

SUPPLEMENTARY TABLE S2. GENES USED IN CONSENSUS PATHWAY DATABASE PATHWAY GENE STUDY

Proteomics (BAL)	ACTG1 (S21), AHSB (S14), ANXA1 (S42), ANXA2 (S14), ANXA3 (S42), ANXA5 (S14, S21), APOA1 (S21), ARHGDIB (S14), B2M (S21), C3 (S21), C4 (S21), C9 (S21), COL1A1 (S14), COL3A1 (S14), COL5A1 (S14), COTL1 (S21), CP (S14, S21), CST2 (S21), CST4 (S21), ENO1 (S14), EZR (S14), FABP4 (S21), FABP5 (S21), FGA (S21), FLNA (S14), FTH1 (S14), FTL (S14, S21), GAPDHL6 (S14), GPI (S14), GSTP1 (S21), HBB (S21), HINT1 (S21), HPX (S14, S21), HRG (S14, S21), HSPG2 (S21), MUC5AC (S14), MYH9 (S14), PDIA3 (S21), PFN1 (S14), PGAM1 (S14), PGK1 (S14), PPIA (S21), PRDX2 (S21), PRDX5 (S21), RBP4 (S21), S100A8 (S21), S100A9 (S21), S100A12 (S21), SAA1 (S21), SERPINA1 (S14, S21), SFTP1 (S21), SOD3 (S21), STMN1 (S14), TMSB4X (S14), TPI1 (S21), TPM (S21), TTR (S21), TXN (S14), VASP (S14)
Proteomics (PAXgene)	BPI (S22), CD24 (S22), LCN2 (S22), MME (S22), MMP8 (S22), OLFM4 (S22), RBP7 (S22), STMN1, UTS2 (S22)
Gene Expression (Microarray)	ADMR (S1, S17), ADPRH (S1), AREG (S1), ARG2 (S17), ARPC4 (S17), AQP1 (S1, S17), ATF3 (S17), BHLHB2 (S1, S17), BTG1 (S1, S17), BTG2 (S17), CCL2 (S1), CDKN1A (S1, S17), CEBPB (S1), CEBPD (S17), COX2 (S1), CXCR4 (S1), CYCS (S17), DNAJA1 (S17), EGFR (S17), EIF2S1 (S17), EST (S1), F3 (S1, S17), FGA (S1), GABRD (S1), GADD45A (S1, S17), GAPD (S1), GBP2 (S17), GCLC (S17), GJA1 (S1, S17), HSPA8 (S17), IFIT1 (S43), IFRD1 (S17), IFIT3 (S43), IL13 (S1), IL1B (S1, S17), IL1R2 (S1, S17, S19), IL6 (S1, S17), ISG15 (S43), KCNJ6 (S1), LGALS3 (S1, S17), MAT2A (S1), MX1 (S43), NR4A1 (S17), PLAUR (S1, S17), PRKAR2A (S1), PTGS2 (S17), S100A9 (S17), S100A12 (S19), SERPINE1 (S1, S17), TCF21 (S1, S17), TFF2 (S1, S17), YWHAZ (S1, S17)
Gene Expression (PBMC)	ARG (S17), <sup>a</sup> ANXA3, <sup>a</sup> ATF3, <sup>a</sup> BNIP3L (S38), CEACAM1, <sup>a</sup> CEACAM8, <sup>a</sup> CCT7 (S7), CCT8 (S7), CHUK, <sup>a</sup> CSDE1 (S7), CXCL2, <sup>a</sup> CXCL8, <sup>a</sup> CYBA (S7), CSDE1 (S7), DDIT3, <sup>a</sup> DEF4A, <sup>a</sup> DNAJA3 (S7), DNAJB6 (S7), DNAJB9 (S7), DNAJB11 (S7), DNAJC5 (S7), DNAJC8 (S7), DUSP2, <sup>a</sup> DUSP4, <sup>a</sup> FGL2 (S38), FTH1 (S7), <sup>a</sup> GADD45a (S38), GCLM (S7), GPR177 (S38), GSR (S7), GSTP1 (S7), HBEGF, <sup>a</sup> HSP90AB1, <sup>a</sup> HSPA1A (S38), IL1B, <sup>a</sup> IL1R2, <sup>a</sup> IL8 (S38), JUN, <sup>a</sup> LCN2, <sup>a</sup> LY75 (S38), KEAP1 (S7), MGAM, <sup>a</sup> MME (S38), MMP8, <sup>a</sup> MMP9, <sup>a</sup> NCF1 (S7), NR4A2, <sup>a</sup> NR4A3, <sup>a</sup> OLFM4, <sup>a</sup> OSM, <sup>a</sup> PI3 (S38), PIGF (S38), PLAUR, <sup>a</sup> PLK2, <sup>a</sup> POLB (S38), PRDX2 (S7), PRDX3 (S7), PRDX5 (S7), PTGS2 (S38), RNASE3, <sup>a</sup> SGK (S38), SIK1, <sup>a</sup> SOD2 (S7), STAT1 (S38), TBCC (S38), TCN1, <sup>a</sup> TNFAIP3, <sup>a</sup> VEGFA <sup>a</sup>
Genetic Sequencing (Candidate Gene)	ABCB1 (S36), ACE (S29, S36), ADIPOQ (S32), ADIPOR1 (S32), ADIPOR2 (S32), AGER (S35), AGT (S36), AGTR1 (S36), AHR (S36), CAT (S36), CSF2 (S25), CSF2RB (S25), CXCL2 (S44), CYP1A1 (S36), DIO2 (S40), GCLC (S36), HMGB1 (S25), IL10 (S33), IL4 (S18), IL6 (S4, S31), IREK3 (S20), LRRC16A (S26), MAP3K1 (S41), MIF (S6), MTHFR (S36), MYLK (S15), NAMPT/PBEF (S10, S16), NFE2L2 (S45), NOS3 (S36), NOX4 (S25), PHD2 (S39), PI3 (S37), S1P1 (S9), S1PR3 (S27), SOD2 (S36), SPB (S5, S34), SFTPB (S34), TLR1 (S2), TNF (S33), VEGF (S3, S36)
GWAS	ABCC1 (S13), ADA (S12), ADRBK2 (S13), ARSD (S28), BCL11A (S13), CBS (S12), CHIT1 (S12), DYNC2H1 (S24), EPAS1 (S39), FAAH (S13), FER (S23, S30), FLT1 (S24), FZD2 (S12), GPR98 (S12), GRM3 (S13), HEATR1 (S8), HSPG2 (S13), HTR2A (S13), IL1RN (S12), IL8RA (S13), ISG15 (S13), ITGA1 (S24), KLK2 (S13), MAP3K6 (S13), PDE4B (S13), POPDC3 (S13), PPF1A1 (S11), PRKAG2 (S13), SELPLG (S8), SFRS16 (S13), TACR2 (S8), TGFB2 (S12), TNFRSF11A (S13), UGT2B7 (S12), VLDLR (S12), VWF (S13), XKR3 (S28), ZNF335 (S28)

<sup>a</sup>Unpublished data.

GWAS, genome-wide association study; PBMC, peripheral blood mononuclear cell.

## Supplementary Data

### Supplementary References

- S1. Bhargava M, Becker TL, Viken KJ, Jagtap PD, Dey S, Steinbach MS, Wu B, Kumar V, Bitterman PB, Ingbar DH, and Wendt CH. Proteomic profiles in acute respiratory distress syndrome differentiates survivors from non-survivors. *PLoS One* 9: e109713, 2014.
- S2. Bime C, Poongkunran C, Borgstrom M, Natt B, Desai H, Parthasarathy S, and Garcia JGN. Racial differences in mortality from severe acute respiratory failure in the United States, 2008–2012. *Ann Am Thorac Soc* 13: 2184–2189, 2016.
- S3. Calfee CS, Gallagher D, Abbott J, Thompson BT, Matthay MA, and the NAN. Plasma angiopoietin-2 in clinical acute lung injury: prognostic and pathogenetic significance. *Crit Care Med* 40: 1731–1737, 2012.
- S4. Chen J, Zhang Z, and Cai L. Diabetic cardiomyopathy and its prevention by nrf2: current status. *Diab Metab J* 38: 337–345, 2014.
- S5. Chow C-W, Abreu MTH, Suzuki T, and Downey GP. Oxidative stress and acute lung injury. *Am J Respir Cell Mol Biol* 29: 427–431, 2003.
- S6. Cohen MJ, Brohi K, Calfee CS, Rahn P, Chesebro BB, Christiaans SC, Christiaans, Carles M, Howard M, Pittet J-F. Early release of high mobility group box nuclear protein 1 after severe trauma in humans: role of injury severity and tissue hypoperfusion. *Crit Care* 13: R174, 2009.
- S7. D'Alessio FR, Craig JM, Singer BD, Files DC, Mock JR, Garibaldi BT, Fallica J, Tripathi A, Mandke P, Gans JH, Limjunyawong N, Sidhaye VK, Heller NM, Mitzner W, King LS, and Aggarwal NR. Enhanced resolution of experimental ARDS through IL-4-mediated lung macrophage reprogramming. *Am J Physiol Lung Cell Mol Physiol* 310: L733–L746, 2016.
- S8. Devaney J, Contreras M, and Laffey JG. Clinical review: gene-based therapies for ALI/ARDS: where are we now? *Crit Care* 15: 224, 2011.
- S9. Eklund L and Saharinen P. Angiopoietin signaling in the vasculature. *Exp Cell Res* 319: 1271–1280, 2013.
- S10. Flores C, Ma S-F, Maresso K, Wade MS, Villar J, and Garcia JGN. IL6 gene-wide haplotype is associated with susceptibility to acute lung injury. *Transl Res* 152: 11–17, 2008.
- S11. Gao L, Flores C, Fan-Ma S, Miller EJ, Moitra J, Moreno L, Wadgaonkar R, Simon B, Brower R, Sevransky J, Tuder RM, Maloney JP, Moss M, Shanholtz C, Yates CR, Meduri GU, Ye SQ, Barnes KC, and Garcia JGN. Macrophage migration inhibitory factor in acute lung injury: expression, biomarker, and associations. *Transl Res* 150: 18–29, 2007.
- S12. Gao L, Tsai YJ, Grigoryev DN, and Barnes KC. Host defense genes in asthma and sepsis and the role of the environment. *Curr Opin Allergy Clin Immunol* 7: 459–467, 2007.
- S13. Garcia JGN and Sznajder JI. Healthcare disparities in patients with acute respiratory distress syndrome. toward equity. *Am J Respir Crit Care Med* 188: 631–632, 2013.
- S14. Goldman JL, Sammani S, Kempf C, Saadat L, Letsiou E, Wang T, Moreno-Vinasco L, Rizzo AN, Fortman JD, and Garcia JGN. Pleiotropic effects of interleukin-6 in a “two-hit” murine model of acute respiratory distress syndrome. *Pulm Circ* 4: 280–288, 2014.
- S15. Hästbacka J, Linko R, Tervahartiala T, Varpula T, Hovilehto S, Parviainen I, Vaara ST, Sorsa T, and Pettilä V. Serum MMP-8 and TIMP-1 in critically ill patients with acute respiratory failure: TIMP-1 is associated with increased 90-day mortality. *Anesth Analg* 118: 790–798, 2014.
- S16. Herwig R, Hardt C, Lienhard M, and Kamburov A. Analyzing and interpreting genome data at the network level with ConsensusPathDB. *Nat Protoc* 11: 1889, 2016.
- S17. Jabaudon M, Futier E, Roszyk L, Chalus E, Guerin R, Petit A, Mrozek S, Perbet S, Cayot-Constantin S, Chartier C, Sapin V, Bazin J-E, and Constantin J-M. Soluble form of the receptor for advanced glycation end products is a marker of acute lung injury but not of severe sepsis in critically ill patients. *Crit Care Med* 39: 480–488, 2011.
- S18. Janz DR and Ware LB. Biomarkers of ALI/ARDS: pathogenesis, discovery, and relevance to clinical trials. *Semin Respir Crit Care Med* 34: 537–548, 2013.
- S19. Jia SH, Li Y, Parodo J, Kapus A, Fan L, Rotstein OD, and Marshall JC. Pre-B cell colony-enhancing factor inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis. *J Clin Invest* 113: 1318–1327, 2004.
- S20. Kamburov A, Stelzl U, Lehrach H, and Herwig R. The ConsensusPathDB interaction database: 2013 update. *Nucleic Acids Res* 41: D793–D800, 2013.
- S21. Kangelaris KN, Calfee CS, May AK, Zhuo H, Matthay MA, and Ware LB. Is there still a role for the lung injury score in the era of the Berlin definition ARDS? *Ann Intens Care* 4: 4, 2014.
- S22. Lin Z, Pearson C, Chinchilli V, Pietschmann SM, Luo J, Pison U, and Floros J. Polymorphisms of human SP-A, SP-B, and SP-D genes: association of SP-B Thr131Ile with ARDS. *Clin Genet* 58: 181–191, 2001.
- S23. Meyer NJ, Feng R, Li M, Zhao Y, Sheu C-C, Tejera P, Gallop R, Bellamy S, Rushefski M, Lanken PN, Aplenc R, O'Keefe GE, Wurfel MM, Christiani DC, and Christie JD. IL1RN coding variant is associated with lower risk of acute respiratory distress syndrome and increased plasma IL-1 receptor antagonist. *Am J Respir Crit Care Med* 187: 950–959, 2013.
- S24. Meyer NJ. Beyond SNPs—genetics, genomics and other ‘omic approaches to ARDS. *Clin Chest Med* 35: 673–684, 2014.
- S25. Ryu H, Lee J, Zaman K, Kubilis J, Ferrante RJ, Ross BD, Neve R, and Ratan RR. Sp1 and Sp3 are oxidative stress-inducible, antideath transcription factors in cortical neurons. *J Neurosci* 23: 3597, 2003.
- S26. Shen K, Ramirez B, Mapes B, Shen GR, Gokhale V, Brown ME, Santarsiero B, Ishii Y, Dudek SM, Wang T, and Garcia JGN. Structure–function analysis of the non-muscle myosin light chain kinase (nmMLCK) isoform by NMR spectroscopy and molecular modeling: influence of MYLK variants. *PLoS One* 10: e0130515, 2015.
- S27. Shibuya M. Vascular endothelial growth factor and its receptor system: physiological functions in angiogenesis and pathological roles in various diseases. *J Biochem* 153: 13–19, 2013.

- S28. Shirasawa M, Fujiwara N, Hirabayashi S, Ohno H, Iida J, Makita K, and Hata Y. Receptor for advanced glycation end-products is a marker of type I lung alveolar cells. *Genes Cells* 9: 165–174, 2004.
- S29. Shortt K, Chaudhary S, Grigoryev D, Heruth DP, Venkitachalam L, Zhang LQ, and Ye SQ. Identification of novel single nucleotide polymorphisms associated with acute respiratory distress syndrome by exome-seq. *PLoS One* 9: e111953, 2014.
- S30. Soubrier F, Chung WK, Machado R, Grünig E, Aldred M, Geraci M, Loyd JE, Elliott CG, Trembath RC, Newman JH, and Humbert M. Genetics and genomics of pulmonary arterial hypertension. *J Am Coll Cardiol* 62: D13–D21, 2013.
- S31. Steinberg K, Hudson L, Goodman R, Hough C, Lanke P, Hyzy R, Thompson B, Ancukiewicz M, and National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med* 354: 1671–1684, 2006.
- S32. Sun X, Ma S-F, Wade MS, Acosta-Herrera M, Villar J, Pino-Yanes M, Zhou T, Liu B, Belvitch P, Moitra J, Han Y-J, Machado R, Noth I, Natarajan V, Dudek SM, Jacobson JR, Flores C, and Garcia JGN. Functional promoter variants in sphingosine 1-phosphate receptor 3 associate with susceptibility to sepsis-associated acute respiratory distress syndrome. *Am J Physiol Lung Cell Mol Physiol* 305: L467–L477, 2013.
- S33. The ADTF. Acute respiratory distress syndrome: the berlin definition. *JAMA* 307: 2526–2533, 2012.
- S34. Tired L, Rigat B, Visvikis S, Breda C, Corvol P, Cambien F, and Soubrier F. Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin I-converting enzyme (ACE) gene controls plasma ACE levels. *Am J Hum Genet* 51: 197–205, 1992.
- S35. Tsai M-K, Wang H-MD, Shiang J-C, Chen IH, Wang C-C, Shiao Y-F, Liu W-S, Lin T-J, Chen T-M, and Chen Y-H. Sequence variants of ADIPOQ and association with type 2 diabetes mellitus in Taiwan Chinese Han population. *Sci World J* 2014: 650393, 2014.
- S36. Uchida T, Shirasawa M, Ware LB, Kojima K, Hata Y, Makita K, Mednick G, Matthay ZA, and Matthay MA. Receptor for advanced glycation end-products is a marker of type I cell injury in acute lung injury. *Am J Respir Crit Care Med* 173: 1008–1015, 2006.
- S37. Varley I, Hughes DC, Greeves JP, Stellingwerff T, Ranson C, Fraser WD, and Sale C. RANK/RANKL/OPG pathway: genetic associations with stress fracture period prevalence in elite athletes. *Bone* 71: 131–136, 2015.
- S38. Villarino AV, Kanno Y, and O’Shea JJ. Mechanisms of Jak/STAT signaling in immunity and disease. *J Immunol* 194: 21–27, 2015.
- S39. Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che J, Frazier A, Yang H, Ivanova S, Borovikova L, Manogue KR, Faist E, Abraham E, Andersson J, Andersson U, Molina PE, Abumrad NN, Sama A, and Tracey KJ. HMG-1 as a late mediator of endotoxin lethality in mice. *Science* 285: 248, 1999.
- S40. Wang T, Brown ME, Kelly GT, Camp SM, Mascarenhas JB, Sun X, Dudek SM, and Garcia JGN. Myosin light chain kinase (MYLK) coding polymorphisms modulate human lung endothelial cell barrier responses via altered tyrosine phosphorylation, spatial localization, and lamellipodial protrusions. *Pulm Circ* 8: 2045894018764171, 2018.
- S41. Wei Y, Wang Z, Su L, Chen F, Tejera P, Bajwa EK, Wurfel MM, Lin X, and Christiani DC. Platelet count mediates the contribution of a genetic variant in LRRC16A to ARDS risk. *Chest* 147: 607–617, 2015.
- S42. Wolfson RK, Mapes B, and Garcia JGN. Excessive mechanical stress increases HMGB1 expression in human lung microvascular endothelial cells via STAT3. *Microvasc Res* 92: 50–55, 2014.
- S43. Wu J, Liu Z, Meng K, and Zhang L. Association of adiponectin gene (ADIPOQ) rs2241766 polymorphism with obesity in adults: a meta-analysis. *PLoS One* 9: e95270, 2014.
- S44. Wurfel MM. Microarray-based analysis of ventilator-induced lung injury. *Proc Am Thorac Soc* 4: 77–84, 2007.
- S45. Wurfel MM, Gordon AC, Holden TD, Radella F, Strout J, Kajikawa O, Ruzinski JT, Rona G, Black RA, Stratton S, Jarvik GP, Hajjar AM, Nickerson DA, Rieder M, Sevransky J, Maloney JP, Moss M, Martin G, Shanholtz C, Garcia JGN, Gao L, Brower R, Barnes KC, Walley KR, Russell JA, and Martin TR. Toll-like receptor 1 polymorphisms affect innate immune responses and outcomes in sepsis. *Am J Respir Crit Care Med* 178: 710–720, 2008.