

Supplementary Tables

Table S1: Asthma seed genes. The seed genes were compiled from the following sources:

| Sources | Genes | References (PubMed ids) |
|---|---|--|
| Literature, as compiled in Vercelli et al 2008 | FCER1B,HLA-DRB1,HLA-DQB1,HLA-DPB1,STAT6,NR3C1,GFRA2,GATA2,SH2B3,IKZF2,GSTM1,GSTP1,GSTT1,FLG,IL10,IL18,CTLA4,HAVCR1,GPRA,NAT2,NOS1,CMA1,ACE,TBXA2R,CTA,SCGB1A1 | 18301422 |
| Chemokines pathway-Drug target-genes | CCL17,CCL22,CCL2,CD200,CX3CR1,CXCR1,CXCR2,IL8,CCL11,CCL11,TNFRSF4,TNFSF4,ICOS,C5CHRNA3TRPA1TRPV1HRH4 | |
| Co-stim pathways-Drug target-genes | TNFRSF4,TNFSF4,ICOS | |
| Complement pathways-Drug target-genes | C5 | |
| GPCR-ligand inflammatory mediators -Drug target-genes | CHRNA3,TRPA1,TRPV1,HRH4,PTGDS,GPR44,HNMT,PTGER2 | |
| Growth factors-Drug target-genes | F2RL1,FGF2,PDGFB | |
| Inflammatory signaling -Drug target-genes | CSF2,IKBKB,NGF,PDE4,PIK3CA,STAT1,MAPK14,MAPK8,MMP12,SYK,IRAK3,OSM,TNFA | |
| Leukotriene pathway-Drug target-genes | ALOX5AP,LTB4R2,LTA4H,LTC4S,ALOX5,IFNB1,TLR7,TLR3,TLR9,TLR4 | |
| Pathogen response -Drug target-genes | IFNB1,TLR7,TLR3,TLR9,TLR4 | |
| Proteases-Drug target-genes | MMP9,TPSAB1,SPINK5,ELANE | |
| Structural Genes/Mucosal Epithelial pathways -Drug target-genes | CTNNA3,MUC7,TGFB1,CLCA1,MUC5AC | |
| Th17-Drug target-genes | IL17,IL23A,IL6 | |
| Th2-Drug target-genes | IL13RA2,IL4,IL33,IL4R,IL9,IL25 | |
| Drug target-genes | ADORA2A,SRC,CD28,IL21,IL22,EGF,CD40 | |
| GWAS-Genes | | |
| Asthma | EDN1,GSDMA,GSDMB,HLA-DQA1,IL18R1,IL2RB,MAVS,MYB,PDE11A,PDE4D,RAD50,RORA,SCG3,SLC22A5,SMAD3,VDR, | 21103062, 20860503, 20622879, 20159242, 20032318,19714205,21103062 |
| Childhood Asthma | CRB1,DENND1B,CHCHD9,TLE4,ADAM33,CCL5 | 62 |
| Plasma eosinophil count | IL1RL1,IL5,TSLP | 19198610 |
| YKL-40 levels | CHI3L1 | 18403759 |

Table S2: Gene expression data. Sources of the differential expression gene sets used for the bioinformatics validation of the DIAMOND module.

| Data | Name | Title of study | Differentially expressed genes | Analysis type | adj.p-value | reference | Year |
|----------|-------|---|----------------------------------|-----------------------|--|---|------|
| GSE470 | AEF | Asthma exacerbatory factors [Homo sapiens] | 111 genes | Data from paper | | Am J Respir Cell Mol Biol. 2008 ,38:324-36 | 2003 |
| GSE473 | PHL | PGA Human CD4+ Lymphocytes | 361 genes | Data from paper | | Am J Respir Cell Mol Biol. 2008 ,38:324-36 | 2003 |
| GSE3004 | ACA | Effects of allergen challenge on airway epithelial cell gene expression | 63 genes | Data from paper | p<0.01 | Am J Respir Cell Mol Biol. 2008 ,38:324-36. | 2005 |
| GSE16032 | SPAEC | Gene expression data from severe asthmatic children PBMC profiles during acute exacerbation versus convalescence [Homo sapiens] | 135 genes | Linear models (Limma) | p<0.05 (Benjamini & Hochberg (False discovery rate)) | | 2009 |
| GSE18965 | FPSDR | Decreased fibronectin production significantly contributes to dysregulated repair of asthmatic epithelium | 1487 genes | Data from paper | | Am J Respir Cell Mol Biol. 2008 ,38:324-36 | 2010 |
| GSE31773 | PSA | Comparison of mRNA expression in circulating T-cells from patients with severe asthma [Homo sapiens] | 554 genes | Linear models (Limma) | p<0.02 (Benjamini & Hochberg (False discovery rate)) | | 2011 |
| GSE4302 | GWPAE | Genome-Wide Profiling of Airway Epithelial Cells in Asthmatics, Smokers and Healthy Controls | 187 genes | data from paper | | Proc Natl Acad Sci U S A 2007, 104:15858-63 | 2007 |
| GSE23611 | | | | | | | |
| GSE2125 | IAM | isolated alveolar macrophages [Homo sapiens] | 1580 (smokers)/1998 (Nonsmokers) | Linear models (Limma) | p<0.02 (Benjamini & Hochberg (False discovery rate)) | | 2003 |
| CSPC | CSPC | | 452 genes | Data from paper | p<0.05 | Am J Respir Cell Mol Biol. 2008 ,38:324-36 | 2000 |

Table S3: Asthma-specific pathways. Thirty-five asthma related pathways identified by the GeneGO Meta-Core software and their total number of genes.

| GeneGo pathways | Number of genes |
|--|-----------------|
| IFN-gamma and Th2 cytokines-induced inflammatory signaling in normal and asthmatic airway epithelium | 173 |
| IL-17 and IL-17F-induced inflammatory signaling in normal and asthmatic airway epithelium | 120 |
| Interleukins-induced inflammatory signaling in normal and asthmatic airway epithelium | 136 |
| Lysophospholipid mediators-induced inflammatory signaling in normal and asthmatic airway epithelium | 533 |
| Proteases and EGFR-induced mucin synthesis in normal and asthmatic epithelium | 345 |
| TNF-alpha-induced inflammatory signaling in normal and asthmatic airway epithelium | 259 |
| Hypertrophy of asthmatic airway smooth muscle cells | 238 |
| TGF-beta 1-mediated induction of EMT in normal and asthmatic airway epithelium | 245 |
| Probable BMP4-mediated induction of EMT in airway epithelium | 113 |
| Disruption of apoptosis, proliferation and shedding of epithelial cells in asthma | 317 |
| Disruption of epithelial layer restitution in asthma | 171 |
| Induction of mucin secretion in airway goblet cells by purinergic receptors | 342 |
| Inflammatory factors-induced expression of mucins in normal and asthmatic epithelium | 210 |
| Prostaglandins and leukotrienes-mediated induction of expression of mucins in normal and asthmatic epithelium | 225 |
| Retinoic acid maintains mucocilliary differentiation and mucins expression in normal and asthmatic airway epithelium | 141 |
| Th2-cytokines-induced expression of mucins in asthma | 194 |
| Th2-cytokines-induced mucous metaplasia in asthma | 165 |
| MAPK-mediated proliferation of normal and asthmatic smooth muscle cells | 247 |
| MAPK-independent pathway of regulation proliferation of normal and asthmatic smooth muscle cells | 333 |
| Extracellular matrix-regulated proliferation of airway smooth muscle cells in asthma | 179 |
| Cytokine production by Th17 cells | 199 |
| Immune response_Th1 and Th2 cell differentiation | 213 |
| Immune response_IL-17 signaling pathways | 350 |
| Immune response_PGE2 signaling in immune response | 196 |
| Immune response_NF-AT signaling and leukocyte interactions | 337 |
| Immune response_Histamine signaling in dendritic cells | 288 |
| Immune response_TREM1 signaling pathway | 330 |
| Immune response_MIF in innate immunity response | 204 |
| Development_Regulation of epithelial-to-mesenchymal transition (EMT) | 318 |
| Immune response_Histamine H1 receptor signaling in immune response | 281 |
| Normal and pathological TGF-beta-mediated regulation of cell proliferation | 158 |
| Immune response_CCR3 signaling in eosinophils | 381 |
| Immune response_IL-15 signaling | 351 |
| Immune response_IL-13 signaling via JAK-STAT | 132 |
| Immune response_IL-4 signaling pathway | 319 |

Table S4: Comorbidity analysis. List of all diseases with increased comorbidity with asthma and the number of their associated genes. The *p*-value (Fisher's exact test) gives the enrichment of the 350 DIAMOnD genes with the disease-associated genes

| Comorbid disease to asthma | number of all disease genes in interactome | Number of found genes in 350 | P-value | RR |
|---|--|------------------------------|----------|-------------|
| Disorders involving the immune mechanism | 45 | 7 | 3.50E-04 | 2.141628613 |
| Congenital anomalies of the integument, Ichthyosis congenita | 71 | 6 | 2.00E-02 | 2.181108365 |
| Diseases of white blood cells | 20 | 4 | 2.70E-03 | 1.951404493 |
| Disorders of lipid metabolism, Lipodystrophy | 5 | 3 | 2.60E-04 | 2.137210606 |
| Other endocrine disorders | 10 | 3 | 2.80E-03 | 1.551643308 |
| Disorders involving the immune mechanism, Combined immunity deficiency | 17 | 3 | 1.30E-02 | 2.759940969 |
| Overweight, obesity and other hyperalimantation | 26 | 3 | 4.20E-02 | 2.119876087 |
| Cardiomyopathy, Other primary cardiomyopathies | 31 | 2 | 2.40E-01 | 1.620611052 |
| Cardiomyopathy | 32 | 2 | 2.50E-01 | 1.607315797 |
| Chronic airway obstruction, not elsewhere classified | 1 | 1 | 3.00E-02 | 2.422866403 |
| Contact dermatitis and other eczema | 1 | 1 | 3.00E-02 | 1.646203094 |
| Diseases of white blood cells, Eosinophilia | 1 | 1 | 3.00E-02 | 4.554252927 |
| Disorders involving the immune mechanism, Hypogammaglobulinemia, unspecified | 1 | 1 | 3.00E-02 | 4.19521066 |
| Poisoning by water, mineral, and uric acid metabolism drugs | 1 | 1 | 3.00E-02 | 8.095143306 |
| Strabismus and other disorders of binocular eye movements, Other and unspecified heterotropia | 1 | 1 | 3.00E-02 | 2.013630401 |
| Other diseases of lung, Other diseases of lung, not elsewhere classified | 2 | 1 | 5.90E-02 | 2.589269223 |
| Other disorders of thyroid, Other specified disorders of thyroid | 2 | 1 | 5.90E-02 | 1.631167268 |
| Other diseases of lung | 3 | 1 | 8.70E-02 | 2.589269223 |
| Anxiety, dissociative and somatoform disorders | 4 | 1 | 1.10E-01 | 2.331397137 |
| Diseases of white blood cells, Functional disorders of polymorphonuclear neutrophils | 4 | 1 | 1.10E-01 | 1.951404493 |
| Lipoma, Lipoma, unspecified site | 4 | 1 | 1.10E-01 | 1.67355976 |
| Migraine, Migraine, unspecified | 4 | 1 | 1.10E-01 | 1.667642309 |
| Other disorders of bone and cartilage, Other and unspecified disorders of bone and cartilage | 4 | 1 | 1.10E-01 | 1.884875851 |
| Migraine | 5 | 1 | 1.40E-01 | 1.667642309 |
| Postinflammatory pulmonary fibrosis | 6 | 1 | 1.70E-01 | 2.229826227 |
| Disorders of tooth development and eruption | 10 | 1 | 2.60E-01 | 1.652392976 |
| Other disorders of bone and cartilage | 16 | 1 | 3.90E-01 | 2.110697713 |

Table S6: GWAS analysis. DIAMOND genes with p -values < 0.05 in both Gabriel and EVE GWAS data.

| Gene | SNP_GABRIEL | P-value | SNP_EVE | P-value2 |
|----------|-------------|----------|------------|----------|
| IL5 | rs2069812 | 0.0035 | rs736801 | 0.0015 |
| IL4R | rs1805012 | 0.00058 | rs2107357 | 0.0045 |
| CD200 | rs4682103 | 0.000086 | rs2895395 | 0.0046 |
| HLA-G | rs2517826 | 0.01 | rs3900925 | 0.0012 |
| ICOS | rs11571312 | 0.00068 | rs2081725 | 0.0013 |
| HLA-DRB1 | rs3129763 | 2.28E-05 | rs2516049 | 0.0038 |
| BCL2 | rs2849382 | 0.0042 | rs4987768 | 0.00061 |
| PLA2G4A | rs6665890 | 0.01 | rs642508 | 0.0013 |
| RARA | rs2715556 | 0.002 | rs2715553 | 0.0033 |
| PPARA | rs11090910 | 0.01 | rs6008197 | 0.0001 |
| IRS2 | rs12584136 | 0.0091 | rs9515116 | 0.001 |
| IRF1 | rs12521868 | 6.29E-07 | rs13164856 | 0.00025 |
| PAK1 | rs7109180 | 0.00025 | rs10899379 | 0.01 |
| SMAD4 | s7244227 | 0.012 | rs17663887 | 0.025 |
| TOP2A | rs2715556 | 0.0028 | rs2715553 | 0.0033 |
| CIITA | rs17229044 | 0.0003 | rs3743976 | 0.002 |
| CAMK2A | rs1432833 | 0.00042 | rs4704525 | 0.0025 |
| RET | rs752978 | 0.015 | rs2251674 | 0.0018 |
| DOK1 | rs759075 | 0.0013 | rs10210396 | 0.24 |

Table S8: Enrichment of steroid response genes (differentially expressed) in asthma disease module exclusive of GCR pathway genes.

| Data set | Total DE genes | In Module | Outside Module | p-value | DIAMOnD genes | p-value-D |
|-----------------|-----------------------|------------------|-----------------------|----------------|----------------------|------------------|
| Normal DE genes | 628 | 47 | 424 | 7.64E-09 | 37 | 5.06E-08 |
| Asthma DE genes | 562 | 42 | 377 | 4.40E-08 | 33 | 2.65E-07 |

| Normal | | | | Asthmatic | | | |
|---|-------------|------------|-----------------|---|-------------|------------|-----------------|
| Pathway | Fold change | raw-pvalue | Pathway-p-value | Pathway | Fold change | raw-pvalue | Pathway-p-value |
| BIOCARTA_IGF1_PATHWAY | | | 0.0013 | REACTOME_GAB1_SIGNALOSOME | | | 0.006 |
| IGF1R | 1.5038 | 0.0093 | | PAG1 | 1.942 | 0.0022 | |
| PIK3R1 | 3.6779 | 1.05E-06 | | GAB1 | 1.683 | 0.0055 | |
| RAF1 | 1.5218 | 0.0167 | | PIK3R1 | 3.928 | 0.0008 | |
| RASA1 | -1.681 | 3.01E-05 | | BIOCARTA_EGF_PATHWAY | | | 0.024 |
| JUN | -2.0269 | 2.63E-05 | | JUN | -2.395 | 0.0094 | |
| BIOCARTA_CDMAC_PATHWAY | | | 0.0033 | JAK1 | 1.551 | 0.0048 | |
| JUN | -2.0269 | 2.63E-05 | | PIK3R1 | 3.928 | 0.0008 | |
| RAF1 | 1.5218 | 0.0167 | | RASA1 | -1.554 | 0.0123 | |
| NFKBIA | 2.1694 | 4.15E-05 | | BIOCARTA_NGF_PATHWAY | | | 0.025 |
| MYC | 1.5295 | 0.0498 | | JUN | -2.395 | 0.0094 | |
| BIOCARTA_NGF_PATHWAY | | | 0.0051 | NGF | -3.092 | 0.0186 | |
| RAF1 | 1.5218 | 0.0167 | | PIK3R1 | 3.928 | 0.0008 | |
| JUN | -2.0269 | 2.63E-05 | | BIOCARTA_PDGF_PATHWAY | | | 0.025 |
| NGF | -3.2549 | 4.37E-06 | | JUN | -2.395 | 0.0094 | |
| PIK3R1 | 3.6779 | 1.05E-06 | | JAK1 | 1.551 | 0.0048 | |
| BIOCARTA_EGF_PATHWAY | | | 0.0075 | PIK3R1 | 3.928 | 0.0008 | |
| RAF1 | 1.5218 | 0.0167 | | RASA1 | -1.554 | 0.0123 | |
| JUN | -2.0269 | 2.63E-05 | | BIOCARTA_IGF1_PATHWAY | | | 0.038 |
| JAK1 | 1.516 | 0.0007 | | JUN | -2.395 | 0.0094 | |
| PIK3R1 | 3.6779 | 1.05E-06 | | PIK3R1 | 3.928 | 0.0008 | |
| RASA1 | -1.681 | 3.01E-05 | | RASA1 | -1.554 | 0.0123 | |
| REACTOME_GAB1_SIGNALOSOME | | | 0.0085 | BIOCARTA_INSULIN_PATHWAY | | | 0.043 |
| PAG1 | 2.2155 | 9.58E-05 | | JUN | -2.395 | 0.0094 | |
| GAB1 | 1.8742 | 0.0083 | | PIK3R1 | 3.928 | 0.0008 | |
| PIK3R1 | 3.6779 | 1.05E-06 | | RASA1 | -1.554 | 0.0123 | |
| BIOCARTA_PDGF_PATHWAY | | | 0.0086 | BIOCARTA_IL6_PATHWAY | | | 0.043 |
| RAF1 | 1.5218 | 0.0167 | | JUN | -2.395 | 0.0094 | |
| JUN | -2.0269 | 2.63E-05 | | JAK1 | 1.551 | 0.0048 | |
| JAK1 | 1.516 | 0.0007 | | IL6 | -6.769 | 0.0082 | |
| PIK3R1 | 3.6779 | 1.05E-06 | | BIOCARTA_TPO_PATHWAY | | | 0.053 |
| RASA1 | -1.681 | 3.01E-05 | | JUN | -2.395 | 0.0094 | |
| BIOCARTA_INSULIN_PATHWAY | | | 0.0108 | PIK3R1 | 3.928 | 0.0008 | |
| JUN | -2.0269 | 2.63E-05 | | RASA1 | -1.554 | 0.0123 | |
| PIK3R1 | 3.6779 | 1.05E-06 | | BIOCARTA_TRKA_PATHWAY | | | 0.067 |
| RAF1 | 1.5218 | 0.0167 | | NGF | -3.092 | 0.0186 | |
| RASA1 | -1.681 | 3.01E-05 | | PIK3R1 | 3.928 | 0.0008 | |
| BIOCARTA_IL6_PATHWAY | | | 0.0108 | BIOCARTA_CDMAC_PATHWAY | | | 0.111 |
| JUN | -2.0269 | 2.63E-05 | | JUN | -2.395 | 0.0094 | |
| JAK1 | 1.516 | 0.0007 | | 4792 | 2.673 | 0.0216 | |
| RAF1 | 1.5218 | 0.0167 | | BIOCARTA_HER2_PATHWAY | | | 0.187 |
| IL6 | -5.5181 | 4.43E-06 | | PIK3R1 | 3.928 | 0.0008 | |
| BIOCARTA_GLEEVEC_PATHWAY | | | 0.0127 | IL6 | -6.769 | 0.0082 | |
| JUN | -2.0269 | 2.63E-05 | | BIOCARTA_IL2_PATHWAY | | | 0.187 |
| PIK3R1 | 3.6779 | 1.05E-06 | | JUN | -2.395 | 0.0094 | |
| RAF1 | 1.5218 | 0.0167 | | JAK1 | 1.551 | 0.0048 | |
| MYC | 1.5295 | 0.0498 | | BIOCARTA_GLEEVEC_PATHWAY | | | 0.200 |
| BIOCARTA_TPO_PATHWAY | | | 0.014748449 | JUN | -2.395 | 0.0094 | |
| JUN | -2.0269 | 2.63E-05 | | PIK3R1 | 3.928 | 0.0008 | |
| PIK3R1 | 3.6779 | 1.05E-06 | | REACTOME_ACTIVATION_OF_THE_AP1_FAMILY_OF_TRANSCRIPTION_FACTORS | | | 0.307 |
| RAF1 | 1.5218 | 0.0167 | | JUN | -2.395 | 0.0094 | |
| RASA1 | -1.681 | 3.01E-05 | | | | | |
| BIOCARTA_HER2_PATHWAY | | | 0.057218252 | | | | |
| PIK3R1 | 3.6779 | 1.05E-06 | | | | | |
| RAF1 | 1.5218 | 0.0167 | | | | | |
| IL6 | -5.5181 | 4.43E-06 | | | | | |
| BIOCARTA_IL2_PATHWAY | | | 0.057218252 | | | | |
| JUN | -2.0269 | 2.63E-05 | | | | | |
| JAK1 | 1.516 | 0.0007 | | | | | |
| RAF1 | 1.5218 | 0.0167 | | | | | |
| BIOCARTA_TRKA_PATHWAY | | | 0.082399119 | | | | |
| NGF | -3.2549 | 4.37E-06 | | | | | |
| PIK3R1 | 3.6779 | 1.05E-06 | | | | | |
| BIOCARTA_GH_PATHWAY | | | 0.102176826 | | | | |
| PIK3R1 | 3.6779 | 1.05E-06 | | | | | |
| RAF1 | 1.5218 | 0.0167 | | | | | |
| GHR | 1.6017 | 0.0001 | 0.178011116 | | | | |
| BIOCARTA_EPO_PATHWAY | | | | | | | |
| JUN | -2.0269 | 2.63E-05 | | | | | |
| RAF1 | 1.5218 | 0.0167 | | | | | |
| REACTOME_ACTIVATION_OF_THE_AP1_FAMILY_OF_TRANSCRIPTION_FACTORS | | | 0.338313276 | | | | |
| JUN | -2.0269 | 2.63E-05 | | | | | |

Table S9: Twenty pathways with the highest enrichment with genes found to be differentially expressed in normal and asthmatic fibroblast cells under glucocorticoid treatment. Column 1 gives the pathway and the contained differentially expressed genes, columns 2 and 3 the raw *p*-value and fold-change of the differential expression analysis and column 4 the pathway enrichment *p*-value (Fisher's exact test).

| Disease | GSE id | ID | adj.P.Val | P.Value | t | B | logFC | Gene.symbol |
|------------------------------|----------|-------------|-----------|----------|------------|-----------|------------|-------------|
| crohn's | GSE3365 | 207112_s_at | 1.70E-01 | 7.67E-02 | -1.788299 | -5.074263 | -0.3484484 | GAB1 |
| Hashimoto | | | | | | | | |
| Grave's | | | | | | | | |
| Celiac | GSE11501 | ILMN_17816 | 0.91559 | 6.68E-01 | -0.430133 | -6.08368 | -0.0081987 | GAB1 |
| Ankylosing spondylitis | GSE25101 | | | | | | | |
| Multiple Sclerosis | GSE21942 | 226002_at | 1.09E-03 | 5.15E-05 | -4.76 | 1.81 | -3.84E-01 | GAB1 |
| Psoriasis | GSE14905 | 229114_at | 5.92E-06 | 5.16E-07 | -5.71 | 5.80187 | -7.30E-01 | GAB1 |
| Rheumatoid Arthritis | GSE2053 | 15704 | 0.98317 | 9.13E-01 | -0.1137671 | -6.0394 | -0.0865509 | GAB1 |
| Systemic Lupus Erythematosus | GSE46923 | 214987_at | 0.3899 | 5.30E-02 | -2.2080186 | -4.1683 | -0.6638811 | GAB1 |
| Type 1 Diabetes | GSE17635 | GI_4503850 | 0.619878 | 4.36E-01 | 0.793898 | -5.8525 | 0.12736474 | GAB1 |
| Ulcerative Colitis | GSE3365 | 214987_at | 1.04E-01 | 2.38E-02 | 2.310773 | -3.91248 | 0.5716394 | GAB1 |

Table S10: Case vs control differential expression analysis using Gene Expression Omnibus (GEO) data set. Differential expression analysis was done using the limma package in Bioconductor. We find GAB1 not differentially expressed in most of the inflammatory-related diseases.

We also check the GAB1 differentially expressed status in Disease-connect data that include 996 datasets with 4,273 subsets and 20,915 samples. Differentially expressed genes are defined as genes with t-test P-values $< 1e-6$ for each subset pair (disease-connect.org).