整合多基因風險分數以預測慢性蕁麻疹

Integrated Polygenic Risk Score for predicting chronic urticaria

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Background

Urticaria patients experience skin symptoms of redness, swelling, and itching. If these symptoms persist for over 6 weeks, it's termed chronic urticaria (CU). Based on 2009-2012 data from the National Health Insurance Research Database (NHIRD), CU's prevalence in Taiwan ranges from 0.69% to 0.79% [1], making it a prevalent skin condition. CU lacks curative drugs, with its recurrent nature severely impacting patients' quality of life and society's economic burden. However, genetic and epidemiological research on chronic urticaria, particularly in the Taiwanese population, are limited. This study aims to link chronic urticaria with specific genetic markers or diseases, facilitating early prevention and screening through precision medicine.

Materials

Taiwan Precision Medicine Initiative (TPMI) data

From the database of the Taiwan Precision Medicine Initiative, in which Taichung Veterans General Hospital participated, medical records, genetic information, and medication histories of 63,542 participants were obtained.

PGS Catalog database

The PGS Catalog is an openly accessible repository of documented polygenic scores (PGS). According to the PGS Catalog database, this study initially gathered 54 PGS associated with chronic urticaria-related conditions. PGS are also referred to as polygenic risk scores (PRS)[2].

Methods

Genome-wide association studies (GWAS)

The aggregated data were subjected to analysis using PLINK. Subsequently, the outcomes of the GWAS data were utilized to generate a Manhattan plot through the LocusZoom website to identify significant correlated SNPs pertinent to chronic urticaria.

Logistic regression analysis

The medical records were translated into phenotype-defined case and control groups based on ICD-9 codes. Additionally, a logistic regression analysis was conducted to evaluate the relationship between phenotypes and chronic urticaria patients, while accounting for age and gender as covariates in the analysis.

Survival Analysis

The various significant associated phenotypic conditions obtained from the aforementioned steps were designated as case groups, and their cumulative hazard of developing chronic urticaria was calculated.

Results

Table 1 shows that, after removing urticaria-related cases from the TPMI dataset, a 1:10 matched control group was formed based on age and gender distribution of the case group, totaling 11,341 individuals. Gender and age distributions were similar between groups. **Figure 1** illustrates the GWAS association data generated from the TPMI dataset using the PLINK toolset. As observed from the Manhattan plot, no gene loci significantly correlated with chronic urticaria were identified.

(Table 1) Comparison of matched samples

	case	control	p-value
n	1031	10310	
age (mean(SD))	46.35 (13.75)	46.38 (13.69)	0.943
sex = M (%)	27.3	27.1	0.939

(Figure 1)
Manhattan plot of GWAS for chronic urticaria
(Dotted Line : p=5E-08)

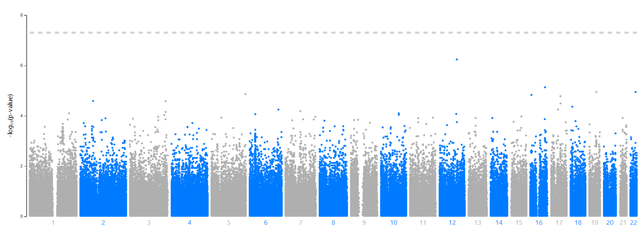
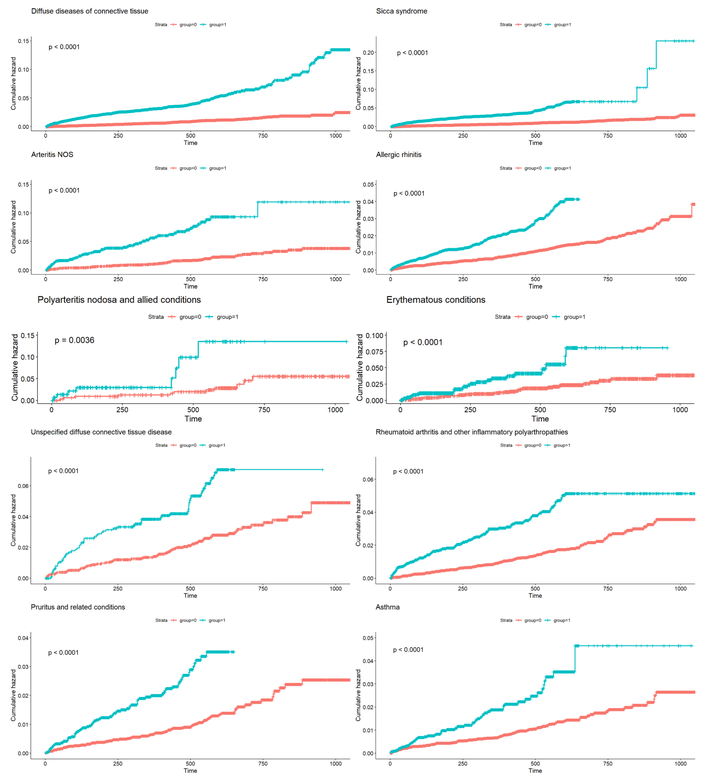


Table 2 presents 20 phenotypes significantly associated with CU along with their odds ratios, excluding 3 types confounded by misdiagnosis with CU (highlighted with green lines). Based on these relevant phenotypes, **Figure 2** categorizes patients into groups according to the presence or absence of each individual phenotype, demonstrating significant differences in the cumulative risk of developing chronic urticaria between the groups (with the x-axis measured in weeks). Employing these associated phenotypes' available PRS, an optimized PRS for precise chronic urticaria screening is integrated, as shown in Figure 3.

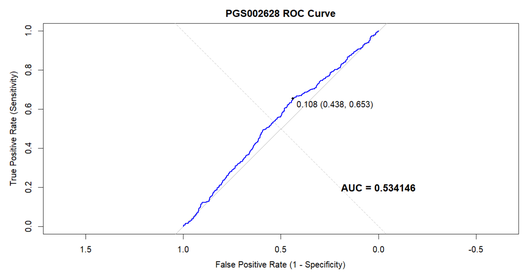
(Table 2) Phenotypes significantly linked to CU

No.	phenotype	description	OR	p-value
1	709	Diffuse diseases of connective tissue	8.00578	2.6903E-109
2	709.2	Sicca syndrome	8.7462	2.3486E-105
3	446.9	Arteritis NOS	8.98748	9.72133E-51
4	476	Allergic rhinitis	3.70509	1.81155E-49
5	446	Polyarteritis nodosa and allied conditions	7.77837	1.74248E-48
6	695	Erythematous conditions	3.87396	7.66151E-43
7	716	Other arthropathies	4.18063	2.28153E-41
8	709.7	Unspecified diffuse connective tissue disease	7.32653	1.19236E-40
9	939	Atopic/contact dermatitis due to other or unspecified	541.777	9.88258E-34
10	695.4	Lupus (localized and systemic)	3.75539	1.56216E-33
11	714	Rheumatoid arthritis and other inflammatory polyarthropathies	3.69929	2.14082E-33
12	695.42	Systemic lupus erythematosus	3.69463	3.32886E-32
13	946	Anaphylactic shock NOS	6021.11	5.58009E-31
14	694	Dyschromia and Vitiligo	11.0353	1.15942E-29
15	698	Pruritus and related conditions	4.98001	2.06975E-27
16	930	Allergic reaction to food	1463.57	2.69157E-27
17	495	Asthma	3.80872	4.29294E-27
18	743	Osteoporosis, osteopenia and pathological fracture	4.60057	1.61612E-26
19	743.11	Osteoporosis NOS	4.63044	3.91502E-26
20	743.1	Osteoporosis	4.61588	4.72571E-26
21	246	Other disorders of thyroid	6.00775	8.0499E-26
22	716.1	Unspecified polyarthropathy or polyarthritis	4.39732	1.17921E-25
23	694.3	Vascular disorders of skin	29.5923	7.93515E-25

(Figure 2) Cumulative hazard plot



(Figure 3) the ROC curve and AUC



Discussion & Conclusion

This study did not identify significant genetic loci associated with CU. Despite integrating relevant phenotypes to develop a PRS for chronic urticaria screening, its AUC remained low. Possible reasons include limited sample size, non-significant genetic effects on CU, or exclusion of relevant genes from the gene chip used. While genetic prediction of CU risk in unaffected individuals is not feasible, the study's clinical observations provide valuable advice and reference for patients and clinicians. Individuals with conditions such as Sicca syndrome, systemic lupus erythematosus, arteritis, allergic rhinitis, rheumatoid arthritis, systemic sclerosis, pruritus, or asthma are at a heightened risk of developing chronic urticaria in the future.. Early adjustments to lifestyle, diet, or suitable treatments are recommended to mitigate CU risk and prevent its occurrence.

The prevention of CU still necessitates further genetic research, such as the optimization of gene chip designs tailored for the Taiwanese population, as well as the accumulation of more clinical evidence. These efforts would empower patients to take charge of their future healthcare plans and management.

References

1. Chia-yu chu, Yung-tsu cho, Jhih-hua jiang, Eve i-chun lin, & Chao-hsiun tang. (2017, July 15). *Epidemiology and Comorbidities of Patients with Chronic Urticaria in Taiwan: A Nationwide Population-Based Study*. Journal of Dermatological Science. https://doi.org/10.1016/j.jdermsci.2017.07.006
2. https://www.pgscatalog.org/