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Review Article

The *PTPN22* as Master Regulation in Autoimmune Diseases and Its Susceptibility to Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is a long-term autoimmune condition that causes joint inflammation, resulting in pain, tenderness, expansion, and even joint malformation. It mostly causes inflammation and thickening of the synovium, the membrane that lines the joints. Joint erosion, cartilage breakdown, and function loss are all possible outcomes of RA over time. Though it can affect any joint in the body, it usually affects the smaller joints in the hands and feet. A significant role can be played by genetic ability in the progress of rheumatoid arthritis. The review's subject, "*PTPN22*" (sometimes referred to as "LYP in humans or PEP in mice"), is the typical non receptor PTP belonging to the proline rich subgroup of Type I. PTPN22 is a "major negative regulator of T-cell receptor (TCR) signal transduction" which is mostly express in the immune cells. Interestingly, a mutation in this gene has been related to the onset of many autoimmune disorders. Several genetic variants have been identified that contribute to the risk of developing RA, including rs2476601. This review discussed the *PTPN22* as master regulation of immune system and the role of rs2476601 in RA.

Keywords: *PTPN22*, Rheumatoid Arthritis, Rs2476601.

INTRODUCTION

PTPN22 is a gene that encodes a protein called lymphoid tyrosine phosphatase (LYP), that elaborate regulating the activation of the cells that involved in immune system (Tizaoui *et al*., 2021). The rs2476601 variant of the PTPN22 gene has been correlated with an increased risk of evolving autoimmune diseases. It is thought that variant has the ability to affect the function of immune cells, leading to dysregulated immune responses and inflammation in RA (Bufalo *et al*., 2021).

Studies have indicated connections between certain genetic variations (PTPN22 rs2476601) and the likelihood of developing rheumatoid arthritis. It's crucial to remember that environmental variables and gene-environment interactions also play major roles in the development of RA, therefore genetic factors alone do not define the disease's course. Improved diagnosis, prognosis, and tailored treatments for this complicated inflammatory disease may result from our growing understanding of the genetic underpinnings of rheumatoid arthritis.

Autoimmune Disease

Autoimmune diseases are caused via losing of patience to self-antigens (Watad *et al*., 2019). Autoimmune disorders are characterized by the presence of a94utoimmunity and pathological conditions, as well as self-reactive immune components. The occurrence of autoimmune disorders and autoimmunity is rapidly cumulative in numerous portions of the world, potentially due to fluctuations in our exposure to environmental factors. Available data suggests that these increases are caused by significant changes in our diets, exposure to xenobiotic, air contamination, contagions, individual lifestyles, pressure, and climate change (Miller, 2023).

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The presence of self-reactive immune components is called autoimmunity. When combined with clinical symptoms, it is an autoimmune disorder (Suurmond and Diamond, 2015). Despite recommendations, there are currently no generally accepted criteria for defining autoimmunity or specific autoimmune diseases (De Leo *et al*., 2023, Rojas *et al*., 2022).

Rheumatoid Arthritis

A malfunctioning immune system characterizes rheumatoid arthritis (RA), a chronic inflammatory ailment that primarily affects numerous peripheral joints (Abed and Saud, 2023). It's an autoimmune disease affecting 1% of people and is twice as likely to affect women as men (van der Woude and van der Helm-van, 2018).

The origin of the term "rheumatoid arthritis" comes from the Greek phrase that describes inflammation and fluid build-up in the joints (Al-Rubaye *et al*., 2017, Senthelal *et al*., 2022). The "French physician Augustin Jacob Landré-Beauvais" was the first to recognize and classify this crippling illness in 1880. "Landré-Beauvais", who called the condition "asthenic gout" saw the disease's notable symptoms and hypothesized that it affected women more frequently(Landré-Beauvais, 2001).

The name "rheumatoid arthritis" was later invented by the British doctor "Dr. Alfred Baring Garrod" in 1859 (Garrod, 1876). Importantly, researchers now know that the worldwide incidence of RA is less than 1% (Aletaha and Smolen, 2018, Safiri *et al*., 2019). The disease is most common in people between the ages of 40 and 50, and its incidence increases with age. Women are affected three to five times more often than men (Radu and Bungau, 2021, Sparks *et al*., 2016).

Rheumatoid Arthritis Risk Factors

Evidence shows that many environmental and genetic factors are associated with a higher risk of developing rheumatoid arthritis (RA). Genetic factors known as "shared epitopes", female gender, family history of RA, and smoking appear to be strongly associated with it. Mucosal inflammation and microbiology are also receiving accelerated attention as possible causes of RA (Deane *et al*., 2017).

Genetic and Familial Risk Factors for RA

A growing body of evidence suggests that genetics may be an important factor in the development of RA. These include the fact that RA often runs in families; This results in an estimated familial risk contribution of 40% to 50% in seropositive RA, with a significant risk in first-degree relatives (FDR) (Frisell *et al*., 2016).

Family history is still important during genome-wide studies (GWAS) because it is the only population-level indicator of the likely etiology of serious diseases before the affected genes are identified. Familial risk factors can be evaluated before initiating a gene screening study to determine the possibility of identifying candidate genes (Davies *et al*., 2019, Hemminki *et al*., 2017).

In recent years, RA susceptibility has been associated with HLA-DRB1 alleles (Deighton *et al*., 1989, Raychaudhuri, 2010, Arango *et al*., 2017). Large-scale genetic analyses have identified more than 100 loci associated with the development of RA. Non-receptor protein tyrosine phosphatase type 22 (*PTPN22*) has the subsequent robust association with RA and activates lymphoid tyrosine phosphatase, or Lyp, a key regulator of T cell receptor signaling (Okada *et al*., 2014).

Environmental Risk Factors for RA

RA has been linked to many dietary, behavioral, and environmental factors. The environment with the strongest and most reliable relationship with RA is smoking; however, most of these relationships are found in individual studies or conflicting results emerge across multiple studies. Many studies have shown a link between smoking and RA (Mosalmanzadeh *et al*., 2020, Sundström *et al*., 2015). The above changes may affect specific genes following posttranscriptional changes, either directly or indirectly through epigenetic mechanisms affecting genes that are linked to susceptibility (Firestein and McInnes, 2017, Kotrulev *et al*., 2023).

Gene – Environment Interactions

These results are supported by gene-environment interaction studies. Smoking and other bronchial irritants such as silica increase the risk of rheumatoid arthritis in people with HLA-DR4 alleles susceptibility (de Hair *et al*., 2012, Arleevskaya *et al*., 2022).

Many viral infections (Parvovirus B19, Hepatitis B, Hepatitis C, Chikungunya and other alphaviruses, human immunodeficiency virus (HIV) and some other viruses), mycobacterial infections (Poncet's disease, leprosy, and tubercular septic arthritis) brucellosis, Lyme disease are represented the most common diseases associated with RA. Widespread

travel and tourism, high-risk sexual behavior, and the use of immunosuppressive drugs and chemotherapy have led to the spread of the disease in areas where it had not previously been reported. (Sharma and Sharma, 2022).

Genetic Factors

The scientific world has come a long way in comprehending the genesis of RA in the past several years. Recent research links the genesis of RA to genetics, food and microbiota, obesity, respiratory exposures, and their interactions. Moreover, aberrant glycosylation and "anti-posttranslationally modified protein antibodies (AMPAs)" might be further indicators of RA. Ultimately, functional genomics methods link RA to the decline of certain macrophage subsets and the growth of synovial fibroblasts (Kronzer and Davis, 2021).

LA-DRB1, HLA-DPB1, HLA-DOA, PADI4, PTPN22, CTLA4, IL2RA, STAT4, TRAF1-C5, CD40, CCR6, IRF4, BACH2, RAD51B, DPP4, RBFOX1, PADI2, CDK4RAP2, LBH, COG6, TYK2, PADI4 and GATA3 are the most significant genes currently associated with RA susceptibility (Khidhir *et al*., 2023, Fan *et al*., 2023).

Human Leukocyte Antigen

Human leukocyte antigen (HLA)-DRB1 is the most important genetic risk factor for RA. Many studies have reported the association of HLA polymorphisms with susceptibility to RA (Furukawa *et al*., 2015, Wysocki *et al*., 2020, Klimenta *et al*., 2019)

Non HLA Genes

RA develops as a result of "Single Nucleotide Polymorphisms" (SNP) in non-HLA genes. It has been shown that SNPS in the genes TRAF1 (rs3761847), CD40 (rs4810485), PTPN22 (rs2476601), PADI4 (rs2240340), and STAT4 (rs7574865) are risk factors for the onset of autoimmune disorders, including RA (Dedmon, 2020, Eyre *et al*., 2017, Karami *et al*., 2019, Budlewski *et al*., 2023).

The frequency of RA varies among populations, most likely as a result of differences in genetic backgrounds. Genetic variables are important and represent probably 70% of the cause of RA susceptibility and symptom manifestation (Yip and Navarro-Millán, 2021).

HLA-DRB1 alleles, which have attributed to at least 30% of the overall genetic foundation of RA and are characterized in the majority of genetic research as the leading cause of RA, have been linked primarily to an increased risk of developing RA (Dedmon, 2020, Wysocki *et al*., 2020). This study reviewed PTPN22 as the most important non-HLA gene which linked to many autoimmune diseases included RA.

Protein Tyrosine Phosphatases Non-Receptor 22

As a master regulator of the immune system, protein tyrosine phosphatases non-receptor 22 (PTPN22) controls pertinent immunological responses and functions as a "negative regulator of signaling pathways" via the "T cell receptor" (TCR) and "B cell receptor" (BCR) (Armitage *et al.*, 2021). Protein tyrosine phosphatases (PTPs) have diverse roles as negative regulators of stimulatory signaling cascades and are widely recognized as key to maintaining immune cellular homeostasis (Siminovitch 2004).

Protein Tyrosine Phosphatases Non-Receptor Proteins

"Tyrosyl phosphorylation" is an essential component of several physiological signaling pathways. It is a perpetual and changeable process (Chen *et al*., 2017). The PTPs are a class of enzymes that catalyze "the dephosphorylation of tyrosine residues" (Perla *et al*., 2023). Encoded by 103 genes, PTPs are sorted into four major superfamily classes, and every single PTP was denominated an official gene name by The Human Genome Organization in Nomenclature Committee.

According to the latter system, 17 non-receptor PTPs which belong to the biggest family class I, are designated PTPN, followed by a number (Chen *et al.*, 2020). A growing body of research indicates that the interaction between members of the "PTPN gene family" affects a wide range of physiological functions, including immune response, migration, metabolism, and cell division (Yu and Zhang, 2018).

For instance, "PTPN22" is crucial for controlling autophagy and the "NLR family's pyrin domain-containing three inflammasome expression" (Spalinger *et al*., 2017). It is encouraging that PTPN genes may be used as predictive, diagnostic, and potentially curative markers (Zhang, 2017).

Protein Tyrosine Phosphatases Non-Receptor 22 Structure

The components of "PTPN22" are as follows: residues 1–300 make up the N-terminal "PTP catalytic domain"; residues 301–600 make up the middle inter domain region; and residues 601–807 make up the C-terminus (Jassim *et al*., 2022).

The "catalytic domain of PTPN22's crystal structure" has been identified (Nian *et al*., 2022) providing information on the regulation mechanisms and function of the enzyme. "The PTPN22 catalytic domain" has characteristics with other PTPs, including a core eight-stranded "β-sheet" that is surrounded by two "α-helices" on one side and "six α-helices" on the other (Du *et al*., 2014). Four poly-proline motifs (P1–P4) are present in the C-terminal region of "PTPN22. P1 has been demonstrated to bind Csk, a crucial enzyme in T-cell signalling (Burn, 2014, Jassim *et al*., 2022).

Protein Tyrosine Phosphatases Non-Receptor 22 Gene

Among non-HLA genes, the main RA susceptibility factor is the PTPN22 gene on chromosome (Huraib *et al*., 2020). A missense cytosine to thymine substitution at nucleotide position 1858 (rs2476601) of this gene leads to substitution of tryptophan (W) for arginine (R) at residue 620 of the protein product (Ghorban *et al*., 2019, AL-Tarboolii *et al*., 2016). The resulting gain of function, with enhanced regulation of T-cell receptor (TCR) signaling during thymic selection, permits autoantigen specific T cells to escape clonal deletion, thereby predisposing to autoimmunity (Handel *et al*., 2018).

This gene's polymorphism is found in an "SNP", where a change from cytosine to Thymine (rs2476601) occurs at nucleotide (1858), resulting in a change at codon (620) from tryptophan (W) to arginine (R)(Alswat *et al*., 2018). Not only does RA seem to be affected by the SNP in the *PTPN22* gene, but also a variety of other autoimmune diseases. The correlation between "this gene in RA" and several other autoimmune illnesses is contributing to the swift advancement in the analysis of this gene's pathways and a deeper comprehension of autoimmune disorders (Okada *et al*., 2018).

The onset, "propagation, and termination of cellular signaling cascades" are regulated by the state of protein tyrosine phosphorylation. The amount of tyrosine phosphorylation in cells is regulated by PTPs and the inverse activity of "protein tyrosine kinases" (PTKs) (Gonçalves, 2021, Al-Aghbar *et al*., 2022).

"Type I diabetes, rheumatoid arthritis, and lupus" are among the autoimmune disorders linked to the single nucleotide polymorphism C1858T in the LYP, a crucial regulator of TCR signalling (Castro-Sanchez *et al*., 2020). This polymorphism replaces an "R with a W" in the LYP P1 Pro-rich motif, which binds to the "CSK SH3 domain", another TCR signaling negative regulator. It was suggested that LYP and CSK bind constitutively to block LCK and consequently TCR signaling based on the investigation of the mouse homologue, Pep (Bai *et al*., 2023, Song, 2022).

Protein Tyrosine Phosphatases Non-Receptor 22 "R620W Variant"

A genetic variant in the gene PTPN22 (R620W, rs2476601) is strongly associated with increased risk for multiple autoimmune diseases and linked to altered TCR regulation and T cell activation. PTPN22 rs2476601 contributes to autoimmunity risk by permitting increased TCR signaling and activation in mildly self-reactive T cells, thereby potentially expanding the self-reactive T cell pool and skewing this population toward an inflammatory phenotype (Anderson *et al*., 2023).

Based on data obtained in T lymphocytes, LYPW has been proposed to be a gain-of-function variant with increased phosphatase activity that reduces early T cell signaling parameters such as Ca^{2+} mobilization and LCK phosphorylation (de la Puerta *et al*., 2013).

The SNP causes amino acid 620 to change from arginine in the "normal" allele (R620) to tryptophan in the allele linked to the illness (W620) (Burn, 2014). On the C-terminal region of LYP, residue 620 is situated in "the first of four proline-rich motifs" (referred to as P1–P4). Remarkably, "the interaction between LYP" and the CSK Src homology 3 (SH3) domain depends on R620 of the predominant allele (Stanford *et al*., 2012). preventing W620, a minor allele, from joining CSK (Vang *et al*., 2012).

W620 is a "gain-of-function" mutant with around 50% more catalytic activity and a greater inhibitory effect on TCR signaling, which is according to research conducted using primary T cells (Vang *et al*., 2018).

Protein Tyrosine Phosphatases Non-Receptor 22 and Autoimmunity

Numerous studies have connected *PTPN22* R620W to "idiopathic inflammatory myopathies, Addison's illness, juvenile rheumatoid arthritis, generalized vitiligo, systemic lupus erythematosus, immune thrombocytopenia, Grave's disease, and juvenile rheumatoid arthritis" (Song *et al*., 2022).

According to HAMADI and SALEH and Bahrami *et al*., this SNP in PTPN22 is most frequent among Northern Europeans and most widespread in Scandinavia. Despite the very complicated results, instinct would appear to suggest that the typical PTPN22 activity would be lost in the lack of this PTPN22-Csk association (HAMADI and SALEH, 2020, Bahrami *et al*., 2020). Although some research (Knipper *et al*., 2020, Perry *et al*., 2021) showed that "*PTPN22* R620W"

functioned as a "gain-of-function mutant", other studies (Armitage *et al*., 2021) have revealed that this variation represents a loss in function.

Protein Tyrosine Phosphatases Non-Receptor 22 and RA

Lymphoid protein tyrosine phosphatase, the protein product of PTPN22, is an enzyme that is only present in immune cells and is crucial in decreasing the reactivity of T and B-cell receptors. The most potent genetic predisposition factor for RA that is not HLA is PTPN22. Begovich and colleagues presented the first study on the strong correlation between the PTPN22 1858T allele and RA in 2004 (Hegab *et al*., 2016, Stanford and Bottini, 2014, Begovich *et al*., 2004).

It is demonstrated that the homozygous PTPN22 1858C variation doubles the risk of RA compared to the 1858T variant, indicating that this variant is a co-dominant allele (Tizaoui *et al*., 2021, Tizaoui *et al*., 2022). Data in RA indicate that the PTPN22 risk allele has a dose impact (Tang *et al*., 2016). The correlation between the PTPN22 variation and the risk of RA as well as its clinical characteristics was the subject of much research.

Anti-citrullinated protein antibodies (ACPA) are linked to seropositive conditions and the PTPN22 R620W allele (Salama *et al*., 2014, Sardana *et al*., 2023) early disease development and erosive disorders. PTPN22 C1858T was more prevalent in RF-positive patients compared to RF-negative patients in a stratified meta-analysis. It was also more prevalent in patients who had anti-CCP antibodies than in those who did not (Tizaoui *et al*., 2022)

While *PTPN22* 1858T is linked to both seropositive and seronegative autoantibody RA, the majority of research has found that PTPN22 is more strongly connected with RF-positive or ACPA-positive RA (Elshazli and Settin, 2015, Tizaoui *et al*., 2022). PTPN22 1858T is only significant across the genome in patients with ACPA-positive RA, according to a GWAS (Hegab *et al*., 2016). Though this mutation is significant in people descended from Europe, it is extremely uncommon in Asian communities, and as a result, it is unlikely to significantly increase the risk of RA in those populations. (Nabi *et al*., 2016, Laufer *et al*., 2019).

The insufficient binding of the W620 variant with the interacting receptor (SRC kinase) and the imbalanced interactions give strong hints regarding the inadequate control of T cell activation and/or the inadequate removal of autoimmune clones, which are characteristic of several autoimmune diseases.

CONCLUSION

The functional mutation in *PTPN22* (rs2476601) affects the overall shape, charge, and receptor interactions, making one more susceptible to RA and indicating that the gene is a master regulator gene in autoimmune diseases.

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