

Supplementary Table 1:

Top gene-sets associated with COPD in COPDGene and GenKOLS.

Full list of all 42 gene-sets that reached nominal significance in COPDGene and GenKOLS. Gene-sets are given together with their p-values for the two studies. METAINFO: GENE-SET – name of the gene-set, for a detailed description please see MsigDB, N_all – number of genes in this gene list (MsigDB). COPDGene / GenKOLS / ECLIPSE: N_in – number of successfully incorporated genes per gene-set, P – p-value for gene-set, Pcorr – results of analysis without known COPD genes in the gene-sets. Combined: P – p-value for gene-set after meta-analysis of COPDGene and GenKOLS study results, Pcorr – results of meta-analysis without known COPD genes in the gene-sets. Gene-sets highlighted in bold demonstrated a nominally significant p-value across all studied samples.

Supplementary Table 2:

REACTOME PRESYNAPTIC NICOTINIC ACETYLCHOLINE RECEPTORS pathway gene list and corresponding FORGE gene-based results in COPDGene and GENKOLS.

This pathway was the top pathway associated with COPD case-control status in both COPDGene and in GenKOLS. The FORGE gene-based results are displayed for both studies. METAINFO: GENE – HUGO gene name, CHR – chromosome, START – start position in base pairs from the start of the chromosome, STOP – stop position in base pairs from the start of the chromosome; COPDGene / GenKOLS / ECLIPSE: N – number of SNPs annotated to this gene for the respective study, Min P – p-value for the SNP with the lowest p-value (of all SNPs annotated to the gene), Gene P – gene-based p-value for this gene from FORGE analyses. Combined: Gene P – gene-based p-value for this gene from meta-analysis of COPDGene and GenKOLS single study p-values. Genes are highlighted in bold if they surpass the experiment-wide significance level ($1E-06$) for the gene-based analyses or a SNP annotated to the gene ($5E-08$) in the discovery population (COPDGene). Genes are highlighted in italics if they reached nominal significance for the gene-based discovery (COPDGene) and replication (GenKOLS) results. All p-values achieving nominal significance are shaded in grey.

Supplementary Figure 1: a. dmGWAS consensus module generated using the COPDGene results that replicated in GenKOLS. Node color is proportional to p-value significance where the lighter the node shading the smaller the p-value from the gene-based analysis in FORGE. **b.** dmGWAS analysis repeated excluding *UBC* using COPDGene results that replicated in GenKOLS.

Supplementary Figure 2: dmGWAS consensus networks that were generated when the FORGE p-values in COPDGene and GenKOLS were shuffled and run in dmGWAS 10 times.

METAINFO

GENE-SET

REACTOME_PRESYNAPTIC_NICOTINIC_ACETYLCHOLINE_RECEPTORS
REACTOME_ACETYLCHOLINE_BINDING_AND_DOWNSTREAM_EVENTS

REACTOME_HIGHLY_CALCIIUM_PERMEABLE_POSTSYNAPTIC_NICOTINIC_ACETYLCHOLINE_RECEPTORS
REACTOME_TRANSMISSION_ACROSS_CHEMICAL_SYNAPSES

HOOI_ST7_TARGETS_UP

REACTOME_NEUROTRANSMITTER_RECEPTOR_BINDING_AND_DOWNSTREAM_TRANSMISSION_IN_
THE_POSTSYNAPTIC_CELL

NICOTINIC_ACETYLCHOLINE_ACTIVATED_CATION_SELECTIVE_CHANNEL_ACTIVITY

NICOTINIC_ACETYLCHOLINE_GATED_RECEPTOR_CHANNEL_COMPLEX

REACTOME_SIGNALING_BY_FGFR1_FUSION_MUTANTS

REACTOME_REGULATION_OF_SIGNALING_BY_CBL

GSE12366_GC_BCELL_VS_PLASMA_CELL_UP

NIKOLSKY_BREAST_CANCER_15Q26_AMPLICON

AMINE_BINDING

GSE17721_LPS_VS_CPG_2H_BMDM_UP

V\$FOXO3_01

SENESE_HDAC2_TARGETS_UP

KEGG_OLFACTORY_TRANSDUCTION

SHETH_LIVER_CANCER_VS_TXNIP_LOSS_PAM1

VANOEVERLEN_MYOGENESIS_SIN3A_TARGETS

KEGG_FOCAL_ADHESION

ACETYLCHOLINE_BINDING

REACTOME_NEURONAL_SYSTEM

BIOCARTA_GLEEVEC_PATHWAY

CHIARADONNA_NEOPLASTIC_TRANSFORMATION_KRAS_CDC25_DN

FARMER_BREAST_CANCER_CLUSTER_8

KEGG_SYSTEMIC_LUPUS_ERYTHEMATOSUS

GSE2706_LPS_VS_R848_AND_LPS_2H_STIM_DC_DN

KATSANOUELAVL1_TARGETS_UP

YAO_TEMPORAL_RESPONSE_TO_PROGESTERONE_CLUSTER_9

REACTOME_APC_C_CDH1_MEDIATED_DEGRADATION_OF_CDC20_AND_OTHER_APC_C_CDH1_

TARGETED_PROTEINS_IN_LATE_MITOSIS_EARLY_G1

REACTOME_DESTABILIZATION_OF_MRNA_BY_AUF1_HNRNP_D0

KANG_AR_TARGETS_UP

NIKOLSKY_BREAST_CANCER_16Q24_AMPLICON

REACTOME_SIGNALING_BY_HIPPO

GSE36476_CTRL_VS_TSST_ACT_16H_MEMORY_CD4_TCELL_OLD_DN

POTASSIUM_CHANNEL_REGULATOR_ACTIVITY

GCCNNNWTAAR_UNKNOWN

ZWANG_EGF_PERSISTENTLY_UP

REACTOME_CDT1_ASSOCIATION_WITH_THE_CDC6_ORC_ORIGIN_COMPLEX

V\$EGR1_01

MODY_HIPPOCAMPUS_POSTNATAL

GSE20366_CD103_POS_VS_CD103_KLRG1_DP_TREG_DN

Discovery										
N_all	COPDGene				GenKOLS				Combined	
	N	Ncorr	P	Pcorr	N	Ncorr	P	Pcorr	P	Pcorr
12	12	9	3.2E-04	0.11	12	9	0.0066	0.12	2.8E-05	0.10
16	14	11	5.4E-04	0.11	14	11	0.0056	0.094	4.3E-05	0.088
13	11	8	0.0024	0.34	11	8	0.0055	0.12	2.1E-04	0.35
186	172	169	0.0029	0.015	172	169	0.0060	0.016	2.8E-04	0.0033
94	80	80	0.0050	0.0050	80	80	0.031	0.031	0.0016	0.0016
137	126	123	0.0053	0.032	126	123	0.016	0.043	0.0010	0.014
11	11	9	0.0083	0.268	11	9	0.016	0.11	0.0017	0.26
11	11	9	0.0083	0.268	11	9	0.016	0.11	0.0017	0.26
19	18	18	0.011	0.011	18	18	0.006	0.0059	0.0013	0.0013
18	18	18	0.012	0.012	18	18	0.035	0.035	0.0043	0.0043
200	177	177	0.013	0.013	177	177	0.0054	0.0054	0.0014	0.0014
22	21	21	0.014	0.014	21	21	0.0085	0.0085	0.0020	0.0020
23	21	18	0.015	0.340	21	18	0.027	0.19	0.0046	0.43
200	188	188	0.016	0.016	187	187	0.030	0.030	0.0052	0.0052
245	226	226	0.017	0.017	226	226	0.030	0.030	0.0054	0.0054
114	110	110	0.017	0.017	110	110	0.0040	0.0040	0.0016	0.0016
389	356	356	0.018	0.018	357	357	0.043	0.043	0.0078	0.0078
229	213	213	0.019	0.019	213	213	0.012	0.012	0.0035	0.0035
220	211	211	0.020	0.020	211	211	0.0075	0.0075	0.0028	0.0028
201	191	191	0.025	0.025	191	191	0.013	0.013	0.0052	0.0052
17	17	14	0.026	0.52	17	14	0.0086	0.104	0.0042	0.56
279	262	259	0.027	0.074	262	259	0.045	0.082	0.012	0.052
23	23	23	0.030	0.030	23	23	0.035	0.035	0.011	0.011
51	47	47	0.030	0.030	47	47	0.0085	0.0085	0.0050	0.0050
7	7	7	0.033	0.033	7	7	0.023	0.023	0.010	0.0099
140	121	121	0.034	0.034	122	122	0.050	0.050	0.016	0.016
200	137	136	0.034	0.058	137	136	0.0022	0.0032	0.003	0.0069
169	160	160	0.035	0.035	160	160	0.026	0.026	0.011	0.011
76	71	71	0.037	0.037	71	71	0.033	0.033	0.014	0.014
72	62	62	0.037	0.037	62	62	0.041	0.041	0.016	0.016
53	49	49	0.038	0.038	49	49	0.041	0.041	0.017	0.017
17	15	15	0.039	0.039	15	15	0.0030	0.0030	0.0039	0.0039
53	50	50	0.040	0.040	50	50	0.0092	0.0092	0.0073	0.0073
22	19	19	0.041	0.041	19	19	0.0071	0.0071	0.0065	0.0065
200	192	192	0.041	0.041	192	192	0.029	0.029	0.014	0.014

14	13	13	0.042	0.042	13	13	0.0025	0.0025	0.0040	0.0040
149	134	134	0.042	0.042	134	134	0.028	0.028	0.015	0.015
32	29	29	0.045	0.045	29	29	0.0071	0.0071	0.0075	0.0075
56	53	53	0.046	0.046	53	53	0.047	0.047	0.022	0.022
269	251	251	0.047	0.047	251	251	0.0034	0.0034	0.0054	0.0053
63	58	58	0.049	0.049	58	58	0.046	0.046	0.023	0.023
200	187	187	0.049	0.048	187	187	0.045	0.045	0.023	0.022

Replication
ECLIPSE

N	Ncorr	P	Pcorr
12	9	0.87	0.96
14	11	0.84	0.94
11	8	0.75	0.90
172	169	0.46	0.50
80	80	0.79	0.79
126	123	0.68	0.73
11	9	0.92	0.96
11	9	0.92	0.96
18	18	0.69	0.69
18	18	0.15	0.15
177	177	0.94	0.94
21	21	0.076	0.076
21	18	0.44	0.57
188	188	0.52	0.52
226	226	0.032	0.031
110	110	0.26	0.26
359	359	0.83	0.82
213	213	0.43	0.43
212	212	0.54	0.54
191	191	0.15	0.15
17	14	0.62	0.76
262	259	0.93	0.94
23	23	0.31	0.31
47	47	0.59	0.59
7	7	0.22	0.22
122	122	0.70	0.69
137	136	0.39	0.39
160	160	0.69	0.69
71	71	0.22	0.22
62	62	0.43	0.43
49	49	0.39	0.39
15	15	0.14	0.14
50	50	0.0062	0.0062
19	19	0.95	0.95
192	192	0.30	0.30

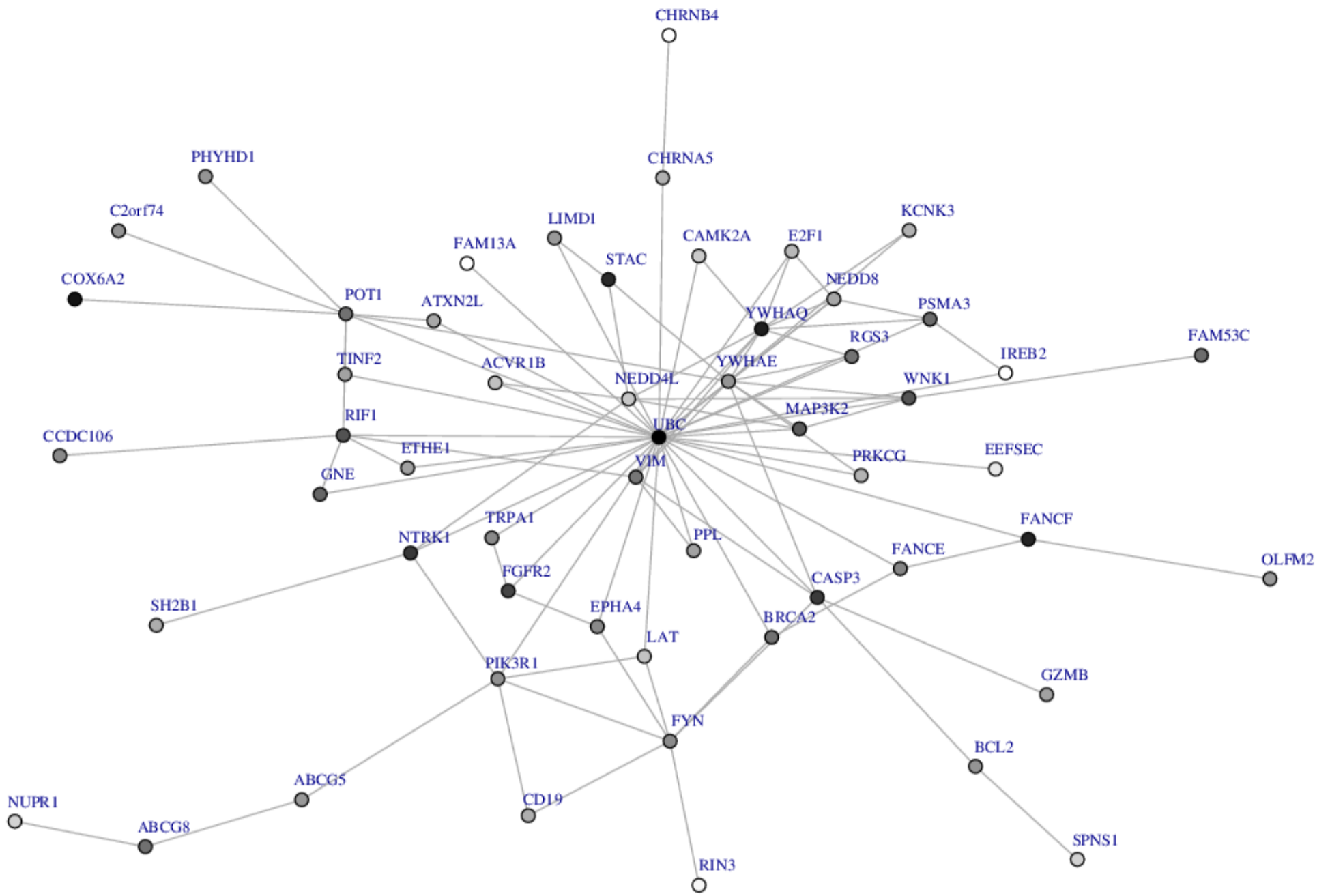
13	13	0.92	0.92
134	134	0.17	0.16
29	29	0.88	0.88
53	53	0.32	0.32
251	251	0.022	0.021
58	58	0.29	0.28
187	187	0.90	0.90

METAINFO

COPDGene

GENE	CHR	START	STOP	N	Min P	Gene P	N
CHRNA1	2	175612320	175629200	37	0.17	0.50	36
CHRNA2	8	27317279	27337400	71	0.042	0.84	71
CHRNA3	15	78885394	78913637	54	1.3E-08	1.7E-05	54
CHRNA4	20	61975420	62009753	36	0.048	0.80	35
CHRNA5	15	78857862	78887611	44	4.7E-08	0.0011	44
CHRNA2	1	154540257	154552502	22	0.15	0.41	22
CHRNA3	8	42552519	42592550	37	0.012	0.18	38
CHRNA4	15	78916461	79012628	81	1.3E-08	1.0E-06	82
CHRND	2	233390703	233401377	25	0.018	0.16	25
CHRNE	17	4801069	4806369	19	0.012	0.067	19
CHRNG	2	233404437	233412546	29	0.013	0.063	29
CHRNA6	8	42607763	42651535	28	0.022	0.085	30

y				Replication		
	GenKOLS		Combined	ECLIPSE		
	Min P	Gene P	Gene P	N	Min P	Gene P
	0.10	0.50	0.99	39	0.075	0.16
	3.4E-04	0.33	0.51	75	0.010	0.86
	3.8E-04	0.0027	6.5E-07	60	0.059	0.17
	0.073	0.74	0.29	36	0.068	0.70
	2.6E-04	0.0093	1.3E-04	52	0.059	0.25
	0.078	0.23	0.58	23	0.093	0.79
	0.052	0.079	0.14	39	0.17	0.57
	7.1E-04	0.0080	1.0E-07	86	0.16	0.52
	0.078	0.21	0.21	27	0.12	0.96
	0.030	0.50	0.19	20	0.17	0.89
	0.078	0.33	0.12	33	0.11	0.43
	0.038	0.15	0.089	32	0.077	1

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