Applying Artificial Intelligence to Identify Common Targets for Treatment of Asthma, Eczema, and Food Allergy

Bonnie Hei Man Liu[1,¶], Andre Rayner[2,¶], Andrew R. Mendelsohn[3], Anastasia Shneyderman[1], Michelle Chen[1], Frank W. Pun[1,*]

[1] Insilico Medicine Hong Kong Ltd., Hong Kong Science and Technology Park, Hong Kong
[2] Henry Gunn High School, Palo Alto, CA, USA
[3] Regenerative Sciences Institute, Sunnyvale, CA, USA

* Corresponding author: Frank W. Pun
Email: frank.pun@insilico.com

¶ These authors contributed equally to this work.

Abstract

Allergic disorders are common diseases marked by the abnormal immune response towards foreign antigens that are not pathogens. Often patients with food allergy also suffer from asthma and eczema. Given the similarities of these diseases and a shortage of effective treatments, developing novel therapeutics against common targets of multiple allergies would offer an efficient and cost-effective treatment for patients. Herein, we employed the artificial intelligence-driven target discovery platform, PandaOmics, to identify common targets for treating asthma, eczema, and food allergy. Thirty-two case-control comparisons were generated from 15, 11, and 6 transcriptomics datasets related to asthma (558 cases, 315 controls), eczema (441 cases, 371 controls), and food allergy (208 cases, 106 controls) respectively, and allocated into three meta-analyses for target identification. Top-100 high-confidence targets and Top-100 novel targets were prioritized by PandaOmics for each allergic disease. Six common high-confidence targets (i.e., *IL4R*, *IL5*, *JAK1*, *JAK2*, *JAK3*, and *NR3C1*) across all three allergic diseases have approved drugs for treating asthma and eczema. Based on the targets' dysregulated expression profiles and their mechanism of action in allergic diseases, three potential therapeutic targets were proposed. *IL5* was selected as a high-confidence target due to its strong involvement in allergies. *PTAFR* was identified for drug repurposing, while *RNF19B* was selected as a novel target for therapeutic innovation. Analysis of the dysregulated pathways commonly identified across asthma, eczema, and food allergy revealed the well-characterized disease signature and novel biological processes that may underlie the pathophysiology of allergies. Altogether, our study dissects the shared pathophysiology of allergic disorders and reveals the power of artificial intelligence in the exploration of novel therapeutic targets.

Introduction

Allergies, particularly in children, play a critical role in the overall health and well-being. The prevalence of food allergy worldwide has risen from about 2% in 1950 to over 7% in 2020(1). In the US alone, over 170 foods are reported to elicit an allergic response(2). Allergic reactions can significantly impact a child's development and quality of life, with reactions ranging from mild hives to anaphylactic reactions and even death(3, 4). Pathologically, food allergy can be Immunoglobulin E (IgE)-mediated, non-IgE-mediated, or mixed, with the underlying mechanisms for non-IgE-mediated reactions remaining poorly defined. Besides food allergy, asthma and eczema are generally considered as allergic diseases, with the three often coexisting among children globally(5, 6). The term 'atopic march' denotes the increased occurrence of allergic disorders, such as asthma and food allergy, after the development of atopic dermatitis(7), suggesting the need for developing treatments that address multiple allergies simultaneously. This approach would enhance patient compliance and make drug development more effective.

Traditional drug discovery approaches are tedious and expensive, often taking 5 to 10 years of intense research and costing millions of dollars with a low probability of success. However, with the availability of large and high-dimensional data derived from multi-omics analysis of healthy volunteers and patients' tissue samples, as well as data on compounds, publications, grants, and clinical trials, artificial intelligence (AI) has emerged as a powerful technology to automate data analysis and accelerate novel therapeutic target identification(8, 9). In particular, machine learning and deep learning can contribute significantly to the prediction of novel therapeutic targets and the repurposing of existing drugs(10, 11, 12, 13). Applying AI-driven approaches not only significantly reduces the time and cost spent on drug development, but may also improve the success rate of clinical trials to remarkably benefit the patients(14).

In the current study, we used PandaOmics, an AI-driven target discovery platform, as a primary tool to analyze publicly available datasets and search for potential therapeutic targets in asthma, eczema, and food allergy. As shown in Figure 1, transcriptomics datasets for asthma, eczema, and food allergy were retrieved from public repositories and uploaded onto PandaOmics to undergo target identification, differential gene expression, and pathway analyses. Eleven common unique targets were selected across the three indications and further evaluated with their potential in treating these allergies. Among them, *IL5* was selected as a high-confidence target due to its strong involvement in allergies. *PTAFR* demonstrated its promise for drug

repurposing, while *RNF19B* offered a high potential for novel therapeutic intervention. This piece of work indicated the potential of AI in driving a rapid target discovery process.

Materials and Methods

Dataset and comparison selection

Bulk transcriptomics datasets with bronchial epithelial and skin tissues were selected for target identification for asthma and eczema, respectively, while target identification for food allergy was performed using datasets with blood or immune cells. As a result, 15, 11, and 6 relevant datasets were selected for asthma, eczema, and food allergy, respectively. Samples from 5 out of 6 datasets selected for food allergy were collected from children and adolescents, while the remaining one was with a mixture of samples from adolescents and adults. All samples used in the eczema-related datasets were from adults. For asthma, 13 and 1 datasets were generated from samples collected from adults and children, respectively. No age information was retrieved for the remaining dataset for asthma. They were retrieved from Gene Expression Omnibus (GEO) and ArrayExpress databases and processed before being uploaded onto PandaOmics for target identification. One case-control comparison was generated from each of the datasets selected. Case-control comparisons for target identification were listed in Table 1. Normal relevant tissue from healthy individuals was chosen as the controls.

Table 1. Transcriptomics case-control comparisons for asthma, eczema, and food allergy.

Serie	Type	Platform	Tissue Source	Experimental design	# Case	# Control	Year	PMID
Asthma meta-analysis								
GSE4302	Microarray	GPL570	Bronchial epithelium	Asthma vs Healthy	42	28	2006	17898169
GSE41649	Microarray	GPL96	Bronchial epithelium	Asthma vs Healthy	4	4	2012	19842841
GSE41861	Microarray	GPL570	Bronchial epithelium	Asthma vs Healthy	51	30	2012	-
GSE43696	Microarray	GPL6480	Bronchial epithelium	Asthma vs Healthy	88	20	2013	24518246
GSE63142	Microarray	GPL6480	Bronchial epithelium	Asthma vs Healthy	128	27	2014	25338189
GSE64913	Microarray	GPL570	Bronchial epithelium	Asthma vs Healthy	22	37	2015	28045928
GSE89809	Microarray	GPL13158	Bronchial epithelium	Asthma vs Healthy	38	18	2016	28933920
GSE104468	Microarray	GPL21185	Bronchial epithelium	Asthma vs Healthy	12	12	2017	28294656
GSE179156	Microarray	GPL570	Bronchial epithelium	Asthma vs Healthy	38	29	2021	34233672
GSE85567	RNA-seq	GPL11154	Bronchial epithelium	Asthma vs Healthy	57	28	2016	27942592
GSE109484	RNA-seq	GPL16791	Bronchial epithelium	Asthma vs Healthy	33	14	2018	29548336
GSE101720	RNA-seq	GPL18573	Bronchial epithelium	Asthma vs Healthy	14	18	2017	30190271
GSE106388	RNA-seq	GPL18573	Bronchial epithelium	Asthma vs Healthy	15	4	2017	-
GSE118761	RNA-seq	GPL11154	Bronchial epithelium	Asthma vs Healthy	21	29	2018	32113981
GSE158752	RNA-seq	GPL18573	Bronchial epithelium	Asthma vs Healthy	25	17	2020	32531372
Eczema meta-analysis								
GSE58558	Microarray	GPL570	Skin	Eczema vs Healthy	18	17	2014	24786238
GSE59294	Microarray	GPL570	Skin	Eczema vs Healthy	16	7	2014	25482871
GSE99802	Microarray	GPL570	Skin	Eczema vs Healthy	59	53	2018	30121291
GSE130588	Microarray	GPL570	Skin	Eczema vs Healthy	51	42	2019	30194992
GSE133385	Microarray	GPL570	Skin	Eczema vs Healthy	30	30	2019	31356921
GSE133477	Microarray	GPL570	Skin	Eczema vs Healthy	79	40	2019	31419544
GSE140684	Microarray	GPL570	Skin	Eczema vs Healthy	31	21	2019	27304428
GSE121212	RNA-seq	GPL16791	Skin	Eczema vs Healthy	21	27	2019	30641038
GSE137430	RNA-seq	GPL20301	Skin	Eczema vs Healthy	40	39	2020	32428528
GSE141571	RNA-seq	GPL20301	Skin	Eczema vs Healthy	39	41	2020	32428543
GSE157194	RNA-seq	GPL21290	Skin	Eczema vs Healthy	57	54	2020	32615169
Food allergy meta-analysis								
GSE88796	Microarray	GPL10558	PBMC*	Food allergy vs Healthy	65	28	2016	27788149
GSE171660	Microarray	GPL13607	Whole blood	Food allergy vs Healthy	11	9	2021	-
GSE114065	RNA-seq	GPL20301	T cells	Food allergy vs Healthy	65	36	2018	30120223
GSE165316	RNA-seq	GPL24676	B cells	Food allergy vs Healthy	18	9	2021	34466226
GSE189149	RNA-seq	GPL24676	T cells	Food allergy vs Healthy	30	18	2021	-
GSE196495	RNA-seq	GPL16791	T cells	Food allergy vs Healthy	19	6	2022	35266148

* PBMC stands for Peripheral Blood Mononuclear Cells.

In addition, GSE41861 and GSE158752 that have information on disease severity, were selected for identifying indicators for disease severity. There were 10, 81 and 30 samples for severe asthma, mild/moderate asthma, and healthy control in GSE41861, while GSE158752 contained 25, 25, and 17 samples isolated from patients with severe asthma, mild/moderate asthma, and healthy individuals. Three comparisons were generated for each dataset, comparing the expression differences between severe asthma and controls, mild/moderate asthma and controls, as well as asthma samples with different severities (S4 Table).

Target identification by PandaOmics

To perform target identification for the three indications with PandaOmics, the 15, 11, and 6 case-control comparisons for asthma, eczema, and food allergy were allocated into 3 independent meta-analyses, which were shown in Table 1. PandaOmics ranked the targets for each disease with a combination of multiple AI scores derived from omics and text data. These AI and bioinformatic models were validated with the Time Machine approach to ensure the identification of truly novel targets for the disease of interest(15). The Omics AI scores include thirteen models representing the target-disease association based on molecular connections between the proposed target and the selected disease. Most of these scores are calculated in real time according to the input of datasets. On the other hand, Text-based AI scores, KOL scores, and Financial scores are calculated from literature and publicly available databases. Scores of each of the models are given on a normalized scale from 0 to 1, with higher scores corresponding to better target-disease association as predicted by the model. Detailed definitions of the scores were described in the User manual section of PandaOmics (https://insilico.com/pandaomics/help). The Metascore (final ranking) provided a list of targets/genes along with the disease of interest for human evaluation and consideration.

To generate therapeutic targets with various degrees of novelty, two settings of filters and scores were employed to obtain a list of targets with high confidence and novelty, respectively. Targets with high confidence in the allergy indications were prioritized based on the Omics, Text-based, Financial, and KOL scores. On the other hand, only the Omics scores were employed for novel target identification. Targets belonging to druggable classes and not regarded as essential genes according to the Therapeutic Target Database (TTD) were selected for further evaluation to avoid potential toxicity.

Pathway analysis

The assessment of signaling pathway activation status was performed by the proprietary single network model iPANDA incorporated in PandaOmics(16). In general, iPANDA utilized the data from differential gene expression and pathway topology decomposition to rapidly identify sets of biological relevant pathway signatures with notable noise reduction. The Reactome database serves as the basis of the hierarchical organization of signaling pathways(17). Pathway activation or suppression was indicated by the positive or negative iPANDA score, respectively.

Statistical analysis

Differential expression analysis was performed using the eBayes function in Limma package(18). Gene expression changes among the healthy cohort and different severity groups of asthma patients were plotted on box-plots, and two-tailed t-test was used to estimate the statistical significance.

Results

Biological processes are commonly dysregulated in allergies

In view of the interconnection between asthma, eczema, and food allergies, dysregulated signaling pathways in the case-control comparisons for the three diseases were compared to determine the commonly dysregulated mechanisms for allergies using the iPANDA algorithm. Pathways were organized based on the hierarchical structure provided by the Reactome database, with each of them corresponding to one top-level pathway. One hundred and thirty-one signaling pathways were identified as unidirectionally dysregulated in all three diseases, with 104 being activated and 27 being inhibited. The biological processes with the highest number of activated pathways included signal transduction (17%), gene expression (transcription) (13%), immune system (13%), and metabolism of proteins (10%) (Fig. 2A). The details of dysregulated pathways were listed in S1 Table.

Targets associated with FDA-approved drugs for three allergy indications are highly ranked in PandaOmics

To understand the effectiveness of PandaOmics in revealing potential therapeutic targets for allergies, the United States Food and Drug Administration (FDA)-approved drugs for asthma, eczema, and food allergy, and their associated targets were retrieved via literature search and

clinical trial result evaluation. No drug has been approved for food allergy by the FDA. Eighteen targets were associated with twenty-six compounds approved for treating asthma and eczema (Table 2). The ranking of these targets under the high confidence setting for each indication in PandaOmics was stated in Table 2, with six of them (i.e., *IL4R*, *IL5*, *JAK1*, *JAK2*, *JAK3*, and *NR3C1*) ranked as the Top-100 targets across all three allergic diseases. *IL13* and *TYK2* were also top-ranked in eczema and food allergy, and asthma and eczema, respectively.

Table 2. A list of targets across three allergic diseases with associated FDA-approved drugs.

Target	Rank			Indication(s)	FDA-approved drugs for asthma, eczema or food allergy
	Asthma	Eczema	Food allergy		
ADRB2	112	144	148	Asthma	Albuterol sulfate, Mometasone furoate, Salmeterol xinafoate, Vilanterol
ALOX5	127	44	151	Asthma	Zileuton
CHRM3	402	1631	2391	Asthma	Umeclidinium
CYSLTR1	229	105	378	Asthma	Montelukast sodium, Zafirlukast
FKBP1A	350	307	1159	Eczema	Pimecrolimus, Tacrolimus
IL13	212	88	10	Eczema	Tralokinumab-ldrm
IL4R	31	1	4	Asthma, eczema	Dupilumab
IL5	47	48	56	Asthma	Mepolizumab, Reslizumab
JAK1	16	26	83	Eczema	Abrocitinib, Ruxolitinib, Upadacitinib
JAK2	1	15	18	Eczema	Ruxolitinib, Upadacitinib
JAK3	58	4	91	Eczema	Upadacitinib
NR3C1	14	11	66	Asthma	Beclomethasone dipropionate, Ciclesonide, Fluticasone furoate, Fluticasone propionate, Formoterol fumarate, Prednisone
				Eczema	Desonide
PDE4A	543	410	4454	Eczema	Crisaborole
PDE4B	231	275	897	Eczema	Crisaborole
PDE4C	672	857	3404	Eczema	Crisaborole
PDE4D	485	409	793	Eczema	Crisaborole
TSLP	164	133	7	Asthma	Tezepelumab-ekko
TYK2	22	36	135	Eczema	Upadacitinib

Even though most of these drugs were approved for only one specific indication, given that the target is often found in other allergic indications, one could further evaluate the repurposing of these drugs. Besides, the successful retrieval of the known therapeutic targets for allergies indicated the feasibility of identifying targets with adequate therapeutic value using PandaOmics.

Interleukin-5 - a high-confidence therapeutic target for allergies

Top-100 high-confidence targets and Top-100 novel targets were prioritized by PandaOmics for each allergic disease. Expression profiles of these targets in allergic patients and healthy individuals were further analyzed, giving 115, 178, and 107 unique dysregulated targets for asthma, eczema, and food allergies, respectively (Fig. 1). Eleven targets (i.e., *CLOCK*, *DCTPP1*, *IFNG*, *IL5*, *PSMA2*, *PSMA4*, *PTAFR*, *RNF19B*, *TGFB1*, *UBE2F*, and *VDR*) were commonly dysregulated across three tested allergy indications (Fig. 3A). All of them were upregulated in the allergies when compared with the healthy controls. Amongst these targets, Interleukin-5 (*IL5*) was selected as a promising high-confidence therapeutic target for allergies. It is a pathogenic target frequently reported in the tested allergy indications(19, 20, 21, 22, 23, 24). Its upregulation was detected in 13 out of 15, 10 out of 11, and 5 out of 5 comparisons for asthma, eczema, and food allergy (S2 Table). *IL5* ranked 54th, 68th, and 56th in the meta-analysis of asthma, eczema, and food allergy, respectively. Out of the thirteen Omics models, five (i.e., Knockouts, Pathways, Relevance, Heterogenous graph walk, and Matrix factorization) scored 0.8 or above, meaning *IL5* was prioritized by the corresponding models across the tested indications (Fig. 3B).

Through mediating the maturation, proliferation, activation, and migration of eosinophils via JAK/STAT, NF-κB, and PI3K pathways(25), IL5 serves as an influential pro-inflammatory cytokine. In asthma, IL5 coordinates type 2 inflammation, a phenotype observed in 50-70% of asthma patients(26). Its dysregulation is also implicated in airway remodeling, such as increasing airway fibrotic response(27) and thickening of the reticular basement membrane(19). It is noteworthy that three antibody inhibitors targeting IL5/IL5R signaling, i.e., mepolizumab, reslizumab, and benralizumab, have been approved for the treatment of asthma. They all offered excellent safety and efficacy profiles in the clinical trials for asthma. The efficacy of these inhibitors in treating food allergy is yet to be determined.

***PTAFR* - a high-confidence target for drug repurposing in allergies**

Beside *IL5*, we selected Platelet Activating Factor Receptor (*PTAFR*) as a potential therapeutic target for drug repurposing (Fig. 3B). PTAFR was ranked as the 1st, 60th, and 35th target in the meta-analysis of asthma, eczema, and food allergy. It performed well (scored ≥ 0.8) in Causal Inference, Heterogenous graph walk, and Matrix factorization models in the three meta-analyses (Fig. 3B). It was significantly overexpressed in patient samples in 5, 10, and 1 comparisons for asthma, eczema, and food allergy, respectively (S2 Table). Functionally, the binding of platelet-activating factor to PTAFR activates PKC and calcium release, which subsequently induces

platelet aggregation, leukocyte reactivity, vasodilation, and inflammation(28). Multiple lines of evidence suggest the potential of inhibiting PTAFR and its signaling to suppress allergic response and inflammation(29, 30, 31). For instance, PTAFR-deficient mice displayed a reduced level of anti-ovalbumin IgE associated with attenuated allergic markers when compared with wild-type mice upon challenges with ovalbumin diet(32). Furthermore, rupatadine, a small molecule inhibitor of PTAFR and histamine H1 receptor(33), is indicated for allergic rhinitis with good long-term safety and tolerability(34, 35). Given it has not been tested in the three indications and its target *PTAFR* was a commonly upregulated gene, rupatadine could be a prospective repurposing candidate for asthma, eczema, and food allergy.

RNF19B - an unreported target for novel therapeutic intervention in allergies

RNF19B, a E3 ubiquitin-protein ligase, was ranked as the Top-20 target and scored ≥ 0.8 in the two Omics models (i.e., Causal Inference and Expression) for the three indications (Fig. 3B). In particular, its overexpression reached statistical significance in all comparisons for eczema ($p < 0.05$) (S2 Table). RNF19B ubiquitinates URKL-1 protein for degradation(36). Despite the fact that there are limited amounts of functional studies for RNF19B, the existing evidence highlights its immunological role by reporting its pivotal contribution to natural killer cell cytotoxicity(37, 38). It is suggested to be a positive regulator of STAT1 and NFκB signalings to mediate innate immunity(39, 40). RNF19B-knockout mice exhibited reduced inflammation, less cytokine production, and defective neutrophils and macrophages during *Streptococcus pneumoniae* infection(41). Considering that allergic inflammation is a hallmark of the three analyzed indications(42) and the strong association between RNF19B and immune regulation, these findings indicate the likelihood of RNF19B involvement in allergic diseases.

Common activated pathways in allergies associated with _IL5_, _PTAFR_, and _RNF19B_

With the aid of the iPANDA algorithm, dysregulated pathways associated with *IL5*, *PTAFR,* and *RNF19B* were also evaluated to dissect their potential roles in allergy (Fig. 2B, S3 Table). The majority of the dysregulated pathways linked to these targets belonged to the immune system. In general, the dysregulated pathways associated with *IL5*, *PTAFR*, and *RNF19B* did not overlap, indicating these targets should have different roles in allergies. Our results were in accordance with the literature and supported the potency of *IL5, PTAFR,* and *RNF19B* as therapeutic targets for allergies.

Upregulation of *PTAFR* could serve as an indicator of disease severity in asthma

Besides exploring the expression profiles in the primary affected tissue, we examined the association between disease severity and the dysregulation of *IL5*, *PTAFR,* and *RNF19B*. Information on disease severity was available in some of the asthma-related datasets; therefore, GSE41861 and GSE158752 were utilized for such analysis. Apart from being significantly overexpressed in asthmatic bronchial epithelial tissues compared to the controls, *PTAFR* was particularly upregulated in samples from severe asthma compared to those with mild/moderate asthma (Fig. 4, S4 Table). These suggested the upregulation of *PTAFR* might serve as a biomarker for asthma severity.

Discussion

AI is revolutionizing the pharmaceutical industry by accelerating every single step of drug development, from the discovery of potential therapeutic targets(8), prediction of protein structures(43), generation of hit compounds(44), to the prediction of drug safety(45) and efficacy(46). The uses of AI in allergy prediction, diagnosis, and medicine were also documented(47, 48, 49). For instance, esophageal mRNA transcripts were analyzed by machine learning strategies (i.e., weighted factor analysis followed by random forest classification) to predict the probability of developing eosinophilic esophagitis during food allergy response with high sensitivity and specificity(50). Given the huge contribution of AI in the healthcare sector, this study applies the generative AI target discovery platform, PandaOmics, to reveal the commonly dysregulated biological processes and, more importantly, to identify targets with high therapeutic values in allergies.

PandaOmics has successfully demonstrated its power in retrieving high-quality therapeutic targets for multiple indications(9, 15, 51). We first evaluated the cellular processes that could serve as common disease-driving mechanisms across asthma, eczema, and food allergy. Immune dysregulation, the well-recognized underlying mechanism of allergies(52, 53), was revealed as one of the commonly dysregulated processes. Specifically, signalings of TRAF, NOD, and interferon were activated. These biological processes were directly associated with allergy development(54, 55, 56, 57). Mitochondrial malfunctioning, indicated by the dysregulation in pathways related to mitochondrial translation, mitochondrial biogenesis, and mitochondrial protein import, was identified as another disease signature. As triggered by allergens, oxidative stress, and reactive oxygen species (ROS) production were induced in the mitochondria, disturbing

cellular bioenergetics and subsequently driving systemic inflammation(58, 59, 60). For instance, upon the oral challenge of peanut extract, the sensitized mice experienced reduced fatty acid oxidation, lower respiration rate, and increased ROS production(61). Antigen-dependent mast cell stimulation in allergies was also a consequence of disrupted mitochondrial dynamics(62). These collectively imply the alignment between our results and the published evidence.

Some groups of dysregulated pathways remain to be explored in allergy. For example, signaling by NTRKs was generally activated across the indications. Upon the binding of neurotrophins, activated NTRK receptors promote neuron growth, differentiation, and survival via the subsequent activation of downstream signaling pathways, i.e., MAPK, PI3K, and PKC(63). In a transcriptome associated study for pediatric asthma, NTRK1 and NTRK2 were the top differentially expressed genes(64). NT4/NTRK2 signaling also served as a cause of chronic airway hyperreactivity due to early-life allergen exposure(65). It is suggested that activation of NTRKs stimulated eosinophilic activity(66, 67). In view of the strong linkage between eosinophilic response and allergies(68), dysregulation of the NTRK pathways is worth additional effort in investigating its linkage with the allergic response.

In view of the successful retrieval of therapeutic targets with approved drugs for allergies, we demonstrated the power of PandaOmics in target discovery for allergic disorders. Three targets (*IL5*, *PTAFR,* and *RNF19B)* with potential therapeutic benefits to allergies were proposed in the study. All three targets were top-ranked in PandaOmics, with relatively consistent expression dysregulation profiles and high druggability. Both IL5 and PTAFR have launched drugs in the markets. It is worthwhile to conduct additional research to explore the possibility of repurposing those drugs for the treatment of allergic conditions. In addition, we observed the correlation between *PTAFR* expression and the severity of asthma. In the two datasets where *PTAFR* was significantly upregulated, the dysregulation of PTAFR is particularly detected in the samples with severe asthma, suggesting PTAFR might serve as an indicator of asthma severity. RNF19B is a novel target for allergic disorders that calls for novel drug development. We recommend experimental validation of these targets for developing or repurposing potential drug candidates to treat common allergic diseases.

In conclusion, we applied PandaOmics, the AI-driven target discovery platform, to identify a number of druggable targets that are common to asthma, eczema, and food allergy, facilitating the possible drug development of efficient and cost-effective therapy for allergy patients. This

study also demonstrated the potential power of AI to aid in drug discovery and the development of efficient and affordable therapies for disease treatment.

ACKNOWLEDGMENTS

We would like to thank Dr. Alex Zhavoronkov and Dr. Feng Ren for reviewing the manuscript and Dr. Xi Long for figure design.

REFERENCE

1. Kari Nadeau, Barnett S. The End of Food Allergy: The First Program to Prevent and Reverse a 21st Century Epidemic: Avery; 2020 September 29.
2. Panel NI-SE, Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1-58.
3. Yu W, Freeland DMH, Nadeau KC. Food allergy: immune mechanisms, diagnosis and immunotherapy. Nat Rev Immunol. 2016;16(12):751-65.
4. Sicherer SH, Warren CM, Dant C, Gupta RS, Nadeau KC. Food Allergy from Infancy Through Adulthood. J Allergy Clin Immunol Pract. 2020;8(6):1854-64.
5. Foong RX, du Toit G, Fox AT. Asthma, Food Allergy, and How They Relate to Each Other. Front Pediatr. 2017;5:89.
6. Bergmann MM, Caubet JC, Boguniewicz M, Eigenmann PA. Evaluation of food allergy in patients with atopic dermatitis. J Allergy Clin Immunol Pract. 2013;1(1):22-8.
7. Maiello N, Comberiati P, Giannetti A, Ricci G, Carello R, Galli E. New Directions in Understanding Atopic March Starting from Atopic Dermatitis. Children (Basel). 2022;9(4).
8. You Y, Lai X, Pan Y, Zheng H, Vera J, Liu S, et al. Artificial intelligence in cancer target identification and drug discovery. Signal Transduct Target Ther. 2022;7(1):156.
9. Pun FW, Leung GHD, Leung HW, Liu BHM, Long X, Ozerov IV, et al. Hallmarks of aging-based dual-purpose disease and age-associated targets predicted using PandaOmics AI-powered discovery engine. Aging (Albany NY). 2022;14(6):2475-506.
10. Dara S, Dhamercherla S, Jadav SS, Babu CM, Ahsan MJ. Machine Learning in Drug Discovery: A Review. Artif Intell Rev. 2022;55(3):1947-99.
11. Zhang Y, Ye T, Xi H, Juhas M, Li J. Deep Learning Driven Drug Discovery: Tackling Severe Acute Respiratory Syndrome Coronavirus 2. Front Microbiol. 2021;12:739684.
12. Aliper A, Plis S, Artemov A, Ulloa A, Mamoshina P, Zhavoronkov A. Deep Learning Applications for Predicting Pharmacological Properties of Drugs and Drug Repurposing Using Transcriptomic Data. Mol Pharm. 2016;13(7):2524-30.

13. Zhavoronkov A, Ivanenkov YA, Aliper A, Veselov MS, Aladinskiy VA, Aladinskaya AV, et al. Deep learning enables rapid identification of potent DDR1 kinase inhibitors. Nat Biotechnol. 2019;37(9):1038-40.
14. Weissler EH, Naumann T, Andersson T, Ranganath R, Elemento O, Luo Y, et al. The role of machine learning in clinical research: transforming the future of evidence generation. Trials. 2021;22(1):537.
15. Pun FW, Liu BHM, Long X, Leung HW, Leung GHD, Mewborne QT, et al. Identification of Therapeutic Targets for Amyotrophic Lateral Sclerosis Using PandaOmics - An AI-Enabled Biological Target Discovery Platform. Front Aging Neurosci. 2022;14:914017.
16. Ozerov IV, Lezhnina KV, Izumchenko E, Artemov AV, Medintsev S, Vanhaelen Q, et al. In silico Pathway Activation Network Decomposition Analysis (iPANDA) as a method for biomarker development. Nat Commun. 2016;7:13427.
17. Sidiropoulos K, Viteri G, Sevilla C, Jupe S, Webber M, Orlic-Milacic M, et al. Reactome enhanced pathway visualization. Bioinformatics. 2017;33(21):3461-7.
18. Ritchie ME, Phipson B, Wu D, Hu Y, Law CW, Shi W, et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res. 2015;43(7):e47.
19. Pelaia C, Paoletti G, Puggioni F, Racca F, Pelaia G, Canonica GW, et al. Interleukin-5 in the Pathophysiology of Severe Asthma. Front Physiol. 2019;10:1514.
20. Metcalfe JR, D'Vaz N, Makrides M, Gold MS, Quinn P, West CE, et al. Elevated IL-5 and IL-13 responses to egg proteins predate the introduction of egg in solid foods in infants with eczema. Clin Exp Allergy. 2016;46(2):308-16.
21. Yamamoto S, Hamasaki Y, Ishii E, Ichimaru T, Miyazaki S. Unbalanced production of interleukin-5 and interleukin-2 in children with atopic dermatitis. Ann Allergy Asthma Immunol. 1997;78(5):517-23.
22. Kondo S, Yazawa H, Jimbow K. Reduction of serum interleukin-5 levels reflect clinical improvement in patients with atopic dermatitis. J Dermatol. 2001;28(5):237-43.
23. Bae SJ, Tanaka Y, Hakugawa J, Katayama I. Interleukin-5 involvement in ovalbumin-induced eosinophil infiltration in mouse food-allergy model. J Dermatol Sci. 1999;21(1):1-7.
24. Vandezande LM, Wallaert B, Desreumaux P, Tsicopoulos A, Lamblin C, Tonnel AB, et al. Interleukin-5 immunoreactivity and mRNA expression in gut mucosa from patients with food allergy. Clin Exp Allergy. 1999;29(5):652-9.
25. Kouro T, Takatsu K. IL-5- and eosinophil-mediated inflammation: from discovery to therapy. Int Immunol. 2009;21(12):1303-9.

26. Brusselle GG, Koppelman GH. Biologic Therapies for Severe Asthma. N Engl J Med. 2022;386(2):157-71.
27. Tanaka H, Komai M, Nagao K, Ishizaki M, Kajiwara D, Takatsu K, et al. Role of interleukin-5 and eosinophils in allergen-induced airway remodeling in mice. Am J Respir Cell Mol Biol. 2004;31(1):62-8.
28. Lordan R, Tsoupras A, Zabetakis I, Demopoulos CA. Forty Years Since the Structural Elucidation of Platelet-Activating Factor (PAF): Historical, Current, and Future Research Perspectives. Molecules. 2019;24(23).
29. Palgan K, Bartuzi Z. Platelet activating factor in allergies. Int J Immunopathol Pharmacol. 2015;28(4):584-9.
30. Patel PS, Kearney JF. CD36 and Platelet-Activating Factor Receptor Promote House Dust Mite Allergy Development. J Immunol. 2017;199(3):1184-95.
31. Kihara Y, Ishii S, Kita Y, Toda A, Shimada A, Shimizu T. Dual phase regulation of experimental allergic encephalomyelitis by platelet-activating factor. J Exp Med. 2005;202(6):853-63.
32. Batista NV, Fonseca RC, Perez D, Pereira RV, de Lima Alves J, Pinho V, et al. Lack of Platelet-Activating Factor Receptor Attenuates Experimental Food Allergy but Not Its Metabolic Alterations regarding Adipokine Levels. Biomed Res Int. 2016;2016:8601359.
33. Sudhakara Rao M, Dwarakanatha Reddy D, Murthy PS. Rupatadine: pharmacological profile and its use in the treatment of allergic rhinitis. Indian J Otolaryngol Head Neck Surg. 2009;61(4):320-32.
34. Valero A, de la Torre F, Castillo JA, Rivas P, del Cuvillo A, Antepara I, et al. Safety of rupatadine administered over a period of 1 year in the treatment of persistent allergic rhinitis: a multicentre, open-label study in Spain. Drug Saf. 2009;32(1):33-42.
35. Hide M, Suzuki T, Tanaka A, Aoki H. Long-term safety and efficacy of rupatadine in Japanese patients with itching due to chronic spontaneous urticaria, dermatitis, or pruritus: A 12-month, multicenter, open-label clinical trial. J Dermatol Sci. 2019;94(3):339-45.
36. Fortier JM, Kornbluth J. NK lytic-associated molecule, involved in NK cytotoxic function, is an E3 ligase. J Immunol. 2006;176(11):6454-63.
37. Kozlowski M, Schorey J, Portis T, Grigoriev V, Kornbluth J. NK lytic-associated molecule: a novel gene selectively expressed in cells with cytolytic function. J Immunol. 1999;163(4):1775-85.
38. Hoover RG, Gullickson G, Kornbluth J. Impaired NK cytolytic activity and enhanced tumor growth in NK lytic-associated molecule-deficient mice. J Immunol. 2009;183(11):6913-21.

39. Lawrence DW, Kornbluth J. E3 ubiquitin ligase NKLAM ubiquitinates STAT1 and positively regulates STAT1-mediated transcriptional activity. Cell Signal. 2016;28(12):1833-41.
40. Lawrence DW, Gullickson G, Kornbluth J. E3 ubiquitin ligase NKLAM positively regulates macrophage inducible nitric oxide synthase expression. Immunobiology. 2015;220(1):83-92.
41. Lawrence DW, Kornbluth J. Reduced inflammation and cytokine production in NKLAM deficient mice during Streptococcus pneumoniae infection. PLoS One. 2018;13(3):e0194202.
42. Nakayama T. Introduction to "allergic inflammation". Immunol Rev. 2017;278(1):5-7.
43. Ren F, Ding X, Zheng M, Korzinkin M, Cai X, Zhu W, et al. AlphaFold accelerates artificial intelligence powered drug discovery: efficient discovery of a novel CDK20 small molecule inhibitor. Chem Sci. 2023;14(6):1443-52.
44. Ivanenkov YA, Polykovskiy D, Bezrukov D, Zagribelnyy B, Aladinskiy V, Kamya P, et al. Chemistry42: An AI-Driven Platform for Molecular Design and Optimization. J Chem Inf Model. 2023;63(3):695-701.
45. Basile AO, Yahi A, Tatonetti NP. Artificial Intelligence for Drug Toxicity and Safety. Trends Pharmacol Sci. 2019;40(9):624-35.
46. He D, Liu Q, Wu Y, Xie L. A context-aware deconfounding autoencoder for robust prediction of personalized clinical drug response from cell-line compound screening. Nature Machine Intelligence. 2022;4:879-92.
47. Ferrante G, Licari A, Fasola S, Marseglia GL, La Grutta S. Artificial intelligence in the diagnosis of pediatric allergic diseases. Pediatr Allergy Immunol. 2021;32(3):405-13.
48. Shamji MH, Ollert M, Adcock IM, Bennett O, Favaro A, Sarama R, et al. EAACI guidelines on environmental science in allergic diseases and asthma - Leveraging artificial intelligence and machine learning to develop a causality model in exposomics. Allergy. 2023.
49. Bulfamante AM, Ferella F, Miller AM, Rosso C, Pipolo C, Fuccillo E, et al. Artificial intelligence, machine learning, and deep learning in rhinology: a systematic review. Eur Arch Otorhinolaryngol. 2023;280(2):529-42.
50. Sallis BF, Erkert L, Monino-Romero S, Acar U, Wu R, Konnikova L, et al. An algorithm for the classification of mRNA patterns in eosinophilic esophagitis: Integration of machine learning. J Allergy Clin Immunol. 2018;141(4):1354-64 e9.
51. Mkrtchyan GV, Veviorskiy A, Izumchenko E, Shneyderman A, Pun FW, Ozerov IV, et al. High-confidence cancer patient stratification through multiomics investigation of DNA repair disorders. Cell Death Dis. 2022;13(11):999.
52. Durham SR, Shamji MH. Allergen immunotherapy: past, present and future. Nat Rev Immunol. 2022:1-12.

53. Goretzki A, Lin YJ, Schulke S. Immune metabolism in allergies, does it matter?-A review of immune metabolic basics and adaptations associated with the activation of innate immune cells in allergy. Allergy. 2021;76(11):3314-31.
54. Bryce PJ, Oyoshi MK, Kawamoto S, Oettgen HC, Tsitsikov EN. TRAF1 regulates Th2 differentiation, allergic inflammation and nuclear localization of the Th2 transcription factor, NIP45. Int Immunol. 2006;18(1):101-11.
55. Gonzales-van Horn SR, Farrar JD. Interferon at the crossroads of allergy and viral infections. J Leukoc Biol. 2015;98(2):185-94.
56. Ait Yahia S, Audousset C, Alvarez-Simon D, Vorng H, Togbe D, Marquillies P, et al. NOD1 sensing of house dust mite-derived microbiota promotes allergic experimental asthma. J Allergy Clin Immunol. 2021;148(2):394-406.
57. Wong CK, Hu S, Leung KM, Dong J, He L, Chu YJ, et al. NOD-like receptors mediated activation of eosinophils interacting with bronchial epithelial cells: a link between innate immunity and allergic asthma. Cell Mol Immunol. 2013;10(4):317-29.
58. Iyer D, Mishra N, Agrawal A. Mitochondrial Function in Allergic Disease. Curr Allergy Asthma Rep. 2017;17(5):29.
59. Aguilera-Aguirre L, Bacsi A, Saavedra-Molina A, Kurosky A, Sur S, Boldogh I. Mitochondrial dysfunction increases allergic airway inflammation. J Immunol. 2009;183(8):5379-87.
60. Qian L, Mehrabi Nasab E, Athari SM, Athari SS. Mitochondria signaling pathways in allergic asthma. J Investig Med. 2022;70(4):863-82.
61. Trinchese G, Paparo L, Aitoro R, Fierro C, Varchetta M, Nocerino R, et al. Hepatic Mitochondrial Dysfunction and Immune Response in a Murine Model of Peanut Allergy. Nutrients. 2018;10(6).
62. Chelombitko MA, Chernyak BV, Fedorov AV, Zinovkin RA, Razin E, Paruchuru LB. The Role Played by Mitochondria in FcepsilonRI-Dependent Mast Cell Activation. Front Immunol. 2020;11:584210.
63. Bertrand T, Kothe M, Liu J, Dupuy A, Rak A, Berne PF, et al. The crystal structures of TrkA and TrkB suggest key regions for achieving selective inhibition. J Mol Biol. 2012;423(3):439-53.
64. Forno E, Zhang R, Jiang Y, Kim S, Yan Q, Ren Z, et al. Transcriptome-wide and differential expression network analyses of childhood asthma in nasal epithelium. J Allergy Clin Immunol. 2020;146(3):671-5.

65. Aven L, Paez-Cortez J, Achey R, Krishnan R, Ram-Mohan S, Cruikshank WW, et al. An NT4/TrkB-dependent increase in innervation links early-life allergen exposure to persistent airway hyperreactivity. FASEB J. 2014;28(2):897-907.
66. Noga O, Englmann C, Hanf G, Grutzkau A, Guhl S, Kunkel G. Activation of the specific neurotrophin receptors TrkA, TrkB and TrkC influences the function of eosinophils. Clin Exp Allergy. 2002;32(9):1348-54.
67. Nassenstein C, Braun A, Erpenbeck VJ, Lommatzsch M, Schmidt S, Krug N, et al. The neurotrophins nerve growth factor, brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin-4 are survival and activation factors for eosinophils in patients with allergic bronchial asthma. J Exp Med. 2003;198(3):455-67.
68. Fulkerson PC, Rothenberg ME. Targeting eosinophils in allergy, inflammation and beyond. Nat Rev Drug Discov. 2013;12(2):117-29.

DATA AVAILABILITY

The original findings presented in the study are included in the article/supporting material, further inquiries can be directed to the corresponding author.

FINANCIAL DISCLOSURE STATEMENT

The author(s) received no specific funding for this work.

COMPETING INTERESTS

BHML, AS, MC, and FP are affiliated with Insilico Medicine, an artificial intelligence powered drug discovery & development company.

Figure Legend

Figure 1. Study scheme of applying PandaOmics to asthma, eczema, and food allergy. Transcriptomics datasets with bronchial epithelial tissue, skin, and blood for asthma, eczema, and food allergy were retrieved from the public repositories. Case-control comparisons were generated from datasets consisting both samples from patients and healthy individuals, and allocated into three meta-analyses based on their disease types in PandaOmics for target identification (Target ID). Expression profiles of the differentially expressed genes (DEGs) and the list of dysregulated signaling pathways were also obtained from PandaOmics for downstream analysis. After target prioritization by PandaOmics under two novelty settings, followed by DEG analysis, 115, 178, and 107 unique dysregulated targets for asthma, eczema, and food allergy were shortlisted. Among the eleven commonly dysregulated targets in the three indications, targets for proof-of-concept, drug repurposing, and novel therapeutic intervention were selected based on consistency of the dysregulated expression across the comparisons in each indication, relevance to allergies, drug availability, and clinical trial status.

Figure 2. Common activated pathways across asthma, eczema, and food allergy. (A) One hundred and four common activated pathways in asthma, eczema, and food allergy were categorized into twenty biological processes. The percentage of activated pathways in a particular process over all activated pathways was shown next to each bar. Please note that one pathway belonged to two independent biological processes. (B) Common activated pathways associated with IL5, PTAFR, and RNF19B in asthma, eczema, and food allergy were displayed in the dot plot. Presence of a red dot indicated the association between the given target and the pathway.

Figure 3. PandaOmics-derived targets matched up against each other for comparison. (A) Two lists of Top-100 targets with high confidence and novelty for each indication were obtained from PandaOmics. Based on the consistency of the dysregulated expression across the comparisons in each indication, as well as the statistical significance, these 200 unique targets were classified into three groups: upregulated (*left*), downregulated (*right*), and no difference (not shown). Upregulated targets in the three indications were overlapped to identify the shared targets. The same applied to the downregulated targets. Eleven targets were commonly activated across the three allergic indications. (B) Screenshot of the Target ID page of PandaOmics for the meta-analyses for asthma, eczema, and food allergy. *IL5*, *PTAFR*, and *RNF19B* were revealed as the target for proof-of-concept, drug repurposing, and novel therapeutic design, respectively.

Figure 4. Upregulation of PTAFR was particularly observed in severe asthma. Expressions for PTAFR in the two asthma transcriptomics datasets having information on disease severity, i.e. GSE41861 and GSE158752, were displayed in box plots. *$P < 0.05$, ns: not significant. $P < 0.05$ is considered as statistically significant.

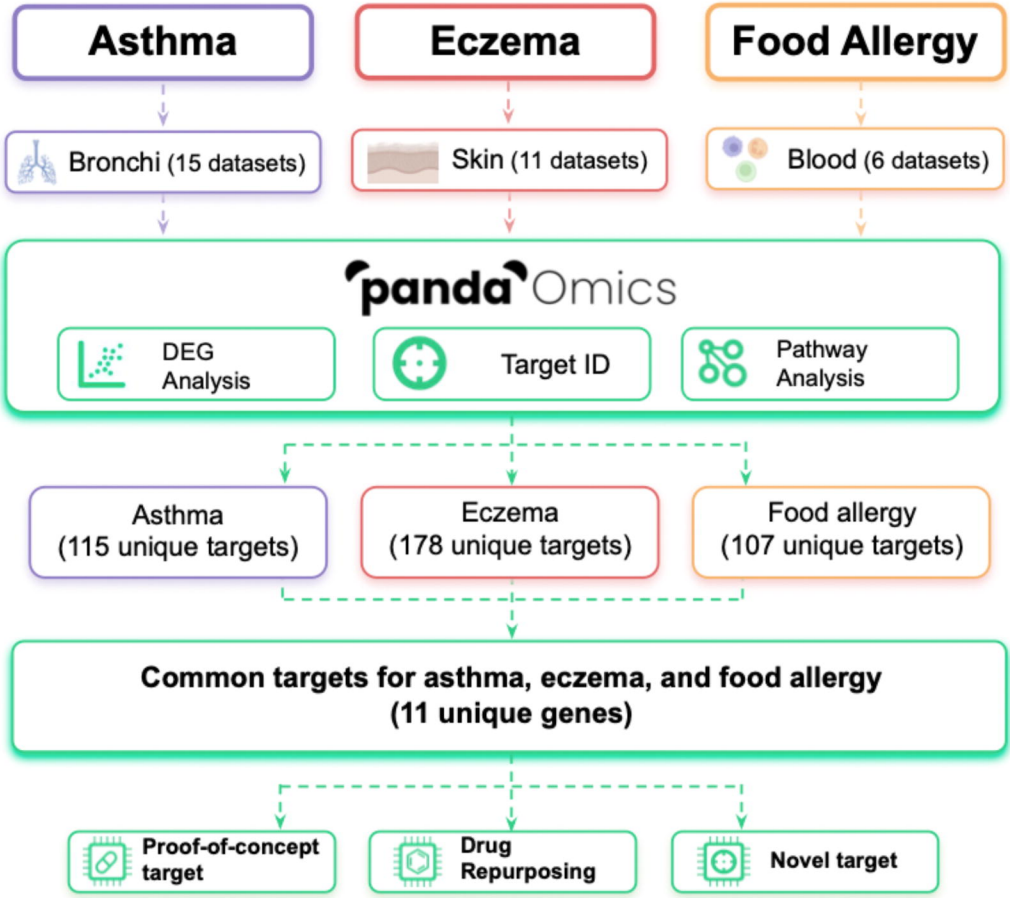
Supplemental Information

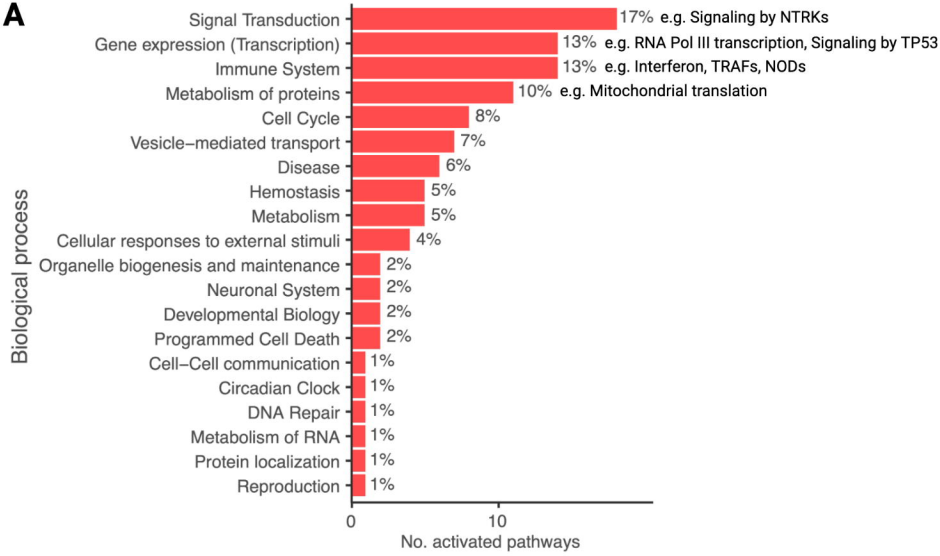
S1 Table. Dysregulated pathways in asthma, eczema, and food allergy groups.

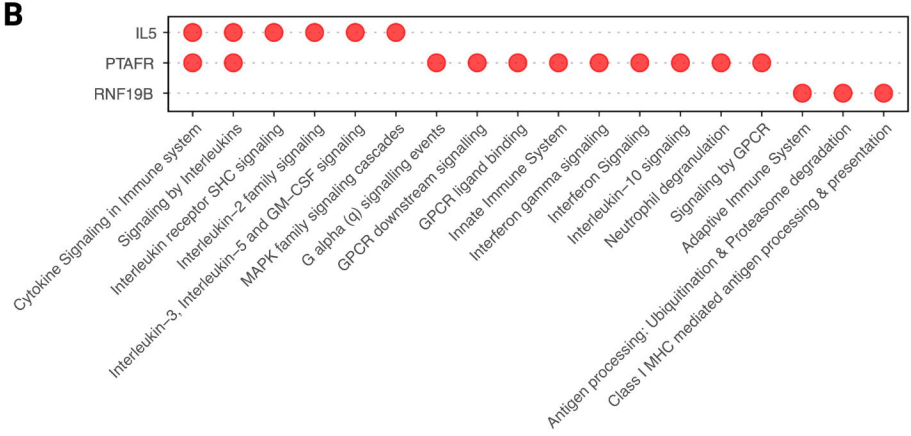
S2 Table. Expression profiles of *IL5*, *PTAFR*, and *RNF19B* in allergies-related bulk transcriptomics comparisons for target identification.

S3 Table. Dysregulated pathways associated with *IL5*, *PTAFR*, and *RNF19B* in allergies-related comparisons.

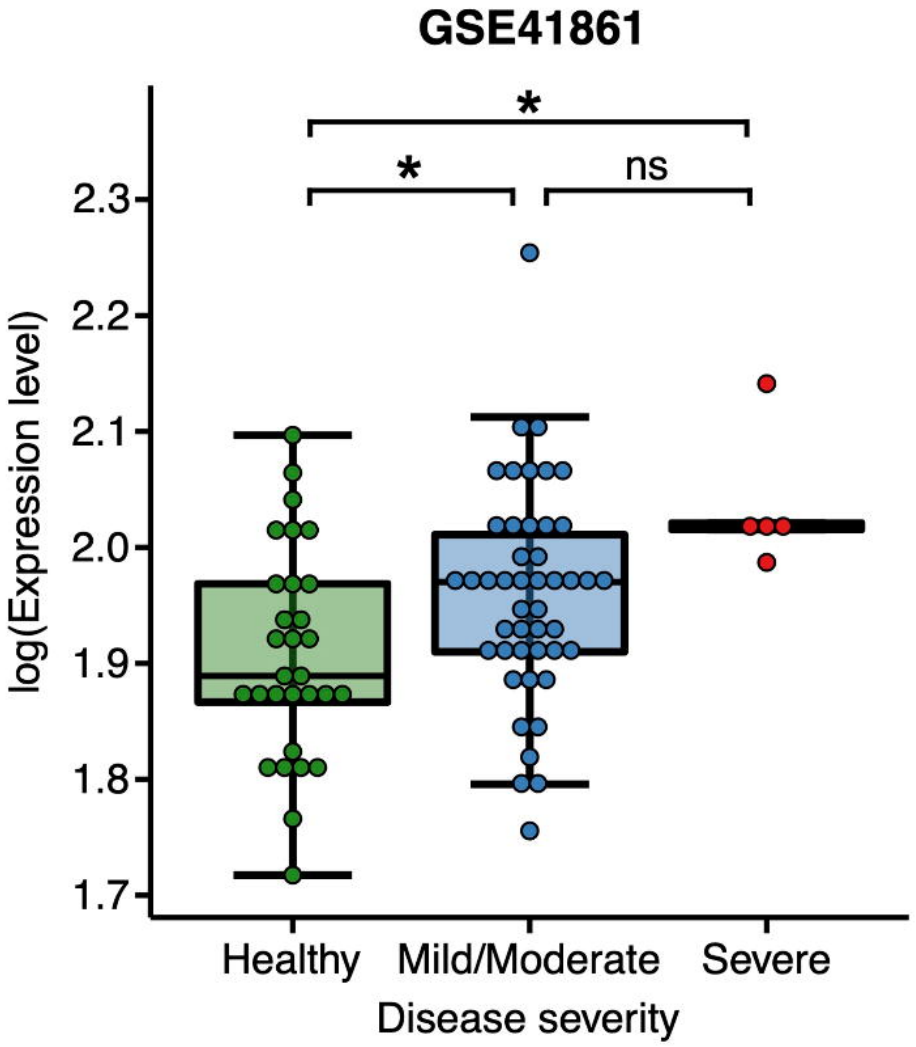
S4 Table. Association between the expressions of *IL5*, *PTAFR*, and *RNF19B* and disease severity in asthma-related bulk transcriptomics comparisons.

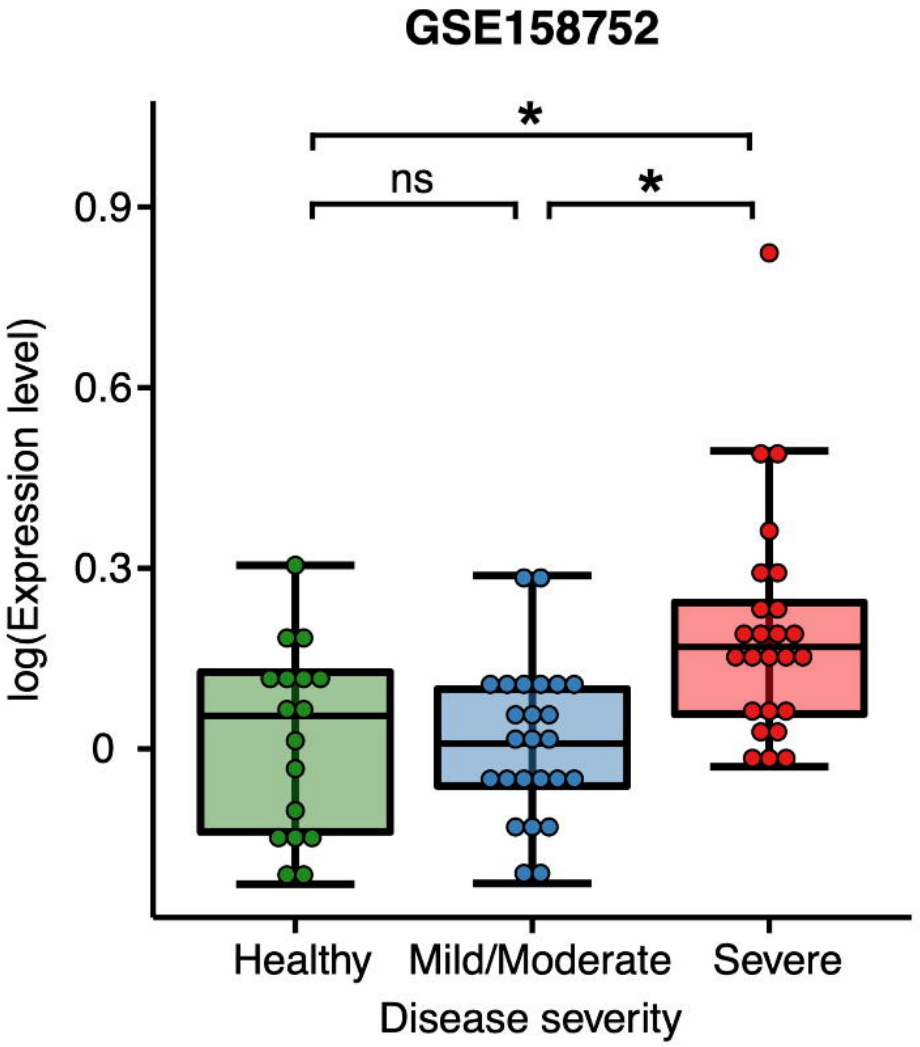

Asthma
Eczema
Food Allergy
Bronchi (15 datasets)
Skin (11 datasets)
Blood (6 datasets)
pandaOmics
DEG Analysis
Target ID
Pathway Analysis
Asthma (115 unique targets)
Eczema (178 unique targets)
Food allergy (107 unique targets)
Common targets for asthma, eczema, and food allergy (11 unique genes)
Proof-of-concept target
Drug Repurposing
Novel target


A
Biological process
Signal Transduction
Gene expression (Transcription)
Immune System
Metabolism of proteins
Cell Cycle
Vesicle−mediated transport
Disease
Hemostasis
Metabolism
Cellular responses to external stimuli
Organelle biogenesis and maintenance
Neuronal System
Developmental Biology
Programmed Cell Death
Cell−Cell communication
Circadian Clock
DNA Repair
Metabolism of RNA
Protein localization
Reproduction
17% e.g. Signaling by NTRKs
13% e.g. RNA Pol III transcription, Signaling by TP53
13% e.g. Interferon, TRAFs, NODs
10% e.g. Mitochondrial translation
8%
7%
6%
5%
5%
4%
2%
2%
2%
2%
1%
1%
1%
1%
1%
1%
0
10
No. activated pathways


B
IL5
PTAFR
RNF19B
Cytokine Signaling in Immune system
Signaling by Interleukins
Interleukin receptor SHC signaling
Interleukin−2 family signaling
Interleukin−5 and GM−CSF signaling
Interleukin−3, Interleukin−5 and GM−CSF signaling
MAPK family signaling cascades
G alpha (q) signalling events
GPCR downstream signalling
GPCR ligand binding
Innate Immune System
Interferon gamma signaling
Interferon Signaling
Interleukin−10 signaling
Neutrophil degranulation
Signaling by GPCR
Adaptive Immune System
Antigen processing: Ubiquitination & Proteasome degradation
Class I MHC mediated antigen processing & presentation

A
Top-100 Upregulated Hits
Food allergy
65
4
15
11
34
96
17
Asthma
Eczema
Common Upregulated targets
CLOCK, DCTPP1, IFNG, IL5, PSMA2, PSMA4, PTAFR, RNF19B, TGFB1, UBE2F, and VDR
Top-100 Downregulated Hits
Food allergy
9
0
3
0
44
31
5
Asthma
Eczema
B
asthma
atopic eczema
food allergy
Data types:
RANK
OMICS SCORES
TEXT-BASED
FINANCIAL
KOL
TISSUE
Small molecule
Antibodies
Safety
Novelty
Structure
Development Level
Target Family
PTAFR
IL5
RNF19B
Tchem
Tclin
Tbio
GPCR
Interleukin
Acyltransferase
Network neighbors
Mutated sub-modules
Disease sub-modules
Causal inference
Overexpression
Knockouts
Mutations
Pathways
Interactome community
Relevance
Expression
Heterogenous graph walk
Matrix factorization
Attention spike
Evidence
Attention score
Trend
Funding per publication
Grant funding
Grant size
Credible attention index
Mean Hirsch
Impact factor
Tissue specificity
Specificity in selected tissue


GSE41861
*
*
ns
2.3
2.2
2.1
2.0
1.9
1.8
1.7
log(Expression level)
Healthy
Mild/Moderate
Severe
Disease severity


GSE158752
*
ns
*
0.9
0.6
0.3
0
log(Expression level)
Healthy
Mild/Moderate
Severe
Disease severity