Patient stratification of two asthma populations reveal distinct genetic and mechanistic differences between T2-high and T2-low asthma

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Introduction & Aims

PrecisionLife is a computational biology company focusing on precision medicine analytics in complex chronic diseases. Our mechanistic patient stratification identifies subgroups of patients who share causal drivers of disease and treatment response, generating biomarkers that inform and de-risk drug discovery and development.

Asthma can be split into two major endotypes (T2-high and T2-low) characterized by distinct molecular drivers. The genetic risk factors and underlying pathology of T2-low asthma are more poorly understood than the T2-driven endotype and there is no clear consensus on the clinical definition, although patients with low eosinophil counts often display a greater proportion of neutrophilic inflammation.

PrecisionLife aimed to identify genetic differences between the two cohorts and further characterize the biological drivers of T2-low asthma.

Methods

PRIMARY DATA:
PrecisionLife analysed genetic datasets constructed from the UK Biobank and GASP study using blood eosinophil data:

 # 1) T2-LOW ASTHMA CASES (UKB = 14,996, GASP = 405)
ICD-10 code, J45.x
Serum eosinophil counts of 0.15 (1,500 cells/mm3) or fewer[1]
 # 2) T2-HIGH ASTHMA CASES (UKB = 7,072, GASP = 271)
ICD-10 code, J45.x
Serum eosinophil counts of 0.35 (3,500 cells/mm3) or more[1]

HEALTHY CONTROLS (n = 21,566)
No evidence of chronic respiratory disease

COMBINATORIAL ANALYSIS:
Each case-control dataset was analysed in the PrecisionLife platform to identify combinations of SNP genotypes that when observed together in a patient are strongly associated with each endotype of asthma.

SNP combinations that have high odds ratios, low *p*-values and high prevalence in cases are prioritised. This process undergoes 1,000 cycles of fully randomized permutations and combinations must meet a specified FDR threshold.

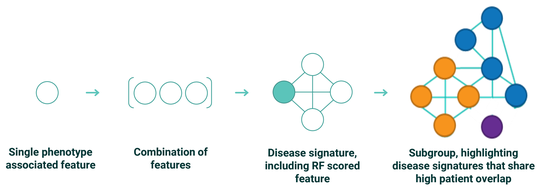
SNPs are scored using a Random Forest algorithm in a 5-fold cross-validation framework and prioritised based on their ability to differentiate cases and controls.

The highest scoring SNPs are then mapped to genes and clustered by the patients they co-occur in to generate a disease architecture.

The results from each dataset (T2-high and T2-low asthma) were compared to identify significant genetic differences between the two.

Results

Figure 1. Combinatorial analysis of genomic data vs GWAS

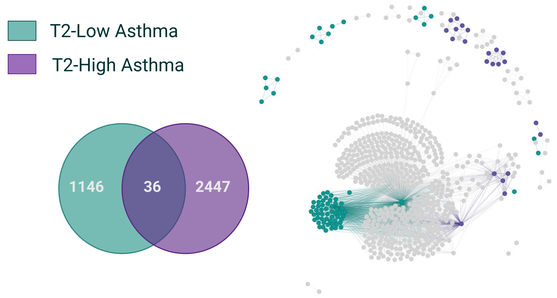


Conceptual representation of features, combinations, disease signatures and communities used to build up the disease architecture in the PrecisionLife combinatorial methodology.

GWAS	Combinatorial Analysis
Single SNP associations must be significant across large groups of patients	Specific combinations of variants associated with each patient subgroup serve as a genetic stratification biomarker
Limited insights unless disease is likely to be caused by a small number of rare variants with large effect sizes (often in gene coding regions affecting protein 3D structure)	Patient subgroups with different causes of disease or even incorrect diagnoses can be distinguished (stratified) by different mechanistic aetiology
Does not account for the effects of interactions between SNPs, genes and metabolic networks	Captures epistatic and non-linear additive effects of all interactions between SNPs, genes, environmental factors and metabolic networks

Figure 2. Key results from PL analysis of T2-high and T2-low UK Biobank and GASP datasets

Venn diagram demonstrating the overlap in the SNPs associated with T2-low and T2-high asthma populations in UK Biobank.



Disease architecture of GASP asthma cohort. Each circle represents a disease-associated SNP genotype, edges represent their co-association in patients in disease signature(s). Turquoise SNPs are significantly associated with T2-low asthma cases, purple SNPs with T2-high asthma, grey SNPs are not specific to either endotype.

Pathway enrichment plot for genes associated with cases categorised with T2-low and T2-high asthma. Gene ratio represents the ratio of genes found in the pathway compared to the genes associated with a community and *p.adjust* represents the p-value adjusted for multiple testing. The dots in the plot are color-coded based on their corresponding *p.adjust* values.

Table 2. 10 prioritised novel drug targets with patient stratification biomarkers in T2-low asthma in UKB and GASP populations

PL TARGET	PL BIOMARKER	MECHANISM IN ASTHMA	TARGET PREVALENCE	LUNG EXPRESSION	LEVEL OF TARGET TRACTABILITY	NOVEL OPPORTUNITY IN ASTHMA
PL-001	✓T2-Low Asthma	Fatty acid inflammation	22%	✓ HIGH	Small molecule tractable	✓
PL-002	✓T2-Low Asthma	ASMC proliferation	30%	✓ HIGH	Tool compounds	✓
PL-003	✓T2-Low Asthma	T cell inflammation	30%	✓ HIGH	Drugs in clinical development	✓
PL-004	✓T2-Low Asthma	Neutrophil inflammation	43%	✓ HIGH	Drugs in clinical development	✓
PL-005	✓T2-Low Asthma	Mucus secretion	24%	✓ HIGH	Tool compounds	✓
PL-006	✓T2-Low Asthma	Inflammation	55%	✓ HIGH	Drugs in clinical development	✓
PL-007	✓T2-Low Asthma	Fatty acid inflammation	10%	✓ HIGH	Small molecule tractable	✓
PL-008	✓T2-Low Asthma	Epithelial barrier function	16%	✓ MEDIUM	Drugs in clinical development	✓
PL-009	✓T2-Low Asthma	T cell inflammation	63%	✓ HIGH	Drugs in clinical development	✓ NOVEL IN T2-LOW TYPE
PL-010	✓T2-Low Asthma	Lung function	11%	✓ MEDIUM	Small molecule tractable	✓

Discussion

PATIENT STRATIFICATION
We demonstrate distinct differences in the biological pathways associated with the genes identified in each asthma endotype when analysed using the PrecisionLife platform.

T2-high:
- T2 cytokine pathways
- HLA region genes

T2-low:
- Neutrophilic inflammation
- Lipid metabolic processes
- Apoptosis
- Metal ion binding

ANALYSIS OF GASP DATASET
PrecisionLife has further demonstrated these mechanistic differences between T2-high and T2-low asthma using genetic data derived of cases from the GASP [the Genetics of Asthma Severity and Phenotypes][2] study and UK Biobank controls.

10 NOVEL DRUG TARGETS WITH PSBs IN T2-LOW ASTHMA
PrecisionLife have prioritised 10 of the most tractable gene targets are specific to T2-low asthma in both UK Biobank and GASP asthma populations. The targets are novel but have strong mechanism of action hypotheses in T2-low asthma development. These can be used for the development of more targeted and efficient treatment strategies to improve asthma control in each endotype.

Conclusion

The results demonstrate that the PrecisionLife combinatorial analysis platform is uniquely able to stratify heterogenous patient populations with complex disease pathologies and replicate these results in independent cohorts. We can use these insights to identify more effective therapeutic strategies, and accompanying biomarker sets to match them to the patient subgroups that are most likely to demonstrate benefit in downstream clinical trials.

References

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