Supplementary Tables

Supplementary Table 1. Haplotype-based FBAT analysis of exertional dyspnoea using the genome-wide significant SNPs rs10165869, rs6725280, rs7607911, rs1865671, rs30102, and rs10168628, where A1 and A2 correspond to the haplotype with all minor and major alleles of 6 SNPs, respectively.

Haplotype	frequency	NINFF*	S-E(S)	Var(S)	Z	P value
A1	0.278	482	77.501	185.445	5.691	1.30E-08
A2	0.651	520	-77.616	197.655	-5.521	3.38E-08

*NINFF number of informative families

Supplementary Table 2. The FBAT results for the genome-wide significant SNPs in the GACRS WGS analysis of exertional dyspnoea and the replication analysis in CAMP.

	Chr	Position	A1	A2	rsID	frequency	NINFF*	S.E.S.	Var.S.	Z	p value
GACRS trios (N=894)	2	236932637	A	G	rs10165869	0.309	561	80.428	180.341	5.989	2.16E-09
	2	236940120	T	C	rs6725280	0.288	562	78.13	175.486	5.898	3.77E-09
	2	236935080	G	A	rs1865671	0.289	564	77.151	174.379	5.842	5.27E-09
	2	236929711	T	C	rs7607911	0.302	569	78.083	179.342	5.831	5.66E-09
	2	236908895	C	G	rs30102	0.304	584	76.225	180.017	5.681	1.37E-08
	2	236933062	A	G	rs10168628	0.336	606	76.898	196.043	5.492	3.97E-08
CAMP trios (N=286, dyspnea: 60.42%)	2	236932637	A	G	rs10165869	0.284	170	18.726	68.288	2.266	0.023445
	2	236940120	T	C	rs6725280	0.267	168	12.27	66.679	1.503	0.132928
	2	236935080	G	A	rs1865671	0.271	172	13.423	68.014	1.628	0.103599
	2	236929711	T	C	rs7607911	0.285	172	17.435	68.467	2.107	0.035107
	2	236908895	C	G	rs30102	0.275	168	16.441	67.900	1.995	0.046018
	2	236933062	A	G	rs10168628	0.338	197	16.772	79.905	1.876	0.060621
CAMP European American (N= 216, dyspnea: 61.21%)	2	236932637	A	G	rs10165869	0.308	135	13.77	56.454	1.833	0.066847
	2	236940120	T	C	rs6725280	0.287	136	8.27	55.512	1.11	0.266992
	2	236935080	G	A	rs1865671	0.288	137	8.958	55.985	1.197	0.231227
	2	236929711	T	C	rs7607911	0.306	136	12.479	56.197	1.665	0.095979
	2	236908895	C	G	rs30102	0.296	134	10.408	55.471	1.397	0.162271
	2	236933062	A	G	rs10168628	0.346	149	14.093	63.622	1.767	0.07726
CAMP African American (N= 28, dyspnea: 55.56%)	2	236932637	A	G	rs10165869	0.116	11	0.887	3.375	0.483	0.629201
	2	236940120	T	C	rs6725280	0.089	8	0.531	2.633	0.328	0.743281
	2	236935080	G	A	rs1865671	0.107	10	0.396	3.135	0.224	0.822818
	2	236929711	T	C	rs7607911	0.116	11	0.887	3.375	0.483	0.629201

	2	236908895	C	G	rs30102	0.098	9	1.022	2.873	0.603	0.546546
	2	236933062	A	G	rs10168628	0.196	14	-2.765	5.023	-1.234	0.217362
CAMP Latinx (N= 19, dyspnea: 63.16%)	2	236932637	A	G	rs10165869	0.365	10	0.719	3.004	0.415	0.678384
	2	236940120	T	C	rs6725280	0.355	10	0.118	3.079	0.067	0.946339
	2	236935080	G	A	rs1865671	0.368	11	0.719	3.44	0.387	0.698392
	2	236929711	T	C	rs7607911	0.368	11	0.719	3.44	0.387	0.698392
	2	236908895	C	G	rs30102	0.355	10	1.141	3.261	0.632	0.527503
	2	236933062	A	G	rs10168628	0.421	13	-1.496	4.047	-0.744	0.4571
CAMP Others (N= 23, dyspnea : 56.52%)	2	236932637	A	G	rs10165869	0.228	14	3.35	5.455	1.435	0.151425
	2	236940120	T	C	rs6725280	0.228	14	3.35	5.455	1.435	0.151425
	2	236935080	G	A	rs1865671	0.228	14	3.35	5.455	1.435	0.151425
	2	236929711	T	C	rs7607911	0.228	14	3.35	5.455	1.435	0.151425
	2	236908895	C	G	rs30102	0.228	15	3.87	6.294	1.542	0.12297
	2	236933062	A	G	rs10168628	0.370	21	6.94	7.213	2.584	0.009767

*NINFF number of informative families

Supplementary Table 3. Significant cis-eQTLs of top SNPs for *ACKR3* (ENSG00000144476.5) in lung tissues. Data Source: GTEx Analysis Release V8 (dbGaP Accession phs000424.v8.p2)

rsID	A1	T-statistic	normalized effect size	p value
rs10165869	G	-2.2	-0.097	0.025
rs6725280	C	-2.6	-0.12	0.0091
rs1865671	A	-2.6	-0.11	0.0097
rs7607911	C	-2.5	-0.1	0.015
rs30102	C	1.9	0.084	0.052
rs10168628	G	-2	-0.082	0.046

TOPMed whole-genome sequencing data

WGS data for GACRS, CAMP, and COPDGene was generated as part of the National Heart, Lung, and Blood Institute (NHLBI) Trans-Omics for Precision Medicine (TOPMed) program[1]. Details on DNA sample handling, quality control, library construction, clustering and sequencing, read processing, and sequence data quality control are described on the TOPMed website (https://www.nhlbiwgs.org/topmed-whole-genome-sequencing-methods-freeze-8). Variant calls were obtained from TOPMed data freeze 8 variant call format files aligned to the GRCh38 genome reference. In our analyses, we included only biallelic SNPs with a minimal depth of coverage of 10 reads that were marked as PASS in the VCF FILTER column.

Acknowledgments: TOPMed Banner Authorship

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