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Molecular Genetic Mechanisms of Chronic Urticaria

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Chronic urticaria (CU) is a common allergic skin disease that requires long-term pharmacological treatment. Some patients with severe CU suffer a poor quality of life. Although the pathogenic mechanisms of CU are not clearly understood, several groups have suggested that genetic mechanisms are involved in various CU cohorts. To further understand the molecular genetic mechanisms of CU, we summarize recent genetic data in this review. Although a few HLA alleles were suggested to be candidate markers in different ethnic groups, further replication studies that apply the recent classification are needed. Genetic polymorphisms in histamine-related genes, including *FcεRI* and *HNMT*, were suggested to be involved in mast cell activation and histamine metabolism. Several genetic polymorphisms of leukotriene-related genes, such as *ALOX5*, *LTC4S*, and the PGE2 receptor gene *PTGER4*, were suggested to be involved in leukotriene overproduction, a pathogenic mechanism. Further investigations using candidate gene approaches and genome-wide association studies (GWAS) will provide new insights into the molecular genetic mechanisms of CU, which will provide new marker genes for differentiation of CU phenotypes and identification of potential therapeutic targets.

Key Words: Chronic urticaria; genetic association; leukotriene; mast cell

Urticaria is a common skin disorder, affecting 15%-30% of the population and leading to consultations at medical facilities. Chronic urticaria (CU) accounts for 25% of urticaria and the point prevalence of CU is 0.5%-1%.[1,2] CU is characterized by the presence of hives, on most days of the week, for over 6 weeks. However, the classification of CU has been updated and the terminology has evolved and become more specific, as a result of increasing understanding of the causes of, and eliciting factors in, urticaria. Despite this increased understanding, appreciable numbers of CU patients are classified as idiopathic, implying an unknown origin.[3] Furthermore, the underlying causes and pathophysiological mechanisms of CU are not fully understood. Allergic diseases are complex, and are regulated by the interaction between genetic and environmental factors. Over the last few years, genetic studies of allergic diseases have become more advanced, especially of asthma. Similar to asthma and other allergic diseases, genetic mechanisms may be associated with the pathogenesis of CU. A study in a large population of patients with CU showed an increased prevalence of the disorder among first-degree relatives compared to the general population.[4] Several recent genetic studies aimed to determine the genetic predisposition to CU. Genetic factors doubtless make important contributions to susceptibility to disease development and progression, especially in particular CU subtypes; *e.g.*, aspirin-intolerant CU.

CLINICAL CHARACTERISTICS OF CU

CU is defined when it occurs spontaneously , without demonstrable provocations, unlike physical and other inducible urticaria.[5] About 40% of patients with CU experience concurrent angioedema.[6] The majority of studies of CU show that females are affected nearly twice as often as males, and that the peak age of manifestation of CU is 20–40 years.[1,7-9] Common provoking factors, such as physical factors, cold, heat, food, food additives, viral infection, psychological factors, endocrine diseases, and drugs, aggravate the symptoms.[3,5,10-13] One of the most common drugs which elicit urticaria is aspirin and other nonsteroidal anti-inflammatory drugs (NSAID).[14,15] Ingestion of aspirin or other NSAIDs, which inhibit cyclooxygenase, exacerbates the underlying conditions of CU and induces hives, namely aspirin-intolerant chronic urticaria (AICU), while patients who develop acute urticaria whenever they are exposed to aspirin/NSAIDs are called as having aspirin-intolerant acute urticaria

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(AIAU). One recent study proposed that AICU be described as aspirin-exacerbated cutaneous disease (AECD), similarly to aspirin-exacerbated respiratory disease (AERD),[16] the prevalence of which may be as high as 27%-35% in patients with CU.[17] AICU is confirmed by oral aspirin challenge test; no reliable *in vitro* test is available.[18] Based on oral challenge tests, CU can be classified as AICU or aspirin-tolerant CU (ATCU).

Genetic epidemiology studies of AICU in a Korean population suggested that atopy and increased serum total IgE levels are major predisposing factors for the AICU phenotype.[19,20] Patients with AICU were found to be younger and to have higher atopy rates, higher total serum IgE levels, and greater associations with a history of asthma compared to those with ATCU (Table 1). AICU had a longer duration of CU symptoms and presented with more severe symptoms requiring higher doses of drugs, including oral corticosteroids. However, no significant differences were noted in the prevalences of serum thyroid autoantibodies and antinuclear antibody (ANA) between AICU and ATCU.[19] Few reports compared the clinical features and pathogenic mechanisms of AIAU and AICU. In those available at present, there were no significant differences in mean age, gender distribution, serum total IgE, or the prevalences of atopy, allergic rhinitis, asthma, or food allergy between the two groups.[21,22] However, levels of a neutrophil activation marker were significantly higher in AIAU patients than in those with AICU.[21] Atopy was also a major predisposing factor for the AIAU phenotype.[22]

THE CANDIDATE GENE APPROACH IN CU

The first target genes identified using the candidate gene approach were those related to mast cell activation and histamine including, *FcεRI*, *HNMT*, *HRH1*, *HRH2*, *TNF-α*, *TGFβ1*, *ADORA3*, and *IL-10*. Also identified were genes related to the arachidonic acid (AA) pathway, including *ALOX5*, *CysLTR1*, *LTC4S*, and *PTGER4*, and HLA class I and II alleles. Other genes that could be involved in CU pathogenesis were *UGT1A6*, *CYP2C9*, *NAT2*, *ACE*, and *PTPN22* (Table 2).

Molecular genetic mechanisms related with mast cell activation and histamine

Mast cells are the major effector cell type that release histamine, cytokines and chemical mediators involved in the pathogenic mechanisms of CU. IgE binds with high affinity to a receptor (FcεRI) on the mast cell surface to induce activation, and CU patients show increased basophil histamine release.[23] Anti-IgE therapy is considered as an effective treatment to control urticaria symptoms in CU patients.[24] Moreover, CU is thought to have an autoimmune background because of the presence of circulating histamine-releasing IgG autoantibodies against FcεRI, which could induce degranulation of basophils and cutaneous mast cells.[25,26] Various types of serum autoantibody, such as ANA and IgGs against thyroglobulin and thyroid peroxidase (TPO), were elevated in sera from CU patients, although it is unknown how these autoantibodies are involved in the pathogenic mechanism.[3,7,27] One recent study demonstrated the presence of highly cytokinergic serum IgE antibodies spe-

Table 1. Comparison of the clinical characteristics of patients with chronic urticaria according to aspirin hypersensitivity

	AICU (n=141)	ATCU (n=153)	*P* value
Sex (male, %)	48.9	47.7	0.907
Age (years)	35.44±11.54	39.39±11.71	0.004
Atopy (%)	72.1	49.3	<0.001
Log serum total IgE (IU/mL)	5.20±1.05	4.69±1.11	<0.001

Age and serum total IgE: Prsented as mean±SD.
AICU, aspirin-intolerant chronic urticaria; ATCU, aspirin-tolerant chronic urticaria

Table 2. Genetic markers significantly associated with chronic urticaria phenotypes

Gene	RefSNP ID	Variation	Clinical phenotype	Country
Histamine- and mast cell-related genes				
FcεRIα	rs2427827	-344C>T	AICU	Korea[33]
FceRIβ	rs569108	E237G	AICU	Korea[34]
FceRIγ	rs11587213	-237A>G	AICU	Korea[34]
HNMT	rs1050891	939A>G	AICU	Korea[37]
TNF-α	rs1799964	Ht: -1031T>C	AIU	Korea[42]
	rs1800630	-863C>A		
	rs1799724	-857C>T		
	rs1800629	-308G>A		
	rs361525	-238G>A		
TGFβ1	rs1800469	-509C>T	CU, AICU	Iran[47]
ADORA3	rs10776727	-1050G>T	AIU	Korea[48]
IL-10	rs1544224	-564C>T		Korea[54]
	rs1800871	-819T>C	AIU	Korea[62]
Arachidonic acid pathway related genes				
ALOX5	rs4986832	-1708G>A	AIU	Korea[70]
	rs2228064	270G>A		
	rs2229136	1728A>G		
CysLTR1	rs321029	-634C>T	AICU	Korea[71]
LTC4S	rs730012	-444A>C	AIU	Poland[74] Venezuela[73]
PTGER4	rs45613037	-1254A>G	AICU	Korea[20]
Other potential mechanisms				
CYP2C9	rs4918758	-1188T>C	AIU	Korea[88]
ACE	rs1799752	Insertion/deletion	CU with angioedema	Turkey[94]
PTPN22	rs2488457	Ht: -1123G/C	CU	Poland[99]
	rs1310182	rs1310182C/T		
	rs3811021	rs3811021C/T		

Both allelic and haplotype associations are shown.

cific for various autoantigens, such as TPO on the mast cell surface, which could activate mast cells.[28] When mast cells are triggered, they release preformed mediators, and subsequently leukotrienes, prostaglandins, cytokines, and chemokines, which aggravate chronic inflammation.[29,30] FcεRI is a tetramer consisting of a ligand-binding α chain, a signal-amplifying β chain, and a signal-transducing γ chain dimer.[31,32] Recent studies have demonstrated their roles in aspects of molecular genetic mechianism of CU. When the genotype frequency of the *FcεRIα* gene was analyzed in CU patients comparing between AICU and ATCU patients, the minor allele *FcεRIα* -344C>T polymorphism showed a higher frequency in patients with AICU than in those with ATCU and normal controls in a Korean population.[33] *In vitro* functional analysis showed that this allele induced significantly higher promoter activity. Moreover, basophils in AICU patients with this allele showed increased histamine-releasing capacity. These findings suggest that this functional polymorphism may modulate FcεRIα expression on mast cells, enhancing histamine release and increasing susceptibility to AICU. A further study of *FcεRIβ* indicated that two genetic polymorphisms, *FcεRIβ* E237G and *FcεRIγ* -237A>G, were associated with atopy rate in AICU patients, but not in ATCU patients, in a Korean population.[34] The AG/GG genotype of the *FcεRIβ* E237G and *FcεRIγ* -237G alleles was associated with risk of atopy in AICU patients. Moreover, histamine release from basophils induced by anti-IgE antibodies was significantly higher in AICU patients with atopy than in those without atopy, suggesting that atopy may contribute to increased histamine release from basophils in AICU patients. These findings suggest that genetic variations in the *FcεRI* gene could modulate expression of this receptor on the mast cell surface, and so histamine release from mast cells/basophils in CU patients, especially those with atopy.

Histamine is formed by the histamine synthesis enzyme, L-histidine decarboxylase and its local action is terminated by histamine N-methyltransferase (HNMT) and diamine oxidase.[35,36] We hypothesized that a genetic variant at *HNMT* (939A>G) is a risk factor for CU.[37] When this polymorphism was assessed in CU patients including AICU and ATCU groups compared to NC group, the frequency of the major allele was significantly higher in AICU group compared to the control group in a Korean population. Moreover, *in vitro* functional analysis showed that the 939A allele was associated with decreased mRNA stability and enzyme activity, indicating that this genetic polymorphism at *HNMT* 939A>G modulates HNMT enzyme activity, thereby contributing to the development of CU. The diverse functions of histamine are mediated by G-protein-coupled H1 to H4 receptors. However, a genetic association study showed that histamine receptor H1 (*HRH1*) (-17C>T) and *HRH2* (543G>A) polymorphisms were not significant risk factors for this type of urticaria.[38]

Tumor necrosis factor (TNF)-α is a proinflammatory cytokine that is synthesized, stored, and released by mast cells during allergic inflammation. TNF-α can be found at the site of urticarial lesions, and several studies have shown upregulation of TNF-α expression in CU patients.[39,40] *TNF-α* genetic variants with high transcriptional activity may upregulate *TNF-α* production by mast cells and so contribute to the pathogenesis of CU. The TNF-α gene is located on chromosome 6 and may interact with the HLA class I and II alleles.[41] Recently, it was demonstrated that *TNF-α* polymorphisms at -1031T>C and -863C>A, and their haplotype, were significantly associated with the aspirin-induced urticaria (AIU) phenotype compared to healthy controls in a Korean population.[42] Moreover, Japanese investigators showed higher levels of *TNF-α* transcription for the -1031C, -863A, and -857T alleles, demonstrating that these three alleles were in significant linkage disequilibrium with HLA-B61, -B39, and -DRB1*0901, and with HLA-B54, -B35, -B59, and -DRB1*0405, respectively.[43]

The multipotent cytokine transforming growth factor (TGF)-β1 may be related to CU phenotypes due to its positive and negative effects on mast cell function. TGF-β1 is expressed by airway epithelial cells, eosinophils, Th2 lymphocytes, macrophages, and fibroblasts.[44] Studies of the effects of TGFβ1 on mast cell effector functions showed that TGF-β1 inhibits FcεRI expression and degranulation of mast cells.[45,46] Genetic effects of *TGFβ1* in different allergic disorders, including CU, have been described. The major allele frequency at *TGFβ1* -509C>T was significantly higher in CU patients in an Iranian population.[47] In contrast, the minor allele frequency of -509C>T was significantly higher in AICU patients in a Korean population, and this allele tended to be associated with a lower serum level of TGF-β1.[48,49] The minor allele of this variant, *TGFβ1* -509T, was identified as a risk factor in patients with AERD and asthma in two studies.[49,50] Patients carrying the minor allele had lower serum TGF-β1 levels and higher transcriptional activity. These findings suggest that *TGFβ1* genetic variants could be involved in the modulation of mast cell function and may contribute to the development of CU.

Adenosine is an endogenous nucleoside that can be released from stimulated mast cells.[51] It increases cutaneous vasopermeability and edema formation by activating A2B (ADORA2B) and A3 receptors (ADORA3) expressed on human mast cells, and facilitates the release of histamine, prostaglandins, leukotrienes, and proinflammatory cytokines.[52,53] Two functional genetic variants of the adenosine A3 receptor (*ADORA3*) gene at -1050G>T and -564C>T have been identified as genetic risk factors for AIU, including AICU, in a Korean population; *ADORA3* -1050G>T and haplotype 1 (TC; -1050T and -564C) showed significant associations in AIU patients.[54] Moreover, this haplotype showed higher promoter activity and increased basophil histamine release, indicating that the *ADORA3* gene polymorphism could enhance histamine release through increased *ADORA3* expression in CU patients.

Interleukin (IL)-10 is an anti-inflammatory cytokine that is expressed in a wide range of cells of the adaptive and innate im-

mune systems and that plays an essential role in the regulation of immune responses.[55-57] Moreover, it has been shown to induce pro- and anti-inflammatory responses.[55] The genetic variants -1082A/G, -819C/T, and 592A/C in the promoter region of the *IL-10* gene have been described frequently in association with cutaneous diseases, while their influence on IL-10 production is unclear.[58-61] A genetic association of -819T>C in *IL-10* with AIU, including both AIAU and AICU, was identified in a Korean population.[62] The authors demonstrated a significantly higher frequency of the major allele of *IL-10* -819T>C in those with AIU phenotypes. Some evidence indicates that IL-10 can suppress FcεRI expression in human skin-derived mast cells.[63] This effect was confirmed in mouse mast cells since IL-10 suppressed both signaling molecule and IgE-mediated cytokine production. A similar study demonstrated that mast cell-derived IL-10 could limit leukocyte infiltration, epidermal hyperplasia, and epidermal necrosis in a mouse model.[64] This evidence indicates that downregulation of IL-10 production as a result of genetic predisposition may facilitate mast cell degranulation and aggravate CU.

Genes involved in the arachidonic acid pathway

Aberrant arachidonic acid (AA) metabolism, especially cyclooxygenase (COX) and arachidonate 5-lipoxygenase (5-LO or ALOX5) pathways, account for the susceptibility to CU phenotypes following the ingestion of aspirin or NSAIDs.[65] The *ALOX5* gene encodes the enzyme 5-LO, which acts with arachidonate 5-lipoxygenase-activating protein (ALOX5AP/FLAP) to catalyze the first two steps in synthesis of leukotriene A4 (LTA4).[66] LTA4 is converted to a variety of leukotrienes, such as LTC4, LTD4, and LTE4, by leukotriene C4 synthase (LTC4S). Cysteinyl leukotrienes bind to and activate two receptors belonging to the G-protein-coupled receptors (GPCR) superfamily, CysLTR1 and CysLTR2, with different affinities. In contrast, prostaglandins and thromboxanes are synthesized via the COX pathway and show inhibitory effects on the release of CysLTs from activated mast cells.[67] Prostaglandin E2 (PGE2) binds to a specific group of four GPCR subtypes, EP1- EP4, which are expressed on the mast cell surface and responsible for PGE2 activity.[68]

Recently, AA pathway-related genetic variants were studied in NSAID-induced acute urticaria patients among two different Spanish populations.[69] Genetic variants in *ALOX5AP* (218A>G), *ALOX15* (-272C>A), *PTGDR* (-549T>C), *PTGER1* (-1013A>C and -804C>T), *PTGER2* (-72G>A), and *CysLTR1* (927C>T) showed significant associations with this clinical phenotype.

Most genetic studies of this pathway have focused on whether these genetic polymorphisms can be used to differentiate two major phenotypes of aspirin hypersensitivity, AERD and AIU. Genetic variants in *ALOX5* (-1708G>A, 270G>A and 1728A>G) and *ALOX5AP* (218A>G) were identified in a Korean population, with *ALOX5* -1708G>A, haplotype 1 (GGA; -1708G, 270G, and 1728A) and haplotype 2 (AGA; -1708A, 270G, 1728A) differing significantly between AIU and AERD phenotypes.[70] Similarly, a significant association was noted for the *CysLTR1* -634C>T variant and the AICU phenotype compared to AERD.[71] Moreover, haplotype 2 (TCG: -634T, -475C, and -336G) showed higher promoter activity compared to other haplotypes haplotypes. These findings suggest that the contributions of *ALOX5* and *CysLTR1* genetic variants differ between AICU and AERD.

Leukotriene C4 synthase (LTC4S) is a terminal enzyme in the leukotriene pathway and is responsible for the production of CysLTs, the levels of which are characteristically increased after aspirin exposure in AICU patients.[29,65,72] Genetic variability in the functional polymorphism in *LTC4S*, which increases the expression of this gene, has been reported in different ethnic groups. The *LTC4S* -444A>C genetic variant was significantly associated with AIU in a Venezuelan population, as well with the cutaneous clinical pattern and a low skin response to histamine.[73] Elsewhere, in a Polish population, the variant allele of the *LTC4S* -444A>C polymorphism was inherited in families with AIU.[74] Attempts to replicate this association in Spanish[75] and Korean populations were unsuccessful.[71]

A genetic variant in the PGE2 receptor subtype EP4 (*PTGER4*) at -1254A>G was significantly associated with AICU in a Korean population.[20] The minor allele of this polymorphism had a high frequency in AICU patients, and showed lower *PTGER4* promoter activity with decreased expression of PTGER4 in human mast cells. That this functional variant modulates *PTGER4* gene expression was confirmed by lower transcriptional regulation of *PTGER4*, suggesting that PTGER4 expression could lose its protective effect after aspirin exposure in subjects carrying this risk allele, which contributes to the development of AICU.

HLA class I and class II alleles

HLA class I and II alleles, which may affect MHC binding capacity, are well known genetic markers of CU phenotypes in various ethnic groups (Table 3). HLA class I alleles have been investigated less often than HLA class II alleles. A possible protective role for HLA-A24 (Turkey)[76] and -A33 (Poland)[77] was identified in CU. However, the HLA antigens HLA-Bw4 (Turkey),[76] -B14 (Brazil),[78] and -B44 (Poland and Turkey)[77,79] may be responsible for susceptibility to CU. Notably, the prevalence of HLA-B14 was higher in patients with CU with high IgG to TPO levels.[78] AICU and HLA class I antigen showed a strong correlation in an Italian population.[80] HLA-B44 and -Cw5 allele frequencies are higher in AICU, while HLA-A11, -B13, -Cw4 and Cw7 allele frequencies are lower in patients with AICU. HLA class II alleles and CU were further investigated in a variety of ethnic groups. Significantly higher frequencies of HLA-DQ1 (Turkey),[76] -DQB1*0302 (UK),[81] -DRB1*01 (Turkey),[79] -DRB1*04 (UK, Turkey and Poland),[77,81,82] -DRB1*0901 (China),[83] -DRB1*12 (China),[83] and -DRB1*15 (Turkey)[79] were noted in CU patients. However, HLA-DRB1*15 (UK),[81] -DQB1*06 (UK),[81] and -DQB1*05 (China)[83] were found to be protective factors in CU patients.

Table 3. Genetic markers of HLA class I and II regions associated with chronic urticaria phenotypes

	HLA class I				HLA class II			
	Risk	Ethnic group	Protective	Ethnic group	Risk	Ethnic group	Protective	Ethnic group
Chronic urticaria	Bw4	Turkey[76]	A24	Turkey[76]	DRB1*01	Turkey[79]	DRB1*15	UK[81]
	B14	Brazil[78]	A33	Poland[77]	DRB1*04	UK[81]	DQB1*06	UK[81]
						Turkey[82]		
						Poland[77]		
	B44	Turkey[79]			DRB1*0901	China[83]	DQB1*05	China[83]
		Poland[77]			DRB1*12	China[83]		
					DRB1*15	Turkey[79]		
					DQ1	Turkey[76]		
					DQB1*0302	UK[81]		
ASA-intolerant chronic urticaria	B44	Italy[80]	A11	Italy[80]	Ht: DRB1*1302	Korea[84]		
	Cw5	Italy[80]	B13	Italy[80]	DQB1*0609			
			Cw4	Italy[80]	DPB1*0201			
			Cw7	Italy[80]				

Both allelic and haplotype associations are shown.

When HLA class I and II alleles were evaluated in Korean patients with AIU using a high-resolution technique, the frequency of the HLA-DRB1*1302-DQB1*0609-DPB1*0201 haplotype was significantly higher in the patient group.[84] Although studies using a high-resolution technique in a larger CU cohort, followed by *in vitro* functional studies, are essential, these findings suggest the potential involvement of HLA alleles in CU phenotypes.

Two HLA class II alleles, HLA-DQB1*0609 and -DRB1*1302, showed significant associations with the prevalence of serum specific IgE antibodies to staphylococcal enterotoxins A (SEA) and B (SEB) in AICU patients,[85] suggesting that patients carrying these HLA alleles may be more susceptible to a Th2 immune response induced by staphylococcal superantigens, which may contribute to the development of AICU.

Other potential genetic mechanisms

Variation in genes encoding acetyl salicylic acid-metabolizing enzymes may affect drug responses and the risk of developing drug intolerance. In humans, aspirin is rapidly deacetylated to salicylic acid. The major enzymes involved in acetylsalicylic acid metabolism are polymorphic enzymes responsible for hydroxylation and glucuronidation of the drug, and include uridine diphosphate (UDP)-glucuronosyltransferase UGT1A6, cytochrome P450 CYP2C9, and N-acetyltransferase 2 (NAT2). Two common variant alleles of *UGT1A6*, with amino acid changes at positions 181 (T181A) and 184 (R184S), result in an enzyme activity that is reduced to 30%-50% of the wild-type allele.[86] In addition, two variants of *CYP2C9* alleles, *CYP2C9*2* (R144C) and *CYP2C9*3* (I359L), yield slow metabolizing enzymes with 5-30% of the activity of the wild-type.[87] Due to differences in metabolic efficacy between wild-type and variant phenotypes, it is tempting to reason that carriers of these variants differ in their metabolism in a way that influences aspirin hypersensitivity and CU. Evaluation of genetic polymorphisms with major metabolizing activity, including *CYP2C9* -1188T>C, *CYP2C9*3* A1075C, *UGT1A6* T181A A>G, *UGT1A6* R184S A>C, *NAT2* -9796T>A, *NAT2* 197G>A, *NAT2* 286A>G, *NAT2* -9601A>G, and *NAT2* -9306A>G, in Korean patients with AIU[88] suggests that the *CYP2C9* -1188T>C variant may contribute to AIU development by modulating the metabolizing activity of its encoded enzyme.

Angiotensin-converting enzyme (ACE) is widely expressed in the skin and is a major proteolytic peptidase that degrades substance P.[89] Substance P is a well-known neuropeptide with the capacity to provoke the release of histamine from skin mast cells. Intradermal injection of substance P induces wheal and flare reactions in normal human skin.[90, 91] Genetic variation in the *ACE* gene has been studied in patients with angioedema and CU patients with angioedema.[92-94] Insertion/deletion polymorphisms of the *ACE* gene showed statistically significant associations with angioedema in CU in a Turkish cohort.[94] Although this was a single report with no follow-up studies, the findings suggest that this polymorphism contributes to susceptibility to angioedema in CU patients.

Autoimmune mechanisms are known to be involved in the pathogenesis of CU. One candidate autoimmune mechanism is protein tyrosine phosphatase 22 (PTPN22), which is considered to be an inhibitor of the immunological responses of both T and B cells.[95] PTPN22 is expressed by B cells, T cells, and dendritic cells, and is present mainly in the cytoplasm, as well as in the nucleus.[95] Genetic variation in this gene has been reported in various autoimmune disorders, including rheumatoid arthritis, type I diabetes, and systemic lupus erythematosus.[96-98] Functional variants of this gene may decrease the ability of

PTPN22 to reduce antigen-receptor signaling, leading to compromised central and peripheral tolerance.[95] PTPN22 was reported to contribute to CU susceptibility in a Polish population.[99] The prevalences of the *PTPN22* promoter polymorphism -1123G>C, and its haplotype construct including rs2488457C, rs1310182T and 3811021T, showed significant associations with CU. However, the *PTPN22* polymorphism 1858C>T did not show an association with CU in autologous serum skin test-positive patients.[100] Further association studies of other autoimmune markers in a variety of CU cohorts are needed.

CONCLUSIONS

We summarized the molecular genetic mechanisms underlying CU phenotypes. Because CU is a heterogeneous disease, the phenotype is at present not well-defined and related clinical parameters have not been fully evaluated in each study. Further investigations using GWASs and candidate gene approaches with applying immunologic evaluations should follow. This will improve understanding of the molecular genetic mechanisms underlying CU, facilitate the development of marker genes for differentiation of the various CU phenotypes, and identify potential therapeutic targets.

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