**Supplemental table E4. Leading edge genes of the 25 pathways that are most enriched in the SEO-COPD vs control comparison**

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| --- | --- | --- | --- | --- |
| #1) GOCC:  Immunoglobulin complex\* | #2) GOMF:  Antigen binding\* | #3) GOCC:  Immunoglobulin complex circulating\* | #4) GOBP:  Phagocytosis recognition\* | #5) GOMF: Immunoglobulin receptor binding\* |
| **IGLV2-11**  IGLC2  **IGLV2-14**  **IGHV1-18**  **CD79A**  IGLV6-57  IGKV1-27  IGLV1-40  *+55 more* | **IGLV2-11**  IGLC2  **IGLV2-14**  **IGHV1-18**  IGLV6-57  IGLV1-40  IGHA1  IGKV1-17  *+59 more* | IGLC2  **IGHV1-18**  IGHA1  IGHG3  IGHV2-70  IGHV3-73  JCHAIN  IGHV3-21  *+27 more* | IGLC2  **IGHV1-18**  **PTX3**  IGHA1  MFGE8  IGHG3  IGHV2-70  IGHV3-73  *+32 more* | IGLC2  **IGHV1-18**  IGHA1  IGHG3  IGHV2-70  IGHV3-73  JCHAIN  IGHV3-21  *+27 more* |
| #6) GOBP:  Humoral immune response mediated by circulating immunoglobulin\* | #7) GOBP:  Humoral immune response\* | #8) GOBP:  Complement activation\* | #9) GOBP:  B-cell receptor signaling pathway\* | #10) GOBP:  Regulation of B-cell activation\* |
| C7  C1S  IGLC2  **IGHV1-18**  SERPING1  C1R  IGHA1  IGHG3  *+35 more* | C7  C1S  **GATA6**  IGLC2  **IGHV1-18**  SERPING1  BCL2  C1R  *+78 more* | C7  C1S  IGLC2  **IGHV1-18**  SERPING1  C1R  IGHA1  A2M  *+39 more* | IGLC2  **IGHV1-18**  **CD79A**  BMX  BCL2  IGHA1  MS4A1  CTLA4  *+37 more* | IGLC2  **IKZF3**  **IGHV1-18**  MZB1  BCL2  IGHA1  TNFAIP3  CTLA4  *+54 more* |
| #11) GOBP: Positive regulation of B-cell activation\* | #12) GOCC: Blood microparticle | #13) GOBP:  B-cell activation\* | #14) GOMF:  Glycosaminoglycan binding§ | #15) GOMF:  Extracellular matrix structural constituent‡ |
| IGLC2  **IGHV1-18**  BCL2  IGHA1  TNFRSF13C  IGHG3  IGHV2-70  IGHV3-73  *+42 more* | C1S  IGLC2  SERPING1  C1R  IGHA1  IGKV1-17  A2M  HSPA2  *+38 more* | IGLC2  **IKZF3**  **IGHV1-18**  **CD79A**  LAX1  MZB1  BCL2  IGHA1  *+87 more* | **ADAMTS15**  PTPRS  **SMOC2**  FGF7  **FBN1**  SULF1  CCN5  FGFR4  *+61 more* | **PODN**  **SPON1**  **EMILIN1**  **FBN1**  **FBLN1**  COL6A1  SRPX2  MFGE8  *+55 more* |
| #16) GOBP: B-cell mediated immunity\* | #17) GOBP: Adaptive immune response\* | #18) GOBP:  Membrane invagination\* | #19) GOBP: Antimicrobial humoral response\* | #20) GOCC:  External side of plasma membrane† |
| C7  C1S  IGLC2  **IGHV1-18**  SERPING1  C1R  IGHA1  IGHG3  *+46 more* | C7  **PRDM1**  **IGLV2-11**  C1S  IGLC2  **IGLV2-14**  **IGHV1-18**  **CD79A**  *+147 more* | **RHOH**  IGLC2  **IGHV1-18**  IGHA1  MFGE8  THBS1  IGHG3  IGHV2-70  *+33 more* | **GATA6**  IGHA1  CXCL10  RARRES2  JCHAIN  TF  IGHM  CXCL11  *+7 more* | **CXCL12**  **ITGA7**  IGLC2  **IGHV1-18**  **CD79A**  CXCR4  CD69  GFRA1  *+131 more* |
| #21) GOBP: Cell recognition\* | #22) GOBP: Immunoglobulin production\* | #23) GOBP: Antigen receptor mediated signaling pathway\* | #24) GOMF: Cytokine binding† | #25) GOMF: Heparin binding§ |
| IGLC2  **IGHV1-18**  **PTX3**  CXCR4  IGHA1  MFGE8  CCL19  IGHG3  *+52 more* | **IGLV2-11**  **IGLV2-14**  IGLV6-57  IGKV1-27  MZB1  IGLV1-40  IGKV1-17  IGLV3-10  *+34 more* | IGLC2  **IGHV1-18**  **CD79A**  LAX1  BMX  BCL2  IGHA1  CD3E  *+67 more* | CXCR4  CHRDL1  A2M  THBS1  TGFB3  LTBP1  CCR7  IL1R1  *+43 more* | **ADAMTS15**  PTPRS  **SMOC2**  FGF7  **FBN1**  CCN5  FGFR4  SAA1  *+44 more* |

Leading edge genes of the 25 pathways with the highest normalized enrichment score (NES) from the SEO-COPD vs control gene set enrichment analysis. Rank in GSEA result list given for each pathway. Leading edge genes in pathways ordered on rank, only first eight shown per pathway. Genes that overlap with the 105 SEO-COPD gene signature are marked in bold. \*Blue: pathway is in the Adaptive immune system cluster. †Green: pathway is in the Chemotaxis and cytokine signaling cluster. ‡Red: pathway is in the Extracellular matrix organization cluster. §Yellow: pathway is in the Glycosaminoglycan binding cluster. See **figure 2** for clusters and **figure 3** for corresponding cluster colors and leading edge overlap.