

SUPPLEMENTAL MATERIAL

Napier et al., <http://dx.doi.org/10.1084/jem.20160027>

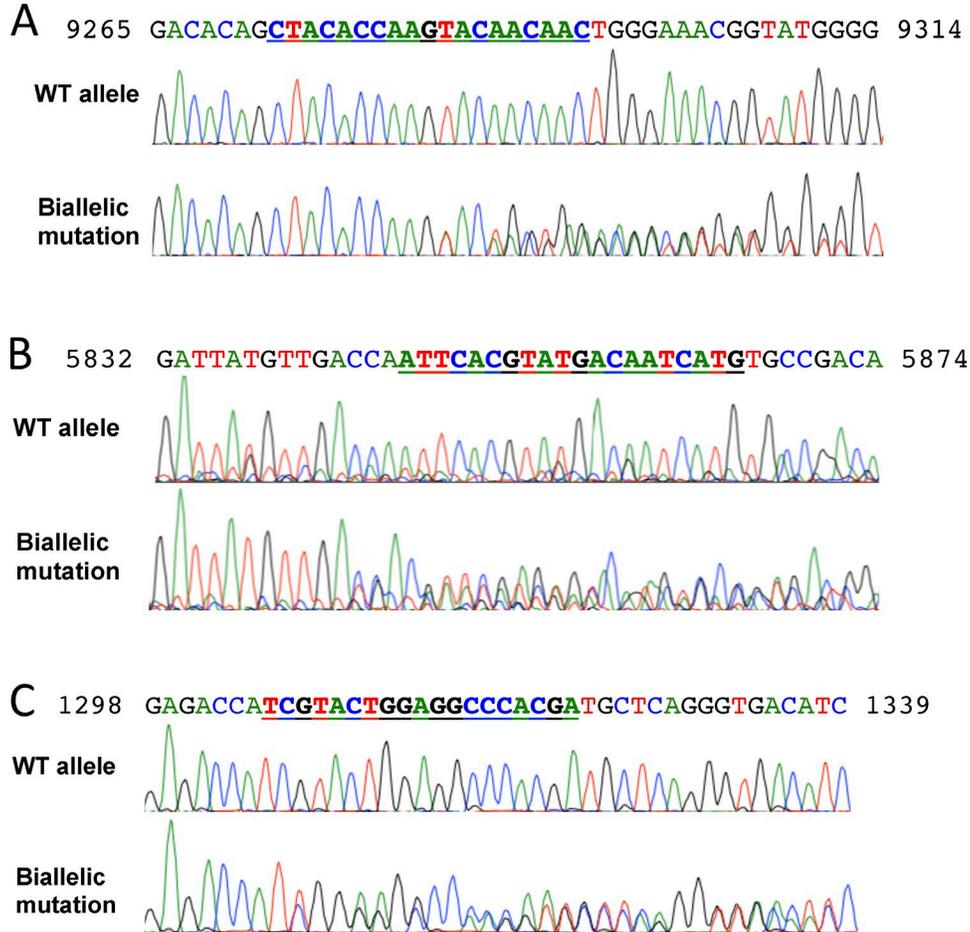


Figure S1. **Biallelic mutations using CRISPR-Cas9 in RAW cells.** Electropherograms of WT versus biallelic mutants in RAW cells for genes (A) Cpb1, (B) C3aR, and (C) C3.

WT	CTCTCTT <u>CACAGAT</u> CACTTGTCCTA
C3aR <sup>-/-</sup>	CTCTCTT <u>CACAGAT</u> CACTTGTCCTA
C3 <sup>-/-</sup>	CTCTCTT <u>CACAGAT</u> CACTTGTCCTA

Figure S2. **C3aR<sup>-/-</sup> and C3<sup>-/-</sup> BMDMs harbor a WT copy of caspase-11.** Caspase-11 from WT, C3aR-deficient (C3aR<sup>-/-</sup>), and C3-deficient (C3<sup>-/-</sup>) BMDMs was sequenced and analyzed for the presence or absence of a 5-bp deletion found in Sv129 mice (sequence underlined).

Table S1. Top 100 enriched hits in the CRISPR-Cas9 screen

Rank	Gene	Hit well	negLogP	Rank	Gene	Hit well	negLogP
1	<i>B4galnt1</i>	3	5.48	64	<i>Coasy</i>	1	3.099
2	<i>Il11ra1</i>	3	4.838	65	<i>Adamts16</i>	2	3.069
3	<i>Acbd5</i>	4	4.829	66	<i>Lamc3</i>	1	3.069
4	<i>Acsf6</i>	3	4.618	67	<i>Olf916</i>	3	3.067
5	<i>Ccdc151</i>	5	4.501	68	<i>Kcnj10</i>	2	3.059
6	<i>Ric8b</i>	5	4.501	69	<i>St3gal5</i>	3	3.049
7	<i>Zmiz1</i>	2	4.473	70	<i>Phpp2</i>	1	3.041
8	<i>Pip5k1a</i>	1	4.245	71	<i>Cylc1</i>	3	3.035
9	<i>Prkcb</i>	2	4.184	72	<i>Zranb3</i>	3	3.035
10	<i>Prss1</i>	1	4.166	73	<i>Pepd</i>	2	3.029
11	<i>Shisa3</i>	2	4.157	74	<i>Olf904</i>	3	3.025
12	<i>Zik1</i>	4	4.056	75	<i>Grm1</i>	3	3.023
13	<i>Cyp4f15</i>	2	3.941	76	<i>Gfod1</i>	1	3.015
14	<i>Adck5</i>	3	3.92	77	<i>Cox10</i>	1	3
15	<i>Olf953</i>	4	3.908	78	<i>Tmem9</i>	2	2.994
16	<i>Gen1</i>	4	3.898	79	<i>Fbxl16</i>	1	2.99
17	<i>Vmn1r40</i>	1	3.865	80	<i>Olf9140</i>	3	2.979
18	<i>B3galt4</i>	2	3.817	81	<i>Ifi44</i>	1	2.966
19	<i>Aldh8a1</i>	2	3.792	82	<i>Atp2c1</i>	2	2.964
20	<i>3110079O15Rik</i>	2	3.778	83	<i>Sclt1</i>	3	2.959
21	<i>Acmsd</i>	4	3.769	84	<i>Tlr11</i>	3	2.952
22	<i>Dcaf12</i>	2	3.713	85	<i>1700016M24Rik</i>	4	2.948
23	<i>2810405K02Rik</i>	3	3.689	86	<i>Chi3l1</i>	4	2.948
24	<i>Nfs1</i>	4	3.673	87	<i>Gm7168</i>	4	2.948
25	<i>Ccdc41</i>	3	3.649	88	<i>Tc2n</i>	4	2.948
26	<i>Cpsf7</i>	3	3.649	89	<i>Tmem161b</i>	4	2.948
27	<i>Suv39h1</i>	3	3.632	90	<i>Vsig1</i>	4	2.948
28	<i>Pcdha9</i>	3	3.586	91	<i>Trem14</i>	1	2.944
29	<i>Jmjd4</i>	2	3.546	92	<i>Krt14</i>	2	2.941
30	<i>Memo1</i>	1	3.546	93	<i>Myh11</i>	1	2.923
31	<i>Fam194a</i>	3	3.496	94	<i>Mill1</i>	3	2.92
32	<i>Fam83g</i>	3	3.47	95	<i>Fbxo11</i>	2	2.905
33	<i>Abhd15</i>	1	3.467	96	<i>D17Wsu104e</i>	2	2.883
34	<i>Mfn1</i>	2	3.455	97	<i>Mpz11</i>	1	2.883
35	<i>1110021J02Rik</i>	3	3.447	98	<i>A4gnt</i>	2	2.865
36	<i>Tmem136</i>	4	3.425	99	<i>Atp6ap2</i>	1	2.865
37	<i>Lingo3</i>	1	3.4	100	<i>Olf958</i>	3	2.86
38	<i>Prss27</i>	3	3.389				
39	<i>Dmbt1</i>	3	3.379				
40	<i>Sftpd</i>	3	3.368				
41	<i>C4b</i>	1	3.342				
42	<i>Plau</i>	3	3.322				
43	<i>Cpb1</i>	2	3.313				
44	<i>Scnn1g</i>	2	3.295				
45	<i>Map3k3</i>	1	3.291				
46	<i>Slc25a14</i>	3	3.287				
47	<i>Dir2</i>	4	3.248				
48	<i>Mlc1</i>	4	3.248				
49	<i>Tsc22d4</i>	3	3.246				
50	<i>C1s</i>	1	3.245				
51	<i>Arf1</i>	1	3.228				
52	<i>Mapre3</i>	1	3.204				
53	<i>Rasa4</i>	3	3.2				
54	<i>Lmx1a</i>	2	3.181				
55	<i>Paqr5</i>	3	3.17				
56	<i>Pram1</i>	1	3.166				
57	<i>Anpep</i>	2	3.159				
58	<i>Apcs</i>	3	3.149				
59	<i>Tmem235</i>	3	3.129				
60	<i>Impa2</i>	3	3.12				
61	<i>Tmem97</i>	3	3.12				
62	<i>Sdcbp</i>	2	3.109				
63	<i>Vmn1r38</i>	2	3.105				

Table S2. gRNAs for each CRISPR-Cas9 KO cell line (Continued)

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Primer name	Sequence
Casp11-gRNA-F	caccgCTGAACGCAGTGACAAGCGT
Casp11-gRNA-R	aaacACGCTTGTCACCTGCGTTCAGc
Casp1-gRNA-F	caccgTGTCTCTAAAAAGGGCCCC
Casp1-gRNA-R	aaacGGGGCCCTTTTTAGAGACAc
Cpb1-gRNA-F	caccgCTACCCAAGTACAACAAC
Cpb1-gRNA-R	aaacGTTGTTGACTTGGGTAGC
C3-gRNA-F	caccgCCGCCAAGAATCGCTACTTC
C3-gRNA-R	aaacGAAGTAGCGATTCTGGCGGc
C3aR-gRNA-F	caccgCCGTACCCAGCGGGTTTCTT
C3aR-gRNA-R	aaacAGGAAACCCGCTGGGTACGGc
Casp11-seq-F	GACTAAGTTGATTCCAAGCTC
Casp11-seq-R	GATTCTGAGACCTACCTATG
Casp1-seq-F	AACAGACAAGATCCTGAGGG
Casp1-seq-R	GTCATCCTTGGTGAGACTG
Cpb1-seq-F	GTGATTGATACCAGAATCTG
Cpb1-seq-R	GAGAACATACATGTTACGTC
C3-seq-F	GTGGAGATCAGAGCTGTGCT
C3-seq-R	CTCTCTTCTGAAGCCTAGC
C3aR-seq-F	CTGGACATATGAATGACAGGTC
C3aR-seq-R	GTGATGTTATTGCCATCAGC

Table S3. Sequences for each set of primers used in qRT-PCR

Sequence	Reference
ACAATGCTGAACGCAGTGAC	Φ
CTGGTTCCTCCATTTCCAGA	Φ
ACAAGGCACGGGACCTATG	#
TCCCAGTCAGTCTGGAAATG	#
TCCAGTTGCCTTCTGGGAC	*
AGTCTCCTCTCCGACTTGT	*
GATCGGTCCCAAAGGATG	*
TGGTTTGTGAGTGTGAGGTC	*
ATTTCTCCAGCACTGGGTGG	*
CACTGTCTGCTGGTGGAGTT	*
CCTTGGTGAAGGACTGAGC	*
CAACGTTCTCCGTTCTTTGC	*

Φ, Lupfer, 2014; #, Vande Walle, 2014; \*, Made for this study.

Table S4. Cohorts used in our multi-cohort analysis

Year	PMID	Author	Accession	Control	Condition	Tissue	Platforms included	Controls used here	Cases used here
2005	15655079	Reghunathan et al., 2005	GSE1739	Healthy Adults	Adults hospitalized with SARS	PBMC	GPL201	4	10
2006	17105821	Ramilo et al., 2007	GSE6269	Healthy Children	Hospitalized with <i>E. coli</i> , <i>S. aureus</i> , <i>S. pneumo</i> , or influenza	PBMC	GPL96	7	136
2008	18631455	Chaussabel et al., 2008	GSE11907	Healthy controls	Hospitalized with <i>E. coli</i> , <i>S. aureus</i> , or influenza	PBMC	GPL96	0	56
2009	19424507	Ardura et al., 2009	GSE16129	Healthy children	Hospitalized with acute <i>S. aureus</i> infection	PBMC	GPL96, GPL6106	29	97
2012	22398282	Ioannidis et al., 2012	GSE34205	Healthy infants	Hospitalized with influenza or RSV	PBMC	GPL570	22	79
2014	24667684	Severino et al., 2014	GSE48080	Healthy adults	Adults with community-acquired pneumonia in ICU	PBMC	GPL4133	3	20
2015	26162090	Brand et al., 2015	GSE69606	Baseline control (4–6 wk after infection)	Patients hospitalized with RSV	PBMC	GPL570	17	26

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