

**Table S7. Summary of 113 orientation-determined genes in 784 DEGs.**

Gene symbol	Entrez ID	The direction of gene expression conducive to influenza virus clearance or host resistance	
		Direction	References
<i>B2M</i>	567	↓	[1]
<i>CAMP</i>	820	↑	[2]
<i>CASP1</i>	834	↑	[3]
<i>CTSD</i>	1509	↓	[4]
<i>CTSG</i>	1511	↓	[5]
<i>GADD45A</i>	1647	↓	[6]
<i>DUSP3</i>	1845	↓	[5]
<i>EEF1G</i>	1937	↓	[4]
<i>EEF2</i>	1938	↓	[4,7]
<i>EIF4B</i>	1975	↓	[4]
<i>SERPINB1</i>	1992	↑	[8]
<i>ACSL4</i>	2182	↓	[9]
<i>FKBP5</i>	2289	↓	[9,10]
<i>FYB</i>	2533	↑	[11]
<i>HIST1H2BD</i>	3017	↓	[6]
<i>HLA-A</i>	3105	↓	[9]
<i>HLA-B</i>	3106	↓	[4]
<i>DNAJA1</i>	3301	↑	[12]
<i>HSPA1B</i>	3304	↓	[4]
<i>IFI35</i>	3430	↓	[13]
<i>IFIT2</i>	3433	↓	[9]
<i>IL1B</i>	3553	↑	[14]
<i>CXCL10</i>	3627	↓	[15]
<i>IRF1</i>	3659	↓	[9]
<i>IRF5</i>	3663	↓	[16]
<i>IRF7</i>	3665	↑	[17]
<i>KPNB1</i>	3837	↓	[1,5]
<i>LGALS3BP</i>	3959	↓	[4,9,12]
<i>LGALS9</i>	3965	↓	[9]
<i>MAP3K5</i>	4217	↑	[18]
<i>MPO</i>	4353	↓	[19]
<i>MX1</i>	4599	↑	[20]
<i>MYD88</i>	4615	↑	[21]
<i>NAIP</i>	4671	↓	[1]
<i>NFIL3</i>	4783	↓	[9]
<i>NFKBIA</i>	4792	↓	[9]
<i>OAS1</i>	4938	↓	[9]
<i>PAK2</i>	5062	↓	[5]

<i>PDGFA</i>	5154	↓	[9]
<i>PIK3CG</i>	5294	↑	[22]
<i>PLEK</i>	5341	↓	[6]
<i>EIF2AK2</i>	5610	↑	[23]
<i>PSMA4</i>	5685	↓	[4]
<i>PSMB9</i>	5698	↓	[6,9]
<i>PSME2</i>	5721	↓	[4]
<i>RPL3</i>	6122	↓	[4]
<i>RPS3</i>	6188	↓	[1]
<i>RPS4X</i>	6191	↓	[24]
<i>RPS5</i>	6193	↓	[1,24]
<i>RPS8</i>	6202	↓	[24]
<i>CCL2</i>	6347	↓	[25]
<i>SELPLG</i>	6404	↓	[1]
<i>SGK1</i>	6446	↓	[5]
<i>SIAH2</i>	6478	↓	[5]
<i>SLC1A3</i>	6507	↓	[9,26]
<i>SMARCD3</i>	6604	↓	[5]
<i>TRIM21</i>	6737	↓	[1]
<i>STAT1</i>	6772	↑	[27]
<i>STAT2</i>	6773	↑	[28]
<i>SVIL</i>	6840	↓	[9]
<i>TOP2A</i>	7153	↓	[7]
<i>TXK</i>	7294	↓	[5]
<i>SF1</i>	7536	↓	[4]
<i>TRIM25</i>	7706	↓	[9]
<i>HIST1H4H</i>	8365	↓	[6]
<i>OASL</i>	8638	↑	[29]
<i>EIF4G3</i>	8672	↓	[4]
<i>SIGLEC5</i>	8778	↓	[1]
<i>CFLAR</i>	8837	↓	[5]
<i>ISG15</i>	9636	↑	[30]
<i>TRIM14</i>	9830	↓	[1]
<i>SCO2</i>	9997	↑	[12]
<i>TRIM22</i>	10346	↓	[9]
<i>IFITM3</i>	10410	↑	[31]
<i>ATG7</i>	10533	↓	[32]
<i>RBCK1</i>	10616	↓	[5,9]
<i>MYL12A</i>	10627	↓	[4]
<i>NFAT5</i>	10725	↓	[5]
<i>MTHFD2</i>	10797	↓	[9]
<i>CKAP4</i>	10970	↓	[4]
<i>IRAK3</i>	11213	↑	[33]
<i>CBX3</i>	11335	↓	[4]
<i>FTSJ2</i>	23070	↓	[7]

ZFYVE26	23503	↓	[9]
RPL13A	23521	↓	[9]
TNPO3	23534	↓	[5]
DDX58	23586	↑	[34]
CLEC5A	23601	↓	[35]
IL17RA	23765	↓	[36]
IFIT5	24138	↓	[9]
CNIH4	29097	↓	[4]
SHISA5	51246	↑	[12]
TLR7	51284	↑	[37]
RIN2	54453	↑	[38]
GNL3L	54552	↓	[10]
ZRANB1	54764	↑	[12]
HERC6	55008	↓	[6,10]
NAGK	55577	↓	[5]
APOB48R	55911	↓	[6]
RETN	56729	↓	[1]
C21orf7	56911	↓	[1]
TAOK1	57551	↓	[5]
RNF213	57674	↑	[12]
SQRDL	58472	↓	[6]
RRAGD	58528	↑	[12]
RTP4	64108	↓	[9]
NCAPG	64151	↓	[4]
NADK	65220	↓	[5]
C16orf57	79650	↓	[6]
CXorf21	80231	↓	[5]
ZBP1	81030	↑	[39]
PARP10	84875	↓	[6]
JDP2	122953	↓	[6]

### Supplementary References

1. Karlas, A.; Machuy, N.; Shin, Y.; Pleissner, K.-P.; Artarini, A.; Heuer, D.; Becker, D.; Khalil, H.; Ogilvie, L.A.; Hess, S.; et al. Genome-Wide RNAi Screen Identifies Human Host Factors Crucial for Influenza Virus Replication. *Nature* **2010**, *463*, 818–822, doi:10.1038/nature08760.
2. Barlow, P.G.; Svoboda, P.; Mackellar, A.; Nash, A.A.; York, I.A.; Pohl, J.; Davidson, D.J.; Donis, R.O. Antiviral Activity and Increased Host Defense against Influenza Infection Elicited by the Human Cathelicidin LL-37. *PLoS One* **2011**, *6*, e25333, doi:10.1371/journal.pone.0025333.
3. Thomas, P.G.; Dash, P.; Aldridge, J.R.; Ellebedy, A.H.; Reynolds, C.; Funk, A.J.; Martin, W.J.; Lamkanfi, M.; Webby, R.J.; Boyd, K.L.; et al. The Intracellular Sensor NLRP3 Mediates Key Innate and Healing Responses to Influenza A Virus via the Regulation of Caspase-1. *Immunity* **2009**, *30*, 566–575, doi:10.1016/j.immuni.2009.02.006.
4. Watanabe, T.; Kawakami, E.; Shoemaker, J.E.; Lopes, T.J.S.; Matsuoka, Y.; Tomita, Y.; Kozuka-Hata, H.; Gorai, T.; Kuwahara, T.; Takeda, E.; et al. Influenza Virus-Host Interactome Screen as a Platform for Antiviral Drug Development. *Cell Host Microbe* **2014**, *16*, 795–805, doi:10.1016/j.chom.2014.11.002.

5. König, R.; Stertz, S.; Zhou, Y.; Inoue, A.; Hoffmann, H.-H.; Bhattacharyya, S.; Alamares, J.G.; Tscherne, D.M.; Ortigoza, M.B.; Liang, Y.; et al. Human Host Factors Required for Influenza Virus Replication. *Nature* **2010**, *463*, 813–817, doi:10.1038/nature08699.
6. Han, J.; Perez, J.T.; Chen, C.; Li, Y.; Benitez, A.; Kandasamy, M.; Lee, Y.; Andrade, J.; tenOever, B.; Manicassamy, B. Genome-Wide CRISPR/Cas9 Screen Identifies Host Factors Essential for Influenza Virus Replication. *Cell Rep* **2018**, *23*, 596–607, doi:10.1016/j.celrep.2018.03.045.
7. Li, B.; Clohisey, S.M.; Chia, B.S.; Wang, B.; Cui, A.; Eisenhaure, T.; Schweitzer, L.D.; Hoover, P.; Parkinson, N.J.; Nachshon, A.; et al. Genome-Wide CRISPR Screen Identifies Host Dependency Factors for Influenza A Virus Infection. *Nat Commun* **2020**, *11*, 164, doi:10.1038/s41467-019-13965-x.
8. Farley, K.; Stolley, J.M.; Zhao, P.; Cooley, J.; Remold-O'Donnell, E. A SerpinB1 Regulatory Mechanism Is Essential for Restricting Neutrophil Extracellular Trap Generation. *J Immunol* **2012**, *189*, 4574–4581, doi:10.4049/jimmunol.1201167.
9. Shapira, S.D.; Gat-Viks, I.; Shum, B.O.V.; Dricot, A.; de Grace, M.M.; Wu, L.; Gupta, P.B.; Hao, T.; Silver, S.J.; Root, D.E.; et al. A Physical and Regulatory Map of Host-Influenza Interactions Reveals Pathways in H1N1 Infection. *Cell* **2009**, *139*, 1255–1267, doi:10.1016/j.cell.2009.12.018.
10. Sui, B.; Bamba, D.; Weng, K.; Ung, H.; Chang, S.; Van Dyke, J.; Goldblatt, M.; Duan, R.; Kinch, M.S.; Li, W.-B. The Use of Random Homozygous Gene Perturbation to Identify Novel Host-Oriented Targets for Influenza. *Virology* **2009**, *387*, 473–481, doi:10.1016/j.virol.2009.02.046.
11. Li, C.; Jiao, S.; Wang, G.; Gao, Y.; Liu, C.; He, X.; Zhang, C.; Xiao, J.; Li, W.; Zhang, G.; et al. The Immune Adaptor ADAP Regulates Reciprocal TGF- $\beta$ 1-Integrin Crosstalk to Protect from Influenza Virus Infection. *PLoS Pathog* **2015**, *11*, e1004824, doi:10.1371/journal.ppat.1004824.
12. Ward, S.E.; Kim, H.S.; Komurov, K.; Mendiratta, S.; Tsai, P.-L.; Schmolke, M.; Satterly, N.; Manicassamy, B.; Forst, C.V.; Roth, M.G.; et al. Host Modulators of H1N1 Cytopathogenicity. *PLoS One* **2012**, *7*, e39284, doi:10.1371/journal.pone.0039284.
13. Gounder, A.P.; Yokoyama, C.C.; Jarjour, N.N.; Bricker, T.L.; Edelson, B.T.; Boon, A.C.M. Interferon Induced Protein 35 Exacerbates H5N1 Influenza Disease through the Expression of IL-12p40 Homodimer. *PLoS Pathog* **2018**, *14*, e1007001, doi:10.1371/journal.ppat.1007001.
14. Schmitz, N.; Kurrer, M.; Bachmann, M.F.; Kopf, M. Interleukin-1 Is Responsible for Acute Lung Immunopathology but Increases Survival of Respiratory Influenza Virus Infection. *J Virol* **2005**, *79*, 6441–6448, doi:10.1128/JVI.79.10.6441-6448.2005.
15. Ichikawa, A.; Kuba, K.; Morita, M.; Chida, S.; Tezuka, H.; Hara, H.; Sasaki, T.; Ohteki, T.; Ranieri, V.M.; dos Santos, C.C.; et al. CXCL10-CXCR3 Enhances the Development of Neutrophil-Mediated Fulminant Lung Injury of Viral and Nonviral Origin. *Am J Respir Crit Care Med* **2013**, *187*, 65–77, doi:10.1164/rccm.201203-0508OC.
16. Forbester, J.L.; Clement, M.; Wellington, D.; Yeung, A.; Dimonte, S.; Marsden, M.; Chapman, L.; Coomber, E.L.; Tolley, C.; Lees, E.; et al. IRF5 Promotes Influenza Virus-Induced Inflammatory Responses in Human Induced Pluripotent Stem Cell-Derived Myeloid Cells and Murine Models. *J Virol* **2020**, *94*, e00121-20, doi:10.1128/JVI.00121-20.
17. Hatesuer, B.; Hoang, H.T.T.; Riese, P.; Trittel, S.; Gerhauser, I.; Elbahesh, H.; Geffers, R.; Wilk, E.; Schughart, K. Deletion of Irf3 and Irf7 Genes in Mice Results in Altered Interferon Pathway Activation and Granulocyte-Dominated Inflammatory Responses to Influenza A Infection. *J Innate Immun* **2017**, *9*, 145–161, doi:10.1159/000450705.
18. Okazaki, T.; Higuchi, M.; Takeda, K.; Iwatsuki-Horimoto, K.; Kiso, M.; Miyagishi, M.; Yanai, H.; Kato, A.; Yoneyama, M.; Fujita, T.; et al. The ASK Family Kinases Differentially Mediate Induction of Type I Interferon and Apoptosis during the Antiviral Response. *Sci Signal* **2015**, *8*, ra78, doi:10.1126/scisignal.aab1883.
19. Sugamata, R.; Dobashi, H.; Nagao, T.; Yamamoto, K.-I.; Nakajima, N.; Sato, Y.; Aratani, Y.; Oshima, M.; Sata, T.; Kobayashi, K.; et al. Contribution of Neutrophil-Derived Myeloperoxidase in the Early Phase of Fulminant Acute Respiratory Distress Syndrome Induced by Influenza Virus Infection. *Microbiol Immunol* **2012**, *56*, 171–182, doi:10.1111/j.1348-0421.2011.00424.x.
20. Pavlovic, J.; Arzet, H.A.; Hefti, H.P.; Frese, M.; Rost, D.; Ernst, B.; Kolb, E.; Staeheli, P.; Haller, O. Enhanced Virus Resistance of Transgenic Mice Expressing the Human MxA Protein. *J Virol* **1995**, *69*, 4506–4510, doi:10.1128/JVI.69.7.4506-4510.1995.

21. Ito, T.; Allen, R.M.; Carson, W.F.; Schaller, M.; Cavassani, K.A.; Hogaboam, C.M.; Lukacs, N.W.; Matsukawa, A.; Kunkel, S.L. The Critical Role of Notch Ligand Delta-like 1 in the Pathogenesis of Influenza A Virus (H1N1) Infection. *PLoS Pathog* **2011**, *7*, e1002341, doi:10.1371/journal.ppat.1002341.
22. Nobs, S.P.; Schneider, C.; Heer, A.K.; Huotari, J.; Helenius, A.; Kopf, M. PI3K $\gamma$  Is Critical for Dendritic Cell-Mediated CD8 $^{+}$  T Cell Priming and Viral Clearance during Influenza Virus Infection. *PLoS Pathog* **2016**, *12*, e1005508, doi:10.1371/journal.ppat.1005508.
23. Balachandran, S.; Roberts, P.C.; Brown, L.E.; Truong, H.; Pattnaik, A.K.; Archer, D.R.; Barber, G.N. Essential Role for the DsRNA-Dependent Protein Kinase PKR in Innate Immunity to Viral Infection. *Immunity* **2000**, *13*, 129–141, doi:10.1016/s1074-7613(00)00014-5.
24. Hao, L.; Sakurai, A.; Watanabe, T.; Sorensen, E.; Nidom, C.A.; Newton, M.A.; Ahlquist, P.; Kawaoka, Y. Drosophila RNAi Screen Identifies Host Genes Important for Influenza Virus Replication. *Nature* **2008**, *454*, 890–893, doi:10.1038/nature07151.
25. Lai, C.; Wang, K.; Zhao, Z.; Zhang, L.; Gu, H.; Yang, P.; Wang, X. C-C Motif Chemokine Ligand 2 (CCL2) Mediates Acute Lung Injury Induced by Lethal Influenza H7N9 Virus. *Front Microbiol* **2017**, *8*, 587, doi:10.3389/fmicb.2017.00587.
26. Brass, A.L.; Huang, I.-C.; Benita, Y.; John, S.P.; Krishnan, M.N.; Feeley, E.M.; Ryan, B.J.; Weyer, J.L.; van der Weyden, L.; Fikrig, E.; et al. The IFITM Proteins Mediate Cellular Resistance to Influenza A H1N1 Virus, West Nile Virus, and Dengue Virus. *Cell* **2009**, *139*, 1243–1254, doi:10.1016/j.cell.2009.12.017.
27. Davidson, S.; Crotta, S.; McCabe, T.M.; Wack, A. Pathogenic Potential of Interferon A $\beta$  in Acute Influenza Infection. *Nat Commun* **2014**, *5*, 3864, doi:10.1038/ncomms4864.
28. Gopal, R.; Lee, B.; McHugh, K.J.; Rich, H.E.; Ramanan, K.; Mandalapu, S.; Clay, M.E.; Seger, P.J.; Enelow, R.I.; Manni, M.L.; et al. STAT2 Signaling Regulates Macrophage Phenotype During Influenza and Bacterial Super-Infection. *Front Immunol* **2018**, *9*, 2151, doi:10.3389/fimmu.2018.02151.
29. Silverman, R.H. Viral Encounters with 2',5'-Oligoadenylate Synthetase and RNase L during the Interferon Antiviral Response. *J Virol* **2007**, *81*, 12720–12729, doi:10.1128/JVI.01471-07.
30. Lai, C.; Struckhoff, J.J.; Schneider, J.; Martinez-Sobrido, L.; Wolff, T.; García-Sastre, A.; Zhang, D.-E.; Lenschow, D.J. Mice Lacking the ISG15 E1 Enzyme UBE1L Demonstrate Increased Susceptibility to Both Mouse-Adapted and Non-Mouse-Adapted Influenza B Virus Infection. *J Virol* **2009**, *83*, 1147–1151, doi:10.1128/JVI.00105-08.
31. Kenney, A.D.; McMichael, T.M.; Imas, A.; Chesarino, N.M.; Zhang, L.; Dorn, L.E.; Wu, Q.; Alfaour, O.; Amari, F.; Chen, M.; et al. IFITM3 Protects the Heart during Influenza Virus Infection. *Proc Natl Acad Sci U S A* **2019**, *116*, 18607–18612, doi:10.1073/pnas.1900784116.
32. Lu, Q.; Yokoyama, C.C.; Williams, J.W.; Baldridge, M.T.; Jin, X.; DesRochers, B.; Bricker, T.; Wilen, C.B.; Bagaitkar, J.; Loginicheva, E.; et al. Homeostatic Control of Innate Lung Inflammation by Vici Syndrome Gene Epg5 and Additional Autophagy Genes Promotes Influenza Pathogenesis. *Cell Host Microbe* **2016**, *19*, 102–113, doi:10.1016/j.chom.2015.12.011.
33. Seki, M.; Kohno, S.; Newstead, M.W.; Zeng, X.; Bhan, U.; Lukacs, N.W.; Kunkel, S.L.; Standiford, T.J. Critical Role of IL-1 Receptor-Associated Kinase-M in Regulating Chemokine-Dependent Deleterious Inflammation in Murine Influenza Pneumonia. *J Immunol* **2010**, *184*, 1410–1418, doi:10.4049/jimmunol.0901709.
34. Kandasamy, M.; Suryawanshi, A.; Tundup, S.; Perez, J.T.; Schmolke, M.; Manicassamy, S.; Manicassamy, B. RIG-I Signaling Is Critical for Efficient Polyfunctional T Cell Responses during Influenza Virus Infection. *PLoS Pathog* **2016**, *12*, e1005754, doi:10.1371/journal.ppat.1005754.
35. Teng, O.; Chen, S.-T.; Hsu, T.-L.; Sia, S.F.; Cole, S.; Valkenburg, S.A.; Hsu, T.-Y.; Zheng, J.T.; Tu, W.; Bruzzone, R.; et al. CLEC5A-Mediated Enhancement of the Inflammatory Response in Myeloid Cells Contributes to Influenza Virus Pathogenicity In Vivo. *J Virol* **2017**, *91*, e01813-16, doi:10.1128/JVI.01813-16.
36. Crowe, C.R.; Chen, K.; Pociask, D.A.; Alcorn, J.F.; Krivich, C.; Enelow, R.I.; Ross, T.M.; Witztum, J.L.; Kolls, J.K. Critical Role of IL-17RA in Immunopathology of Influenza Infection. *J Immunol* **2009**, *183*, 5301–5310, doi:10.4049/jimmunol.0900995.
37. Shinya, K.; Okamura, T.; Sueta, S.; Kasai, N.; Tanaka, M.; Ginting, T.E.; Makino, A.; Einfeld, A.J.; Kawaoka, Y. Toll-like Receptor Pre-Stimulation Protects Mice against Lethal Infection with Highly Pathogenic Influenza Viruses. *Virol J* **2011**, *8*, 97, doi:10.1186/1743-422X-8-97.

38. Heaton, B.E.; Kennedy, E.M.; Dumm, R.E.; Harding, A.T.; Sacco, M.T.; Sachs, D.; Heaton, N.S. A CRISPR Activation Screen Identifies a Pan-Avian Influenza Virus Inhibitory Host Factor. *Cell Rep* **2017**, *20*, 1503–1512, doi:10.1016/j.celrep.2017.07.060.
39. Thapa, R.J.; Ingram, J.P.; Ragan, K.B.; Nogusa, S.; Boyd, D.F.; Benitez, A.A.; Sridharan, H.; Kosoff, R.; Shubina, M.; Landsteiner, V.J.; et al. DAI Senses Influenza A Virus Genomic RNA and Activates RIPK3-Dependent Cell Death. *Cell Host Microbe* **2016**, *20*, 674–681, doi:10.1016/j.chom.2016.09.014.