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Genes and Gene Polymorphisms Associated with Henoch-Schönlein purpura

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Abstract: Henoch-Schönlein purpura (HSP) is the most common vasculitis among children, which its overall incidence rate is higher in boys than girls. This syndrome can affect skin, joints, gastrointestinal (GI) tract, kidney and, in rare cases CNS and scrotum. Genetic and environmental factors are considered to be possible triggers. HSP is typically self-limited, and most patients recover without therapy, however, severe intestinal bleeding or intussusception, intermittent hematuria, proteinuria and chronic kidney disease may occur in a small number of cases. In recent years, attempts have been made to identify genetic polymorphisms that may be associated with the development of HSP or with its severity. Many of these evaluated cytokines or cell adhesion molecules involved in the modulation of inflammatory pathways and endothelial cell activation. A few number of research work on a limited number of patients have been done and the results are varying among different ethnic groups. We review association studies on HSP to identify which genes or genetic polymorphisms significantly increase the risk of the disease.

Key words: Henoch-Schönlein purpura, Association, Gene Polymorphism

INTRODUCTION

Henoch-Schönlein purpura (HSP) is the most common childhood small vessel vasculitis (He X. et al., 2012). Due to presence of immunoglobulin A (IgA)-immune complex deposition in tissue it is also known as IgA vacuities (Audemard-Verger A. et al., 2015 ; Rai A. et al. 1999). Although the disease occurs in all ages, it is rare among adults. In children it has an incidence of 10-20 per 100000, while 90% of patients are younger than 10 years (Dillon MJ. et al., 2007 ; Reamy BV. et al., 2009). This auto-inflammatory disease characterized by palpable purpura, abdominal pain, joint and renal impairment or injury. (Dillon MJ. et al., 2007 ; Reamy BV. et al., 2009 ; Daripally VK. et al., 2012 ; Raquel Lo´pez-Mejı´as FG et al., 2015). The majority of patients (94%) have a self-limited disease, but severe intestinal bleeding, leukocytoclasia and also in the long term, severe nephrotic - nephritic syndrome are predictable. (Reamy BV. et al., 2009 ; Daripally VK. et al., 2012 ; Raquel Lo´pez-Mejı´as FG et al., 2015 ; He X. et al., 2013). It has been reported in all populations but Blacks have a lower incidence than Asian and Caucasian. The peak of the disease is varies- winter, autumn, spring- and boys affected more than girls in a 1.2-2 ratio. (He X. et al., 2013 ; Outi J. et al., 2013). The etiology of HSP is not completely understood, but infectious and non-infectious agents such as several bacteria, viruses and protozoa, drugs, vaccination, food and certain toxins like insect bites have been reported as a trigger of the disease. (Outi J. et al., 2013 ; Rigante D. et al., 2013).Furthermore, several reports of occurrence the disease in the members of the same family suggesting genetic basis of the disease. (Outi J. et al., 2013). There are several potential candidates

for genetic causes of disease such as cytokines and cell adhesion molecules involved in inflammatory responses. (Outi J. et al., 2013 ; Rigante D. et al., 2013 ; Dinarello CA. , 2000).

In this review, we summarize the association studies in the literature. In order to find those articles that has assessed the correlation between gene polymorphisms and the incidence or manifestation of HSP, we collected data through PubMed, Rheumatology International and the Google search engine using the following search strategy (gene polymorphisms associated with Henoch-Schönlein purpura). We included all English articles and we focused on HSP and not Henoch-Schönlein purpura nephritis (HSPN), however time of publishing and country were not limited.

Major Histocompatibility Complex (MHC) Gene Family

MHC gene families occur in many species and they are highly polymorphic, due to their main role in presenting processed peptide antigens on cell surface. In human, as they first identified using alloantibody against leukocytes they are called Human Leukocyte Antigen (HLA). (Choo SY. , 2007) They are in cluster form, located on short arm of chromosome 6 and consist of more than 200 genes. This complex is categorized into three basic groups: class I, class II, and class III (Janeway CA Jr TP. et al., 2001 ; Moreland LW. , 2004).

Because of their role in helping immune system recognizing foreign antigen, and their highest level of allelic polymorphism among our entire known genes, they are the principal candidate for increasing incidence of many autoimmune diseases, hence their association with HSP has been investigated and reported in the literature frequently (S.M. Ren GLY, 2012)

MHC class I

Some of these reports have shown the association of MHC-A and -B alleles with HSP. In China, a total of 35 alleles (14 alleles of HLA-A and 21 alleles of HLA- B) between Han (50 cases, 96 controls) and Mongolian (56 cases, 66 controls) population were studied and the result showed HLA-A*11(*1101) and HLA -B*15(*1501) are associated with susceptibility to HSP in Mongolian children and HLA-A*26(*2601), HLA-B*35(*3503) and HLA-B*52 are associated with susceptibility to HSP in Han children. HLA-B*07 and HLA -B*40 may be protective genes in Mongolian children.[15] HLA-A2, -A11, and -B35 in a study in Turkey were significantly increased in patients, while HLA- A1, -B49, and -B50 were significantly decreased. (Peru H. et al., 2008). In Northwest Spain, HLA-B*58 was reported as increasing risk factor for purpuric nephritis, (S.M. Ren GLY., 2012) while in another study on 349 patients HLAB*41:02 had an association with HSP, regardless of patients HLA-DRB1 status (Lopez-Mejias R. , 2015).

MHC class II

MHC class II have been studied in few countries. Some reports have shown the association of HLA- DQB1 and -DRB1 alleles with HSP, including HLA-DQB1*0301 in Han population from Northern China, HLA-DRB1*01 in Northwest Spain, Spanish Caucasian and Italy and DRB1*11 in Italy, India and Turkey, also HLA-DRB1*07 in Italy and Northwest Spain, DRB1*10 and DRB1*17 in Turkey and DRB1*0301 in Spanish Caucasian are reported as protective factors. (S.M. Ren GLY., 2012 ; Amoli MM.et al., 2002 ; Soylemezoglu O. et al., 2008 ; Soylemezoglu O. et al., 2008 ; Amoli MM. et al., 2001 ; Amoroso A.et al., 1997 ; Aggarwal R. et al., 2014 ; Lopez-Mejias R. et al., 2014)

MHC class III

Complement Factor 4 (C4)

C4 is a part of our complement system, which plays an important role in immune system. Complement activation can contribute to inflammation-mediated tissue damage, while complement deficiencies result in the

development of a number of autoimmunity including: HSP and childhood diabetes mellitus (Stefansson Thors V. et al., 2005).

56 patients and 92 controls from Iceland attended the study for analyzing C4 null alleles (C4A*Q0 and C4B*Q0). The result showed a significant increase of the phenotype C4B*Q0 but not C4A*Q0. Frequency of C4 null alleles was not significant neither between HSP patients and controls nor between HSPN and HSP patients (Stefansson Thors V. et al., 2005).

Pro- and Anti-inflammatory genes

Pro-inflammatory cytokines such as interleukin (IL)-1ß, IL-6, and tumor necrosis factor alpha (TNF-α), mainly are producing by activated macrophages. They up-regulate the inflammatory reactions and generally make the disease worse (Dinarello CA. , 2000)

On the contrary, the anti-inflammatory cytokines including: IL-1 receptor antagonist (IL-1RA), IL-4, IL-10, IL-11 and IL-13, regulate the human immune response, reduce inflammation and promote healing. (Dinarello CA. , 2000 ; Choo SY. , 2007 ; Janeway CA Jr TP. et al., 2001 ; Moreland LW. , 2004 ; S.M. Ren GLY. , 2012 ; Amoli MM.et al., 2002 ; Soylemezoglu O. et al., 2008 ; Soylemezoglu O. et al., 2008 ; Amoli MM. et al., 2001 ; Amoroso A.et al., 1997 ; Aggarwal R. et al., 2014 ; Lopez-Mejias R. et al., 2014)

Some cytokines under various conditions can function as pro-inflammatory or anti-inflammatory such as leukemia inhibitory factor (LIF), interferon-alpha (IFN-α), IL-6, and transforming growth factor (TGF)-ß. Specific cytokine receptors for IL-1, TNF-α, and IL-18 also work as suppressors for pro-inflammatory cytokines (Dinarello CA. , 2000 ; Choo SY. , 2007 ; Janeway CA Jr TP. et al., 2001 ; Moreland LW. , 2004 ; S.M. Ren GLY. , 2012 ; Amoli MM.et al., 2002 ; Soylemezoglu O. et al., 2008 ; Soylemezoglu O. et al., 2008 ; Amoli MM. et al., 2001 ; Amoroso A.et al., 1997 ; Aggarwal R. et al., 2014 ; Lopez-Mejias R. et al., 2014 ; Stefansson Thors V. et al., 2005 ; Zhang J-M. et al., 2007)

Mediterranean fever (MEFV) gene

MEFV gene encodes a protein with 781- amino acid known as pyrin (Manukyan G. et al., 2016). Pyrin has a role in the regulation of IL-1ß production and caspase-1 activation, which interacts with a subunit of NF-kappaB, activate it and affect the expression of many genes involved in the innate immune response. Therefore, this gene is an appropriate candidate for association study in auto-inflammatory disorders like HSP (Altug U. et al., 2013)

Several case study research has shown the higher frequency of certain MEFV mutations with HSP. In Turkey, a total of three association research has been done. In the first study in 2008, 80 patients were screened for exon 10 and E148Q mutation of MEFV. The result showed that 34% of them were heterozygous for one of these mutations: M694V, M680I, V726A and E148Q. The edema and arthritis in patients with MEFV mutation were higher than patients without MEFV mutation ($p<0.05$) (Ozcakar ZB. et al., 2008).

Another research group in Turkey investigated on 76 pediatrics. Exon 2 and exon 10 of the MEFV gene were screened by direct sequencing. The total of 25 mutations in 18 patients were founded, which 13 of them were heterozygous and/or compound heterozygous, and 5 were homozygous (Dogan CS. et al., 2013)

Last research was done in 2013. The genome of 68 patients were analyzed for 12 MEFV mutations (E148Q, P369S, F479L, M680I [G/C], M680I [G/A], I692del, M694V, M694I, K695R, V726A, A744S, R761H). 26% of patients had MEFV mutation which among them 22% were heterozygous or compound heterozygous and one

of them was homozygous for E148Q/E148Q mutation. Disease manifestation was significantly higher in patients with MEFV mutation ($p<0.05$) (Altug U. et al., 2013).

In 2010 in China, four MEFV variants (E148Q, P369S, M694V, and M680I) were studied among 78 cases and 189 controls and the result showed E148Q has an association with HSP and joint involvement (He X. et al., 2010).

In one study in Slovenia on 102 Caucasian children with HSP and 105 controls, 6 patients and 7 healthy individuals had the heterozygous mutation. Therefore, no significant difference was found neither in the frequency of the mutations among patients nor in the disease manifestation (Kolnik M TN. et al., 2012).

In Egypt in a study on 60 HSP patients and 30 healthy individuals, MEFV gene were screened for 12 MEFV mutations (E148Q in exon 2, P369S in exon 3, F479L in exon 5, M6801 [G/C], M6801 [G/A], 1692del [2076–2078], M694V, M6941, K695R, V726A, A744S, R761H in exon 10). The result showed that 61.7% of patients had at least one MEFV mutation compared to 36.7% of controls ($p<0.05$). V726A was the most frequent mutation among patients. No significant difference between clinical manifestation were observed (Salah S. et al., 2014)

In Iran, 50 Azeri Turkish patients were studied for M694V, V726A, M680I, and A744S mutations. From 24% with mutation, 22% showed M694V mutation which suggests this allele has higher frequency among Iranian Azeri patients (Nikibakhsh AA. et al., 2012).

Interleukin-8 (IL-8)

IL-8 is a pro-inflammatory chemokine produced by a variety of tissue and blood cells and activates neutrophils inducing: chemotaxis and degranulation. Its role in the pathogenesis of some autoimmune and inflammatory diseases has been reported (Xu H. et al., 2016 ; Bickel M. et al., 1993 ; Waugh DJ. 2008).

There have been few studies that have investigated the association of IL-8 and HSP. In China, 192 patients with HSP and 202 healthy controls were studied for +781 C/T Polymorphism, in Turkey, 115 patients and 108 controls were studied for 2767 A/G polymorphism and in Northwestern Spain, 50 patients and 50 controls were studied. Although none of these research showed significant correlation, in Northwestern Spain and China frequency of allele A in patients with kidney involvement was higher ($p<0.05$) (Xu H. et al., 2016; Tabel Y. et al., 2011 ; Amoli MM. et al., 2002).

interleukin 17 (IL-17)

Among six known types of IL-17, IL-17A and IL-17F are mainly produced by Th17 cells and both known for their function in mediating pro-inflammatory responses. IL-17A has a role in the regulation of local tissue inflammation and immunity to intracellular pathogens, while IL-17F has more function in immunity to extracellular pathogens. They both have been linked to many autoimmune diseases, including rheumatoid arthritis (RA), and HSP (Jin W. et al., 2013 ; Xu H. et al., 2016)

A group of researchers in China studied 148 pediatric patients and 202 healthy individuals which 73 of patients were suffered from HSPN. Three polymorphisms of IL-17A (rs2275913G/A, rs8193037G/A, rs3819025G/A) and two of IL-17F (rs763780C/T, rs9463772C/T) were studied. Among them IL17A rs2275913 AA genotype and A allele was correlated with HSP and A allele of IL-17A (rs3819025) increased risk of HSPN, while IL17A rs2275913 GG genotype showed protective role (Xu H. et al., 2016).

The interleukin-1 receptor antagonist (IL-1ra)

IL-1 is known as a pro-inflammatory cytokine responsible for inflammation. One of the mechanisms of its regulation is IL-1RA, which is a competitive inhibitor of IL-1. The IL-1ra gene is polymorphic, and it has been shown that those who carry both alleles of IL-1ra allele 2 (IL1RN*2) have a more prolonged and severe pro-inflammatory immune response than those with other IL-1ra genotypes (Arend WP. et al., 1998 ; Witkin SS. et al., 2002 ; Krishnan BR., 1999). This has been shown in two unrelated research on HSP. Although, ILRN*2 has shown no association with HSP in Northwest Spain and China, its frequency was higher in patients who developed renal manifestation ($p<0.05$) (Amoli MM. et al., 2002 ; Liu ZH et al., 1997).

Interleukin 1-beta (IL-1ß)

IL-1ß is considered a prototypic multifunctional cytokine that has function in pain, inflammation and autoimmune conditions and plays an important role in various chronic and acute inflammatory diseases (Ren K & Torres R. , 2009 ; Church LD. et al., 2008 ; Li L. et al., 2008).

IL-1ß gene (-511 C/T) in the Northwest Spain among 49 Caucasian patients and 148 controls has shown an association with severe renal manifestation but not HSP (Amoli MM. et al., 2004).

Transforming Growth Factor-beta (TGF-ß)

TGF-ß is a multifunctional cytokine and has role in the control of proliferation and differentiation of several cells. Pathological dysregulation of TGF-ß has been shown to play a critical role in many diseases, including: cancer, atherosclerosis, and some autoimmune diseases (Yang YH et al., 2004 ; Wang W. et al., 2005).

29 patients and 36 controls in Chinese population were studied and the result showed the frequencies of TGF-ß -509 genotypes TT, TC, and CC were significantly different in patients and controls, however, the allelic difference was not significant (Yang YH et al., 2004).

Interferon-Gamma (IFN-γ)

IFN-γ gene consists of four exons and three introns. Among them single nucleotide polymorphism (SNP) at position +874A/T on the first interferon has been identified as a possible binding site for kappa B, which can change the overall expression and secretion of IFN-γ and finally determine the outcome of the infection (Ghasemian N. & Shahbazi M., 2016)

In one study in China, the research group genotyped IFN-γ +874 A/T polymorphism in 97 patients and in 97 control subjects. They could not find any association between IFN-γ +874 A/T gene polymorphism and HSP or HSPN (Xu H. et al., 2014)

Other cytokines such as TNF-α-308 polymorphism in the Chinese population and Interleukin 6 (IL-6) promoter polymorphism at position -174 among Northwest Spain patients have been studied and no correlation has been found (Amoli MM. et al., 2004 ; Wang W. et al., 2005)

Regulation of Endothelial Gene Expression

Endothelial cells are the main regulators in inflammation. Their activation in injury or infection, control the adhesion and migration of inflammatory cells, as well as leaking the fluid out of blood vessels into the damaged tissue. Therefore, mediators that act on endothelial cells, adhesion molecules and cytokines which change its permeability are needed to be tightly regulated to allow for a controlled inflammatory response and are appropriate candidates for association study (Pober JS. et al., 2007; Kadl A. 2005).

Renin-angiotensin system gene (RAS)

RAS is considered as a coordinated hormonal cascade which plays a key role in controlling various functions such as blood pressure. RAS modulate the cellular synthesis of several molecules such as cytokines, chemokines and transcription factors (Capettini LS et al., 2012)

Angiotensin Converting Enzyme (ACE) and Angiotensinogen (AGT)

One of the main RAS regulators is ACE which creates angiotensin II (Ang II). It also has a role in regulating kallikrein-kininogen system by inactivating bradykinin. ACE has an important role in inflammatory process; therefore, it has been widely studied to detect its association with various autoimmune diseases such as HSP (Rashed L. et al., 2015)

AGT is involved in the activation cascade of RAS in response to low blood pressure. Because of affecting the basal transcription rate of AGT, AGT (M235T) polymorphism is known as a functional genotype. Its association with the pathogenesis of several inflammatory and auto- inflammatory diseases has been studied (Shamaa MM. et al., 2015).

In Japan 59 patients with HSPN were studied for ACE DD and non-DD genotypes and the result showed the DD genotype in these patients was significantly higher than the Japanese population as a whole, while other studies from Italy and UK showed no significant correlation neither with HSP nor with HSPN; however, in Italy patients with D/D genotype had a slightly higher rate of proteinuria (Dudley J. et al., 2000 ; Yoshioka T. et al., 1998 ; Amoroso A.et al., 1998).

142 pediatrics and 217 controls from West China were studied for four RAS gene polymorphisms (ACE I/D, M235T (rs699), T174M (rs4762), A1166C) and the result showed the correlation of three of them (ACE I/D, M235T, T174M) with HSP. The group has concluded the AGT gene is consistently correlated with the severity of renal complications. M235T was associated with the severity of renal complication in HSP but not associated with renal involvement. ACE I/D, however, was associated with severity of renal complications and renal involvement (Desong L. et al., 2010)

In Turkey two studies has been done. In the first one, 114 children with HSP and 164 healthy controls were included. They showed that AGT (M235T) polymorphism was significantly different in genotypic frequency and its frequency was higher in patients with renal involvement ($p<0.05$).

In another study 139 pediatrics and 159 controls were studied and the result showed no correlation between AGT M235T and HSP or HSPN. However, it supported those with ACE I/D polymorphism are more susceptible to HSP (Ozkaya O. et al., 2006 ; Nalbantoglu S. et al., 2013)

Nitric Oxide Synthase II (NOS2A)

NOS2A encodes inducible Nitric oxide synthase (iNOS) which play an important role in the pathophysiology of inflammatory diseases and septic shock.

In Northwest Spain, 58 patients and 251 controls were studied for a multi-allelic (CCTTT)n and for the bi-allelic TAAA repeats in the promoter region of NOS2A gene. Patients had significantly higher frequency of the NOS2A CCTTTn alleles compared to controls and this frequency were even more significant comparing HSPN with controls, while NOS2A TAAA repeat polymorphism showed no difference (Martin J. et al., 2005)

Vascular Endothelial Growth Factor (VEGF)

The VEGF gene encodes a protein with the same name which is a potent inducer of capillary permeability and stimulates angiogenesis. Therefore, When VEGF is overexpressed, it can contribute to disease. Its association with HSP has been studied in a few countries (Mortaza Bonyadi EN. et al.,2014 ; Rueda B. et al., 2006)

Thirty Iranian Azeri Turkish pediatrics and fifty healthy individuals attended a study and -634G/C polymorphism of VEGF gene was genotyped. CC genotype in VEGF -634G/C polymorphism showed significant difference (Mortaza Bonyadi EN. et al.,2014).

In another research, 57 patients and 226 controls from Northwest Spain were studied for -1154G→A and -634 G→C VEGF gene polymorphism. No significant differences in the allele or genotype frequencies of both VEGF polymorphisms were observed; however, -1154 G and -634 C alleles showed association with HSPN (Rueda B. et al., 2006).

Table 1: gene polymorphisms associated with HSP

Ethnicity	Polymorphism	Year	Patients (N)	Controls (N)	Association	Manifestation association	Ref
Turkish	HLA-A*02, -A*11	2008	110	250	YES	NO	[16]
Mongolian	HLA -A*1101	2012	56	66	YES	NO	[15]
Han	HLA-A*2601, -B*3503	2012	50	96	YES	SGIB, Edema	[15]
Turkish	HLA-B*3503	2008	110	250	YES	NO	[16]
Spanish	HLA-B*41	2015	349	335	YES	NO	[17]
Mongolian	HLA-B*58	2012	56	66	YES	NO	[15]
Han	HLA-DQB1*0301	2006	NA	NA	YES	NS	[15]
Caucasian	HLA-DRB1*01	2001	50	50	YES	NO	[21]
Caucasian	HLA- DRB1*01	2002	58	145	YES	NS	[18]
Italian	HLA-DRB1*01, - DRB1*11	1997	152	NA	YES	NS	[22]
Turkish	HLA-DRB1*11	2008	110	250	YES	NO	[20]
Indian	HLA -DRB1*11	2014	43	53	YES	GII & RI	[23]
Icelanders	C4B*Q0	2005	56	92	YES	NO	[25]

Chinese	MEFV(E148Q)	2010	78	189	YES	JI	[31]
Egyptian	MEFV(E148Q, M694V, M680I, P369S, A744S, K695R, M694I, F479L, R761H, I692del)	2014	60	30	YES	NO	[32]
Chinese	TGF-ß(C-509T)	2004	29	36	YES	---	[51]
Chinese	ACE I/D	2010	142	217	YES	RI	[63]
Turkish	ACE I/D	2013	139	159	YES	NO	[65]
Chinese	AGT, M235T	2010	142	217	YES	NO	[63]
Caucasian	NOS2A, (CCTTT)n	2005	58	251	YES	RI	[66]
Azeri	VEGF(-634G/C)	2014	50	---	YES, CC	NO	[67]
Turkish	PON1(Q/R192)	2009	46	28	YES, QQ	NO	[69]
Chinese	IL-17 (rs2275913)	2016	146	202	YES, AA, A	NO	[41]

MHC, major histocompatibility complex; MEFV, Mediterranean fever gene; IL, interleukin; IL-1ra, the interleukin-1 receptor antagonist, TGF-ß, transforming growth factor-beta; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor alpha, ACE, angiotensin converting enzyme; AGT, angiotensinogen; NOS2A, nitric oxide synthase II; VEGF, vascular endothelial growth factor; N, number; Ref, reference; GII, gastrointestinal involvement; SGIB, severe gastrointestinal bleeding; RI, renal involvement; JI, joint involvement; NA, not available; NS, not studied.

Paraoxonase 1 (PON1)

The PON1 gene encodes PON1 enzyme which is associated with circulating high-density lipoprotein (HDL) and has the ability to prevent the generation of pro-inflammatory oxidized phospholipids. Two polymorphisms have been defined in the coding region of the PON1 gene (Q/R192, L/M55). PON1 activity and polymorphisms were found to be associated with several diseases such as systemic lupus erythematosus and rheumatoid arthritis (Yilmaz A. et al., 2009)

It has been shown that in HSP patients there is a relationship between the serum PON1 activity and HSP; therefore, in a study in Turkey the association of PON1(L/M55, Q/R192) and HSP was tested. 46 cases and 34 controls involved in the study and the result showed QQ genotype has correlation with the disease while MM genotype was found protective. No significance of those alleles and nephritis was observed (Yilmaz A. et al., 2009).

Table 2. protective polymorphisms

Ethnicity	Polymorphism	Year	Patients (N)	Controls (N)	Association	Ref

Turkish	HLA-A*01, -B*49, -B*50	2008	110	250	NO, Protective	[16]
Caucasian	HLA -DRB1*0301	2014	342	303	NO, Protective	[24]
Italian	HLA -DRB1*07	1997	152	NA	NO, Protective	[22]
Caucasian	HLA -DRB1*07	2001	50	NA	NO, Protective	[21]
Caucasian	HLA -DRB1*07	2002	58	96	NO, Protective	[18]
Caucasian	HLA -DRB1*07	2014	342	303	NO, Protective	[24]
Turkish	HLA -DRB1*10 , -DRB1*17	2008	110	250	NO, Protective	[20]
Turkish	PON1(L/M55)	2009	46	34	NO, MM Protective	[69]

PON1, paraoxonase 1; N, number; Ref, reference; NA, not available.

Cytotoxic T lymphocyte-associated molecule-4 (CTLA-4)

CTLA-4 also known as CD152 is encoded by a gene with the same name. CTLA-4 regulates T cell activation and targets the co-stimulatory molecules CD80/CD86. It is found in regulatory T cells, transmits an inhibitory signal to T cells and is expressed at highest levels after activation. SNPs in the CTLA-4 gene have been reported to be associated with a higher risk of some of rheumatic autoimmune diseases (Kormendy D. et al., 2013).

100 patients and 196 healthy controls in Turkish population enrolled in the study. CTLA-4 +49 A/G genotype was analyzed with respect to HLA-DRB1 typing. The HLA-DRB1*13-positive patients showed a significant difference in A/G heterozygosity and nephrotic range proteinuria. While in regards to other HLA-DRB1 gene polymorphisms, no association was demonstrated (oylemezoglu O. et al., 2008)

Conclusions

Autoimmune and multifunctional disorders result from the interaction of several genetic variations and environmental triggers. Each individual has several alleles of susceptibility to autoimmune diseases; however, only if many of them be combined in one person, s/he will manifest the disease. In this study, we have collected all related gene polymorphism studies and risk of HSP. The result has shown that there are associations between several genetic polymorphisms and HSP or its manifestation, such as HLA-DRB1*01, DRB1*11 and MEFV mutation E148Q (table 1), and some of them have a protective role (table 2). However, Different racial/ethnical groups differ in genetic factors. Therefore, there are racial/ethnical variation in the prevalence of HSP among individuals. As a result, these studies require follow-up studies in new populations with large sample sizes and characterizing genetic distances between populations.

Genome-wide association studies for identifying numerous genetic variations and a thorough understanding of the contribution of variation within the genome is also valuable. This genetic information could eventually be used as a predictive model for determining a patient's risk for HSP.

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