

**Multi-omics Mendelian randomization using different molecular traits to identify novel drug targets on complex diseases**

Appendix



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|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| European ancestry conditional SNP: 7650(7105 pQTLs)(1992 protein) | | | | | | | |
| after mapping with EA summary data: 6614(6107 pQTLs)(1311 protein) | | | | | | | |
| after 0.6 LD clumping: 6144(5974 pQTLs)(1310 protein) | | | | | | | |
| Removing weak instruments (F-statistics<10) 5418(5285 pQTLs)(1310 protein) | | | | | | | |
| match with Asthma outcome | match with COPD outcome | match with Gout outcome | match with POAG outcome | match with VTE outcome | match with IPF outcome | match with Stroke outcome | match with HF outcome |
| 4894 pQTLs (1297 protein) | 4895 pQTLs (1297 protein) | 4896 pQTLs (1297 protein) | 4893 pQTLs (1297 protein) | 4894 pQTLs (1297 protein) | 4896 pQTLs (1297 protein) | 4895 pQTLs (1297 protein) | 4898 pQTLs (1297 protein) |
| after Steiger filtering | after Steiger filtering | after Steiger filtering | after Steiger filtering | after Steiger filtering | after Steiger filtering | after Steiger filtering | after Steiger filtering |
| 4870 pQTLs (1294 protein) | 4774 pQTLs (1288 protein) | 4774 pQTLs (1288 protein) | 4729 pQTLs (1290 protein) | 4744 pQTLs (1291 protein) | 4577 pQTLs (1278 protein) | 4749 pQTLs (1289 protein) | 4824 pQTLs (1294 protein) |

Table S : Summary of data processing for the European pQTLs

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| African ancestry conditional SNP: 4246(4129 pQTLs)(1605 protein) | | | | | | | |
| after mapping with AA summary data: 3900(3793 pQTLs)(1312 protein) | | | | | | | |
| after 0.6 LD clumping: 3875(3785 pQTLs)(1311 protein) | | | | | | | |
| Removing weak instruments (F-statistics<10) 3550(3473 pQTLs)(1311 protein) | | | | | | | |
| match with Asthma outcome | match with COPD outcome | match with Gout outcome | match with POAG outcome | match with VTE outcome | match with IPF outcome | match with Stroke outcome | match with HF outcome |
| 3173 pQTLs (1263 protein) | 3173 pQTLs (1263 protein) | 3173 pQTLs (1263 protein) | 3050 pQTLs (1246 protein) | 3173 pQTLs (1263 protein) | 3162 pQTLs (1261 protein) | 3168 pQTLs (1263 protein) | 3173 pQTLs (1263 protein) |
| after Steiger filtering | after Steiger filtering | after Steiger filtering | after Steiger filtering | after Steiger filtering | after Steiger filtering | after Steiger filtering | after Steiger filtering |
| 3151 pQTLs (1263 protein) | 3108 pQTLs (1254 protein) | 3070 pQTLs (1252 protein) | 2790 pQTLs (1204 protein) | 3083 pQTLs (1249 protein) | 2421 pQTLs (1132 protein) | 3041 pQTLs (1253 protein) | 3089 pQTLs (1251 protein) |

Table S : Summary of data processing for the African pQTLs

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Endpoint | name | Sex | Dataset | Biobank | Ancestry | Case | Control | N\_total | N\_SNPs |
| Idiopathic pulmonary fibrosis | IPF | Bothsex | Total | 2 | 1 | 169 | 8,368 | 8,537 | 18,058,634 |
| Primary open-angle glaucoma | POAG | Bothsex | Total | 3 | 1 | 483 | 26,323 | 26,806 | 15,534,506 |
| Heart failure | HF | Bothsex | Total | 4 | 1 | 1,367 | 29,835 | 31,202 | 24,631,161 |
| Venous thromboembolism | VTE | Bothsex | Total | 4 | 1 | 1,466 | 31,042 | 32,508 | 24,935,323 |
| Stroke | Stroke | Bothsex | Total | 4 | 1 | 1,161 | 24,416 | 25,577 | 21,994,124 |
| Gout | Gout | Bothsex | Total | 6 | 1 | 1,312 | 33,902 | 35,214 | 25,056,505 |
| Chronic obstructive pulmonary disease | COPD | Bothsex | Total | 6 | 1 | 1,978 | 27,704 | 29,682 | 23,889,093 |
| Asthma | Asthma | Bothsex | Total | 6 | 1 | 5,051 | 27,607 | 32,658 | 24,660,533 |
| Idiopathic pulmonary fibrosis | IPF | Female | Total | NR | NR | NR | NR | NR | NR |
| Primary open-angle glaucoma | POAG | Female | Total | 2 | 1 | 249 | 12,361 | 12,610 | 15,313,506 |
| Heart failure | HF | Female | Total | 2 | 1 | 542 | 12,211 | 12,753 | 16,366,512 |
| Venous thromboembolism | VTE | Female | Total | 4 | 1 | 795 | 18,306 | 19,101 | 22,266,615 |
| Stroke | Stroke | Female | Total | 3 | 1 | 639 | 14,459 | 15,098 | 19,332,406 |
| Gout | Gout | Female | Total | 2 | 1 | 405 | 13,731 | 14,136 | 17,064,891 |
| Chronic obstructive pulmonary disease | COPD | Female | Total | 5 | 1 | 1,060 | 15,990 | 17,050 | 21,218,274 |
| Asthma | Asthma | Female | Total | 5 | 1 | 3,408 | 15,993 | 19,401 | 22,046,242 |
| Idiopathic pulmonary fibrosis | IPF | Male | Total | NR | NR | NR | NR | NR | NR |
| Primary open-angle glaucoma | POAG | Male | Total | 2 | 1 | 155 | 7,705 | 7,860 | 14,154,062 |
| Heart failure | HF | Male | Total | 3 | 1 | 466 | 10,006 | 10,472 | 19,265,630 |
| Venous thromboembolism | VTE | Male | Total | 2 | 1 | 18,392 | 276,146 | 294,538 | 19,167,224 |
| Stroke | Stroke | Male | Total | 2 | 1 | 347 | 7,737 | 8,084 | 14,526,945 |
| Gout | Gout | Male | Total | 4 | 1 | 648 | 9,713 | 10,361 | 17,289,485 |
| Chronic obstructive pulmonary disease | COPD | Male | Total | 4 | 1 | 692 | 10,385 | 11,077 | 19,835,727 |
| Asthma | Asthma | Male | Total | 5 | 1 | 1,362 | 10,733 | 12,095 | 20,105,752 |

Table S : Information of the GBMI African-specific GWASs

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Endpoint | name | Sex | Dataset | Biobank | Ancestry | Case | Control | N\_total | N\_SNPs |
| Idiopathic pulmonary fibrosis | IPF | Bothsex | Total | 8 | 1 | 5,229 | 750,630 | 755,859 | 45,621,626 |
| Primary open-angle glaucoma | POAG | Bothsex | Total | 11 | 1 | 11,922 | 946,349 | 958,271 | 46,421,873 |
| Heart failure | HF | Bothsex | Total | 9 | 1 | 28,795 | 772,854 | 801,649 | 46,480,843 |
| Venous thromboembolism | VTE | Bothsex | Total | 6 | 1 | 15,970 | 681,106 | 697,076 | 44,258,755 |
| Stroke | Stroke | Bothsex | Total | 12 | 1 | 15,842 | 842,678 | 858,520 | 46,916,547 |
| Gout | Gout | Bothsex | Total | 10 | 1 | 20,702 | 823,829 | 844,531 | 47,218,578 |
| Chronic obstructive pulmonary disease | COPD | Bothsex | Total | 11 | 1 | 51,644 | 750,635 | 802,279 | 45,532,064 |
| Asthma | Asthma | Bothsex | Total | 13 | 1 | 101,311 | 1,118,682 | 1,219,993 | 47,156,680 |
| Idiopathic pulmonary fibrosis | IPF | Female | Total | 5 | 1 | 1,281 | 324,340 | 325,621 | 30,122,297 |
| Primary open-angle glaucoma | POAG | Female | Total | 8 | 1 | 3,055 | 358,334 | 361,389 | 30,378,775 |
| Heart failure | HF | Female | Total | 6 | 1 | 6,414 | 339,114 | 345,528 | 30,796,627 |
| Venous thromboembolism | VTE | Female | Total | 4 | 1 | 6,210 | 290,495 | 296,705 | 27,492,256 |
| Stroke | Stroke | Female | Total | 9 | 1 | 4,786 | 374,631 | 379,417 | 31,014,093 |
| Gout | Gout | Female | Total | 6 | 1 | 2,569 | 357,103 | 359,672 | 31,030,676 |
| Chronic obstructive pulmonary disease | COPD | Female | Total | 8 | 1 | 16,868 | 329,201 | 346,069 | 29,908,839 |
| Asthma | Asthma | Female | Total | 9 | 1 | 38,075 | 339,423 | 377,498 | 31,152,977 |
| Idiopathic pulmonary fibrosis | IPF | Male | Total | 5 | 1 | 1,701 | 262,944 | 264,645 | 28,658,316 |
| Primary open-angle glaucoma | POAG | Male | Total | 8 | 1 | 2,758 | 295,037 | 297,795 | 29,005,259 |
| Heart failure | HF | Male | Total | 6 | 1 | 10,288 | 278,037 | 288,325 | 29,315,684 |
| Venous thromboembolism | VTE | Male | Total | 4 | 1 | 7,080 | 243,671 | 250,751 | 26,399,801 |
| Stroke | Stroke | Male | Total | 9 | 1 | 5,744 | 303,338 | 309,082 | 29,517,405 |
| Gout | Gout | Male | Total | 7 | 1 | 9,249 | 294,636 | 303,885 | 29,727,215 |
| Chronic obstructive pulmonary disease | COPD | Male | Total | 8 | 1 | 18,392 | 276,146 | 294,538 | 29,077,843 |
| Asthma | Asthma | Male | Total | 9 | 1 | 23,890 | 284,962 | 308,852 | 29,843,298 |

Table S : Information of the GBMI European-specific GWASs

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SOMAmerID | Entrez Gene | P | Heterogeneity | Pleiotropy | Outcome | LD\_r2 | Coloc\_prob | Coloc\_overall | Ancestry |
| SeqId\_11387\_3 | ATF6B | 3.43E-24 | TRUE | TRUE | Asthma | 42% | 0% | Not colocalized | EA |
| SeqId\_4440\_15 | FCRL3 | 3.05E-33 | TRUE | TRUE | Asthma | 100% | 0% | Colocalized | EA |
| SeqId\_4440\_15 | FCRL3 | 0.00E+00 | TRUE | TRUE | COPD | 100% | 7% | Colocalized | EA |
| SeqId\_4440\_15 | FCRL3 | 0.00E+00 | TRUE | TRUE | Gout | 1% | 0% | Not colocalized | EA |
| SeqId\_4440\_15 | FCRL3 | 1.06E-70 | TRUE | TRUE | HF | 100% | 0% | Colocalized | EA |
| SeqId\_4440\_15 | FCRL3 | 0.00E+00 | TRUE | TRUE | IPF | 6% | 15% | Not colocalized | EA |
| SeqId\_4440\_15 | FCRL3 | 1.23E-09 | TRUE | TRUE | POAG | 8% | 4% | Not colocalized | EA |
| SeqId\_4440\_15 | FCRL3 | 0.00E+00 | TRUE | TRUE | Stroke | 2% | 1% | Not colocalized | EA |
| SeqId\_4440\_15 | FCRL3 | 0.00E+00 | TRUE | TRUE | VTE | 1% | 1% | Not colocalized | EA |
| SeqId\_4964\_67 | ERAP1 | 9.07E-12 | FALSE | TRUE | COPD | 100% | 1% | Colocalized | EA |

Table S : Protein-disease assocaitions passed FDR < 0.05 but with evidence of horizontal pleiotropy in European ancestry

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SOMAmerID | Entrez Gene | P | Heterogeneity | Pleiotropy | Outcome | LD\_r2 | Coloc\_prob | Coloc\_overall | Ancestry |
| SeqId\_14133\_93 | IL1R2 | 2.29E-02 | TRUE | TRUE | Asthma | 7% | 0% | Not colocalised | EA |
| SeqId\_4234\_8 | IL1RL1 | 1.67E-02 | TRUE | TRUE | Asthma | 61% | 0% | Not colocalised | EA |
| SeqId\_12378\_71 | TAPBP | 1.94E-02 | TRUE | TRUE | Asthma | 63% | 0% | Not colocalised | EA |
| SeqId\_7916\_10 | S100A7 | 2.44E-03 | FALSE | TRUE | Asthma | 36% | 0% | Not colocalised | EA |
| SeqId\_5353\_89 | IL1RN | 7.90E-03 | TRUE | TRUE | Asthma | 97% | 4% | Colocalised | EA |
| SeqId\_12436\_84 | GSTO1 | 1.65E-02 | FALSE | TRUE | COPD | 99% | 95% | Colocalised | EA |
| SeqId\_4407\_10 | MST1 | 2.92E-03 | TRUE | TRUE | COPD | 100% | 34% | Colocalised | EA |
| SeqId\_15388\_24 | FCGR3A | 3.37E-02 | TRUE | TRUE | COPD | 99% | 63% | Colocalised | EA |
| SeqId\_5722\_78 | PRCP | 4.58E-02 | TRUE | TRUE | Gout | 31% | 25% | Not colocalised | EA |
| SeqId\_18922\_27 | CD68 | 1.25E-02 | FALSE | TRUE | Gout | 2% | 30% | Not colocalised | EA |
| SeqId\_4989\_7 | FGG | 4.08E-03 | TRUE | TRUE | VTE | 100% | 0% | Colocalised | EA |
| SeqId\_8244\_16 | FUT8 | 5.85E-03 | FALSE | TRUE | VTE | 70% | 77% | Colocalised | EA |
| SeqId\_3077\_66 | F10 | 4.82E-03 | TRUE | TRUE | VTE | 97% | 40% | Colocalised | EA |
| SeqId\_4878\_3 | F10 | 1.66E-02 | TRUE | TRUE | VTE | 97% | 40% | Colocalised | EA |
| SeqId\_3580\_25 | SERPINA1 | 2.65E-03 | TRUE | TRUE | IPF | 88% | 99% | Colocalised | EA |
| SeqId\_3290\_50 | CD109 | 2.81E-02 | FALSE | TRUE | IPF | 100% | 4% | Colocalised | EA |
| SeqId\_19557\_3 | KLB | 4.58E-02 | FALSE | TRUE | HF | 100% | 1% | Colocalised | EA |

Table S : Protein-disease assocaitions passed MR P-value <0.05 but with evidence of horizontal pleiotropy in European ancestry

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Protein-disease MR information | | Drugbank information | | | OpenTargets information | | MR evidence from this study | Evidence synthesis |
| Protein(Gene) | Outcome | Drugbank ID(name) | Molecular action | Current clinical indication(s) | Overall score | Genetic score |
| Angiotensin-converting enzyme(ACE) | Chronic obstructive pulmonary disease | DB00492(Fosinopril) | Inhibitor | Hypertension, chronic obstructive pulmonary disease | 0.4 | 0 | 1.64×10-3 | Validating efficacy in African ancestry |
| Coagulation Factor VII(F7) | Stroke | DB00036(Coagulation factor VIIa Recombinant Human) | Inhibitor | Hemophilia A and B | 0 | 0 | 2.42×10-3 | Repurposing |
| Allograft inflammatory factor 1(AIF1) | Heart failure | DB03147(Flavin adenine dinucleotide) | Unknown | Vitamin B2 deficiency | 0.03 | 0 | 2.67×10-3 | Repurposing |
| Coagulation Factor XI(F11) | Venous thromboembolism | DB00100(Coagulation Factor XI) | Ligand | Hemophilia B, Hereditary angioedema | 0.49 | 0.79 | 6.14×10-61 | Repurposing |
| Kallikrein B1(KLKB1) | Venous thromboembolism | DB05311(Ecallantide) | Inhibitor | Hereditary angioedema | 0.05 | 0.08 | 4.59×10-15 | Repurposing |
| Endoplasmic Reticulum Aminopeptidase 1(ERAP1) | Primary open-angle glaucoma | DB11781(Tosedostat) | Inhibitor | Acute myeloid leukemia, pancreas cancer, multiple myeloma, and pancreatic cancer | 0 | 0 | 9.19×10-14 | Repurposing |
| TNF Superfamily Member 12(TNFSF12) | Asthma | N/A(BIIB-023\*) | Inhibitor | Lupus nephritis | 0.01 | 0 | 1.50×10-7 | Repurposing |
| Interleukin 7 Receptor(IL7R) | Asthma | DB08895(Tofacitinib) | Inhibitor | Rheumatoid and psoriatic arthritis | 0.5 | 0.79 | 3.71×10-3 | Repurposing |

Table S : Drug target validation and repurposing opportunities

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| MR a estimate of effect on disease | Cases/controls | | MR signals with FDR b <0.05 and colocalization evidence | |
| European ancestry | African ancestry | European ancestry | African ancestry |
| Idiopathic pulmonary fibrosis (IPF) | 4,066/751,962 | 168/8,364 | 3 | 0 |
| Primary open-angle glaucoma (POAG) | 11,657/957,371 | 483/26,323 | 3 | 0 |
| Heart failure (HF) | 27,064/796,602 | 970/16,823 | 0 | 0 |
| Venous thromboembolism (VTE) | 15,907/696,395 | 1031/16,743 | 17 | 1 |
| Stroke | 15,520/852,432 | 1,161/24,411 | 2 | 0 |
| Gout | 20,512/843,507 | 1,313/33,896 | 4 | 0 |
| Chronic obstructive pulmonary disease (COPD) | 51,231/800,577 | 1,978/27,699 | 2 | 0 |
| Asthma | 100,736/1,219,215 | 5,054/2,7599 | 14 | 0 |
| Total MR results |  |  | 45 | 1 |
| Multi-ancestry and ancestry-specific MR results | Cases/controls | | Ancestry-specific MR signals with FDR<0.05 | |
| European ancestry | African ancestry | European ancestry | African ancestry |
| Idiopathic pulmonary fibrosis (IPF) | 4,066/751,962 | 168/8,364 | 4 | 0 |
| Primary open-angle glaucoma (POAG) | 11,657/957,371 | 483/26,323 | 9 | 1 |
| Heart failure (HF) | 27,064/796,602 | 970/16,823 | 7 | 1 |
| Venous thromboembolism (VTE) | 15,907/696,395 | 1031/16,743 | 18 | 1 |
| Stroke | 15,520/852,432 | 1,161/24,411 | 4 | 3 |
| Gout | 20,512/843,507 | 1,313/33,896 | 9 | 2 |
| Chronic obstructive pulmonary disease (COPD) | 51,231/800,577 | 1,978/27,699 | 10 | 2 |
| Asthma | 100,736/1,219,215 | 5,054/2,7599 | 28 | 2 |
| Total MR results |  |  | 89 | 12 |
| a MR: Mendelian Randomization, b FDR: False Discovery Rate | | | | |

Table S : Summary of proteome-wide MR results in European and African ancestries