoto’s thyroiditis, but PTPN22 C1858T mutation was not confirmed [69].

2.7. PTPN22 C1858T in Autoimmune Skin Diseases

A study showed not only the significant association of the PTPN22 C1858T with patients with psoriasis arthritis (PsA) (Odds ratio, 1.49; 95% confidence interval, 1.10–2.02) but also showed a greater number of deformed joints [70]. While most susceptibility loci identified in psoriasis (PsO) tend to be equally associated with skin psoriasis and with PsA, the 1858T allele PTPN22 is weakly associated with general skin psoriasis whereas its association with PsA is statistically highly significant [71]. This suggests that PTPN22 may influence more cells and pathways influenced in PsA, which has additional components in its pathogenesis compared to skin-restricted. Bowes et al. suggested that the differential association of PTPN22 Trp620 with PsA vs. PsO depends on alterations in the function of CD8 T cells, which have been known to be influenced by PTPN22 [71,72]. The known role of PTPN22 in CD8 memory T cell function and IL-17-producing Th17 cell differentiation suggests the possibility that PTPN22-W620 contributes to differential phenotypes of Th17 in PsA vs. PsO or AS [73,74].

The T allele of the single nucleoid polymorphism (SNP) rs2476601 in the PTPN22 gene is a risk factor for developing alopecia areata. However, more robust studies defining the ethnic background of the population of origin are required, so that the risk identified in the present study can be validated [75]. The PTPN22 1858T allele of SNP rs2476601 is also reported to be associated with an increased risk of generalized vitiligo [76–78].

2.8. PTPN22 C1858T in Other Autoimmune Conditions

Intriguingly, the allele was protective against two autoimmune disorders, Crohn’s disease (CD) and Behçet’s disease (BD) [79]. However, these reports did not contain large sample sizes, and in some cases, these associations have failed to replicate. In addition, there were no noteworthy findings by FPRP or BFDP in one study (two comparisons) of BD and one study (three comparisons) of AITD [6]. No association was observed between rs2476601 and autoimmune diseases of the liver and the bile duct, such as autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis, but further investigation is needed as not many studies were conducted [49,80,81].

Unlike in RA studies, the association with systemic sclerosis (SSc) is not affected by the presence of autoantibodies, as meta-analysis did not reveal a difference in allele frequency when comparing anti-centromere antibody seropositive and seronegative or
anti-topoisomerase I autoantibody seropositive and seronegative SSc [38,82]. Bayesian approaches including two studies with three allelic comparisons analyzed the genetic impact of psoriasis (PsO) and did not verify noteworthiness by means of both FPRP and BFDP estimations [6]. Three studies including patients with SSc analyzed seven genotypic and allelic comparisons and did not show noteworthiness in terms of FPRP and BFDP estimations. Findings from patients with SS and AS included two studies, only one study for each, and did not verify noteworthiness by means of FPRP and BFDP estimations. However, a GWAS meta-analysis including one comparison showed noteworthy results for PsA [6]. It should be noted that meta-analyses from PsO, SS, SSc, and AS patients had several limitations related to the number and population size of included studies. Therefore, meta-analyses with larger sizes including different ethnicities and clinical features would give significant results.

A single case-control study that reported an association of PTPN22 C1858T with idiopathic inflammatory myopathy in white individuals suggested that after stratification analysis the association was restricted to polymyositis and juvenile dermatomyositis, and not to dermatomyositis or myositis overlapping with another connective tissue disease [83]. In addition, PTPN22 1858T was not associated with dermatomyositis in a GWAS of patients with adult or juvenile dermatomyositis [84]. In the case of GD and MG, it is widely recognized that the disease-associated autoantibodies are pathogenic. A direct role for autoantibodies is less clear for Hashimoto’s thyroiditis, vitiligo, and rheumatoid arthritis, although recent studies suggest that the anti-citrulline antibodies may contribute directly to joint inflammation [85]. Interestingly, many of these PTPN22-associated diseases also appear to cluster together in families, suggesting that the PTPN22 association reflects the involvement of common pathways in these disorders [86,87]. The C1858T polymorphism could contribute to the development of GD and HT in children, with a strong indication that females are pre-disposed to developing the disease and the T allele is the main risk factor [88]. Re-analysis of previous results by Bayesian approaches reported that among three studies from subjects with MG reporting five allelic comparisons, four (80%) of the five comparisons had noteworthy findings by FPRP or BFDP. Out of three studies with five comparisons included from patients with vitiligo, four (80%) of the five comparisons had noteworthy findings by FPRP or BFDP. For Addison’s disease, out of the three comparisons, two were noteworthy in terms of BFDP. For patients with endometriosis, one study with three co-dominant comparisons did not verify noteworthiness, except for one finding which was noteworthy by using BFDP. There were no noteworthy findings by FPRP or BFDP in one comparison of alopecia areata [6]. Re-analysis from patients with CD including five studies revealed that two (40%) of the five comparisons had noteworthy findings by FPRP or BFDP [6].

At the functional level, several studies tried to explain how PTPN22 contributes to CD. PTPN22 regulates intracellular signaling events and is induced by IFN-γ in human monocytes [89]. Knock-down of PTPN22 alters the activation of inflammatory signal transducers, increasing the secretion of Th17-related inflammatory mediators [90]. This might explain on a functional level how the reduced PTPN22 expression found in CD patients contributes to CD pathology. Spalinger et al. showed that TNFα levels are elevated in CD patients, decreasing PTPN22 expression significantly; thus, TNFα is likely to play an even more important role in CD pathogenesis than IFN-γ [90]. In concordance with these findings, the C1858T polymorphism, which causes a gain of function, is protective in CD and attenuates the expression of proinflammatory cytokines [91,92]. PTPN22 also is involved in the regulation of Src kinase and negatively controls the p38-MAPK/IL-6 pathway [93]. p38-MAPK activation and IL-6 secretion by antigen-presenting cells (APC) play a crucial role in the differentiation of CD4+ naive T cells into Th17 cells that are more and more regarded as the driving force of CD [94].
3. Other Polymorphisms in the PTPN22 Gene Are Associated with Autoimmune Diseases

Not only the C1858T polymorphism but other PTPN22 gene variants also have been investigated to be associated with autoimmune disorders. These associations especially are more prominent in specific populations with low frequency of the C1858T polymorphism and they are associated with resistance to certain autoimmune diseases, indicating the complexity of most autoimmune diseases [95]. In the Asian population, a systemic search for SNPs allowed identifying five SNPs in the PTPN22 gene, while C1858T was not found (vide supra). Among these, two SNPs, G1123C and C2740T, showed allele frequencies of more than 5% [96].

The G1123C polymorphism (rs2488457) is located in the 5′ promoter region of PTPN22, and its function has not yet been characterized. The impact of this non-coding SNP on the transcription, stability, or translation of the mRNA remains to be fully clarified. It has been found that the SNP is associated with RA, JIA, the onset of acute T1D in Japanese and Korean subjects, latent autoimmune diabetes in Chinese patients, and UC [96–100]. Interestingly, rs2488457 was recently reported as a potential cis-expression quantitative trait loci (eQTLs) in whole blood from Spanish RA patients, and another study demonstrated that PTPN22 expression is significantly decreased in whole blood from RA patients carrying the risk alleles of SNPs C1858T and G1123C compared to healthy controls [101,102].

The second (rs33996649) is a rare missense G788A mutation that does not co-occur with C1858T and encodes an R263Q substitution in the catalytic domain of the protein [103]. PTPN22 G788A encodes a loss-of-function Arg263Gln substitution that changes the conformation of the active site and results in the reduced catalytic activity of PTPN22 [103]. Therefore, the 788A allele displays a pattern of autoimmune disease association that is distinct from the 1858T allele in European populations. Single studies have so far shown no associations with SSc, GCA, IgA vasculitis, uveitis, or GD [64,104]. In contrast to 1858T, the 788A allele protects against both SLE and RA [104]. The 788A allele reduced risk for UC, which 1858T does not associate with, and the 788A does not associate with CD, with which the 1858T is protective against [92,104].

Recently, Gong et al., by using whole-exome sequencing in a Chinese Hashimoto’s thyroiditis pedigree, identified an extremely rare missense mutation in PTPN22 (NM_015967.5; c. 77A > G; p. Asn26Ser) [69]. The missense mutation PTPN22 (N26S) is located in the classical catalytic domain of the N-terminal protein tyrosine phosphatase. Little is known regarding its specific function; however, co-segregation analysis confirmed that all patients in this family were female, and authors linked this variant to Hashimoto’s thyroiditis [69]. Considering the female predominance in most of the autoimmune disorders associated with the PTPN22 Trp620 variant, Nielsen et al. investigated the existence of cis-acting or sex-specific trans-acting factor/s (e.g., sex hormones) affecting the allele-specific expression of the PTPN22 Arg620Trp polymorphism [105]. They report no effect of sex or pregnancy status on the relative expression of the PTPN22 1858T allele, indicating the absence of sex-specific trans-acting factor/s (e.g., sex hormones) [105].

Many SNPs were studied to assess the association between ethnicity and susceptibility to different autoimmune diseases. A Japanese study identified nine SNPs in the PTPN22 gene and found minor alleles at rs1217412, rs1217388, rs1217407, and rs2488458 less frequent in autoimmune hepatitis patients compared with controls [80]. This is in contrast with a genome-wide association study where PTPN22 was not related to autoimmune hepatitis patients of European descent [106]. In a study based on the Chinese Han population, rs1217414 and rs3811021 showed a strong association with both SLE and RA, while rs3765598 had a significant association with SLE only [107].
Table 1. Summary of the PTPN22 C1858T polymorphism with different types of autoimmune diseases.

| Type of Diseases | Summary of Immunologic Functions | References |
|------------------|----------------------------------|------------|
| T1DM             | PTPN22 variant produces Lyp R620W protein which increases the number of autoreactive B cells, promoting the autoimmune reactions by internalizing and presenting autoantigens to T lymphocytes. | [12,13] |
|                  | In T1DM patients with PTPN22 variants, expansion of B cell along with reduced B cell receptor signaling and resistance to apoptosis were found. | [14] |
|                  | PTPN22 1858T variant disturbs the homeostasis of B cells and Toll-like receptor 9 mediated response, and also the cytokine production. | [15] |
|                  | PTPN22 variant increases the number of Treg cells then modulates the threshold of T cell activation. | [21] |
|                  | Overexpression of PTPN22 encodes Pep-decreased TCR-mediated effector cell responses then prevents the disease process. | [22] |
|                  | On the contrary, PTPN22 knocked-down mice showed an acceleration of T1DM by elevating the titer of insulin. | [23] |
| RA               | Lack of PTPN22 function activates the antigen-specific, class-II-restricted CD4+ T cells and effector T cells, contributing inflammatory process in the synovium, accelerating the RA progress. | [44,45] |
|                  | Increased number of antibodies also promotes osteoclastogenesis and bone resorption. | [44] |
|                  | PTPN22 Trp620-expressing human cells have lack of production of TLR-induced IFN production, have lowered threshold for TCR signaling. | [46,47] |
| SLE              | In the C1858T polymorphism of PTPN22, the risk of SLE increased by lowering IFN-gamma rate and higher serum IFN-α activity. | [57] |
|                  | The 1858T variant may enhance IFN-α-mediated JAK-STAT signaling, and the increasing number of Pep and IFN-α results in dysfunctional hematopoiesis. | [58] |
|                  | PTPN22*W polymorphism influences TCR signaling and augments the TCR-initiated response to promote autoimmunity. | [59] |
|                  | Patients with SLE showed abnormality in TCR/CD3 monoclonal antibody stimulation. | [60] |

4. Conclusions

To sum up, we can conclude that the SNPs of PTPN22 play an important role in the onset of autoimmune diseases including T1DM, RA, JIA, PsA, SLE, SSC, AIID, and different forms of vasculitis. Not only the most well-known polymorphism of PTPN22 at position 1858 called the PTPN22 C1858T SNP has significant variant characteristics, but also new variants in a variety of genes, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4), tumor necrosis factor (TNF), interferon regulatory factor 5 (IRF5), etc., are recently reported to be associated with autoimmune disorders (Table 1). Recent large-scale GWAS studies support the strength of genetic factors on autoimmunity; nevertheless, this still needs to be supported with additional research.

Author Contributions: Conceptualization, K.T. and J.H.K.; methodology, K.T.; validation and investigation, K.T., J.I.S., G.H.J., J.W.Y., S.P. and J.H.K.; writing—original draft preparation, K.T. and J.H.K.; writing—review and editing, J.I.S., S.Y.H., S.J.P., A.K. and L.S.; supervision, S.J.P., A.K. and L.S.; project administration, K.T. and J.H.K.; funding acquisition, J.I.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.
References

1. Scherlinger, M.; Mertz, P.; Sagez, F.; Meyer, A.; Felten, R.; Chatelus, E.; Javier, R.-M.; Sordet, C.; Martin, T.; Korganow, A.-S.; et al. Worldwide trends in all-cause mortality of auto-immune systemic diseases between 2001 and 2014. *Autoimmun. Rev.* 2020, 19, 102531. [CrossRef]

2. Hayter, S.M.; Cook, M.C. Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. *Autoimmun. Rev.* 2012, 11, 754–765. [CrossRef] [PubMed]

3. Lerner, A.; Jeremias, P.; Matthias, T. The world incidence and prevalence of autoimmune diseases is increasing. *Int. J. Celiac Dis.* 2015, 3, 151–155. [CrossRef]

4. Cho, J.H.; Feldman, M.D. Heterogeneity of autoimmune diseases: Pathophysiologic insights from genetics and implications for new therapies. *Nat. Med.* 2015, 21, 730–738. [CrossRef]

5. Gregersen, P.K.; Olsson, L.M. Recent advances in the genetics of autoimmune disease. *Annu. Rev. Immunol.* 2009, 27, 363–391. [CrossRef]

6. Tizaoui, K.; Kim, S.H.; Jeong, G.H.; Kronbichler, A.; Lee, K.S.; Lee, K.H.; Shin, J.I. Association of PTPN22 1858C/T Polymorphism with Autoimmune Diseases: A Systematic Review and Bayesian Approach. *J. Clin. Med.* 2019, 8, 347. [CrossRef] [PubMed]

7. Siminovich, K.A. PTPN22 and autoimmune disease. *Nat. Genet.* 2004, 36, 1248–1249. [CrossRef] [PubMed]

8. Bottini, N.; Musumeci, L.; Alonso, A.; Rahmouni, S.; Nika, K.; Rostamkhani, M.; MacMurray, J.; Meloni, G.F.; Lucarelli, P.; Pellecchia, M.; et al. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. *Nat. Genet.* 2004, 36, 337–338. [CrossRef] [PubMed]

9. Huraiib, G.B.; Harthi, F.A.; Arfin, M.; Al-Asmari, A. The Protein Tyrosine Phosphatase Non-Receptor Type 22 (PTPN22) Gene Polymorphism and Susceptibility to Autoimmune Diseases. In *The Recent Topics in Genetic Polymorphisms*; Mahmut Çalışkan, O.E., Gül, Ö., Eds.; IntechOpen: London, UK, 2020.

10. Tizaoui, K.; Terrazzino, S.; Cargnin, S.; Lee, K.H.; Gauckler, P.; Li, H.; Shin, J.I.; Kronbichler, A. The role of PTPN22 in the pathogenesis of autoimmune diseases: A comprehensive review. *Semin. Arthritis Rheum.* 2021, 51, 513–522. [CrossRef] [PubMed]

11. Heneberg, P.; Kocková, L.; Čečáková, M.; Daňková, P.; Černá, M. Autoimmunity-Associated PTPN22 Polymorphisms in Latent Autoimmune Diabetess of the Adult Differ from Those of Type 1 Diabetes Patients. *Int. Arch. Allergy Immunol.* 2018, 177, 57–68. [CrossRef]

12. Slomchik, M.J. Sites and stages of autoreactive B cell activation and regulation. *Immunity* 2008, 28, 18–28. [CrossRef] [PubMed]

13. Menard, L.; Saadoun, D.; Isnardi, I.; Ng, Y.-S.; Meyers, G.; Massad, C.; Price, C.; Abraham, C.; Motaghedi, R.; Buckner, J.H.; et al. The PTPN22 allele encoding an R620W variant interferes with the removal of developing autoreactive B cells in humans. *J. Clin. Investig.* 2011, 121, 3635–3644. [CrossRef] [PubMed]

14. Habib, T.; Funk, A.; Rieck, M.; Brahmandam, A.; Dai, X.; Panigrahi, A.K.; Prak, E.T.L.; Meyer-Bahlburg, A.; Sanda, S.; Sanda, S.; Greenbaum, C.; et al. Altered B cell homeostasis is associated with type I diabetes and carriers of the PTPN22 allelic variant. *J. Immunol.* 2012, 188, 487–496. [CrossRef] [PubMed]

15. Perri, V.; Pellergrino, M.; Ceccacci, F.; Scipioni, A.; Petrini, S.; Gianechetti, E.; Russo, A.L.; de Santis, S.; Mancini, G.; Fierabracci, A. Use of short interfering RNA delivered by cationic liposomes to enable efficient down-regulation of PTPN22 gene in human T lymphocytes. *PLoS ONE* 2017, 12, e0175784. [CrossRef]

16. Vang, T.; Congia, M.; Macis, M.D.; Musumeci, L.; Orrù, V.; Zavattari, P.; Nika, K.; Tautz, L.; Taskén, K.; Cucca, F.; et al. Autoimmune-associated lymphoid tyrosine phosphatase is a gain-of-function variant. *Nat. Genet.* 2005, 37, 1317–1319. [CrossRef] [PubMed]

17. Long, S.A.; Rieck, M.; Sanda, S.; Bollyky, J.B.; Samuels, P.L.; Goland, R.; Ahmann, A.; Rabinovitch, A.; Aggarwal, S.; Phippard, D.; et al. Rapamycin/IL-2 combination therapy in patients with type 1 diabetes augments Tregs yet transiently impairs beta-cell function. *Diabetes 2012*, 61, 2340–2348. [CrossRef]

18. Pellergrino, M.; Ceccacci, F.; Petrini, S.; Scipioni, A.; de Santis, S.; Cappa, M.; Mancini, G.; Fierabracci, A. Exploiting novel tailored immunotherapies of type 1 diabetes: Short interfering RNA delivered by cationic liposomes enables efficient down-regulation of variant PTPN22 gene in T lymphocytes. *Antiviral Res.* 2015, 119, 443–452. [CrossRef] [PubMed]

19. Caligiuri, P.; Danzov, J.; Grey, A.; Heneberg, P.; ˇCerná, M. Autoimmunity-Associated PTPN22 Polymorphisms in Latent Autoimmune Diabetess of the Adult Differ from Those of Type 1 Diabetes Patients. *Int. Arch. Allergy Immunol.* 2018, 177, 57–68. [CrossRef]

20. Garg, G.; Tyler, J.R.; Yang, J.H.; Cutler, A.J.; Downes, K.; Pekalski, M.; Bell, G.L.; Nutland, S.; Peakman, M.; Todd, J.A.; et al. Type 1 diabetes-associated IL2RA variation lowers IL-2 signaling and contributes to diminished CD4+CD25+ regulatory T cell function. *J. Immunol.* 2012, 188, 4644–4653. [CrossRef]

21. Fousteri, G.; Jofra, T.; Debernardis, I.; Stanford, S.M.; Laurenzi, A.; Bottini, N.; Battaglia, M. The protein tyrosine phosphatase PTPN22 controls forkhead box protein 3 T regulatory cell induction but is dispensable for T helper type 1 cell polarization. *Clin. Exp. Immunol.* 2014, 178, 178–189. [CrossRef]

22. Yeh, L.-T.; Miaw, S.-C.; Lin, M.-H.; Chou, F.-C.; Shieh, S.-J.; Chuang, Y.-P.; Lin, S.-H.; Chang, D.-M.; Sytwu, H.-K. Different modulation of Ptpn22 in effector and regulatory T cells leads to attenuation of autoimmune diabetes in transgenic nonobese diabetic mice. *J. Immunol.* 2013, 191, 594–607. [CrossRef] [PubMed]
31. Lee, A.T.; Li, W.; Liew, A.; Bombardier, C.; Weisman, M.; Massarotti, E.M.; Kent, J.; Wolfe, F.; Begovich, A.B.; Gregersen, P.K.; et al. CRISPR-Cas9-mediated modification of the NOD mouse genome with Ptprn22R619W mutation increases autoimmune diabetes. *Diabetes* **2016**, *65*, 2134–2138. [CrossRef] [PubMed]

24. Zheng, P.; Kissler, S. PTPN22 silencing in the NOD model indicates the type 1 diabetes-associated allele is not a loss-of-function variant. *Diabetes* **2013**, *62*, 896–904. [CrossRef] [PubMed]

27. Tang, S.; Peng, W.; Wang, C.; Tang, H.; Zhang, Q. Association of the PTPN22 gene (+1858C/T, −1123G/C) polymorphisms with type 1 diabetes mellitus: A systematic review and meta-analysis. *Diabetes Res. Clin. Pract.* **2012**, *97*, 446–452. [CrossRef] [PubMed]

26. Maine, C.J.; Hamilton-Williams, E.E.; Cheung, J.; Stanford, S.M.; Bottini, N.; Wicker, L.S.; Sherman, L.A. PTPN22 alters the development of regulatory T cells in the thymus. *J. Immunol.* **2012**, *188*, 5267–5275. [CrossRef] [PubMed]

25. Brownlie, R.J.; Miosge, L.A.; Vassilakos, D.; Svensson, L.M.; Cope, A.; Zamoyska, R. Lack of the phosphatase PTPN22 increases adhesion of murine regulatory T cells to improve their immunosuppressive function. *Sci. Signal.* **2012**, *5*, ra87. [CrossRef] [PubMed]

28. Begovich, A.B.; Carlton, V.E.; Honigberg, L.A.; Schrodi, S.J.; Chokkalingam, A.P.; Alexander, H.C.; Ardlie, K.G.; Huang, Q.; Smith, A.M.; Sporke, J.M.; 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.* **2004**, *75*, 330–337. [CrossRef] [PubMed]

29. Steer, S.; Lad, B.; Grunmly, J.A.; Kingsley, G.H.; Fisher, S.A. Association of R602W in a protein tyrosine phosphatase gene with a high risk of rheumatoid arthritis in a British population: Evidence for an early onset/disease severity effect. *Arthritis Care Res.* **2005**, *52*, 358–360. [CrossRef]

30. Hinks, A.; Barton, A.; John, S.; Bruce, I.; Hawkins, C.; Griffiths, C.; Donn, R.; Thomson, W.; Silman, A.; Worthington, J. Association between the PTPN22 gene and rheumatoid arthritis and juvenile idiopathic arthritis in a UK population: Further support that PTPN22 is an autoimmunity gene. *Arthritis Care Res.* **2005**, *52*, 1694–1699. [CrossRef]

31. Lee, A.T.; Li, W.; Liew, A.; Bombardier, C.; Weisman, M.; Massarotti, E.M.; Kent, J.; Wolfe, F.; Begovich, A.B.; Gregersen, P.K. The PTPN22 R620W polymorphism associates with RF positive rheumatoid arthritis in a dose-dependent manner but not with HLA-SE status. *Genes Immun.* **2005**, *6*, 129–133. [CrossRef] [PubMed]

32. Simkins, H.M.A.; Merriman, M.E.; Highton, J.; Chapman, P.T.; O’Donnell, J.L.; Jones, P.B.B.; Gow, P.J.; McLean, L.; Pokorny, V.; Harrison, A.A.; et al. Association of the PTPN22 locus with rheumatoid arthritis in a New Zealand Caucasian cohort. *Arthritis Care Res.* **2005**, *52*, 2222–2225. [CrossRef] [PubMed]

33. Gregersen, P.K. Pathways to gene identification in rheumatoid arthritis: PTPN22 and beyond. *Immune Rev.* **2005**, *204*, 74–86. [CrossRef] [PubMed]

34. Goeb, V.; Dieude, P.; Daveau, R.; Thomas-L’Otellier, M.; Jouen, F.; Hau, F.; Boumier, P.; Tron, F.; Gilbert, D.; Fardellone, P.; et al. Contribution of PTPN22 1858T, TNFRII 196R and HLA-shared epitope alleles with rheumatoid factor and anti-citrullinated protein antibodies to early rheumatoid arthritis diagnosis. *Rheumatology* **2008**, *47*, 1208–1212. [CrossRef] [PubMed]

35. Johansson, M.; Arlestig, L.; Hallmans, G.; Rantapää-Dahlqvist, S. PTPN22 polymorphism and anti-cyclic citrullinated peptide antibodies in combination strongly predicts future onset of rheumatoid arthritis and has a specificity of 100% for the disease. *Arthritis Care Res.* **2005**, *52*, 2222–2225. [CrossRef] [PubMed]

36. Lie, B.A.; Viken, M.K.; Ødegård, S.; van der Heijde, D.; Landewé, R.; Uhlig, T.; Kvien, T.K. Associations between the PTPN22 1858C→T polymorphism and radiographic joint destruction in patients with rheumatoid arthritis: Results from a 10-year longitudinal study. *Ann. Rheum. Dis.* **2007**, *66*, 1604–1609. [CrossRef] [PubMed]

37. Karlson, E.W.; Chibnik, L.B.; Cui, J.; Plenge, R.M.; Glass, R.J.; Maher, N.E.; Parker, A.N.; Roubenoff, R.; Izsaimova, E.S.; Coblyn, J.S.; et al. Associations between human leukocyte antigen, PTPN22, CTLA4 genotypes and rheumatoid arthritis phenotype. *Ann. Rheum. Dis.* **2007**, *66*, 1604–1609. [CrossRef] [PubMed]

38. Zheng, J.; Ibrahim, S.; Petersen, F.; Yu, X. Meta-analysis reveals an association of PTPN22 C1858T with autoimmune diseases, which depends on the localization of the affected tissue. *Genes Immun.* **2012**, *13*, 641–652. [CrossRef] [PubMed]

39. Padyukov, L.; Seielstad, M.; Ong, R.T.H.; Ding, B.; Ronnelid, J.; Sedighzadeh, M.; Alfredsson, L.; Klareskog, L.; Epidemiological Investigation of Rheumatoid Arthritis (EIRA) Study Group. A genome-wide association study suggests contrasting associations in ACPA-positive versus ACPA-negative rheumatoid arthritis. *Ann. Rheum. Dis.* **2011**, *70*, 259–265. [CrossRef]

40. Marinou, I.; Healy, J.; Mewar, D.; Moore, D.J.; Dickson, M.C.; Binks, M.H.; Montgomery, D.S.; Walters, K.; Wilson, A.G. Association of interleukin-6 and interleukin-10 genotypes with radiographic damage in rheumatoid arthritis is dependent on the localization of the affected tissue. *Genes Immun.* **2012**, *13*, 641–652. [CrossRef] [PubMed]

41. Taylor, L.H.; Twigg, S.; Worthington, J.; Emery, P.; Morgan, A.W.; Wilson, A.G.; Teare, M.D. Metaanalysis of the association of smoking and PTPN22 R620W genotype on autoantibody status and radiological erosions in rheumatoid arthritis. *J. Rheumatol.* **2013**, *40*, 1048–1053. [CrossRef]

42. Harrison, P.; Pointon, J.J.; Farrar, C.; Brown, M.A.; Wordsworth, B.P. Effects of PTPN22 C1858T polymorphism on susceptibility and clinical characteristics of British Caucasian rheumatoid arthritis patients. *Rheumatology* **2006**, *45*, 1009–1011. [CrossRef] [PubMed]
43. Orozco, G.; Sánchez, E.; González-Gay, M.A.; López-Nevo, M.A.; Torres, B.; Cáliz, R.; Ortego-Centeno, N.; Jiménez-Alonso, J.; Pascual-Salcedo, D.; Balsa, A.; et al. Association of a functional single-nucleotide polymorphism of PTPN22, encoding lymphoid protein phosphatase, with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis Rheum.* 2005, 52, 219–224. [CrossRef] [PubMed]

44. Harre, U.; Georgess, D.; Bang, H.; Bozec, A.; Axmann, R.; Ossipova, E.; Jakobsson, P.-J.; Baum, W.; Nimmerjahn, F.; Szarka, E.; et al. Induction of osteoclastogenesis and bone loss by human autoantibodies against citrullinated vimentin. *J. Clin. Investig.* 2012, 122, 1791–1802. [CrossRef] [PubMed]

45. Geronzy, J.J.; Zettl, A.; Weyand, C.M. T cell receptor repertoire in rheumatoid arthritis. *Int. Rev. Immunol.* 1998, 17, 339–363. [CrossRef]

46. Sood, S.; Brownlie, R.J.; Garcia, C.; Cowan, G.; Salmond, R.J.; Sakaguchi, S.; Zamoyska, R. Loss of the protein tyrosine phosphatase protein phosphatase PEP negatively regulates IFN-alpha receptor signaling. *J. Exp. Med.* 2005, 202, 1695–1707. [CrossRef] [PubMed]

47. Wang, Y.; Shaked, I.; Stanford, S.M.; Zhou, W.; Curtsinger, J.M.; Mikulski, Z.; Shaheen, Z.R.; Cheng, G.; Sawatzke, K.; Kariuki, S.N.; Crow, M.K.; Niewold, T.B. The PTPN22 C1858T polymorphism is associated with skewing of cytokine profiles toward high interferon-alpha activity and low tumor necrosis factor alpha levels in patients with lupus. *Arthritis Care Res.* 2013, 65, 292–299. [CrossRef] [PubMed]

48. Abbasifard, M.; Imani, D.; Bagheri-Hosseinabadi, Z. PTPN22 gene polymorphism and susceptibility to rheumatoid arthritis (RA): Updated systematic review and meta-analysis. *J. Gene Med.* 2020, 22, e3204. [CrossRef]

49. Vassilopoulos, D.; Kovacs, B.; Tsokos, G.C. TCR/CD3 complex-mediated signal transduction pathway in T cells and T cell lines. *Int. Rev. Immunol.* 2012, 31, 155–169. [CrossRef] [PubMed]

50. Hinks, A.; Eyre, S.; Ke, X.; Barton, A.; Martin, P.; Flynn, E.; Packham, J.; Worthington, J.; Thomson, W.; Childhood arthritis prospective study (CAPS); et al. Overlap of disease susceptibility loci for rheumatoid arthritis and juvenile idiopathic arthritis. *Ann. Rheum. Dis.* 2010, 69, 1049–1053. [CrossRef]

51. Lee, Y.H.; Bae, S.-C.; Song, G.G. The association between the functional PTPN22 1858 C/T and MIF -173 C/G polymorphisms and juvenile idiopathic arthritis: A meta-analysis. *Inflamm. Res.* 2012, 61, 411–415. [CrossRef]

52. Ellis, J.A.; Chavez, R.A.; Pezic, A.; Ponsonby, A.-L.; Akikusa, J.D.; Allen, R.C.; Munro, J.E. Independent replication analysis of genetic loci with previous evidence of association with juvenile idiopathic arthritis. *Pediatr. Rheumatol.* 2013, 11, 12. [CrossRef] [PubMed]

53. Kyogoku, C.; Langefeld, C.D.; Ortmann, W.A.; Lee, A.; Selby, S.; Carlton, V.E.H.; Chang, M.; Ramos, P.; Baechler, E.C.; Batliwalla, F.M.; et al. Genetic association of the R620W polymorphism of protein tyrosine phosphatase PTPN22 with human SLE. *Am. J. Hum. Genet.* 2004, 75, 504–507. [CrossRef] [PubMed]

54. Chung, S.A.; Taylor, K.E.; Graham, R.R.; Nititham, J.; Lee, A.T.; Ortmann, W.A.; Jacob, C.O.; Alarcón-Riquelme, M.E.; Tsao, B.P.; Harley, J.B.; et al. Differential genetic associations for systemic lupus erythematosus based on anti-dsDNA autoantibody production. *PloS Genet.* 2011, 7, e1001323. [CrossRef] [PubMed]

55. Kariuki, S.N.; Crow, M.K.; Niewold, T.B. The PTPN22 C1858T polymorphism is associated with skewing of cytokine profiles toward high interferon-alpha activity and low tumor necrosis factor alpha levels in patients with lupus. *Arthritis Care Res.* 2008, 58, 2818–2823. [CrossRef]

56. Holmes, D.A.; Suto, E.; Lee, W.P.; Ou, Q.; Gong, Q.; Smith, H.R.; Caplazi, P.; Chan, A.C. Autoimmunity-associated protein tyrosine phosphatase PEP negatively regulates IFN-alpha receptor signaling. *J. Exp. Med.* 2015, 212, 1081–1093. [CrossRef] [PubMed]

57. Cao, Y.; Liu, K.; Tian, Z.; Hogan, S.L.; Yang, J.; Poulton, C.J.; Falk, R.J.; Li, W. PTPN22 R620W polymorphism and ANCA disease risk in white populations: A metaanalysis. *J. Rheumatol.* 2015, 42, 292–299. [CrossRef] [PubMed]

58. Jagiello, P.; Aries, P.; Arning, L.; Wagenleiter, S.E.; Csernok, E.; Hellmich, B.; Gross, W.L.; Epplen, J.T. The PTPN22 620W allele is a risk factor for Wegener’s granulomatosis. *Arthritis Rheum.* 2005, 52, 4039–4043. [CrossRef] [PubMed]
64. Serrano, A.; Márquez, A.; Mackie, S.L.; Carmona, F.D.; Solans, R.; Miranda-Filloy, J.A.; Hernández-Rodriguez, J.; Cid, M.C.; Castañeda, S.; Morado, I.; et al. Identification of the PTPN22 functional variant R620W as susceptibility genetic factor for giant cell arteritis. *Ann. Rheum. Dis.* 2013, 72, 1882–1886. [CrossRef]

65. Baranathan, V.; Stanford, M.R.; Vaughan, R.W.; Kondeatis, E.; Graham, E.; Fortune, F.; Madanat, W.; Kanawati, C.; Ghabra, M.; Murray, P.I.; et al. The association of the PTPN22 620W polymorphism with Behcet’s disease. *Ann. Rheum. Dis.* 2007, 66, 1531–1533. [CrossRef]

66. Bottini, N.; Peterson, E.J. Tyrosine phosphatase PTPN22: Multifunctional regulator of immune signaling, development, and disease. *Annu. Rev. Immunol.* 2014, 32, 83–119. [CrossRef] [PubMed]

67. Wu, H.; Wan, S.; Qu, M.; Ren, B.; Liu, L.; Shen, H. The relationship between PTPN22 R620W polymorphisms and the susceptibility to Autoimmune Thyroid Diseases: An Updated Meta-analysis. *Immunol. Invest.* 2022, 51, 438–451. [CrossRef] [PubMed]

68. Luo, L.; Cai, B.; Liu, F.; Hu, X.; Wang, L. Association of Protein Tyrosine Phosphatase Nonreceptor 22 (PTPN22) C1858T gene polymorphism with susceptibility to autoimmune thyroid diseases: A meta-analysis. *Endocr. J.* 2012, 59, 439–445. [CrossRef]

69. Gong, L.; Liu, B.; Wang, J.; Pan, H.; Qi, A.; Zhang, S.; Wu, J.; Yang, P.; Wang, B. Novel missense mutation in PTPN22 in a Chinese pedigree with Hashimoto’s thyroiditis. *BMC Endocr. Disord.* 2018, 18, 76. [CrossRef] [PubMed]

70. Juneblad, K.; Johansson, M.; Kautt, A.-L.; Prestvik, G.; Alenius, G.-M. Association between the PTPN22 +1858 C/T polymorphism and psoriatic arthritis. *Arthritis Res. Ther.* 2011, 13, R45. [CrossRef]

71. Budu-Aggrey, A.; Lohr, S.; Bowes, J.; Uebe, S.; Bruce, I.; Feletar, M.; Marzo-Ortega, H.; Helliswell, P.; Ryan, A.; Kane, D.; et al. PTPN22 is associated with susceptibility to psoriatic arthritis but not psoriasis: Evidence for a further PsA-specific risk locus. *Ann. Rheum. Dis.* 2015, 74, 1882–1885. [CrossRef]

72. Mehlehp-Williams, E.R.; Bevan, M.J. Memory CD8+ T cells exhibit increased antigen threshold requirements for recall proliferation. *J. Exp. Med.* 2014, 211, 345–356. [CrossRef]

73. Vang, T.; Landskron, J.; Viken, M.K.; Oberprieler, N.; Torgersen, K.M.; Mustelin, T.; Tasken, K.; Tautz, L.; Rickert, R.C.; Lie, B.A. The autoimmune-predisposing variant of lymphoid tyrosine phosphatase favors T helper 1 responses. *Hum. Immunol.* 2013, 74, 574–585. [CrossRef] [PubMed]

74. Benham, H.; Norris, P.; Goodall, J.; Wechalekar, M.D.; FitzGerald, O.; Szentpetery, A.; Smith, M.; Thomas, R.; Gaston, H. Th17 and Th22 cells in psoriatic arthritis and psoriasis. *Arthritis Res. Ther.* 2013, 15, R136. [CrossRef] [PubMed]

75. Gil-Quinones, S.R.; Sepulveda-Pachon, I.T.; Vanegas, G.S.; Gutierrez-Castaneda, L.D. Effect of PTPN22, FAS/FASL, IL2RA and CTLA4 genetic polymorphisms on the risk of developing alopecia areata: A systematic review of the literature and meta-analysis. *PLoS ONE* 2021, 16, e0258499. [CrossRef] [PubMed]

76. Canton, I.; Akhtar, S.; Gavalias, N.G.; Gawkrodger, D.J.; Blomhoff, A.; Watson, P.F.; Weetman, A.P.; Kemp, E.H. A single-nucleotide polymorphism in the gene encoding lymphoid protein tyrosine phosphatase (PTPN22) confers susceptibility to generalised vitiligo. *Genes Immun.* 2005, 6, 584–587. [CrossRef] [PubMed]

77. LaBerge, G.S.; Bennett, D.C.; Fain, P.R.; Spritz, R.A. PTPN22 is genetically associated with risk of generalized vitiligo, but CTLA4 is not. *J. Investig. Dermatol.* 2008, 128, 1757–1762. [CrossRef] [PubMed]

78. Laddha, N.C.; Dwivedi, M.; Shajil, E.; Prajapati, H.; Marfatia, Y.; Platt, H.; Cid, M.C.; Cid, A.; Cid, I.; Cid, F.; et al. Association of PTPN22 1858C/T polymorphism with susceptibility to autoimmune thyroid diseases: A meta-analysis. *Endocr. J.* 2012, 59, 439–445. [CrossRef]

79. Galeazzi, M.; Gasbarrini, G.; Ghirardello, A.; Grandemange, S.; Hoffman, H.M.; Manna, R.; Podsiadlo, M.; Punzi, L.; Sebastiani, G.D.; Tautz, L.; et al. Autoimmune-associated variations of lymphoid tyrosine phosphatase favor T helper 1 responses. *Hum. Immunol.* 2013, 74, 574–585. [CrossRef] [PubMed]

80. Umemura, T.; Joshita, S.; Yamazaki, T.; Komatsu, M.; Katsuyama, Y.; Yoshizawa, K.; Tanaka, E.; Ota, M. Genetic Association of PTPN22 Polymorphisms with Autoimmune Hepatitis and Primary Biliary Cholangitis in Japan. *J. Exp. Med.* 2014, 211, 345–356. [CrossRef] [PubMed]

81. Milkiewicz, P.; Pache, I.; Buwaneswaran, H.; Liu, X.; Coltescu, C.; Heathcote, E.J.; Siminovitch, K.A. The PTPN22 1858T variant is not associated with primary biliary cirrhosis. *Tissue Antigens* 2006, 67, 434–437. [CrossRef]

82. Diaz-Gallo, L.; Gourh, P.; Broen, J.; Simeon, C.; Fonollosa, V.; Ortego-Centeno, N.; Agarwal, S.; Vonk, M.; Coenen, M.; Riembekan, G.; et al. Analysis of the influence of PTPN22 expression in psoriasis vulgaris patients. *Ann. Rheum. Dis.* 2011, 70, 454–462. [CrossRef] [PubMed]

83. Chino, H.; Platt, H.; Lamb, I.A.; Betteridge, Z.; Sunawaruna, H.; Fertig, N.; Varsani, H.; Davidson, J.; Oddie, C.V.; McHugh, N.J.; et al. The protein tyrosine phosphatase N22 gene is associated with juvenile and adult idiopathic inflammatory myopathy independent of the HLA 8.1 haplotype in British Caucasian patients. *Arthritis Care Res.* 2008, 58, 3247–3254. [CrossRef]

84. Miller, F.W.; Cooper, R.G.; Vencovsky, J.; Rider, L.; Danko, K.; Wedderburn, L.; Lundberg, I.; Fuchman, L.M.; Reed, A.M.; Ytterberg, S.R.; et al. Genome-wide association study of dermatomyositis reveals genetic overlap with other autoimmune disorders. *Arthritis Care Res.* 2013, 65, 3239–3247. [CrossRef] [PubMed]

85. Kuhn, K.A.; Kulik, L.; Tomooka, B.; Brachskler, K.J.; Arend, W.P.; Robinson, W.H.; Holers, V.M. Antibodies against citrullinated proteins enhance tissue injury in experimental autoimmune arthritis. *J. Clin. Investig.* 2006, 116, 961–973. [CrossRef] [PubMed]

86. Criswell, L.A.; Peiffer, K.A.; Lum, R.F.; Gonzalez, B.; Novitzke, J.; Kern, M.; Moser, K.L.; Begovich, A.B.; Carlton, V.E.; Li, W.; et al. Analysis of families in the multiple autoimmune disease genetics consortium (MADGIC) collection: The PTPN22 620W allele associates with multiple autoimmune phenotypes. *Am. J. Hum. Genet.* 2005, 76, 561–571. [CrossRef]

87. Lin, J.-P.; Cash, J.M.; Doyle, S.Z.; Peden, S.; Kanik, K.; Amos, C.I.; Bale, S.J.; Wilder, R.L. Familial clustering of rheumatoid arthritis with other autoimmune diseases. *Hum. Genet.* 1998, 103, 475–482. [CrossRef]
