Genome-wide meta-analysis implicates variation affecting mast cell biology in urticaria

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Conflicts of interest: SMM is a sub-investigator and CT is a principal and (national) chief investigator on the Pfizer-funded ALLEGRO clinical trial in alopecia areata. CT provides consulting services to Pfizer; and has received speaker fees from Leo Pharma.

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Abstract

Background: Urticaria is characterized by inappropriate mast cell degranulation that leads to the development of wheals and/or angioedema. Twin and family studies indicate that there is a substantial heritable component to urticaria risk.

Objective: To identify genomic loci at which common genetic variation influence urticaria susceptibility.

Methods: Genome-wide association studies (GWAS) of urticaria (including all subtypes) from three European cohorts (UK Biobank, FinnGen, and the HUNT Study) were combined through statistical meta-analysis (14,306 urticaria cases and 650,664 controls). Cases were identified from electronic healthcare records from primary and/or secondary care. To identify putative causal variants and genes, statistical fine-mapping, colocalization, and interrogation of publicly available single-cell transcriptome sequencing resources were performed.

Results: Genome-wide significant associations ($p < 5 \times 10^{-8}$) were identified at six independent loci. These included two previously reported association signals at 1q44 and the human leucocyte antigen region on chromosome 6. Genes with expected or established roles in mast cell biology were associated with the other four genome-wide association signals (*GCSAML*, *FCER1A, TPSAB1,* and *CBLB*). Colocalization of association signals consistent with the presence of shared causal variants was observed between urticaria susceptibility and increased expression of *GCSAML* (posterior probability (PP_{coloc}) = 0.89) and *FCER1A* (PP_{coloc} = 0.91) in skin.

Conclusion: Common genetic variation influencing the risk of developing urticaria was identified at six genomic loci. The relationship of genes with roles in mast cell biology with several association signals implicates genetic variability of specific components of mast cell function in the development of urticaria.

Key Messages

- Common genetic variation at six loci influences genetic susceptibility to urticaria.
- The relationship of genes with established roles in mast cell biology with several association signals implicates genetic variability affecting mast cell function in the development of urticaria.

Capsule summary

This genome-wide meta-analysis identifies common genetic variation at six genomic loci that associate with urticaria susceptibility and suggests that biological variation in mast cell biology is an important mechanism through which this genetic variation acts.

Abbreviations

AU	acute urticaria
CIndU	chronic inducible urticaria
CSU	chronic spontaneous urticaria
CU	chronic urticaria
GWAS	genome-wide association study
GTEx	Genotype-Tissue Expression project
HLA	human leucocyte antigen
HUNT	Trøndelag Health Study
ICD9	International Classification of Diseases (9th Revision)
ICD10	International Classification of Diseases (10th Revision)
MHC	major histocompatibility complex
OR	odds ratio
PP	posterior probability
QTL	quantitative trait locus

Introduction

Urticaria is characterized by aberrant cutaneous mast cell degranulation and the recurrent development of wheals and/or angioedema[1,2]. Acute urticaria (AU) constitutes recurrent wheals and/or angioedema occurring for less than six weeks, while chronic urticaria (CU) entails daily or almost daily symptoms for six weeks or more[1]. CU is subclassified into chronic spontaneous urticaria (CSU), where no consistent trigger is identified, or chronic inducible urticaria (CIndU) wherein symptoms are triggered by specific physical stimuli (e.g., mechanical, thermal or solar electromagnetic radiation) or non-physical phenomena (e.g., exertion via exercise)[1]. Urticaria exhibits epidemiological heterogeneity, with prevalence estimates ranging from ≤ 14% for AU and 0.02–2.7% for CSU, to less than 100 reported cases for certain CIndUs (e.g., heat urticaria)[3,4]. Importantly, the collective frequency of urticaria and poor responses (~50%) to first-line treatments in CU mean that it poses a significant global health burden[5,6].

The contribution of genetic variation to urticaria susceptibility has been demonstrated in family and twin studies. Lifetime risk of any type of urticaria in offspring of parents who both experienced episodes of urticaria is 8.8-fold higher than individuals whose parents had no previous history[7], while twin studies estimate urticaria to be ~60% heritable[8]. The frequent co-occurrence of several urticaria subtypes also implies a shared susceptibility across disease subtypes[4].

To date, three genome-wide association studies (GWAS) of urticaria have been performed. Two specifically focused on CSU, identifying a total of six independent urticaria risk loci in European and Han Chinese populations, and with both implicating the extended major histocompatibility complex (MHC) on chromosome 6[9,10]. Urticaria (including all subtypes) was also one of 220 traits included in a large genetic study in the Japanese population[11]. This GWAS identified two further urticaria susceptibility loci at chromosome 1q44 and 11p15.4[11].

The current study aims to identify specific genomic loci at which genetic variation influences susceptibility to urticaria by performing a series of case-control GWAS in European ancestry cohorts and combining the results via statistical meta-analysis.

Results/Discussion

We performed an inverse variance weighted fixed-effects meta-analysis, incorporating GWAS for urticaria (including all subtypes) performed in two European cohorts (UK Biobank and the Trøndelag Health Study (HUNT); **Methods**) and summary statistics obtained from a similar urticaria GWAS in FinnGen[12-14]. Urticaria cases within these cohorts were identified from primary and/or secondary care electronic healthcare records using International Classification of Diseases (9th and 10th Revisions) (ICD9/ICD10) codes, which were either directly encoded or systematically mapped from an alternative coding scheme. Individuals with no record of urticaria were classified as controls. A total of 11,261,454 variants were analyzed for 14,306 cases and 650,664 controls across the three studies[12-14]. The genomic inflation factor was less than 1.05 in each GWAS and 1.04 in the final meta-analysis, indicating effective control of potential sources of systematic bias. Genetic variants with genome-wide significant evidence of association ($p < 5 \times 10^{-8}$) were observed at six independent loci (**Figure 1** and **Table 1**).

We evaluated the evidence of association in our urticaria meta-analysis for each of the six genomic loci previously reported to contribute to CSU risk (**Table E1**). Within the MHC region, we found nominally significant evidence of association for a variant previously associated with CSU by Zhang *et al.* (rs9378141, odds ratio (OR) 0.99, $p = 0.016$)[10], while observing genome-wide significant evidence of association for a different lead variant (rs139299944, OR 1.10, $p = 6.9 \times 10^{-14}$). We performed a detailed analysis of classical MHC alleles through imputation and association testing in UK Biobank. The strongest evidence of association with urticaria was observed for a class II human leucocyte antigen (HLA) allele (HLA-DQB1*02:01, $p = 2.5 \times 10^{-6}$, **Table E2**). This finding differs from the CSU association reported by Chang *et al.*,[9] where the risk allele mapped to the presence of an arginine codon at position 56 of HLA-DQA1. Nevertheless, our observations are consistent with a role for antigen presentation via class II MHC and autoimmunity in urticaria[15], with risk alleles differing across urticaria subtypes.

There was no evidence of association at the 11p15.4 locus previously reported in an analysis by Sakaue *et al.* of all urticaria subtypes in a Japanese population (rs11030639, OR 0.99, $p = 0.279$)[11]. However, the other reported susceptibility locus in that study at 1q44 has the strongest evidence of association with urticaria in the current meta-analysis[11]. Statistical fine-mapping to define the causal variant at this locus identified a 95% credible set comprising two variants. Both variants lie within the boundaries of *GCSAML*, which encodes the cytosolic germinal

center associated signaling and motility-like protein and which has a putative role in immune cell signaling and motility. rs74227709, an intronic variant in *GCSAML*, was the most likely causal variant (OR 1.25, $p = 2.6 \times 10^{-21}$, posterior probability (PP) = 0.64), while the second is a splice donor variant predicted to disrupt splicing of the canonical *GCSAML* transcript typically expressed in skin (rs56043070, OR 1.25, $p = 6.4 \times 10^{-21}$, PP = 0.36). We hypothesized that increased urticaria susceptibility at the 1q44 locus might be due to cutaneous expression of an alternative *GCSAML* transcript, but this was not supported by analysis of splice quantitative trait loci (QTL) of *GCSAML* in skin from the Genotype-Tissue Expression project (GTEx). Nevertheless, colocalization was observed between the urticaria association signal and *GCSAML* transcript abundance QTL in non-sun-exposed skin ($PP_{coloc} = 0.89$), with urticaria risk alleles being associated with increased *GCSAML* expression (**Figure 2**). Analysis of a publicly available single-cell RNA sequencing dataset also revealed that *GCSAML* is expressed almost exclusively in skin by mast cells (**Figure 3, Figure E1**)[16], providing supportive evidence that the effect of this locus may be exerted via a direct effect on mast cell function.

In addition to the genome-wide significant associations at two of the previously reported urticaria susceptibility loci, we report a further four risk loci. At 1q23.2 (lead variant rs6703348, OR 1.08, $p = 3.6 \times 10^{-8}$), colocalization analyses indicated that this association signal shares a common causal variant with an expression QTL for *FCER1A* in both sun-exposed ($PP_{coloc} = 0.93$) and non-sun-exposed skin ($PP_{coloc} = 0.91$), with the urticaria risk allele being associated with increased *FCER1A* expression in both tissues (**Figure 4**). *FCERA1* encodes a subunit of the high-affinity IgE receptor whose expression on the cell surface of mast cells is well-documented, as is its role in IgE-dependent mast cell activation[17]. It is also expressed in several types of cutaneous immune cell, e.g., Langerhans cells, and plays an established role in several allergic diseases (**Figure E1**)[18].

The biological mechanisms impacted by the associated genetic variation at each of the remaining three association signals are less clearly defined. At 16p13, the lead variant (rs118070675, OR 1.18, $p = 2.8 \times 10^{-10}$) is an intronic variant in *CACNA1H* (calcium voltage-gated channel subunit alpha1 H). This variant lies less than 35 kb upstream of *TPSAB1* (tryptase alpha/beta 1, **Figure E2**), a gene that encodes key enzymes in mast cell granules and which may potentiate mast cell activation through cleavage of their cell surface receptors, e.g., G-protein coupled receptors[19,20]. Furthermore, increased gene copy numbers of *TPSAB1* are

associated with elevated serum tryptase in the UK population and more variably with mast cell-mediated symptoms[21,22]. Such variants are absent from available imputation panels and its relevance to urticaria risk will therefore require dedicated investigation. At 3q13.11, the 95% credible set comprised 40 variants. However, the lead variant (rs35834008, OR 1.11, $p = 3.5 \times 10^{-14}$) is located in an intron of *CBLB*, whose gene product negatively regulates signal transduction from cell surface receptors on immune cells, including the high-affinity IgE receptor on mast cells, for which it downregulates phosphorylation of the receptor itself and the signalling molecules required for mast cell degranulation and cytokine gene transcription[23]. Interestingly, analysis of the UK Biobank cohort revealed no evidence of epistasis between rs35834008 and the lead variant at 1q23.2, where *FCER1A* is a putative causal gene. Finally, fine-mapping of the association signal at 12q15 strongly supported rs73141533 (OR 1.41, $p = 3.8 \times 10^{-8}$) as the causal variant (PP = 0.94). Publicly available ChIP-Seq experiments in human tissues demonstrate transcription factor binding at this location, e.g., ESR1, GATA4 and MYOG, indicating that this variant likely has biological sequelae, and although there is evidence of *ESR1* expression in human cutaneous mast cells, the mechanisms by which it influences urticaria risk are unclear[24,25].

This study represents one of the largest genetic studies of urticaria ever undertaken and provides striking insights into genetic mechanisms contributing to disease risk. Our findings are consistent with the previously proposed role of antigen presentation by MHC class II molecules in CSU, in addition to highlighting a novel association with HLA-DQB1 in the UK Biobank cohort. Our results also suggest that genetic predisposition to urticaria is mediated through genetic control of mast cell function. This model is supported by the causal associations ascertained via integration of functional data and/or the spatial proximity of genes with proposed roles in mast cell biology at four of our six susceptibility loci (*GCSAML*, *FCER1A, TPSAB1,* and *CBLB*). Inclusion of all urticaria subtypes in this meta-analysis facilitated investigation of shared genetic risk factors amongst urticaria subtypes. However, it is possible that some association signals are driven by specific forms of urticaria. Due to limitations in the ICD9/ICD10 classification of urticaria, our study could not interrogate this phenomenon further, and there is an urgent need for deeply phenotyped urticaria datasets to allow nuanced questions of genetic heterogeneity to be addressed.

In conclusion, this genome-wide meta-analysis has identified common variants at six genomic loci associated with urticaria and implicates biological variation in mast cell biology as a key mechanism through which this genetic variation impacts disease risk.

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Tables

Table 1. Lead variants at each of the six independent genome-wide significant association signals

rsID	Chr	Pos	Band	RA	PA	RAF_{Case}	RAF_{Ctrl}	OR_{UKB} (95% CI)	P_{UKB}	OR_{FG} (95% CI)	P_{FG}	OR_{HUNT} (95% CI)	P_{HUNT}	OR_{MA} (95% CI)	P_{MA}	95% CS SNPs	Lead SNP PP	Candidate Gene
rs6703348	1	159291683	1q23.2	C	G	0.747	0.730	1.06 (1.03-1.11)	9.2×10^{-4}	1.11 (1.06-1.15)	1.1×10^{-6}	0.97 (0.86-1.11)	0.691	1.08 (1.05-1.11)	3.6×10^{-8}	93	0.31	*FCER1A*
rs74227709	1	247722588	1q44	A	G	0.079	0.065	1.23 (1.16-1.30)	2.4×10^{-12}	1.28 (1.18-1.39)	2.7×10^{-9}	1.32 (1.06-1.64)	0.012	1.25 (1.19-1.31)	2.6×10^{-21}	2	0.64	*GCSAML*
rs35834008	3	105387230	3q13.11	C	A	0.711	0.692	1.10 (1.06-1.15)	1.5×10^{-7}	1.11 (1.06-1.15)	2.4×10^{-7}	1.13 (0.99-1.28)	0.069	1.11 (1.08-1.14)	3.5×10^{-14}	40	0.06	*CBLB*
rs139299944	6	32602665	6p21.32	C	CT	0.611	0.594	1.08 (1.04-1.11)	3.4×10^{-5}	1.12 (1.08-1.16)	1.8×10^{-9}	1.33 (1.11-1.60)	0.002	1.10 (1.07-1.13)	6.9×10^{-14}	-	-	*HLA-DQA1*
rs73141533	12	68184407	12q15	C	A	0.991	0.988	1.43 (1.21-1.69)	3.5×10^{-5}	1.39 (1.15-1.67)	5.3×10^{-4}	1.33 (0.80-2.21)	0.270	1.41 (1.25-1.59)	3.8×10^{-8}	2	0.94	-
rs118070675	16	1256902	16p13.3	C	G	0.948	0.939	1.18 (1.10-1.26)	4.7×10^{-6}	1.20 (1.10-1.30)	1.6×10^{-5}	1.10 (0.85-1.44)	0.462	1.18 (1.12-1.25)	2.8×10^{-10}	19	0.22	*CACNA1H*

NOTE. All genomic positions are reported in relation to Genome Reference Consortium Human Build 37. 95% CI, 95% confidence interval; Chr, chromosome; CS, credible set; FG, FinnGen; HUNT, Trøndelag Health Study; MA, meta-analysis; OR, odds ratio; P, p-value; PA, protective allele; PAF, protective allele frequency; PP, posterior probability; Pos, genomic position; RA, risk allele; RAF, risk allele frequency; rsID, Reference SNP cluster ID; SNP, single nucleotide polymorphism; UKB, UK Biobank

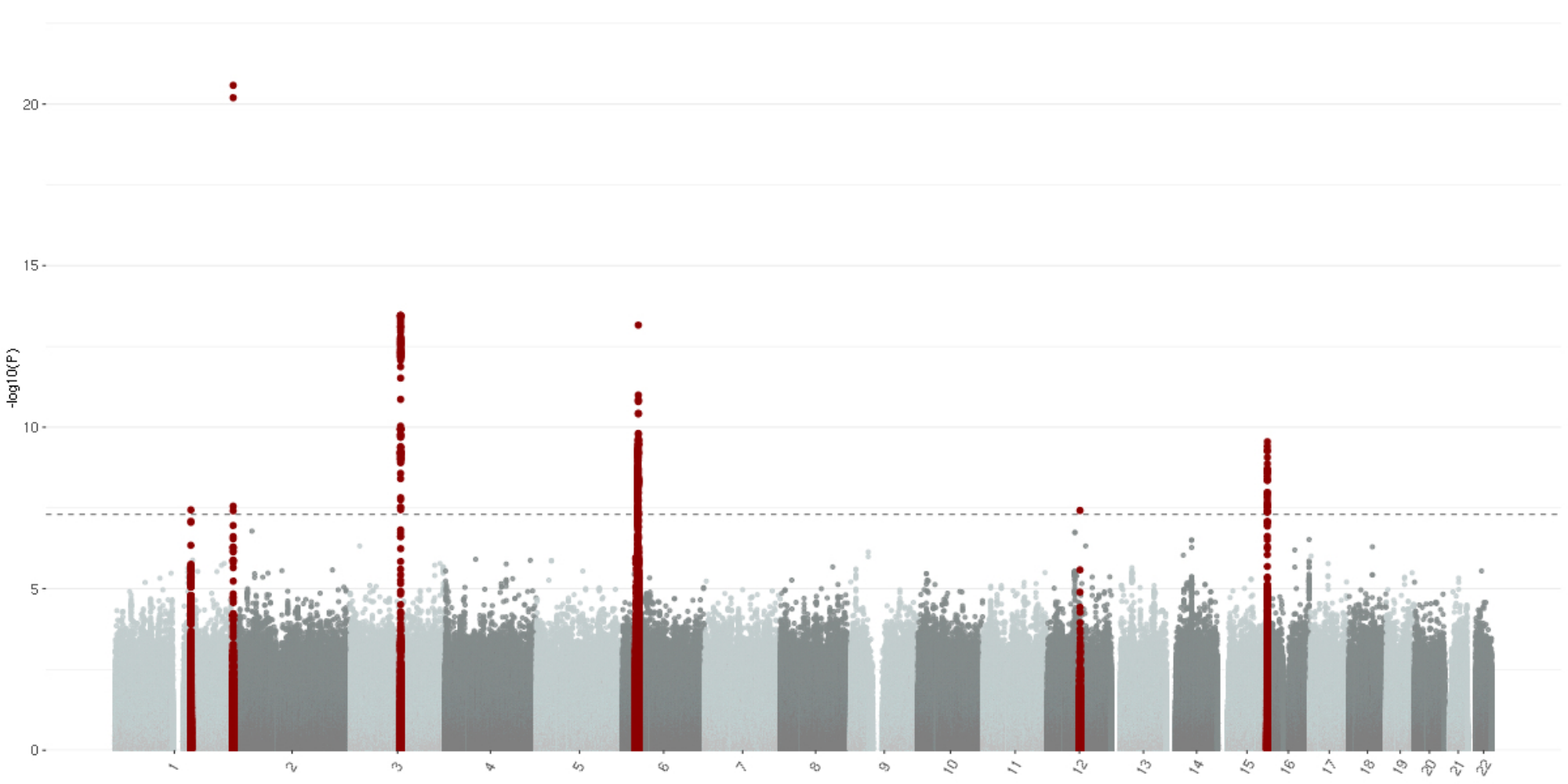
Figure Legends

Figure 1. Manhattan plot illustrating evidence of association of genetic variants with urticaria susceptibility. Each point represents a variant ordered by chromosome and base position on the X-axis, with the evidence of association on the Y-axis represented as $-\log_{10}$(p-value) (not adjusted for multiple comparisons). The dashed line indicates the genome-wide significance threshold ($p = 5 \times 10^{-8}$).

Figure 2. Regional association plot of urticaria susceptibility association signal at 1q44 and eQTL for *GCSAML* in non-sun-exposed skin. The lead variant for the urticaria association signal (rs74227709) is shown in purple while the colors of the other variants indicate linkage disequilibrium (r^2) with the lead variant. *eQTL, expression quantitative trait locus.*

Figure 3. *GCSAML* mRNA expression in human skin. (a) Uniform Manifold Approximation and Projection (UMAP) plot of single-cell RNA sequencing data from cells isolated from breast skin of healthy adults (n = 5)[16], with mast cells highlighted in black. (b) Log2 normalised expression of *GCSAML* showing localization of expression to the mast cell cluster.

Figure 4. Regional association plot of urticaria susceptibility association signal at 1q23.2 and eQTL for *FCER1A* in non-sun-exposed skin. The lead variant for the urticaria association signal (rs6703348) is shown in purple while the colors of the other variants indicate linkage disequilibrium (r^2) with the lead variant. *eQTL, expression quantitative trait locus.*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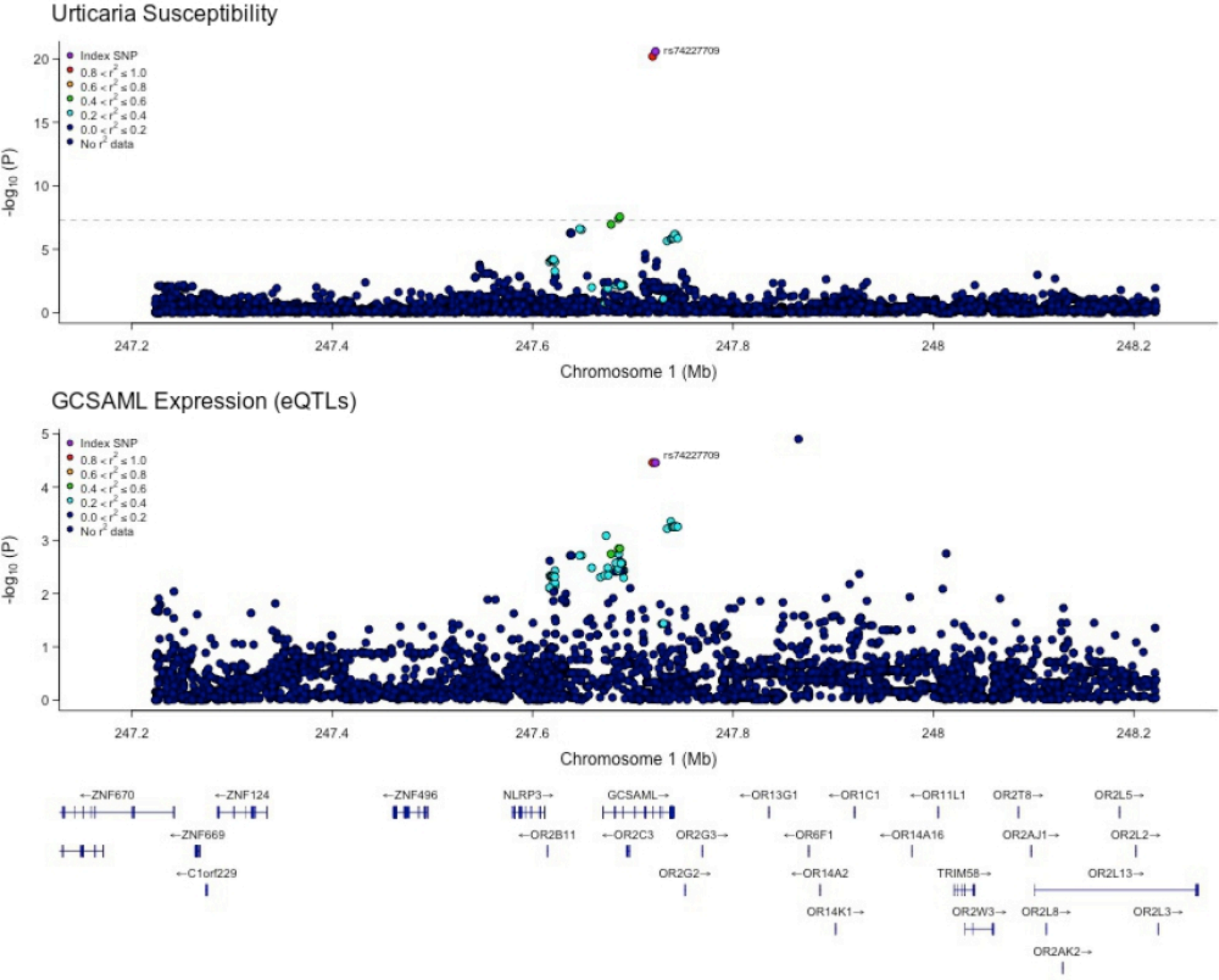
Urticaria Susceptibility
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0.6 < r² ≤ 0.8
0.4 < r² ≤ 0.6
0.2 < r² ≤ 0.4
0.0 < r² ≤ 0.2
No r² data
rs74227709
-log10 (P)
20
15
10
5
0
247.2
247.4
247.6
247.8
248
248.2
Chromosome 1 (Mb)
GCSAML Expression (eQTLs)
Index SNP
0.8 < r² ≤ 1.0
0.6 < r² ≤ 0.8
0.4 < r² ≤ 0.6
0.2 < r² ≤ 0.4
0.0 < r² ≤ 0.2
No r² data
rs74227709
-log10 (P)
5
4
3
2
1
0
247.2
247.4
247.6
247.8
248
248.2
Chromosome 1 (Mb)
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←ZNF124
←ZNF496
NLRP3→
GCSAML→
←OR13G1
←OR1C1
←OR11L1
OR2T8→
OR2L5→
←ZNF669
←OR2B11
←OR2C3
OR2G3→
←OR6F1
←OR14A16
OR2AJ1→
OR2L2→
←C1orf229
OR2G2→
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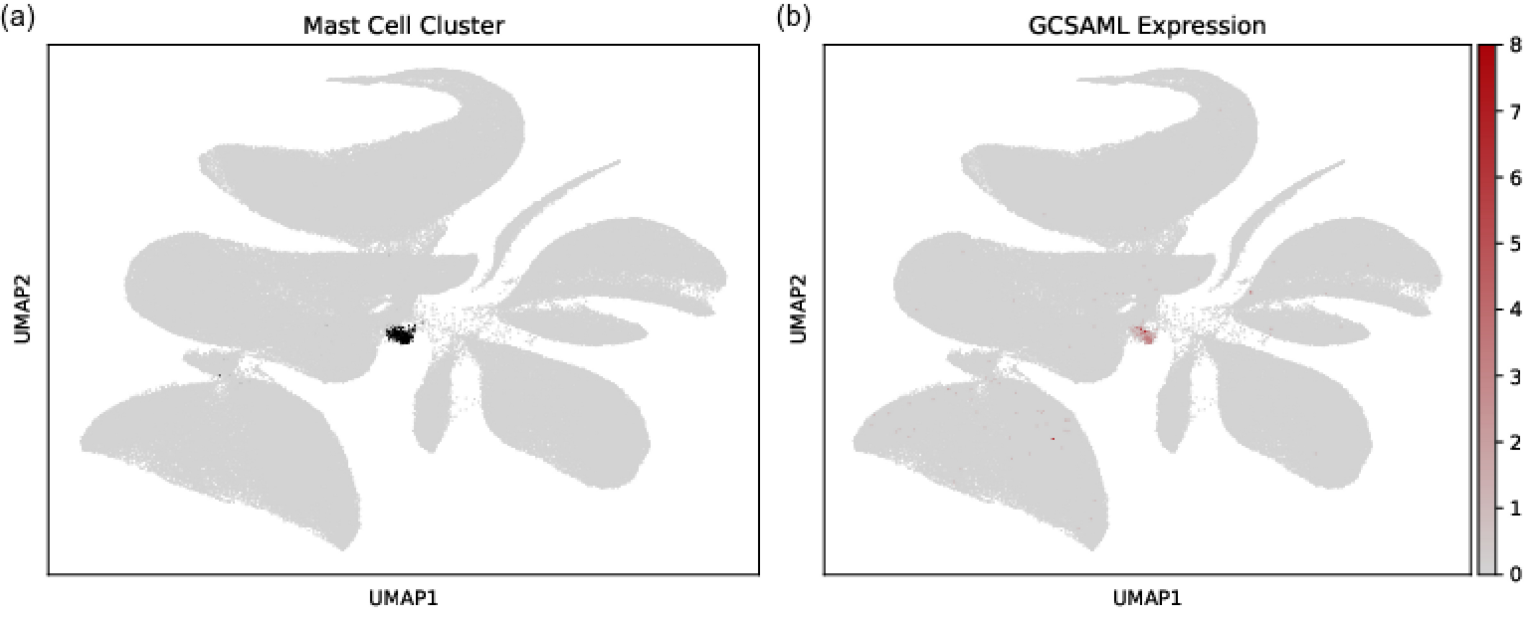
OR2AK2→


(a)
Mast Cell Cluster
UMAP2
UMAP1
(b)
GCSAML Expression
UMAP2
UMAP1
8
7
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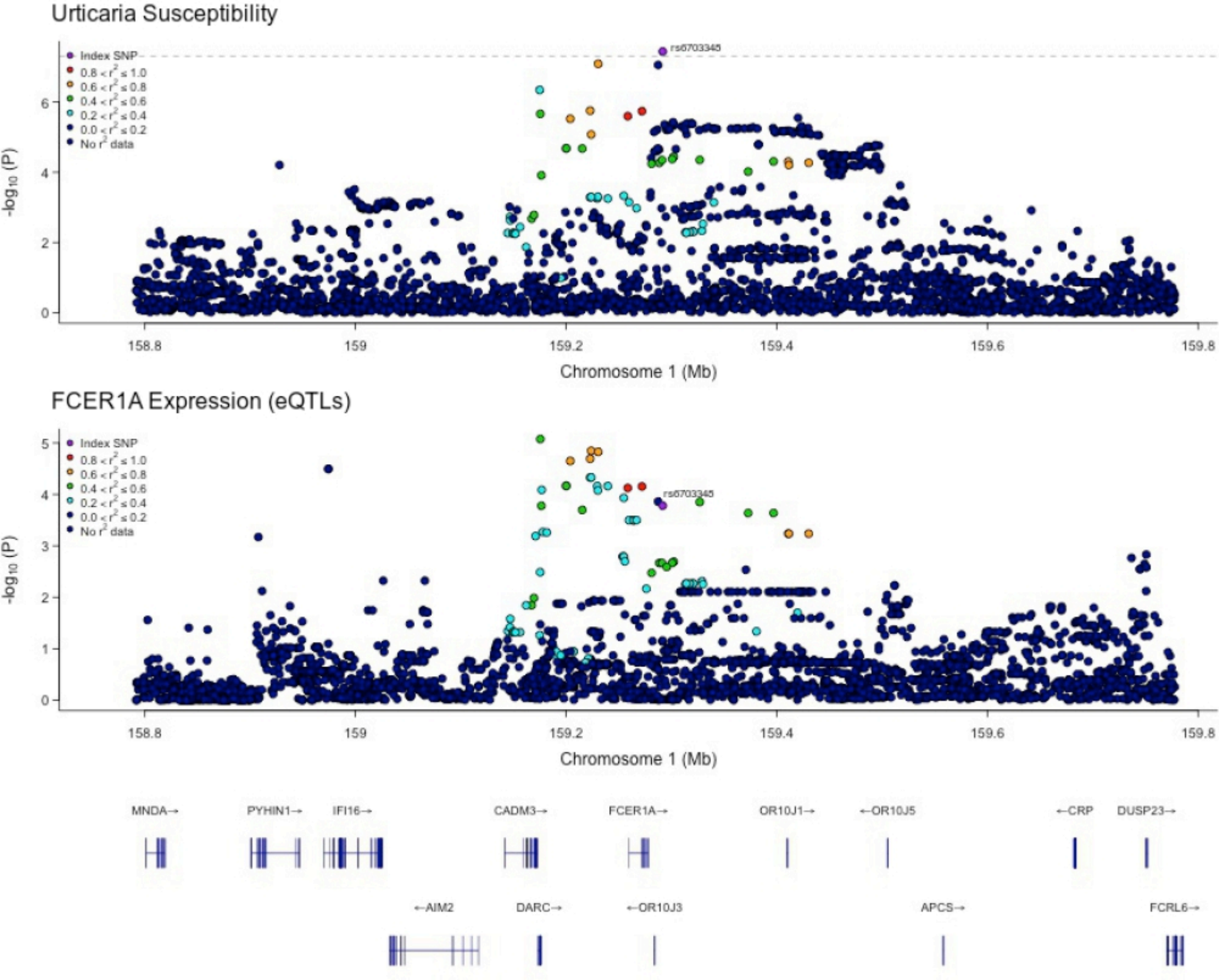
Urticaria Susceptibility
Index SNP
0.8 < r² ≤ 1.0
0.6 < r² ≤ 0.8
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No r² data
rs6703345
-log10 (P)
0
2
4
6
158.8
159
159.2
159.4
159.6
159.8
Chromosome 1 (Mb)
FCER1A Expression (eQTLs)
Index SNP
0.8 < r² ≤ 1.0
0.6 < r² ≤ 0.8
0.4 < r² ≤ 0.6
0.2 < r² ≤ 0.4
0.0 < r² ≤ 0.2
No r² data
rs6703345
-log10 (P)
0
1
2
3
4
5
158.8
159
159.2
159.4
159.6
159.8
Chromosome 1 (Mb)
MNDA→
PYHIN1→
IFI16→
CADM3→
FCER1A→
OR10J1→
←OR10J5
←CRP
DUSP23→
←AIM2
DARC→
←OR10J3
APCS→
FCRL6→

Methods

Cohort descriptions

UK Biobank is a longitudinal observational study that includes genetic, lifestyle and primary/secondary healthcare information from more than 500,000 UK participants and is available to researchers following an approval process (approved research ID: 15147)[1]. The UK Biobank study was approved by the National Health Service (NHS) National Research Ethics Service (Reference: 11/NW/0382), and all participants provided written informed consent to participate in the study. FinnGen data consists of 260,405 Finnish individuals from FinnGen Data Freeze 6, which includes prospective epidemiological and disease-based cohorts as well as hospital biobank samples (https://finngen.gitbook.io/documentation/v/r6/)[2]. The data were linked by unique national personal identification numbers to national hospital discharge, death, and medication reimbursement registries. The Ethical Review Board of the Hospital District of Helsinki and Uusimaa approved the FinnGen study protocol (Reference: HUS/990/2017). Participation in FinnGen utilizing biobank samples is always voluntary and sample donors are free to alter their consent to biobank research at any time. The Trøndelag Health Study (HUNT) is a population-based cohort study carried out at four time points over approximately 40 years (HUNT1 (1984-1986), HUNT2 (1995-1997), HUNT3 (2006-2008) and HUNT4 (2017-2019)) and incorporates over 250,000 individuals[3]. Participants from HUNT2 and HUNT3 are included in the current study (n = 69,420). Participation in HUNT is based on informed consent, and the study has been approved by the Norwegian Data Protection Authority and the Regional Committee for Medical and Health Research Ethics in Central Norway (Reference: 27420).

Case ascertainment

A dermatologist (SMM) working with a clinical coding team in a tertiary hospital identified all International Classification of Diseases (9th and 10th Revisions) (ICD9/ICD10) codes that could map to the EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI clinical classification of urticaria, including acute and chronic subtypes[4]. ICD9/ICD10 codes that referred to non-mast cell-mediated urticaria- or angioedema were excluded. Of note, the classification of urticaria subtypes within the ICD9/ICD10 system does not clearly map to its classification by EAACI/GA^{2}LEN/EuroGuiDerm/APAAACI guidelines and analyses of specific urticaria subtypes

were not performed. The ICD10 codes used to identify cases in UK Biobank (secondary care records only) and FinnGen were L50.0 ("allergic urticaria"), L50.1 ("idiopathic urticaria"), L50.2 ("urticaria due to cold/heat"), L50.3 ("dermographic urticaria"), L50.4 ("vibratory urticaria"), L50.5 ("cholinergic urticaria"), L50.6 ("contact urticaria"), L50.8 ("other urticaria, including chronic and recurrent"), L50.9 ("urticaria, unspecified"), and L56.3 ("solar urticaria"). Additional cases in UK Biobank were identified from linked primary care records using a series of primary care read codes that were systematically mapped from the above ICD10 classifications based on the Technology Reference Update Distribution from NHS Digital. These comprised primary care read v2 codes and CTv3 codes (**Table E3**). Data access restrictions in the FinnGen cohort precluded specific inclusion of L56.3 ("solar urticaria") in the genome-wide association study (GWAS) summary statistics. Those excluded cases accounted for 16 individuals in total. For the HUNT cohort, all ICD9 codes corresponding to the above ICD10 classification (708.0, 708.1, 708.2, 708.3, 708.4, 708.4, 708.8 and 708.9) were used to define urticaria cases. There were no ICD9 codes corresponding specifically to L50.6 ("contact urticaria") or L56.3 ("solar urticaria").

Genome-wide association studies

UK Biobank genotyping was performed using the Affymetrix UK BiLEVE and UK Biobank Axiom arrays. Genotyping and initial quality control were performed by the UK Biobank central team[1]. Based on the quality control metrics provided, we removed samples if they were non-European, exhibited gender mismatch, excess relatedness, heterozygosity or missingness > 5%. We then extracted participants that were unrelated and of white British ancestry (to minimize the potential impact of population stratification), followed by removal of additional individuals with low call rates (< 98%) in well-called (> 90%) markers. This produced a final sample size of 33,694. Genome-wide imputation was undertaken by the UK Biobank central team using IMPUTE2 software and UK10K haplotype reference panel merged with the 1,000 Genomes Phase 3 reference panel[5]. Imputed variants with imputation $r^2 > 0.7$ and minor allele frequency > 0.5% were included in further analyses. We performed a GWAS of urticaria (7,570 cases and 329,124 controls) using logistic regression in PLINK v2.0 with the age, sex, genotyping batch, and the first 20 ancestry principal components as co-variates (**Table E4** and **Figure E3**)[6]. Imputation of classical human leucocyte antigen (HLA) alleles was also performed by the UK Biobank central team and their association with urticaria disease status was tested using the same model and covariates as the

primary GWAS in PLINK v1.9[6]. Testing for epistasis between lead variants identified in the meta-analysis was also performed in the UK Biobank cohort using PLINK v1.9[6].

For the FinnGen cohort, summary statistics for a publicly available urticaria GWAS (6,168 cases and 252,688 controls) were downloaded from the FinnGen server (Data Freeze 6)[2]. These summary statistics were lifted over from Genome Reference Consortium Human Build 38 (GRCh38) to Genome Reference Consortium Human Build 37 (GRCh37) using the UCSC LiftOver tool (downloaded 11 June 2020; http://genome.ucsc.edu). 15,753,026 variants were successfully lifted over. The original data from this cohort were produced and processed by the FinnGen study investigators (detailed at https://finngen.gitbook.io/documentation/v/r6/). Briefly, samples were genotyped using Illumina (Illumina Inc., San Diego, CA, USA) and Affymetrix arrays (Thermo Fisher Scientific, Santa Clara, CA, USA). For sample-wise quality control, individuals with ambiguous gender, high genotype missingness (>5%), excess heterozygosity (± 4 standard deviations) and non-Finnish ancestry were removed. For variant-wise quality control, variants with high missingness (> 2%), low Hardy-Weinberg equilibrium p-values ($< 1 \times 10^{-6}$) and minor allele count < 3 were removed. Genome-wide genotype imputation used a population-specific Sequencing Initiative Suomi (SISu; https://sisuproject.fi/) v3 reference panel performed with Beagle 4.1 (version 08Jun17.d8b). Phenotypic data used to define disease endpoints in this cohort were derived from various nationwide registries linked to unique national personal identification numbers and harmonized over different ICD Revisions. SAIGE (r3 release) software was used for running the GWAS for each phenotype (**Table E4** and **Figure E3**). This model included age, sex, genotyping batch and 10 principal components as co-variates.

For the HUNT cohort, participants (aged > 20 years) from the HUNT2 and HUNT3 studies only were genotyped using one of three different Illumina HumanCoreExome arrays (HumanCoreExome12 v1.0, HumanCoreExome12 v1.1 and UM HUNT Biobank v1.0). Sample and variant quality control was performed using standard practices and have been reported elsewhere[7]. All variants were imputed from a merged reference panel constructed from the Haplotype Reference Consortium (HRC) panel (v1.1) and a local reference panel based on 2,202 whole-genome sequenced HUNT participants using Minimac3[8], resulting in 24.9 million variants. The individuals included in the analyses were of European ancestry. An urticaria GWAS (568

cases and 68,852 controls) was run using SAIGE version 0.35.8.3 and included age, sex, genotyping batch, and the first four ancestry principal components as co-variates (**Figure E3**).

Meta-analysis

A fixed-effects (inverse variance-weighted) meta-analysis was conducted using METAL on 664,970 individuals (14,306 urticaria cases and 650,664 controls) from the three GWAS described above[9]. All variants were aligned to GRCh37 and provided with a unique identifier that consisted of a concatenation of the chromosome, basepair position, and variant alleles. Discrepancies in naming conventions for effect and non-effect alleles across the datasets were accounted for. A total of 11,261,454 variants present in two or more datasets were included in the final analysis. The linkage disequilibrium (LD) score regression intercept and genomic inflation factor were calculated using LDSC software with default settings and precomputed LD scores derived from 1,000 Genomes data[10]. Genome-wide significant variants were determined using a p-value threshold of 5.0×10^{-8}. Lead variants for each association signal were defined as the most significant genome-wide significant variant (lowest p-value) within a 500 kb genomic window.

Fine-mapping

Statistical fine-mapping was performed at each association signal using the R package coloc, which uses approximate Bayes' factors as described by Wakefield[11]. Variants within 500 kb of the lead variant were used as input, and the prior probability for each variant was set at 1×10^{-4}. The resulting posterior probabilities represent the probability of each variant being causal for urticaria, under the assumption that a single causal variant underlies the association signal. These posterior probabilities were used to define 95% credible sets, which were the minimum set of variants whose combined posterior probabilities were ≥ 0.95.

Colocalization

Colocalization between urticaria association signals and skin *cis* expression quantitative trait loci (eQTLs) from The Genotype-Tissue Expression (GTEx) Project were examined using a Bayesian test for colocalization and implemented in the R package coloc, with a prior probability of colocalization of 1×10^{-4}. GTEx data were obtained from the GTEx Portal via https://console.cloud.google.com/storage/browser/gtex-resources/GTEx_Analysis_v8_QTLs on

1st November 2022. Candidate eQTLs were defined as any variant within 500 kb of an urticaria risk locus that was also associated with variation in expression of a nearby gene ($p < 1 \times 10^{-4}$). Following the analysis, a posterior probability > 50% was taken as evidence of colocalization. Analyses of splice quantitative trait loci from GTEx were performed only for the 1q44 locus using the same methodology.

Exploration of putative causal variants and genes

Several publicly available bioinformatic resources and tools were used to explore putative causal variants and genes. Ensembl Variant Effect predictor (VEP) was used to annotate variants with publicly available meta-data, including their consequences, population allele frequencies and pathogenicity predictions[12]. EMBL-EBI Expression Atlas and The Human Protein Atlas were used to explore tissue- and cell-specific expression of putative causal genes[13,14]. Single-cell sequencing analysis expression of *GCSAML* in healthy human skin was explored through re-analysis of publicly available data using Scanpy packages in Python[15]. Cell clusters of interest were determined by the authors' cell annotations and the identity of the cell cluster representing mast cells was confirmed by examining the expression of well-known marker genes.

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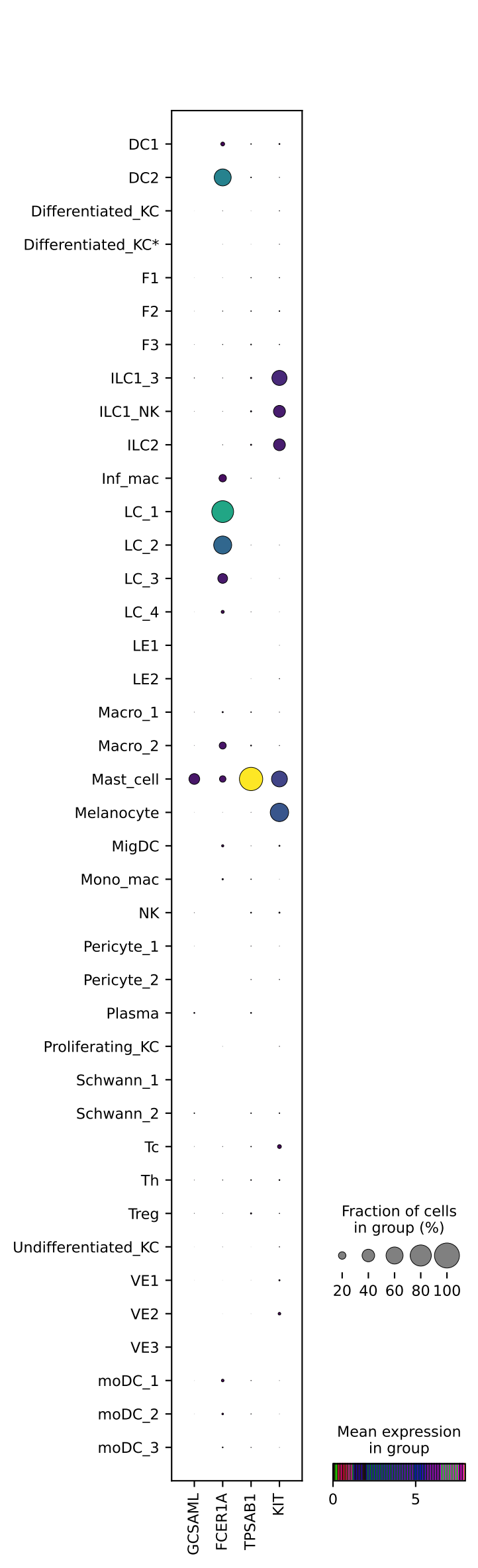
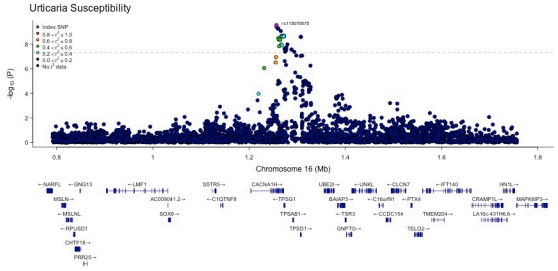
Online Repository Figure Legends

Figure E1. *GCSAML* and *FCER1A* expression in human skin. Dotplot of mean log2 normalised expression of *GCSAML* and *FCER1A* in a single-cell RNA sequencing healthy skin dataset[16]. *DC, dendritic cell; F, fibroblast; ILC, innate lymphoid cell; Inf, inflammatory; KC, keratinocyte; LC, Langerhans cell; LE, lymphatic endothelium; Macro, macrophage; MigDC, migratory DC; Mono-mac, monocyte-derived macrophage; NK, natural killer cell; Plasma, plasma cell; Schwann, Schwann cell; Tc, cytotoxic T-cell; Th, T-helper cell; Treg, regulatory T-cell; VE, vascular endothelium; moDC, monocyte-derived DC.*

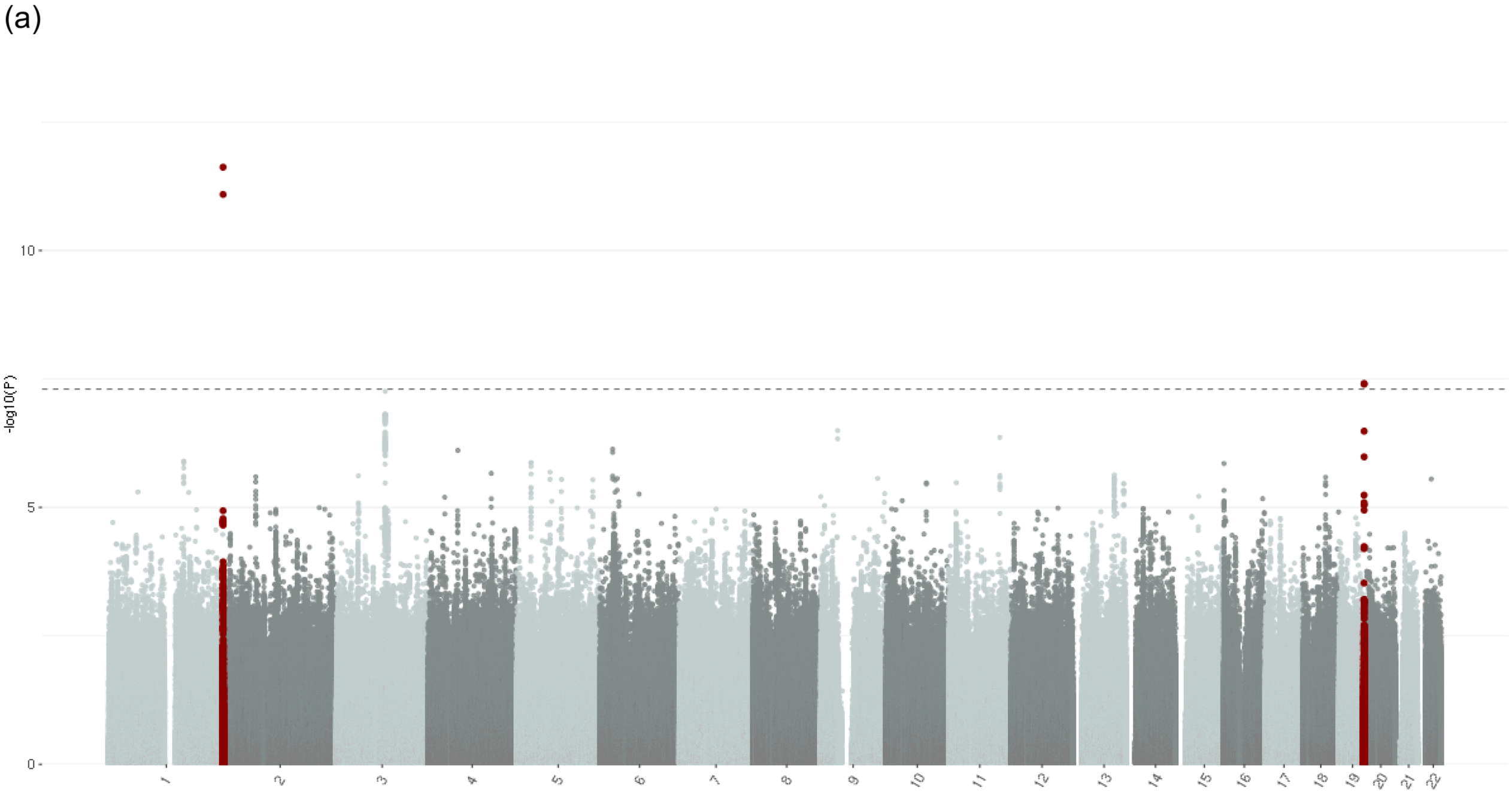
Figure E2. Regional association plot of urticaria genome-wide meta-analysis at genomic locus 16p13.3. The lead variant for the urticaria association signal (rs118070675) is shown in purple while the colors of the other variants indicate linkage disequilibrium (r^2) with the lead variant.

Figure E3. Manhattan plots illustrating evidence of association of genetic variants with urticaria susceptibility in three separate cohorts (a) UK Biobank, (b) FinnGen, and (c) HUNT. Each point represents a variant ordered by chromosome and base position on the X-axis, with the evidence of association on the Y-axis represented as $-\log_{10}$(p-value) (not adjusted for multiple comparisons). The dashed line indicates the genome-wide significance threshold ($p = 5 \times 10^{-8}$).


DC1
DC2
Differentiated_KC
Differentiated_KC*
F1
F2
F3
ILC1_3
ILC1_NK
ILC2
Inf_mac
LC_1
LC_2
LC_3
LC_4
LE1
LE2
Macro_1
Macro_2
Mast_cell
Melanocyte
MigDC
Mono_mac
NK
Pericyte_1
Pericyte_2
Plasma
Proliferating_KC
Schwann_1
Schwann_2
Tc
Th
Treg
Undifferentiated_KC
VE1
VE2
VE3
moDC_1
moDC_2
moDC_3
GCSAML
FCER1A
TPSAB1
KIT
Fraction of cells in group (%)
20 40 60 80 100
Mean expression in group
0
5


Urticaria Susceptibility
rs115075075
Index SNP
0.8 < r² ≤ 1.0
0.6 < r² ≤ 0.8
0.4 < r² ≤ 0.6
0.2 < r² ≤ 0.4
0.0 < r² ≤ 0.2
No r² data
-log10 (P)
0
2
4
6
8
0.8
1
1.2
1.4
1.6
1.8
Chromosome 16 (Mb)
←NARFL
←GNG13
MSLN→
←MSLNL
←RPL39D1
CHTF18→
PRR25→
H1
←LMF1
AC009041.2→
SOX8→
SSTR5→
←C1QTNF8
CACNA1H→
←TPSG1
TPSAB1→
TPSD1→
UBE2E→
←JUND
BAIAP3→
←TSR3
GNPTG→
←CLCN7
←C16orf91
←PTX4
←CCDC154
TMEM204→
TELO2→
←IFT140
CRAMP1L→
LA16c-431H6.6→
HN1L→
MAPK3IP3→

(a)


10
5
0
-log10(P)
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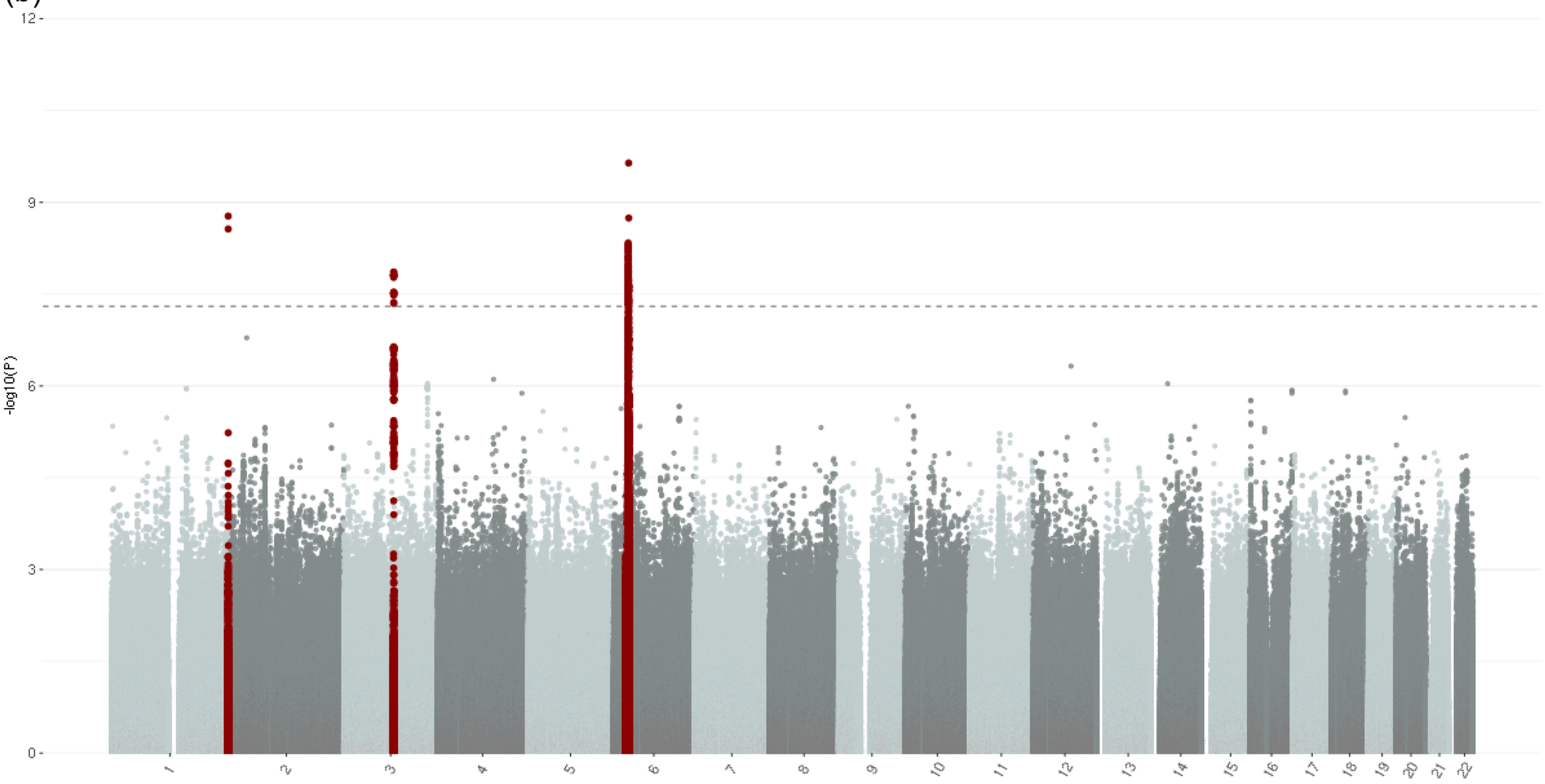
21
22

(b)


12
9
6
3
0
-log10(P)
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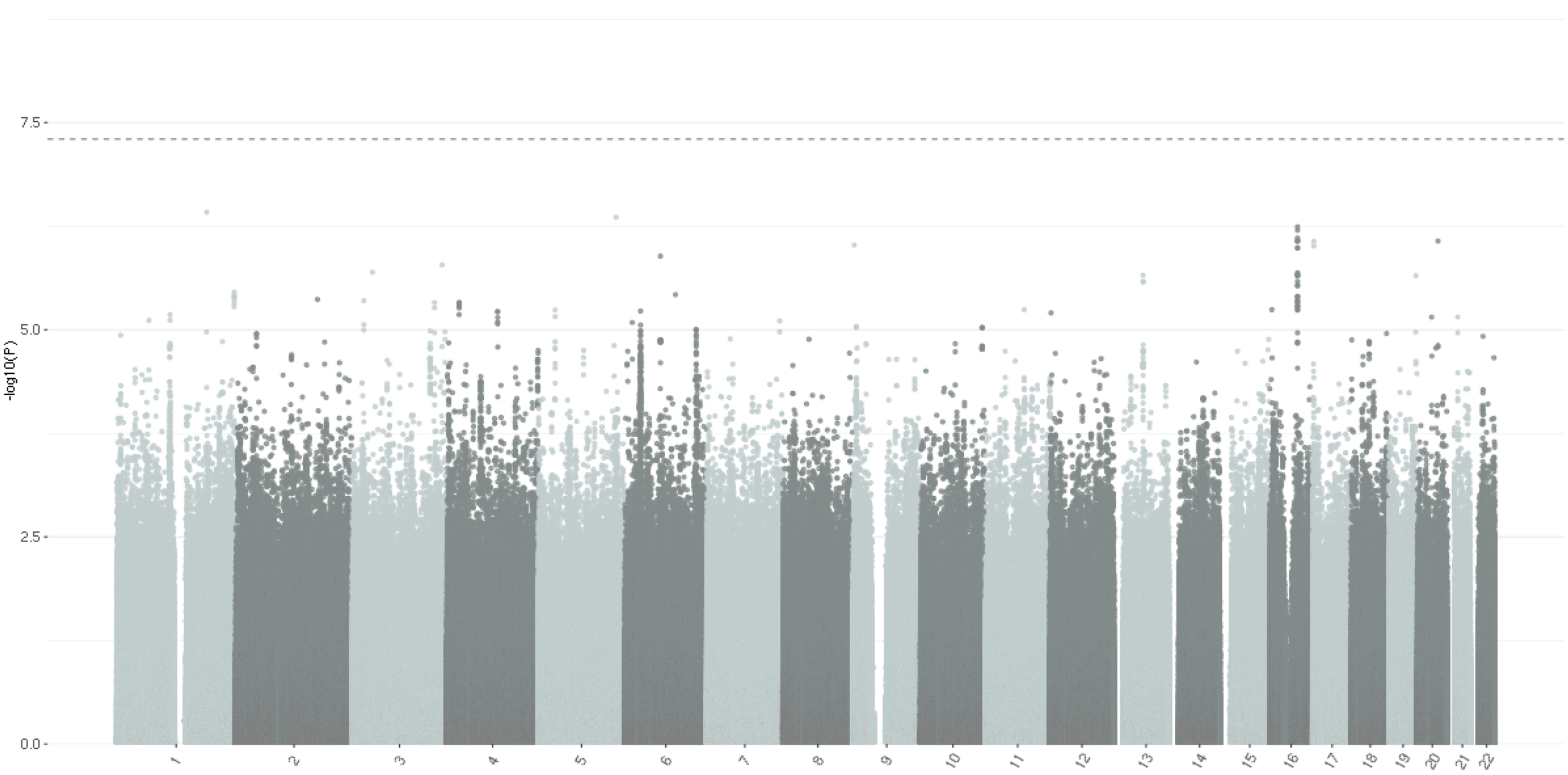
(c)


7.5
5.0
2.5
0.0
-log10(P)
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Supplementary Tables

Table E1. Evidence of association amongst variants reported by published genome-wide association studies of urticaria

rsID	Chr	Pos	Band	RA[a]	PA[a]	OR_{GWAS}	P_{GWAS}	OR_{MA}	P_{MA}
Chronic spontaneous urticaria (Chang *et al.*[1])									
rs1097296	1	226943488	1q42.12	C	T	1.44	1.6×10^{-8}	0.99	0.580
rs34141382	6	32608478	6p21.32	C	T	1.74	5.0×10^{-13}	1.03	0.247
Chronic spontaneous urticaria (Zhang *et al.*[2])									
rs434124	19	54809336	19q13.42	C	G	1.90	2.0×10^{-15}	1.00	0.959
rs34398108[b]	14	106169056	14q32.33	G	A	1.63	2.7×10^{-10}	1.00	0.771
rs73075571	3	46649711	3p21.31	G	A	1.63	2.7×10^{-10}	0.96	0.272
rs9378141	6	29938368	6p22.1	C	A	1.41	5.7×10^{-9}	0.99	0.016
rs3789612	1	114414108	1p13.2	T	C	2.01	1.9×10^{-9}	0.92	0.139
Urticaria, including all subtypes (Sakaue *et al.*[3])									
rs56043070	1	247719769	1q44	A	G	1.24	7.0×10^{-12}	1.25	6.4×10^{-21}
rs11030639	11	4039056	11p15.4	G	A	1.10	2.7×10^{-9}	0.99	0.279

NOTE. All genomic positions are reported in relation to Genome Reference Consortium Human Build 37. [a] Denotes reported risk and protect alleles in previous GWAS of urticaria. [b] Proxy single nucleotide polymorphism for rs61986182 ($r^2 = 0.89$ in European populations), which was unavailable in the meta-analysis datasets. Chr, chromosome; GWAS, genome-wide association study; MA, meta-analysis; OR, odds ratio; P, p-value; PA, protective allele; Pos, genomic position; RA, risk allele; rsID, Reference SNP cluster ID.

Table E2. Human leucocyte antigen region associations with urticaria in UK Biobank

Allele	AF	OR (95% CI)	P
HLA-DQB1*02:01	0.147	1.09 (1.06-1.13)	2.5×10^{-6}
HLA-DRB1*03:01	0.144	1.09 (1.05-1.13)	6.7×10^{-6}
HLA-A*02:01	0.263	0.93 (0.90-0.96)	1.4×10^{-5}
HLA-B*08:01	0.137	1.08 (1.04-1.11)	1.7×10^{-4}
HLA-DRB1*13:01	0.051	0.90 (0.84-0.97)	0.002
HLA-A*03:01	0.140	1.06 (1.02-1.10)	0.003
HLA-DQA1*01:03	0.059	0.92 (0.86-0.97)	0.003
HLA-DQB1*06:03	0.052	0.91 (0.85-0.97)	0.003
HLA-A*01:01	0.187	1.05 (1.02-1.09)	0.004
HLA-DQA1*05:01	0.231	1.04 (1.01-1.07)	0.015

NOTE. The ten classical HLA alleles with lowest association p-value are reported. 95% CI, 95% confidence interval; AF, allele frequency; OR, odds ratio; P, p-value.

16 **Table E3. Read codes used to identify urticaria cases from primary care data in UK Biobank**

Read code	Description	Corresponding ICD10 code
ctv3		
Xa8Ef	Bullous urticaria	L50
2F8..	O/E - weals present	L50
M28..	Urticaria	L50
SN51.	Angio-oedema	L50
X75uX	Weal, Urticarial rash, Nettle rash, Hives	L50
M280.	Urticaria: [allergic] or [drug induced]	L50.0
XE1BR	Allergic urticaria	L50.0
M281.	Idiopathic urticaria	L50.1
Xa8EW	Acute idiopathic urticaria	L50.1
Xa8EX	Chronic idiopathic urticaria	L50.1
Xa8EY	Idiopathic micropapular urticaria	L50.1
Xa8Ea	Idiopathic cold urticaria	L50.1
M282.	Urticaria due to cold and heat	L50.2
M2820	Cold urticaria, Cold-induced angio-oedema-urticaria	L50.2
M2821	Heat urticaria, Thermal urticaria	L50.2
M282z	Urticaria due to cold and heat NOS	L50.2
X508P	Physical urticaria	L50.2
X508T	Familial cold urticaria	L50.2
X508U	Cold reflex urticaria	L50.2
X508V	Delayed cold sensitivity	L50.2
Xa8Ea	Idiopathic cold urticaria	L50.2
Xa8Eb	Cold urticaria with agglutinins	L50.2
Xa8Ec	Cold urticaria with cryoglobulins	L50.2
X508Q	Symptomatic dermographism	L50.3
XE2aJ	Dermographism, Dermographic urticaria, Dermographia	L50.3
M284.	Vibratory urticaria	L50.4
M285.	Cholinergic urticaria, Cholinergic angio-oedema-urticaria	L50.5
X508W	Persisting cholinergic urticaria	L50.5
X506B	Non-immunological contact urticaria, Contact urticaria	L50.6
M28y.	(Other specified urticaria) or (nettle rash), Other specified urticaria, Nettle rash	L50.8
M28y0	Urticaria geographica	L50.8
M28y1	Menstrual urticaria	L50.8
M28y2	Urticaria persistans	L50.8
M28yz	Other specified urticaria NOS	L50.8
Myu40	[X]Other urticaria	L50.8
X508N	Drug-induced urticaria	L50.8
X508R	Delayed dermographism	L50.8
X508S	Delayed pressure urticaria, Pressure angio-oedema-urticaria	L50.8
X508Z	Reflex urticaria	L50.8
X508b	Aquagenic urticaria, Aquagenic angio-oedema-urticaria	L50.8
XE1BS	Other specified urticaria	L50.8
2F8..	O/E - weals present	L50.9
M28..	Urticaria, Nettle rash, Hives	L50.9
M28z.	(Urticaria NOS) or (hives), Urticaria NOS, Hives	L50.9
X75uX	Weal, Urticarial rash, Nettle rash, Hives	L50.9
XE1BT	Urticaria NOS	L50.9
Xa8Ef	Bullous urticaria	L50.9
X5050	Solar urticaria, Sunlight-induced angio-oedema-urticaria	L56.3

v2		
M28..	Urticaria	L50
M280.	Allergic urticaria, Drug induced urticaria	L50.0
M281.	Idiopathic urticaria	L50.1
M282.	Urticaria due to cold and heat	L50.2
M2820	Cold urticaria	L50.2
M2821	Thermal urticaria, heat urticaria	L50.2
M282z	Urticaria due to cold and heat NOS	L50.2
M287.	Physical urticaria	L50.2
M283.	Dermatographic urticaria, factitial urticaria	L50.3
M284.	Vibratory urticaria	L50.4
M285.	Cholinergic urticaria	L50.5
M286.	Contact urticaria	L50.6
M28y.	Other specified urticaria, Nettle rash	L50.8
M28y0	Urticaria geographica	L50.8
M28y1	Menstrual urticaria	L50.8
M28y2	Urticaria persistans	L50.8
M28yz	Other specified urticaria NOS	L50.8
Myu40	[X]Other urticaria	L50.8
M28z.	Urticaria NOS, Hives	L50.9
M12A2	Solar urticaria	L56.3

NOTE. ICD10, International Classification of Diseases (10th Revision).

Table E4. Lead variants in individual genome-wide association studies of urticaria (UK Biobank, FinnGen)

rsID	Chr	Pos	Band	RA	PA	RAF_{Case}	RAF_{Ctrl}	OR_{GWAS} (95% CI)	P_{GWAS}	Candidate Gene
UK Biobank										
rs74227709	1	247722588	1q44	A	G	0.087	0.071	1.23 (1.16-1.30)	2.4×10^{-12}	*GCSAML*
rs59290587	19	54553956	19q13.42	G	A	0.697	0.677	1.10 (1.06-1.14)	3.9×10^{-8}	*VSTM1*
FinnGen										
rs56043070	1	247719769	1q44	A	G	0.067	0.054	1.28 (1.18-1.39)	1.7×10^{-9}	*GCSAML*
rs6787175	3	105416421	3q13.11	C	G	0.55	0.523	1.11 (1.07-1.15)	1.4×10^{-8}	*CBLB*
rs1980496	6	32340070	6p21.32	T	C	0.326	0.298	1.14 (1.09-1.18)	2.3×10^{-10}	*TSPBP1-AS1*

NOTE. All genomic positions are reported in relation to Genome Reference Consortium Human Build 37. No variants reached genome-wide significance in the HUNT cohort. 95% CI, 95% confidence interval; Chr, chromosome; OR, odds ratio; P, p-value; PA, protective allele; Pos, genomic position; RA, risk allele; RAF, risk allele frequency; rsID, Reference SNP cluster ID

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