

A genome-wide association study of chronic spontaneous urticaria risk and heterogeneity



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Background: Chronic spontaneous urticaria (CSU) is a dermatologic condition characterized by spontaneous, pruritic hives and/or angioedema that persists for 6 weeks or longer with no identifiable trigger. Antihistamines and second-line therapies such as omalizumab are effective for some CSU patients, but others remain symptomatic, with significant impact on quality of life. This variable response to treatment and autoantibody levels across patients highlight clinically heterogeneous subgroups. **Objective:** We aimed to highlight pathways involved in CSU by investigating the genetics of CSU risk and subgroups. **Methods:** We performed a genome-wide association study (GWAS) of 679 CSU patients and 4446 controls and a GWAS of chronic urticaria (CU)-index, which measures IgG autoantibodies levels, by comparing 447 CU index-low to 183 CU index-high patients. We also tested whether polygenic scores for autoimmune-related disorders were associated with CSU risk and CU index. **Results:** We identified 2 loci significantly associated with disease risk. The strongest association mapped to position 56 of *HLA-DQA1* ($P = 1.69 \times 10^{-9}$), where the arginine residue was associated with increased risk (odds ratio = 1.64). The second association signal colocalized with expression-quantitative trait loci for *ITPKB* in whole blood ($P_{\text{colocalization}} = .997$). The arginine residue at position 56 of *HLA-DQA1* was also associated with increased risk of CU index-high ($P = 6.15 \times 10^{-5}$, odds ratio = 1.86), while the *ITPKB* association was not ($P = .64$). Polygenic scores for 3 autoimmune-related disorders (hypothyroidism, type 1 diabetes, and vitiligo) were associated with CSU risk and CU index ($P < 2.34 \times 10^{-3}$, odds ratio > 1.72). **Conclusion:** A GWAS of CSU identified 2 genome-wide significant loci, highlighting the shared genetics between CU

index and autoimmune disorders. (J Allergy Clin Immunol 2023;151:1351-6.)

Key words: Genome-wide association studies, chronic spontaneous urticaria

Chronic spontaneous urticaria (CSU) is a dermatologic condition with an overall prevalence of 0.5% to 1%.¹ It is characterized by spontaneous, pruritic hives and/or angioedema that persists for longer than 6 weeks despite antihistamine treatment.^{2,3} Mast cell and basophil degranulation are integral to the etiology of CSU. Although not all mediators of this degranulation are known, some factors point to an autoimmune basis. Specifically, the presence in some patients of IgG autoantibodies to FcεRI and IgE, and IgE with specificities to autoantigens suggest degranulation is elicited by autoantibody-mediated FcεRI/IgE cross-linking.⁴ Omalizumab, a recombinant monoclonal antibody that targets IgE, is an approved therapy for CSU patients.⁵⁻⁷ A subset of patients do not achieve well-controlled status with this therapy,⁸ indicating additional disease mediators are involved that can be targeted therapeutically.

Over the past 20 years, results from thousands of genome-wide association studies (GWASs) on numerous diseases have shed light on disease biology. A family study of CSU supports the notion that it is a heritable disorder,⁹ and several candidate single nucleotide polymorphism (SNP) analyses in small cohorts (fewer than 200 cases) have been reported, although with limited replication.^{10,11}

To investigate the genetics of CSU risk and heterogeneity, we performed a GWAS of 679 CSU patients who were participants of 4 CSU clinical trials.⁵⁻⁷

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METHODS

Samples

CSU patients in this GWAS were obtained from CSU clinical trial participants from the following trials: ASTERIA I ([ClinicalTrials.gov NCT01287117](https://clinicaltrials.gov/NCT01287117)), ASTERIA II (NCT01292473), GLACIAL (NCT01264939),⁵⁻⁷ and SHASTA (NCT03693625). GLACIAL, ASTERIA I, and ASTERIA II were conducted from 2011 to 2012. SHASTA was conducted from 2018 to 2019. Inclusion and exclusion criteria were comparable across CSU studies, with the exception of GLACIAL (NCT01264939), which permitted H₁ antihistamine treatment up to 4 times above the approved dose (see the Note in this article's Online Repository at www.jacionline.org). Clinical characteristics and general demographics are available in Table E1 and the Note in the Online Repository. Controls were either participants in non-CSU clinical trials (n = 4388) or healthy volunteers (n = 58) (see Table E2 in the Online Repository). All data used in this study were generated from clinical trial participants who signed informed consent forms approved by the ethics committee or institutional review board

Abbreviations used

CSU: Chronic spontaneous urticaria
 CU: Chronic urticaria
 eQTL: Expression quantitative trait loci
 GWAS: Genome-wide association study
 LD: Linkage disequilibrium
 MAF: Minor allele frequency
 MHC: Major histocompatibility complex
 PRS: Polygenic risk score
 SNP: Single nucleotide polymorphism

responsible for the country or site where the trial participants donated samples for research. Informed consent included use of these data for genetic research.

Samples were genotyped with the Infinium Global Screening Array (v2) by Illumina (San Diego, Calif) and imputed using Beagle (v5.1)¹² and the 1000 Genomes Project reference panel (GRCh38 aligned version). All samples had a genotyping rate of >0.98; only samples with majority European ancestry (fraction ancestry >0.70), estimated using the supervised mode of ADMIXTURE,^{13,14} were retained for analysis. We additionally removed 17 related samples ($Z_0 \geq 0.4$), 19 individuals with excess heterozygosity (≥ 6 standard deviations from the mean), and 58 samples that were excluded on the basis of iterative principal component analysis outlier removal (default parameters as provided by Eigensoft¹⁵). We excluded variants with imputation quality <0.3, Hardy-Weinberg equilibrium $P < 1 \times 10^{-6}$, and minor allele frequency (MAF) <0.005. After performing these quality control measures, we retained 10,077,611 variants across 679 CSU patients and 4,446 non-CSU controls for analysis. Although we used the full control set for the risk analysis, we only retained 3,406 controls that were not flagged by the reverse regression method for the HLA allele and polygenic risk score (PRS) analyses.

Statistical methods

Variant-level association analyses were performed in PLINK (v1.90b6.16).^{16,17} All association analyses corrected for genetic sex and the first 5 principal components. Genetic sex was estimated from X-chromosome heterozygosity via PLINK. Principal components were generated with Eigensoft (v6.1.4)¹⁵ on a set of linkage disequilibrium (LD)-pruned variants and regions of long-range LD excluded.

Because of the heterogeneous nature of our controls, we used a method that utilizes reverse regression and a Bayesian spike and slab to flag control groups that may contribute to association signals.¹⁸ Further details are provided in the Note in the Online Repository.

HLA alleles were imputed with HIBAG using provided reference panels.¹⁹ Alleles with a minimum frequency of >0.01 were retained for analysis. Variable amino acid position inference and association analyses, assuming a dominant inheritance model, was carried out in R using the MiDAS package.²⁰ Independently associated alleles were determined by iterative conditional analyses on the most significant alleles until no further alleles are associated with $P_{\text{adjusted}} < .05$. Multiple testing correction was carried out via Bonferroni correction. All analyses corrected for genetic sex and the first 5 principal components.

Heritability was estimated using LD score regression as implemented in the LDSC tool (v1.0.1).²¹ The CSU risk GWAS summary statistics were harmonized and subset to variants overlapping HapMap3 variants using the 'munge_sumstats.py' function. To calculate heritability (h^2) on the liability scale, we assumed a CSU prevalence of 1%.² We used precomputed LD scores from 1000 Genomes Project samples of European ancestry, as linked to by LDSC (github.com/bulik/ldsc/wiki/LD-Score-Estimation-Tutorial).

Bayesian colocalization analysis was performed by the 'coloc' package.²² For each region, we input P values and MAFs for variants within 1 megabase of the most significantly associated variants and assumed default prior probabilities to estimate colocalization probabilities. MAFs were estimated

from the samples used in this GWAS. We obtained summary statistics for expression quantitative trait loci (eQTL) from GTEx (v8).²³

PRS analysis was performed and scores generated for 15 diseases and 12 blood cell-type traits using PRS-CS²⁴ (see Table E3 in the Online Repository at www.jacionline.org). Only variants in each GWAS overlapping variants in our study were used as input to PRS-CS. Furthermore, we estimated 2 PRS for each trait/disease, one for which we included the major histocompatibility complex (MHC) region (GRCh37 coordinates – chromosome 6:28,477,797–33,448,354), and another in which variants within 3 megabases of the MHC were excluded. Association with CSU risk and CU index subgroup were carried out in R by the 'glm' function with the "family = binomial" parameter.

RESULTS**Study overview**

We included 679 patients with clinically defined CSU and 4446 non-CSU controls of majority European ancestry (fraction ancestry >0.70). CSU patients were diagnosed by physician assessment and were refractory to antihistamine treatment for at least 6 weeks. Controls included healthy volunteers as well as individuals from clinical trials of other diseases (age-related macular degeneration, amyotrophic lateral sclerosis, cancer, hepatic insufficiency, Parkinson disease, schizophrenia, nonalcoholic fatty liver disease, and ulcerative colitis) (Tables E1 and E2). All samples were genotyped on the Illumina Global Screening Array and imputed using the 1000 Genomes Project reference panel. Association analyses were corrected for genetic sex and ancestry (first 5 principal components) (see Fig E1 and the Note in this article's Online Repository at www.jacionline.org).

Two loci significantly associated with CSU

We tested for association with CSU at 10,077,611 variants with MAF >0.5% that passed quality-control filters. There was no inflation of test statistics ($\lambda_{GC} = 1.02$). The common-variant SNP heritability (h^2) of CSU estimated by LD score regression²¹ is 0.160 (standard error = 0.114), assuming a prevalence of 1%.² We found 2 loci significantly ($P < 5 \times 10^{-8}$) associated with CSU (Fig 1, Table I, and, in the Online Repository at www.jacionline.org, Tables E3 and E4). The most significantly associated region was located in the major histocompatibility complex (MHC) (rs34141382, odds ratio of C allele = 1.74, $P = 4.98 \times 10^{-13}$) (see Fig E2 in the Online Repository). Because of the heterogeneous nature of our controls, we applied the reverse regression method¹⁸ to flag variants where diseases represented in our control samples may have contributed to the association signal. Although this method flagged a subset of the controls as contributing to the MHC signal, the association remained highly significant despite removing the flagged controls from the analysis ($P = 1.75 \times 10^{-10}$) and when comparing cases to more homogeneous controls (see Tables E5 and E6 as well as the Note in the Online Repository). Furthermore, the MAF observed in controls (0.12) was more comparable to the MAF in an external reference data set such as gnomAD (MAF_{non-Finnish-European} = 0.16) than the MAF in study cases (0.22).

To refine the observed MHC associations, we imputed HLA class I and II alleles and inferred variable amino acid positions across the HLA genes using HIBAG.¹⁹ We tested for association with CSU risk by comparing the 679 CSU patients to 3406 controls that were not flagged by the reverse regression method. The most significant association was at position 56 of

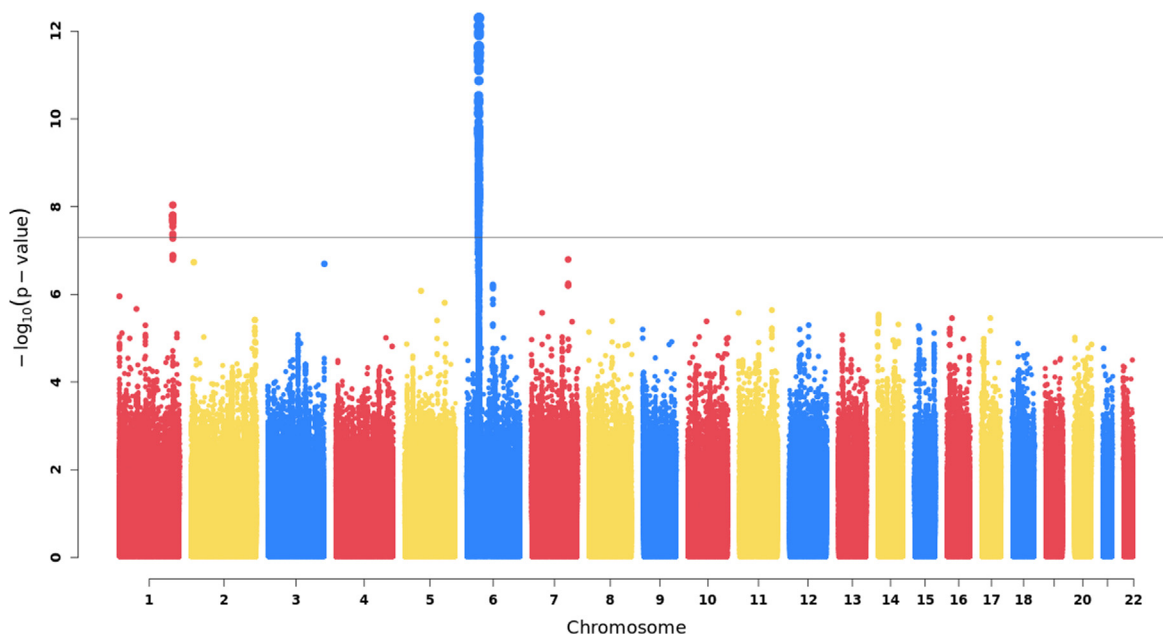


FIG 1. CSU risk GWAS Manhattan plot. Two-sided P values comparing 679 CSU patients to 4446 non-CSU controls. Black line represents the significance threshold after multiple testing correction ($P = 5 \times 10^{-8}$).

TABLE I. Sentinel SNPs for 2 loci significantly associated in this GWAS comparing 679 CSU patients to 4446 non-CSU controls

CHR	BP	SNP	EA	NEA	OR (95% CI)	P	RAF (controls/cases)
1	226755787	rs1097296	C	T	1.44 (1.27-1.64)	1.57×10^{-8}	0.59/0.67
6	32640701	rs34141382	C	T	1.74 (1.50-2.03)	4.98×10^{-13}	0.12/0.22

BP, GRCh38 coordinates; CHR, chromosome; CI, confidence interval; EA, effect allele; NEA, noneffect allele; OR, odds ratio; RAF, risk allele frequency. Two-sided unadjusted P values are reported.

TABLE II. HLA alleles and variable amino acid positions significantly associated with CSU risk

Allele	OR (95% CI)	P	Allele frequency (cases/controls)
DQA1_56	1.64 (1.41-1.91)	1.69×10^{-9}	0.23/0.14
DQA1*03:03	1.69 (1.32-2.16)	3.01×10^{-5}	0.09/0.05
DRB1*04:04	1.82 (1.35-2.45)	9.72×10^{-5}	0.05/0.03
DQB1*03:02	1.50 (1.21-1.84)	1.56×10^{-4}	0.13/0.09
DQA1*03:01	1.49 (1.20-1.84)	2.41×10^{-4}	0.12/0.09

Association statistics for alleles significantly associated with CSU risk are provided. The OR and allele frequencies listed for variable amino acid for DQA1 at position 56 is with respect to the arginine residue. CI, Confidence interval; OR, odds ratio. Two-sided unadjusted P values are provided.

HLA-DQA1 ($P = 1.69 \times 10^{-9}$) (Table II, and see Tables E7-E9 in the Online Repository at www.jacionline.org), where the arginine residue was associated with increased risk of CSU (odds ratio = 1.64). No further positions were independently associated in a conditional analysis including position 56 as a covariate.

The second genome-wide significant signal mapped to an index SNP near *ITPKB* (rs1097296, $P = 1.57 \times 10^{-8}$, odds ratio of C allele = 1.44) (see Fig E3 in the Online Repository at www.jacionline.org). Reverse regression did not flag any controls contributing to this signal (Note in the Online Repository), and conditioning on the index SNP, rs1097296, did not reveal any independent associations with $P < 1 \times 10^{-6}$. Although rs1097296 is a *cis*-eQTL in GTEx for several genes nearby (see Table E10 in the Online Repository), colocalization analysis to

estimate the probability of a shared causal variant between the association and eQTL signal only supported a shared causal variant between the CSU risk signal and the *ITPKB* eQTL in whole blood ($P = .997$) (see Table E11 in the Online Repository). At this locus, the CSU risk allele (C) is associated with increased expression of *ITPKB* in blood.

CU index-stratified analyses highlight the autoimmune basis of CU index

The Chronic Urticaria (CU)-index test measures the presence and function of serum IgG autoantibodies via a basophil histamine release assay. Roughly 90% of CSU patients with CU index ≥ 10 are symptomatic despite use of antihistamines and leukotriene

receptor agonists.²⁵ To investigate whether genetic differences underlie the CU index, we classified the CSU patients in our study into a high (≥ 10 , $n = 183$) or low (< 10 , $n = 447$) CU index²⁵ subgroup for 630 samples with available data (see Fig E4 in the Online Repository at www.jacionline.org). The Note in the Online Repository provides the results with the CU index cutoff equal to 5, the median of this population. A logistic regression analysis comparing CU index–low to CU index–high patients did not identify any associations meeting genome-wide significance (see Fig E5 in the Online Repository). Of the loci significantly associated with CSU risk, the SNP near *ITPKB* (rs1097296) was not associated with CU index ($P = .64$), and the risk allele frequency (RAF) was similar across CSU subgroups (RAF_{CU index–low} = 0.67, RAF_{CU index–high} = 0.68) (see Table E12 in the Online Repository). In contrast, the HLA index SNP was associated with CU index ($P = 6.02 \times 10^{-6}$), and the RAF for the index variant (rs34141382) was greater in CU index–high than in CU index–low patients (RAF_{CU index–high} = 0.30, RAF_{CU index–low} = 0.19) (see Tables E12 and E13 in the Online Repository). Across HLA alleles and variable amino acid positions, position 56 of *HLA-DQA1* was most significantly associated with CU index ($P = 6.15 \times 10^{-5}$) (see Table E14 in the Online Repository). At this position, the frequency of the arginine residue was higher in CU index–high patients (0.30) compared to CU index–low patients (0.20).

Shared genetics with autoimmune disorders

Several autoimmune disorders have been shown to be more frequent in CSU patients,⁴ such as Hashimoto thyroiditis. We investigated whether pleiotropy between CSU and CU index with autoimmune disorders extended beyond the MHC region. To do this, we estimated PRS for 9 autoimmune disorders or disorders with a potential autoimmune basis (Table E3). PRS were estimated with PRS-CS²⁴ using publicly available GWAS, and individuals from our study were scored with PLINK.¹⁷ We also included 3 allergic traits as well as 3 additional “control” traits (coronary artery disease, COVID-19, and type 2 diabetes) for which there is little overlapping biology with CSU, and we thus did not expect to see an association. All together, we tested 15 PRS for association with CU index and CSU risk. To minimize confounding from our control samples, we also excluded controls that were flagged earlier by the reverse regression analysis.

CSU risk was significantly associated with 4 autoimmune-related PRS (hypothyroidism, rheumatoid arthritis, type 1 diabetes, and vitiligo) and a composite PRS for allergic disease (hay fever, eczema, and asthma) ($P < 1.67 \times 10^{-3}$, correcting for 15 PRS and 2 phenotypes) (see Table E15 in the Online Repository at www.jacionline.org). These risk associations became more significant when variants in the MHC were included in the PRS calculation (Table E15). Three of the autoimmune-related PRS were also significantly associated with CU index (hypothyroidism, type 1 diabetes, and vitiligo) (Fig 2, Table E15), with greater autoimmune risk associated with the CU index–high group.

Last, considering the crucial role of various immune cells in CSU, we tested whether CSU risk or CU index may also share genetics with loci underlying cell count measures. We used the same methods as above to estimate PRS for cell count measures using a large-scale blood cell count GWAS.²⁶ We found that the eosinophil PRS was significantly associated with CSU risk

($P = 6.1 \times 10^{-4}$) after multiple testing correction for 12 blood cell count measures and 2 CSU-related phenotypes, but we did not observe associations of blood cell count PRS with CU index (Table E15).

DISCUSSION

The activation and degranulation of mast cells and basophils play key roles in the pathogenesis of CSU. Although the exact mechanisms are unknown, one theory suggests degranulation is elicited by autoantibody-mediated FcεRI/IgE cross-linking.⁴ Indeed, up to 50% of CSU patients test positive for the presence of autoantibodies or other histamine-releasing factors, and CSU patients are likely to have autoimmune comorbidities such as rheumatoid arthritis and type 1 diabetes²⁷ compared to individuals without CSU. In this GWAS study of CSU, we found 2 loci significantly associated with CSU risk that may shed light on factors mediating CSU pathogenesis. The most significant association mapped to the MHC region, which builds on previously reported smaller candidate gene studies that show nominal significance for association of HLA alleles with CSU risk.^{10,11}

Furthermore, we identified a novel locus that is an eQTL for *ITPKB*, where the risk allele is associated with increased *ITPKB* expression in the blood. A role for *ITPKB* has been suggested for several diseases, including autoimmune disease²⁸ and severe immunodeficiency disorder.²⁹ Inositol 1,4,5-trisphosphate kinase B (*ITPKB*) is part of a family of kinases that phosphorylates inositol (1,4,5), a secondary messenger involved in calcium signaling via a process called store-operated calcium entry.³⁰ Inositol (1,4,5) regulation is involved in neuronal signaling³¹ and immune cell function, including mast cell and basophil degranulation.³⁰ A potential role for *ITPKB* in CSU could be through elevated store-operated calcium entry–dependent mast cell and basophil degranulation releasing pruritogenic mediators (eg, histamine) directly activating receptors on peripheral sensory neurons. Murine genetic models have highlighted the role of *ITPKB* in limiting neutrophil, natural killer, and T-cell function, and myelopoiesis.³² *ITPKB* inhibition is also efficacious in preclinical models of autoimmune disease,²⁸ suggesting that *ITPKB* may play a role in the loss of tolerance in CSU and potentiates calcium-dependent secretory responses in mast cells.³³ Taken together, this information highlights a potential dual role of *ITPKB* in CSU via immune and neuronal cell types. Future mechanistic studies confirming the role of *ITPKB* in the etiology and pathology of CSU may yield insights into new treatments.

By investigating the genetics of CU index, we identified shared genetics between 3 autoimmune-related disorders and CU index that extended beyond the MHC. These results provide a genetic basis for clinical observations that CSU patients are more likely to experience autoimmune comorbidities; the results also highlight the autoimmune genetic nature underlying patient heterogeneity measured by CU index.

There are several limitations to this study. First is the lack of a replication cohort. Although ICD-based CSU patients can be defined in biobank studies (eg, UK Biobank), information on the CU index status would be missing, barring replication of our CU index–stratified findings. Therefore, full replication of our results is not yet possible until additional genetic data are available from other CSU cohorts. Second, because our study focused on individuals of European ancestry, studies in individuals of non-European ancestry are needed to confirm whether our results hold

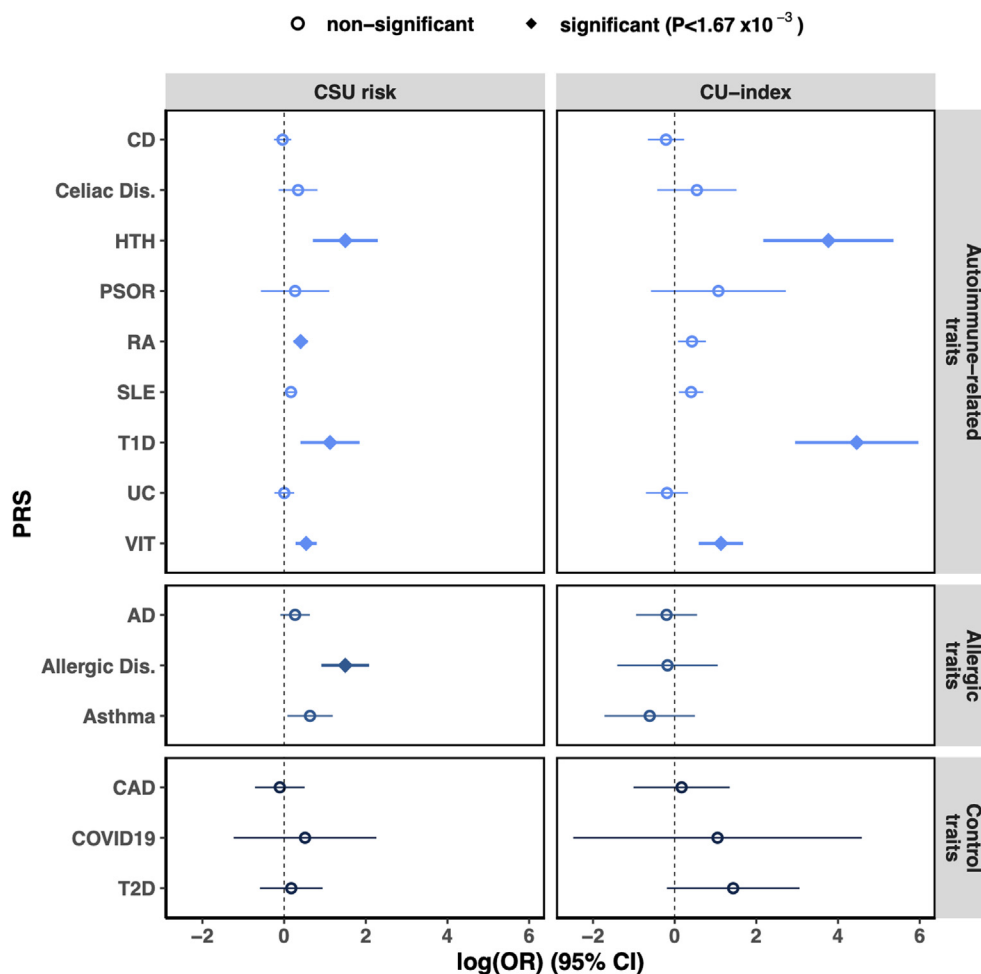


FIG 2. Association of PRS for 15 disorders with CSU and CU index risk. The log(odds ratio) is plotted on the x-axis, with bars indicating 95% confidence intervals. Associations passing multiple testing correction ($P < 1.67 \times 10^{-3}$) are displayed as *solid diamonds*. Corresponding association statistics are available in Table E15. AD, Atopic dermatitis; Allergic dis, allergic diseases; CAD, coronary artery disease; CD, Crohn disease; COVID-19, hospitalized COVID-19; HTH, hypothyroidism; MS, multiple sclerosis; PSOR, psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; T2D, type 2 diabetes; UC, ulcerative colitis.

in other populations. A recently reported GWAS of CSU in individuals of East Asian ancestry found 5 loci significantly associated with CSU risk.³⁴ Although this study also found an association mapping to the MHC, their index variant (rs9378141) is not in LD with our index variant (rs34141382) in individuals of East Asian or European ancestry. We also do not see evidence of association with the 3 other loci for which we could test for an association in our study (see Table E16 in the Online Repository at www.jacionline.org), although most of these loci had higher frequencies in individuals of East Asian ancestry. This highlights the importance of studying the genetics of disease risk in multiple ancestries.

In summary, in this GWAS of a cohort of clinically well-characterized CSU patients, we identified 2 loci significantly associated with CSU risk and identified a genetic basis for autoimmune comorbidities underlying CU index–high patients.

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Key messages

- GWAS analysis of CSU identified 2 loci significantly associated with risk that map to the MHC region and a region near *ITPKB*.
- Stratifying the results by CU index highlighted the shared genetics between several autoimmune disorders and CU index.

REFERENCES

1. Maurer M, Abuzakouk M, Berard F, Canonica W, Oude Elberink H, Gimenez-Arnanau A, et al. The burden of chronic spontaneous urticaria is substantial: real-world evidence from ASSURE-CSU. *Allergy* 2017;72:2005-16.
2. Maurer M, Weller K, Bindslev-Jensen C, Gimenez-Arnanau A, Bousquet PJ, Bousquet J, et al. Unmet clinical needs in chronic spontaneous urticaria. A GA²LEN task force report. *Allergy* 2011;66:317-30.
3. Bernstein JA, Lang DM, Khan DA, Craig T, Dreyfus D, Hsieh F, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol* 2014;133:1270-7.

4. Kolkhir P, Church MK, Weller K, Metz M, Schmetzer O, Maurer M. Autoimmune chronic spontaneous urticaria: what we know and what we do not know. *J Allergy Clin Immunol* 2017;139:1772-81.e1.
5. Kaplan A, Ledford D, Ashby M, Canvin J, Zazzali JL, Conner E, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol* 2013;132:101-9.
6. Maurer M, Rosen K, Hsieh HJ, Saini S, Grattan C, Gimenez-Arnau A, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013;368:924-35.
7. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Bulbul Baskan E, Bradley MS, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol* 2015;135:67-75.
8. Kaplan A, Ferrer M, Bernstein JA, Antonova E, Trzaskoma B, Raimundo K, et al. Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticaria. *J Allergy Clin Immunol* 2016;137:474-81.
9. Asero R. Chronic idiopathic urticaria: a family study. *Ann Allergy Asthma Immunol* 2002;89:195-6.
10. Losol P, Yoo HS, Park HS. Molecular genetic mechanisms of chronic urticaria. *Allergy Asthma Immunol Res* 2014;6:13-21.
11. Bozek A, Krajewska J, Filipowska B, Polanska J, Rachowska R, Grzanka A, et al. HLA status in patients with chronic spontaneous urticaria. *Int Arch Allergy Immunol* 2010;153:419-23.
12. Browning BL, Zhou Y, Browning SR. A one-penny imputed genome from next-generation reference panels. *Am J Hum Genet* 2018;103:338-48.
13. Alexander DH, Novembre J, Lange K. Fast model-based estimation of ancestry in unrelated individuals. *Genome Res* 2009;19:1655-64.
14. Bansal V, Libiger O. Fast individual ancestry inference from DNA sequence data leveraging allele frequencies for multiple populations. *BMC Bioinformatics* 2015;16:4.
15. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet* 2006;38:904-9.
16. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* 2015;4:7.
17. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 2007;81:559-75.
18. Tom J, Chang D, Wuster A, Mukhyala K, Cuenco K, Cowgill A, et al. Enabling genome-wide association testing with multiple diseases and no healthy controls. *Gene* 2019;684:118-23.
19. Zheng X, Shen J, Cox C, Wakefield JC, Ehm MG, Nelson MR, et al. HIBAG-HLA genotype imputation with attribute bagging. *Pharmacogenomics J* 2014;14:192-200.
20. Migdal M, Ruan DF, Forrest WF, Horowitz A, Hammer C. MiDAS—meaningful immunogenetic data at scale. *PLoS Comput Biol* 2021;17:e1009131.
21. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics Consortium, et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* 2015;47:291-5.
22. Giambartolomei C, Vukcevic D, Schadt EE, Franke L, Hingorani AD, Wallace C, et al. Bayesian test for colocalisation between pairs of genetic association studies using summary statistics. *PLoS Genet* 2014;10:e1004383.
23. GTEx Consortium. Human genomics. The Genotype-Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. *Science* 2015;348:648-60.
24. Ge T, Chen CY, Ni Y, Feng YA, Smoller JW. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat Commun* 2019;10:1776.
25. Biagtan MJ, Viswanathan RK, Evans MD, Mathur SK. Clinical utility of the Chronic Urticaria Index. *J Allergy Clin Immunol* 2011;127:1626-7.
26. Astle AJ, Elding H, Jiang T, Allen D, Ruklika D, Mann AL, et al. The allelic landscape of human blood cell trait variation and links to common complex disease. *Cell* 2016;167:1415-29.e19.
27. Bracken SJ, Abraham S, MacLeod AS. Autoimmune theories of chronic spontaneous urticaria. *Front Immunol* 2019;10:627.
28. Miller AT, Dahlberg C, Sandberg ML, Wen BG, Beisner DR, Hoerter JA, et al. Inhibition of the inositol kinase Itpkb augments calcium signaling in lymphocytes and reveals a novel strategy to treat autoimmune disease. *PLoS One* 2015;10:e0131071.
29. Almutairi A, Wallace JG, Jaber F, Alosaimi MF, Jones J, Sallam MTH, et al. Severe combined immunodeficiency caused by inositol-trisphosphate 3-kinase B (ITPKB) deficiency. *J Allergy Clin Immunol* 2020;145:1696-9.e6.
30. Siraganian RP, de Castro RO, Barbu EA, Zhang J. Mast cell signaling: the role of protein tyrosine kinase Syk, its activation and screening methods for new pathway participants. *FEBS Lett* 2010;584:4933-40.
31. Kennedy MB, Beale HC, Carlisle HJ, Washburn LR. Integration of biochemical signalling in spines. *Nat Rev Neurosci* 2005;6:423-34.
32. Elich M, Sauer K. Regulation of hematopoietic cell development and function through phosphoinositides. *Front Immunol* 2018;9:931.
33. Stokes AJ, Shimoda LM, Lee JW, Rillero C, Chang YT, Turner H. Fcεpsilon RI control of Ras via inositol (1,4,5) trisphosphate 3-kinase and inositol tetrakisphosphate. *Cell Signal* 2006;18:640-51.
34. Zhang L, Qiu L, Wu J, Qi Y, Gao X, He C, et al. GWAS of chronic spontaneous urticaria reveals genetic overlap with autoimmune diseases, not atopic diseases. *J Invest Dermatol* 2022.