

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

**4,800**

Open access books available

**122,000**

International authors and editors

**135M**

Downloads

Our authors are among the

**154**

Countries delivered to

**TOP 1%**

most cited scientists

**12.2%**

Contributors from top 500 universities



**WEB OF SCIENCE™**

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.

For more information visit [www.intechopen.com](http://www.intechopen.com)



## Chapter

# The Protein Tyrosine Phosphatase Non-Receptor Type 22 (PTPN22) Gene Polymorphism and Susceptibility to Autoimmune Diseases

*Ghaleb Bin Huraib, Fahad Al Harthi, Misbahul Arfin  
and Abdulrahman Al-Asmari*

## Abstract

The protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene located on chromosomes 1p 13.3–13 encodes a lymphoid-specific tyrosine phosphatase (Lyp) which is involved in autoimmunity by preventing spontaneous T-cell activation and T-cell development and inactivating T-cell receptor-associated kinases and their substrates. Several single nucleotide polymorphisms (SNPs) have been identified in PTPN22, but only one PTPN22 C1858T has been intensively studied in relation to autoimmune diseases. The PTPN22 C1858T functional polymorphism is a strong non-HLA risk factor for several autoimmune diseases and considered to play an important role in etiology of diseases due to significant production of autoantibodies. However, available literature on PTPN22 C1858T polymorphism and autoimmune diseases shows inconsistencies and ethnic variations. Therefore, further genetic studies on patients suffering from various autoimmune diseases from different ethnicities and PTPN22 gene polymorphisms are expected to help better understand the pathogenesis and will contribute to the development of more targeted therapies and biomarkers.

**Keywords:** PTPN22, genetic, polymorphism, autoimmune diseases

## 1. Introduction

Genetic polymorphisms are variations in DNA found in 1% or more of the population which may alter the structure and function of protein through a single nucleotide base substitution in a gene's coding region. It may alter the gene expression either by affecting mRNA stability when occurring in a gene's 3'-untranslated region or by changing transcription factor binding when occurring in the 5'-promoter region. A polymorphism does not have any effect on the protein product when it occurs within DNA regions that are not involved in gene transcription or translation but serves as the basis for genetic linkage analysis [1].

The information on genetic polymorphisms facilitates to explain pathologic mechanisms and help in identifying individuals at risk. It also helps us to find novel targets for drug treatment. The protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) gene is an important predisposing gene for human autoimmune diseases. The alterations in *PTPN22* render a person susceptible and lead to the development of several autoimmune diseases. Many single nucleotide polymorphisms (SNPs) have been identified in *PTPN22*, but only one non-synonymous SNP has been intensively studied in relation to autoimmune diseases. This SNP C1858T (rs2476601) in exon 14 of the *PTPN22* gene has been associated with a number of autoimmune diseases and considered as a risk factor due to significant production of autoantibodies [2, 3].

The *PTPN22* C1858T variant has been studied in autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), type 1 diabetes mellitus, juvenile idiopathic arthritis (JIA), inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, vitiligo, systemic sclerosis (SSc), Graves' disease (GD), myasthenia gravis (MG), Addison's disease, psoriasis, psoriatic arthritis (PsA), Behcet's disease (BD), endometriosis, autoimmune thyroid disease (AITD), giant cell arteritis (GCA), alopecia areata (AA), and Sjögren's syndrome. The association of *PTPN22* C1858T genetic polymorphism is very significant and noteworthy in some autoimmune diseases, while in other it is less significant [3]. However, available literature on *PTPN22* C1858T polymorphism and autoimmune diseases shows inconsistencies and ethnic variations exist.

## **2. *PTPN22* gene**

*PTPN22* gene is located on chromosomes 1p13.3–p13.1 and encodes a lymphoid-specific tyrosine phosphatase (Lyp). Lyp is an intracellular protein tyrosine phosphatase, bound to the SH3 domain of the C-terminal Src kinase (Csk) through a proline-rich motif. It is believed to suppress kinases mediating T-cell activation [4]. Lyp plays an important role in B-cell signaling, besides functioning as a negative regulator of T cells. It works in signaling cascade at various levels and targets several signaling intermediates involved in T-cell receptor signaling [5, 6]. After HLA, *PTPN22* gene is the second-most important predisposing gene for human autoimmune diseases.

The minor allele 1858T in the *PTPN22* locus has a strong and consistent genetic association with autoimmune diseases. In *PTPN22* C1858T (rs2476601), cytosine changes to thymidine at nucleotide 1858, resulting in an amino acid change from arginine to tryptophan at codon 620 (R620W), located in the polyproline-binding motif P1 [7, 8]. Yet there is no consensus whether C1858T polymorphism is a gain- or loss-of-function variant. The C1858T has been reported as a susceptibility locus associated with several autoimmune diseases. It was first reported in type 1 diabetes mellitus (T1DM) [7].

*PTPN22* C1858T polymorphism has been suggested to increase Lyp protein activity which in turn inhibits T-cell signaling and results in a failure to delete autoreactive T cells during thymic selection. The association of this polymorphism is restricted to disorders that have a strong autoantibody component as it results in immune responses against autoantigens [8].

With the advent of new genotyping and molecular biology techniques, a huge amount of data are available for analysis. A large number of genes associated with diseases have been identified by the GWAS, candidate gene, and epidemiological

studies. Therefore, the focus should be on the way genetic associations are reported. Even in the overlapping meta-analyses on the same topic, the limitations such as inclusion and exclusion criteria and number of included studies result in consistency of association results of genes, although the meta-analysis has been considered as a powerful approach to identify true-positive association of genes with disease.

The PTPN22 C1858T variant has been studied in several autoimmune or autoimmunity-related diseases in different ethnic populations worldwide.

### 3. Autoimmune diseases

Autoimmune diseases are pathological conditions identified by abnormal autoimmune responses and characterized by autoantibodies and T-cell responses to self-molecules by immune system reactivity. Human autoimmune diseases occur frequently (affecting in aggregate more than 5% of the population worldwide) and impose a significant burden of morbidity and mortality on the human population [9].

The etiology of autoimmune diseases involves both genetic and environmental factors. Familial clustering is known in autoimmune diseases with higher rate of concordance in monozygotic twins as compared to dizygotic twins [10–12]. Most autoimmune diseases are multigenic, with multiple susceptibility genes working in concert to produce the disease; however, a few autoimmune diseases are caused by mutations in a single gene. Even in such cases other genes modify the severity of disease. On the other hand, some individuals with these mutations do not manifest the disease.

The genetic polymorphisms also occur in normal population and are compatible with a normal immune function. However, when these polymorphisms occur with

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Mexican	187/223	CT	Susceptible	[20]
Indian (Tamils)	264/264	CT	Susceptible	[25]
Indian (Gujarati)	126/140	C1858T	No association	[32]
English	165/304	C1858T	Susceptible	[29]
Romanian	–	T-allele	Susceptible	[30]
European*	2094/3613	T-allele	Susceptible	[28]
Asian		T-allele	No association	
Turkish	107/112	C1858T	No association	[27]
European*	1800/3269	T-allele	Susceptible	[26]
Asian		T-allele	No association	
Jordanian	55/85	C1858T	No association	[33]
Egyptian	100/120	C1858T	No association	[34]
Caucasian#	1514/2813	C1858T	Susceptible	[31]
European				

\*Meta-analysis.

#Genome-wide association study.

**Table 1.**  
 Association of PTPN22 C1858T polymorphism with vitiligo susceptibility.

other susceptibility genes, they develop autoimmunity [13, 14]. The extent of risk is not same for all such genes, and some of the genes confer a much higher level of risk than others [9].

The results of various association studies of PTPN22 C1858T variant with some of the autoimmune diseases are summarized in **Tables 1–18**.

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Mexican	64/225	T-allele	Susceptible	[41]
Belgian-German	435/628	C1858T	Susceptible	[39]
English	196/507	C1858T	Susceptible	[38]
Mixed*	1129/1702	T and CT	Susceptible	[43]
Mixed*	365/173	C1858T	Susceptible	[42]
Egyptian	103/100	CT, TT	Susceptible	[40]
Iranian	69/69	T-allele	No association	[44]

\*Meta-analysis.

**Table 2.**  
*Association of PYPN22 C1858T polymorphism with alopecia susceptibility.*

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Saudi	106/200	T-allele, CT	Susceptible	[53]
German	375 + 418/376 + 561	C1858T	No association	[57]
English	647/566	C1858T	No association	[58]
Caucasian	1146	C1858T	No association	[59]
Mixed*	3334/5753	T-allele	No association	[56]
Mixed*	1448/1385	C1858T	No association	[55]
Cretan (Greek)	173/348	T-allele	No association	[60]

\*Meta-analysis.

**Table 3.**  
*Association of PTPN22 C1858T polymorphism with psoriasis susceptibility.*

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Toronto (admixed)	207/199	T-allele	Susceptible	[61]
Swedish	291/725	T-allele	Susceptible	[62]
Mixed <sup>#</sup>	1177/2155	C1858T	Susceptible	[63]
UK	455/595	C1858T	No association	[65]
Newfoundland	238/149	T-allele	No association	[61]
German	375/376	T-allele	No association	[66]

<sup>#</sup>Genome-wide association study.

**Table 4.**  
*Association of PTPN22 C1858T polymorphism with psoriatic arthritis susceptibility.*

Population	Case/ controls	Genotype/allele/ polymorphism	Association	References
American (European ancestry)	647/751	C1858T	Susceptible	[67]
Australian	324/568	C1858T	Susceptible	[70]
Australian	413/690 1608/9284	C1858T	Susceptible in females	[71]
Greek	128/221	C1858T	Susceptible	[73]
Egyptian	60/40	T-allele	Susceptible	[75]
UK	661/595	C1858T	Susceptible	[65]
Czechs	130/400	T-allele	Susceptible	[72]
European	809/3535	C1858T	Susceptible	[69]
Norwegian	320/555	C1858T	Susceptible	[74]
Mixed*	4552/10,161	C1858T	Susceptible	[77]
Mixed*	4238/6012	C1858T	Susceptible	[76]
Finish	230	T-allele	No association	[78]
Hungarian	150/200	T-allele	No association	[79]

\*Meta-analysis.

**Table 5.**  
*Association of PTPN22 C1858T polymorphism with juvenile idiopathic arthritis susceptibility.*

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Spanish	826/1036	T-allele	Susceptible	[96]
Italian	396/477	T-allele	Susceptible	[92]
Turkish	323/426	C1858T	Susceptible	[97]
Colombian	298/308	T-allele	Susceptible	[86]
Colombian	413/434	T-allele	Susceptible	[87]
Egyptian	150/150	T-allele	Susceptible	[89]
Egyptian	394/398	C1858T	Susceptible	[90]
Egyptian	112/122	T-allele	Susceptible	[88]
Egyptian	100/114	C1858T	No association	[100]
Algerian	110/197	C1858T	Susceptible	[85]
Mexican	315/315	C1858T	Susceptible	[95]
Mexican	364/387	C1858T	Susceptible	[94]
Mexican	309/347	T-allele	Susceptible	[93]
UK	886/595	C1858T	Susceptible	[65]
Iranian	120/120	C1858T	Susceptible	[91]
Iranian	120/120	T-allele	Susceptible	[84]
Iranian	405/467	C1858T	No association	[101]
Chinese Han	358/564	C1858T	No association	[99]
Chinese-Yunnan	192/288	C1858T	No association	[98]

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Caucasian*	27,205/27,677	C1858T	Susceptible	[103]
Asian*		C1858T	No association	
European*	29 studies	C1858T	Susceptible	[104]
Asian and African		C1858T	No association	
Mixed*	11,727/12,640	T-allele	Susceptible	[105]
Mixed*	3209/3692	C1858T	Susceptible	[106]
Mixed*	20,344/21,828	C1858T	Susceptible	[76]
Mixed*	13 studies	T-allele	Susceptible	[107]
Mixed*	17,961/18,611	C1858T	Susceptible	[102]
Mixed*	34 studies	C1858T	Susceptible	[108]
Mixed*	36 studies	T-allele	Susceptible	[2]

\*Meta-analysis.

**Table 6.**  
Association of PTPN22 C1858T polymorphism with RA susceptibility.

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Spanish	338/1036	T-allele	Susceptible	[96]
Swedish	571/1042	C1858T	Susceptible	[120]
American	525/1961	C1858T	Susceptible	[116]
Crete	328/427	C1858T	Susceptible	[119]
Colombian	94/434	T-allele	Susceptible	[87]
Colombian	143/308	T-allele	Susceptible	[86]
Polish	135/201	CT, T-allele	Susceptible	[122]
Polish	150/300	C1858T	Susceptible	[121]
Mixed*	6 studies	T-allele	susceptible	[107]
Mixed*	772/1092	C1858T	Susceptible	[126]
Mixed*	9120/11724	C1858T	Susceptible	[128]
Mixed*	11 studies	CT, TT	Susceptible	[125]
Mixed*	14 studies	T-allele	Susceptible	[2]
Mixed*	3868/7458	T-allele, TT	Susceptible	[127]
European-Americans	3936/3491	C1858T	Susceptible	[118]
Hispanics	1492/807	C1858T	No association	[118]
African-Americans	1527/1811	C1858T	No association	[118]
Asians	1265/1260	C1858T	No association	[118]
Egyptian	170/241	C1858T	Susceptible	[124]
Egyptian	40/20	CT	Susceptible	[123]
Egyptian	60/60	C1858T	No association	[133]
European-American	1680/1467	T-allele	Susceptible	[117]
Mexican	500/355	T-allele	Susceptible	[134]

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Mexican mestizos	150/150	C1858T	No association	[130]
Turkish	158/155	C1858T	No association	[131]
Turkish	137/160	C1858T	No association	[132]
Chinese Han	713/672	C1858T	No association	[99]
Chinese	40/20	C1858T	No association	[129]

\*Meta-analysis.

**Table 7.**  
 Association of PTPN22 C1858T polymorphism with SLE susceptibility.

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Egyptian	60/60	C1858T	Susceptible	[133]
German	140/100	T-allele	Susceptible	[138]
Mixed*	3764/3328	C1858T	Susceptible	[139]
Japanese	456/221	T-allele	No association	[143]
Japanese	334/179	C1858T	No association	[144]
Korean	212/225	T-allele	No association	[145]
Polish	149/200	C1858T	No association	[147]
Jordanian Arab	204/2016	C1858T	No association	[146]

\*Meta-analysis.

**Table 8.**  
 Association of PTPN22 C1858T polymorphism with AITD susceptibility.

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Latin-American	83/336	C1858T	Susceptible	[148]
Polish	166/154	C1858T	Susceptible	[149]
Polish	290/310	T-allele	Susceptible	[150]
Polish	735/1216	C1858T	No association	[154]
English	768/768	C1858T	Susceptible	[140]
English	549/429	C1858T	Susceptible	[151]
English	901/833	C1858T	Susceptible	[152]
Mixed*	3 studies	T-allele	Susceptible	[2]
Mixed*	3764/3328	C1858T	Susceptible	[139]
Indian Kashmiri	135/150	C1858T	No association	[155]
Chinese Han <sup>#</sup>	5904/5866	C1858T	No association	[153]

\*Meta-analysis.

<sup>#</sup>Genome-wide association study.

**Table 9.**  
 Association of PTPN22 C1858T polymorphism with Graves' disease susceptibility.



Population	Case/controls	Genotype/allele/ polymorphism	Association	Reference
Tunisian	164/100	C1858T	Susceptible	[163]
Moroccan	195/311	C1858T	No association	[167]
Spanish	1903CD, 1677UC/ 3111	C1858T	Protective to CD	[165]
New Zealanders	315/4081	C1858T	No association with CD	[168]
Czech	345/501	C1858T	No association	[169]
Canadian	455/190	C1858T	No association with CD	[170]
Canadian	249/207	T-allele	No association with CD	[171]
British	514/374	C1858T	No association	[172]
Spanish	1113/812	C1858T	No association	[173]
German	146	C1858T	No association with CD	[174]
Mixed*	8182/13356	C1858T	Susceptible to CD	[164]
Meta-analysis		C1858T	Protective to CD	[2]
Italian	649/256	C1858T	No association	[175]

\*Meta-analysis.

**Table 10.**  
Association of PTPN22 C1858T polymorphism with IBD (CD + UC) susceptibility.

Population	Case/controls	Genotype/allele/ polymorphism	Association	References
Saudi	372/372	T-allele	Susceptible	[184]
German	220/239	C1858T	Susceptible	[185]
Egyptian	150/165	T-allele	Susceptible	[186]
Egyptian	120/120	T-allele	Susceptible	[187]
Kuwaiti Arabs	253/2014	T-allele	Susceptible	[188]
Chinese	202/240	C1858T	Susceptible	[189]
Chinese	364/719	C1858T	No association	[178]
Brazilian	612/792	C1858T	Susceptible	[190]
Brazilian	205/308	C1858T	Susceptible	[191]
Polish	215/236	C1858T	Susceptible	[192]
Polish	147/327	C1858T	Susceptible	[193]
Russian	27/62 families	C1858T	Susceptible	[194]
Croatian	102/193	T-allele	Susceptible	[195]
Caucasian	140/100	T-allele	Susceptible	[138]
Caucasian	8677	C1858T	Susceptible	[196]
Caucasian	113	C1858T	Susceptible	[197]
Czechs	372/400	T-allele	Susceptible	[72]
Iranian (Azeri)	160/271	T-allele	Susceptible	[72]

Population	Case/controls	Genotype/allele/ polymorphism	Association	References
Iranian	99/100	C1858T	Susceptible	[84]
Iranian	144/197	C1858T	No association	[181]
Estonian	170/230	T-allele	Susceptible	[198]
Italian	271/89	C1858T	Susceptible	[199]
Spanish	316/554	T-allele	Susceptible	[200]
Colorado	753/662	CT, TT	Susceptible	[201]
Colombian	110/308	T-allele	Susceptible	[86]
Colombian	197 families	C1858T	Susceptible	[202]
International children	257	C1858T	Associated with proinsulin levels	[203]
Mixed*	6 studies	C1858T	Susceptible	[107]
Mixed*	19,495/25,341	C1858T	Susceptible	[204]
Mixed*	22,485/35,292	C1858T	Susceptible in Caucasian	[205]
Mixed*	11 studies	T-allele	Susceptible in European	[206]
Mixed*	16,240/17,997	C1858T	Susceptible	[207]
Mixed*	8869/20,829	C1858T	Susceptible	[208]
Mixed*	10 studies	C1858T	Susceptible	[209]
Indian	145/210	T-allele	Susceptible	[210]
Indian	129/109	C1858T	No association	[180]
Greek	130/135	C1858T	No association	[179]

\*Meta-analysis.

**Table 11.**  
 Association of PTPN22 C1858T polymorphism with T1DM susceptibility.

Population	Case/ controls	Genotype/allele/ polymorphism	Association	References
French	659/504	T-allele	Susceptible	[216]
French	121/103	C1858T	No association	[218]
Mixed White, Black, Hispanic	1120/716	C1858T	Susceptible	[217]
Caucasian	3422/3638	C1858T	Susceptible	[214]
Mixed*	4367/4771	C1858T	Susceptible	[107]
Columbian	101/434	T-allele	No association	[87]
Spanish	54/55	C1858T	No association	[219]

\*Meta-analysis.

**Table 12.**  
 Association of PTPN22 C1858T polymorphism with systemic sclerosis susceptibility.

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Swedish	409/1557	C1858T	Susceptible	[228]
German	125/301	C1858T	Susceptible	[229]
European	649/	C1858T	Susceptible	[230]
Mixed*	2802/3730	C1858T	Susceptible	[221]
Hungarian, German	282/379	T-allele	Susceptible	[231]
French	470/296	C1858T	Susceptible	[232]
European#	532/2128	C1858T	Susceptible	[235]
Chinese	79/50	C1858T	No association	[2]
Turkish	416/293	C1858T	No association	[234]
Italian	356/439	C1858T	No association	[233]

\*Meta-analysis.  
#Genome-wide association study.

**Table 13.**  
*Association of PTPN22 C1858T polymorphism with myasthenia gravis susceptibility.*

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Spanish	404/1517	C1858T	No association	[243]
Turkish	134/177	C1858T	No association	[242]
UK and Middle East	270/203	C1858T	Protective	[241]
Mixed*	1922/11,505	C1858T	No association	[76]

\*Meta-analysis.

**Table 14.**  
*Association of PTPN22 (C1858T) polymorphism with Behcet's disease susceptibility.*

Population	Case/controls	Genotype/allele/polymorphism	Association	Reference
Italian	132/232	C1858T	Susceptible	[252]
Italian	132/359	T-allele	Susceptible	[253]
Italian	130/250	C1858T	Susceptible	[254]
Brazilian	140/180	C1858T	Susceptible	[255]
Mixed*	971/1181	T-allele	Susceptible	[246]
Polish	171/310	C1858T	No association	[248]

\*Meta-analysis.

**Table 15.**  
*Association of PTPN22 C1858T polymorphism with endometriosis susceptibility.*

Population	Case/controls	Genotype/allele/polymorphism	Association	References
German	199/399	T-allele	Susceptible	[259]
British	641/9115	C1858T	Susceptible	[260]
Italian	344/945	C1858T	Susceptible	[261]

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Mixed*	1399/9934	C1858T	Susceptible in White	[262]
Mixed*	1922/11,505	C1858T	Susceptible	[76]

\*Meta-analysis.

**Table 16.**

Association of PTPN22 C1858T polymorphism with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis susceptibility.

Population	Case/Controls	Genotype/allele/polymorphism	Association	References
Spanish	95/229	C1858T	No association	[263]
Spanish, German, Norwegian	911/8136	C1858T	Susceptible	[265]
European	1651/15,306	C1858T	Susceptible	[266]
Australian	209/455	T-allele	Susceptible	[267]

**Table 17.**

Association of PTPN22 C1858T polymorphism with giant cell arteritis susceptibility.

Population	Case/controls	Genotype/allele/polymorphism	Association	References
Norwegian	332/990	T-allele	Susceptible	[269]
UK and Polish	338/665	T-allele	Susceptible	[270]
English	104/429	C1858T	Susceptible	[151]
Mixed*	6 studies	T-allele	Susceptible	[2]
German	121/239	C1858T	No association	[185]
Mixed*	2 studies	C1858T	No association	[107]

\*Meta-analysis.

**Table 18.**

Association of PTPN22 C1858T polymorphism with Addison's disease susceptibility.

#### 4. Vitiligo

Vitiligo is an acquired, autoimmune skin disorder characterized by melanocyte loss resulting into progressive depigmentation of the skin and hair [15, 16]. The prevalence of vitiligo varies considerably with ethnicity and it affects 0.1–2% of the population worldwide [15, 17]. Vitiligo is associated with an elevated risk of several other autoimmune diseases [18–20].

Vitiligo commonly shows familial aggregation and multifactorial mode of inheritance. It is a polygenic disease, and several genes related to autoimmunity have been reported to be associated with the pathogenesis of vitiligo [20–25].

Various published reports on PTPN22 C1858T polymorphism support the association of the T-allele and vitiligo susceptibility in different ethnic populations (Table 1). However, available literature on the PTPN22 C1858T polymorphism and

vitiligo susceptibility is inconsistent [25–28]. It has been reported to be a risk factor for vitiligo in English, Romanian, North American, Mexican, and South Indian Tamil populations [20, 25, 29, 30]. PTPN22 C1858T polymorphism is strongly associated with vitiligo susceptibility in Saudis also [in press]. A genome-wide association study indicates that PTPN22 C1858T is associated with vitiligo in European-derived white patients [Jin et al. 2010]. A meta-analysis utilizing data from different ethnicities shows an association of PTPN22 C1858T with vitiligo in European but not in Asian population [28].

In contrast, no significant association of PTPN22 C1858T polymorphism with susceptibility to generalized vitiligo was found in Indian Gujarat population, Jordanian, Egyptian female, and Turkish population [27, 32–34]. Available literature shows that the variant of PTPN22 C1858T is responsible for increased risk of vitiligo in Caucasian patients; however, among non-Caucasians/Asians, inconsistency exists, and even the two populations of same country differ in association of PTPN22 C1858T with vitiligo indicating the role of ethnicity. The heterozygous CT genotype of the PTPN22 C1858T has a strong association with non-segmental vitiligo in South Indian Tamils, while there is no association of this polymorphism in Indian Gujarat population [25, 32]. This difference in the results of this polymorphism in Asians or non-Caucasians can be attributed to ethnic differences.

## **5. Alopecia areata (AA)**

AA is a dermatological condition in which hair is lost from certain or all areas of the body, typically from certain areas of the scalp, more frequent in young ones [35]. The characteristic feature of AA is circular or oval bald spots which may progress and spread to the entire scalp (alopecia totalis) or entire body (alopecia universalis). Sometimes hair loss is localized to the sides and lower back of the scalp which is known as alopecia ophiasis [36]. The prevalence of AA in the general population varies between 0.1 and 6.9% depending on the ethnic group [37].

Alopecia areata is an autoimmune disease mediated by T cells to the hair follicles. There are enough evidences indicating that AA is a complex multigenetic trait with components of inherited predisposition. Molecular biology studies have led to the identification of a number of candidate genes in humans that confer susceptibility to AA. Recently, PTPN22 gene has been reported to be an additional immunoregulatory gene associated with AA. PTPN22 C1858T polymorphism has been associated with susceptibility of AA in Belgian, English, Egyptian, German, and Mexican populations (**Table 2**) [38–43]. Two meta-analyses have also indicated an association with AA susceptibility [42, 43]. However, no association of PTPN22 C1858T has been found in Iranian patients [44].

## **6. Psoriasis**

Psoriasis is a chronic, complex autoimmune disease with characteristic reddish patches covered by silvery-white scales. It affects approximately 120–180 million people worldwide [45]. The prevalence of psoriasis varies significantly depending mainly on race, geographical location, genetics, environmental factors, and ethnicity [46–50].

The etiology of psoriasis involves both genetic and environmental factors indicating a multifactorial nature. Moreover, a number of characteristic features of psoriasis are also found in other autoimmune diseases indicating a common etiology [51, 52].

Though the pathogenesis of psoriasis and comorbidities has been studied at the molecular level and a number of gene loci have been associated with susceptibility/severity of psoriasis [50–53], genes identified till date to be associated with it do not fully account for it. Psoriasis is highly heritable, and it has been suggested in several association studies that skin barrier function, innate and adaptive immunity, and gene-gene and gene-environment interactions are involved in the pathogenesis of psoriasis [52].

Recently an association of T-allele of the PTPN22 C1858T with susceptibility to psoriasis in Saudi population was reported (**Table 3**) [53]. Earlier it has been suggested that *PTPN22* may be among the true psoriasis susceptibility risk genes [54]. However, another study analyzed 15 SNPs from 7 putative psoriasis-risk genes and could not find any significant association of PTPN22 C1858T polymorphism with psoriasis. On the other hand, they found a significant association with another polymorphism (rs3789604) in *PTPN22* gene and suggested that *PTPN22* is one of the significant risk genes for psoriasis [55]. Chen and Chang [56] reported a strong association of PTPN22 + 1858T allele with PsA but no association with psoriasis and suggested that attention should be given to the studies dealing with gene-environment interaction besides keeping in consideration the clinical heterogeneity of the disease and population stratification.

Earlier Hüffmeier et al. [57] found gender variations in susceptibility of PTPN22 (+1858T allele) with psoriasis and suggested that other susceptibility locus/loci within noncoding regions of *PTPN22* or its proximity might exist and act independently as a risk factor. They excluded the direct link of T-allele in psoriasis susceptibility in German psoriasis patients.

## 7. Psoriatic arthritis

PsA is a chronic inflammatory arthritis associated with psoriasis. PsA is a chronic skin and joint condition that considerably affects patient's quality of life. PsA is a complex disease with environmental and genetic risk factors contributing to it. Several studies have demonstrated different associations of genetic polymorphisms in the pathogenic process of PsA.

PTPN22 C1858T polymorphism has also been strongly associated with PsA (**Table 4**) in Toronto admix and Swedish population [61, 62]. Several non-HLA loci including *PTPN22* have been suggested to affect the susceptibility to PsA [63, 64]. A complete genetic overlap has been suggested between psoriasis and PsA susceptibility loci as about a third of people who have psoriasis gets PsA. It has been noticed that subjects with severe psoriasis have a greater chance of getting PsA and about 40% of patients with PsA have relatives with it or with psoriasis, while other earlier studies reported no association of PTPN22 C1858T polymorphism and PsA in Newfoundland, the UK, and German Caucasian [57, 61, 65]. Though no significant differences were observed in allele distribution with different manifestations of disease, there is gender difference, and male PsA patients has higher frequency of T-allele than in the subgroup of female patients [66].

## 8. Juvenile idiopathic arthritis

JIA is the most common inflammatory disease of the joints in children. Its etiology is complex and involves both genetic and environmental factors. It has been suggested that genetic factors play a significant role in the susceptibility to JIA [67]. While associations between JIA and variants in HLA are well established,

non-HLA genetic variants also play a role in JIA susceptibility and have increasingly been identified by genome-wide and candidate gene studies [68, 69]. Many of the genetic associations have been confirmed recently by the International JIA Immunochip consortium, and several novel loci have also been identified showing a genome-wide association.

Several reports indicate that PTPN22 C1858T polymorphism has been consistently associated with JIA (**Table 5**). PTPN22 C1858T polymorphism is associated with JIA in Australians [70, 71], Americans of European ancestry [67], Czech [72], Europeans [69], Greek [73], Norwegians [74], UK population [65], and Egyptians [75]. Two separate meta-analyses also indicated that PTPN22 C1858T is associated with susceptibility to JIA [76, 77]. However, it is not associated with JIA in Finnish and Hungarian patients [78, 79]. These variations may be due to ethnic variations; however, methodological error in genotyping cannot be ruled out.

## **9. Rheumatoid arthritis**

RA is a chronic autoimmune disorder of bone joints caused by the complex interplay between several factors like body physiology and the environment with genetic background [80, 81]. RA is characterized by synovial inflammation, hyperplasia, cartilage and bone destruction, autoantibody production (rheumatoid factor), anticyclic citrullinated peptide (CCP), and the decreased quality of life [82]. Its prevalence is approximately 0.51% worldwide and afflicts people of all races.

RA shares a number of pathogenic mechanisms with other autoimmune disorders. More than 100 loci have been associated with RA as shown in a meta-analysis of GWAS. Out of these majority (97%) are located in the noncoding region, and the remaining 3% are in various non-HLA genes including PTPN22 (Trp620Arg) [83].

Several studies have been performed on the association of PTPN22 C1858T variants with RA susceptibility in different ethnic populations (**Table 6**). Various studies have demonstrated that allelic heterogeneity distribution has an increasing north-south gradient in the frequencies of the 1858T alleles in different European populations [84]. PTPN22 C1858T polymorphism has been associated with susceptibility to RA in Algerian [85], Colombian [86, 87], Egyptian [88–90], Iranian [84, 91], Italian [92], Mexican [93–95], Spanish [96], Turkish [97], and UK Caucasian populations [65].

On the other hand, some studies reported that it is not associated with RA in Chinese [98, 99], Egyptian [100], and Iranian populations [101]. A number of meta-analyses have also shown that T-allele of PTPN22 C1858T is associated with RA susceptibility in Caucasians but not in Asians and Africans (**Table 6**) [102–104]. The different allele frequency of T-allele is very important in determining the population attributable risk of this allele for the autoimmune diseases in different populations. It also affects any suggested screening or predictive testing protocol for these diseases [101]. The absence of this association in Asians undermines the importance of this locus as a susceptibility locus for the RA and other autoimmune diseases.

## **10. Systemic lupus erythematosus**

SLE is a heterogeneous autoimmune inflammatory disease characterized by loss of self-tolerance with hyperactivation of autoreactive T and B cells with a predominance of Th2 inflammatory response [109]. The SLE incidence rate varies from 1 to 10 per 100,000 person/years, and the prevalence varies from 20 to 70 per 100,000

persons. SLE affects more than 300,000 people in the United States (USA) and millions worldwide [110]. It is characterized by multisystem involvement, autoantibody formation, and dysregulation of the complement system. The onset of SLE is postulated to be triggered by environmental and hormonal factors in genetically susceptible individuals [111, 112].

The genetic contribution to the development of SLE is considerably high, which is estimated to be 66% of heritability in twin studies. Genome-wide association studies (GWASs) have greatly improved our understanding of the genetic basis of SLE [113]. A high-density SNP analysis has identified and facilitated to focus on disease-associated loci where patients and healthy controls exhibit different frequencies of trait-associated alleles which are potential disease-causal variants or their proxies [113]. To date, about 100 SLE susceptibility loci have been identified, mostly in European and Asian populations [112], explaining the heritability of SLE up to around 30% [114, 115]. The highly polygenic etiology of SLE is supported by a large number of disease-associated loci that have modest effect sizes but surpass the genome-wide significance threshold for the genetic association with SLE as reviewed by Kwon et al. [112].

PTPN22 C1858T polymorphism has been associated with the pathogenesis of SLE in various populations (**Table 7**). This polymorphism is significantly associated with susceptibility to SLE in American [116–118], Columbian [86, 87], Crete [119], Spanish [96], Swedish [120], Polish [121, 122], Egyptian populations [123, 124].

Several meta-analyses also indicated that PTPN22 C1858T polymorphism is associated with SLE susceptibility [2, 107, 125–128]. On the other hand, it is not associated with SLE in Asians [118], Chinese [99, 129], Hispanics, African-Americans [118], Mexican mestizos [130], and Turkish patients [131, 132].

## 11. Autoimmune thyroid disease

Autoimmune thyroid disease (AITD) is a complex disease which includes GD and Hashimoto's thyroiditis (HT). Its susceptibility is influenced by both genetic and environmental factors. The interaction of specific susceptibility genes and environmental exposures have been associated with AITD [135]. Both GD and HT are characterized by the production of thyroid autoantibodies and the invasion of thyroid lymphocytes. AITD is found in 5% of the general population and is one of the most prevalent autoimmune diseases. The incidence of GD and HT is influenced by genetic factors as well as environmental factors including geographical locations [136]. Approximately 37% of families with AITD exhibit either of these two disorders [137].

Previous molecular studies on genetic etiology of AITD have expanded the field of thyroid autoimmunity. Previous studies have shown that PTPN22 C1858T is associated with AITD [138, 139] (**Table 8**). Some reports have indicated a positive correlation [140–142], while others have indicated no correlation between PTPN22 C1858T and AITD in Japanese [143, 144], Korean [145], Jordanian, [146], and Polish populations [147].

PTPN22 C1858T polymorphism has been associated with GD (**Table 9**). It is susceptible to GD in Latin-American [148], Polish [149, 150], and English Caucasian populations [140, 151, 152]. Two separate meta-analyses confirmed the association of PTPN22 + 1858C/T polymorphism with Graves' disease [2, 139]. However, some reports have indicated no correlation between PTPN22 + 1858C/T and Graves' disease in Chinese Han, Polish, and Indian Kashmiri populations [153–155].

Jacobson et al. [156] reported that the PTPN22 + 1858C/T is related to the occurrence of HT. Another variant in PTPN22 gene has been found to be associated



with HT using whole-exome sequencing [157] indicating the role of *PTPN22* in autoimmune thyroid disease. However, the functional mechanism involved in the association remains to be found out.

## **12. Inflammatory bowel disease**

IBD is a complex, multifactorial, chronic inflammatory disorder of the gastrointestinal tract in which immune dysregulation caused by genetic and/or environmental factors plays an important role. IBD refers to two chronic inflammatory disorders of the gastrointestinal tract: UC and CD.

The IBD is a complex autoimmune disease. Its etiology is characterized by immune dysregulation caused by genetic and/or environmental factors [158, 159]. A genetically susceptible person develops IBD as a result of the immunogenic responses against environmental factors and/or microbes inhabiting the distal ileum and colon. It is believed that genetic factors contribute significantly to the pathogenesis of IBD [160–162]. Genome-wide scans performed in patients with IBD have failed to find a major unique susceptibility locus and have prompted the general agreement that these diseases are polygenic entities in which several genes may contribute to susceptibility [162].

Sfar et al. [163] reported an association of *PTPN22* C1858T polymorphism with IBD in Tunisian patients. Recently a meta-analysis utilizing 8182 patients and 13,356 controls indicated that this is associated with CD susceptibility only and there is no association with UC [164]. No association of *PTPN22* C1858T polymorphism with IBD was found in British, Canadian, Czech, German, Italian, Moroccan, New Zealander, and Spanish populations (**Table 10**). Another study on Spanish patients showed that this polymorphism is protective to CD while there is no association with UC [165]. A meta-analysis also indicated that *PTPN22* C1858T polymorphism is associated with reduced susceptibility to CD with no association with UC [2]. Despite the association of *PTPN22* C1858T SNP with CD and several different autoimmune disorders, a role for this polymorphism in susceptibility to IBD does not establish.

Thus, it is plausible that this genetic discrepancy in *PTPN22* influences a range of diseases in which the phenotypic spectrum includes an aberrant or hyperactive immune response [5, 166]. However, these variations in the association reports of *PTPN22* C1858T polymorphism with IBD may be due to ethnic variations in genetic makeup of the different populations. It has been suggested that the presence of T-allele of *PTPN22* C1858T makes an individual susceptible to autoimmune diseases by helping the production of antibodies associated with these diseases, resulting in the disease development [116].

## **13. Type 1 diabetes mellitus**

Type 1 diabetes is an autoimmune disease in which the insulin-producing cells are attacked by the body's defense system resulting in no insulin or very little insulin production. Although the exact cause of the T1DM is not clear yet, it has been associated with both genetic and environmental factors. It usually develops in children or young adults but can affect people of all age group. The patient will die if there is no access to insulin. Therefore, daily injection of insulin is required to control the blood glucose levels in patients with T1DM.

The International Diabetes Federation (IDF) has reported that there were 382 million people living with diabetes worldwide in 2013 and this number is expected

to rise to 592 million by 2035 [176]. Most people with diabetes live in low- and middle-income countries, where rapid changes in lifestyle have increased the prevalence of diabetes, cardiovascular diseases, and cancer, and these countries are expected to experience the greatest increase in cases of diabetes in the next 20 years. The global prevalence of diabetes was reported as 8.8% of the world's population (95% confidence interval 7.2–11.3%) in 2017, and it is expected to increase to 9.9% in 2045 [177]. At present in every seventh second, someone dies from diabetes or its complications. Fifty percent of these deaths are under the age of 60 years.

According to a report, 424.9 million people were having diabetes worldwide in 2017 which is expected to increase to 628.6 million people in 2045. The prevalence of diabetes is continuously increasing since the IDF Diabetes Atlas first was launched in 2000, and about 50% of the diabetes cases remain undiagnosed especially in developing countries which is a matter of concern [177].

A positive association between PTPN22 C1858 T polymorphism and susceptibility to the development of T1DM has been reported in a large number of studies from several populations (**Table 11**) with the exception of a few such as a single study from Chinese [178], Greek [179], Indian [180], and Iranian populations [181] where no association was found.

The review by Prezioso et al. [182] evaluated the role of the PTPN22 C1858 T in the prognosis of disease. On the basis of the potential role of C1858 T as a target for tertiary prevention trials and new therapeutic strategies, such as the Lyp inhibitors, they suggested that PTPN22 can be a promising target for therapeutic interventions and identification of at-risk subjects in autoimmune diseases such as T1DM.

It has been shown that several SNPs could potentially contribute to susceptibility to various autoimmune disorders including T1DM. However, 1858C/T SNP is the most stable, where T-allele correlates with T1DM (**Table 11**) [7, 142, 152, 183]. Habib et al. [211] demonstrate a role of PTPN22 1858T in signaling defects in both transitional and naïve B cells in healthy subjects resulting in an increased resistance to BCR-driven apoptosis in these cells and peripheral reservoir of autoreactive cells [212].

## 14. Systemic sclerosis

SSc is a complex disease with an autoimmune origin in which extensive fibrosis, vascular alterations, and autoantibodies against various cellular antigens are among the principal features [213]. Although the etiopathogenesis is not yet well understood, the results of numerous genetic association studies support genetic contributions as an important factor to SSc.

SSc occurs in persons who are genetically predisposed and have faced specific environmental factors with or without other randomly distributed factors [214, 215]. It has been consistently associated with the major histocompatibility complex variants. Non-HLA genes associated with immunity have also been associated with SSc susceptibility [214].

In spite of these findings, the complete genetic background of SSc, the nature of its genetic determinants, and how they contribute to SSc susceptibility and clinical manifestations are poorly understood. Interestingly, PTPN22 has emerged as an important genetic risk factor for human autoimmunity. The PTPN22 C1858T polymorphism in SSc has also been investigated and shows a trend of association (**Table 12**). It has been associated with SSc susceptibility in French [216], Caucasian [214], and White, Black, and Hispanic American [217]. A meta-analysis showed that PTPN22 1858T is susceptible to SSc [107]. Some other report shows the absence of any association between this polymorphism and SSc in French [218], Columbian [87], and Spanish [219].

## 15. Myasthenia gravis

MG is an antibody-mediated autoimmune disease against antigens at the neuromuscular junction. Both genetic and environmental factors contribute to the susceptibility of MG. The annual incidence of MG is reported to be 0.25–4 patients per 100,000 population, with the first peak of onset around the second and third decades of life and the second peak around the fifth and sixth decades [220, 221]. The exact mechanism of the autoimmunity in MG is unknown. It is caused mostly by the autoantibodies directed toward the skeletal muscle acetylcholine receptor (AChR), but there are cases in which autoimmune attack targets non-AChR components of the postsynaptic muscle endplate [222–225]. It has been suggested that genetic factors might play an important role in the development of MG [226–227]. Some studies showed that PTPN22 C1858T polymorphism is associated with MG risk (**Table 13**).

PTPN22 C1858T polymorphism is associated with MG susceptibility in Swedish [228], German [229], European [230], Hungarian [231], and French patients [232]. However, the association between this polymorphism and the risk of MG was controversial and inconclusive in Chinese, Italian, and Turkish patients [2, 233, 234].

## 16. Behcet's diseases

BD is characterized by recurrent orogenital ulcers, cutaneous inflammation, and uveitis. It is a chronic autoimmune/inflammatory disorder with typical mucocutaneous and ocular manifestations. It also targets musculoskeletal, nervous, vascular, and gastrointestinal systems [236]. The prevalence of BD varies with geographical locations. It is more prevalent in countries along the silk route, particularly in the East Asia and the Middle East. Prevalence is highest in Turkey, followed by Egypt, Morocco, Iraq, Saudi Arabia, Japan, Iran, Korea, and China [237, 238]. Available reports indicate that autoimmunity, genetic factors, and environmental factors are involved in the pathogenesis of BD; however, the specific etiology remains to be determined [236, 239, 240].

Being an autoimmune disease, BD is considered to be affected by PTPN22 C1858T polymorphism. However, there is no significant association of this gene in susceptibility to BD (**Table 14**). Baranathan et al. [241] suggested that PTPN22 C1858T is inversely associated with BD in the UK population indicating its protective role in BD. However, this does not hold for Middle Eastern patients in whom PTPN22 C1858T expression does not associate with BD, possibly due to a very low prevalence of the polymorphism in this population.

The prevalence of PTPN22 C1858T is very low in the general population, and the absence of any correlation with BD indicates that PTPN22 C1858T polymorphism has a limited role in the pathogenesis of autoimmunity [242]. Recently Ortiz-Fernández [243] also could not find any association of PTPN22 C1858T polymorphism with BD in Spanish patients.

## 17. Endometriosis

Endometriosis is a chronic inflammatory disease and one of the most common benign gynecological disorders. It is a condition in which a tissue that is histologically similar to the endometrium, with glands and/or stroma, grows outside the uterine cavity [244]. It presents a multisystem involvement affecting several

organs, most commonly in the peritoneum and pelvis, especially the ovaries, and less often in the rectovaginal septum. This results in pelvic pain, dysmenorrhea, and infertility [245].

Although various hypotheses have been proposed to explain the etiology of endometriosis, the explanation of symptoms and presence of ectopic endometrial tissue and stroma at various sites is not very clear [246].

The etiology of endometriosis is complex and characterized by genetic and environmental factors similar to other autoimmune diseases. The immunological changes such as an increase in the number and cytotoxicity of macrophages, increase in the activity of B lymphocytes, abnormalities in the functions and concentrations of B and T lymphocytes, and reduction in the number or the activity of natural killer cells have been indicated in endometriosis. Anti-endometrial and anti-ovary antibodies have been also found in endometriosis [247]. As genetic factors and immunological predispositions are involved in the etiology of the disease, therefore the variants of genes associated with autoimmune diseases are possible candidates for endometriosis development [247]. PTPN22 C1858T polymorphism and its association with endometriosis have been studied in only three populations (Brazilian, Italian, and Polish) so far (**Table 15**).

The PTPN22 C1858T polymorphism has been reported to be associated with altered risk of endometriosis in Italian and Brazilian populations, but no significant association was found in Polish patients. However, on exploratory analyses Płoski et al. [248] suggested that the T-allele and the TT genotype may be associated with the prevalence of double positivity for antinuclear antibody (ANA) and anti-cardiolipin autoantibody (ACA).

A meta-analysis showed overall increased risk associations of up to 5.6-fold in endometriosis. In the presence of endometriosis, the PTPN22 C1858T polymorphism may cooperate with clinical and genetic factors to influence the course of disease and immune reactions. These cooperative interactions could result in a statistical association between PTPN22 C1858T and endometriosis [246].

The lymphoid tyrosine phosphatase enzyme is encoded by *PTPN22* gene and is a regulator of signaling through the T-cell receptor and forms a complex with the kinase Csk in T cells. The variant of PTPN22 C1858T polymorphism does not bind kinases properly and results in a gain-of-function enzyme [246, 249, 250]. The increased inhibition of T-cell receptor signaling caused by the PTPN22 C1858T polymorphism could predispose toward autoimmunity, either by affecting the thymic deletion of autoreactive T cells or by affecting the development or function of peripheral regulatory T cells [251].

## **18. Antineutrophil cytoplasmic antibody-associated vasculitis**

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an uncommon inflammatory disease, characterized by inflammation in small- to medium-sized vessels, necrosis, and association with detectable circulating ANCAs. Though the manifestations in the lungs and kidneys are common, any organ or system can be affected. AAV refers to a group of small-vessel vasculitis, including granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA, formerly Churg-Strauss syndrome) [256].

AAV is a complex disease with both genetic and environmental factors involved in pathogenesis [257]. There is increasing evidence that susceptibility loci are shared between autoimmune diseases. The candidate gene association studies and the GWASs have shown the genetic basis of AAV. The significant association of AAV

with HLA polymorphisms has confirmed the central role of autoimmunity in the development of AAV. All the three main subtypes mentioned above have been reported to be associated with distinct HLA variants [258].

The role of PTPN22 C1858T in AAV provided the basis for the three main PTPN22 genetic association studies performed so far (**Table 16**). The first, which included a German cohort, showed an association of this variant with the disease; the association was even more significant in the ANCA-positive subgroup [259]. This result has been subsequently replicated in two independent cohorts of British [260] and Italian AAV patients [261]. However, the study on Italian patients showed that the association is restricted to the GPA patients only, as almost similar frequency of the T-allele of PTPN22 C1858T was found in the MPA or the EGPA patients and controls.

Three independent meta-analyses indicated that PTPN22 C1858T polymorphism is significantly associated with susceptibility of AAV in Caucasian population [76, 262].

## **19. Giant cell arteritis**

GCA is a form of vasculitis. It is very common in elderly people and may cause blindness and stroke [263]. The environmental, infectious, and genetic risk factors have been associated with GCA development; however, the pathogenesis is not clear yet. PTPN22 is a gene of interest which is proposed to be an “archetypal non-HLA autoimmunity gene” [251, 264]. The T-allele of a functional PTPN22 C1858T polymorphism has been reported to be associated with biopsy-proven GCA in Spanish patients (**Table 17**), with supporting data from three replicate Northern European studies [265]. Recently, this observation has been extended with additional patients and controls and studies encompassing European, Scandinavian, UK, and American patients [266], though an earlier report from Spanish patients does not support the potential involvement of PTPN22 gene polymorphism in the susceptibility or clinical expression of GCA [263].

Though Lester et al. [267] could not find any significant difference in the distribution of alleles and genotypes of PTPN22 C1858T polymorphism between patients and control groups, they suggested that there is a significant association between the minor allele of PTPN22 C1858T polymorphism and GCA.

## **20. Autoimmune Addison’s disease (AAD)**

AAD occurs due to autoimmune destruction of the adrenal cortex. Approximately half of the patients have additional autoimmune components. The prevalence of AAD varies from 110 to 144 cases per million in the developed countries. In adult patients, AAD is the most common etiological form (80%), followed by post-tuberculosis AD (10–15%) and vascular, neoplastic, or rare genetic forms (5%) [268]. AAD commonly coexists with thyroid autoimmunity and/or type I diabetes and is called as autoimmune polyendocrine syndrome type II (APS II).

Several genetic determinants have long been suspected to be involved in various autoimmune diseases. PTPN22 C1858T polymorphism has been studied in AAD patients with inconsistent results (**Table 18**). Velaga et al. [151] reported an association for the T-allele in patients from northeast England, whereas Kahles et al. [185] found no association in German patients. This inconsistency may be due to small sample size. The 1858T allele is associated with susceptibility to AAD in Norwegians [269], UK cohort, and the Polish population [270]. Meta-analysis of the results,

together with those from three other populations, showed that the 1858T allele is associated with AAD susceptibility.

Confounding factors must be considered particularly when polymorphisms identified in one study cannot be duplicated in a similar ethnic group. One confounding factor is population stratification. This may occur with an unbalanced ethnic admixture.

It is clear that the inheritance of a coding variant of *PTPN22* gene is associated with increased susceptibility to autoimmunity. The mechanism by which the *PTPN22* C1858T variant modulates disease risk has been studied. *PTPN22* is capable of both enzymatic activities and adaptor functions. It exerts its effects in multiple biochemical pathways and cell types. *PTPN22* regulates signaling through both antigen and innate immune receptors. It is involved in the development and activation of lymphocyte, establishment of tolerance, and innate immune cell-mediated host defense and immunoregulation. The *PTPN22* C1858T variant protein is involved in the pathogenesis of autoimmunity at multiple levels. The action of *PTPN22* C1858T during immature B-cell selection disrupts the establishment of a tolerant B-cell repertoire and alters mature T-cell responsiveness. When an autoimmune attack initiates tissue injury, the *PTPN22*C1858T fosters inflammation by regulating the level of cytokines produced by a myeloid cell.

## 21. Conclusion

The *PTPN22* C1858T is one of the strongest and most consistent genetic associations with autoimmune diseases. However, available literature on *PTPN22* C1858T polymorphism and autoimmune diseases shows ethnic variations. It is conceivable that the relation of any locus with the autoimmune disease will be small as interactions between gene and gene and gene and environment might also be operating. Further well-designed studies from different populations and cohorts to detect small genetic risk will help in drawing better conclusion on the development of autoimmune diseases. Therefore, further genetic studies on patients suffering from various autoimmune diseases from different ethnicities and *PTPN22* gene polymorphisms are expected to help better understand the pathogenesis and will contribute to the development of more targeted therapies and biomarkers.

## Acknowledgements

Authors wish to thank the MSD administration for facilities and support.

## Conflict of interest

No conflicts of interests.

# IntechOpen

## Author details

Ghaleb Bin Huraib<sup>1</sup>, Fahad Al Harthi<sup>2</sup>, Misbahul Arfin<sup>3</sup>  
and Abdulrahman Al-Asmari<sup>3\*</sup>

<sup>1</sup> Medical Services Department for Armed Forces, Riyadh, Saudi Arabia

<sup>2</sup> Department of Dermatology, Prince Sultan Military Medical City, Riyadh, Saudi Arabia

<sup>3</sup> Scientific Research Center, Medical Services Department for Armed Forces, Riyadh, Saudi Arabia

\*Address all correspondence to: [abdulrahman.alasmari@gmail.com](mailto:abdulrahman.alasmari@gmail.com)  
and [misbahularfin@yahoo.com](mailto:misbahularfin@yahoo.com)

## IntechOpen

---

© 2020 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Weber JL, Broman KW. Genotyping for human whole-genome scans: Past, present, and future. *Advances in Genetics*. 2001;**42**:77-96. DOI: 10.1016/S0065-2660(01)42016-5
- [2] 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 and Immunity*. 2012;**13**(8):641-652. DOI: 10.1038/gene.2012.46
- [3] Tizaoui K, Kim SH, Jeong GH, et al. Association of PTPN22 1858C/T polymorphism with autoimmune diseases: A systematic review and Bayesian approach. *Journal of Clinical Medicine*. 2019;**8**(3):347. Published 12 March 2019. DOI: 10.3390/jcm8030347
- [4] Cohen S, Dadi H, Shaoul E, Sharfe N, Roifman CM. Cloning and characterization of a lymphoid-specific, inducible human protein tyrosine phosphatase, Lyp. *Blood*. 1999;**93**: 2013-2024
- [5] Vang T, Congia M, Macis MD, et al. Autoimmune-associated lymphoid tyrosine phosphatase is a gain-of-function variant. *Nature Genetics*. 2005;**37**(12):1317-1319. DOI: 10.1038/ng1673
- [6] Arechiga AF, Habib T, He Y, et al. Cutting edge: The PTPN22 allelic variant associated with autoimmunity impairs B cell signaling. *Journal of Immunology*. 2009;**182**:3343-3347
- [7] Bottini N, Musumeci L, Alonso A, et al. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. *Nature Genetics*. 2004;**36**(4):337-338. DOI: 10.1038/ng1323
- [8] Bottini N, Vang T, Cucca F, Mustelin T. Role of PTPN22 in type 1 diabetes and other autoimmune diseases. *Seminars in Immunology*. 2006;**18**:207-213
- [9] Singh SP, Wal P, Wal A, Srivastava V, Tiwari R, Sharma RD. Understanding autoimmune disease: An update review. *International Journal of Pharmaceutical Technology and Biotechnology*. 2016;**3**(3):51-65
- [10] Ortonne JP. Recent developments in the understanding of pathogenesis of psoriasis. *The British Journal of Dermatology*. 1999;**140**(Suppl 54):1-7
- [11] Kukreja A, Maclaren NK. Autoimmunity and diabetes. *The Journal of Clinical Endocrinology and Metabolism*. 1999;**84**:4371-4378
- [12] Gregersen PK. Genetic analysis of rheumatic diseases. In: Kelley WN, Harris ED Jr, Ruddy S, Sledge CN, editors. *Textbook of Rheumatology*. 5th ed. Vol. 1. Philadelphia: W.B. Saunders; 1997. pp. 209-211
- [13] Encinas JA, Kuchroo VK. Mapping and identification of autoimmunity genes. *Current Opinion in Immunology*. 2000;**12**:691-697
- [14] Becker KG. Comparative genetics of type I diabetes and autoimmune disease: Common loci, common pathways? *Diabetes*. 1999;**48**:1353-1358
- [15] Sehgal VN, Srivastava G. Vitiligo: Compendium of clinico-epidemiological features. *Indian Journal of Dermatology, Venereology and Leprology*. 2007;**73**(3): 149-156
- [16] Guerra L, Dellambra E, Brescia S, Raskovic D. Vitiligo: pathogenetic hypotheses and targets for current therapies. *Current Drug Metabolism*. 2010;**11**(5):451-467
- [17] Krüger C, Schallreuter KU. A review of the worldwide prevalence of vitiligo



in children/adolescents and adults. *International Journal of Dermatology*. 2012;**51**(10):1206-1212

[18] Jin Y, Bennett DC, Amadi-Myers A, Holland P, Riccardi SL, Gowan K, et al. Vitiligo-associated multiple autoimmune disease is not associated with genetic variation in AIRE. *Pigment Cell Research*. 2007;**20**(5):402-404

[19] van Geel N, Speeckaert M, Brochez L, Lambert J, Speeckaert R. Clinical profile of generalized vitiligo patients with associated autoimmune/ autoinflammatory diseases. *Journal of the European Academy of Dermatology and Venereology*. 2014;**28**(6):741-746

[20] Garcia-Melendez ME, Salinas-Santander M, Sanchez-Dominguez C, Gonzalez-Cardenas H, Cerda-Flores RM, Ocampo-Candiani J, et al. Protein tyrosine phosphatase PTPN22 + 1858C/T polymorphism is associated with active vitiligo. *Experimental and Therapeutic Medicine*. 2014;**8**(5):1433-1437

[21] Spritz RA. The genetics of generalized vitiligo and associated autoimmune diseases. *Pigment Cell Research*. 2007;**20**:271-278

[22] Pehlivan S, Ozkinay F, Alper S, Onay H, Yuksel E, Pehlivan M, et al. Association between IL4 (-590), ACE (I)/(D), CCR5 (Delta32), CTLA4 (+49) and IL1-RN (VNTR in intron 2) gene polymorphisms and vitiligo. *European Journal of Dermatology*. 2009;**19**(2):126-128

[23] Zamani M, Tabatabaiefar MA, Mosayyebi S, Mashaghi A, Mansouri P. Possible association of the CD4 gene polymorphism with vitiligo in an Iranian population. *Clinical and Experimental Dermatology*. 2010;**35**(5):521-524

[24] Ochoa-Ramírez LA, Becerra-Loaiza DS, Díaz-Camacho SP, Muñoz-Estrada

VF, Ríos-Burgueño ER, Prado-Montes de Oca E, et al. Association of human beta-defensin 1 gene polymorphisms with nonsegmental vitiligo. *Clinical and Experimental Dermatology*. 2019;**44**(3):277-282. DOI: 10.1111/ced.13697

[25] Rajendiran KS, Rajappa M, Chandrashekar L, Thappa DM. Association of PTPN22 gene polymorphism with non-segmental vitiligo in South Indian Tamils. *Postepy Dermatologii I Alergologii*. 2018;**35**(3):280-285

[26] Song GG, Kim JH, Lee YH. The CTLA-4 +49 A/G, CT60 A/G and PTPN22 1858 C/T polymorphisms and susceptibility to vitiligo: a meta-analysis. *Molecular Biology Reports*. 2013;**40**(4):2985-2993

[27] Akbas H, Dertlioglu SB, Dilmec F, Atay AE. Lack of association between PTPN22 Gene +1858 C>T polymorphism and susceptibility to generalized vitiligo in a Turkish population. *Annals of Dermatology*. 2014;**26**(1):88-91

[28] Agarwal S, Changotra H. Association of protein tyrosine phosphatase, non-receptor type 22 +1858C→T polymorphism and susceptibility to vitiligo: Systematic review and meta-analysis. *Indian Journal of Dermatology, Venereology and Leprology*. 2017;**83**(2):183-189

[29] Cantón I, Akhtar S, Gavalas NG, Gawkrödger DJ, Blomhoff A, Watson PF, et al. A single-nucleotide polymorphism in the gene encoding lymphoid protein tyrosine phosphatase (PTPN22) confers susceptibility to generalised vitiligo. *Genes and Immunity*. 2005;**6**:584-587

[30] Laberge GS, Birlea SA, Fain PR, Spritz RA. The PTPN22 – 1858C>T (R620W) functional polymorphism is associated with generalized vitiligo in the Romanian population. *Pigment Cell*

& Melanoma Research. 2008;**21**:  
206-208

[31] Jin Y, Birlea SA, Fain PR, Gowan K, Riccardi SL, Holland PJ, et al. Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo. *The New England Journal of Medicine*. 2010; **362**(18):1686-1697

[32] Laddha NC, Dwivedi M, Shajil EM, Prajapati H, Marfatia YS, Begum R. Association of PTPN22 1858C/T polymorphism with vitiligo susceptibility in Gujarat population. *Journal of Dermatological Science*. 2008;**49**:260-262

[33] Alkhateeb A, Qarqaz F, Al-Sabah J, Al Rashaideh T. Clinical characteristics and PTPN22 1858C/T variant analysis in Jordanian Arab vitiligo patients. *Molecular Diagnosis & Therapy*. 2010; **14**:179-184

[34] Elmongy NN, Abu Khalil RE. PTPN22 gene polymorphism in Egyptian females with non-segmental vitiligo. *Comparative Clinical Pathology*. 2013;**22**(5):961-964

[35] Galán-Gutiérrez M, Rodríguez-Bujaldón A, Moreno-Giménez JC. Update on the treatment of alopecia areata. *Actas Dermo-Sifiliográficas*. 2009;**100**:266-276. (In Spanish)

[36] Hordinsky MK. Overview of alopecia areata. *The Journal of Investigative Dermatology. Symposium Proceedings*. 2013;**16**(1):S13-S15. DOI: 10.1038/jidsymp.2013.4

[37] Alzolibani AA. Epidemiologic and genetic characteristics of alopecia areata (part 1). *Acta Dermatovenerologica Alpina, Panonica, et Adriatica*. 2011;**20**: 191-198

[38] Kemp EH, McDonagh AJ, Wengraf DA, et al. The non-synonymous C1858T substitution in the PTPN22 gene is associated with

susceptibility to the severe forms of alopecia areata. *Human Immunology*. 2006;**67**(7):535-539. DOI: 10.1016/j.humimm.2006.04.006

[39] Betz RC, König K, Flaquer A, et al. The R620W polymorphism in PTPN22 confers general susceptibility for the development of alopecia areata. *The British Journal of Dermatology*. 2008; **158**(2):389-391. DOI: 10.1111/j.1365-2133.2007.08312.x

[40] El-Zawahry BM, Azzam OA, Zaki NS, Abdel-Raheem HM, Bassiouny DA, Khorshied MM. PTPN22 gene polymorphism in Egyptian alopecia areata patients and its impact on response to diphencyprone immunotherapy. *Gene*. 2013;**523**(2): 147-151. DOI: 10.1016/j.gene.2013.03.070

[41] Salinas-Santander M, Sánchez-Domínguez C, Cantú-Salinas C, et al. Association between PTPN22 C1858T polymorphism and alopecia areata risk. *Experimental and Therapeutic Medicine*. 2015;**10**(5):1953-1958. DOI: 10.3892/etm.2015.2728

[42] Bhanusali DG, Sachdev A, Olson MA, Gerlach JA, Sinha AA. PTPN22 profile indicates a novel risk group in Alopecia areata. *Human Immunology*. 2014;**75**(1):81-87. DOI: 10.1016/j.humimm.2013.09.003

[43] Lei ZX, Chen WJ, Liang JQ, et al. The association between rs2476601 polymorphism in PTPN22 gene and risk of alopecia areata: A meta-analysis of case-control studies. *Medicine (Baltimore)*. 2019;**98**(20):e15448. DOI: 10.1097/MD.00000000000015448

[44] Moravvej H, Tabatabaei-Panah PS, Abgoon R, et al. Genetic variant association of PTPN22, CTLA4, IL2RA, as well as HLA frequencies in susceptibility to alopecia areata. *Immunological Investigations*. 2018;

47(7):666-679. DOI: 10.1080/08820139.2018.1480032

[45] Icen M, Crowson CS, McEvoy MT, Dann FJ, Gabriel SE, Maradit KH. Trends in incidence of adult-onset psoriasis over three decades: a population-based study. *Journal of the American Academy of Dermatology*. 2009;**60**(3):394-401. DOI: 10.1016/j.jaad.2008.10.062

[46] Dogra S, Yadav S. Psoriasis in India: Prevalence and pattern. *Indian Journal of Dermatology, Venereology and Leprology*. 2010;**76**(6):595-601. DOI: 10.4103/0378-6323.72443

[47] Ding X, Wang T, Shen Y, et al. Prevalence of psoriasis in China: A population-based study in six cities. *European Journal of Dermatology*. 2012;**22**(5):663-667. DOI: 10.1684/ejd.2012.1802

[48] Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: Analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. *International Journal of Dermatology*. 2014;**53**(6):676-684. DOI: 10.1111/ijd.12070

[49] Loo CH, Chan YC, Lee KQ, Tharmalingam P, Tan WC. Clinical profile, morbidity and outcome of adult patients with psoriasis at a district hospital in Northern Malaysia. *The Medical Journal of Malaysia*. 2015;**70**(3):177-181

[50] Al Harthi F, Huraib GB, Zouman A, Arfin M, Tariq M, Al-Asmari A. Apolipoprotein E gene polymorphism and serum lipid profile in Saudi patients with psoriasis. *Disease Markers*. 2014;**2014**:239645. DOI: 10.1155/2014/239645

[51] Elder JT. Genome-wide association scan yields new insights into the immunopathogenesis of psoriasis. *Genes*

and Immunity. 2009;**10**(3):201-209. DOI: 10.1038/gene.2009.11

[52] Elder JT, Bruce AT, Gudjonsson JE, et al. Molecular dissection of psoriasis: integrating genetics and biology. *The Journal of Investigative Dermatology*. 2010;**130**(5):1213-1226. DOI: 10.1038/jid.2009.319

[53] Scarpa R, Altomare G, Marchesoni A, Balato N, Matucci Cerinic M, Lotti T, et al. Psoriatic disease: Concepts and implications. *Journal of the European Academy of Dermatology and Venereology*. 2010;**24**(6):627-630. DOI: 10.1111/j.1468-3083.2010.03574.x

[54] Li Y, Chang M, Schrodin SJ, et al. The 5q31 variants associated with psoriasis and Crohn's disease are distinct. *Human Molecular Genetics*. 2008;**17**(19):2978-2985. DOI: 10.1093/hmg/ddn196

[55] Li Y, Liao W, Chang M, et al. Further genetic evidence for three psoriasis-risk genes: ADAM33, CDKAL1, and PTPN22. *The Journal of Investigative Dermatology*. 2009;**129**(3):629-634. DOI: 10.1038/jid.2008.297

[56] Chen YF, Chang JS. PTPN22 C1858T and the risk of psoriasis: A meta-analysis. *Molecular Biology Reports*. 2012;**39**(8):7861-7870. DOI: 10.1007/s11033-012-1630-z

[57] Hüffmeier U, Steffens M, Burkhardt H, et al. Evidence for susceptibility determinant(s) to psoriasis vulgaris in or near PTPN22 in German patients. *Journal of Medical Genetics*. 2006;**43**(6):517-522. DOI: 10.1136/jmg.2005.037515

[58] Smith RL, Warren RB, Eyre S, Ke X, Young HS, Allen M, et al. Polymorphisms in the PTPN22 region are associated with psoriasis of early onset. *The British Journal of*

Dermatology. 2008;**158**(5):962-968.  
DOI: 10.1111/j.1365-2133.2008.08482.x

[59] Nistor I, Nair RP, Stuart P, et al. Protein tyrosine phosphatase gene PTPN22 polymorphism in psoriasis: Lack of evidence for association. *The Journal of Investigative Dermatology*. 2005;**125**(2):395-396. DOI: 10.1111/j.0022-202X.2005.23802.x

[60] Zervou MI, Castro-Giner F, Sidiropoulos P, Boumpas DT, Tosca AD, Krueger-Krasagakis S. The protein tyrosine phosphatase, non-receptor type 22 R620W polymorphism does not confer susceptibility to psoriasis in the genetic homogeneous population of Crete. *Genetic Testing and Molecular Biomarkers*. 2010;**14**(1):107-111

[61] Butt C, Peddle L, Greenwood C, Hamilton S, Gladman D, Rahman P. Association of functional variants of PTPN22 and tp53 in psoriatic arthritis: a case-control study. *Arthritis Research & Therapy*. 2006;**8**(1):R27. DOI: 10.1186/ar1880

[62] Juneblad K, Johansson M, Rantapää-Dahlqvist S, Alenius GM. Association between the PTPN22 +1858 C/T polymorphism and psoriatic arthritis. *Arthritis Research and Therapy*. 2011;**13**(2):R45. Published Mar 16, 2011. DOI: 10.1186/ar3284

[63] Bowes J, Loehr S, Budu-Aggrey A, et al. PTPN22 is associated with susceptibility to psoriatic arthritis but not psoriasis: Evidence for a further PsA-specific risk locus. *Annals of the Rheumatic Diseases*. 2015;**74**(10):1882-1885. DOI: 10.1136/annrheumdis-2014-207187

[64] Budu-Aggrey A, Bowes J, Barton A. Identifying a novel locus for psoriatic arthritis. *Rheumatology (Oxford, England)*. 2016;**55**(1):25-32. DOI: 10.1093/rheumatology/kev273

[65] Hinks A, Barton A, John S, et al. 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 and Rheumatism*. 2005;**52**(6):1694-1699. DOI: 10.1002/art.21049

[66] Hüffmeier U, Reis A, Steffens M, et al. Male restricted genetic association of variant R620W in PTPN22 with psoriatic arthritis. *The Journal of Investigative Dermatology*. 2006;**126**(4):932-935. DOI: 10.1038/sj.jid.5700179

[67] Kaalla MJ, Broadaway KA, Rohani-Pichavant M, et al. Meta-analysis confirms association between TNFA-G238A variant and JIA, and between PTPN22-C1858T variant and oligoarticular, RF-polyarticular and RF-positive polyarticular JIA. *Pediatric Rheumatology Online Journal*. 2013;**11**(1):40. Published Oct 25, 2013. DOI: 10.1186/1546-0096-11-40

[68] Hinks A, Eyre S, Ke X, Barton A, Martin P, Flynn E, et al. Overlap of disease susceptibility loci for rheumatoid arthritis and juvenile idiopathic arthritis. *Annals of the Rheumatic Diseases*. 2010;**69**(6):1049-1053. DOI: 10.1136/ard.2009.110650

[69] Thompson SD, Sudman M, Ramos PS, Marion MC, Ryan M, Tsoras M, et al. The susceptibility loci juvenile idiopathic arthritis shares with other autoimmune diseases extend to PTPN2, COG6, and ANGPT1. *Arthritis and Rheumatism*. 2010;**62**(11):3265-3276. DOI: 10.1002/art.27688

[70] Ellis JA, Chavez RA, Pezic A, Ponsonby AL, Akikusa JD, Allen RC, et al. Independent replication analysis of genetic loci with previous evidence of association with juvenile idiopathic arthritis. *Pediatric Rheumatology Online Journal*. 2013;**11**(1):12. DOI: 10.1186/1546-0096-11-12

- [71] Chiaroni-Clarke RC, Li YR, Munro JE, et al. The association of PTPN22 rs2476601 with juvenile idiopathic arthritis is specific to females. *Genes and Immunity*. 2015;**16**(7): 495-498. DOI: 10.1038/gene.2015. 32
- [72] Cinek O, Hradsky O, Ahmedov G, Slavcev A, Kolouskova S, Kulich M, et al. No independent role of the –1123 G>C and +2740 A>G variants in the association of PTPN22 with type 1 diabetes and juvenile idiopathic arthritis in two Caucasian populations. *Diabetes Research and Clinical Practice*. 2007; **76**(2):297-303. DOI: 10.1016/j.diabres.2006.09.009
- [73] Goulielmos GN, Chiaroni-Clarke RC, Dimopoulou DG, et al. Association of juvenile idiopathic arthritis with PTPN22 rs2476601 is specific to females in a Greek population. *Pediatric Rheumatology Online Journal*. 2016; **14**(1):25. DOI: 10.1186/s12969-016-0087-3
- [74] Viken MK, Amundsen SS, Kvien TK, Boberg KM, Gilboe IM, Lilleby V, et al. Association analysis of the 1858C>T polymorphism in the PTPN22 gene in juvenile idiopathic arthritis and other autoimmune diseases. *Genes and Immunity*. 2005; **6**(3):271-273. DOI: 10.1038/sj.gene.6364178
- [75] Soliman YA, Hashaad NI, Emam SM, Mohamed RR. Role of PTPN22 1858 C/T polymorphisms in juvenile idiopathic arthritis in Egyptian patients. *The Egyptian Journal of Immunology*. 2017;**24**(1):95-104
- [76] Lee YH, Bae SC, Song GG. The association between the functional PTPN22 1858 C/T and MIF –173 C/G polymorphisms and juvenile idiopathic arthritis: a meta-analysis. *Inflammation Research*. 2012;**61**(5):411-415. DOI: 10.1007/s00011-012-0447-5
- [77] DI Y, Zhong S, Wu L, Li Y, Sun N. The association between PTPN22 genetic polymorphism and juvenile idiopathic arthritis (JIA) susceptibility: An updated meta-analysis. *Iranian Journal of Public Health*. 2015;**44**(9): 1169-1175
- [78] Seldin MF, Shigeta R, Laiho K, Li H, Saila H, Savolainen A, et al. Finnish case-control and family studies support PTPN22 R620W polymorphism as a risk factor in rheumatoid arthritis, but suggest only minimal or no effect in juvenile idiopathic arthritis. *Genes and Immunity*. 2005;**6**(8):720-722
- [79] Pazar B, Gergely P Jr, Nagy ZB, Gombos T, Pozsonyi E, Rajczy K, et al. Role of HLA-DRB1 and PTPN22 genes in susceptibility to juvenile idiopathic arthritis in Hungarian patients. *Clinical and Experimental Rheumatology*. 2008; **26**(6):1146-1152
- [80] Chaudhari K, Rizvi S, Syed BA. Rheumatoid arthritis: current and future trends. *Nature Reviews Drug Discovery*. 2016;**15**(5):305-306. DOI: 10.1038/nrd.2016.21
- [81] Angelotti F, Parma A, Cafaro G, Capecchi R, Alunno A, Puxeddu I. One year in review 2017: Pathogenesis of rheumatoid arthritis. *Clinical and Experimental Rheumatology*. 2017; **35**(3):368-378
- [82] McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *The New England Journal of Medicine*. 2011;**365**(23):2205-2219. DOI: 10.1056/NEJMra1004965
- [83] Shaik NA, Banaganapalli B. Computational molecular phenotypic analysis of PTPN22 (W620R), IL6R (D358A), and TYK2 (P1104A) gene mutations of rheumatoid arthritis. *Frontiers in Genetics*. 2019;**10**:168. DOI: 10.3389/fgene.2019.00168
- [84] Abbasi Z, Kazemi Nezhad SR, Pourmahdi-Broojeni M, Rajaei E. Association of PTPN22 rs2476601

- polymorphism with rheumatoid arthritis and celiac disease in Khuzestan province. Southwestern Iran. Iranian Biomedical Journal. 2017;**21**(1):61-66. DOI: 10.6091/.21.1.61
- [85] Fodil M, Benzaoui A, Zemani-Fodil F, et al. Association of PTPN22 (rs2476601) and STAT4 (rs7574865) polymorphisms with rheumatoid arthritis in the Western Algerian population. *Acta Reumatológica Portuguesa*. 2015;**40**(1):56-62
- [86] Gomez LM, Anaya JM, Gonzalez CI, Pineda-Tamayo R, Otero W, Arango A, et al. PTPN22 C1858T polymorphism in Colombian patients with autoimmune diseases. *Genes and Immunity*. 2005;**6**: 628-631. DOI: 10.1038/sj.gene.6364261
- [87] Ramirez M, Quintana G, Diaz-Gallo LM, et al. The PTPN22 C1858T variant as a risk factor for rheumatoid arthritis and systemic lupus erythematosus but not for systemic sclerosis in the Colombian population. *Clinical and Experimental Rheumatology*. 2012; **30**(4):520-524
- [88] Salama A, Elshazli R, Elsaid A, Settin A. Protein tyrosine phosphatase non-receptor type 22 (PTPN22) +1858 C>T gene polymorphism in Egyptian cases with rheumatoid arthritis. *Cellular Immunology*. 2014;**290**(1):62-65. DOI: 10.1016/j.cellimm.2014.05.003
- [89] Raslan HM, Attia HR, Salama I, et al. Association of PTPN22 1858C→T polymorphism, HLA-DRB1 shared epitope and autoantibodies with rheumatoid arthritis. *Rheumatology International*. 2016;**36**(8):1167-1175. DOI: 10.1007/s00296-016-3511-6
- [90] Hegab MM, Abdelwahab AF, El-Sayed Yousef AM, et al. CD28 and PTPN22 are associated with susceptibility to rheumatoid arthritis in Egyptians. *Human Immunology*. 2016; **77**(6):522-526. DOI: 10.1016/j.humimm.2016.04.018
- [91] Hashemi M, Atabaki M, Daneshvar H, Zakeri Z, Eskandari-Nasab E. Association of PTPN22 rs2476601 and EGFR rs17337023 Gene polymorphisms and rheumatoid arthritis in Zahedan, Southeast Iran. *International Journal of Immunogenetics*. 2013;**40**(4):299-305
- [92] Totaro MC, Tolusso B, Napolioni V, et al. PTPN22 1858C>T polymorphism distribution in Europe and association with rheumatoid arthritis: Case-control study and meta-analysis. *PLoS One*. 2011;**6**(9):e24292. DOI: 10.1371/journal.pone.0024292
- [93] Torres-Carrillo NM, Ruiz-Noa Y, Martínez-Bonilla GE, et al. The +1858C/T PTPN22 gene polymorphism confers genetic susceptibility to rheumatoid arthritis in Mexican population from the Western Mexico. *Immunology Letters*. 2012;**147**(1-2):41-46. DOI: 10.1016/j.imlet.2012.05.007
- [94] Rincón JF, Cano DL, Morales SJ, Jiménez ML, Cobos RE, Bello JR. The functional PTPN22 C1858T polymorphism confers risk for rheumatoid arthritis in patients from Central Mexico. *Clinical Rheumatology*. 2016;**35**(6):1457-1462. DOI: 10.1007/s10067-016-3223-z
- [95] Ruiz-Noa Y, Padilla-Gutiérrez JR, Hernández-Bello J, et al. Association of PTPN22 haplotypes (-1123G>C/+1858C>T) with rheumatoid arthritis in Western Mexican population. *International Journal of Genomics*. 2017; **2017**:8753498. DOI: 10.1155/2017/8753498
- [96] Orozco G, Sánchez E, González-Gay MA, et al. Association of a functional single-nucleotide polymorphism of PTPN22, encoding lymphoid protein phosphatase, with rheumatoid arthritis and systemic lupus erythematosus. *Arthritis and Rheumatism*. 2005;**52**(1):219-224. DOI: 10.1002/art.20771

- [97] Ates A, Karaaslan Y, Karatayli E, et al. Association of the PTPN22 gene polymorphism with autoantibody positivity in Turkish rheumatoid arthritis patients. *Tissue Antigens*. 2011; **78**(1):56-59. DOI: 10.1111/j.1399-0039.2011.01675.x
- [98] Li Q, Lin KQ, Li Q, et al. Association of polymorphisms of PTPN22 and PADI4 genes with rheumatoid arthritis in Yunnan. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*. 2013; **30**(1):111-115. DOI: 10.3760/cma.j.issn.1003-9406.2013.01.027
- [99] Tang L, Wang Y, Zheng S, Bao M, Zhang Q, Li J. PTPN22 polymorphisms, but not R620W, were associated with the genetic susceptibility of systemic lupus erythematosus and rheumatoid arthritis in a Chinese Han population. *Human Immunology*. 2016; **77**(8): 692-698. DOI: 10.1016/j.humimm.2016.04.021
- [100] El-Lebedy D, Raslan H, Ibrahim A, Ashmawy I, El-Aziz SA, Mohammed AM. Association of STAT4 rs7574865 and PTPN22 rs2476601 polymorphisms with rheumatoid arthritis and non-systemically reacting antibodies in Egyptian patients. *Clinical Rheumatology*. 2017; **36**(9):1981-1987. DOI: 10.1007/s10067-017-3632-7
- [101] Ahmadloo S, Taghizadeh M, Akhiani M, Salimzadeh A, Keramatipour M. Single Nucleotide Polymorphism rs 2476601 of PTPN22 Gene and Susceptibility to Rheumatoid Arthritis in Iranian Population. *Iranian Journal of Allergy, Asthma, and Immunology*. 2015; **14**(4):437-442
- [102] Song GG, Bae SC, Kim JH, Lee YH. The PTPN22 C1858T polymorphism and rheumatoid arthritis: A meta-analysis. *Rheumatology International*. 2013; **33**(8):1991-1999. DOI: 10.1007/s00296-013-2679-2
- [103] Nabi G, Akhter N, Wahid M, et al. Meta-analysis reveals PTPN22 1858C/T polymorphism confers susceptibility to rheumatoid arthritis in Caucasian but not in Asian population. *Autoimmunity*. 2016; **49**(3):197-210. DOI: 10.3109/08916934.2015.1134514
- [104] Elshazli R, Settin A. Association of PTPN22 rs2476601 and STAT4 rs7574865 polymorphisms with rheumatoid arthritis: A meta-analysis update. *Immunobiology*. 2015; **220**(8): 1012-1024. DOI: 10.1016/j.imbio.2015.04.003
- [105] Nong LM, Ren KW, Xu NW, Zhou D. 1858 C/T polymorphism of the protein tyrosine phosphatase nonreceptor 22 gene and rheumatoid arthritis risk in Europeans: A meta-analysis. *Archives of Medical Research*. 2011; **42**(8):698-702. DOI: 10.1016/j.arcmed.2011.12.001
- [106] Plant D, Flynn E, Mbarek H, et al. Investigation of potential non-HLA rheumatoid arthritis susceptibility loci in a European cohort increases the evidence for nine markers. *Annals of the Rheumatic Diseases*. 2010; **69**(8): 1548-1553. DOI: 10.1136/ard.2009.121020
- [107] Lee YH, Rho YH, Choi SJ, et al. The PTPN22 C1858T functional polymorphism and autoimmune diseases—A meta-analysis. *Rheumatology (Oxford, England)*. 2007; **46**(1):49-56. DOI: 10.1093/rheumatology/kel170
- [108] Jiang Y, Zhang R, Zheng J, et al. Meta-analysis of 125 rheumatoid arthritis-related single nucleotide polymorphisms studied in the past two decades. *PLoS One*. 2012; **7**(12):e51571. DOI: 10.1371/journal.pone.0051571
- [109] Meza-Meza MR, Vizmanos-Lamotte B, Muñoz-Valle JF, et al. Relationship of excess weight with clinical activity and dietary intake deficiencies in systemic lupus erythematosus patients. *Nutrients*.

2019;**11**(11):E2683. Published Nov 6,  
2019. DOI: 10.3390/nu11112683

[110] Carter EE, Barr SG, Clarke AE. The global burden of SLE: Prevalence, health disparities and socioeconomic impact. *Nature Reviews Rheumatology*. 2016; **12**(10):605-620. DOI: 10.1038/nrrheum.2016.137

[111] Mak A, Tay SH. Environmental factors, toxicants and systemic lupus erythematosus. *International Journal of Molecular Sciences*. 2014;**15**(9): 16043-16056. Published Sep 11, 2014. DOI: 10.3390/ijms150916043

[112] Kwon YC, Chun S, Kim K, Mak A. Update on the genetics of systemic lupus erythematosus: genome-wide association studies and beyond. *Cells*. 2019;**8**(10):1180. Published Sep 30, 2019. DOI: 10.3390/cells8101180

[113] Buniello A, MacArthur JAL, Cerezo M, et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics 2019. *Nucleic Acids Research*. 2019;**47**(D1):D1005-D1012. DOI: 10.1093/nar/gky1120

[114] Morris DL, Sheng Y, Zhang Y, et al. Genome-wide association meta-analysis in Chinese and European individuals identifies ten new loci associated with systemic lupus erythematosus. *Nature Genetics*. 2016;**48**(8):940-946. DOI: 10.1038/ng.3603

[115] Sun C, Molineros JE, Looger LL, et al. High-density genotyping of immune-related loci identifies new SLE risk variants in individuals with Asian ancestry. *Nature Genetics*. 2016;**48**(3):323-330. DOI: 10.1038/ng.3496

[116] Kyogoku C, Langefeld CD, Ortmann WA, et al. Genetic association of the R620W polymorphism of protein tyrosine phosphatase PTPN22 with human SLE. *American Journal of*

*Human Genetics*. 2004;**75**(3):504-507. DOI: 10.1086/423790

[117] Kaufman KM, Kelly JA, Herring BJ, et al. Evaluation of the genetic association of the PTPN22 R620W polymorphism in familial and sporadic systemic lupus erythematosus. *Arthritis and Rheumatism*. 2006;**54**(8): 2533-2540. DOI: 10.1002/art.21963

[118] Namjou B, Kim-Howard X, Sun C, et al. PTPN22 association in systemic lupus erythematosus (SLE) with respect to individual ancestry and clinical sub-phenotypes. *PLoS One*. 2013;**8**(8): e69404. DOI: 10.1371/journal.pone.0069404

[119] Eliopoulos E, Zervou MI, Andreou A, et al. Association of the PTPN22 R620W polymorphism with increased risk for SLE in the genetically homogeneous population of Crete. *Lupus*. 2011;**20**(5):501-506. DOI: 10.1177/0961203310392423

[120] Reddy MV, Johansson M, Sturfelt G, et al. The R620W C/T polymorphism of the gene PTPN22 is associated with SLE independently of the association of PDCD1. *Genes and Immunity*. 2005;**6**(8):658-662. DOI: 10.1038/sj.gene.6364252

[121] Piotrowski P, Lianeri M, Wudarski M, Lacki JK, Jagodziński PP. Contribution of the R620W polymorphism of protein tyrosine phosphatase non-receptor 22 to systemic lupus erythematosus in Poland. *Clinical and Experimental Rheumatology*. 2008;**26**(6): 1099-1102

[122] Ostanek L, Ostanek-Pańska M, Bobrowska-Snarska D, et al. PTPN22 1858C>T gene polymorphism in patients with SLE: Association with serological and clinical results. *Molecular Biology Reports*. 2014;**41**(9): 6195-6200. DOI: 10.1007/s11033-014-3498-6



- [123] Moez P, Soliman E. Association of PTPN22 gene polymorphism and systemic lupus erythematosus in a cohort of Egyptian patients: Impact on clinical and laboratory results. *Rheumatology International*. 2012; **32**(9):2753-2758. DOI: 10.1007/s00296-011-2063-z
- [124] Elghzaly AA, Metwally SS, El-Chennawi FA, et al. IRF5, PTPN22, CD28, IL2RA, KIF5A, BLK and TNFAIP3 genes polymorphisms and lupus susceptibility in a cohort from the Egypt Delta; relation to other ethnic groups. *Human Immunology*. 2015; **76**(7):525-531. DOI: 10.1016/j.humimm.2015.06.001
- [125] Lea WW, Lee YH. The association between the PTPN22 C1858T polymorphism and systemic lupus erythematosus: A meta-analysis update. *Lupus*. 2011; **20**(1):51-57. DOI: 10.1177/0961203310381774
- [126] Shi L, Wei Y, Xun W, Han D. Meta-analysis of the correlation between PTPN22 gene polymorphisms and susceptibility to systemic lupus erythematosus. *Asia-Pacific Journal of Public Health*. 2013; **25**(4 Suppl):22S-29S. DOI: 10.1177/1010539513496268
- [127] de Lima SC, Adelino JE, Crovella S, de Azevedo Silva J, Sandrin-Garcia P. PTPN22 1858C>T polymorphism and susceptibility to systemic lupus erythematosus: a meta-analysis update. *Autoimmunity*. 2017; **50**(7):428-434. DOI: 10.1080/08916934.2017.1385774
- [128] Hu LY, Cheng Z, Zhang B, et al. Associations between PTPN22 and TLR9 polymorphisms and systemic lupus erythematosus: A comprehensive meta-analysis. *Archives of Dermatological Research*. 2017; **309**(6): 461-477. DOI: 10.1007/s00403-017-1745-0
- [129] Peng XB, Ou LN. Correlation between PTPN22 gene polymorphism and systemic lupus erythematosus in Chinese Han patients. *Nan Fang Yi Ke Da Xue Xue Bao*. 2010; **30**(10): 2390-2391
- [130] Machado-Contreras JR, Muñoz-Valle JF, Cruz A, Salazar-Camarena DC, Marín-Rosales M, Palafox-Sánchez CA. Distribution of PTPN22 polymorphisms in SLE from western Mexico: correlation with mRNA expression and disease activity. *Clinical and Experimental Medicine*. 2016; **16**(3): 399-406. DOI: 10.1007/s10238-015-0359-0
- [131] Zervou MI, Vazgiourakis VM, Yilmaz N, et al. TRAF1/C5, eNOS, C1q, but not STAT4 and PTPN22 gene polymorphisms are associated with genetic susceptibility to systemic lupus erythematosus in Turkey. *Human Immunology*. 2011; **72**(12): 1210-1213. DOI: 10.1016/j.humimm.2011.09.003
- [132] Aksoy R, Duman T, Keskin O, Düzgün N. No association of PTPN22 R620W gene polymorphism with rheumatic heart disease and systemic lupus erythematosus. *Molecular Biology Reports*. 2011; **38**(8):5393-5396. DOI: 10.1007/s11033-011-0692-7
- [133] Hamza RT, Awwad KS, Temsah KA, Hamed AI. R620W polymorphism of protein tyrosine phosphatase PTPN22 in Egyptian children and adolescents with systemic lupus erythematosus: relation to thyroid autoimmunity. *International Journal of Adolescent Medicine and Health*. 2013; **25**(2):143-149. DOI: 10.1515/ijamh-2013-0022
- [134] Baca V, Velázquez-Cruz R, Salas-Martínez G, Espinosa-Rosales F, Saldaña-Alvarez Y, Orozco L. Association analysis of the PTPN22 gene in childhood-onset systemic lupus erythematosus in Mexican population. *Genes and Immunity*. 2006; **7**(8): 693-695. DOI: 10.1038/sj.gene.6364350

- [135] Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. *Autoimmunity Reviews* 2015; **14**(2):174-180. DOI: 10.1016/j.autrev.2014.10.016
- [136] Tomer Y, Davies TF. Searching for the autoimmune thyroid disease susceptibility genes: from gene mapping to gene function. *Endocrine Reviews*. 2003;**24**(5):694-717. DOI: 10.1210/er.2002-0030
- [137] Tomer Y, Ban Y, Concepcion E, et al. Common and unique susceptibility loci in Graves and Hashimoto diseases: results of whole-genome screening in a data set of 102 multiplex families. *American Journal of Human Genetics*. 2003;**73**(4):736-747. DOI: 10.1086/378588
- [138] Dultz G, Matheis N, Dittmar M, Röhrig B, Bender K, Kahaly GJ. The protein tyrosine phosphatase non-receptor type 22 C1858T polymorphism is a joint susceptibility locus for immune thyroiditis and autoimmune diabetes. *Thyroid*. 2009;**19**(2):143-148. DOI: 10.1089/thy.2008.0301
- [139] 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. *Endocrine Journal*. 2012;**59**(5):439-445. DOI: 10.1507/endocrj.ej11-0381
- [140] Heward JM, Brand OJ, Barrett JC, Carr-Smith JD, Franklyn JA, Gough SC. Association of PTPN22 haplotypes with Graves' disease. *The Journal of Clinical Endocrinology and Metabolism*. 2007; **92**(2):685-690. DOI: 10.1210/jc.2006-2064
- [141] Gu LQ, Zhu W, Zhao SX, et al. Clinical associations of the genetic variants of CTLA-4, Tg, TSHR, PTPN22, PTPN12 and FCRL3 in patients with Graves' disease. *Clinical Endocrinology*. 2010;**72**(2):248-255. DOI: 10.1111/j.1365-2265.2009.03617.x
- [142] Zhebrun D, Kudryashova Y, Babenko A, et al. Association of PTPN22 1858T/T genotype with type 1 diabetes, Graves' disease but not with rheumatoid arthritis in Russian population. *Aging (Albany, NY)*. 2011;**3**(4):368-373. DOI: 10.18632/aging.100305
- [143] Ban Y, Tozaki T, Taniyama M, et al. Association of the protein tyrosine phosphatase nonreceptor 22 haplotypes with autoimmune thyroid disease in the Japanese population. *Thyroid*. 2010; **20**(8):893-899. DOI: 10.1089/thy.2010.0104
- [144] Ban Y, Tozaki T, Taniyama M, Tomita M, Ban Y. The codon 620 single nucleotide polymorphism of the protein tyrosine phosphatase-22 gene does not contribute to autoimmune thyroid disease susceptibility in the Japanese. *Thyroid*. 2005;**15**(10):1115-1118. DOI: 10.1089/thy.2005.15.1115
- [145] Lee HS, Kang J, Yang S, Kim D, Park Y. Susceptibility influence of a PTPN22 haplotype with thyroid autoimmunity in Koreans. *Diabetes/Metabolism Research and Reviews*. 2011;**27**(8):878-882. DOI: 10.1002/dmrr.1265
- [146] Alkhateeb A, Marzouka NA, Tashtoush R. Variants in PTPN22 and SMOC2 genes and the risk of thyroid disease in the Jordanian Arab population. *Endocrine*. 2013;**44**(3):702-709. DOI: 10.1007/s12020-013-9908-z
- [147] Krupińska J, Urbanowicz W, Kaczmarczyk M, et al. Association between genetic mutations and the development of autoimmune thyroiditis in patients with chronic hepatitis C treated with interferon alpha. *Thyroid Research*. 2012;**5**(1):10. DOI: 10.1186/1756-6614-5-10

- [148] López-Cano DJ, Cadena-Sandoval D, Beltrán-Ramírez O, et al. The PTPN22 R263Q polymorphism confers protection against systemic lupus erythematosus and rheumatoid arthritis, while PTPN22 R620W confers susceptibility to Graves' disease in a Mexican population. *Inflammation Research*. 2017;**66**(9):775-781. DOI: 10.1007/s00011-017-1056-0
- [149] Wawrusiewicz-Kurylonek N, Koper-Lenkiewicz OM, Gościk J, Myśliwiec J, Pawłowski P, Krętowski AJ. Association of PTPN22 polymorphism and its correlation with Graves' disease susceptibility in Polish adult population- A preliminary study. *Molecular Genetics & Genomic Medicine*. 2019;**7**(6):e661. DOI: 10.1002/mgg3.661
- [150] Skórka A, Bednarczyk T, Bar-Andziak E, Nauman J, Ploski R. Lymphoid tyrosine phosphatase (PTPN22/LYP) variant and Graves' disease in a Polish population: association and gene dose-dependent correlation with age of onset. *Clinical Endocrinology*. 2005;**62**(6):679-682. DOI: 10.1111/j.1365-2265.2005.02279.x
- [151] Velaga MR, Wilson V, Jennings CE, et al. The codon 620 tryptophan allele of the lymphoid tyrosine phosphatase (LYP) gene is a major determinant of Graves' disease. *The Journal of Clinical Endocrinology and Metabolism*. 2004;**89**(11):5862-5865. DOI: 10.1210/jc.2004-1108
- [152] Smyth D, Cooper JD, Collins JE, et al. Replication of an association between the lymphoid tyrosine phosphatase locus (LYP/PTPN22) with type 1 diabetes, and evidence for its role as a general autoimmunity locus. *Diabetes*. 2004;**53**(11):3020-3023. DOI: 10.2337/diabetes.53.11.3020
- [153] Xue L, Pan C, Gu Z, et al. Genetic heterogeneity of susceptibility gene in different ethnic populations: Refining association study of PTPN22 for Graves' disease in a Chinese Han population. *PLoS One*. 2013;**8**(12):e84514. DOI: 10.1371/journal.pone.0084514
- [154] Jurecka-Lubieniecka B, Ploski R, Kula D, et al. Association between age at diagnosis of Graves' disease and variants in genes involved in immune response. *PLoS One*. 2013;**8**(3):e59349. DOI: 10.1371/journal.pone.0059349
- [155] Shehjar F, Afroze D, Misgar RA, Malik SA, Laway BA. PTPN22 1858 C/T exon polymorphism is not associated with graves' disease in Kashmiri population. *Indian Journal of Endocrinology and Metabolism*. 2018;**22**(4):457-460. DOI: 10.4103/ijem.IJEM\_105\_18
- [156] Jacobson EM, Tomer Y. The genetic basis of thyroid autoimmunity. *Thyroid*. 2007;**17**(10):949-961. DOI: 10.1089/thy.2007.0153
- [157] Gong L, Liu B, Wang J, et al. Novel missense mutation in PTPN22 in a Chinese pedigree with Hashimoto's thyroiditis. *BMC Endocrine Disorders*. 2018;**18**(1):76. Published Nov 1, 2018. DOI: 10.1186/s12902-018-0305-8
- [158] Strober W, Fuss I, Mannon P. The fundamental basis of inflammatory bowel disease. *The Journal of Clinical Investigation*. 2007;**117**(3):514-521. DOI: 10.1172/JCI30587
- [159] Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. *Nature*. 2007;**448**(7152):427-434. DOI: 10.1038/nature06005
- [160] Kim ES, Kim WH. Inflammatory bowel disease in Korea: Epidemiological, genomic, clinical, and therapeutic characteristics. *Gut and Liver*. 2010;**4**:1-14
- [161] Waterman M, Xu W, Stempak JM, et al. Distinct and overlapping genetic loci in Crohn's disease and ulcerative

colitis: Correlations with pathogenesis. Inflammatory Bowel Diseases. 2011;17:1936-1942

[162] Al-Meghaiseb ES, Al-Robayan AA, Al-Otaibi MM, Arfin M, Al-Asmari AK. Association of tumor necrosis factor- $\alpha$  and - $\beta$  gene polymorphisms in inflammatory bowel disease. Journal of Inflammation Research. 2016;9:133-140. DOI: 10.2147/JIR.S101225

[163] Sfar I, Ben Aleya W, Mouelhi L, et al. Lymphoid tyrosine phosphatase R620W variant and inflammatory bowel disease in Tunisia. World Journal of Gastroenterology. 2010;16(4):479-483. DOI: 10.3748/wjg.v16.i4.479

[164] Hedjoudje A, Cheurfa C, Briquez C, Zhang A, Koch S, Vuitton L. rs2476601 polymorphism in *PTPN22* is associated with Crohn's disease but not with ulcerative colitis: A meta-analysis of 16,838 cases and 13,356 controls. Annals of Gastroenterology. 2017;30(2):197-208. DOI: 10.20524/aog.2017.0121

[165] Diaz-Gallo LM, Espino-Paisán L, Fransen K, et al. Differential association of two *PTPN22* coding variants with Crohn's disease and ulcerative colitis. Inflammatory Bowel Diseases. 2011;17(11):2287-2294. DOI: 10.1002/ibd.21630

[166] Begovich AB, Carlton VE, Honigberg LA, et al. A missense single-nucleotide polymorphism in a gene encoding a protein tyrosine phosphatase (*PTPN22*) is associated with rheumatoid arthritis. American Journal of Human Genetics. 2004;75(2):330-337. DOI: 10.1086/422827

[167] Zaid Y, Senhaji N, Bakhtaoui FZ, et al. The *PTPN22* C1858T (R620W) functional polymorphism in inflammatory bowel disease. BMC Research Notes. 2018;11(1):783. DOI: 10.1186/s13104-018-3875-7

[168] Morgan AR, Han DY, Huebner C, Lam WJ, Fraser AG, Ferguson LR.

*PTPN2* but not *PTPN22* is associated with Crohn's disease in a New Zealand population. Tissue Antigens. 2010;76(2):119-125. DOI: 10.1111/j.1399-0039.2010.01493.x

[169] Hradsky O, Lenicek M, Dusatkova P, et al. Variants of *CARD15*, *TNFA* and *PTPN22* and susceptibility to Crohn's disease in the Czech population: high frequency of the *CARD15* 1007fs. Tissue Antigens. 2008;71(6):538-547. DOI: 10.1111/j.1399-0039.2008.01047.x

[170] van Oene M, Wintle RF, Liu X, et al. Association of the lymphoid tyrosine phosphatase R620W variant with rheumatoid arthritis, but not Crohn's disease, in Canadian populations. Arthritis and Rheumatism. 2005;52(7):1993-1998. DOI: 10.1002/art.21123

[171] De Jager PL, Sawcer S, Waliszewska A, et al. Evaluating the role of the 620W allele of protein tyrosine phosphatase *PTPN22* in Crohn's disease and multiple sclerosis. European Journal of Human Genetics. 2006;14(3):317-321. DOI: 10.1038/sj.ejhg.5201548

[172] Prescott NJ, Fisher SA, Onnie C, et al. A general autoimmunity gene (*PTPN22*) is not associated with inflammatory bowel disease in a British population. Tissue Antigens. 2005;66(4):318-320. DOI: 10.1111/j.1399-0039.2005.00494.x

[173] Martín MC, Oliver J, Urcelay E, et al. The functional genetic variation in the *PTPN22* gene has a negligible effect on the susceptibility to develop inflammatory bowel disease. Tissue Antigens. 2005;66(4):314-317. DOI: 10.1111/j.1399-0039.2005.00428.x

[174] Wagenleiter SE, Klein W, Griga T, Schmiegel W, Epplen JT, Jagiello P. A case-control study of tyrosine phosphatase (*PTPN22*) confirms the lack of association with Crohn's disease. International Journal of

Immunogenetics. 2005;**32**(5):323-324. DOI: 10.1111/j.1744-313X.2005.00534.x

[175] Latiano A, Palmieri O, Valvano MR, et al. Evaluating the role of the genetic variations of PTPN22, NFKB1, and FcGR11A genes in inflammatory bowel disease: A meta-analysis. *Inflammatory Bowel Diseases*. 2007;**13**(10):1212-1219. DOI: 10.1002/ibd.20185

[176] Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Research and Clinical Practice*. 2014;**103**(2):137-149. DOI: 10.1016/j.diabres.2013.11.002

[177] International Diabetes Federation. *IDF Diabetes Atlas*. 8th ed. Brussels, Belgium: International Diabetes Federation; 2017. <http://www.diabetesatlas.org>

[178] Pei Z, Chen X, Sun C, et al. A novel single nucleotide polymorphism in the protein tyrosine phosphatase N22 gene (PTPN22) is associated with Type 1 diabetes in a Chinese population. *Diabetic Medicine*. 2014;**31**(2):219-226. DOI: 10.1111/dme.12331

[179] Giza S, Goulas A, Gbandi E, et al. The role of PTPN22 C1858T gene polymorphism in diabetes mellitus type 1: First evaluation in Greek children and adolescents. *BioMed Research International*. 2013;**721604**:2013. DOI: 10.1155/2013/721604

[180] Baniyasi V, Das SN. No evidence for association of PTPN22 R620W functional variant C1858T with type 1 diabetes in Asian Indians. *Journal of Cellular and Molecular Medicine*. 2008;**12**(3):1061-1062. DOI: 10.1111/j.1582-4934.2008.00222.x

[181] Almasi S, Aliparasti MR, Yazdchi-Marandi L, et al. Analysis of PTPN22 C1858T gene polymorphism in cases

with type 1 diabetes of Azerbaijan, Northwest Iran. *Cellular Immunology*. 2014;**292**(1-2):14-18. DOI: 10.1016/j.cellimm.2014.08.007

[182] Prezioso G, Comegna L, Di Giulio C, Franchini S, Chiarelli F, Blasetti A. C1858T polymorphism of protein tyrosine phosphatase non-receptor type 22 (PTPN22): An eligible target for prevention of type 1 diabetes?. *Expert Review of Clinical Immunology* 2017;**13**(3):189-196. DOI: 10.1080/1744666X.2017.1266257

[183] Kawasaki E, Awata T, Ikegami H, et al. Systematic search for single nucleotide polymorphisms in a lymphoid tyrosine phosphatase gene (PTPN22): Association between a promoter polymorphism and type 1 diabetes in Asian populations. *American Journal of Medical Genetics. Part A*. 2006;**140**(6):586-593. DOI: 10.1002/ajmg.a.31124

[184] Alswat KA, Nasr A, Al Dubayee MS, et al. The potential role of PTPN-22 C1858T gene polymorphism in the pathogenesis of type 1 diabetes in Saudi population. *Immunological Investigations*. 2018;**47**(5):521-533. DOI: 10.1080/08820139.2018.1458109

[185] Kahles H, Ramos-Lopez E, Lange B, Zwermann O, Reincke M, Badenhoop K. Sex-specific association of PTPN22 1858T with type 1 diabetes but not with Hashimoto's thyroiditis or Addison's disease in the German population. *European Journal of Endocrinology*. 2005;**153**(6):895-899. DOI: 10.1530/eje.1.02035

[186] Abdelrahman HM, Sherief LM, Abd Elrahman DM, Alghobashy A, Elsaadani HF, Mohamed RH. The association of PTPN22 (rs2476601) and IL2RA (rs11594656) polymorphisms with T1D in Egyptian children. *Human Immunology*. 2016;**77**(8):682-686. DOI: 10.1016/j.humimm.2016.06.006

- [187] El Fotoh WMMA, El Razek Midan DA, El Shalakany AH. Role of C1858T polymorphism of Lymphoid Tyrosine Phosphatase in Egyptian children and adolescents with type 1. *Current Diabetes Reviews*. 2018;**10**:2174. DOI: 10.2174/1573399814666180709102533
- [188] Haider MZ, Rasoul MA, Al-Mahdi M, Al-Kandari H, Dhaunsi GS. Association of protein tyrosine phosphatase non-receptor type 22 gene functional variant C1858T, HLA-DQ/DR genotypes and autoantibodies with susceptibility to type-1 diabetes mellitus in Kuwaiti Arabs. *PLoS One*. 2018;**13**(6): e0198652. Published Jun 20, 2018. DOI: 10.1371/journal.pone.0198652
- [189] Liu HW, Xu RY, Sun RP, et al. Association of PTPN22 gene polymorphism with type 1 diabetes mellitus in Chinese children and adolescents. *Genetics and Molecular Research*. 2015;**14**(1):63-68. DOI: 10.4238/2015.January.15.8
- [190] Mainardi-Novo DT, Santos AS, Fukui RT, et al. The PTPN22 1858T allele but not variants in the proximal promoter region of IL-21 gene is associated with the susceptibility to type 1 diabetes and the presence of autoantibodies in a Brazilian cohort. *Clinical and Experimental Immunology*. 2013;**172**(1):16-22. DOI: 10.1111/cei.12030
- [191] Tavares NA, Santos MM, Moura R, et al. Association of TNF- $\alpha$ , CTLA4, and PTPN22 polymorphisms with type 1 diabetes and other autoimmune diseases in Brazil. *Genetics and Molecular Research*. 2015;**14**(4):18936-18944. DOI: 10.4238/2015.December.28.42
- [192] Fichna M, Zurawek M, Januszkiewicz-Lewandowska D, Fichna P, Nowak J. PTPN22, PDCD1 and CYP27B1 polymorphisms and susceptibility to type 1 diabetes in Polish patients. *International Journal of Immunogenetics*. 2010;**37**(5):367-372. DOI: 10.1111/j.1744-313X.2010.00935.x
- [193] Pawłowicz M, Filipów R, Krzykowski G, et al. Coincidence of PTPN22 c.1858CC and FCRL3 -169CC genotypes as a biomarker of preserved residual  $\beta$ -cell function in children with type 1 diabetes. *Pediatric Diabetes*. 2017;**18**(8):696-705. DOI: 10.1111/pedi.12429
- [194] Lavrikova EI, Nikitin AG, Seregin IA, et al. Association of the C1858T polymorphism of the PTPN22 gene with type 1 diabetes. *Molekuliarnaia Biologiya (Mosk)*. 2009;**43**(6):1040-1043
- [195] Korolija M, Renar IP, Hadzija M, et al. Association of PTPN22 C1858T and CTLA-4 A49G polymorphisms with type 1 diabetes in croatians. *Diabetes Research and Clinical Practice*. 2009;**86**(3):e54-e57. DOI: 10.1016/j.diabres.2009.09.012
- [196] Törn C, Hadley D, Lee HS, et al. Role of type 1 diabetes-associated SNPs on risk of autoantibody positivity in the TEDDY study. *Diabetes*. 2015;**64**(5): 1818-1829. DOI: 10.2337/db14-1497
- [197] Blasetti A, Di Giulio C, Tumini S, et al. Role of the C1858T polymorphism of protein tyrosine phosphatase non-receptor type 22 (PTPN22) in children and adolescents with type 1 diabetes. *The Pharmacogenomics Journal*. 2017;**17**(2):186-191. DOI: 10.1038/tpj.2016.6
- [198] Douroudis K, Prans E, Haller K, et al. Protein tyrosine phosphatase non-receptor type 22 gene variants at position 1858 are associated with type 1 and type 2 diabetes in Estonian population. *Tissue Antigens*. 2008;**72**(5):425-430. DOI: 10.1111/j.1399-0039.2008.01115.x
- [199] Saccucci P, Del Duca E, Rapini N, et al. Association between PTPN22 C1858T and type 1 diabetes: a replication in continental Italy. *Tissue*

Antigens. 2008;**71**(3):234-237. DOI: 10.1111/j.1399-0039.2007.00987.x

[200] Santiago J, Martinez A, de la Calle H, Fernandez-Arquero M, Figueredo MA, de la Concha E, et al. Susceptibility to type 1 diabetes conferred by the PTPN22 C1858T polymorphism in the Spanish population. *BMC Medical Genetics*. 2007;**8**:54

[201] Steck AK, Liu SY, McFann K, et al. Association of the PTPN22/LYP gene with type 1 diabetes. *Pediatric Diabetes*. 2006;**7**(5):274-278. DOI: 10.1111/j.1399-5448.2006.00202.x

[202] Rodríguez A, Alfaro JM, Balthazar V, Pineda TN. Association analysis of PTPN22, CTLA4 and IFIH1 genes with type 1 diabetes in Colombian families. *Journal of Diabetes*. 2015;**7**(3): 402-410. DOI: 10.1111/1753-0407.12192

[203] Nielsen LB, Pörksen S, Andersen ML, et al. The PTPN22 C1858T gene variant is associated with proinsulin in new-onset type 1 diabetes. *BMC Medical Genetics*. 2011;**12**:41. DOI: 10.1186/1471-2350-12-41

[204] Xuan C, Lun LM, Zhao JX, et al. PTPN22 gene polymorphism (C1858T) is associated with susceptibility to type 1 diabetes: A meta-analysis of 19,495 cases and 25,341 controls. *Annals of Human Genetics*. 2013;**77**(3):191-203. DOI: 10.1111/ahg.12016

[205] Wang XF, Chen ZX, Shao YC, et al. Population-based and family-based studies on the protein tyrosine phosphatase non-receptor 22 gene polymorphism and type 1 diabetes: A meta-analysis. *Gene*. 2013;**517**(2): 191-196. DOI: 10.1016/j.gene.2012.12.076

[206] Lee YH, Song GG. Meta-analysis of the family-based association between the PTPN22 C1858T polymorphism and type 1 diabetes. *Molecular Biology*

*Reports*. 2013;**40**(1):211-215. DOI: 10.1007/s11033-012-2051-8

[207] Peng H, Zhou M, Xu WD, et al. Association of PTPN22 C1858T polymorphism and type 1 diabetes: A meta-analysis. *Immunological Investigations*. 2012;**41**(5):484-496. DOI: 10.3109/08820139.2012.664226

[208] Ramu D, Perumal V, Paul SFD. Association of common type 1 and type 2 diabetes gene variants with latent autoimmune diabetes in adults: A meta-analysis. *Journal of Diabetes*. 2019; **11**(6):484-496. DOI: 10.1111/1753-0407.12879

[209] Dong F, Yang G, Pan HW, et al. The association of PTPN22 rs2476601 polymorphism and CTLA-4 rs231775 polymorphism with LADA risks: A systematic review and meta-analysis. *Acta Diabetologica*. 2014;**51**(5):691-703. DOI: 10.1007/s00592-014-0613-z

[210] Kumar N, Kaur G, Kanga U, Tandon N, Caillat-Zucman S, Mehra NK. Association of PTPN22 +1858C/T polymorphism with Type 1 diabetes in the North Indian population. *International Journal of Immunogenetics*. 2014;**41**(4):318-323. DOI: 10.1111/iji.12129

[211] Habib T, Funk A, Rieck M, et al. Altered B cell homeostasis is associated with type I diabetes and carriers of the PTPN22 allelic variant. *Journal of Immunology*. 2012;**188**(1):487-496. DOI: 10.4049/jimmunol.1102176

[212] Duty JA, Szodoray P, Zheng NY, et al. Functional anergy in a subpopulation of naive B cells from healthy humans that express autoreactive immunoglobulin receptors. *The Journal of Experimental Medicine*. 2009;**206**(1):139-151. DOI: 10.1084/jem.20080611

[213] Sobolewski P, Maślińska M, Wiczorek M, et al. Systemic

- sclerosis—multidisciplinary disease: Clinical features and treatment. *Reumatologia*. 2019;**57**(4):221-233. DOI: 10.5114/reum.2019.87619
- [214] Diaz-Gallo LM, Gourh P, Broen J, et al. Analysis of the influence of PTPN22 gene polymorphisms in systemic sclerosis [published correction appears in *Ann Rheum Dis*. 2011 Aug;**70**(8):1520]. *Annals of the Rheumatic Diseases*. 2011;**70**(3):454-462. DOI: 10.1136/ard.2010.130138
- [215] Agarwal SK, Tan FK, Arnett FC. Genetics and genomic studies in scleroderma (systemic sclerosis). *Rheumatic Disease Clinics of North America*. 2008;**34**(1):17-v. DOI: 10.1016/j.rdc.2007.10.001
- [216] Dieudé P, Guedj M, Wipff J, et al. The PTPN22 620W allele confers susceptibility to systemic sclerosis: findings of a large case-control study of European Caucasians and a meta-analysis. *Arthritis and Rheumatism*. 2008;**58**(7):2183-2188. DOI: 10.1002/art.23601
- [217] Gourh P, Tan FK, Assassi S, et al. Association of the PTPN22 R620W polymorphism with anti-topoisomerase I- and anticentromere antibody-positive systemic sclerosis. *Arthritis and Rheumatism*. 2006;**54**(12):3945-3953. DOI: 10.1002/art.22196
- [218] Wipff J, Allanore Y, Kahan A, et al. Lack of association between the protein tyrosine phosphatase non-receptor 22 (PTPN22)\*620W allele and systemic sclerosis in the French Caucasian population. *Annals of the Rheumatic Diseases*. 2006;**65**(9):1230-1232. DOI: 10.1136/ard.2005.048181
- [219] Balada E, Simeón-Aznar CP, Serrano-Acedo S, et al. Lack of association of the PTPN22 gene polymorphism R620W with systemic sclerosis. *Clinical and Experimental Rheumatology*. 2006;**24**(3):321-324
- [220] Burns TM. History of outcome measures for myasthenia gravis. *Muscle & Nerve*. 2010;**42**(1):5-13. DOI: 10.1002/mus.21713
- [221] Xiong X, Xiang M, Cheng X, Huang Y. PTPN22 R620W polymorphism is associated with myasthenia gravis risk: A systematic review and meta-analysis. *Medical Science Monitor*. 2015;**21**:2567-2571. DOI: 10.12659/MSM.894307
- [222] Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. *Lancet Neurology*. 2009;**8**(5):475-490. DOI: 10.1016/S1474-4422(09)70063-8
- [223] Olate S, Muñoz D, Neumann S, Pozzer L, Cavalieri-Pereira L, de Moraes M. A descriptive study of the oral status in subjects with Sjögren's syndrome. *International Journal of Clinical and Experimental Medicine*. 2014;**7**(4):1140-1144
- [224] Wahono CS, Rusmini H, Soelistyoningsih D, et al. Effects of 1,25(OH)2D3 in immune response regulation of systemic lupus erythematosus (SLE) patient with hypovitamin D. *International Journal of Clinical and Experimental Medicine*. 2014;**7**:22-31
- [225] Yuksel S, Pancar Yuksel E, et al. Abnormal nail fold capillaroscopic findings in patients with coronary slow flow phenomenon. *International Journal of Clinical and Experimental Medicine*. 2014;**7**:1052-1058
- [226] Deitiker PR, Oshima M, Smith RG, et al. Association with HLA DQ of early onset myasthenia gravis in Southeast Texas region of the United States. *International Journal of Immunogenetics*. 2011;**38**:55-62
- [227] Nikolic AV, Andric ZP, Simonovic RB, et al. High frequency of



DQB1\*05 and absolute absence of DRB1\*13 in muscle-specific tyrosine kinase positive myasthenia gravis. *European Journal of Neurology*. 2015; **22**(1):59-63

[228] Lefvert AK, Zhao Y, Ramanujam R, Yu S, Pirskanen R, Hammarström L. PTPN22 R620W promotes production of anti-AChR autoantibodies and IL-2 in myasthenia gravis. *Journal of Neuroimmunology*. 2008;**197**(2): 110-113. DOI: 10.1016/j.jneuroim.2008.04.004

[229] Chuang WY, Ströbel P, Belharazem D, et al. The PTPN22 gain-of-function+1858T(+) genotypes correlate with low IL-2 expression in thymomas and predispose to myasthenia gravis. *Genes and Immunity*. 2009;**10**(8):667-672. DOI: 10.1038/gene.2009.64

[230] Gregersen PK, Kosoy R, Lee AT, et al. Risk for myasthenia gravis maps to a (151) Pro→Ala change in TNIP1 and to human leukocyte antigen-B\*08. *Annals of Neurology*. 2012;**72**(6):927-935. DOI: 10.1002/ana.23691

[231] Greve B, Hoffmann P, Illes Z, et al. The autoimmunity-related polymorphism PTPN22 1858C/T is associated with anti-titin antibody-positive myasthenia gravis. *Human Immunology*. 2009;**70**(7): 540-542. DOI: 10.1016/j.humimm.2009.04.027

[232] Vandiedonck C, Capdevielle C, Giraud M, et al. Association of the PTPN22\*R620W polymorphism with autoimmune myasthenia gravis. *Annals of Neurology*. 2006;**59**(2):404-407. DOI: 10.1002/ana.20751

[233] Provenzano C, Ricciardi R, Scuderi F, et al. PTPN22 and myasthenia gravis: replication in an Italian population and meta-analysis of literature data. *Neuromuscular Disorders*. 2012;**22**(2):131-138. DOI: 10.1016/j.nmd.2011.09.003

[234] Kaya GA, Coşkun AN, Yılmaz V, et al. The association of PTPN22 R620W polymorphism is stronger with late-onset AChR-myasthenia gravis in Turkey. *PLoS One*. 2014;**9**(8):e104760. Published Aug 13, 2014. DOI: 10.1371/journal.pone.0104760

[235] Seldin MF, Alkhairy OK, Lee AT, et al. Genome-wide association study of late-onset myasthenia gravis: Confirmation of *TNFRSF11A* and identification of *ZBTB10* and three distinct HLA associations. *Molecular Medicine*. 2016;**21**(1):769-781. DOI: 10.2119/molmed.2015.00232

[236] Cho SB, Cho S, Bang D. New insights in the clinical understanding of Behçet's disease. *Yonsei Medical Journal*. 2012;**53**(1):35-42. DOI: 10.3349/ymj.2012.53.1.35

[237] Al-Okaily F, Arfin M, Al-Rashidi S, Al-Balawi M, Al-Asmari A. Inflammation-related cytokine gene polymorphisms in Behçet's disease. *Journal of Inflammation Research*. 2015; **8**:173-180. DOI: 10.2147/JIR.S89283

[238] Davatchi F, Chams-Davatchi C, Shams H, et al. Behçet's disease: Epidemiology, clinical manifestations, and diagnosis. *Expert Review of Clinical Immunology*. 2017;**13**(1):57-65. DOI: 10.1080/1744666X.2016.1205486

[239] Kaya Tİ. Genetics of Behçet's disease. *Pathology Research International*. 2012;**2012**:912589. DOI: 10.1155/2012/912589

[240] Al-Okaily F, Al-Rashidi S, Al-Balawi M, Mustafa M, Arfin M, Al-Asmari A. Genetic association of HLA-A\*26, -A\*31, and -B\*51 with Behçet's disease in Saudi patients. *Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders*. 2016;**9**: 167-173. DOI: 10.4137/CMAMD.S39879

[241] Baranathan V, Stanford MR, Vaughan RW, et al. The association of the PTPN22 620W polymorphism with

Behçet's disease. *Annals of the Rheumatic Diseases*. 2007;**66**(11): 1531-1533. DOI: 10.1136/ard.2007.073866

[242] Sahin N, Bicakcigil M, Atagunduz P, Direskeneli H, Saruhan-Direskeneli G. PTPN22 gene polymorphism in Behçet's disease. *Tissue Antigens*. 2007;**70**(5):432-434. DOI: 10.1111/j.1399-0039.2007.00928.x

[243] Ortiz-Fernández L, Montes-Cano MA, García-Lozano JR, et al. PTPN22 is not associated with Behçet's disease. Study spanning the complete gene region in the Spanish population and meta-analysis of the functional variant R620W. *Clinical and Experimental Rheumatology*. 2016;**34**(6 Suppl 102): S41-S45

[244] Giudice LC, Kao LC. Endometriosis. *Lancet*. 2004; **364**(9447):1789-1799. DOI: 10.1016/S0140-6736(04)17403-5

[245] Cramer DW, Missmer SA. The epidemiology of endometriosis. *Annals of the New York Academy of Sciences*. 2002;**955**:11-406. DOI: 10.1111/j.1749-6632.2002.tb02761.x

[246] Pabalan N, Jarjanazi H, Christofolini DM, Bianco B, Barbosa CP. Association of the protein tyrosine phosphatase non-receptor 22 polymorphism (PTPN22) with endometriosis: A meta-analysis. *Einstein (Sao Paulo)*. 2017;**15**(1):105-111. DOI: 10.1590/S1679-45082017RW3827

[247] Bianco B, André GM, Vilarino FL, et al. The possible role of genetic variants in autoimmune-related genes in the development of endometriosis. *Human Immunology*. 2012;**73**(3): 306-315. DOI: 10.1016/j.humimm.2011.12.009

[248] Płoski R, Dziunycz P, Kostrzewa G, Roszkowski PI, Barcz E, Zabek J, et al. PTPN22/LYP 1858C>T gene polymorphism and susceptibility to

endometriosis in a Polish population. *Journal of Reproductive Immunology*. 2009;**79**(2):196-200

[249] Vang T, Miletic AV, Bottini N, Mustelin T. Protein tyrosine phosphatase PTPN22 in human autoimmunity. *Autoimmunity*. 2007; **40**(6):453-461 (Review)

[250] Gregersen PK. Gaining insight into PTPN22 and autoimmunity. *Nature Genetics*. 2005;**37**(12):1300-1302

[251] Gregersen PK, Lee HS, Batliwalla F, Begovich AB. PTPN22: setting thresholds for autoimmunity. *Seminars in Immunology*. 2006;**18**(4):214-223. (Review)

[252] Ammendola M, Bottini N, Pietropolli A, Saccucci P, Gloria-Bottini F. Association between PTPN22 and endometriosis. *Fertility and Sterility*. 2008;**89**(4):993-994. DOI: 10.1016/j.fertnstert.2007.04.008

[253] Gloria-Bottini F, Ammendola M, Saccucci P, Pietropolli A, Magrini A, Bottini E. The association of PTPN22 polymorphism with endometriosis: Effect of genetic and clinical factors. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*. 2013;**169**(1):60-63

[254] Gloria-Bottini F, Ammendola M, Saccucci P, Neri A, Magrini A, Bottini E. The effect of ACP1, ADA6 and PTPN22 genetic polymorphisms on the association between p53 codon 72 polymorphism and endometriosis. *Archives of Gynecology and Obstetrics*. 2016;**293**(2):399-402. DOI: 10.1007/s00404-015-3827-6

[255] Gomes FM, Bianco B, Teles JS, Christofolini DM, Souza AM de, Guedes AD, et al. PTPN22 C1858T polymorphism in women with endometriosis. *American Journal of Reproductive Immunology*. 2010;**63**(3): 227-232

- [256] Shi L. Anti-neutrophil cytoplasmic antibody-associated vasculitis: Prevalence, treatment, and outcomes. *Rheumatology International*. 2017; **37**(11):1779-1788. DOI: 10.1007/s00296-017-3818-y
- [257] Willcocks LC, Lyons PA, Rees AJ, Smith KG. The contribution of genetic variation and infection to the pathogenesis of ANCA-associated systemic vasculitis. *Arthritis Research & Therapy*. 2010; **12**(1):202. DOI: 10.1186/ar2928
- [258] Alberici F, Martorana D, Vaglio A. Genetic aspects of anti-neutrophil cytoplasmic antibody-associated vasculitis. *Nephrology, Dialysis, Transplantation*. 2015; **30**(Suppl 1):i37-i45. DOI: 10.1093/ndt/gfu386
- [259] Jagiello P, Aries P, Arning L, et al. The PTPN22 620W allele is a risk factor for Wegener's granulomatosis. *Arthritis and Rheumatism*. 2005; **52**(12):4039-4043. DOI: 10.1002/art.21487
- [260] Carr EJ, Niederer HA, Williams J, et al. Confirmation of the genetic association of CTLA4 and PTPN22 with ANCA-associated vasculitis. *BMC Medical Genetics*. 2009; **10**:121. Published Dec 1, 2009. DOI: 10.1186/1471-2350-10-121
- [261] Martorana D, Maritati F, Malerba G, et al. PTPN22 R620W polymorphism in the ANCA-associated vasculitides. *Rheumatology (Oxford, England)*. 2012; **51**(5):805-812. DOI: 10.1093/rheumatology/ker446
- [262] Cao Y, Liu K, Tian Z, et al. PTPN22 R620W polymorphism and ANCA disease risk in white populations: A metaanalysis. *The Journal of Rheumatology*. 2015; **42**(2):292-299. DOI: 10.3899/jrheum.131430
- [263] González-Gay MA, Pina T. Giant cell arteritis and polymyalgia rheumatica: An update. *Current Rheumatology Reports*. 2015; **17**(2):6. DOI: 10.1007/s11926-014-0480-1
- [264] Stanford SM, Bottini N. PTPN22: The archetypal non-HLA autoimmunity gene. *Nature Reviews Rheumatology*. 2014; **10**(10):602-611. DOI: 10.1038/nrrheum.2014.109
- [265] Serrano A, Márquez A, Mackie SL, et al. Identification of the PTPN22 functional variant R620W as susceptibility genetic factor for giant cell arteritis. *Annals of the Rheumatic Diseases*. 2013; **72**(11):1882-1886. DOI: 10.1136/annrheumdis-2013-203641
- [266] Carmona FD, Mackie SL, Martín JE, et al. A large-scale genetic analysis reveals a strong contribution of the HLA class II region to giant cell arteritis susceptibility. *American Journal of Human Genetics*. 2015; **96**(4):565-580. DOI: 10.1016/j.ajhg.2015.02.009
- [267] Lester S, Hewitt AW, Ruediger CD, et al. PTPN22 R620W minor allele is a genetic risk factor for giant cell arteritis. *RMD Open*. 2016; **2**(1):e000246. Published Apr 7, 2016. DOI: 10.1136/rmdopen-2016-000246
- [268] Betterle C, Morlin L. Autoimmune Addison's disease. *Endocrine Development*. 2011; **20**:161-172. DOI: 10.1159/000321239
- [269] Skinningsrud B, Husebye ES, Gervin K, et al. Mutation screening of PTPN22: Association of the 1858T-allele with Addison's disease. *European Journal of Human Genetics*. 2008; **16**(8):977-982. DOI: 10.1038/ejhg.2008.33
- [270] Roycroft M, Fichna M, McDonald D, et al. The tryptophan 620 allele of the lymphoid tyrosine phosphatase (PTPN22) gene predisposes to autoimmune Addison's disease. *Clinical Endocrinology*. 2009; **70**(3):358-362. DOI: 10.1111/j.1365-2265.2008.03380.x