Chapter

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

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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#	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]

#*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[#]	5904/5866	C1858T	No association	[153]

[*] *Meta-analysis.*
[#] *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 exits, 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 Finish 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 PTPT22 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 TPN22C1858T 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.

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Conflict of interest

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