

Online Supplement

Methods

Identification cohort: nasal epithelial brushes

COPD patients: COPD patients participated in a multicenter, randomized, longitudinal study with the aim to compare the efficacy of beclomethasone/formoterol and budesonide/formoterol (FAIR study, ClinicalTrials.gov registration number NCT01351792). Exclusion criteria were the presence of an asthma diagnosis, long-term oxygen therapy, pregnancy, clinically unstable concurrent disease (as judged by the investigator), a COPD exacerbation within 2 months prior to the first study visit and reversibility of the FEV₁ >15% and >200mL of initial FEV₁.

Controls: Controls participated in a cross-sectional study with the aim to obtain normal values of inflammatory variables (NORM study, ClinicalTrials.gov registration number NCT00848406). Normal pulmonary function was defined by a FEV₁/FVC > lower limit of normal, absence of bronchial hyperresponsiveness and reversibility of the FEV₁% predicted to salbutamol <10%. For the present study, we used only data of controls > 40 years. Current smokers had a smoking history of at least 10 pack years. Exclusion criteria were the use of inhaled or oral corticosteroids, upper respiratory tract infection, clinically unstable concurrent disease (as judged by the investigator) or pregnancy.

Comparator cohorts: bronchial epithelial brushes

For bronchial brushes (cohort 1), the same linear regression model as published previously was used to identify differentially expressed genes between COPD and controls[1].

For bronchial brushes (cohort 2), the same linear regression model as used for the nasal gene expression analysis was used to identify differentially expressed genes between COPD and controls.

For both comparator cohorts, bronchial airway gene expression was ranked according to the strength and direction of the association with COPD, and compared to the set of genes significant altered in the nasal epithelial of individuals with COPD compared to those without COPD at FDR < 0.01.

Nasal epithelial brushing

Nasal epithelial brushes in COPD patients were performed at the first study visit with subjects using their daily medication without having received study treatment. First, subjects were asked to blow their nose in order to remove mucus. To numb the nasal mucous membrane, 1 ml lidocaine 1% was sprayed in the right nostril. The lateral area underneath the inferior turbinate was brushed for 3 seconds. Next, the brush was placed in an Eppendorf tube containing RNA-protect fluid (Qiagen, Hilden, Germany) and stored at -80° Celsius until processing.

RNA isolation

Total RNA was isolated from nasal brushes using the miRNeasy kit (Qiagen, Hilden, Germany) according to the protocol of the manufacturer. In short, QIAzol Lysis Reagent was added to the samples to induce lysis. Then, chloroform was added and after centrifuging the sample, the aqueous phase was mixed with 100% ethanol and transferred to a RNeasy® Mini column. The sample was washed once with RWT buffer fluid and two times with RPE buffer fluid. Finally, after adding RNase-free water, the sample was centrifuged and the RNA fractions

were eluted from the column. Quantity and purity of the RNA was assessed with a NanoDrop 1000 UV-Vis spectrophotometer (Thermo Scientific, Breda, Netherlands) and RNA integrity of the fractions was assessed with an Agilent 2100 BioAnalyzer.

RNA processing and microarray hybridization

To minimize technical variation due to batch effects, we evenly distributed nasal epithelial samples from COPD patients and healthy controls across the different batches, thereby taking into account gender, age and smoking status.

In short, 200ng high molecular weight RNA (i.e. >200 nucleotides) from nasal epithelial brushes was reverse transcribed (Whole Transcript cDNA Synthesis Kit, Affymetrix, Santa Clara, CA). The obtained cDNA was used for *in vitro* transcription (IVT) (Whole Transcript cDNA Amplification Kit, Affymetrix, Santa Clara, CA), purification (GeneChip Sample Cleanup Module, Affymetrix, Santa Clara, CA) and reverse transcription resulting in single-stranded DNA with incorporation of dUTP. Using uracil DNA glycosylase (UDG), and apurinic/apyrimidinic endonuclease 1 (APE 1), the single-stranded DNA was fragmented and labeled with DNA Labeling Reagent which is covalently linked to biotin with terminal deoxynucleotidyl transferase (TdT) (Whole Transcript Terminal Labeling Kit, Affymetrix, Santa Clara, CA). Quality control of IVT and cDNA fragmentation was performed using the mRNA Nano Assay in the Agilent 2100 BioAnalyzer.

Microarray hybridization to Affymetrix Human Gene 1.0 ST Arrays was performed at the Boston University Microarray Core Facility. The labeled cDNA was hybridized to Affymetrix Human Gene 1.0 ST Arrays for 16 to 18 hours in the GeneChip Hybridization Oven 640 at 45°Celsius with rotation at 60 r.p.m. Washing and staining of the hybridized samples was

performed using the Affymetrix Fluidics Station 450 (Hybridization Washing and Staining Kit, Affymetrix, Santa Clara, CA): the samples were first stained with streptavidin (SAPE), followed by administration of a biotinylated goat anti-streptavidin antibody in order to induce signal amplification and finally a second SAPE staining. Immediately after staining, the microarrays were scanned using Affymetrix GeneArray Scanner 3000 7G Plus (Affymetrix, Santa Clara, CA).

Quality control, data normalization and principal component analysis

Normalization was performed with the Robust Multichip Average algorithm using the 'affy' package of 'R' statistical software and Entrez Gene Chip Definition File hugene10sthentrezgpdf 17.1.0.

The quality of the microarray hybridization was assessed by means of Normalized Unscaled Standard Error (NUSE) plots and Relative Log Expression (RLE) plots as previously described [1]. To account for technical variation within the microarray data after the quality control, a principal component (PC) analysis was performed on the normalized microarray data of the COPD patients and controls (nasal epithelium) and microarray data of cohort 2 (bronchial epithelium) together. To prevent filtering out important clinical variables with the PC analysis, we first adjusted all data for known confounders (age, sex, smoking status, RNA integrity number (RIN)), disease specific variables (FEV₁% predicted) and tissue type (i.e. nasal or bronchial). Next, we performed a PC analysis on the residuals of this analysis to identify PCs accounting for technical variation.

The number of principal components that together explained at least 50% of the variance of the data, were included as covariates in further analyses. This approach resulted in the inclusion of the first 4 principal components, which together explained 52% of the variance.

Results

Identification cohort: nasal epithelial brushes

Nasal samples from 36 current smokers with COPD and 23 current smokers without COPD were hybridized to microarrays. We excluded 1 microarray from a patient with COPD from the analysis due to missing smoking history information, and 5 additional microarrays (4 COPD patients and 1 control) based on quality metrics.

Figure E1

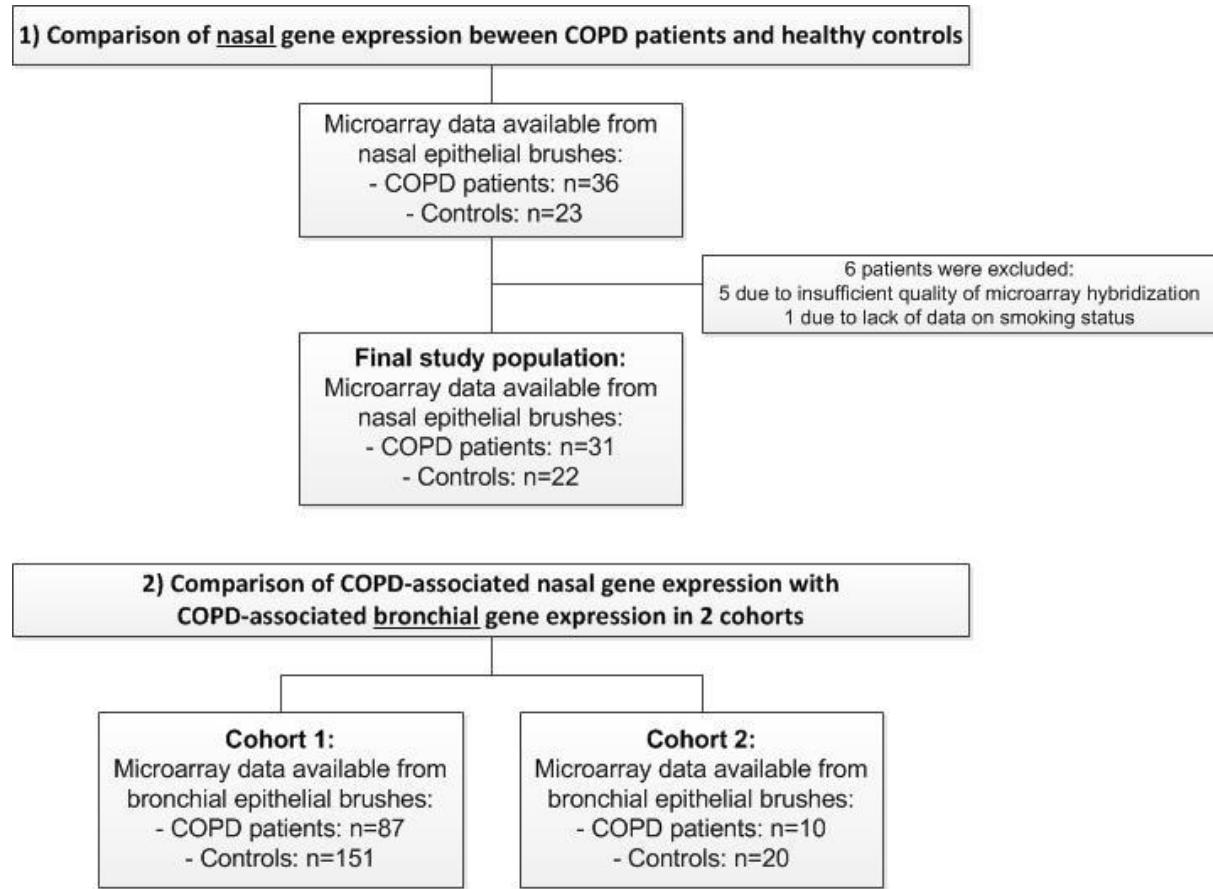
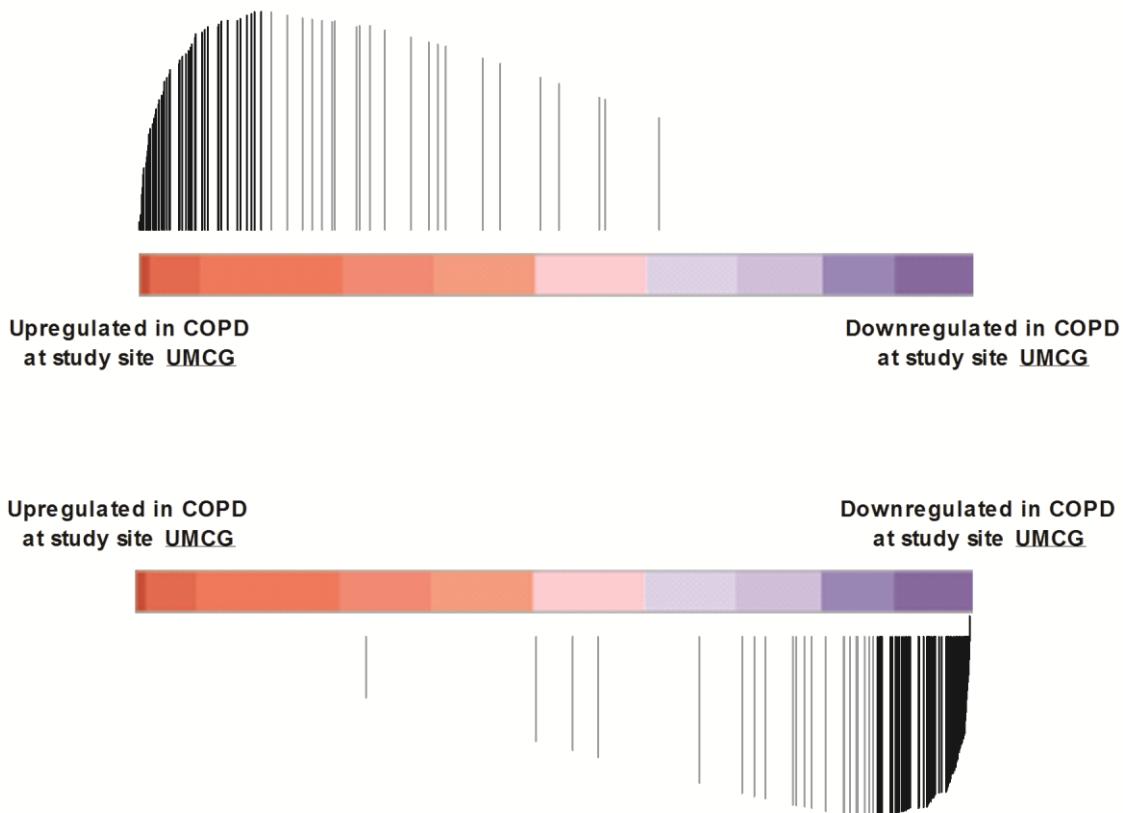


Table E1: COPD-associated up- and downregulated genes in nasal epithelium (n=135)

Upregulated genes (n=21)			Downregulated genes (n=114)		
gene name	t value	FDR p value	gene name	t value	FDR p value
<i>SHROOM1</i>	5.23	0.0026	<i>NPHP1</i>	-7.21	0.0001
<i>STARD13</i>	5.08	0.0035	<i>CFAP206</i>	-7.17	0.0001
<i>CMTM1</i>	5.01	0.0040	<i>C11orf70</i>	-6.41	0.0006
<i>SHC4</i>	4.92	0.0046	<i>CCDC113</i>	-6.12	0.0010
<i>RRBP1</i>	4.88	0.0050	<i>CSE1L</i>	-6.10	0.0010
<i>ARHGEF16</i>	4.85	0.0051	<i>FAM83B</i>	-6.03	0.0011
<i>MUC1</i>	4.86	0.0051	<i>LTV1</i>	-5.95	0.0011
<i>TEP1</i>	4.77	0.0055	<i>GMNN</i>	-5.95	0.0011
<i>TRIM3</i>	4.75	0.0057	<i>SERPINB5</i>	-5.72	0.0019
<i>GPRC5C</i>	4.69	0.0062	<i>AKAP14</i>	-5.70	0.0019
<i>SDF4</i>	4.66	0.0065	<i>LRRC49</i>	-5.66	0.0019
<i>LOC727721</i>	4.58	0.0076	<i>CDKN2AIP</i>	-5.66	0.0019
<i>ZNF521</i>	4.53	0.0085	<i>CAPS</i>	-5.54	0.0024
<i>CAPN10</i>	4.54	0.0085	<i>RPAP3</i>	-5.53	0.0024
<i>CREB3L1</i>	4.50	0.0088	<i>HSPB1</i>	-5.51	0.0024
<i>MYOM1</i>	4.50	0.0089	<i>TEKT1</i>	-5.48	0.0024
<i>CHPF2</i>	4.47	0.0091	<i>PAK1IP1</i>	-5.48	0.0024
<i>MAN1B1</i>	4.48	0.0091	<i>APPL1</i>	-5.43	0.0024
<i>LEPRE1</i>	4.46	0.0093	<i>KIFAP3</i>	-5.43	0.0024
<i>ANKRD10-IT1</i>	4.43	0.0096	<i>CCDC65</i>	-5.42	0.0024
<i>DCAF8</i>	4.44	0.0096	<i>IQCA1</i>	-5.41	0.0024
			<i>EIF3M</i>	-5.41	0.0024
			<i>CDC20</i>	-5.36	0.0025
			<i>RAB38</i>	-5.35	0.0025
			<i>RSPH1</i>	-5.35	0.0025
			<i>MDH1B</i>	-5.34	0.0025
			<i>ADGB</i>	-5.33	0.0025
			<i>AK7</i>	-5.31	0.0025
			<i>ZNF474</i>	-5.31	0.0025
			<i>CAPSL</i>	-5.28	0.0026
			<i>WDR66</i>	-5.25	0.0026
			<i>CRABP2</i>	-5.25	0.0026
			<i>NEK10</i>	-5.24	0.0026
			<i>CCDC39</i>	-5.24	0.0026
			<i>NR1D2</i>	-5.23	0.0026
			<i>CCDC176</i>	-5.22	0.0026
			<i>KPNA3</i>	-5.21	0.0026
			<i>DUSP11</i>	-5.15	0.0031
			<i>WDR96</i>	-5.14	0.0031
			<i>DSC2</i>	-5.13	0.0032
			<i>KRT13</i>	-5.08	0.0035
			<i>C10orf107</i>	-5.07	0.0035
			<i>RABL5</i>	-5.06	0.0035
			<i>LDLRAD1</i>	-5.06	0.0035
			<i>EIF2S1</i>	-5.04	0.0037
			<i>LCA5</i>	-5.02	0.0039
			<i>YBX3</i>	-5.00	0.0040
			<i>MTA3</i>	-4.97	0.0043
			<i>GMPS</i>	-4.97	0.0043
			<i>APEX1</i>	-4.96	0.0044
			<i>SERPINB4</i>	-4.94	0.0045
			<i>CETN2</i>	-4.93	0.0045
			<i>ENO4</i>	-4.91	0.0048
			<i>C15orf26</i>	-4.88	0.0050
			<i>MORN2</i>	-4.88	0.0050

<i>ATP5C1</i>	-4.86	0.0051
<i>HIST1H3B</i>	-4.84	0.0052
<i>DSP</i>	-4.83	0.0053
<i>ARMC3</i>	-4.82	0.0055
<i>ERH</i>	-4.81	0.0055
<i>NAE1</i>	-4.79	0.0055
<i>PBK</i>	-4.79	0.0055
<i>GSTA2</i>	-4.79	0.0055
<i>HIST1H2BM</i>	-4.79	0.0055
<i>MYL12B</i>	-4.78	0.0055
<i>HIST1H1B</i>	-4.77	0.0055
<i>CDKL1</i>	-4.77	0.0055
<i>MMP10</i>	-4.77	0.0055
<i>EFCAB1</i>	-4.77	0.0055
<i>DPM1</i>	-4.76	0.0055
<i>S100A2</i>	-4.76	0.0055
<i>HIST1H3G</i>	-4.76	0.0055
<i>SPA17</i>	-4.73	0.0058
<i>PSMG2</i>	-4.73	0.0058
<i>MRPL9</i>	-4.71	0.0062
<i>CDC5L</i>	-4.70	0.0062
<i>UQCRC2</i>	-4.70	0.0062
<i>SULT2B1</i>	-4.69	0.0062
<i>SLC25A5</i>	-4.69	0.0062
<i>APOO</i>	-4.67	0.0065
<i>WDR16</i>	-4.66	0.0065
<i>DSC3</i>	-4.66	0.0065
<i>KRT5</i>	-4.65	0.0066
<i>HN1</i>	-4.64	0.0067
<i>FAM183A</i>	-4.62	0.0072
<i>WDR63</i>	-4.61	0.0072
<i>MTMR2</i>	-4.61	0.0073
<i>ARMC4</i>	-4.60	0.0074
<i>CLCA4</i>	-4.59	0.0074
<i>STX2</i>	-4.58	0.0076
<i>CDK1</i>	-4.56	0.0082
<i>C8orf37</i>	-4.54	0.0085
<i>IQUB</i>	-4.54	0.0085
<i>GTPBP8</i>	-4.53	0.0085
<i>VDAC3</i>	-4.52	0.0086
<i>KRT14</i>	-4.52	0.0087
<i>MNS1</i>	-4.51	0.0087
<i>APOBEC3B</i>	-4.51	0.0087
<i>RPL22L1</i>	-4.51	0.0087
<i>KIAA1430</i>	-4.48	0.0091
<i>LRRIQ1</i>	-4.48	0.0091
<i>PIFO</i>	-4.48	0.0091
<i>C1orf158</i>	-4.46	0.0093
<i>PDE12</i>	-4.46	0.0093
<i>LARP7</i>	-4.45	0.0095
<i>ANXA1</i>	-4.45	0.0095
<i>BNC1</i>	-4.44	0.0095
<i>KCNRG</i>	-4.44	0.0096
<i>MORN5</i>	-4.43	0.0096
<i>PKP1</i>	-4.43	0.0097
<i>SPATA18</i>	-4.42	0.0097
<i>PSMA1</i>	-4.42	0.0098
<i>SERPINB13</i>	-4.42	0.0098
<i>S100A10</i>	-4.41	0.0098

A) COPD-associated genes UPregulated in nasal epithelium.
Sub-analysis comparing COPD patients recruited at other study sites versus those recruited at the UMCG.



B) COPD-associated genes DOWNregulated in nasal epithelium.
Sub-analysis comparing COPD patients recruited at other study sites versus those recruited at the UMCG.

Figure E2: Gene set enrichment analysis showing that COPD-associated nasal gene expression in the subset of COPD patients recruited at other study sites, is comparable with COPD patients recruited at the UMCG. Gene expression of UMCG COPD patients was ranked according to the strength and direction of the association with COPD, and compared to the set of genes significantly altered in the nasal epithelial of COPD patients from other study sites at FDR < 0.1. A) Upregulated COPD-associated genes in nasal epithelium in the subset of COPD patients from other study sites are significantly enriched among upregulated genes in the subset of COPD patients from the UMCG ($FDR_{GSEA} < 0.001$); B) Downregulated COPD-associated genes in nasal epithelium in the subset of COPD patients from other study sites are significantly enriched among downregulated genes in the subset of COPD patients from the UMCG ($FDR_{GSEA} < 0.001$).

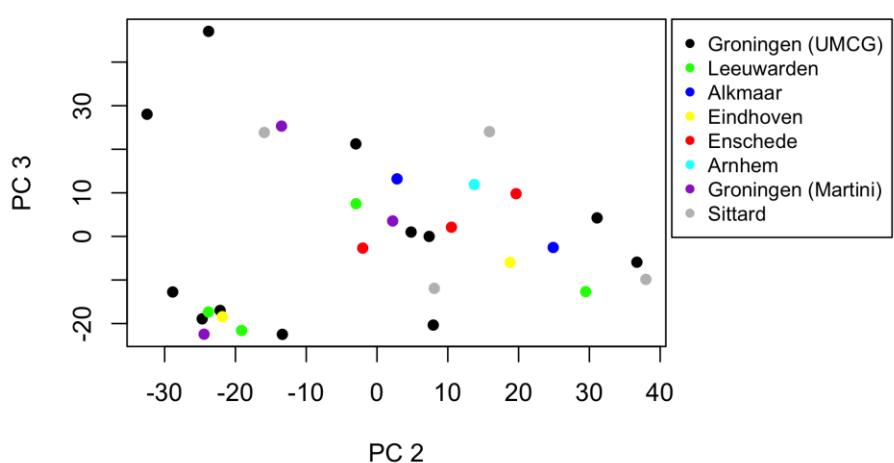
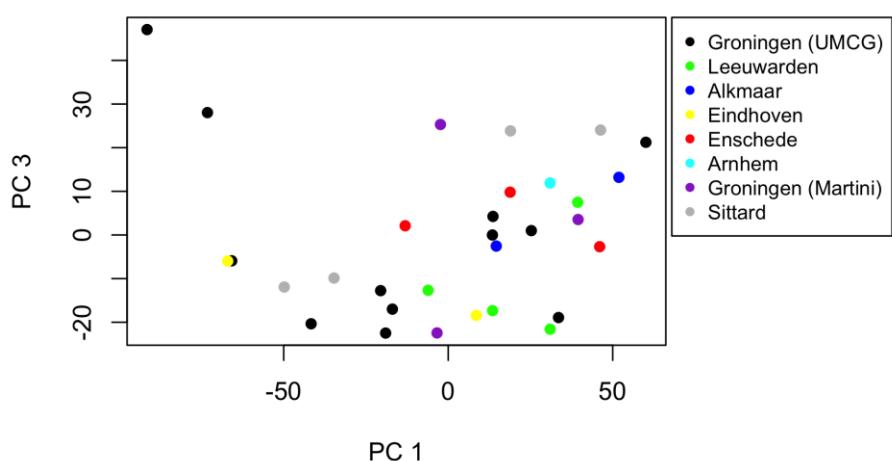
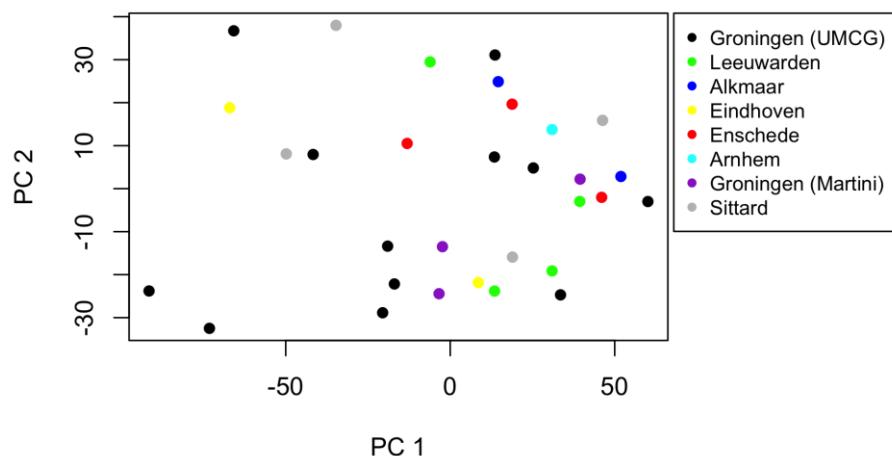


Figure E3: Plots of principal component analysis of only COPD patients colored by study site.
PC1= principal component 1; PC2=principal component 2; PC3=principal component 3.

Table E2: Overlapping COPD-associated genes (FDR<0.01) in both nasal and bronchial epithelium (cohort 1)

Upregulated genes (n=9)	Downregulated genes (n=19)
<i>ARHGEF16</i>	<i>AK7</i>
<i>CAPN10</i>	<i>ARMC3</i>
<i>CHPF2</i>	<i>ARMC4</i>
<i>CREB3L1</i>	<i>C6orf165</i>
<i>GPRC5C</i>	<i>C8orf37</i>
<i>MUC1</i>	<i>CCDC113</i>
<i>RRBP1</i>	<i>CDKL1</i>
<i>SDF4</i>	<i>CETN2</i>
<i>TEP1</i>	<i>CSE1L</i>
	<i>ENO4</i>
	<i>GSTA2</i>
	<i>IQCA1</i>
	<i>KCNRG</i>
	<i>KIFAP3</i>
	<i>LRRC49</i>
	<i>MDH1B</i>
	<i>PIFO</i>
	<i>TEKT1</i>
	<i>WDR16</i>

Table E3: KEGG pathways enriched for genes that are UPregulated in COPD (FDR_{GSEA} ≤0.25) in nasal and bronchial epithelium (cohort 1 and cohort 2)

Nasal epithelium	FDR q-val	Bronchial epithelium (cohort 1)	FDR q-val	Bronchial epithelium (cohort 2)	FDR q-val
KEGG_TASTE_TRANSDUCTION	0.00	KEGG_O_GLYCAN BIOSYNTHESIS	0.00	KEGG_GLYCOSAMINOGLYCAN BIOSYNTHESIS_CHONDROITIN_SULFATE	0.01
KEGG_GLYCOSAMINOGLYCAN_DEGRADATION	0.01	KEGG_GLYCOPHOSPHOLIPID_BIOSYNTHESIS_LACTO_AND_NEOLACTO_SERIES	0.00	KEGG_O_GLYCAN BIOSYNTHESIS	0.02
KEGG_O_GLYCAN_BIOSYNTHESIS	0.01	KEGG_P53_SIGNALING_PATHWAY	0.01	KEGG_NEUROACTIVE_LIGAND_RECECTOR_INTERACTION	0.03
KEGG_GLYCOPHOSPHOLIPID_BIOSYNTHESIS_LACTO_AND_NEOLACTO_SERIES	0.04	KEGG_APOPTOSIS	0.01	KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_HEPARAN_SULFATE	0.09
KEGG_OTHER_GLYCAN_DEGRADATION	0.08	KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_KERATAN_SULFATE	0.01	KEGG_LINOLEIC_ACID_METABOLISM	0.09
KEGGADIPOCYTOKINE_SIGNALING_PATHWAY	0.07	KEGG_ENDOCYTOSIS	0.01	KEGG_GLYCOPHOSPHOLIPID_BIOSYNTHESIS_LACTO_AND_NEOLACTO_SERIES	0.11
KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_KERATAN_SULFATE	0.09	KEGG_LINOLEIC_ACID_METABOLISM	0.01	KEGG_GLYCOSAMINOGLYCAN_DEGRADATION	0.10
KEGG_LYSOSOME	0.11	KEGG_N_GLYCAN_BIOSYNTHESIS	0.01	KEGG_GLYCOPHOSPHOLIPID_BIOSYNTHESIS_GANGLIO_SERIES	0.13
KEGG_GLYCOPHOSPHOLIPID_BIOSYNTHESIS_GANGLIO_SERIES	0.13	KEGG_GRAFT_VERSUS_HOST_DISEASE	0.02		
KEGG_NITROGEN_METABOLISM	0.13	KEGG_CHRONIC_MYELOID_LEUKEMIA	0.03		
KEGG_OLFFACTORY_TRANSDUCTION	0.18	KEGG_NATURAL_KILLER_CELL_MEDiated_CYTOTOXICITY	0.03		
KEGG_NEUROACTIVE_LIGAND_RECECTOR_INTERACTION	0.18	KEGG_INOSITOL_PHOSPHATE_METABOLISM	0.03		
KEGG_N_GLYCAN_BIOSYNTHESIS	0.21	KEGG_SMALL_CELL_LUNG_CANCER	0.04		
KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_HEPARAN_SULFATE	0.21	KEGG_FC_GAMMA_R_MEDiated_PHAGOCYTOSIS	0.04		
		KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	0.05		
		KEGG_T_CELL_RECECTOR_SIGNALING_PATHWAY	0.05		
		KEGG_BLADDER_CANCER	0.05		
		KEGG_EETHER_LIPID_METABOLISM	0.05		
		KEGG_PANCREATIC_CANCER	0.05		
		KEGG_EPITHELIAL_CELL_SIGNALING_IN_Helicobacter_pylori_INFECTIOn	0.05		
		KEGG_TYPE_I_DIABETES_MELLITUS	0.05		
		KEGG_VIRAL_MYOCARDITIS	0.05		
		KEGG_CYTOSOLIC_DNA_SENSING_PATHWAY	0.05		
		KEGG_RETINOL_METABOLISM	0.05		
		KEGG_PHOSPHATIDYLINOSITOL_SIGNALING_SYSTEM	0.05		
		KEGG_ARACHIDONIC_ACID_METABOLISM	0.05		
		KEGG_TOLL_LIKE_RECECTOR_SIGNALING_PATHWAY	0.06		
		KEGG_AUTOIMMUNE_THYROID_DISEASE	0.06		
		KEGG_REGULATION_OF_ACTIN_CYTOSKELETON	0.06		
		KEGG_VIBRIO_CHOLERAE_INFECTION	0.06		
		KEGG_GLYOXYLATE_AND_DICARBOXYLATE_METABOLISM	0.07		
		KEGG_PROSTATE_CANCER	0.07		
		KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION	0.07		
		KEGG_INSULIN_SIGNALING_PATHWAY	0.07		
		KEGG_ACUTE_MYELOID_LEUKEMIA	0.07		
		KEGG_PATHWAYS_IN_CANCER	0.07		
		KEGG_NOD_LIKE_RECECTOR_SIGNALING_PATHWAY	0.07		
		KEGG_HUNTINGTONS_DISEASE	0.07		
		KEGG_ALLOGRAFT_REJECTION	0.08		
		KEGG_AMINO_SUGAR_AND_NUCLEOTIDE_SUGAR_METABOLISM	0.08		
		KEGG_LEISHMANIA_INFECTION	0.08		
		KEGG_CHEMOKINE_SIGNALING_PATHWAY	0.08		
		KEGG_MAPK_SIGNALING_PATHWAY	0.09		
		KEGG_ERBB_SIGNALING_PATHWAY	0.10		
		KEGG_PRIMARY_IMMUNODEFICIENCY	0.10		
		KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450	0.11		
		KEGG_VEGF_SIGNALING_PATHWAY	0.11		
		KEGG_ALZHEIMERS_DISEASE	0.12		
		KEGG_PARKINSONS_DISEASE	0.12		
		KEGG_CYTOKINE_CYTOKINE_RECECTOR_INTERACTION	0.11		
		KEGG_RENAL_CELL_CARCINOMA	0.11		
		KEGG_AMYOTROPHIC_LATERAL_SCLEROSIS_ALS	0.12		
		KEGG_NON_SMALL_CELL_LUNG_CANCER	0.13		
		KEGG_B_CELL_RECECTOR_SIGNALING_PATHWAY	0.13		

KEGG_INTESTINAL_IMMUNE_NETWORK_FOR_IGA_PRODUCTION	0.13
KEGG_STARCH_AND_SUCROSE_METABOLISM	0.14
KEGG_AXON_GUIDANCE	0.15
KEGG_ENDOMETRIAL_CANCER	0.16
KEGG_COMPLEMENT_AND_COAGULATION_CASCADES	0.16
KEGG_ONE_CARBON_POOL_BY_FOLATE	0.16
KEGG_GLIOMA	0.16
KEGG_SPHINGOLIPID_METABOLISM	0.17
KEGG_GNRH_SIGNALING_PATHWAY	0.17
KEGG_GLYCEROPOHOSPHOLIPID_METABOLISM	0.16
KEGG_GALACTOSE_METABOLISM	0.17
KEGG_VASOPRESSIN_REGULATED_WATER_REABSORPTION	0.17
KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY	0.17
KEGG_FRUCTOSE_AND_MANNOSE_METABOLISM	0.18
KEGG_PATHOGENIC_ESCHERICHIA_COLI_INFECTION	0.18
KEGG_SYSTEMIC_LUPUS_ERYTHEMATOSUS	0.18
KEGG_BASE_EXCISION_REPAIR	0.19
KEGG_THYROID_CANCER	0.19
KEGG_DORSO_VENTRAL_AXIS_FORMATION	0.19
KEGG_GAP_JUNCTION	0.20
KEGG_JAK_STAT_SIGNALING_PATHWAY	0.21
KEGG_STEROID_HORMONE BIOSYNTHESIS	0.21
KEGG_PROTEASOME	0.21
KEGG_MELANOMA	0.22
KEGG_GLYCOSAMINOGLYCAN_BIOSYNTHESIS_HEPARAN_SULFATE	0.22
KEGG_NOTCH_SIGNALING_PATHWAY	0.23
KEGG_CELL_CYCLE	0.23
KEGG_PYRIMIDINE_METABOLISM	0.23

Table E4: KEGG pathways enriched for genes that are DOWNregulated in COPD (FDR_{GSEA} ≤0.25) in nasal and bronchial epithelium (cohort 1 and cohort 2)

Nasal epithelium	FDR q-val	Bronchial epithelium (cohort 1)	FDR q-val	Bronchial epithelium (cohort 2)	FDR q-val
KEGG_RIBOSOME	0.00	KEGG_MISMATCH_REPAIR	0.06	KEGG_SYSTEMIC_LUPUS_ERYTHEMATOSUS	0.01
KEGG_CELL_CYCLE	0.00	KEGG_NUCLEOTIDE_EXCISION_REPAIR	0.04	KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION	0.01
KEGG_PROTEASOME	0.00	KEGG_RNA_DEGRADATION	0.06	KEGG_DORSO_VENTRAL_AXIS_FORMATION	0.02
KEGG_SYSTEMIC_LUPUS_ERYTHEMATOSUS	0.00	KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION	0.06	KEGG_GRAFT_VERSUS_HOST_DISEASE	0.06
KEGG_SPLICEOSOME	0.00	KEGG_DNA_REPLICATION	0.09	KEGG_VIRAL_MYOCARDITIS	0.06
KEGG_PARKINSONS_DISEASE	0.00	KEGG_OLFACTOORY_TRANSDUCTION	0.15	KEGG_AUTOIMMUNE_THYROID_DISEASE	0.05
KEGG_HUNTINGTONS_DISEASE	0.00	KEGG_PRIMARY_BILE_ACID BIOSYNTHESIS	0.20	KEGG_CELL_CYCLE	0.06
KEGG_DNA_REPLICATION	0.00	KEGG_TIGHT_JUNCTION	0.21	KEGG_ALLOGRAFT_REJECTION	0.05
KEGG_OXIDATIVE_PHOSPHORYLATION	0.00	KEGG_PROPANOATE_METABOLISM	0.20	KEGG_RNA_DEGRADATION	0.06
KEGG_CITRATE_CYCLE_TCA_CYCLE	0.00			KEGG_PRION_DISEASES	0.08
KEGG_RNA_DEGRADATION	0.00			KEGG_PROTEASOME	0.08
KEGG_NUCLEOTIDE_EXCISION_REPAIR	0.00			KEGG_ENDOMETRIAL_CANCER	0.08
KEGG_ALZHEIMERS_DISEASE	0.00			KEGG_COLORECTAL_CANCER	0.08
KEGG_OOCYTE_MEIOSIS	0.00			KEGG_OOCYTE_MEIOSIS	0.08
KEGG_PATHOGENIC_ESCHERICHIA_COLI_INFECTION	0.00			KEGG_CELL_ADHESION_MOLECULES_CAMS	0.08
KEGG_P53_SIGNALING_PATHWAY	0.00			KEGG_INTESTINAL_IMMUNE_NETWORK_FOR_IGA_PRODUCTION	0.08
KEGG_MISMATCH_REPAIR	0.00			KEGG_PATHOGENIC_ESCHERICHIA_COLI_INFECTION	0.07
KEGG_GLUTATHIONE_METABOLISM	0.00			KEGG_THYROID_CANCER	0.08
KEGG_SMALL_CELL_LUNG_CANCER	0.02			KEGG_LEISHMANIA_INFECTION	0.07
KEGG_PROGESTERONE_MEDIANED_OOCYTE_MATURATION	0.03			KEGG_ADHERENS_JUNCTION	0.07
KEGG_PYRUVATE_METABOLISM	0.03			KEGG_TYPE_I_DIABETES_MELLITUS	0.07
KEGG_BASAL_TRANSCRIPTION_FACTORS	0.04			KEGG_RNA_POLYMERASE	0.07
KEGG_BASE_EXCISION_REPAIR	0.04			KEGG_GLYCOLYLPHOSPHATIDYLINOSITOL_GPI_ANCHOR_BIOSYNTHESIS	0.08
KEGG_AMINOACYL_TRNA BIOSYNTHESIS	0.06			KEGG GLUTATHIONE_METABOLISM	0.08
KEGG_BUTANOATE_METABOLISM	0.09			KEGG_RENAL_CELL_CARCINOMA	0.08
KEGG_METABOLISM_OF_XENOBIOTICS_BY_CYTOCHROME_P450	0.10			KEGG_PROPANOATE_METABOLISM	0.09
KEGG_COLORECTAL_CANCER	0.10			KEGG_ASTHMA	0.09
KEGG_DRUG_METABOLISM_CYTOCHROME_P450	0.10			KEGG_TGF_BETA_SIGNALING_PATHWAY	0.10
KEGG_VALINE_LEUCINE_AND_ISOLEUCINE_DEGRADATION	0.11			KEGG ubiquitin_MEDiated_proteolysis	0.13
KEGG_PYRIMIDINE_METABOLISM	0.12			KEGG_P53_SIGNALING_PATHWAY	0.14
KEGG_GLYCOLYSIS_GLUCONEOGENESIS	0.12			KEGG_VASOPRESSIN_REGULATED_WATER_REABSORPTION	0.15
KEGG ubiquitin_MEDiated_proteolysis	0.13			KEGG_SPHINGOLIPID_METABOLISM	0.15
KEGG_TIGHT_JUNCTION	0.13			KEGG_ACUTE_MYELOID_LEUKEMIA	0.15
KEGG_BLADDER_CANCER	0.13			KEGG_BASAL_TRANSCRIPTION_FACTORS	0.15
KEGG_PROPANOATE_METABOLISM	0.13			KEGG_T_CELL_RECEPATOR_SIGNALING_PATHWAY	0.16
KEGG_ARRHYTHMOGENIC_RIGHT_VENTRICULAR_CARDIOMYOPATHY_ARVC	0.14			KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	0.16
KEGG_REGULATION_OF_ACTIN_CYTOSKELETON	0.14			KEGG_ALZHEIMERS_DISEASE	0.16
KEGG_GLIOMA	0.15			KEGG_RENIN_ANGIOTENSIN_SYSTEM	0.17
KEGG_ADHERENS_JUNCTION	0.15			KEGG_PEROXISOME	0.17
KEGG_ASTHMA	0.15			KEGG_leukocyte_transendothelial_migration	0.17
KEGG_PROSTATE_CANCER	0.22			KEGG_DNA_REPLICATION	0.19
				KEGG_HUNTINGTONS_DISEASE	0.18
				KEGG_B_CELL_RECEPATOR_SIGNALING_PATHWAY	0.23
				KEGG_HEDGEHOG_SIGNALING_PATHWAY	0.23
				KEGG_ARRHYTHMOGENIC_RIGHT_VENTRICULAR_CARDIOMYOPATHY_ARVC	0.24
				KEGG_MELANOGENESIS	0.24
				KEGG_TIGHT_JUNCTION	0.24
				KEGG_PATHWAYS_IN_CANCER	0.25

Table E5: GO term analyses (GORilla) for genes DOWNregulated in COPD in nasal epithelium (FDR<0.05)

Gene Ontology Process	P-value	FDR q-value
microtubule-based process	1.5E-16	2.24E-12
rRNA processing	1.09E-14	8.1E-11
translational initiation	2.33E-14	1.15E-10
rRNA metabolic process	1.34E-13	4.98E-10
posttranscriptional regulation of gene expression	3.26E-12	9.69E-9
organelle organization	9.06E-12	2.24E-8
cilium movement	1.85E-11	3.93E-8
chromosome segregation	2.47E-11	4.6E-8
mitotic cell cycle process	3.22E-11	5.32E-8
cellular component organization or biogenesis	4.17E-11	6.2E-8
cellular component assembly	4.87E-11	6.59E-8
cellular component organization	1.13E-10	1.4E-7
regulation of cell cycle G2/M phase transition	1.56E-10	1.78E-7
microtubule-based movement	2.76E-10	2.93E-7
cellular macromolecular complex assembly	5.34E-10	5.29E-7
regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle	5.77E-10	5.36E-7
ncRNA processing	7.13E-10	6.24E-7
regulation of mitotic cell cycle phase transition	9.77E-10	8.07E-7
positive regulation of ubiquitin-protein ligase activity involved in regulation of mitotic cell cycle transition	1.32E-9	1.03E-6
organelle assembly	1.33E-9	9.92E-7
regulation of cell cycle phase transition	1.53E-9	1.08E-6
regulation of G2/M transition of mitotic cell cycle	1.83E-9	1.24E-6
cell cycle process	3.32E-9	2.15E-6
negative regulation of ubiquitin-protein ligase activity involved in mitotic cell cycle	4.64E-9	2.87E-6
positive regulation of ubiquitin protein ligase activity	4.93E-9	2.93E-6
regulation of cell cycle process	8.87E-9	5.07E-6
negative regulation of cell cycle process	1.18E-8	6.52E-6
negative regulation of mitotic cell cycle phase transition	1.4E-8	7.42E-6
negative regulation of ubiquitin protein ligase activity	1.45E-8	7.42E-6
negative regulation of mitotic cell cycle	1.51E-8	7.47E-6
positive regulation of protein ubiquitination involved in ubiquitin-dependent protein catabolic process	1.61E-8	7.72E-6
regulation of ubiquitin protein ligase activity	1.89E-8	8.77E-6
anaphase-promoting complex-dependent catabolic process	2.06E-8	9.29E-6
regulation of protein ubiquitination involved in ubiquitin-dependent protein catabolic process	2.12E-8	9.29E-6
regulation of cell cycle	2.76E-8	1.17E-5
cellular macromolecule catabolic process	2.84E-8	1.17E-5
negative regulation of cell cycle phase transition	3.26E-8	1.31E-5
cilium organization	3.57E-8	1.4E-5
regulation of translation	3.77E-8	1.44E-5
negative regulation of ubiquitin-protein transferase activity	4.04E-8	1.5E-5
negative regulation of cell cycle	4.39E-8	1.59E-5
motile cilium assembly	4.66E-8	1.65E-5
chromosome organization	6.26E-8	2.16E-5
regulation of mitotic cell cycle	6.62E-8	2.24E-5
positive regulation of ubiquitin-protein transferase activity	7.2E-8	2.38E-5
nuclear-transcribed mRNA catabolic process	9.61E-8	3.11E-5
RNA catabolic process	1.11E-7	3.5E-5
negative regulation of macromolecule metabolic process	1.23E-7	3.8E-5
regulation of cellular amide metabolic process	2.45E-7	7.44E-5
mRNA catabolic process	2.83E-7	8.43E-5
ncRNA metabolic process	3.03E-7	8.84E-5
negative regulation of protein modification by small protein conjugation or removal	3.14E-7	8.99E-5
protein-DNA complex assembly	3.36E-7	9.43E-5
negative regulation of G2/M transition of mitotic cell cycle	4.09E-7	1.13E-4
single-organism organelle organization	4.35E-7	1.18E-4
mitotic cell cycle	4.72E-7	1.25E-4
negative regulation of cell cycle G2/M phase transition	5.43E-7	1.42E-4
RNA processing	5.74E-7	1.47E-4
viral process	6.92E-7	1.74E-4

Table E5 continued

Gene Ontology Process	P-value	FDR q-value
symbiosis, encompassing mutualism through parasitism	6.92E-7	1.71E-4
establishment of protein localization to endoplasmic reticulum	7.15E-7	1.74E-4
negative regulation of gene expression	7.65E-7	1.84E-4
regulation of ubiquitin-protein transferase activity	7.71E-7	1.82E-4
negative regulation of protein ubiquitination	7.94E-7	1.85E-4
cell division	8.5E-7	1.94E-4
SRP-dependent cotranslational protein targeting to membrane	9.02E-7	2.03E-4
positive regulation of cellular protein catabolic process	9.67E-7	2.15E-4
macromolecular complex subunit organization	1.01E-6	2.21E-4
cell projection organization	1.11E-6	2.39E-4
regulation of mRNA stability	1.19E-6	2.52E-4
plasma membrane bounded cell projection organization	1.81E-6	3.8E-4
cotranslational protein targeting to membrane	1.84E-6	3.79E-4
protein modification by small protein removal	1.89E-6	3.85E-4
macromolecular complex assembly	1.94E-6	3.9E-4
macromolecule catabolic process	2.3E-6	4.56E-4
interspecies interaction between organisms	2.53E-6	4.95E-4
protein localization to endoplasmic reticulum	2.54E-6	4.9E-4
protein targeting to ER	2.74E-6	5.22E-4
regulation of RNA stability	2.78E-6	5.22E-4
protein-DNA complex subunit organization	2.92E-6	5.43E-4
cell cycle	3.86E-6	7.08E-4
positive regulation of proteolysis involved in cellular protein catabolic process	4.44E-6	8.05E-4
regulation of cellular amine metabolic process	4.72E-6	8.46E-4
nuclear-transcribed mRNA catabolic process, nonsense-mediated decay	5.02E-6	8.88E-4
microtubule organizing center organization	5.04E-6	8.81E-4
translation	5.63E-6	9.74E-4
plasma membrane bounded cell projection assembly	6.12E-6	1.05E-3
microtubule bundle formation	6.55E-6	1.11E-3
regulation of cellular protein catabolic process	7.03E-6	1.17E-3
regulation of transcription from RNA polymerase II promoter in response to hypoxia	7.06E-6	1.17E-3
cell projection assembly	8.21E-6	1.34E-3
negative regulation of transferase activity	8.41E-6	1.36E-3
negative regulation of metabolic process	8.95E-6	1.43E-3
nucleobase-containing compound catabolic process	9.61E-6	1.52E-3

NB: GO terms in bold represent biological processes at the bottom of the hierarchical diagram created by GOrilla, i.e. the most specific pathways. Only pathways with a p-value < p-value < 1E-5 are shown.

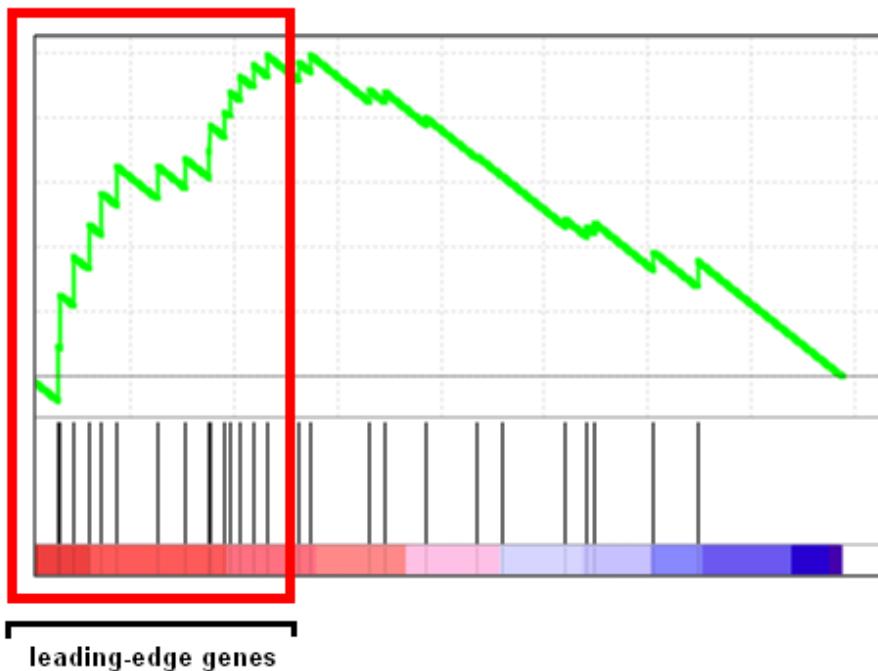


Figure E4: Example of the leading-edge subset, consisting of those genes that contribute the most to the enrichment of pathways; in the figure the leading-edge genes are ranked before the point at which the running sum (represented by the green line) reaches its highest point.

Table E6: Leading-edge genes of the 2 significantly enriched UPregulated KEGG pathways in nasal and bronchial epithelium (cohort 1 and cohort 2)

O-Glycan biosynthesis			Glycosphingolipid biosynthesis		
Nasal	Bronchial (cohort 1)	Bronchial (cohort 2)	Nasal	Bronchial (cohort 1)	Bronchial (cohort 2)
<i>GALNT4</i>	<i>GALNT4</i>	<i>GALNT4</i>	<i>FUT3</i>	<i>FUT3</i>	<i>FUT3</i>
<i>GALNT5</i>	<i>GALNT5</i>	<i>GALNT5</i>	<i>FUT6</i>	<i>FUT6</i>	<i>FUT6</i>
<i>GALNT6</i>	<i>GALNT6</i>	<i>GALNT6</i>	<i>ST3GAL3</i>	<i>ST3GAL3</i>	<i>ST3GAL3</i>
<i>GALNT7</i>	<i>GALNT7</i>	<i>GALNT7</i>	<i>B4GALT4</i>	<i>B4GALT4</i>	<i>ST3GAL4</i>
<i>GALNT12</i>	<i>GALNT12</i>	<i>GALNT12</i>	<i>B3GNT3</i>	<i>B3GNT3</i>	<i>B3GNT3</i>
<i>B3GNT6</i>	<i>B3GNT6</i>	<i>B3GNT6</i>	<i>ABO</i>	<i>ABO</i>	<i>ABO</i>
<i>ST6GALNAC1</i>	<i>ST6GALNAC1</i>	<i>ST6GALNAC1</i>	<i>FUT2</i>	<i>FUT2</i>	-
<i>GCNT3</i>	<i>GCNT3</i>	-	<i>ST3GAL4</i>	<i>ST3GAL4</i>	-
<i>GALNT3</i>	-	<i>GALNT3</i>	<i>B4GALT1</i>	<i>B4GALT1</i>	-
<i>GALNTL6</i>	-	<i>GALNTL6</i>	<i>B4GALT3</i>	<i>B4GALT3</i>	-
<i>GALNT9</i>	-	<i>GALNT9</i>	<i>FUT4</i>	-	<i>FUT4</i>
<i>ST3GAL1</i>	-	<i>ST3GAL1</i>	<i>B3GNT4</i>	-	<i>B3GNT4</i>
<i>WBSCR17</i>	-	<i>WBSCR17</i>	-	<i>B4GALT2</i>	<i>B4GALT2</i>
<i>GALNT8</i>	-	-	-	<i>FUT1</i>	<i>FUT1</i>
<i>GALNT10</i>	-	-	<i>B3GALT5</i>	-	-
<i>GALNT11</i>	-	-	-	<i>B3GALT1</i>	-
<i>C1GALT1C1</i>	-	-	-	<i>B3GNT2</i>	-
<i>ST3GAL2</i>	-	-	-	-	-
<i>C1GALT1</i>	-	-	-	-	-
-	<i>B4GALT5</i>	-	-	-	<i>ST8SIA1</i>
-	<i>GALNT14</i>	-	-	-	<i>FUT5</i>
-	<i>GCNT1</i>	-	-	-	
-	<i>GALNT2</i>	-	-	-	
-	<i>GALNT1</i>	-	-	-	

Table E7: Leading-edge genes of the 3 significantly enriched DOWNregulated KEGG pathways in nasal and bronchial epithelium (cohort 1 and cohort 2)

DNA replication			Propanoate metabolism			RNA degradation			Tight junction		
Nasal	Bronchial (cohort 1)	Bronchial (cohort 2)	Nasal	Bronchial (cohort 1)	Bronchial (cohort 2)	Nasal	Bronchial (cohort 1)	Bronchial (cohort 2)	Nasal	Bronchial (cohort 1)	Bronchial (cohort 2)
<i>POLD2</i>	<i>POLD2</i>	<i>POLD2</i>	<i>SUCLG2</i>	<i>SUCLG2</i>	<i>SUCLG2</i>	<i>PAPOLG</i>	<i>PAPOLG</i>	<i>PAPOLG</i>	<i>CLDN16</i>	<i>CLDN16</i>	<i>CLDN16</i>
<i>PRIM1</i>	<i>PRIM1</i>	<i>PRIM1</i>	<i>HADHA</i>	<i>HADHA</i>	<i>HADHA</i>	<i>LSM3</i>	<i>LSM3</i>	<i>LSM3</i>	<i>CTNNB1</i>	<i>CTNNB1</i>	<i>CTNNB1</i>
<i>RFC3</i>	<i>RFC3</i>	<i>RFC3</i>	<i>LDHB</i>	<i>LDHB</i>	<i>LDHB</i>	<i>CNOT1</i>	<i>CNOT1</i>	<i>CNOT1</i>	<i>EPB41L2</i>	<i>EPB41L2</i>	<i>EPB41L2</i>
<i>RPA1</i>	<i>RPA1</i>	<i>RPA1</i>	<i>ALDH3A2</i>	<i>ALDH3A2</i>	<i>ALDH3A2</i>	<i>SKIV2L2</i>	<i>SKIV2L2</i>	<i>SKIV2L2</i>	<i>PPP2CB</i>	<i>PPP2CB</i>	<i>PPP2CB</i>
<i>MCM2</i>	<i>MCM2</i>	-	<i>ACADM</i>	<i>ACADM</i>	<i>ACADM</i>	<i>CNOT10</i>	<i>CNOT10</i>	<i>CNOT10</i>	<i>PRKCZ</i>	<i>PRKCZ</i>	<i>PRKCZ</i>
<i>RFC5</i>	<i>RFC5</i>	-	-	<i>ALDH9A1</i>	<i>ALDH9A1</i>	<i>DCP1B</i>	<i>DCP1B</i>	<i>DCP1B</i>	<i>VAPA</i>	<i>VAPA</i>	<i>VAPA</i>
<i>RFC1</i>	<i>RFC1</i>	-	-	<i>ACAT2</i>	<i>ACAT2</i>	<i>CNOT6L</i>	<i>CNOT6L</i>	<i>CNOT6L</i>	<i>MPP5</i>	<i>MPP5</i>	-
-	<i>RPA2</i>	<i>RPA2</i>	-	<i>MUT</i>	<i>MUT</i>	<i>DDX6</i>	<i>DDX6</i>	<i>DDX6</i>	<i>PRKCA</i>	<i>PRKCA</i>	-
<i>POLE3</i>	-	<i>POLE3</i>	-	<i>ALDH2</i>	<i>ALDH2</i>	-	<i>WDR61</i>	<i>WDR61</i>	<i>MPDZ</i>	<i>MPDZ</i>	-
<i>RFC2</i>	-	<i>RFC2</i>	-	<i>ACSS1</i>	<i>ACSS1</i>	-	<i>ENO2</i>	<i>ENO2</i>	<i>EPB41L3</i>	<i>EPB41L3</i>	-
<i>RFC4</i>	-	<i>RFC4</i>	-	<i>EHHADH</i>	<i>EHHADH</i>	<i>TTC37</i>	<i>TTC37</i>	-	<i>OCLN</i>	<i>OCLN</i>	-
<i>RNASEH2A</i>	-	<i>RNASEH2A</i>	<i>LDHA</i>	-	<i>LDHA</i>	<i>CNOT2</i>	<i>CNOT2</i>	-	<i>PARD3</i>	<i>PARD3</i>	-
<i>RNASEH2B</i>	-	<i>RNASEH2B</i>	<i>PCCB</i>	-	<i>PCCB</i>	<i>DIS3</i>	<i>DIS3</i>	-	<i>CLDN8</i>	<i>CLDN8</i>	<i>CLDN8</i>
<i>SSBP1</i>	-	<i>SSBP1</i>	<i>SUCLG1</i>	-	<i>SUCLG1</i>	<i>PAPOLA</i>	<i>PAPOLA</i>	-	<i>CLDN18</i>	<i>CLDN18</i>	<i>CLDN18</i>
<i>MCM4</i>	-	<i>MCM4</i>	<i>SUCLA2</i>	-	-	<i>LSM6</i>	<i>LSM6</i>	-	<i>JAM3</i>	<i>JAM3</i>	-
<i>DNA2</i>	-	-	<i>ACAT1</i>	-	-	<i>XRN2</i>	<i>XRN2</i>	-	<i>PARD6B</i>	<i>PARD6B</i>	-
<i>FEN1</i>	-	-	-	<i>LDHAL6A</i>	-	<i>EXOSC9</i>	<i>EXOSC9</i>	-	<i>ZAK</i>	<i>ZAK</i>	-
<i>LIG1</i>	-	-	-	<i>LOC283398</i>	-	<i>EXOSC1</i>	<i>EXOSC1</i>	-	<i>CLDN9</i>	<i>CLDN9</i>	-
<i>MCM5</i>	-	-	-	<i>MCEE</i>	-	<i>EXOSC8</i>	<i>EXOSC8</i>	-	<i>ASH1L</i>	-	<i>ASH1L</i>
<i>MCM6</i>	-	-	-	<i>ALDH6A1</i>	-	<i>EXOSC2</i>	<i>EXOSC2</i>	-	<i>ACTG1</i>	-	<i>ACTG1</i>
<i>MCM7</i>	-	-	-	-	<i>ABAT</i>	<i>EXOSC3</i>	-	<i>ACTN4</i>	-	<i>ACTN4</i>	-
<i>PCNA</i>	-	-	-	-	<i>HIBCH</i>	<i>EXOSC4</i>	-	<i>AKT3</i>	-	<i>AKT3</i>	-
<i>POLA2</i>	-	-	-	-	<i>LDHC</i>	<i>EXOSC5</i>	-	<i>AMOTL1</i>	-	<i>AMOTL1</i>	-
<i>POLD4</i>	-	-	-	-	-	<i>LSM4</i>	<i>LSM4</i>	-	<i>CDK4</i>	-	<i>CDK4</i>
<i>POLR2</i>	-	-	-	-	-	<i>LSM5</i>	<i>LSM5</i>	-	<i>CLDN1</i>	-	<i>CLDN1</i>
-	<i>PRIM2</i>	-	-	-	-	<i>CNOT8</i>	-	<i>CNOT8</i>	<i>CLDN4</i>	-	<i>CLDN4</i>
-	<i>RNASEH1</i>	-	-	-	-	<i>CNOT7</i>	-	<i>CNOT7</i>	<i>CSNK2B</i>	-	<i>CSNK2B</i>
-	<i>RPA3</i>	-	-	-	-	<i>HSPD1</i>	-	<i>HSPD1</i>	<i>F11R</i>	-	<i>F11R</i>
-	-	<i>MCM3</i>	-	-	-	<i>EXOSC7</i>	-	-	<i>MYL9</i>	-	<i>MYL9</i>
-	-	<i>POLA1</i>	-	-	-	<i>HSPA9</i>	-	-	<i>PPP2CA</i>	-	<i>PPP2CA</i>
-	-	-	-	-	-	<i>ENO1</i>	-	-	<i>CASK</i>	-	-
-	<i>PRIM2</i>	-	-	-	-	<i>EDC3</i>	-	-	<i>MLLT4</i>	-	-
-	<i>RNASEH1</i>	-	-	-	-	<i>LSM1</i>	<i>CNOT4</i>	-	<i>TJP1</i>	-	-
-	<i>RPA3</i>	-	-	-	-	-	<i>RQCD1</i>	-	<i>YES1</i>	-	-
-	-	<i>MCM3</i>	-	-	-	-	<i>PNPT1</i>	-	<i>GNA13</i>	-	-
-	-	<i>POLA1</i>	-	-	-	-	<i>PAPOLB</i>	-	<i>MYH14</i>	-	-
-	-	-	-	-	-	-	<i>DCP2</i>	-	<i>MYH9</i>	-	-
-	-	-	-	-	-	-	<i>ZCCHC7</i>	-	<i>MYL12A</i>	-	-
-	-	-	-	-	-	-	<i>EXOSC10</i>	-	<i>MYL12B</i>	-	-
-	-	-	-	-	-	-	-	<i>PATL1</i>	<i>NRAS</i>	-	-
-	-	-	-	-	-	-	-	-	<i>PARD6G</i>	-	-
-	-	-	-	-	-	-	-	-	<i>PPP2R2A</i>	-	-

Table E7 continued

Nasal	Tight junction	
	Bronchial (cohort 1)	Bronchial (cohort 2)
<i>PPP2R2C</i>	-	-
<i>PTEN</i>	-	-
<i>RAB13</i>	-	-
<i>SRC</i>	-	-
-	<i>CLDN22</i>	-
-	<i>PRKCB</i>	-
-	<i>MYH10</i>	-
-	<i>PRKCD</i>	-
-	<i>EXOC4</i>	-
-	<i>CSNK2A1</i>	-
-	<i>MAGI1</i>	-
-	<i>PPP2R2D</i>	-
-	<i>PRKCH</i>	-
-	<i>PRKCE</i>	-
-	<i>CGN</i>	-
-	<i>RAB3B</i>	-
-	<i>CSNK2A2</i>	-
-	<i>MAGI2</i>	-
-	<i>INADL</i>	-
-	-	<i>MYH2</i>
-	-	<i>CLDN3</i>
-	-	<i>AKT1</i>
-	-	<i>ACTB</i>
-	-	<i>MYH11</i>
-	-	<i>MYH6</i>
-	-	<i>MYH7B</i>
-	-	<i>PPP2R1A</i>
-	-	<i>SPTAN1</i>
-	-	<i>RHOA</i>

References

1. Steiling K, van den Berge M, Hijazi K, Florido R, Campbell J, Liu G, et al. A dynamic bronchial airway gene expression signature of chronic obstructive pulmonary disease and lung function impairment. *Am J Respir Crit Care Med.* 2013;187: 933-942.