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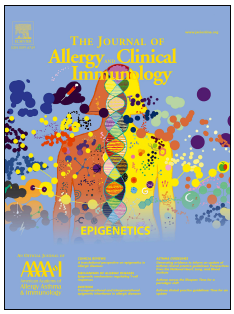

IL-17-high asthma with features of a psoriasis immunophenotype

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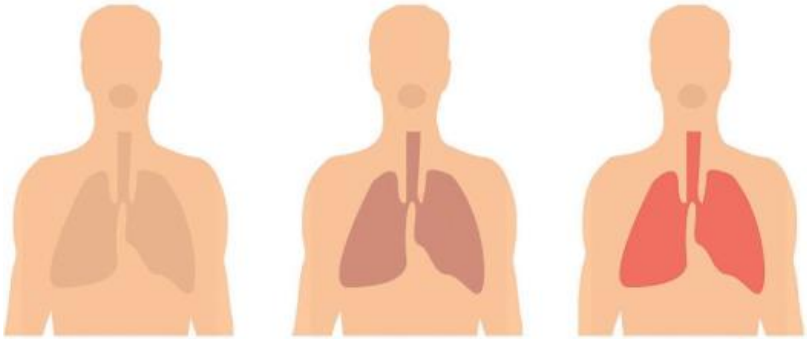
IL-17-high asthma with features of a psoriasis immunophenotype

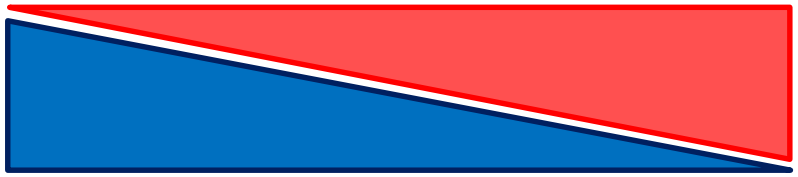
U-BIOPRED cohort
n=91 epithelial brushings or biopsies



Clinical phenotype
Nasal polyps
Smoking
Antibiotic use

Clinical phenotype
FeNO
Exacerbations

IL-17 High



IL-13 High

Gene expression shared with psoriasis
IDO1
IL1B
DEFB4B
S100A8, S100A9
PI3
CXCL3, CXCL8
CXCL10, CCL20

Epithelial Gene Expression Profile

T cell infiltration

Neutrophilia

Eosinophilia

Gene signature
SERPINB2
POSTN
CLCA1

IL-17-high asthma with features of a psoriasis immunophenotype

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ABSTRACT

Background: The role of interleukin-17 immunity is well established in inflammatory diseases like psoriasis and inflammatory bowel disease but not in asthma where further study is required.

Objective: To undertake a deep-phenotyping study of asthmatics with up-regulated interleukin-17 immunity.

Methods: Whole genome transcriptomic analysis was performed using epithelial brushings, bronchial biopsies (91 asthmatics patients and 46 healthy controls) and whole blood samples (n=498) from the U-BIOPRED cohort. Gene signatures induced *in vitro* by interleukin-17 and interleukin-13 in bronchial epithelial cells were used to identify patients with interleukin-17-high and interleukin-13-high phenotypes of asthma.

Results: 22 out of 91 patients were identified with interleukin-17 and 9 patients with interleukin-13 gene signatures. The interleukin-17-high asthmatics were characterised by risk of frequent exacerbations, airway (sputum and mucosal) neutrophilia, decreased lung microbiota diversity and urinary biomarker evidence of activation of the thromboxane B2 pathway. In pathway analysis, the differentially expressed genes in interleukin-17-high patients were shared with those reported as altered in psoriasis lesions, and included genes regulating epithelial barrier function and defence mechanisms, such as interleukin-1β, interleukin-6, interleukin-8, and beta-defensin.

Conclusion: The interleukin-17-high asthma phenotype, characterized by bronchial epithelial dysfunction, upregulated anti-microbial and inflammatory response, resembles the immunophenotype of psoriasis, including activation of the thromboxane B2 pathway which should be considered as a biomarker for this phenotype in further studies, including clinical trials targeting interleukin-17.

Clinical implications: This study points to shared mechanisms between asthma and psoriasis, with implications for treatments targeting interleukin-17-driven mechanisms.

Capsule summary: This study provides evidence of an interleukin-17-driven asthma phenotype sharing features with psoriasis, and provides a rationale for testing drugs targeting this pathway in interleukin-17-high asthmatics.

Key words: Interleukin-17, asthma, bronchial biopsies, bronchial brushings, biomarkers, psoriasis

Abbreviations:

IL-17: interleukin-17

ILC3: type 3 innate immune lymphoid cells

NK: natural killer

GMCSF: granulocyte colony-stimulating factor

U-BIOPRED: Unbiased BIOmarkers for the PREDiction of respiratory disease outcomes

FEV_1: forced expiratory volume in one second

FeNO: fraction of exhaled nitric oxide

NGS: next generation sequencing

IPA: ingenuity pathway analysis

TDA: topological data analysis

DEG: differentially expressed gene

ICAM-1: intercellular adhesion molecule 1

RAR: retinoic acid receptor

RORC: RAR-related Orphan Receptor C

DDP4: dipeptidyl peptidase-4

BC: cluster derived from transcriptomic data in whole blood

FDR: false detection rate

OUT: operational taxonomic unit

NTHi: non-typeable haemophilus influenza

ACQ: asthma control questionnaire

CLDN: claudin

INTRODUCTION

Asthma presents in variable clinical forms that can be stratified into multiple clinical phenotypes driven by distinct pathological mechanisms that define so-called asthma endotypes(1, 2). This stratified approach to asthma is useful for both advancing the understanding of disease pathogenesis and optimising treatment with inhaled corticosteroids (3, 4) and biologics (5, 6). Type-2 (T2) interleukins (IL), 4, 5, and 13, are pivotal in asthma, driving the isotype switch to the production of immunoglobulin E, eosinophilia, mast cell activation, and airways remodelling(7). Trials with T2 biologics have shown that T2 cytokines play key roles in a significant proportion of asthmatics, particularly those with prominent eosinophilic inflammation(8). However, substantial numbers of patients do not respond to T2 biologics(9), suggesting the presence of T2-independent mechanisms.

The role of IL-17 in asthma is unclear. IL-17 immunity has been associated with asthma exacerbations(10, 11), but it is not understood whether it is a driver of an asthma phenotype or a marker of mucosal defence responses to microbial stimulus. In a study of 51 asthmatics with a range of clinical severities, Choy *et al*. identified a group characterised by high expression of genes in the bronchial epithelium demonstrated to be up-regulated *in vitro* by IL-17A(12). In these patients, epithelial T17 and T2 gene signatures were inversely correlated, suggesting that they are mutually exclusive. IL-17 is produced by T17 cells, γδT-cells and innate cells, such as type 3 innate lymphoid cells (ILC3), natural killer (NK) cells and NK T-cells(13). The IL-17 family consists of six members, with antimicrobial activity associated mainly with IL-17A, IL-17F and IL-17A/F heterodimer members(14). IL-17 is co-regulated by the transcription factor retinoid-related orphan receptor (ROR)γt, and activation of IL-17 or IL-22 receptors expressed on bronchial epithelial cells induces neutrophil chemotactic factors such as granulocyte-macrophage colony-stimulating factor (GMCSF), and chemokine CXC ligand (CXCL) 8, cytokines like IL-6, and the antimicrobial peptides β-defensins and S100 proteins(15).

The aim of this study was to advance the understanding of the clinical features and molecular mechanisms of asthmatics characterized by up-regulation of IL-17. We used the large transcriptomics and clinical datasets from the U-BIOPRED (Unbiased BIOmarkers for the PREDiction of respiratory disease outcomes) study and stratified patients according to epithelial and mucosal expression of IL-13 and IL-17 gene signatures described by Woodruff et al. and Choy et al., respectively(12, 16). As the secretion of IL-17 is not limited to T-cells and we do not know the source of these cytokines modulating the lung epithelium, we used the definition of IL-17 instead of T17 gene signature. Systemic activation of IL-17 immunity was assessed in blood by analysing the transcriptomic dataset derived from whole blood microarray analysis. We applied cluster analysis to the bronchial and blood transcriptomic datasets and compared the identified groups in respect of clinical characteristics that define asthma severity, namely levels of symptoms and frequency of exacerbations, and looked for biomarkers in blood and urine in the large U-BIOPRED dataset of serum proteins and urinary eicosanoids.

METHODS

Study design and methods

The design, participants and sample collection methods in the U-BIOPRED study, engaging 16 clinical centres in 11 European countries, have been published(17). The study was approved by the ethics committee for each participating clinical institution (registered on ClinicalTrials.gov: NCT01982162). All participants gave written informed consent.

Severe asthmatics had uncontrolled symptoms defined by the Global Initiative for Asthma (GINA) guidelines and/or frequent exacerbations (>2/year) despite high-dose inhaled corticosteroids (⩾1000 μg fluticasone propionate per day or equivalent dose of other ICS) and were under follow-up by a respiratory physician for at least 6 months prior to enrolment to optimise asthma control and assess medication adherence (Table E1). Mild to moderate asthmatics had controlled or partially controlled symptoms (defined by GINA), while on treatment with <500 μg of fluticasone propionate/day or equivalent (Table E1). Healthy controls had no history of asthma, wheeze or other chronic respiratory disease and pre-bronchodilator FEV_1⩾80% of predicted.

All participants underwent spirometry, exhaled nitric oxide (FeNO) measurement, sputum induction(18) and assessment for atopy. Whole blood samples from 246 severe non-smoking asthmatics, 88 severe smoking asthmatics, 77 mild-moderate non-smoking asthmatics and 87 healthy non-smokers underwent transcriptomic analysis and urine samples were collected for lipid mediator measurement. Bronchial brushings and biopsies were performed in 91 asthmatics with severe or mild-to-moderate asthma; all were non-smokers for >12 months, with <5 pack-years history. Biopsies were processed for immunohistochemistry. Biopsies, brushings and whole blood samples were analysed for whole genome expression using the HT HG-U133+ PM microarray platform (Affymetrix Plus 2.0) as previously described(19). Sputum samples were also subjected to 16S rRNA sequencing and NGS based metagenomic analysis.

Statistical analysis

Gene expression data were analysed by general linear model based statistical tests and hierarchical clustering of transcriptomics data was performed using the average linkage and Euclidean metric methods with each variable normalized to mean 0 and variance, using Qlucore Omics Explorer 3.3 software. Clinical variables and biomarker data were compared by Kruskal-Wallis test using Spotfire 7.0.2. Correlations were tested with the Spearman's r statistics. Gene expression data from blood were analysed by topological data analysis (TDA) performed in Ayasdi Core software (11)(20, 21). Function and pathway enrichment analysis was performed using Ingenuity Pathway Analysis (IPA) package. Unless otherwise stated, clinical data were considered significant if $p<0.05$. For global unbiased analysis of omics data, Benjamini-Hochberg multiple correction for the rate of false positives was applied.

For more details on methods see online repository.

RESULTS

Gene expression in the epithelium

Hierarchical clustering based on IL-13 and IL-17 gene signatures defines 3 asthma groups

A total of 85 brushings and 68 bronchial biopsies with high quality RNA were obtained from 91 participants; while some participants provided both sample types, for some participants only one sample type was obtained or yielded good quality RNA. Hierarchical clustering, using the IL-13 and IL-17 gene signatures, applied separately to data from brushings and biopsies, revealed in total 10 patients with an IL-13-high phenotype and 22 asthmatics with an IL-17-high phenotype (Figures 1A and B, Table E2). One participant had simultaneously high expression of both IL-13-high and IL-17-high phenotypes (Figures 1A and B), while none of the others had simultaneous high expression of both IL-13 and IL-17 gene signatures. Thus, IL-17 and IL-13 gene expression scores correlated negatively (rho=-0.646, $p<0.0001$) (figure 1 D). Sixty participants did not show either the IL-13 or IL-17 gene signatures and were defined, accordingly, as IL-13/IL-17 low phenotype, indicating that their lung cytokine environment may be less polarized.

Additional clustering performed with the combined set of eight genes from the IL-13- and IL-17-signatures confirmed distinct IL-13-high (n=13) and IL-17-high (n=13) clusters, with no clear cluster of patients with simultaneously high expression of both signatures (Figure 1C). These clusters consisted, largely, of the same subjects identified by hierarchical clustering using separate gene signatures.

Differentially expressed epithelial genes (DEGs) in the IL-17-high group reveals dysregulation of epithelial barrier mechanisms

A complete list of DEGs in brushings from IL-17high subjects was generated by excluding mRNAs differentially expressed in the comparison between IL-13high (n=9) and healthy participants (n=64) ($p<0.05$) from the list of genes differentially expressed when comparing IL-17-high (n=22) and all

other participants (comprising IL-13high (n=9), IL-13/IL-17-low (n=54) and healthy (n=64) participants ($q<0.05$)). Comparison with all other participants identified 797 DEGs either over- or under-expressed in the IL-17high group with $q<0.05$ (for complete list of DEGs see Table E3 in the online repository), including host defence genes CCL20 (q=0.0004), IL-1β (q=0.0009), IL-6 (q=0.0003), IL-8 (q=0.0003), TL2R (q=0.00013), β-defensin (q=0.00065), S100A8 (q=0.0009), S100A9 (q=0.0006), and ICAM-1 (q=0.0003), many of which, (e.g. CCL20, IL-1β, β-defensin, IL-6 and IL-8), are associated with T17-pathway activation(22, 23). IPA Regulator Effects Analysis, restricted to immune, infection and inflammatory disease, identified IL-17A as the regulator with the highest consistency score (Table 1).

Expression of RORC, the gene for Nuclear Receptor ROR-γ, a regulator of IL-17 and IL-22, was decreased in the IL-17-high group ($q<0.003$), possibly a sign of negative transcriptional regulation. Other host defence DEGs included SAA4 and TREM1 (q=0.0004, 0.0008) and genes for StAR-related lipid transfer domain protein 7 (STARD7) and IL-33, an alarmin cytokine with a crucial role in innate immunity, inflammation and T2 responses(24). Expression of several key tight junction genes was also significantly lower (CLDN1 (q=0.0004), CLDN8, OCLN), CTNNB1 (q=0.0021).

IL-17-high phenotype-associated DEGs overlap with dysregulated genes in psoriasis

Canonical Pathway Analysis identified “Role of IL-17 in psoriasis” as the pathway with the greatest overlap with the list of 797 DEGs (q=3.6E-04) (Table 2), supported by the Disease and Function enrichment analysis, identifying 79 genes previously implicated in psoriasis (p=5.32E-17) (Table E4 in online supplement). 170 of 797 IL-17-high genes mapped to the 3388 psoriasis genes previously published(25) (Figure 2). Genes over-expressed in bronchial epithelial cells of IL-17-high patients (Figure 2C) tended to belong to the genes over-expressed in psoriasis lesions (Figure 2A) and normalized by treatment of psoriasis with the monoclonal antibody against IL-17 Receptor A, brodalumab(25). Genes under-expressed in bronchial epithelial cells in the IL-17-high participants

tended to belong to genes under-expressed in psoriasis and normalized by Brodalumab(25) (Figure 2B).

Epithelial transcripts for dipeptidyl peptidase-4 (DPP4) were significantly lower in the IL-17-high group (Figure E1), a surprising finding given the efficacy of DPP4 inhibition as treatment for psoriasis(26). Furthermore, DPP4 transcripts were higher in the IL-13-high group when compared to the IL-17-high group, pointing to reciprocal expression of DPP4 in the two phenotypes. Consistent with a potential value of DPP4 as a biomarker, similar differences were seen for serum DPP-4 protein (data not shown).

Clinical and pathobiological features of the epithelial IL-17-high group

59% of the IL-17high asthmatics were severe (89% in the IL-13-high and 53% in the IL-13/IL-17-low); 38% had >2 asthma exacerbations in the preceding year, which was higher than in the IL-13/IL-17-low (15%) (p=0.025) but not different from the IL-13-high group (44%) (Table 3). The IL-17-high patients had increased occurrence (43%) of nasal polyps, more significant smoking history, and 27% had been on regular antibiotics, but similar maintenance oral corticosteroid treatment when compared to the other groups.

Consistent with the role of IL-13 in eosinophilic inflammation, the IL-13-high group had elevated serum IL-13 (mean 2.15 pg/ml), sputum and blood eosinophils (49.3 % and 7.9% respectively) (Figure 3) and FeNO and serum periostin (Table 3). In contrast, the IL-17-high phenotype had higher airways neutrophilia both in sputum and bronchial submucosa (Figure 3, Table 3). Immunohistological staining of bronchial biopsies showed increased submucosal T-cell (CD3+ and CD4+) and lower mast cell counts in the IL-17-high compared to the IL-13/IL-17-low -low group, but not when compared to the IL-13-high group (Figure 4).

Gene expression in blood

Application of TDA to blood transcriptomes of participants from the same U-BIOPRED cohort (246 severe non-smoking asthmatics, 88 severe smoking asthmatics, 77 mild to moderate non-smoking asthmatics and 87 healthy non-smokers) identified 9 clusters based on whole blood transcriptomes (BC); BC1, composed of severe asthmatics (10.44% of total cohort) was enriched for IL-17A, IL-21, IL-22 and TGFβ transcripts (Figure 5A), but was also enriched for IL-5. Two other clusters, BCs 2 and 9, were equally enriched for IL-5 and IL-13 transcripts and serum IL-13. Co-localisation of blood gene expression with the three epithelial clusters (Figure 5B) showed no overlap between blood and airway IL-17-high and IL-13-high gene expression, with only two asthmatics present in the bronchial epithelium-based IL-17-high group and BC1.

Asthmatics in BC1 (Figure 5A) had lower FEV_1 (72.21 ± 24.64 % pred. vs. 101.83 ± 12.99 % pred.; $p=1.93E^{-11}$) and higher FeNO (29.81 ± 22.04 vs. 21.72 ± 13.97 ppb; p=0.02), age (51.44 ± 14.73 vs. 39.37 ± 13.71 yr, $p=5.66E^{-06}$), blood neutrophil counts ($5.63x10^9$L vs. 3.44 ± 1.65 $x10^9$L; p=4.97E-08), blood eosinophils (0.31 ± 0.3 vs. 0.14 ± 0.11 $x10^9$L, $3.12E^{-4}$), sputum neutrophils (30.18 ± 36.16 vs. 15.34 ± 23.57 %, $9.92E^{-3}$) and eosinophils (1.67 ± 5.16 vs. 0.09 ± 0.28 %, p=0.03) when compared to healthy controls, but was not different in sputum eosinophils compared to the rest of the cohort.

BC9 (9.43% of total cohort) (Figure 5A), with high IL-13 but not increased IL-17 expression, had a high atopy rate (80% compared to 65% for BC1, and 37% for healthy participants), lower FEV_1 (71.69 ± 24 vs. 101.83 ± 12.99 % pred.; $p=4.46E-^{11}$), age (50.8 ± 15.58 vs. 39.37 ± 13.71 yr, $p=6.08E^{-05}$), and higher blood eosinophil count (0.35 ± 0.33 vs. 0.14 ± 0.11 $x10^9$L, $p = 1.24E^{-4}$) and smoking pack-years (1.65 ± 1.48 vs. 0.38 ± 1.15, p = 0.01) than healthy controls. The other IL-13-high cluster, BC2 (11.84% of total cohort), was characterised by lower FEV_1 (66.04 ± 20.76 vs. 101.83 ± 12.99 % pred.; $p=5.37E^{-13}$), higher blood neutrophils (6.78 ± 2.94 vs. 3.44 ± 1.65 $x10^9$L, p = $5.37E^{-13}$), age (53.03 ± 14.44 vs. 39.37 ± 13.71 yr, $p=3.31E^{-06}$), sputum eosinophils (6.37 ± 14.89 vs.

315 0.09 ± 0.28, p=6.19E^{-04}), but notably no difference in atopy or blood periostin compared to healthy
316 controls.

317 Associations between blood and urine biomarkers and the IL-17-high phenotype

318 An exploratory search of readily available U-BIOPRED blood and urine biomarkers associated with
319 the IL-17-high phenotype by logistic regression identified a number of potential blood transcripts but,
320 when FDR-corrected, none were statistically significant (Table E5). However, urinary 11 dehydro-
321 thromboxane-B2, a degradation of product of thromboxane-B2, was positively associated with the
322 IL-17-high phenotype (z=2.655, p=0.008, FDR q=0.56) (Table E6). Previous studies have shown this
323 biomarker to be raised in both spontaneous and allergen challenge-induced asthma exacerbations(27)
324 (28).

325 Decreased microbial diversity in patients with an IL-17-high phenotype

326 We hypothesised that microbial diversity would be lower in patients with the IL-17-high phenotype,
327 in keeping with reports in neutrophilic asthma(29). Sputum microbiome data were available from
328 24% of the whole adult cohort but only a few participants in this analysis (6/22 IL-17-high (27%),
329 15/60 IL-13/IL-17-low (25%) and 1/10 IL-13-high (11%) subjects). Both 16S- and NGS based
330 metagenomics analysis-derived data were retrieved and analysed in respect of potential differences in
331 microbiota between the three phenotypes and differential analysis was performed using the
332 metagenomics data. The Shannon alpha-diversity index was lower in the IL-17 phenotype compared
333 to the rest of the cohort (p=0.054), with a trend towards reduction when compared to IL-13/IL-17-
334 low asthmatics (p=0.2) (Figure E2). IL-17-high asthmatics showed the lowest diversity index in both
335 the severe and mild to moderate asthmatics (Figure E2). Sputum neutrophil counts correlated
336 inversely with the Shannon alpha-diversity index in the IL-17-high group (R: -0.76, p=0.0825), more
337 strongly than in any of the other separate groups (data not shown). Screening of the complete list of
338 operational taxonomic unit (OUT) abundance data showed no OTUs with clear differences between

339 the phenotypes. Analysing the abundance of *a priori* selected OTUs related to bacterial exacerbation
340 showed lower abundance of *Haemophilus Influenzae* (p=0.039) in the IL-17-high group when
341 compared to all other asthmatics (data not shown). Moraxella species were poorly represented and
342 did not differ between groups (data not shown).

343

DISCUSSION

Using a gene expression signature for IL-17-induced bronchial epithelial activation(12), we have identified a group of asthmatics with an IL-17-high phenotype, comprising about a quarter of patients studied and consisting of similar proportions of mild/moderate and severe asthmatics. A high percentage of these had had >2 exacerbations in the year preceding the study, surgery for nasal polyps and used antibiotics regularly. Their pathobiology was characterized by airway neutrophilia, consistent with the described role of IL-17 in neutrophilic diseases and with IL-17 responses to mucosal bacterial infections, with additional features being mucosal T-cell infiltration and low numbers of mast cells.

Using the epithelial gene signature identified by Choy et al.(12) as an indirect marker of IL-17 pathway activation, we have shown that patients with up-regulated IL-17 immunity exhibit differential expression of several genes previously associated with IL-17 pathway activation. Many of these overlapped with DEGs in psoriasis lesions and are altered when IL-17 signalling is blocked by monoclonal antibody targeting of the IL-17 receptor[25]. Together, these findings give confidence to our approach to identify patients with the IL-17-high phenotype.

When the epithelial DEGs from the T17-high asthmatics were matched against the IPA database, the canonical pathway of psoriasis appeared as the disease with the greatest overlap and significance. High overlap was also seen by Disease and Function enrichment analysis. Because the U-BIOPRED clinical assessment questionnaire did not have specific questions about a past or present diagnosis of psoriasis, we are unable to make any conclusions about co-morbidity of asthma and psoriasis in the current study, although epidemiological studies done by others have pointed to an association between the two diseases in both children and adults(30-32). We speculate, therefore, that mechanisms similar to those in psoriasis may be implicated in the pathobiology of asthmatics with the IL-17-.high phenotype, where bronchial epithelial dysfunction and inflammatory mechanisms would be major drivers defining the clinical outcome. In further support of this link between the two

diseases, increased levels of urinary 11 dehydro-thromboxane-B2 were strongly associated with the IL-17-high phenotype. This breakdown product of thromboxane-2 was recently shown in a psoriasis model to facilitate IL-17 production by Vg4+ γδT-cells, suggesting a pathogenetic role(33).

Patients with the IL-17 phenotype had reduced expression of several genes regulating epithelial tight junctions and mucosal barrier mechanisms, a novel finding suggesting that epithelial leakage is a specific feature of IL-17 asthma. IL-17 and, in particular, IL-22, belonging to IL-17 pathway cytokines, are known to support epithelial homeostasis and anti-microbial responses in the healthy gut and lung mucosa(34). Decreased microbial diversity, an indicator of dysbiosis, was also a feature of IL-17-high asthma, which, together with enhanced IL-17 activation, could be implicated in the observed dysregulated epithelial integrity and the susceptibility to infections and exacerbations in these patients. The increased expression of the anti-microbial peptide, beta-defensin 2, further suggests that microbial alterations may be associated with IL-17 activation. Microbiome analyses were available in a small subgroup of IL-17-high asthmatics, making it impossible to draw possible conclusions about the candidate microbial trigger of IL-17 immunity. A study in a murine asthma model, showing that lipopolysaccharide induces a switch from eosinophilic to neutrophilic inflammation with associated decreases in T2 cytokines and increases in IL-17 and Th17 cells, has suggested that bacteria may drive IL-17 immunity(35). Almost a third of IL-17-high and none of the IL-13-high patients were ex-smokers, suggesting that past cigarette smoke exposure may have influenced the development of the phenotype with altered lung microbiota and neutrophilic airway inflammation. In support of this concept, evidence points to the IL-17 pathway being up regulated in chronic obstructive pulmonary disease (COPD), a disease characterised by neutrophilic inflammation and caused primarily by smoking(36). A recent study of asthmatic smokers, combining an *in vivo* analysis of IL-17A expression and exposure of epithelial cells *ex vivo* to cigarette smoke extract, has supported that smoking induces neutrophilia through IL-17 induction(37). Furthermore, smoking is known to contribute to alterations of microbiota and epithelial barrier function. A mouse model of

COPD has shown that airways neutrophilia, exacerbated by NTHi infection and associated with increased IL-17 production, is inhibited by anti-IL-17A antibody without increasing the microbial burden(38).

It has been suggested that impaired responses to ICS are associated with IL-17 immunity and/or that ICS down-regulation of T2 immunity promotes IL-17 immunity in asthma(39). Our data do not directly support the former concept but suggest that ICS may enable IL-17 immunity to express itself. Using asthma severity as a proxy for poor corticosteroid response, we have found an equal distribution of IL-17-high patients among mild/moderate/severe patients, which does not support the association of the IL-17 phenotype and an impaired treatment response to ICS. While the frequency of IL-17-high patients was 25% in our cohort, we found only one IL-17-high patient in the steroid-free cohort of Woodruff et al.(16). This suggests that ICS treatment may be associated with the development of IL-17 immunity in asthma, possibly because of effective suppression of T2 immunity in the lungs that allows an IL-17 phenotype to emerge. Indeed, both our study and that of Choy et al.(12) suggest no co-existence of IL-13 and IL-17 pathway activation in asthmatic lungs, at least when epithelial responses are used as a marker. In contrast, our analysis of blood showed up-regulation of both IL-13 and IL-17 gene signatures in the same individuals. Together with an earlier report of increased blood T-cells secreting both T2 and T17 cytokines in asthmatics(40), this suggests that T2 and T17 activation can co-exist, at least in blood T-cells. A previous study by Hinks et al., analysing cytokine profiles in airways secretions and airways cells of 60 patients with mild to severe asthma(20) did not show differences in the frequencies of BAL Th17 cells or IL-17+ γδT-cells. The source of IL-17 in the lungs could be T-cells, lung γδT-cells or, according to a recent study, also eosinophils (41). Together with our finding of co-expression of IL-5 and IL-17 in peripheral blood, this suggests the need to revisit the concept of eosinophilic asthma being purely a T2 disease. This may also be needed in nasal polyps where up-regulation of IL-17 immunity polyps has been reported in association with blood eosinophilia(42). Indeed, and in contrast to our study, Choy et al. found

eosinophilia in asthmatics with an IL-17-high gene signature(12). Thus, it cannot be excluded that some IL17-high patients could respond to anti-IL-5 treatments that target IL-5 and eosinophils.

This study has some limitations such as limited availability of sputum samples in the IL-13-high phenotype asthmatics for comparison of granulocyte counts with the IL-17-high phenotype as well as the limited analysis of the microbiome; all of this will require further studies. We also recognize the observational nature of our study but emphasize its importance for future mechanistic studies and clinical trials targeting IL-17. Nevertheless, together with Choy et al., we show that the IL-17 phenotype can be identified reliably, with clinical and immunological features that define a distinct disease phenotype, and because they constituted a quarter of the U-BIOPRED patients, we propose that there is a sufficient case for developing drugs for this phenotype. Past attempts to inhibit IL-17 signalling with the anti-IL-17 receptor A antibody (brodalumab) have failed in respect of the primary outcome while showing possible improvement in asthma symptoms (ACQ) in a select population with highly reversible airway obstruction(43). Similar to the approach taken for biologics targeting T2-high asthma, effective IL-17 pathway blocking would require patient stratification and urine dehydro-thromboxane-B2 in T17-high patients offers a potential biomarker that could be used, possibly in combination with high airway reversibility(43).

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TABLES

TABLE 1. IPA Regulator Effects networks that map to the list of 797 DEGs (IL-17-high vs all other participants, q<0.05)

Regulators	Consistency Score*	Target Molecules in Dataset	Diseases & Functions
IL17A	8.85	CCL20, CD14, CSF3, CXCL3, CXCL8, DEFB4A/DEFB4B, ICAM1, IL1B, IL6, PTGS2	adhesion of immune cells, binding of professional phagocytic cells, inflammatory response, leukocyte migration, response of phagocytes
TLR1	8.66	CXCL8, IL1B, IL6	adhesion of immune cells, cell movement of leukocytes, immune response of cells, inflammatory response, replication of HIV-1
IL18	7.67	CCL4, CXCL10, CXCL11, CXCL8, CXCL9, ICAM1, IL1B, IL6, PTGS2	cell movement of leukocytes, inflammatory response, migration of lymphatic system cells
TLR7	7.24	CCL20, CCL4, CXCL10, CXCL3, CXCL8, CXCL9, ICAM1, IL1B, IL6, MYD88, PLAU	activation of dendritic cells, inflammatory response, leukocyte migration
TBK1	7.16	CXCL10, CXCL11, CXCL8, IL6, IRF7	cell movement of leukocytes, immune response of cells, inflammatory response, migration of lymphatic system cells
TNF	6.95	CCL20, CCL4, CXCL10, CXCL11, CXCL3, CXCL8, CXCL9, DEFB4A/DEFB4B, ICAM1, IL1B, PLAU, S100A8, S100A9, TLR2	adhesion of phagocytes, cell movement of granulocytes, cell movement of T lymphocytes
FOXO1	6.71	CCL20, CXCL10, CXCL8, DEFB4A/DEFB4B, IL6	cell movement of leukocytes, inflammatory response, migration of lymphatic system cells
IFNL1	6.71	CXCL10, CXCL11, CXCL8, CXCL9, IL6	cell movement of leukocytes, inflammatory response, migration of lymphatic system cells
TLR9	6.71	CCL4, CXCL10, CXCL8, CXCL9, IL6	cell movement of leukocytes, inflammatory response, migration of lymphatic system cells
CSF2	6.12	CCR1, CXCL8, ICAM1, IL1B, IL6, TLR2	binding of professional phagocytic cells, cell movement of neutrophils, migration of lymphatic system cells, replication of HIV-1
FOXO3	6.00	CXCL10, CXCL8, DEFB4A/DEFB4B, IL6	cell movement of leukocytes, inflammatory response, migration of lymphatic system cells
Fcer1	6.00	CCL4, CXCL8, IL1B, IL6	adhesion of immune cells, cell movement of leukocytes, inflammatory response

EZH2	5.31	BIRC3, CSF3, CXCL10, CXCL11, CXCL8, IL6	immune response of cells, migration of lymphatic system cells, response of phagocytes
CAMP	5.30	CCL20, CCL4, CXCL10, CXCL8, FPR2, IL1B, IL6, TLR2	cell movement of granulocytes, immune response of cells, migration of lymphatic system cells
ADORA3	5.20	CCL4, CXCL3, CXCL8	cell movement of mononuclear leukocytes, cell movement of neutrophils, chemotaxis of leukocytes
TICAM1	5.20	CXCL10, CXCL11, CXCL8	chemotaxis of leukocytes, migration of lymphatic system cells, migration of mononuclear leukocytes
CD40LG	4.47	CCL20, CXCL8, ICAM1, IL1B, IL6	adhesion of immune cells, cell movement of leukocytes
IKBKB	4.47	CCL4, CXCL8, ICAM1, IL1B, IL6	adhesion of immune cells, cell movement of leukocytes
IRF4	4.47	CCL20, CXCL10, CXCL11, CXCL3, CXCL9	cell movement of mononuclear leukocytes, chemotaxis of leukocytes
CCL5	4.08	ADGRE5, CCL4, CCR1, CXCL8, IL1B, IL6	adhesion of immune cells, cell movement of leukocytes
ERK	4.00	CCL4, CXCL10, CXCL8, ICAM1	migration of lymphatic system cells, migration of mononuclear leukocytes

* The Consistency Score is a measure of how causally consistent and densely connected a Regulator Effects network is. Analysis was applied to the 797 differentially expressed genes unique for the IL-17 high group and was restricted to the following search items: immune, infection and inflammatory diseases.

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TABLE 2. Canonical pathways associated with Th17 biology and host defence

A. Canonical pathways associated with Th17 biology	FDR (q) Benjamini Hochberg	p Fisher exact test	Ratio	Molecules
Role of IL-17A in Psoriasis	3.6E-04	3.5E-06	0.46	S100A8, S100A9, CCL20, DEFB4A/DEFB4B, CXCL3, CXCL8
IL-17A Signalling in Gastric Cells	2.3E-02	1.9E-03	0.20	CXCL11, FOS, CXCL10, CCL20, CXCL8
Differential Regulation of Cytokine Production in Macrophages and T Helper Cells by IL-17A and IL-17F	4.0E-02	3.8E-03	0.22	IL1B, CSF3, CCL4, IL6
Differential Regulation of Cytokine Production in Intestinal Epithelial Cells by IL-17A and IL-17F	8.7E-02	9.3E-03	0.17	IL1B, DEFB4A/DEFB4B, CSF3, CCL4
Role of IL-17F in Allergic Inflammatory Airway Diseases	1.4E-01	1.7E-02	0.12	IL1B, CXCL10, CCL4, IL6, CXCL8
B. Canonical pathways associated with host defence				
TREM1 Signalling	8.1E-05	2.2E-07	0.20	TLR5, TLR7, MYD88, IL1B, IL6, CXCL8, TLR8, FCGR2B, CASP5, TREM1, DEFB4A/DEFB4B, CXCL3, ICAM1, TLR2
Toll-like Receptor Signalling	8.1E-05	3.9E-07	0.19	TLR5, TLR7, MYD88, IL1B, CD14, IRAK3, FOS, TLR8, LY96, IL1RN, TNFAIP3, TRAF4, TLR2, IL33
Communication between Innate and Adaptive Immune Cells	6.5E-04	9.3E-06	0.16	TLR5, TNFSF13B, TLR7, IL1B, CXCL10, FCER1G, IL6, CXCL8, TLR8, IL1RN, CCL4, TLR2, IL33
Interferon Signalling	1.7E-03	4.1E-05	0.22	IFITM1, IFNGR2, IFIT3, IFITM2, MX1, PIAS1, TAP1, TYK2
iNOS Signalling	1.6E-02	9.3E-04	0.16	FOS, LY96, MYD88, CD14, IFNGR2, TYK2, IRAK3
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	1.7E-02	1.1E-03	0.10	TLR5, TLR7, MYD88, IL1B, IL6, C3AR1, CXCL8, TLR8, C1QC, IRF7, OAS3, TLR2, PIK3C2G
Inflammasome pathway	6.8E-02	6.8E-03	0.19	MYD88, IL1B, CASP5, CXCL8

*The significance indicates the probability of association of molecules from the dataset with the canonical pathway by random chance alone.
The 797 DEGs list was used as input.

TABLE 3. Demographic and clinical characteristics of identified clusters

	----------Groups----------			----------Unadjusted p-value----------		
	IL-17-high	IL-13/IL-17-low	IL-13- high	IL-17- high vs IL-13/IL-17- low	IL-17- high vs IL-13- high	IL-13- high vs IL-13/IL-17- low
Study participants	22/91 (24.2)	60/91 (85.9)	9/91 (9.9)			
Age – years	44.8 ± 3.2	45.6 ± 1.9	43.2 ± 5.3	0.8	0.7	0.7
Sex - Female/Male	8/14	38/22	5/4	0.029	0.326	0.653
Severe asthmatic	13/22	32/60	8/9	0.64	0.11	0.44
BMI kg/m^2	25.9 ± 1	29.7 ± 0.8	28.5 ± 4.6	0.006	0.16	0.62
FEV1 % (L)	79.6 ± 4.6	84.3 ± 2.7	73 ± 8.1	0.33	0.49	0.16
Exacerbations/past year	2 ± 0.4	1.2 ± 0.2	2.7 ± 0.96	0.124	0.608	0.127
>2 exacerbations/past year	8/21 (38)	9/60 (15)	4/9 (44.4)	0.025	0.754	0.035
Never smokers	15/22 (68.1)	53/60 (88.3)	9/9 (100)	0.0317	0.054	0.280
Ex-smokers	7/22 (31.8)	7/60 (11.7)	0/9 (0)	0.0317	0.054	0.280
Smoking history - pack years	2.7 ± 0.69	1.4 ± 0.56	0	0.179	n.a.	n.a.
Atopic	19/21 (90)	41/52 (79)	7/9 (78)	0.4	0.7	0.7
Age of onset - % below age 12	12/22	27/57	2/8	0.567	0.151	0.233
Allergic rhinitis	13/21 (61.9)	31/53 (58.5)	4/9 (44.4)	0.787	0.561	0.651
Non-allergic rhinitis	3/19 (15.7)	8/53 (15.1)	3/9 (33.3)	0.942	0.291	0.185
Eczema	12/21 (57.1)	21/55 (38.2)	3/9 (33.3)	0.136	0.232	0.781
Nasal polyps surgery	9/21 (42.9)	8/55 (14.5)	0/9 (0)	0.008	0.018	0.22
GORD diagnosed	6/21 (28.6)	28/55 (50.2)	2/9 (22.2)	0.08	0.72	0.110
Regular treatment – ICS	22/22 (100)	58/60 (96.7)	9/9 (100)	0.386	n.a.[@]	0.578
Regular treatment – OCS	7/22 (31.8)	12/57 (21.1)	2/8 (25)	0.31	0.7	0.8
Regular treatment – Omalizumab	2/21 (9.5)	2/56 (3.6)	0/6 (0)	0.295	0.397	0.611
Regular treatment – Antibiotics including macrolides	6/22 (27.3)	5/57 (8.8)	0/7 (0)	0.032	0.12	0.41
Regular treatment – Macrolides	4/22 (18.2)	4/60 (7)	0/9 (0)	0.119	0.170	0.208
Regular treatment - LT modifier	8/22 (36.4)	16/57 (28.1)	4/8 (50)	0.47	0.5	0.21
Regular treatment – Xanthines	1/21 (4.8)	5/56 (8.9)	1/8 (12.5)	0.746	0.424	0.746
FeNO – ppb	32 (16-46)	40.9 (18.5-55)	59.9 (37.6-69.8)	0.356	0.097	0.172
Blood eosinophils x10e3/µl	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.5 (0.3-0.8)	0.8	0.028	0.012
Blood eosinophils %	3.6 (1.9-5.1)	3.7 (1.8-4.4)	7.9 (3.7-11.1)	0.7	0.025	0.012
Blood neutrophils x10e3/µl	4.7 (2.9-5.7)	4.2 (3.1-5.1)	3.9 (1.9-5.8)	0.892	0.433	0.649
Blood neutrophils %	62.1 (53.9-70.9)	60.2 (53.4-67.8)	53.2 (42.7-58)	0.675	0.555	0.748
Sputum eosinophils %[+]	6.25 (0.5-6.2) (n=12)	3.2 (0.1-4.4) (n=27)	49.3 (45-53.6) (n=2)	0.35	0.0283	0.0193

Sputum neutrophils %[+]	63.7 (52.2-77) (n=12)	48.7(33.3-59.8) (n=27)	38.6 (31.7-45.4) (n=2)	0.045	0.144	0.49

Data are presented as numbers of participants assessed (n), mean ±se, %, n/N (%) or median (interquartile range (q1-q3)). [@] All asthmatics were on ICS, therefore, no statistical analysis was done (n.a). [+]Not all participants produced good quality sputum, so numbers (n) of QC-passed samples are given in parentheses for each group.

FIGURE LEGENDS

Figure 1. IL-13-high and IL-17-high clusters in the U-BIOPRED asthma cohort. Heatmaps show clusters based on gene expression data from 85 brushings and 68 biopsies from 91 asthmatics: mild to moderate (grey bars) and severe (black bars). The IL-13-high and IL-17-high clusters are delineated by pink and turquoise boxes, respectively. A) IL-13-high cluster based on the IL-13 gene signature (POSTN, CLCA1, and SERPINB2) in bronchial brushings (top), n=10, and biopsies (bottom), n=3. B) IL-17-high cluster based on the IL-17 gene signature (CSF3, CXCL1, CXCL2, CXCL3, and CXCL8 (IL-8)) in bronchial brushings (top), n=14, and bronchial biopsies (bottom), n=13. C) Hierarchical clustering of IL-13-high and IL-17- high clusters based on expression levels of the combined IL-17 and IL-13-regulated genes in bronchial brushings. Euclidean distance, average linkage, colour scale is given as log2 fold changes, with a range from −2.0 (blue), via 0.0 (grey) to +2.0 (red). Data from multiple probes were collapsed to single genes using the highest value. Sample IDs are indicated on the x axis. D) Correlation between IL-13 gene and IL-17 gene signature scores. Gene expression score was calculated from normalized and zero-centered gene expression values. Spearman correlation and two tailed p values are shown.

Figure 2. Fold-change values (colour-coded) for 170 genes from three separate differential expression analyses using transcriptomics data from A) Psoriasis skin, lesion vs. non-lesion (for more detail see reference 22), B) Psoriasis skin, lesion before vs. after Brodalumab treatment (reference 22), and C) Asthmatic bronchial epithelial cells, IL-17-high vs. IL-13/IL-17-low, IL-13-high in the current study. Red and blue colours represent over- and under-expression, respectively.

Figure 3. Blood and sputum inflammatory biomarkers distinguishing IL-17-high and IL-13-high clusters. Counts of blood eosinophils (A) and sputum eosinophils (B) and serum IL-13 concentrations (C) are higher in the IL-13-high group as compared to the IL-17-high and IL-13/IL-17-low groups. P

values (Kruskal-Wallis) are indicated for pairwise comparisons. Scatter-plots indicate values of the median and the 25th and 75th percentiles.

Figure 4. Inflammatory cell counts distinguishing IL-17-high and IL-13-high clusters. The percentage of neutrophils in sputum (A), the number of neutrophils in the submucosa (B) and the number of infiltrated CD4+ (C) and CD3+ (D) T cells are higher in the IL-17-high group as compared to the IL-13/IL-17-low group. Number of infiltrated mast cells (E) are lower in the IL-17-high group as compared to the IL-13/IL-17-low group. P values (Kruskal Wallis) are indicated for pairwise comparisons.

Figure 5. Comparison with IL-13-high and IL-17-high blood-based clusters (BC) (see second figure in panel A) identified in blood. A) TDA networks of blood transcriptomics data with heatmap colourings for key asthma-related clinical variables and IL-17 and IL-13 associated gene expression. B) heatmap of the expression of selected IL-17 and IL-13 in blood aligned to IL-17 and IL-13 bronchial brushings cluster assignments. A total of 9 blood-based clusters, seven which were validated by machine learning (ROC AUC of logistic regression models >0.70). The scales (colours) in panel A indicate the relative levels of expression of the gene in question in blood. In panel B, the colours in rows 1-3 indicate membership of the IL-17 and IL-13 high clusters. In the other rows, colour indicate the relative levels of expression of the gene in question in blood.

Figure 1

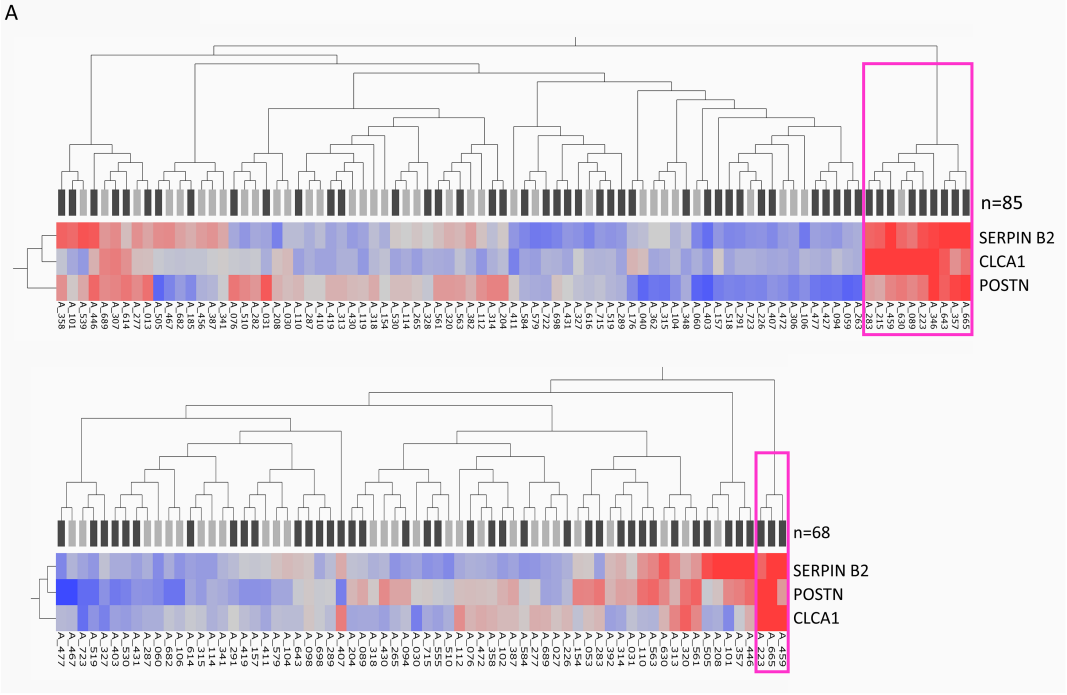


Figure 1

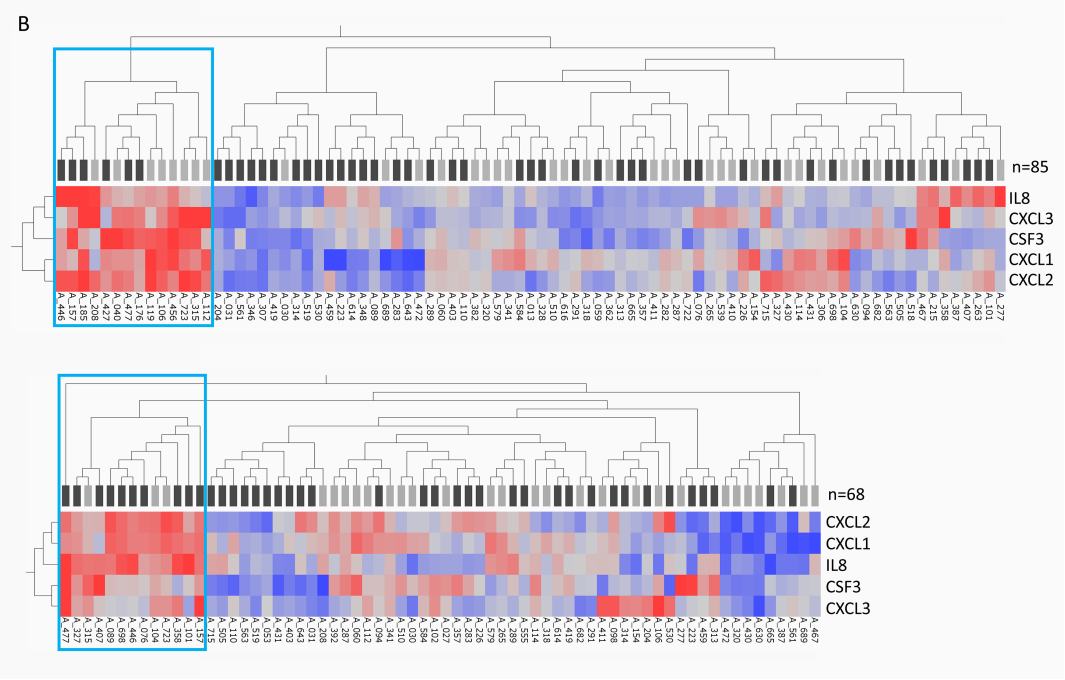


Figure 1

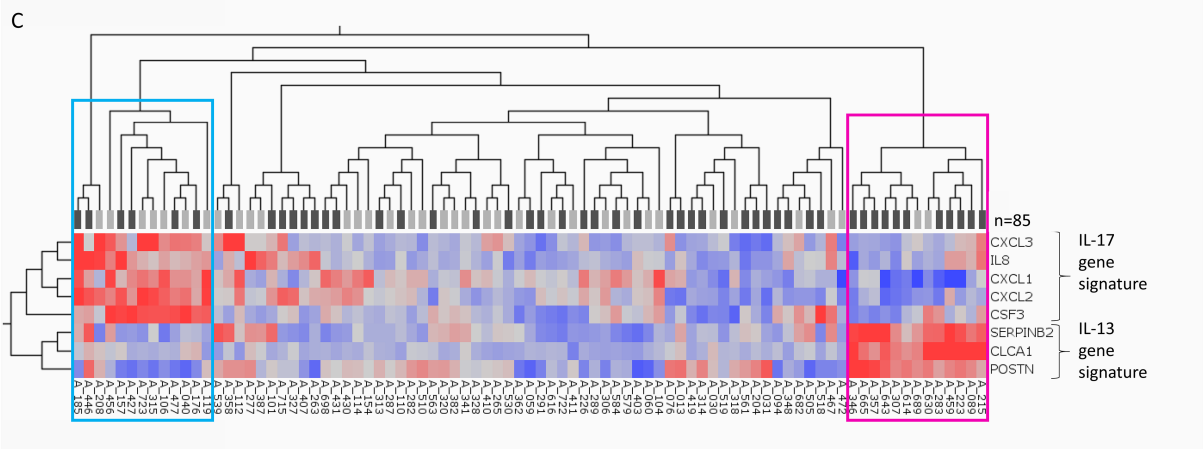


Figure 1

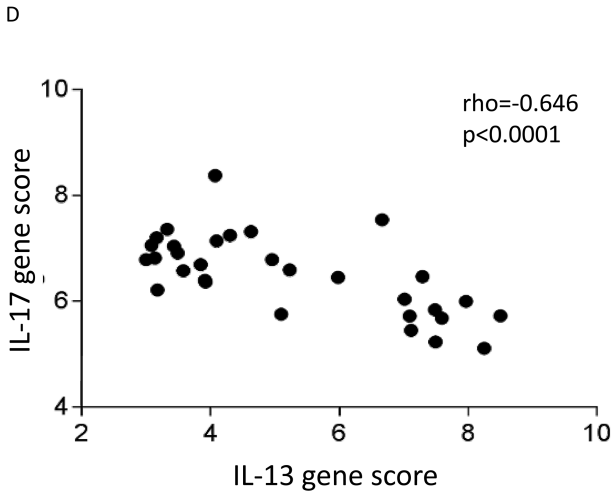


Figure 2

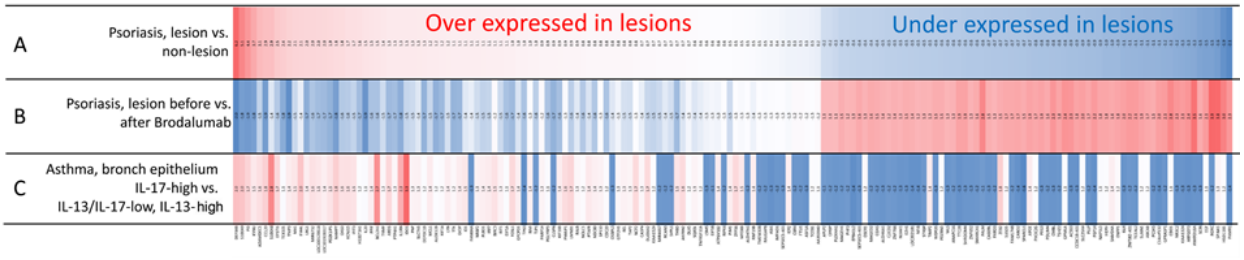


Figure 3

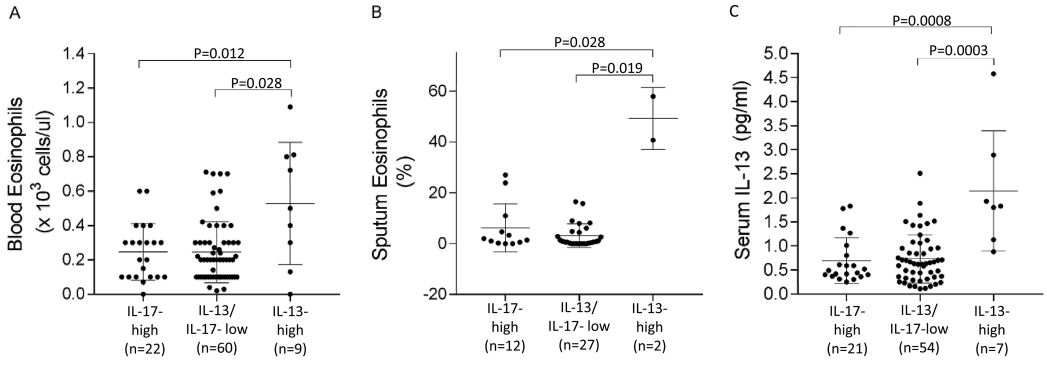


Figure 4

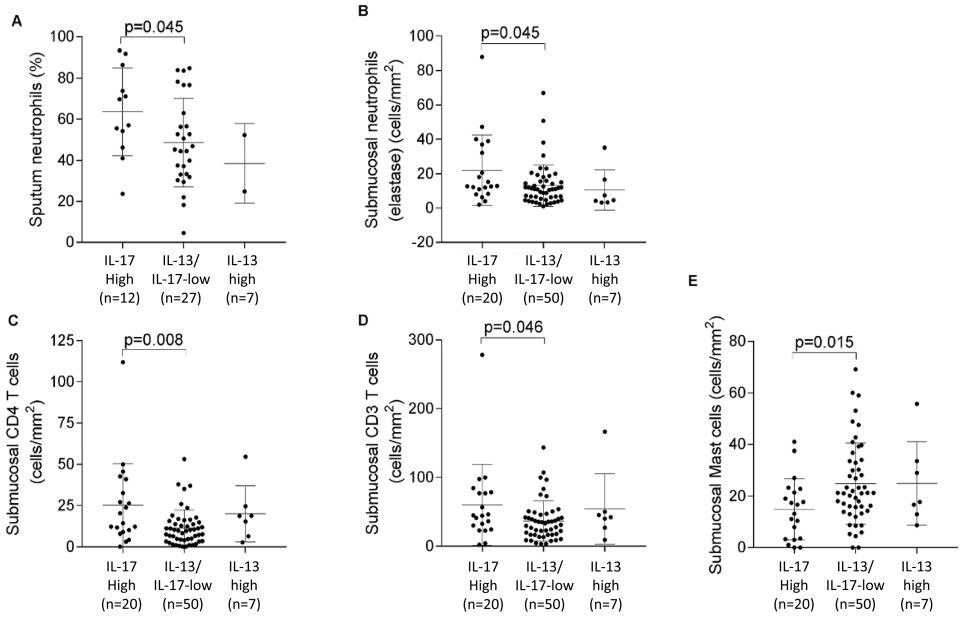


Figure 5A

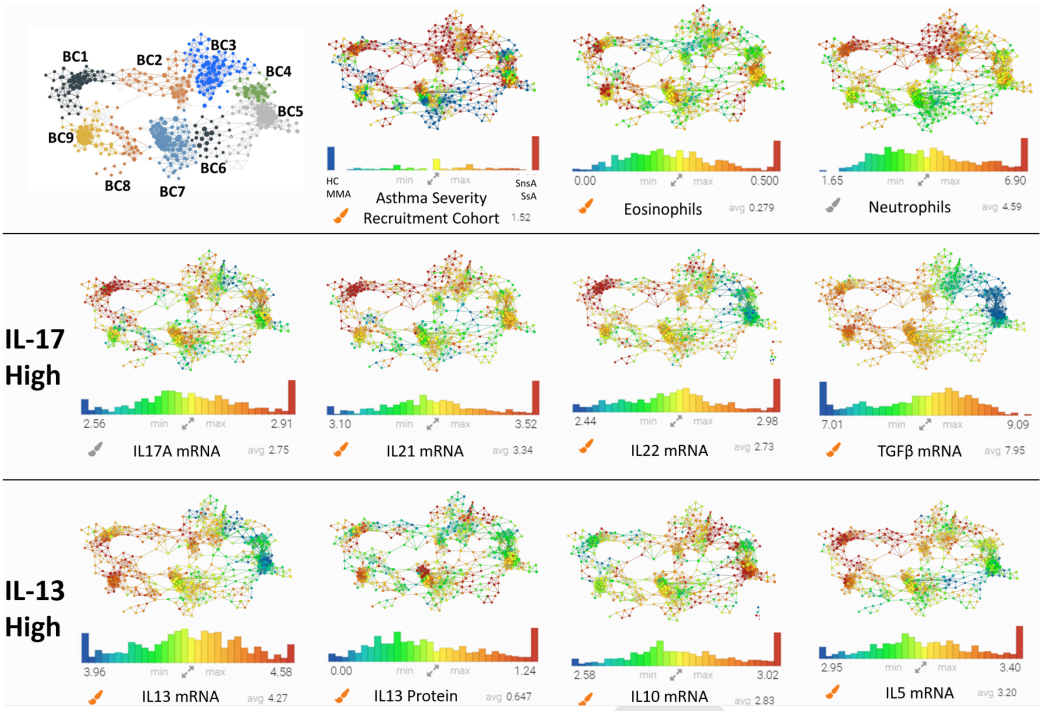
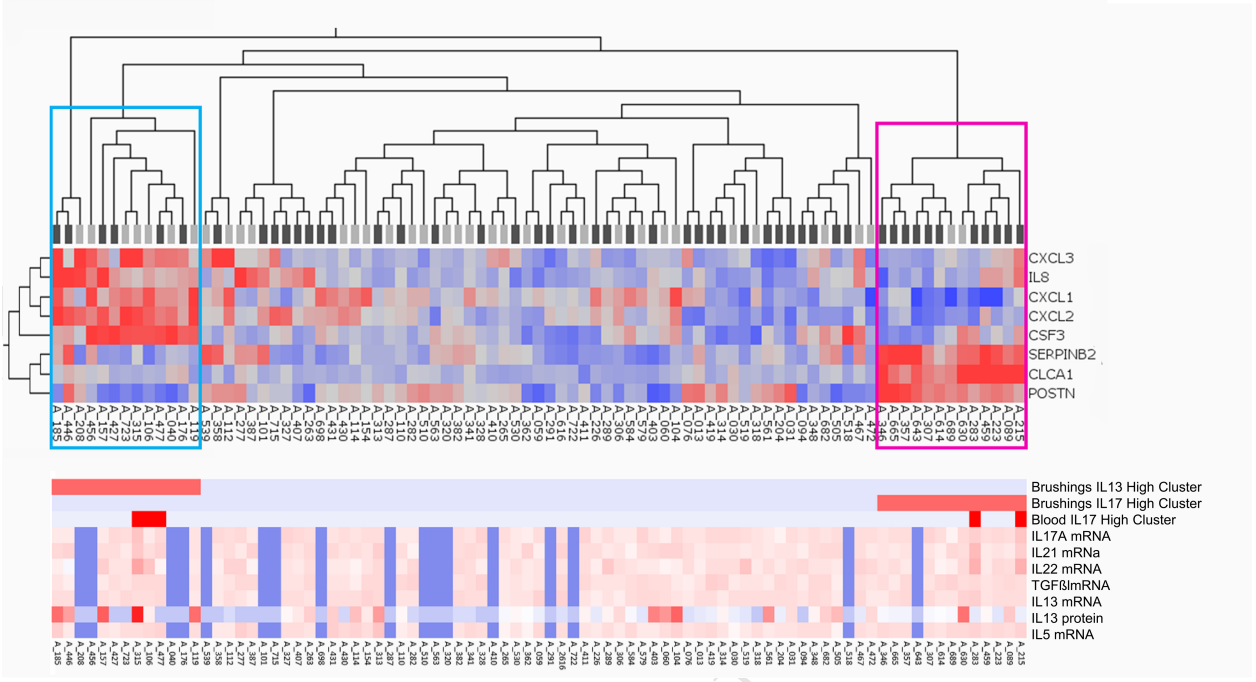
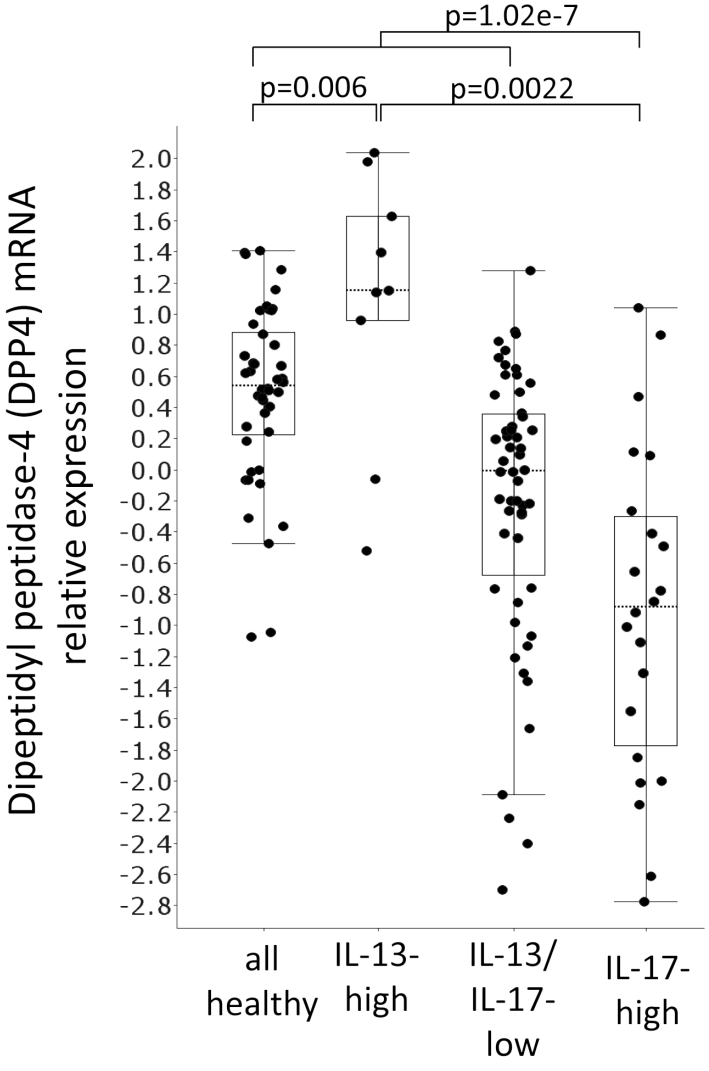


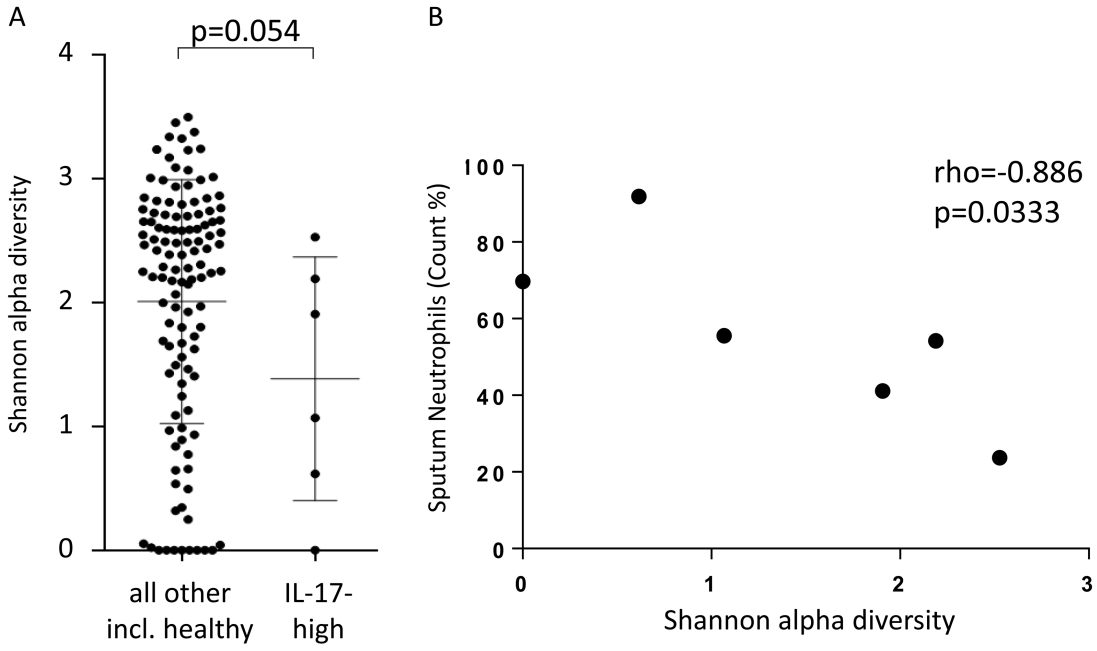
Figure 5B



Supplementary Figure E1



Supplementary Figure E2



METHODS

Study design and patients

The design, participants and sample collection methods in the U-BIOPRED study have been reported in detail(1). Briefly, this was a multicentre prospective cohort study engaging 16 clinical centres in 11 European countries, approved by the ethics committee for each participating clinical institution and adhering to the standards set by International Conference on Harmonisation and Good Clinical Practice (registered on ClinicalTrials.gov: NCT01982162).

All participants gave written informed consent and underwent detailed baseline clinical assessment. Those with severe asthma were additionally required to have been under follow-up by a respiratory physician for at least 6 months prior to enrolment; during this period, assessments were undertaken to optimise asthma control and assess medication adherence [2]. All participants underwent spirometry, haematological profiles and measurement of exhaled nitric oxide levels (FeNO). Induced sputum was attempted and analysed using a standardised operating procedure to provide cell differential counts and supernatant for analysis of protein and lipid biomarkers(2). Allergic status was obtained either by skin prick testing or measurement of specific immunoglobulin (Ig)E to six common aeroallergens. Blood and urine samples were taken for lipidomic, proteomic and transcriptomic analyses for subsequent assessment.

For the purpose of this study, bronchoscopic data were available from 91 asthmatics with either severe or mild-to-moderate asthma, all of whom had been non-smokers for at least the past 12 months, with <5 pack-years smoking history (Table E1). Severe asthmatics had uncontrolled symptoms defined by the Global Initiative for Asthma (GINA) guidelines and/or frequent exacerbations (>2/year) despite high-dose inhaled corticosteroids (⩾1000 μg fluticasone propionate per day or equivalent dose of other ICS). Mild to moderate asthmatics

had controlled or partially controlled asthma symptoms, as defined by GINA, whilst on treatment with <500 μg of fluticasone propionate/day or equivalent. Healthy control samples were from participants with no history of asthma, wheeze or other chronic respiratory disease and pre-bronchodilator $FEV_1 \geqslant 80\%$ of predicted.

Whole blood was also obtained from the wider U-BIOPRED cohort of participants comprising 246 severe non-smoking asthmatics, 88 severe smoking asthmatics, 77 mild to moderate non-smoking asthmatics and 87 healthy non-smoking participants.

Microarray analysis

Transcriptomic data from brushings were obtained using the HT HG-U133+ PM microarray platform (Affymetrix Plus 2.0) as previously described(3), selecting samples providing high quality gene expression data (RNA integrity number (RIN)>9.5). Transcriptomic data from microarray analysis of whole blood have also been reported previously but have not been subjected to specific analysis of T17 and T2 cytokines(4).

Statistical analysis

Gene expression and biomarker data were analysed by General Linear Model (GLM) based statistical tests, using Qlucore Omics Explorer 3.3 software (Qlucore AB, Lund, Sweden). Clinical data, including cell count and immunohistochemistry data, were analysed using statistical tests provided through Spotfire software v 7.01 (TIBCO Palo Alto, California, United States). If not otherwise stated, analysis of clinical data was considered to be hypothesis based and statistical significance reached if $p<0.05$. For global unbiased analysis of omics data, Benjamini-Hochberg multiple correction was used to control for the rate of false positives by calculating adjusted p-values (herein referred to as q-value).

A list of genes that were differentially expressed in brushings specifically from IL-17-high subjects (DEGs) was generated by excluding mRNAs differentially expressed in the comparison between IL-13-high (n=9) and healthy subjects (n=64) ($p<0.05$) from the list of genes that were found to be differentially expressed in the comparison between IL-17-high (n=22) and all the other participants (comprising IL-13-high (n=9), IL-13/IL-17-low (n=54) and healthy (n=64) participants ($q<0.05$, control for age, sex and site code).

Statistical analysis of clinical variables and biomarker data was performed by Kruskal-Wallis test in Spotfire 7.0.2 (TIBCO Spotfire).

Unsupervised clustering of gene expression data

Hierarchical clustering of epithelial gene expression data was performed using the average linkage and Euclidean metric methods, with each variable normalized to mean 0 and variance 1, applying Qlucore Omics Explorer 3 (Qlucore Lund, Sweden). Results were visualized as dendrogram heat maps where the colour scale was given as log2-fold changes, with a range from −2.0 (blue), via 0.0 (grey) to +2.0 (red). Data from multiple probes were collapsed to single genes using the highest value. Transcripts for the IL-13 and IL-17 signatures were selected from previous reports by Woodruff et al.(5) and Choy et al.(6), respectively. Briefly, Woodruff et al. used IL-13 as a T2 cytokine stimulus to stimulate *ex vivo* epithelial cells obtained by research bronchoscopy from mild asthmatics and healthy participants; microarray analysis of the epithelial RNA resulted in the identification of an IL-13 signature (Periostin (POSTN), Chloride channel accessory 1 (CLCA1) and Serpin Family B Member 2 (SERPINB2)). For the IL-17 signature, we used the set of genes shown by Choy et al. to be induced in the epithelium by IL-17 (Colony Stimulating Factor 3 (CSF3), and chemokines CXCL1, CXCL2, CXCL3, and IL-8).

Gene expression data in blood were analysed by Topological data analysis performed in Ayasdi Core software (11), as previously reported(4, 7). Phenotype groups were assigned

based on persistence of structure and conserved groupings of nodes as previously reported(4). Clinical and pathobiological variables were overlaid as meta data onto the generated TDA network to seek associations between clinical features and gene expression.

Immunohistochemistry for submucosal cells in the bronchial biopsies

Glycol methacrylate-embedded sections were stained with specific monoclonal antibodies for T cells (anti-CD3+, -CD4+, -CD8+), neutrophils (anti-neutrophil elastase) and eosinophils (anti-eosinophil cationic protein [EG2]). Cell counts were performed in a blinded fashion and expressed as number of cells/mm^2. Results from this analysis have been presented previously(8) but have not been associated with the IL-17-high phenotype.

Function and Pathway enrichment analysis

A series of different enrichment analyses using the gene expression data was performed by using Ingenuity Pathway Analysis (IPA) package (IPA, QIAGEN Inc). In specific, Ingenuity Regulator Effects Analysis was applied to identify regulatory pathways that could be associated with the gene expression profile unique to the IL-17-high group (the 797 DEGs). To direct the analysis towards pathologically relevant pathways, this analysis was restricted to immune, infection and inflammatory disease and functions categories. The reported Consistency Score was used as a measure of how causally consistent and densely connected a regulator effects network is. Disease and Function enrichment analysis and Canonical Pathway Analysis were applied to explore, in an unbiased fashion, the biology that is most associated with the gene expression profile unique to the IL-17-high group (the 797 DEGs) pathways. The reported p-values associated with a function or a pathway are a measure of the likelihood that the association between the 797 DEGs and a given biological function and/or

disease is due to random chance. Right-tailed Fisher's exact test with the Benjamini-Hochberg multiple correction was used to calculate p-values and control for false positives.

TABLE E1. Demographic and clinical characteristics of assessed U-BIOPRED cohorts

	Severe non-smoking Asthma (SAn)	Mild to moderate non-smoking asthma (MMA)	Non-adjusted p-value	Stat. test
Study participants – n	53	38		
Age – years	49.3 ± 1.9	39.4 ± 2.2	0.0013	KW
Sex - Female/Male	28/25	23/15	0.466	ChiSq
BMI - kg/m^2	30.5 ± 0.9	26.1 ± 0.8	7.41E-004	KW
FEV_1 - % of predicted	74.6 ± 3	92.5 ± 2.7	5.35E-005	KW
Exacerbations in last year	2.3 ± 0.3	0.3 ± 0.1	9.47E-009	KW
Never smokers/Ex-smokers	44/9	33/5		
Smoking history - pack years	2.25 ± 9.6	1.18 ± 0.8		KW
Atopic	38/50 (76)	29/32 (90.6)	0.094	ChiSq
Allergic rhinitis	30/48 (62.5)	18/34 (52.9)	0.387	ChiSq
Non-allergic rhinitis	11/47 (23.4)	3/34 (8.8)	0.0867	ChiSq
Nasal polyps surgery	18/48 (37.3)	2/35 (5.7)	8.26E-004	ChiSq
GORD	28/50 (56)	8/35 (22.9)	0.00234	ChiSq
Regular treatment - ICS	51/53 (96.2)	38/38 (100)	0.226	ChiSq
Regular treatment - OCS	21/49 (42.9)	0/38 (0)	3.6 E-006	ChiSq
Regular treatment - Omalizumab	4/46 (8.7)	0/38 (0)	0.0625	ChiSq
Regular treatment – Antibiotics including macrolides	11/48 (22.9)	0/38 (0)	0.00158	ChiSq
Regular treatment - Macrolides	8/53 (15.1)	0/38 (0)	0.0122	ChiSq
Regular treatment - LT modifier	28/49 (57.1)	0/38 (0)	1.53 E-008	ChiSq
Regular treatment - Xanthines	7/47 (14.8)	0/38 (0)	0.0130	ChiSq
FeNO – ppb	42.4 (19.8-	38.1 (16.7-58.8)	0.214	KW
Blood eosinophils x$10e^3$/µl	0.3 (0.1-0.4)	0.2 (0.1-0.3)	0.267	KW
Blood eosinophils - %	4.3 (1.7-5.3)	3.8 (1.9-4.7)	0.961	KW
Blood neutrophils x$10e^3$/µl	4.8 (3.4-5.8)	3.7 (2.7-4.6)	0.0048	KW
Blood neutrophils - %	61.7 (54.3-	57.5 (51.8-63.9)	0.068	KW
Sputum eosinophils - %	9.1 (0.6-9)	2.0 (0-2.3)	0.0547	KW
Sputum neutrophils - %	55.2 (39.9-	48.4 (32.2-65.6)	0.446	KW

Discontinuous variables are shown as n (%) and continuous variables are shown as mean ± SE or median (interquartile range) depending on data distribution; Chi-Squared (ChiSq) and Kruskal-Wallis (KW) tests were used.

Table E2. Presence of IL-17-high and IL-13 high signatures (+) identified by hierarchical clustering of transcriptomic data from the brushing and/or biopsy samples that were available for each participant. The last column shows categorization into 22 IL-17-high and 9 IL-13 high participants after merging the result from brushings and biopsies data.

PATIENT ID	IL-17 high in Brushings (n=14)	IL-17 high in Biopsies (n=13)	IL-13 high in Brushings (n=10)	IL-13 high in Biopsies (n=3)	Categorization after merging Brushing and Biopsy data
A_040	+				IL-17 high (n=22)
A_106	+				IL-17 high (n=22)
A_112	+				IL-17 high (n=22)
A_119	+				IL-17 high (n=22)
A_176	+				IL-17 high (n=22)
A_185	+				IL-17 high (n=22)
A_208	+				IL-17 high (n=22)
A_427	+				IL-17 high (n=22)
A_456	+				IL-17 high (n=22)
A_157	+	+			IL-17 high (n=22)
A_315	+	+			IL-17 high (n=22)
A_446	+	+			IL-17 high (n=22)
A_477	+	+			IL-17 high (n=22)
A_723	+	+			IL-17 high (n=22)
A_076		+			IL-17 high (n=22)
A_101		+			IL-17 high (n=22)
A_104		+			IL-17 high (n=22)
A_327		+			IL-17 high (n=22)
A_358		+			IL-17 high (n=22)
A_407		+			IL-17 high (n=22)
A_698		+			IL-17 high (n=22)
A_089*		+	+		IL-17 high (n=22)
A_357			+	+	Il-13 high (n=9)
A_643			+	+	Il-13 high (n=9)
A_665			+	+	Il-13 high (n=9)
A_215			+		Il-13 high (n=9)
A_223			+		Il-13 high (n=9)
A_283			+		Il-13 high (n=9)
A_346			+		Il-13 high (n=9)
A_459			+		Il-13 high (n=9)
A_630			+		Il-13 high (n=9)

Footnote: *Only one participant (A_089) displayed both a IL-17 and IL-13 signature. Due to the IL-17 centric nature of this study, A_089 participant was categorized to the IL-17 high group. Therefore, the size of the IL-13-high cluster in statistical analyses is n=9.

Table E3. List of 797 genes differentially expressed in brushings from IL-17-high participants (herein referred to as DEGs). The analysis started by generating a list of genes that were differentially expressed in the comparison between the IL-13-high group (n=9) and the healthy control participants (n=64) ($p<0.05$, controlling for age, sex and site code). These genes were then excluded from the list of genes found to be differentially expressed in the comparison between the IL-17-high group (n=22) and all the other groups (IL-13-high (n=9), IL-13/ IL-17-low (n=54) and healthy (n=64) control participants ($q<0.05$, control for age, sex and site code).

GENE SYMBOL	Description	p-value	q-value (FDR)	Difference (Log2 Fold Change)	Family	ENTREZ GENE ID
AADACL2	arylacetamide deacetylase like 2	1.30E-04	2.88E-03	-0.35	other	344752
AASDH	aminoadipate-semialdehyde dehydrogenase	5.20E-03	1.10E-02	-0.16	enzyme	132949
ABCA8	ATP binding cassette subfamily A member 8	2.51E-04	3.70E-03	0.10	transporter	10351
ABI1	abl interactor 1	3.47E-02	3.88E-02	-0.17	other	10006
ABTB2	ankyrin repeat and BTB domain containing 2	1.11E-03	5.63E-03	0.10	other	25841
ACAD9	acyl-CoA dehydrogenase family member 9	1.24E-02	1.80E-02	0.06	enzyme	28976
ACCN2	acid sensing ion channel subunit 1	5.73E-05	2.70E-03	-0.20	ion channel	41
ACPL2	2-phosphoxylose phosphatase 1	1.51E-02	2.06E-02	-0.12	phosphatase	92370
ACSS3	acyl-CoA synthetase short chain family member 3	7.60E-03	1.33E-02	-0.15	enzyme	79611
ACTL6B	actin like 6B	3.69E-03	9.39E-03	0.15	other	51412
ACVR1C	activin A receptor type 1C	1.98E-02	2.49E-02	0.16	kinase	130399
ACVR2A	activin A receptor type 2A	5.47E-03	1.13E-02	-0.07	kinase	92
ACY1	aminoacylase 1	1.50E-02	2.06E-02	0.10	peptidase	95
ADAMDEC1	ADAM like decysin 1	1.17E-04	2.88E-03	0.33	peptidase	27299
ADH1C	alcohol dehydrogenase 1C (class I), gamma polypeptide	6.57E-03	1.26E-02	-0.11	enzyme	126

ADM	Adrenomedullin	9.13E-04	5.46E-03	0.25	other	133
ADNP	activity dependent neuroprotector homeobox	4.68E-03	1.07E-02	-0.07	transcription regulator	23394
AEBP2	AE binding protein 2	2.47E-03	8.14E-03	-0.14	transcription regulator	121536
AGL	amylo-alpha-1, 6-glucosidase, 4-alpha-glucanotransferase	7.56E-03	1.33E-02	-0.08	enzyme	178
AGPAT4	1-acylglycerol-3-phosphate O-acyltransferase 4	8.42E-03	1.39E-02	0.07	enzyme	56895
AKIRIN2	akirin 2	7.41E-03	1.33E-02	0.15	other	55122
ALDH1L2	aldehyde dehydrogenase 1 family member L2	1.30E-02	1.86E-02	0.10	enzyme	160428
ALDH2	aldehyde dehydrogenase 2 family (mitochondrial)	2.07E-02	2.57E-02	-0.03	enzyme	217
ALDH7A1	aldehyde dehydrogenase 7 family member A1	3.06E-02	3.49E-02	-0.06	enzyme	501
ALDH8A1	aldehyde dehydrogenase 8 family member A1	5.05E-03	1.09E-02	0.13	enzyme	64577
ALDH9A1	aldehyde dehydrogenase 9 family member A1	1.66E-02	2.18E-02	-0.06	enzyme	223
ALOX12B	arachidonate 12-lipoxygenase, 12R type	4.86E-03	1.09E-02	0.09	enzyme	242
ALOX5AP	arachidonate 5-lipoxygenase activating protein	1.34E-01	1.35E-01	0.15	other	241
ANAPC16	anaphase promoting complex subunit 16	4.47E-04	4.53E-03	-0.05	other	119504
ANGPTL4	angiopoietin like 4	8.23E-03	1.38E-02	0.11	other	51129
ANKMY2	ankyrin repeat and MYND domain containing 2	5.13E-03	1.09E-02	-0.09	other	57037
ANKRD18A	ankyrin repeat domain 18A	1.70E-03	6.99E-03	-0.19	other	253650
ANKRD22	ankyrin repeat domain 22	9.65E-03	1.53E-02	0.15	transcription regulator	118932
ANXA4	annexin A4	3.79E-03	9.46E-03	-0.05	other	307
AP4S1	adaptor related protein complex 4 sigma 1 subunit	1.72E-03	7.03E-03	-0.25	other	11154
APLP2	amyloid beta precursor like protein 2	1.03E-02	1.59E-02	-0.02	other	334

APOBEC3A	apolipoprotein B mRNA editing enzyme catalytic subunit 3A	2.62E-03	8.32E-03	0.37	enzyme	200315
APOE	apolipoprotein E	2.82E-02	3.27E-02	0.10	transporter	348
APPL1	adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 1	3.12E-02	3.54E-02	-0.08	other	26060
APPL2	adaptor protein, phosphotyrosine interacting with PH domain and leucine zipper 2	2.38E-02	2.87E-02	-0.07	other	55198
AQP4	aquaporin 4	5.74E-02	6.01E-02	-0.12	transporter	361
AQP9	aquaporin 9	5.49E-03	1.14E-02	0.43	transporter	366
AREG	Amphiregulin	6.39E-03	1.24E-02	0.23	growth factor	374
AREGB	Amphiregulin	3.34E-03	8.96E-03	0.29	growth factor	727738
ARHGAP26	Rho GTPase activating protein 26	1.61E-02	2.14E-02	0.11	other	23092
ARL8A	ADP ribosylation factor like GTPase 8A	2.75E-02	3.20E-02	0.05	enzyme	127829
ASAP1	ArfGAP with SH3 domain, ankyrin repeat and PH domain 1	2.02E-02	2.52E-02	0.20	other	50807
ASB10	ankyrin repeat and SOCS box containing 10	2.86E-03	8.69E-03	0.08	other	136371
ASCL2	achaete-scute family bHLH transcription factor 2	1.14E-02	1.68E-02	0.15	transcription regulator	430
ASCL3	achaete-scute family bHLH transcription factor 3	6.94E-02	7.20E-02	0.09	transcription regulator	56676
ASF1A	anti-silencing function 1A histone chaperone	2.31E-02	2.81E-02	-0.13	other	25842
ASZ1	ankyrin repeat, SAM and basic leucine zipper domain containing 1	7.93E-04	5.45E-03	0.14	transcription regulator	136991
ATF5	activating transcription factor 5	2.09E-02	2.59E-02	0.05	transcription regulator	22809
ATN1	atrophin 1	8.72E-04	5.46E-03	-0.08	transcription regulator	1822
ATP6V0D2	ATPase H+ transporting V0 subunit d2	3.44E-02	3.85E-02	0.16	transporter	245972
ATP6V1B2	ATPase H+ transporting V1 subunit B2	1.00E-02	1.57E-02	0.12	transporter	526

ATP6V1C1	ATPase H+ transporting V1 subunit C1	3.63E-03	9.39E-03	0.15	transporter	528
AVEN	apoptosis and caspase activation inhibitor	8.12E-02	8.29E-02	0.06	other	57099
BATF	basic leucine zipper ATF-like transcription factor	2.26E-04	3.40E-03	0.11	transcription regulator	10538
BCL2A1	BCL2 related protein A1	5.68E-03	1.16E-02	0.44	other	597
BCOR	BCL6 corepressor	6.72E-03	1.27E-02	-0.12	transcription regulator	54880
BEND4	BEN domain containing 4	2.55E-02	3.01E-02	0.12	other	389206
BEST1	bestrophin 1	2.94E-03	8.69E-03	0.21	ion channel	7439
BICD1	BICD cargo adaptor 1	1.47E-02	2.04E-02	0.13	other	636
BIN2	bridging integrator 2	5.31E-03	1.11E-02	0.10	other	51411
BIRC3	baculoviral IAP repeat containing 3	3.66E-03	9.39E-03	0.15	enzyme	330
BMP7	bone morphogenetic protein 7	1.37E-04	2.88E-03	-0.26	growth factor	655
BPIL3	BPI fold containing family B member 6	8.79E-02	8.97E-02	0.06	other	128859
C11orf42	chromosome 11 open reading frame 42	8.95E-02	9.11E-02	0.07	other	160298
C11orf64	long intergenic non-protein coding RNA 301	2.88E-03	8.69E-03	0.19	other	283197
C11orf92	colorectal cancer associated 1	2.41E-03	8.14E-03	-0.08	other	399948
C12orf34	family with sequence similarity 222 member A	6.27E-03	1.23E-02	0.11	other	84915
C13orf27	testis expressed 30	8.42E-04	5.46E-03	0.13	other	93081
C13orf30	family with sequence similarity 216 member B	1.51E-02	2.06E-02	-0.07	other	144809
C14orf132	chromosome 14 open reading frame 132	9.13E-03	1.47E-02	-0.20	other	56967
C14orf4	interferon regulatory factor 2 binding protein like	1.67E-02	2.18E-02	-0.04	other	64207
C19orf77	small integral membrane protein 24	2.92E-02	3.35E-02	0.10	other	284422

C1orf110	coiled-coil domain containing 190	1.90E-03	7.47E-03	-0.08	other	339512
C1orf38	thymocyte selection associated family member 2	7.52E-03	1.33E-02	0.14	other	9473
C1orf52	chromosome 1 open reading frame 52	8.89E-03	1.44E-02	-0.13	other	148423
C1orf84	SZT2, KICSTOR complex subunit	6.43E-04	4.98E-03	-0.14	other	149469
C1QC	complement C1q C chain	4.15E-02	4.51E-02	0.17	peptidase	714
C20orf111	oxidative stress responsive serine rich 1	4.59E-02	4.93E-02	0.07	enzyme	51526
C20orf117	suppressor of glucose, autophagy associated 1	2.42E-03	8.14E-03	0.10	other	140710
C20orf135	abhydrolase domain containing 16B	2.43E-02	2.90E-02	0.06	other	140701
C20orf70	BPI fold containing family A member 2	1.66E-04	2.88E-03	0.16	other	140683
C21orf130	long intergenic non-protein coding RNA 323	2.22E-02	2.71E-02	0.12	other	284835
C2CD2	C2 calcium dependent domain containing 2	1.04E-02	1.59E-02	-0.07	other	25966
C2orf19	KLHL30 antisense RNA 1	6.31E-04	4.98E-03	0.16	other	394261
C2orf64	cytochrome c oxidase assembly factor 5	1.37E-02	1.94E-02	-0.09	other	493753
C3AR1	complement C3a receptor 1	4.89E-03	1.09E-02	0.13	G-protein coupled receptor	719
C5orf4	fatty acid hydroxylase domain containing 2	6.25E-02	6.53E-02	-0.07	other	10826
C6orf130	O-acyl-ADP-ribose deacylase 1	1.64E-02	2.17E-02	-0.05	enzyme	221443
C8orf31	chromosome 8 open reading frame 31 (putative)	2.39E-02	2.87E-02	0.17	other	286122
CAB39L	calcium binding protein 39 like	1.31E-04	2.88E-03	-0.12	kinase	81617
CABP4	calcium binding protein 4	2.09E-03	7.64E-03	0.15	other	57010
CAND2	cullin associated and neddylation dissociated 2 (putative)	2.01E-02	2.51E-02	-0.14	transcription regulator	23066
CAPN12	calpain 12	2.97E-03	8.69E-03	0.07	peptidase	147968

CAPN7	calpain 7	3.20E-02	3.61E-02	-0.06	peptidase	23473
CASP4	caspase 4	3.78E-03	9.46E-03	0.09	peptidase	837
CASP5	caspase 5	1.42E-04	2.88E-03	0.18	peptidase	838
CBR4	carbonyl reductase 4	6.38E-02	6.65E-02	-0.08	enzyme	84869
CBX1	chromobox 1	5.85E-03	1.18E-02	-0.07	transcription regulator	10951
CBX6	chromobox 6	2.71E-04	3.85E-03	-0.09	other	23466
CCDC90B	coiled-coil domain containing 90B	2.63E-03	8.32E-03	-0.17	other	60492
CCL20	C-C motif chemokine ligand 20	2.60E-04	3.77E-03	0.28	cytokine	6364
CCL4	C-C motif chemokine ligand 4	2.85E-02	3.29E-02	0.22	cytokine	6351
CCNJL	cyclin J like	3.19E-03	8.75E-03	0.22	other	79616
CCNYL2	cyclin Y-like 2 (pseudogene)	8.97E-03	1.45E-02	0.14	other	414194
CCR1	C-C motif chemokine receptor 1	2.58E-02	3.03E-02	0.24	G-protein coupled receptor	1230
CCRL2	C-C motif chemokine receptor like 2	1.05E-02	1.60E-02	0.19	G-protein coupled receptor	9034
CD14	CD14 molecule	4.99E-03	1.09E-02	0.19	transmembrane receptor	929
CD163	CD163 molecule	3.95E-03	9.66E-03	0.36	transmembrane receptor	9332
CD177	CD177 molecule	2.51E-03	8.14E-03	0.29	other	57126
CD300A	CD300a molecule	8.67E-03	1.42E-02	0.25	transmembrane receptor	11314
CD3EAP	CD3e molecule associated protein	1.51E-02	2.06E-02	-0.10	other	10849
CD53	CD53 molecule	1.78E-02	2.27E-02	0.24	other	963
CD68	CD68 molecule	1.01E-02	1.57E-02	0.13	other	968
CD81	CD81 molecule	4.92E-03	1.09E-02	-0.05	other	975

CD97	adhesion G protein-coupled receptor E5	2.92E-03	8.69E-03	0.13	G-protein coupled receptor	976
CDC5L	cell division cycle 5 like	6.18E-03	1.22E-02	-0.06	transcription regulator	988
CDH10	cadherin 10	1.13E-02	1.67E-02	0.11	other	1008
CDH18	cadherin 18	3.11E-02	3.53E-02	0.09	other	1016
CDO1	cysteine dioxygenase type 1	3.28E-02	3.70E-02	0.07	enzyme	1036
CDR2L	cerebellar degeneration related protein 2 like	1.44E-01	1.44E-01	0.04	other	30850
CDT1	chromatin licensing and DNA replication factor 1	3.36E-03	8.98E-03	0.10	other	81620
CEACAM3	carcinoembryonic antigen related cell adhesion molecule 3	1.00E-04	2.88E-03	0.15	other	1084
CELF5	CUGBP Elav-like family member 5	1.50E-02	2.06E-02	0.12	other	60680
CEP70	centrosomal protein 70	8.11E-04	5.46E-03	0.08	other	80321
CES5A	carboxylesterase 5A	4.94E-04	4.71E-03	0.13	enzyme	221223
CH25H	cholesterol 25-hydroxylase	9.43E-02	9.57E-02	-0.11	enzyme	9023
CHD3	chromodomain helicase DNA binding protein 3	1.12E-03	5.63E-03	-0.11	enzyme	1107
CHRNB3	cholinergic receptor nicotinic beta 3 subunit	1.03E-02	1.59E-02	0.11	transmembrane receptor	1142
CIRBP	cold inducible RNA binding protein	1.73E-03	7.03E-03	-0.04	translation regulator	1153
CLCA3P	chloride channel accessory 3, pseudogene	4.98E-03	1.09E-02	0.13	other	9629
CLDN1	claudin 1	2.28E-03	7.95E-03	-0.10	other	9076
CLDN6	claudin 6	2.96E-02	3.39E-02	0.09	other	9074
CLEC12B	C-type lectin domain family 12 member B	4.99E-02	5.29E-02	0.08	other	387837
CLIC6	chloride intracellular channel 6	1.47E-03	6.46E-03	-0.07	ion channel	54102
CLK3	CDC like kinase 3	3.30E-03	8.94E-03	0.07	kinase	1198

CMBL	carboxymethylenebutenolidase homolog	1.97E-03	7.53E-03	-0.10	enzyme	134147
CNR2	cannabinoid receptor 2	5.01E-03	1.09E-02	0.12	G-protein coupled receptor	1269
COL20A1	collagen type XX alpha 1 chain	2.50E-02	2.97E-02	0.10	other	57642
COPB1	coatomer protein complex subunit beta 1	6.61E-03	1.26E-02	-0.04	transporter	1315
CREM	cAMP responsive element modulator	5.03E-03	1.09E-02	0.16	transcription regulator	1390
CRX	cone-rod homeobox	1.31E-02	1.87E-02	0.10	transcription regulator	1406
CSF2RB	colony stimulating factor 2 receptor beta common subunit	1.58E-02	2.11E-02	0.34	transmembrane receptor	1439
CSF3	colony stimulating factor 3	7.77E-07	2.06E-04	0.16	cytokine	1440
CSF3R	colony stimulating factor 3 receptor	1.29E-03	6.11E-03	0.33	transmembrane receptor	1441
CSNK2A2	casein kinase 2 alpha 2	3.72E-03	9.45E-03	-0.05	kinase	1459
CTDSP2	CTD small phosphatase 2	2.51E-02	2.97E-02	-0.05	phosphatase	10106
CTNNAL1	catenin alpha like 1	7.30E-02	7.52E-02	-0.07	other	8727
CTNNB1	catenin beta 1	6.57E-03	1.26E-02	-0.05	transcription regulator	1499
CXCL10	C-X-C motif chemokine ligand 10	4.71E-04	4.58E-03	0.39	cytokine	3627
CXCL11	C-X-C motif chemokine ligand 11	1.09E-04	2.88E-03	0.36	cytokine	6373
CXCL3	C-X-C motif chemokine ligand 3	4.74E-08	3.08E-05	0.21	cytokine	2921
CXCL9	C-X-C motif chemokine ligand 9	8.71E-04	5.46E-03	0.27	cytokine	4283
CXCR1	C-X-C motif chemokine receptor 1	1.04E-02	1.59E-02	0.13	G-protein coupled receptor	3577
CYB561D1	cytochrome b561 family member D1	1.92E-03	7.51E-03	-0.12	other	284613
CYorf15A	taxilin gamma pseudogene, Y-linked	1.63E-03	6.84E-03	-0.22	other	246126
CYP2S1	cytochrome P450 family 2 subfamily S member 1	1.52E-02	2.07E-02	-0.07	enzyme	29785

CYP4V2	cytochrome P450 family 4 subfamily V member 2	8.85E-03	1.43E-02	-0.07	enzyme	285440
CYP8B1	cytochrome P450 family 8 subfamily B member 1	1.89E-02	2.39E-02	0.11	enzyme	1582
CYTIP	cytohesin 1 interacting protein	1.03E-02	1.59E-02	0.27	other	9595
DAPL1	death associated protein like 1	7.16E-03	1.32E-02	-0.15	other	92196
DCAF16	DDB1 and CUL4 associated factor 16	5.24E-05	2.70E-03	-0.21	other	54876
DCLK2	doublecortin like kinase 2	1.29E-02	1.84E-02	0.09	kinase	166614
DDB2	damage specific DNA binding protein 2	3.44E-02	3.85E-02	-0.07	other	1643
DDHD2	DDHD domain containing 2	9.63E-04	5.46E-03	-0.12	enzyme	23259
DDX6	DEAD-box helicase 6	1.53E-02	2.07E-02	-0.03	enzyme	1656
DEC1	deleted in esophageal cancer 1	6.78E-03	1.27E-02	0.09	other	50514
DEFB129	defensin beta 129	8.51E-03	1.40E-02	0.10	other	140881
DEFB4A	defensin beta 4A	6.05E-03	1.20E-02	0.26	other	1673
DEPDC1B	DEP domain containing 1B	2.09E-02	2.59E-02	0.15	other	55789
DHFRL1	dihydrofolate reductase 2	3.14E-03	8.75E-03	-0.16	enzyme	200895
DKFZp434L192	uncharacterized protein DKFZp434L192	5.25E-03	1.10E-02	0.11	other	222029
DLG5	discs large MAGUK scaffold protein 5	5.88E-03	1.18E-02	-0.06	other	9231
DLGAP2	DLG associated protein 2	1.45E-03	6.41E-03	0.14	other	9228
DLX5	distal-less homeobox 5	2.57E-02	3.03E-02	0.08	transcription regulator	1749
DOK3	docking protein 3	1.68E-02	2.18E-02	0.08	other	79930
DQX1	DEAQ-box RNA dependent ATPase 1	3.06E-03	8.75E-03	0.14	enzyme	165545
DRD3	dopamine receptor D3	3.55E-02	3.94E-02	0.08	G-protein coupled receptor	1814

DSC3	desmocollin 3	1.05E-02	1.59E-02	-0.17	other	1825
DUOX2	dual oxidase 2	3.17E-02	3.59E-02	0.22	enzyme	50506
DUOXA2	dual oxidase maturation factor 2	1.56E-04	2.88E-03	0.16	other	405753
DUSP1	dual specificity phosphatase 1	2.07E-04	3.28E-03	0.14	phosphatase	1843
DUSP2	dual specificity phosphatase 2	1.43E-05	1.71E-03	0.22	phosphatase	1844
DUSP5	dual specificity phosphatase 5	1.34E-03	6.21E-03	0.25	phosphatase	1847
EBI3	Epstein-Barr virus induced 3	7.94E-02	8.12E-02	0.05	cytokine	10148
EED	embryonic ectoderm development	1.12E-02	1.66E-02	-0.07	transcription regulator	8726
EEF2	eukaryotic translation elongation factor 2	2.37E-03	8.11E-03	-0.02	translation regulator	1938
EFCAB5	EF-hand calcium binding domain 5	1.12E-03	5.63E-03	0.18	other	374786
EFNB3	ephrin B3	2.97E-03	8.69E-03	-0.21	kinase	1949
EGF	epidermal growth factor	6.85E-04	5.20E-03	0.11	growth factor	1950
EGR2	early growth response 2	1.59E-03	6.80E-03	0.18	transcription regulator	1959
EGR3	early growth response 3	1.97E-03	7.53E-03	0.27	transcription regulator	1960
EHD1	EH domain containing 1	2.97E-04	3.88E-03	0.12	other	10938
EIF3L	eukaryotic translation initiation factor 3 subunit L	9.35E-04	5.46E-03	-0.04	other	51386
EIF4B	eukaryotic translation initiation factor 4B	4.43E-03	1.04E-02	-0.05	translation regulator	1975
EIF5A	eukaryotic translation initiation factor 5A	5.20E-02	5.49E-02	0.03	translation regulator	1984
EIF5B	eukaryotic translation initiation factor 5B	7.68E-03	1.33E-02	-0.04	translation regulator	9669
EMB	Embigin	7.26E-02	7.49E-02	-0.04	transporter	133418
EMR2	adhesion G protein-coupled receptor E2	8.04E-05	2.88E-03	0.46	other	30817

ENPP1	ectonucleotide pyrophosphatase/phosphodiesterase 1	2.51E-02	2.97E-02	0.10	enzyme	5167
ENPP6	ectonucleotide pyrophosphatase/phosphodiesterase 6	3.95E-03	9.66E-03	0.13	enzyme	133121
EPAS1	endothelial PAS domain protein 1	1.00E-03	5.46E-03	-0.07	transcription regulator	2034
EPB41L2	erythrocyte membrane protein band 4.1 like 2	1.67E-02	2.18E-02	-0.17	other	2037
EPHB6	EPH receptor B6	5.54E-02	5.81E-02	-0.05	kinase	2051
EPS15	epidermal growth factor receptor pathway substrate 15	2.14E-02	2.62E-02	-0.07	other	2060
EPS8L3	EPS8 like 3	5.75E-02	6.01E-02	0.18	other	79574
EPSTI1	epithelial stromal interaction 1	9.78E-03	1.54E-02	0.19	other	94240
ERMP1	endoplasmic reticulum metallopeptidase 1	5.73E-03	1.17E-02	-0.09	other	79956
ESYT1	extended synaptotagmin 1	1.73E-02	2.23E-02	-0.05	other	23344
EVI2A	ecotropic viral integration site 2A	9.41E-04	5.46E-03	0.23	transmembrane receptor	2123
EXOC4	exocyst complex component 4	2.36E-02	2.85E-02	-0.06	transporter	60412
EXOSC10	exosome component 10	1.08E-02	1.62E-02	-0.15	kinase	5394
EZH1	enhancer of zeste 1 polycomb repressive complex 2 subunit	1.44E-03	6.41E-03	-0.11	enzyme	2145
F2R	coagulation factor II thrombin receptor	1.91E-04	3.17E-03	-0.15	G-protein coupled receptor	2149
FAM101A	refilin A	7.33E-03	1.33E-02	0.07	transporter	144347
FAM113A	PC-esterase domain containing 1A	1.01E-02	1.57E-02	-0.08	other	64773
FAM134A	reticulophagy regulator family member 2	6.23E-03	1.23E-02	-0.07	other	79137
FAM164C	zinc finger C2HC-type containing 1C	1.63E-02	2.15E-02	-0.08	other	79696
FAM168B	family with sequence similarity 168 member B	1.61E-04	2.88E-03	-0.09	other	130074
FAM174B	family with sequence similarity 174 member B	1.66E-02	2.18E-02	-0.07	other	400451

FAM198B	family with sequence similarity 198 member B	1.53E-02	2.07E-02	0.18	other	51313
FAM27D1	family with sequence similarity 27 member D1	5.22E-02	5.50E-02	0.07	other	724094
FAM50B	family with sequence similarity 50 member B	2.83E-02	3.28E-02	-0.05	other	26240
FAM71E1	family with sequence similarity 71 member E1	1.20E-02	1.75E-02	-0.10	other	112703
FAM73A	mitoguardin 1	4.06E-02	4.44E-02	-0.11	other	374986
FAM84A	family with sequence similarity 84 member A	7.56E-05	2.88E-03	-0.10	other	151354
FAM9B	family with sequence similarity 9 member B	8.17E-03	1.38E-02	0.09	other	171483
FBF1	Fas binding factor 1	1.63E-02	2.15E-02	0.06	other	85302
FBXL19	F-box and leucine rich repeat protein 19	2.63E-03	8.32E-03	0.07	enzyme	54620
FCAR	Fc fragment of IgA receptor	2.08E-03	7.64E-03	0.21	transmembrane receptor	2204
FCER1G	Fc fragment of IgE receptor Ig	1.41E-02	1.97E-02	0.35	transmembrane receptor	2207
FCGR1B	Fc fragment of IgG receptor Ib	3.98E-03	9.69E-03	0.23	transmembrane receptor	2210
FCGR2B	Fc fragment of IgG receptor IIb	2.21E-03	7.79E-03	0.29	transmembrane receptor	2213
FCGR2C	Fc fragment of IgG receptor IIc (gene/pseudogene)	2.49E-03	8.14E-03	0.19	transmembrane receptor	9103
FCGR3B	Fc fragment of IgG receptor IIIa	8.61E-03	1.41E-02	0.40	transmembrane receptor	2215
FCHO1	FCH domain only 1	7.26E-03	1.33E-02	0.05	other	23149
FERMT3	fermitin family member 3	5.93E-04	4.98E-03	0.13	enzyme	83706
FGF14	fibroblast growth factor 14	3.62E-03	9.39E-03	-0.15	growth factor	2259
FGF23	fibroblast growth factor 23	2.27E-02	2.77E-02	0.09	growth factor	8074
FGF7	fibroblast growth factor 7	1.25E-03	5.94E-03	0.30	growth factor	2252
FKSG83	vomeronasal 1 receptor 10 pseudogene	1.02E-03	5.46E-03	0.14	other	83954

FMO4	flavin containing monooxygenase 4	1.40E-02	1.96E-02	-0.15	enzyme	2329
FMO6P	flavin containing monooxygenase 6 pseudogene	4.96E-02	5.26E-02	-0.08	other	388714
FOS	Fos proto-oncogene, AP-1 transcription factor subunit	5.87E-04	4.98E-03	0.30	transcription regulator	2353
FOSB	FosB proto-oncogene, AP-1 transcription factor subunit	2.35E-03	8.08E-03	0.21	transcription regulator	2354
FOSL1	FOS like 1, AP-1 transcription factor subunit	1.73E-05	1.71E-03	0.29	transcription regulator	8061
FPR2	formyl peptide receptor 2	2.10E-03	7.64E-03	0.35	G-protein coupled receptor	2358
FRA10AC1	FRA10A associated CGG repeat 1	7.36E-03	1.33E-02	-0.08	other	118924
FSTL4	follistatin like 4	4.07E-03	9.76E-03	0.14	other	23105
FSTL5	follistatin like 5	3.04E-03	8.75E-03	0.14	other	56884
FTHL17	ferritin heavy chain like 17	2.06E-03	7.64E-03	0.11	other	53940
FTSJ1	FtsJ RNA methyltransferase homolog 1	5.12E-02	5.42E-02	-0.08	enzyme	24140
G0S2	G0/G1 switch 2	1.09E-03	5.60E-03	0.27	other	50486
GABRR3	gamma-aminobutyric acid type A receptor rho3 subunit (gene/pseudogene)	1.59E-01	1.59E-01	0.06	transmembrane receptor	200959
GAD2	glutamate decarboxylase 2	1.72E-02	2.22E-02	0.11	enzyme	2572
GADD45B	growth arrest and DNA damage inducible beta	8.27E-04	5.46E-03	0.13	other	4616
GALR2	galanin receptor 2	2.95E-02	3.38E-02	0.06	G-protein coupled receptor	8811
GBP2	guanylate binding protein 2	1.00E-03	5.46E-03	0.22	enzyme	2634
GBP5	guanylate binding protein 5	5.18E-03	1.10E-02	0.11	enzyme	115362
GCM2	glial cells missing homolog 2	3.11E-03	8.75E-03	0.14	transcription regulator	9247
GDF15	growth differentiation factor 15	3.62E-03	9.39E-03	0.20	growth factor	9518
GDF3	growth differentiation factor 3	5.85E-03	1.18E-02	0.10	growth factor	9573

GH1	growth hormone 1	7.08E-03	1.31E-02	0.14	growth factor	2688
GIMAP2	GTPase, IMAP family member 2	1.64E-03	6.85E-03	0.21	other	26157
GK3P	glycerol kinase 3 pseudogene	1.12E-03	5.63E-03	0.12	other	2713
GKN1	gastrokine 1	7.00E-02	7.24E-02	0.08	growth factor	56287
GKN2	gastrokine 2	2.67E-02	3.11E-02	0.15	other	200504
GLA	galactosidase alpha	4.97E-04	4.71E-03	0.11	enzyme	2717
GLCE	glucuronic acid epimerase	5.53E-02	5.81E-02	-0.10	enzyme	26035
GLTSCR2	NOP53 ribosome biogenesis factor	3.54E-03	9.28E-03	-0.03	other	29997
GNL2	G protein nucleolar 2	4.66E-02	4.99E-02	0.04	enzyme	29889
GOLGB1	golgin B1	2.59E-03	8.30E-03	-0.09	other	2804
GOSR1	golgi SNAP receptor complex member 1	2.10E-02	2.59E-02	0.13	transporter	9527
GPCPD1	glycerophosphocholine phosphodiesterase 1	2.91E-04	3.88E-03	0.13	enzyme	56261
GPM6A	glycoprotein M6A	8.17E-03	1.38E-02	0.10	ion channel	2823
GPNMB	glycoprotein nmb	7.26E-03	1.33E-02	0.24	enzyme	10457
GPR113	adhesion G protein-coupled receptor F3	3.33E-02	3.75E-02	0.08	G-protein coupled receptor	165082
GPR17	G protein-coupled receptor 17	2.75E-02	3.20E-02	0.06	G-protein coupled receptor	2840
GPR172A	solute carrier family 52 member 2	5.50E-02	5.79E-02	0.06	transporter	79581
GPR37	G protein-coupled receptor 37	1.99E-05	1.71E-03	0.23	G-protein coupled receptor	2861
GPR63	G protein-coupled receptor 63	3.75E-03	9.46E-03	0.08	G-protein coupled receptor	81491
GPR82	G protein-coupled receptor 82	2.59E-02	3.03E-02	0.15	G-protein coupled receptor	27197
GPRASP1	G protein-coupled receptor associated sorting protein 1	1.08E-02	1.62E-02	-0.17	transporter	9737

GPSM3	G protein signaling modulator 3	3.03E-02	3.47E-02	0.12	other	63940
GRHL2	grainyhead like transcription factor 2	6.23E-03	1.23E-02	-0.06	transcription regulator	79977
GRIN2D	glutamate ionotropic receptor NMDA type subunit 2D	4.32E-02	4.67E-02	0.10	ion channel	2906
GRINA	glutamate ionotropic receptor NMDA type subunit associated protein 1	8.22E-03	1.38E-02	0.07	ion channel	2907
GTF2H1	general transcription factor IIH subunit 1	8.62E-03	1.41E-02	0.09	transcription regulator	2965
GUCY1B2	guanylate cyclase 1 soluble subunit beta 2 (pseudogene)	4.83E-02	5.16E-02	0.08	other	2974
HAMP	hepcidin antimicrobial peptide	4.15E-02	4.51E-02	0.06	other	57817
HAUS8	HAUS augmin like complex subunit 8	1.21E-02	1.75E-02	0.08	other	93323
HCLS1	hematopoietic cell-specific Lyn substrate 1	2.59E-02	3.03E-02	0.14	other	3059
HEPH	Hephaestin	6.73E-03	1.27E-02	0.08	transporter	9843
HERC2	HECT and RLD domain containing E3 ubiquitin protein ligase 2	7.70E-03	1.33E-02	-0.09	enzyme	8924
HERC5	HECT and RLD domain containing E3 ubiquitin protein ligase 5	2.85E-03	8.69E-03	0.25	enzyme	51191
HES5	hes family bHLH transcription factor 5	8.70E-04	5.46E-03	0.17	transcription regulator	388585
HHIP	hedgehog interacting protein	7.51E-02	7.74E-02	0.08	other	64399
HHLA3	HERV-H LTR-associating 3	2.21E-03	7.79E-03	-0.13	other	11147
HIBADH	3-hydroxyisobutyrate dehydrogenase	2.35E-03	8.08E-03	-0.08	enzyme	11112
HIBCH	3-hydroxyisobutyryl-CoA hydrolase	7.40E-04	5.31E-03	-0.11	enzyme	26275
HIST1H1T	histone cluster 1 H1 family member t	2.43E-02	2.90E-02	0.11	other	3010
HIST1H2BC	histone cluster 1 H2B family member c	5.69E-03	1.16E-02	0.24	other	8347
HIST1H2BG	histone cluster 1 H2B family member g	1.59E-02	2.11E-02	0.11	other	8339
HLADMB	major histocompatibility complex, class II, DM beta	5.01E-03	1.09E-02	0.12	transmembrane receptor	3109

HLADOA	major histocompatibility complex, class II, DO alpha	9.41E-04	5.46E-03	0.21	transmembrane receptor	3111
HLF	HLF, PAR bZIP transcription factor	1.75E-02	2.24E-02	-0.15	transcription regulator	3131
HMGN3	high mobility group nucleosomal binding domain 3	3.38E-03	9.00E-03	-0.05	other	9324
HNRNPA3	heterogeneous nuclear ribonucleoprotein A3	2.81E-04	3.86E-03	-0.08	other	220988
HNRNPUL2	heterogeneous nuclear ribonucleoprotein U like 2	2.39E-02	2.87E-02	-0.04	other	221092
HOMEZ	homeobox and leucine zipper encoding	1.00E-02	1.57E-02	-0.17	transcription regulator	57594
HS3ST3A1	heparan sulfate-glucosamine 3-sulfotransferase 3A1	9.43E-04	5.46E-03	0.16	enzyme	9955
HSD11B1	hydroxysteroid 11-beta dehydrogenase 1	5.69E-03	1.16E-02	0.10	enzyme	3290
HSPA2	heat shock protein family A (Hsp70) member 2	3.89E-03	9.63E-03	-0.12	other	3306
ICAM1	intercellular adhesion molecule 1	1.66E-04	2.88E-03	0.21	transmembrane receptor	3383
ID1	inhibitor of DNA binding 1, HLH protein	1.14E-02	1.68E-02	0.15	transcription regulator	3397
IDO1	indoleamine 2,3-dioxygenase 1	1.56E-03	6.72E-03	0.42	enzyme	3620
IER2	immediate early response 2	9.96E-04	5.46E-03	0.10	transcription regulator	9592
IER3	immediate early response 3	2.10E-04	3.28E-03	0.13	other	8870
IER5	immediate early response 5	1.78E-02	2.27E-02	0.11	other	51278
IFFO2	intermediate filament family orphan 2	9.39E-04	5.46E-03	-0.10	other	126917
IFI30	IFI30, lysosomal thiol reductase	9.59E-03	1.53E-02	0.14	enzyme	10437
IFI44L	interferon induced protein 44 like	7.69E-03	1.33E-02	0.30	other	10964
IFIT2	interferon induced protein with tetratricopeptide repeats 2	1.99E-03	7.53E-03	0.21	other	3433
IFIT3	interferon induced protein with tetratricopeptide repeats 3	1.00E-02	1.57E-02	0.18	other	3437
IFITM1	interferon induced transmembrane protein 1	1.37E-03	6.22E-03	0.19	transmembrane receptor	8519

IFITM2	interferon induced transmembrane protein 2	2.65E-03	8.34E-03	0.14	other	10581
IFNGR2	interferon gamma receptor 2	3.21E-03	8.75E-03	0.12	transmembrane receptor	3460
IGSF5	immunoglobulin superfamily member 5	4.54E-02	4.88E-02	0.10	other	150084
IGSF6	immunoglobulin superfamily member 6	7.18E-04	5.30E-03	0.27	transmembrane receptor	10261
IL10RA	interleukin 10 receptor subunit alpha	6.24E-04	4.98E-03	0.19	transmembrane receptor	3587
IL1B	interleukin 1 beta	1.71E-04	2.90E-03	0.34	cytokine	3553
IL1R2	interleukin 1 receptor type 2	4.60E-03	1.06E-02	0.24	transmembrane receptor	7850
IL1RN	interleukin 1 receptor antagonist	2.54E-03	8.19E-03	0.27	cytokine	3557
IL20	interleukin 20	1.54E-02	2.08E-02	0.05	cytokine	50604
IL22RA2	interleukin 22 receptor subunit alpha 2	6.96E-02	7.22E-02	0.04	transmembrane receptor	116379
IL33	interleukin 33	7.09E-03	1.31E-02	-0.12	cytokine	90865
IL3RA	interleukin 3 receptor subunit alpha	4.03E-03	9.74E-03	0.08	transmembrane receptor	3563
IL4I1	interleukin 4 induced 1	7.32E-04	5.30E-03	0.15	enzyme	259307
IL6	interleukin 6	6.28E-04	4.98E-03	0.15	cytokine	3569
IL8	C-X-C motif chemokine ligand 8	6.97E-05	2.88E-03	0.25	cytokine	3576
IMPAD1	inositol monophosphatase domain containing 1	3.17E-03	8.75E-03	-0.09	enzyme	54928
IRAK3	interleukin 1 receptor associated kinase 3	1.45E-02	2.01E-02	0.14	kinase	11213
IRF7	interferon regulatory factor 7	2.50E-03	8.14E-03	0.13	transcription regulator	3665
ISLR	immunoglobulin superfamily containing leucine rich repeat	4.05E-03	9.74E-03	-0.14	other	3671
JUNB	JunB proto-oncogene, AP-1 transcription factor subunit	7.14E-04	5.30E-03	0.13	transcription regulator	3726
KAL1	anosmin 1	9.66E-03	1.53E-02	-0.14	other	3730

KCNJ15	potassium voltage-gated channel subfamily J member 15	6.44E-04	4.98E-03	0.20	ion channel	3772
KCNJ16	potassium voltage-gated channel subfamily J member 16	1.04E-03	5.51E-03	-0.20	ion channel	3773
KCNN2	potassium calcium-activated channel subfamily N member 2	9.10E-03	1.46E-02	0.09	ion channel	3781
KCNV1	potassium voltage-gated channel modifier subfamily V member 1	7.69E-03	1.33E-02	0.11	ion channel	27012
KIAA0146	scaffolding protein involved in DNA repair	8.36E-03	1.38E-02	-0.04	other	23514
KIAA1147	KIAA1147	7.94E-03	1.35E-02	-0.08	other	57189
KIAA1244	ARFGEF family member 3	2.19E-04	3.36E-03	-0.10	other	57221
KIAA1267	KAT8 regulatory NSL complex subunit 1	1.15E-01	1.16E-01	-0.03	other	284058
KIAA1279	KIF1 binding protein	8.27E-03	1.38E-02	-0.09	enzyme	26128
KIAA1324	KIAA1324	1.14E-03	5.66E-03	-0.10	other	57535
KIAA1524	cell proliferation regulating inhibitor of protein phosphatase 2A	4.76E-03	1.08E-02	0.14	other	57650
KIF14	kinesin family member 14	7.39E-03	1.33E-02	0.10	enzyme	9928
KIF18B	kinesin family member 18B	1.59E-03	6.80E-03	0.22	other	146909
KIF21A	kinesin family member 21A	1.37E-03	6.22E-03	-0.07	other	55605
KLC2	kinesin light chain 2	6.39E-02	6.65E-02	0.08	other	64837
KLF2	Kruppel like factor 2	1.41E-02	1.96E-02	0.09	transcription regulator	10365
KLHL11	kelch like family member 11	1.32E-03	6.17E-03	-0.11	other	55175
KMO	kynurenine 3-monooxygenase	1.22E-02	1.77E-02	0.28	enzyme	8564
KRT40	keratin 40	3.48E-02	3.89E-02	0.16	other	125115
KRT5	keratin 5	4.53E-03	1.05E-02	-0.12	other	3852

KRT79	keratin 79	8.40E-03	1.39E-02	0.13	other	338785
KYNU	Kynureninase	5.08E-03	1.09E-02	0.26	enzyme	8942
LAMB2	laminin subunit beta 2	3.25E-02	3.66E-02	-0.07	enzyme	3913
LANCL1	LanC like 1	7.06E-03	1.31E-02	-0.10	other	10314
LAP3	leucine aminopeptidase 3	3.52E-02	3.92E-02	0.09	peptidase	51056
LARP1	La ribonucleoprotein domain family member 1	1.31E-02	1.86E-02	-0.05	translation regulator	23367
LCP1	lymphocyte cytosolic protein 1	1.39E-02	1.95E-02	0.23	other	3936
LCP2	lymphocyte cytosolic protein 2	7.36E-03	1.33E-02	0.39	other	3937
LDHA	lactate dehydrogenase A	1.93E-02	2.44E-02	0.08	enzyme	3939
LDHB	lactate dehydrogenase B	2.99E-03	8.71E-03	-0.05	enzyme	3945
LDHC	lactate dehydrogenase C	7.73E-02	7.93E-02	0.09	enzyme	3948
LENG1	leukocyte receptor cluster member 1	1.20E-03	5.85E-03	0.07	other	79165
LHFPL3	LHFPL tetraspan subfamily member 3	1.68E-02	2.18E-02	0.14	other	375612
LILRA2	leukocyte immunoglobulin like receptor A2	4.74E-03	1.08E-02	0.30	other	11027
LILRA3	leukocyte immunoglobulin like receptor A3	2.65E-02	3.10E-02	0.06	other	11026
LILRA5	leukocyte immunoglobulin like receptor A5	6.27E-03	1.23E-02	0.09	other	353514
LILRB1	leukocyte immunoglobulin like receptor B1	1.16E-02	1.70E-02	0.11	transmembrane receptor	10859
LILRB2	leukocyte immunoglobulin like receptor B2	1.06E-03	5.53E-03	0.18	transmembrane receptor	10288
LILRB3	leukocyte immunoglobulin like receptor B3	3.53E-02	3.92E-02	0.12	transmembrane receptor	11025
LILRB5	leukocyte immunoglobulin like receptor B5	1.72E-02	2.22E-02	0.07	transmembrane receptor	10990
LMBRD2	LMBR1 domain containing 2	4.87E-02	5.18E-02	-0.10	other	92255

LMNB1	lamin B1	2.31E-03	8.02E-03	0.20	other	4001
LOC100127886	LOC100127886	1.70E-05	1.71E-03	0.32	unknown	100127886
LOC100128185	LOC100128185	1.89E-02	2.39E-02	0.13	unknown	100128185
LOC100129104	LOC100129104	6.79E-04	5.20E-03	0.16	unknown	100129104
LOC100129550	long intergenic non-protein coding RNA 2035	3.16E-03	8.75E-03	-0.11	other	100129550
LOC100129890	LOC100129890	2.98E-03	8.69E-03	0.18	unknown	100129890
LOC100131564	CCDC18 antisense RNA 1	3.09E-02	3.52E-02	-0.13	other	100131564
LOC100131642	LOC100131642	1.36E-03	6.22E-03	-0.15	unknown	100131642
LOC100131864	LOC100131864	1.30E-02	1.86E-02	0.09	unknown	100131864
LOC100132815	importin 5 pseudogene 1	7.71E-02	7.92E-02	-0.11	other	100132815
LOC100132891	MSC antisense RNA 1	9.08E-02	9.23E-02	0.07	other	100132891
LOC100132987	long intergenic non-protein coding RNA 856	2.15E-05	1.71E-03	0.15	other	100132987
LOC100271840	LOC100271840	6.64E-03	1.27E-02	0.13	unknown	100271840
LOC100287027	LOC100287027	5.25E-03	1.10E-02	0.09	unknown	100287027
LOC100288617	LOC100288617	1.00E-02	1.57E-02	0.09	unknown	100288617
LOC100288985	LOC100288985	4.49E-04	4.53E-03	0.31	unknown	100288985
LOC100289251	LOC100289251	1.12E-02	1.66E-02	0.09	unknown	100289251
LOC100292909	uncharacterized LOC101060391	1.49E-01	1.50E-01	0.22	other	100292909
LOC100505885	phosphodiesterase 4D interacting protein pseudogene	7.73E-03	1.33E-02	-0.12	other	100505885
LOC100505960	LOC100505960	9.04E-04	5.46E-03	0.19	unknown	100505960
LOC100506090	LOC100506090	2.84E-02	3.29E-02	-0.14	unknown	100506090

LOC100506517	aldehyde dehydrogenase 6 family member A1	3.14E-02	3.56E-02	-0.14	enzyme	100506517
LOC100506748	LOC100506748	5.64E-03	1.16E-02	-0.11	unknown	100506748
LOC100506762	LOC100506762	2.76E-04	3.86E-03	0.23	unknown	100506762
LOC100506828	LOC100506828	7.00E-02	7.24E-02	-0.04	unknown	100506828
LOC100506941	LOC100506941	6.56E-03	1.26E-02	0.13	unknown	100506941
LOC100507123	LOC100507123	3.89E-02	4.26E-02	0.14	unknown	100507123
LOC100507248	LOC100507248	1.76E-03	7.08E-03	0.24	unknown	100507248
LOC100507371	LOC100507371	1.54E-03	6.65E-03	0.11	unknown	100507371
LOC151658	long intergenic non-protein coding RNA 635	5.59E-04	4.98E-03	0.12	other	151658
LOC202181	SUMO interacting motifs containing 1 pseudogene	4.06E-04	4.43E-03	-0.20	other	202181
LOC203274	long intergenic non-protein coding RNA 537	7.35E-03	1.33E-02	-0.15	other	203274
LOC254896	uncharacterized LOC254896	1.68E-02	2.18E-02	0.09	other	254896
LOC283501	ATP11A antisense RNA 1	1.06E-02	1.60E-02	0.09	other	283501
LOC283745	LOC283745	1.93E-03	7.52E-03	0.16	unknown	283745
LOC286002	SLC26A4 antisense RNA 1	1.10E-02	1.64E-02	0.16	other	286002
LOC386758	ZNF582 antisense RNA 1 (head to head)	4.02E-02	4.40E-02	-0.09	other	386758
LOC388387	long intergenic non-protein coding RNA 671	5.13E-02	5.42E-02	0.08	other	388387
LOC441617	trophoblast glycoprotein like	1.05E-02	1.60E-02	0.09	other	441617
LOC441869	ankyrin repeat domain 65	4.70E-03	1.07E-02	-0.05	other	441869
LOC497256	uncharacterized LOC497256	3.86E-02	4.24E-02	0.10	other	497256
LOC553103	MIR3936 host gene	7.33E-03	1.33E-02	-0.21	other	553103

LOC645485	uncharacterized LOC645485	3.82E-03	9.53E-03	0.15	other	645485
LOC646701	developmental pluripotency associated 5 pseudogene 4	9.62E-03	1.53E-02	0.10	other	646701
LOC653602	family with sequence similarity 84 member A	1.62E-03	6.84E-03	-0.27	other	653602
LOC728196	uncharacterized LOC728196	7.07E-03	1.31E-02	-0.10	other	728196
LOC728449	annexin A8 like 1	2.05E-02	2.56E-02	-0.11	other	728449
LPCAT2	lysophosphatidylcholine acyltransferase 2	5.98E-03	1.20E-02	0.25	enzyme	54947
LPL	lipoprotein lipase	1.86E-02	2.36E-02	0.33	enzyme	4023
LRBA	LPS responsive beige-like anchor protein	2.50E-03	8.14E-03	-0.09	other	987
LRG1	leucine rich alpha-2-glycoprotein 1	1.74E-03	7.04E-03	0.15	other	116844
LRRC4	leucine rich repeat containing 4	2.11E-03	7.64E-03	-0.07	other	64101
LRRFIP2	LRR binding FLII interacting protein 2	2.93E-03	8.69E-03	-0.09	other	9209
LSM14A	LSM14A, mRNA processing body assembly factor	8.29E-03	1.38E-02	-0.07	other	26065
LSM5	LSM5 homolog, U6 small nuclear RNA and mRNA degradation associated	2.27E-02	2.77E-02	-0.14	other	23658
LY96	lymphocyte antigen 96	2.85E-03	8.69E-03	0.44	transmembrane receptor	23643
LYN	LYN proto-oncogene, Src family tyrosine kinase	2.79E-03	8.66E-03	0.10	kinase	4067
MAFB	MAF bZIP transcription factor B	2.46E-02	2.93E-02	0.13	transcription regulator	9935
MAFF	MAF bZIP transcription factor F	7.74E-08	3.08E-05	0.37	transcription regulator	23764
MAFG	MAF bZIP transcription factor G	1.53E-03	6.65E-03	0.07	transcription regulator	4097
MAGED2	MAGE family member D2	8.88E-04	5.46E-03	-0.07	other	10916
MAGEH1	MAGE family member H1	1.33E-02	1.88E-02	-0.09	other	28986
MAP1LC3B2	microtubule associated protein 1 light chain 3 beta 2	3.16E-03	8.75E-03	0.10	other	643246

MBIP	MAP3K12 binding inhibitory protein 1	2.41E-02	2.89E-02	-0.10	other	51562
MCL1	MCL1, BCL2 family apoptosis regulator	1.68E-02	2.18E-02	0.09	transporter	4170
MED15	mediator complex subunit 15	4.11E-03	9.84E-03	0.07	transcription regulator	51586
MEIS2	Meis homeobox 2	2.66E-02	3.11E-02	-0.09	transcription regulator	4212
MEIS3P1	Meis homeobox 3 pseudogene 1	1.29E-02	1.84E-02	-0.04	other	4213
METTL3	methyltransferase like 3	3.76E-02	4.13E-02	-0.05	enzyme	56339
MFSD8	major facilitator superfamily domain containing 8	4.45E-03	1.05E-02	-0.10	other	256471
MGAT4C	MGAT4 family member C	2.48E-01	2.48E-01	0.06	enzyme	25834
MGC13053	MGC13053	3.68E-02	4.08E-02	0.08	unknown	84796
MGC34034	long intergenic non-protein coding RNA 1312	5.79E-04	4.98E-03	0.19	other	154089
MGC40069	MGC40069	1.32E-02	1.87E-02	0.12	unknown	348035
MIDN	Midnolin	2.93E-03	8.69E-03	0.07	other	90007
MMP7	matrix metallopeptidase 7	1.37E-04	2.88E-03	0.12	peptidase	4316
MNDA	myeloid cell nuclear differentiation antigen	1.55E-02	2.08E-02	0.22	other	4332
MRPS18A	mitochondrial ribosomal protein S18A	2.14E-03	7.65E-03	0.07	other	55168
MRPS27	mitochondrial ribosomal protein S27	7.50E-03	1.33E-02	-0.04	other	23107
MS4A4A	membrane spanning 4-domains A4A	3.51E-02	3.92E-02	0.31	other	51338
MS4A6A	membrane spanning 4-domains A6A	4.00E-03	9.69E-03	0.19	other	64231
MTMR14	myotubularin related protein 14	7.75E-03	1.33E-02	0.08	phosphatase	64419
MTRF1L	mitochondrial translational release factor 1 like	1.40E-02	1.96E-02	-0.06	translation regulator	54516
MTX3	metaxin 3	7.31E-03	1.33E-02	-0.11	other	345778

MX1	MX dynamin like GTPase 1	4.91E-03	1.09E-02	0.13	enzyme	4599
MX2	MX dynamin like GTPase 2	3.47E-04	4.07E-03	0.24	enzyme	4600
MYD88	myeloid differentiation primary response 88	6.69E-03	1.27E-02	0.12	other	4615
MYH2	myosin heavy chain 2	9.34E-03	1.49E-02	0.14	enzyme	4620
MYO6	myosin VI	1.65E-03	6.85E-03	-0.07	other	4646
NAA11	N(alpha)-acetyltransferase 11, NatA catalytic subunit	4.19E-02	4.54E-02	0.09	enzyme	84779
NAMPT	nicotinamide phosphoribosyltransferase	2.05E-04	3.28E-03	0.18	cytokine	10135
NAP1L1	nucleosome assembly protein 1 like 1	1.39E-03	6.26E-03	-0.21	other	4673
NAP1L2	nucleosome assembly protein 1 like 2	1.74E-02	2.23E-02	-0.16	other	4674
NAP1L3	nucleosome assembly protein 1 like 3	3.19E-03	8.75E-03	0.13	other	4675
NARG2	interactor of little elongation complex ELL subunit 2	4.99E-03	1.09E-02	-0.10	other	79664
NASP	nuclear autoantigenic sperm protein	4.82E-03	1.08E-02	-0.09	other	4678
NBPF10	NBPF member 20	3.44E-03	9.08E-03	-0.04	other	100132406
NBPF12	NBPF member 20	1.05E-02	1.59E-02	-0.04	other	440675
NCF2	neutrophil cytosolic factor 2	7.55E-03	1.33E-02	0.17	enzyme	4688
NCRNA00175	COL18A1 antisense RNA 1	8.31E-03	1.38E-02	0.08	other	378832
NDC80	NDC80, kinetochore complex component	1.38E-02	1.94E-02	0.21	other	10403
NELL2	neural EGFL like 2	3.77E-03	9.46E-03	-0.24	other	4753
NET1	neuroepithelial cell transforming 1	2.03E-05	1.71E-03	-0.06	other	10276
NEURL3	neuralized E3 ubiquitin protein ligase 3	3.70E-02	4.09E-02	-0.11	enzyme	93082
NFIB	nuclear factor I B	8.55E-04	5.46E-03	-0.15	transcription regulator	4781

NFIC	nuclear factor I C	3.67E-03	9.39E-03	-0.05	transcription regulator	4782
NFIL3	nuclear factor, interleukin 3 regulated	1.73E-02	2.23E-02	0.12	transcription regulator	4783
NFIX	nuclear factor I X	2.91E-05	1.93E-03	-0.06	transcription regulator	4784
NFKBIL1	NFKB inhibitor like 1	6.74E-02	7.02E-02	0.04	transcription regulator	4795
NHEG1	neuroblastoma highly expressed 1	3.20E-02	3.61E-02	0.09	other	100294720
NHSL1	NHS like 1	4.20E-04	4.43E-03	-0.18	other	57224
NKAPP1	NFKB activating protein pseudogene 1	1.68E-02	2.18E-02	-0.11	other	158801
NMI	N-myc and STAT interactor	7.70E-03	1.33E-02	0.08	transcription regulator	9111
NMU	neuromedin U	1.69E-02	2.19E-02	0.11	other	10874
NNMT	nicotinamide N-methyltransferase	1.01E-01	1.02E-01	0.05	enzyme	4837
NOLC1	nucleolar and coiled-body phosphoprotein 1	5.78E-03	1.17E-02	0.08	transcription regulator	9221
NPL	N-acetylneuraminate pyruvate lyase	2.92E-02	3.35E-02	0.17	enzyme	80896
NPPB	natriuretic peptide B	4.73E-03	1.08E-02	0.05	other	4879
NPY2R	neuropeptide Y receptor Y2	1.23E-03	5.93E-03	0.11	G-protein coupled receptor	4887
NR1D2	nuclear receptor subfamily 1 group D member 2	5.12E-03	1.09E-02	-0.16	ligand-dependent nuclear receptor	9975
NR3C2	nuclear receptor subfamily 3 group C member 2	5.84E-03	1.18E-02	-0.12	ligand-dependent nuclear receptor	4306
NR4A1	nuclear receptor subfamily 4 group A member 1	6.03E-05	2.70E-03	0.21	ligand-dependent nuclear receptor	3164
NR4A2	nuclear receptor subfamily 4 group A member 2	3.07E-03	8.75E-03	0.14	ligand-dependent nuclear receptor	4929
NRBF2	nuclear receptor binding factor 2	2.01E-02	2.51E-02	0.12	transcription regulator	29982

NTS	Neurotensin	1.08E-03	5.60E-03	-0.23	other	4922
NUAK1	NUAK family kinase 1	4.69E-04	4.58E-03	-0.11	kinase	9891
NUCKS1	nuclear casein kinase and cyclin dependent kinase substrate 1	1.26E-04	2.88E-03	-0.07	kinase	64710
OAF	out at first homolog	1.61E-02	2.14E-02	-0.09	other	220323
OAS3	2'-5'-oligoadenylate synthetase 3	3.71E-02	4.09E-02	0.13	enzyme	4940
OBFC2A	nucleic acid binding protein 1	6.91E-03	1.29E-02	0.19	other	64859
OCA2	OCA2 melanosomal transmembrane protein	7.23E-03	1.33E-02	0.12	transporter	4948
OFCC1	orofacial cleft 1 candidate 1	2.49E-03	8.14E-03	0.13	other	266553
OR5AK4P	olfactory receptor family 5 subfamily AK member 4 pseudogene	1.51E-02	2.06E-02	0.11	other	219525
OR6B1	olfactory receptor family 6 subfamily B member 1	7.34E-03	1.33E-02	0.10	G-protein coupled receptor	135946
OR8D2	olfactory receptor family 8 subfamily D member 2 (gene/pseudogene)	1.85E-02	2.35E-02	0.11	G-protein coupled receptor	283160
OSBPL3	oxysterol binding protein like 3	2.74E-03	8.56E-03	-0.10	transporter	26031
OSGIN2	oxidative stress induced growth inhibitor family member 2	4.14E-02	4.51E-02	0.14	other	734
OXA1L	OXA1L, mitochondrial inner membrane protein	2.30E-02	2.81E-02	-0.04	enzyme	5018
OXTR	oxytocin receptor	4.26E-03	1.01E-02	-0.15	G-protein coupled receptor	5021
P2RY13	purinergic receptor P2Y13	1.37E-03	6.22E-03	0.30	G-protein coupled receptor	53829
PABPC3	poly(A) binding protein cytoplasmic 3	1.25E-02	1.81E-02	-0.03	other	5042
PAG1	phosphoprotein membrane anchor with glycosphingolipid microdomains 1	3.99E-03	9.69E-03	0.22	other	55824
PAICS	phosphoribosylaminoimidazole carboxylase and phosphoribosylaminoimidazolesuccinocarboxamide synthase	2.96E-03	8.69E-03	-0.11	enzyme	10606

PALM	Paralemmin	2.74E-02	3.20E-02	-0.05	other	5064
PAMR1	peptidase domain containing associated with muscle regeneration 1	1.13E-02	1.67E-02	-0.23	peptidase	25891
PARD3	par-3 family cell polarity regulator	1.62E-02	2.14E-02	-0.08	other	56288
PARN	poly(A)-specific ribonuclease	1.10E-02	1.65E-02	-0.08	enzyme	5073
PARP14	poly(ADP-ribose) polymerase family member 14	9.21E-03	1.48E-02	0.08	enzyme	54625
PBX1	PBX homeobox 1	4.14E-04	4.43E-03	-0.12	transcription regulator	5087
PCGF5	polycomb group ring finger 5	1.03E-02	1.58E-02	-0.08	other	84333
PCMTD1	protein-L-isoaspartate (D-aspartate) O-methyltransferase domain containing 1	1.06E-02	1.60E-02	-0.04	enzyme	115294
PCSK5	proprotein convertase subtilisin/kexin type 5	5.22E-03	1.10E-02	-0.09	peptidase	5125
PDLIM4	PDZ and LIM domain 4	3.42E-03	9.08E-03	-0.09	other	8572
PDZK1IP1	PDZK1 interacting protein 1	1.80E-03	7.19E-03	0.13	other	10158
PDZRN3	PDZ domain containing ring finger 3	2.18E-02	2.67E-02	0.07	enzyme	23024
PEG3	paternally expressed 3	5.60E-03	1.16E-02	-0.23	kinase	5178
PENK	Proenkephalin	2.59E-03	8.30E-03	0.11	other	5179
PEX1	peroxisomal biogenesis factor 1	3.15E-03	8.75E-03	-0.12	enzyme	5189
PGLYRP3	peptidoglycan recognition protein 3	3.68E-03	9.39E-03	0.13	transmembrane receptor	114771
PHACTR1	phosphatase and actin regulator 1	1.42E-02	1.98E-02	0.28	other	221692
PHF3	PHD finger protein 3	6.86E-02	7.13E-02	-0.04	other	23469
PHLDA2	pleckstrin homology like domain family A member 2	9.46E-03	1.51E-02	0.07	other	7262
PI3	peptidase inhibitor 3	4.91E-03	1.09E-02	0.18	other	5266

PI4K2B	phosphatidylinositol 4-kinase type 2 beta	7.51E-03	1.33E-02	-0.14	kinase	55300
PIAS1	protein inhibitor of activated STAT 1	4.49E-03	1.05E-02	-0.08	transcription regulator	8554
PIK3AP1	phosphoinositide-3-kinase adaptor protein 1	1.24E-03	5.93E-03	0.28	kinase	118788
PIK3C2G	phosphatidylinositol-4-phosphate 3-kinase catalytic subunit type 2 gamma	1.07E-02	1.60E-02	0.13	kinase	5288
PIM1	Pim-1 proto-oncogene, serine/threonine kinase	1.68E-03	6.96E-03	0.10	kinase	5292
PIM2	Pim-2 proto-oncogene, serine/threonine kinase	1.20E-02	1.75E-02	0.09	kinase	11040
PIM3	Pim-3 proto-oncogene, serine/threonine kinase	2.02E-02	2.52E-02	0.05	kinase	415116
PLA2G7	phospholipase A2 group VII	3.65E-03	9.39E-03	0.17	enzyme	7941
PLAC1	placenta specific 1	4.35E-02	4.69E-02	0.07	other	10761
PLAU	plasminogen activator, urokinase	7.46E-03	1.33E-02	0.21	peptidase	5328
PLBD1	phospholipase B domain containing 1	7.45E-03	1.33E-02	0.12	enzyme	79887
PLEK	Pleckstrin	4.87E-03	1.09E-02	0.24	other	5341
PLEKHA1	pleckstrin homology domain containing A1	7.44E-03	1.33E-02	-0.10	other	59338
PLEKHA8	pleckstrin homology domain containing A8	3.91E-03	9.65E-03	0.13	transporter	84725
PLLP	Plasmolipin	7.68E-03	1.33E-02	-0.09	transporter	51090
PLXND1	plexin D1	5.11E-03	1.09E-02	0.11	transmembrane receptor	23129
PMAIP1	phorbol-12-myristate-13-acetate-induced protein 1	1.08E-03	5.60E-03	0.21	other	5366
PNLIPRP1	pancreatic lipase related protein 1	2.35E-02	2.85E-02	0.06	enzyme	5407
PNOC	Prepronociceptin	1.11E-01	1.12E-01	0.04	other	5368
PNP	purine nucleoside phosphorylase	1.12E-01	1.13E-01	0.08	enzyme	4860
PON3	paraoxonase 3	2.13E-02	2.62E-02	-0.12	enzyme	5446

PPAN	peter pan homolog (Drosophila)	1.30E-01	1.31E-01	0.04	other	56342
PPIF	peptidylprolyl isomerase F	2.20E-03	7.79E-03	0.09	enzyme	10105
PPP1R15A	protein phosphatase 1 regulatory subunit 15A	6.52E-03	1.26E-02	0.10	other	23645
PRAMEF11	PRAME family member 11	4.32E-02	4.67E-02	0.10	other	440560
PRIM1	DNA primase subunit 1	9.97E-04	5.46E-03	-0.22	enzyme	5557
PRO2949	PRO2949	1.75E-02	2.24E-02	0.08	unknown	55412
PROK2	prokineticin 2	5.08E-04	4.71E-03	0.46	other	60675
PRPS1	phosphoribosyl pyrophosphate synthetase 1	7.42E-03	1.33E-02	-0.12	kinase	5631
PRR16	proline rich 16	4.13E-03	9.85E-03	0.10	other	51334
PRSS35	protease, serine 35	1.52E-02	2.07E-02	0.14	peptidase	167681
PSTPIP2	proline-serine-threonine phosphatase interacting protein 2	2.14E-03	7.65E-03	0.31	other	9050
PTAFR	platelet activating factor receptor	1.99E-03	7.53E-03	0.16	G-protein coupled receptor	5724
PTGES	prostaglandin E synthase	7.64E-04	5.39E-03	0.10	enzyme	9536
PTGS2	prostaglandin-endoperoxide synthase 2	2.02E-03	7.56E-03	0.43	enzyme	5743
PTK6	protein tyrosine kinase 6	2.96E-03	8.69E-03	0.13	kinase	5753
PTMS	Parathymosin	1.99E-03	7.53E-03	0.08	other	5763
PTP4A1	protein tyrosine phosphatase type IVA, member 1	3.76E-02	4.13E-02	0.05	phosphatase	7803
PTPN7	protein tyrosine phosphatase, non-receptor type 7	3.58E-03	9.36E-03	0.14	phosphatase	5778
PTPRC	protein tyrosine phosphatase, receptor type C	8.80E-03	1.43E-02	0.26	phosphatase	5788
PURA	purine rich element binding protein A	1.90E-03	7.47E-03	-0.09	transcription regulator	5813
PURB	purine rich element binding protein B	1.49E-02	2.06E-02	-0.06	transcription regulator	5814

PWRN2	Prader-Willi region non-protein coding RNA 2	1.01E-02	1.57E-02	0.10	other	791115
PYGO2	pygopus family PHD finger 2	5.08E-04	4.71E-03	-0.05	other	90780
PYHIN1	pyrin and HIN domain family member 1	1.01E-03	5.46E-03	0.18	other	149628
QPCT	glutaminyl-peptide cyclotransferase	6.32E-03	1.23E-02	0.16	enzyme	25797
RAB20	RAB20, member RAS oncogene family	2.38E-02	2.87E-02	0.09	enzyme	55647
RAB39	RAB39A, member RAS oncogene family	1.02E-02	1.57E-02	0.09	enzyme	54734
RAB8B	RAB8B, member RAS oncogene family	2.11E-02	2.60E-02	0.16	enzyme	51762
RALB	RAS like proto-oncogene B	3.01E-03	8.72E-03	0.09	enzyme	5899
RALGAPB	Ral GTPase activating protein non-catalytic beta subunit	8.89E-04	5.46E-03	-0.10	other	57148
RARRES1	retinoic acid receptor responder 1	3.22E-04	3.90E-03	0.19	other	5918
RASD1	ras related dexamethasone induced 1	5.97E-05	2.70E-03	0.24	enzyme	51655
RASGRP3	RAS guanyl releasing protein 3	7.88E-04	5.45E-03	0.24	other	25780
RASSF9	Ras association domain family member 9	3.48E-03	9.16E-03	-0.09	transporter	9182
RBAK	RB associated KRAB zinc finger	1.54E-02	2.08E-02	-0.10	transcription regulator	57786
RBL2	RB transcriptional corepressor like 2	1.03E-03	5.46E-03	-0.06	other	5934
RBMX	RNA binding motif protein, X-linked	1.83E-03	7.25E-03	-0.39	other	27316
RCAN3	RCAN family member 3	1.57E-02	2.10E-02	-0.05	other	11123
REL	REL proto-oncogene, NF-kB subunit	2.32E-02	2.82E-02	0.09	transcription regulator	5966
RELT	RELT, TNF receptor	4.90E-02	5.21E-02	0.14	transmembrane receptor	84957
RFC1	replication factor C subunit 1	4.85E-02	5.18E-02	-0.09	transcription regulator	5981
RFPL1	ret finger protein like 3	3.25E-03	8.83E-03	0.13	other	5988

RGL4	ral guanine nucleotide dissociation stimulator like 4	8.05E-03	1.36E-02	0.16	other	266747
RILPL2	Rab interacting lysosomal protein like 2	3.44E-03	9.08E-03	0.08	other	196383
RIMKLB	ribosomal modification protein rimK like family member B	2.23E-03	7.82E-03	-0.09	enzyme	57494
RIPK4	receptor interacting serine/threonine kinase 4	2.82E-03	8.69E-03	-0.06	kinase	54101
RIT1	Ras like without CAAX 1	1.05E-02	1.59E-02	0.09	enzyme	6016
RMND1	required for meiotic nuclear division 1 homolog	7.84E-03	1.34E-02	-0.11	other	55005
RNF149	ring finger protein 149	4.41E-03	1.04E-02	0.12	enzyme	284996
RNF175	ring finger protein 175	8.74E-03	1.43E-02	0.11	other	285533
RNF19B	ring finger protein 19B	2.77E-05	1.93E-03	0.14	enzyme	127544
ROBO1	roundabout guidance receptor 1	9.46E-04	5.46E-03	-0.15	transmembrane receptor	6091
ROGDI	rogdi homolog	4.61E-03	1.06E-02	-0.05	other	79641
RORC	RAR related orphan receptor C	1.42E-03	6.36E-03	-0.12	ligand-dependent nuclear receptor	6097
RPL3	ribosomal protein L3	2.24E-03	7.82E-03	-0.04	other	6122
RPL5	ribosomal protein L5	6.71E-03	1.27E-02	-0.04	other	6125
RPS4X	ribosomal protein S4, X-linked	9.81E-04	5.46E-03	-0.03	other	6191
RXFP3	relaxin/insulin like family peptide receptor 3	8.85E-02	9.02E-02	0.07	G-protein coupled receptor	51289
S100A8	S100 calcium binding protein A8	8.30E-03	1.38E-02	0.32	other	6279
S100A9	S100 calcium binding protein A9	1.03E-03	5.46E-03	0.21	other	6280
SAA4	serum amyloid A4, constitutive	8.71E-05	2.88E-03	0.28	transporter	6291
SAMD4A	sterile alpha motif domain containing 4A	2.11E-02	2.60E-02	0.17	translation regulator	23034
SAT1	spermidine/spermine N1-acetyltransferase 1	3.32E-03	8.96E-03	0.04	enzyme	6303

SBNO2	strawberry notch homolog 2	8.59E-04	5.46E-03	0.11	transcription regulator	22904
SCARA3	scavenger receptor class A member 3	9.11E-04	5.46E-03	-0.13	transmembrane receptor	51435
SCGB1C1	secretoglobin family 1C member 1	1.18E-03	5.78E-03	0.13	other	147199
SCIN	Scinderin	3.72E-04	4.17E-03	-0.17	other	85477
SCLT1	sodium channel and clathrin linker 1	4.61E-03	1.06E-02	0.22	transporter	132320
SCN4B	sodium voltage-gated channel beta subunit 4	3.97E-02	4.35E-02	-0.13	ion channel	6330
SDK1	sidekick cell adhesion molecule 1	7.80E-03	1.33E-02	-0.13	other	221935
SEMA5A	semaphorin 5A	6.23E-04	4.98E-03	-0.15	transmembrane receptor	9037
SEPP1	selenoprotein P	2.12E-03	7.64E-03	-0.09	other	6414
SERP1	stress associated endoplasmic reticulum protein 1	3.16E-03	8.75E-03	-0.06	other	27230
SERPINA3	serpin family A member 3	1.08E-04	2.88E-03	0.38	other	12
SERPINB11	serpin family B member 11 (gene/pseudogene)	6.35E-03	1.24E-02	-0.17	other	89778
SERPING1	serpin family G member 1	3.62E-04	4.12E-03	0.19	other	710
SERTAD4	SERTA domain containing 4	4.26E-03	1.01E-02	-0.12	other	56256
SFMBT2	Scm like with four mbt domains 2	2.48E-03	8.14E-03	0.16	other	57713
SHF	Src homology 2 domain containing F	1.47E-04	2.88E-03	-0.14	other	90525
SHROOM4	shroom family member 4	2.66E-03	8.34E-03	-0.14	other	57477
SIGLEC1	sialic acid binding Ig like lectin 1	5.68E-02	5.96E-02	0.09	other	6614
SIGMAR1	sigma non-opioid intracellular receptor 1	3.92E-03	9.65E-03	-0.07	transmembrane receptor	10280
SIRPB1	signal regulatory protein beta 1	9.76E-03	1.54E-02	0.36	other	10326
SLA	Src like adaptor	3.02E-03	8.72E-03	0.16	other	6503

SLAIN1	SLAIN motif family member 1	4.24E-02	4.59E-02	0.11	other	122060
SLAMF9	SLAM family member 9	1.50E-02	2.06E-02	0.08	other	89886
SLC10A4	solute carrier family 10 member 4	2.07E-02	2.57E-02	0.11	transporter	201780
SLC15A3	solute carrier family 15 member 3	6.41E-03	1.24E-02	0.16	transporter	51296
SLC15A4	solute carrier family 15 member 4	4.71E-04	4.58E-03	0.13	transporter	121260
SLC1A7	solute carrier family 1 member 7	3.06E-04	3.88E-03	0.11	transporter	6512
SLC20A2	solute carrier family 20 member 2	2.48E-02	2.94E-02	-0.08	transporter	6575
SLC24A1	solute carrier family 24 member 1	7.81E-02	8.00E-02	-0.07	transporter	9187
SLC25A4	solute carrier family 25 member 4	3.55E-04	4.10E-03	0.16	transporter	291
SLC2A10	solute carrier family 2 member 10	6.02E-03	1.20E-02	-0.09	transporter	81031
SLC2A3	solute carrier family 2 member 3	5.14E-03	1.09E-02	0.20	transporter	6515
SLC31A2	solute carrier family 31 member 2	6.05E-03	1.20E-02	0.16	transporter	1318
SLC35A1	solute carrier family 35 member A1	9.23E-03	1.48E-02	-0.10	transporter	10559
SLC43A2	solute carrier family 43 member 2	1.14E-03	5.66E-03	0.07	transporter	124935
SLC5A10	solute carrier family 5 member 10	6.77E-03	1.27E-02	0.08	transporter	125206
SLC7A5	solute carrier family 7 member 5	1.29E-02	1.84E-02	0.13	transporter	8140
SLCO1B3	solute carrier organic anion transporter family member 1B3	1.09E-01	1.10E-01	0.14	transporter	28234
SMARCA1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 1	3.51E-02	3.92E-02	-0.09	transcription regulator	6594
SMARCA2	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily a, member 2	1.02E-02	1.57E-02	-0.04	transcription regulator	6595
SMEK3P	protein phosphatase 4 regulatory subunit 3C	3.56E-02	3.95E-02	0.09	other	139420

SNAI3	snail family transcriptional repressor 3	4.91E-02	5.21E-02	0.11	transcription regulator	333929
SNTG2	syntrophin gamma 2	1.35E-02	1.91E-02	0.08	other	54221
SNX16	sorting nexin 16	3.20E-03	8.75E-03	0.22	transporter	64089
SOCS3	suppressor of cytokine signaling 3	7.88E-04	5.45E-03	0.11	phosphatase	9021
SOD2	superoxide dismutase 2	1.07E-04	2.88E-03	0.11	enzyme	6648
SORBS3	sorbin and SH3 domain containing 3	4.66E-03	1.07E-02	-0.08	other	10174
SP100	SP100 nuclear antigen	2.46E-02	2.93E-02	0.08	transcription regulator	6672
SP110	SP110 nuclear body protein	6.90E-03	1.29E-02	0.09	other	3431
SP3	Sp3 transcription factor	8.97E-05	2.88E-03	-0.06	transcription regulator	6670
SPARCL1	SPARC like 1	1.30E-03	6.12E-03	-0.31	other	8404
SPATS2	spermatogenesis associated serine rich 2	9.78E-03	1.54E-02	0.08	other	65244
SPI1	Spi-1 proto-oncogene	1.46E-03	6.41E-03	0.14	transcription regulator	6688
SPIB	Spi-B transcription factor	1.51E-02	2.06E-02	0.11	transcription regulator	6689
SPINK1	serine peptidase inhibitor, Kazal type 1	2.86E-02	3.30E-02	0.16	other	6690
SQRDL	sulfide quinone oxidoreductase	1.66E-02	2.18E-02	0.07	enzyme	58472
SREK1	splicing regulatory glutamic acid and lysine rich protein 1	1.34E-03	6.21E-03	-0.12	other	140890
SRGN	Serglycin	8.34E-04	5.46E-03	0.35	other	5552
ST13	ST13, Hsp70 interacting protein	7.93E-03	1.35E-02	-0.04	other	6767
STAG1	stromal antigen 1	5.35E-04	4.90E-03	-0.12	transcription regulator	10274
STAM2	signal transducing adaptor molecule 2	1.29E-02	1.84E-02	-0.03	other	10254
STARD7	StAR related lipid transfer domain containing 7	6.06E-03	1.20E-02	-0.05	other	56910

STRBP	spermatid perinuclear RNA binding protein	1.62E-02	2.14E-02	-0.07	other	55342
STXBP5L	syntaxin binding protein 5 like	1.47E-02	2.04E-02	0.15	other	9515
SULT1B1	sulfotransferase family 1B member 1	2.43E-02	2.90E-02	0.14	enzyme	27284
SUSD5	sushi domain containing 5	2.41E-03	8.14E-03	0.19	other	26032
SYNE2	spectrin repeat containing nuclear envelope protein 2	2.11E-03	7.64E-03	-0.09	other	23224
SYPL1	synaptophysin like 1	3.75E-03	9.46E-03	-0.08	transporter	6856
TAAR8	trace amine associated receptor 8	1.99E-02	2.49E-02	0.09	G-protein coupled receptor	83551
TAP1	transporter 1, ATP binding cassette subfamily B member	1.16E-03	5.69E-03	0.12	transporter	6890
TAP2	transporter 2, ATP binding cassette subfamily B member	2.06E-03	7.64E-03	0.08	transporter	6891
TBC1D2	TBC1 domain family member 2	1.13E-02	1.67E-02	0.06	other	55357
TBX10	T-box 10	4.76E-03	1.08E-02	0.13	transcription regulator	347853
TBXAS1	thromboxane A synthase 1	7.14E-04	5.30E-03	0.10	enzyme	6916
TCEAL2	transcription elongation factor A like 2	2.35E-02	2.85E-02	-0.11	other	140597
TEX101	testis expressed 101	6.54E-03	1.26E-02	0.05	other	83639
THADA	THADA, armadillo repeat containing	1.18E-02	1.73E-02	0.09	other	63892
THBD	Thrombomodulin	2.85E-02	3.29E-02	0.16	transmembrane receptor	7056
THEG	theg spermatid protein	5.78E-03	1.17E-02	0.15	other	51298
TIMP2	TIMP metallopeptidase inhibitor 2	4.66E-02	4.99E-02	0.11	other	7077
TJP1	tight junction protein 1	1.23E-04	2.88E-03	-0.06	other	7082
TLR2	toll like receptor 2	1.24E-04	2.88E-03	0.20	transmembrane receptor	7097
TLR5	toll like receptor 5	8.21E-03	1.38E-02	-0.06	transmembrane receptor	7100

TLR7	toll like receptor 7	1.26E-04	2.88E-03	0.24	transmembrane receptor	51284
TLR8	toll like receptor 8	3.11E-04	3.88E-03	0.18	transmembrane receptor	51311
TMEM131	transmembrane protein 131	5.93E-04	4.98E-03	-0.08	other	23505
TMEM132D	transmembrane protein 132D	1.01E-03	5.46E-03	0.11	other	121256
TMEM140	transmembrane protein 140	4.51E-03	1.05E-02	0.14	other	55281
TMEM149	IGF like family receptor 1	3.10E-03	8.75E-03	0.10	other	79713
TMEM150C	transmembrane protein 150C	6.07E-04	4.98E-03	-0.12	ion channel	441027
TMEM218	transmembrane protein 218	3.08E-03	8.75E-03	-0.11	other	219854
TMEM30B	transmembrane protein 30B	1.57E-02	2.11E-02	-0.06	transporter	161291
TMEM5	ribitol xylosyltransferase 1	2.49E-03	8.14E-03	-0.12	enzyme	10329
TMF1	TATA element modulatory factor 1	2.08E-05	1.71E-03	-0.12	transcription regulator	7110
TNFAIP3	TNF alpha induced protein 3	1.62E-03	6.84E-03	0.19	enzyme	7128
TNFAIP6	TNF alpha induced protein 6	5.46E-03	1.13E-02	0.28	other	7130
TNFRSF10A	TNF receptor superfamily member 10a	1.40E-02	1.96E-02	0.07	transmembrane receptor	8797
TNFRSF11B	TNF receptor superfamily member 11b	6.09E-05	2.70E-03	0.18	transmembrane receptor	4982
TNFSF13B	TNF superfamily member 13b	3.23E-04	3.90E-03	0.30	cytokine	10673
TNIP3	TNFAIP3 interacting protein 3	1.99E-03	7.53E-03	0.28	other	79931
TNRC6B	trinucleotide repeat containing 6B	4.48E-03	1.05E-02	-0.08	other	23112
TOP1P2	DNA topoisomerase I pseudogene 2	1.40E-02	1.96E-02	0.06	other	7152
TOP2B	DNA topoisomerase II beta	5.82E-04	4.98E-03	-0.05	enzyme	7155
TP63	tumor protein p63	3.33E-03	8.96E-03	-0.34	transcription regulator	8626

TPRG1	tumor protein p63 regulated 1	4.44E-02	4.79E-02	-0.15	other	285386
TRAF2	TNF receptor associated factor 2	7.54E-03	1.33E-02	0.08	enzyme	7186
TRAF4	TNF receptor associated factor 4	8.24E-04	5.46E-03	0.06	other	9618
TREM1	triggering receptor expressed on myeloid cells 1	1.94E-02	2.45E-02	0.26	transmembrane receptor	54210
TRIB1	tribbles pseudokinase 1	1.02E-03	5.46E-03	0.13	kinase	10221
TRIM37	tripartite motif containing 37	8.24E-04	5.46E-03	-0.17	enzyme	4591
TRIM39	tripartite motif containing 39	5.14E-03	1.09E-02	-0.08	other	56658
TRIM66	tripartite motif containing 66	7.57E-03	1.33E-02	-0.15	transcription regulator	9866
TRIM78P	TRIM78P	5.54E-04	4.98E-03	0.25	unknown	117852
TSHZ2	teashirt zinc finger homeobox 2	1.80E-03	7.19E-03	-0.08	other	128553
TSPAN12	tetraspanin 12	1.10E-01	1.12E-01	-0.11	other	23554
TSPYL4	TSPY like 4	1.21E-02	1.75E-02	-0.10	other	23270
TTC28	tetratricopeptide repeat domain 28	1.54E-04	2.88E-03	-0.29	other	23331
TTK	TTK protein kinase	1.63E-04	2.88E-03	0.21	kinase	7272
TULP2	tubby like protein 2	2.78E-03	8.64E-03	0.13	enzyme	7288
TXNDC3	NME/NM23 family member 8	4.98E-03	1.09E-02	0.13	kinase	51314
TYK2	tyrosine kinase 2	1.52E-02	2.07E-02	0.05	kinase	7297
TYMP	thymidine phosphorylase	3.33E-04	3.96E-03	0.16	growth factor	1890
UBASH3B	ubiquitin associated and SH3 domain containing B	2.95E-04	3.88E-03	0.12	enzyme	84959
UBE3A	ubiquitin protein ligase E3A	4.67E-02	5.00E-02	-0.04	enzyme	7337
USH2A	Usherin	2.82E-03	8.69E-03	0.13	other	7399

WARS	tryptophanyl-tRNA synthetase	5.38E-03	1.12E-02	0.14	enzyme	7453
VASH1	vasohibin 1	2.87E-03	8.69E-03	0.09	other	22846
WDR35	WD repeat domain 35	6.34E-04	4.98E-03	-0.13	other	57539
WLS	wntless Wnt ligand secretion mediator	8.80E-03	1.43E-02	-0.07	other	79971
VNN2	vanin 2	3.12E-04	3.88E-03	0.18	enzyme	8875
VPS37B	VPS37B, ESCRT-I subunit	1.85E-02	2.35E-02	0.08	other	79720
VSIG4	V-set and immunoglobulin domain containing 4	4.23E-02	4.58E-02	0.20	other	11326
ZADH2	zinc binding alcohol dehydrogenase domain containing 2	6.17E-04	4.98E-03	-0.10	enzyme	284273
ZC3H12A	zinc finger CCCH-type containing 12A	3.97E-04	4.40E-03	0.18	enzyme	80149
ZDHHC7	zinc finger DHHC-type containing 7	5.03E-03	1.09E-02	-0.05	enzyme	55625
ZEB2	zinc finger E-box binding homeobox 2	6.67E-03	1.27E-02	0.32	transcription regulator	9839
ZFP106	zinc finger protein 106	2.52E-02	2.97E-02	-0.05	other	64397
ZFP36	ZFP36 ring finger protein	4.93E-05	2.70E-03	0.11	transcription regulator	7538
ZNF132	zinc finger protein 132	8.75E-03	1.43E-02	-0.18	transcription regulator	7691
ZNF200	zinc finger protein 200	7.66E-03	1.33E-02	0.23	other	7752
ZNF22	zinc finger protein 22	1.20E-02	1.75E-02	-0.08	other	7570
ZNF234	zinc finger protein 234	4.28E-04	4.43E-03	-0.31	other	10780
ZNF251	zinc finger protein 251	2.01E-03	7.56E-03	-0.14	other	90987
ZNF253	zinc finger protein 253	2.42E-03	8.14E-03	-0.04	transcription regulator	56242
ZNF267	zinc finger protein 267	8.15E-03	1.38E-02	0.10	other	10308
ZNF345	zinc finger protein 345	1.22E-04	2.88E-03	-0.27	transcription regulator	25850

ZNF383	zinc finger protein 383	2.42E-02	2.90E-02	-0.10	other	163087
ZNF436	zinc finger protein 436	3.69E-02	4.08E-02	-0.11	other	80818
ZNF503	zinc finger protein 503	7.60E-04	5.39E-03	-0.17	other	84858
ZNF514	zinc finger protein 514	1.35E-04	2.88E-03	-0.15	other	84874
ZNF562	zinc finger protein 562	7.32E-04	5.30E-03	-0.08	other	54811
ZNF645	zinc finger protein 645	1.15E-02	1.69E-02	0.11	other	158506
ZNF652	zinc finger protein 652	4.25E-04	4.43E-03	-0.11	other	22834
ZNF703	zinc finger protein 703	2.49E-03	8.14E-03	-0.08	other	80139
ZNF766	zinc finger protein 766	1.89E-02	2.39E-02	-0.09	other	90321
ZNF780B	zinc finger protein 780B	3.10E-02	3.53E-02	-0.21	other	163131
ZNF789	zinc finger protein 789	3.86E-03	9.58E-03	-0.14	other	285989
ZNF826P	zinc finger protein 826, pseudogene	1.58E-02	2.11E-02	-0.07	other	664701
ZPLD1	zona pellucida like domain containing 1	7.69E-02	7.91E-02	0.07	other	131368

Table E4. List of 79 genes identified in the IL-17-high group associated with psoriasis. The list of 797 DEGs list was analysed by IPA Diseases & Functions enrichment analysis. Of all diseases and function annotations in IPA, "psoriasis" came out with the most significant over representation (p =6.67e-17) and an overlap of 79 genes.

Genes in 797 list HGNC Symbol	Entrez Gene Name	DEGs p-value	DEGsExpr False Discovery Rate (q-value)	DEGs Expr Fold Change (positive value indicate overexpression in IL-17-high)
IDO1	indoleamine 2,3-dioxygenase 1	1.40E-05	2.47E-04	3.286
S100A8	S100 calcium binding protein A8	4.33E-04	9.24E-04	2.834
FOS	Fos proto-oncogene, AP-1 transcription factor subunit	2.34E-05	2.88E-04	2.394
FCGR3A/FCGR3B	Fc fragment of IgG receptor IIIa	1.11E-03	1.61E-03	2.29
CXCL8	C-X-C motif chemokine ligand 8	1.93E-05	2.75E-04	2.22
G0S2	G0/G1 switch 2	3.48E-04	8.39E-04	2.204
IL1B	interleukin 1 beta	3.88E-04	8.79E-04	2.2
AQP9	aquaporin 9	3.14E-04	8.05E-04	2.186
APOBEC3A	apolipoprotein B mRNA editing enzyme catalytic subunit 3A	1.92E-04	6.45E-04	2.127
ADM	Adrenomedullin	4.06E-06	1.30E-04	2.085
DEFB4A/DEFB4B	defensin beta 4A	1.95E-04	6.49E-04	2.036
CXCL10	C-X-C motif chemokine ligand 10	1.26E-04	5.34E-04	1.982
S100A9	S100 calcium binding protein A9	1.53E-04	5.77E-04	1.977
IFI44L	interferon induced protein 44 like	5.97E-04	1.13E-03	1.966
IFITM1	interferon induced transmembrane protein 1	8.76E-05	4.69E-04	1.941

Genes in 797 list HGNC Symbol	Entrez Gene Name	DEGs p-value	DEGsExpr False Discovery Rate (q-value)	DEGs Expr Fold Change (positive value indicate overexpression in IL-17-high)
DUSP1	dual specificity phosphatase 1	2.13E-06	1.08E-04	1.861
TLR2	toll like receptor 2	3.85E-06	1.30E-04	1.843
NAMPT	nicotinamide phosphoribosyltransferase	2.30E-06	1.08E-04	1.826
PTGS2	prostaglandin-endoperoxide synthase 2	1.14E-04	5.13E-04	1.803
GBP2	guanylate binding protein 2	1.15E-04	5.13E-04	1.8
CCL20	C-C motif chemokine ligand 20	4.42E-05	3.73E-04	1.791
ICAM1	intercellular adhesion molecule 1	3.12E-05	3.12E-04	1.79
RARRES1	retinoic acid receptor responder 1	1.82E-04	6.35E-04	1.78
CXCL9	C-X-C motif chemokine ligand 9	1.08E-04	5.12E-04	1.767
PI3	peptidase inhibitor 3	1.75E-03	2.05E-03	1.743
TNFAIP3	TNF alpha induced protein 3	3.53E-05	3.35E-04	1.718
IFI30	IFI30, lysosomal thiol reductase	1.26E-03	1.73E-03	1.701
TNFAIP6	TNF alpha induced protein 6	2.10E-04	6.80E-04	1.687
EPSTI1	epithelial stromal interaction 1	1.94E-04	6.48E-04	1.686
ZFP36	ZFP36 ring finger protein	3.83E-07	4.39E-05	1.674
FOSL1	FOS like 1, AP-1 transcription factor subunit	5.97E-05	4.24E-04	1.666
CXCL3	C-X-C motif chemokine ligand 3	1.32E-09	1.05E-06	1.631
PLAU	plasminogen activator, urokinase	6.90E-05	4.24E-04	1.621

Genes in 797 list HGNC Symbol	Entrez Gene Name	DEGs p-value	DEGsExpr False Discovery Rate (q-value)	DEGs Expr Fold Change (positive value indicate overexpression in IL-17-high)
ADAMDEC1	ADAM like decysin 1	1.37E-07	3.31E-05	1.586
OAS3	2'-5'-oligoadenylate synthetase 3	7.91E-04	1.33E-03	1.558
JUNB	JunB proto-oncogene, AP-1 transcription factor subunit	1.36E-04	5.50E-04	1.533
IFIT3	interferon induced protein with tetratricopeptide repeats 3	5.33E-04	1.08E-03	1.53
CXCL11	C-X-C motif chemokine ligand 11	4.60E-06	1.33E-04	1.528
PDZK1IP1	PDZK1 interacting protein 1	2.75E-04	7.60E-04	1.511
THBD	Thrombomodulin	1.45E-03	1.86E-03	1.498
NR4A2	nuclear receptor subfamily 4 group A member 2	1.07E-03	1.57E-03	1.496
MX1	MX dynamin like GTPase 1	7.75E-04	1.33E-03	1.494
SOD2	superoxide dismutase 2	1.50E-04	5.75E-04	1.493
ID1	inhibitor of DNA binding 1, HLH protein	6.22E-04	1.15E-03	1.48
KYNU	Kynureninase	1.38E-04	5.50E-04	1.455
C3AR1	complement C3a receptor 1	3.12E-04	8.03E-04	1.453
NFIL3	nuclear factor, interleukin 3 regulated	5.04E-04	1.03E-03	1.44
TIMP2	TIMP metallopeptidase inhibitor 2	5.49E-04	1.08E-03	1.431
IRF7	interferon regulatory factor 7	2.05E-05	2.77E-04	1.417
LILRB1	leukocyte immunoglobulin like receptor B1	2.60E-04	7.39E-04	1.402
APOE	apolipoprotein E	1.82E-03	2.09E-03	1.401

Genes in 797 list HGNC Symbol	Entrez Gene Name	DEGs p-value	DEGsExpr False Discovery Rate (q-value)	DEGs Expr Fold Change (positive value indicate overexpression in IL-17-high)
PTPRC	protein tyrosine phosphatase, receptor type C	7.42E-04	1.30E-03	1.401
PPIF	peptidylprolyl isomerase F	1.54E-04	5.77E-04	1.382
IER2	immediate early response 2	5.21E-04	1.06E-03	1.378
NMI	N-myc and STAT interactor	2.45E-04	7.20E-04	1.358
ADGRE5	adhesion G protein-coupled receptor E5	2.91E-04	7.80E-04	1.354
IFNGR2	interferon gamma receptor 2	3.68E-04	8.53E-04	1.321
SOCS3	suppressor of cytokine signaling 3	7.08E-05	4.24E-04	1.296
IL6	interleukin 6	2.69E-05	3.00E-04	1.292
KRT79	keratin 79	3.21E-04	8.13E-04	1.281
PTP4A1	protein tyrosine phosphatase type IVA, member 1	1.36E-03	1.79E-03	1.271
TYMP	thymidine phosphorylase	9.08E-04	1.43E-03	1.254
CASP4	caspase 4	1.46E-03	1.86E-03	1.252
FGF7	fibroblast growth factor 7	5.00E-04	1.02E-03	1.25
ALOX12B	arachidonate 12-lipoxygenase, 12R type	2.39E-04	7.17E-04	1.171
ABCA8	ATP binding cassette subfamily A member 8	7.35E-04	1.29E-03	1.17
EIF5A	eukaryotic translation initiation factor 5A	2.41E-03	2.41E-03	1.145
IL20	interleukin 20	5.98E-04	1.13E-03	1.13
CTNNB1	catenin beta 1	1.99E-03	2.17E-03	-1.166

Genes in 797 list HGNC Symbol	Entrez Gene Name	DEGs p-value	DEGsExpr False Discovery Rate (q-value)	DEGs Expr Fold Change (positive value indicate overexpression in IL-17-high)
TLR5	toll like receptor 5	1.38E-03	1.81E-03	-1.172
MEIS3P1	Meis homeobox 3 pseudogene 1	1.28E-03	1.73E-03	-1.178
RORC	RAR related orphan receptor C (ROR gamma)	1.83E-03	2.09E-03	-1.209
PDLIM4	PDZ and LIM domain 4	2.49E-04	7.20E-04	-1.236
HIBADH	3-hydroxyisobutyrate dehydrogenase	1.71E-04	6.18E-04	-1.239
WLS	wntless Wnt ligand secretion mediator	6.58E-05	4.24E-04	-1.265
DDHD2	DDHD domain containing 2	2.32E-04	7.07E-04	-1.298
NR1D2	nuclear receptor subfamily 1 group D member 2	2.47E-04	7.20E-04	-1.313
KRT5	keratin 5	5.39E-04	1.08E-03	-1.363
IL33	interleukin 33	3.76E-05	3.36E-04	-1.404

Table E5. Logistic regression of gene expression in blood associated with the IL-17-high patient cluster derived from gene expression in the airways. Using logistic regression, the top 10 blood mRNAs which distinguished the IL-17-high from other study participants were identified (in ascending order of FDR-corrected p-value): alpha kinase 2, leucine rich transmembrane and O-methyltransferase domain containing, ankyrin repeat domain 57 pseudogene, peptidase inhibitor 3, desmoplakin, calneuron 1, signal peptidase complex subunit 2, peptidase inhibitor 3, VPS53 GARP complex subunit, olfactory receptor family 5 subfamily K member 1.

Gene	Description	p-value	FDR q-value	Fold change
ALPK2	alpha kinase 2	2.6E-05	0.56	0.10
LRTOMT	leucine rich transmembrane and O-methyltransferase domain containing	3.1E-05	0.56	0.04
LOC389834	ankyrin repeat domain 57 pseudogene	1.8E-04	1.00	-0.15
PI3	peptidase inhibitor 3	2.2E-04	1.00	0.04
DSP	Desmoplakin	2.5E-04	1.00	-0.15
CALN1	calneuron 1	2.7E-04	1.00	0.05
SPCS2	signal peptidase complex subunit 2	2.8E-04	1.00	0.02
PI3	peptidase inhibitor 3	3.6E-04	1.00	0.04
VPS53	VPS53, GARP complex subunit	7.2E-04	1.00	0.04
OR5K1	olfactory receptor family 5 subfamily K member 1	7.5E-04	1.00	-0.04

Table E6. Logistic regression of urinary eicosanoids associated with the IL-17-high patient cluster derived from gene expression in the airways. Using logistic regression, the top 10 urinary eicosanoids which distinguished the IL-17-high from other study participants were identified (in ascending order of FDR-corrected p-value): 11-dehydroTXB2, PGE2, tetranorPGEM, 2,3-dinor-8-isoPGF2a, LTE4, tetranorPGDM, 2,3-dinor-11-B-PGF2a, 2,3-dinorTXB2, 8,12-iso-iPF2a-VI, PGF2a-Norm, 8-isoPGF2a.

Eicosanoid	p-value	FDR q-value	Fold change
11-dehydroTXB2	0.05	0.56	0.60
PGE2	0.40	0.90	-0.21
tetranorPGEM	0.18	0.90	-0.21
2,3-dinor-8-isoPGF2a	0.41	0.90	-0.11
LTE4	0.34	0.90	0.63
tetranorPGDM	0.76	0.91	0.05
2,3-dinor-11-B-PGF2a	0.77	0.91	-0.04
2,3-dinorTXB2	0.57	0.91	0.09
8,12-iso-iPF2a-VI	0.83	0.91	-0.03
PGF2a-Norm	0.79	0.91	0.03
8-isoPGF2a	0.97	0.97	0.00

Declaration of previous reports of data presented in this manuscript.

Transcriptomic data from microarray analysis of whole blood have also been reported previously but have not been subjected to specific analysis of T17 and T2 cytokines(4). Results immunohistochemistry analysis have been presented previously(8) but have not been associated with the IL-17-high phenotype.

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FIGURE LEGENDS

Figure E1. Increased expression of Dipeptidyl peptidase-4 (DPP4) mRNA in brushings from asthma patients in the IL-13- high cluster when compared to IL-13/IL-17-low or IL-17-high group (p=0.0003 and p=0.002, respectively). DPP4 mRNA expression was lower in the IL-17-high group as compared to a group comprising all other asthma and healthy subjects, for which brushing were available (p=1.02e-7). Boxes indicate 25 and 75 percentiles and dotted line indicate mean values. Data shown are not adjusted for age, gender and site code. Y-axis values represent relative expression and are log2 transformed, mean-centred and sigma-normalized.

Figure E2. A) Alpha diversity (expressed as Shannon diversity index, based on NGS data) in the IL-17-high group (n=6) and in the combined group of all severe, mild to moderate asthmatic and healthy participants for which sputum microbiome data were available (n=125). B) Inverse correlations between sputum neutrophil counts and the alpha diversity index in the IL-17-high group.