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A powerful tool with a narrow focus: aiming genome wide association studies at chronic spontaneous urticaria

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Chronic spontaneous urticaria (CSU) is characterized by itchy wheals and/or angioedema that persist or appear intermittently for at least six weeks and can greatly impact quality of life.[1, 2] CSU is increasingly recognized as an immune-mediated chronic inflammatory disorder.[3] A high percentage of patients have symptoms resistant to treatment, requiring a step-up/step-down approach to balance clinical response with treatment risk.[1, 2, 4] The prevalence of CSU is estimated to be 0.5–1% in the US and European counties and up to 4–5% in Asian and South American countries (data are lacking from Africa and other regions), is higher among adults than children and higher among women than men.[1, 2, 4] Different CSU endotypes have been identified, indicating that heterogenous etiologies underlie a common phenotype associated with mast cell degranulation.[2] These include a type I autoallergic endotype and a type IIb autoimmune endotype with overlap between the two groups as well as patients who fit into neither category.[2]

Chang et al. present a genome wide association study (GWAS) in 679 CSU patients from 4 clinical trials investigating omalizumab treatment and nearly 4,500 control patients to assess over 10 million variants for association with CSU risk.[5] The unpredictable and idiopathic nature of CSU, the higher incidence of CSU in first-degree relatives of patients, and the high percentage of CSU patients with symptoms refractory to treatment suggest that GWAS is an apt tool to explore opportunities to expand personalized management. Yet the GWAS by Chang et al. is only the second published. A challenge for CSU GWAS studies is the complex etiological landscape. Multiple pathways contribute to the expressed features of CSU: skin mast cell and basophil activation through autoallergic- or auto-immune-mediated mechanisms; cellular defects in trafficking, signaling and function; and suspected serum and

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plasma factors.[2, 3, 6] Genetic markers for CSU have been observed focusing on a candidate gene or region and include HLA class I and II alleles, histamine- and MC-related genes, genes related to the arachidonic acid pathway, loci in the major histocompatibility complex (MHC) and other targets although results are inconsistent between patient populations that vary by disease characteristics and ethnicity.[6]

The heterogeneity of CSU pathogenic mechanisms despite similar clinical presentations requires careful classification of study participants. Heterogeneity in underlying genetic variants within a study population could bias GWAS results by reducing the statistical power to detect genetic association. Chang et al.[5] increased homogeneity in their study population by including only those with a physician diagnosis who were refractory to antihistamine treatment for at least 6 weeks. Furthermore, the investigators categorized case patients by CU index that measures IgG autoantibody levels using a basophil histamine release assay. While CU index is not a validated tool and is less frequently used than the Urticarial Activity Score, it predicts severity of symptoms and response to treatment with antihistamine, omalizumab and possibly cyclosporine.[7] To address heterogeneity among control patients, the investigators used reverse regression to identify those with diseases not of primary interest that were driving associations and excluded them from a reduced control group used in a second set of analyses. For both CSU and control patients, heterogeneity in genetic ancestry was reduced by including patients with >70% European ancestry.[5]

Chang et al.[5] found associations between loci in the MHC and CSU risk when comparing CSU patients to both the full and reduced control groups, and between loci in the MHC and high CU index among CSU patients (Figure). A second association was found between CSU risk and the inositol-triphosphate 3-kinase B (*ITPKB)* expression quantitative trait loci (eQTL). However, this association was not significant when CSU patients were compared with the reduced control group or for high CU index risk among CSU patients. A second set of analyses involved polygenic risk scores (PRS): genetic variants identified by GWAS are combined into a PRS to estimate lifetime genetic risk of disease. Associations with autoimmune disorders beyond the MHC region were observed between CSU risk and PRSs for 4 autoimmune diseases, a composite PRS for allergic disease, and a PRS for eosinophil cell count expression. Associations between high CU index among CSU patients were found with PRS for 3 autoimmune diseases but not for allergic disease or eosinophil count expression. Unlike many allergic conditions where tissue eosinophilia is accompanied with blood eosinophilia, a percentage of CSU patients have eosinopenia along with higher disease activity and treatment failure.[3, 6] The only other published GWAS study also found autoimmune associations: among Chinese patients and healthy controls, an association with CSU was observed with 5 SNPs related to autoimmune conditions but not with SNPs or PRS linked with atopic conditions.[8] These 5 SNPs did not overlap those found by Chang et al. The GWAS among Chinese patients took a different approach of studying the association of SNPs with different CSU phenotypes and excluded patients with co-morbid autoimmune disease. It is not clear if Chang et al. ascertained autoimmune history in the CSU patients, and if not, this could be a further refinement of their study. There is evidence that patients with type IIb autoimmune CSU (more commonly women and those with high disease activity, treatment resistance, eosinopenia, and comorbid autoimmune conditions) may be affected by different immunologic mechanisms of disease.[3]

Taken together, these first two CSU GWAS reinforce the importance of targeting autoimmune mechanisms for treatment. Implications for further research from the Chang et al. study are evaluation of the specific allele found in the MHC region and exploration of the expression of ITPKB in blood that could be related to mast cell and basophil degranulation to help reveal additional mechanisms of mast cell activation. However, findings are not generalizable to all CSU patients because of the need to focus on a specific subgroup for each GWAS. While not specifically defined, the Chang et al. patient population likely aligned with the type IIb endotype but did not have sufficient sample size to conduct analyses for patients not of European genetic ancestry. The GWAS of CSU that focused on Chinese Han adults found different associations to autoimmune diseases.[8] Differences between these first two GWAS studies could arise from methodologic differences, study groups with different genetic ancestry, or both. The contribution of ancestry to heterogeneity in CSU is not understood but is certainly part of the picture needed to understand which group of patients benefit from each treatment. Similar to other heterogenous conditions, many pathways and treatment options need to be individually and painstakingly illuminated. To understand the landscape, identified subgroups of the CSU patient population need to be continually refined. To this end, genetic data for more diverse CSU patient groups are needed.

Currently, treatment approaches focus on inhibition of mast cell mediators and preventing mast cell activation.[3] GWAS may identify upstream targets and other systems potentially involved, especially for subgroups of patients with symptoms refractory to treatment, as in the study by Chang et al. As mentioned above, the need to precisely characterize participant phenotypes and endotypes to reduce bias means that results from any particular study have limited generalizability. There are other limitations inherent in GWAS that could lead to bias or limit generalizability of findings, including dependence on linkage disequilibrium patterns, small effect sizes and unidentified haplotypes. Additionally, the “upstream” associations identified through GWAS require confirmation using population-based case-control studies. Furthermore, CSU manifestations stemming from mechanisms downstream from the genome are uncovered with other methods. For example, recent transcriptome studies indicate that a number of biologic pathways seen with other inflammatory skin diseases may be involved in CSU.[9] Nevertheless, the strengths of GWAS are much needed and welcomed in the effort to more precisely define and treat this burdensome condition.

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Abbreviations:

CSU	chronic spontaneous urticaria
CU	chronic urticaria
eQTL	expression quantitative trait loci

GWAS	genome-side association study
MHC	major histocompatibility complex
PRS	polygenic risk score
SNP	single nucleotide polymorphism

References

1. Goncalo M, Gimenez-Arnau A, Al-Ahmad M, Ben-Shoshan M, Bernstein JA, Ensina LF, et al. The global burden of chronic urticaria for the patient and society. Br J Dermatol 2021; 184:226–36. [PubMed: 32956489]
2. Kolkhir P, Munoz M, Asero R, Ferrer M, Kocaturk E, Metz M, et al. Autoimmune chronic spontaneous urticaria. J Allergy Clin Immunol 2022; 149:1819–31. [PubMed: 35667749]
3. Kaplan A, Lebwohl M, Gimenez-Arnau AM, Hide M, Armstrong AW, Maurer M. Chronic spontaneous urticaria: Focus on pathophysiology to unlock treatment advances. Allergy 2023; 78:389–401. [PubMed: 36448493]
4. Zuberbier T, Bernstein JA, Maurer M. Chronic spontaneous urticaria guidelines: What is new? J Allergy Clin Immunol 2022; 150:1249–55. [PubMed: 36481045]
5. Chang D, Hammer C, Holweg CTJ, Selvaraj S, Rathore N, McCarthy MI, et al. A genome-wide association study of chronic spontaneous urticaria risk and heterogeneity. J Allergy Clin Immunol 2022.
6. Worm M, Vieths S, Mahler V. An update on anaphylaxis and urticaria. J Allergy Clin Immunol 2022; 150:1265–78. [PubMed: 36481047]
7. Biagtan MJ, Viswanathan RK, Evans MD, Mathur SK. Clinical utility of the Chronic Urticaria Index. J Allergy Clin Immunol 2011; 127:1626–7. [PubMed: 21376378]
8. 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 2023; 143:67–77 e15. [PubMed: 35933036]
9. Ghosh D, Karim R, Zhang X, Singh U, Bernstein JA. Biologic pathways for chronic spontaneous urticaria and their regulation by benralizumab. Allergy 2022; 77:3687–9. [PubMed: 36004497]

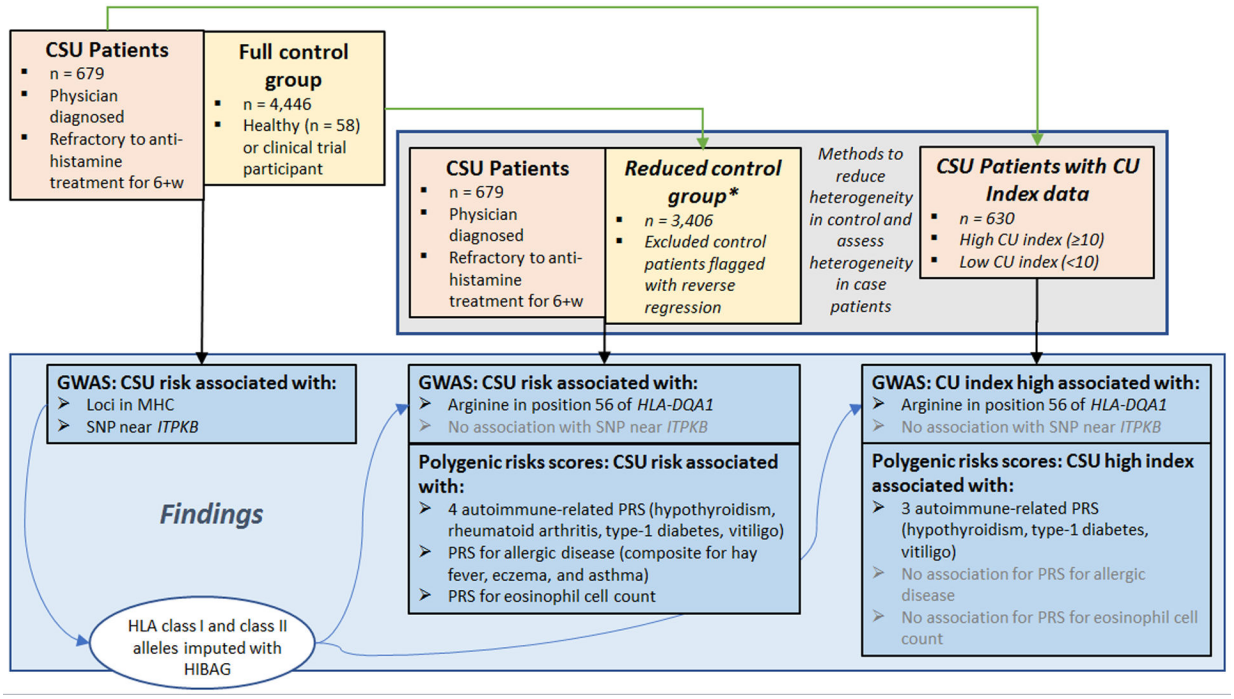

Figure.

Study design and results by Chang et al.[5]

* The investigators used reverse regression to flag control patients with diseases not of primary interest that were driving associations, primarily ulcerative colitis.

CSU: chronic spontaneous urticaria, CU: chronic urticaria, GWAS: genome-wide association study, ITPKB: inositol-triphosphate 3-kinase B, MHC: major histocompatibility complex, PRS: polygenic risk score