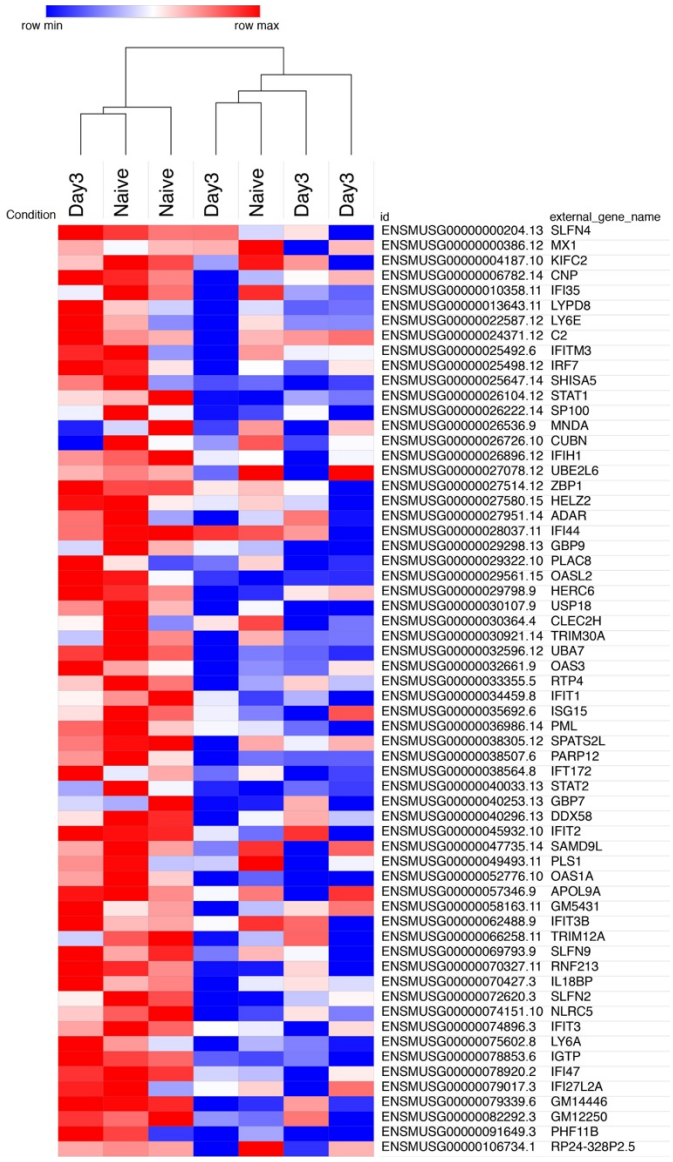

Figure S1. A Heat map of down-regulated genes at 3 dpi. Related to Figure 1.
Wild-type mice were infected with 10^6 plaque forming units (PFU) of CR6 perorally. At 3 dpi, ileum from the infected mice and the littermate control mice were collected for mRNA sequencing.

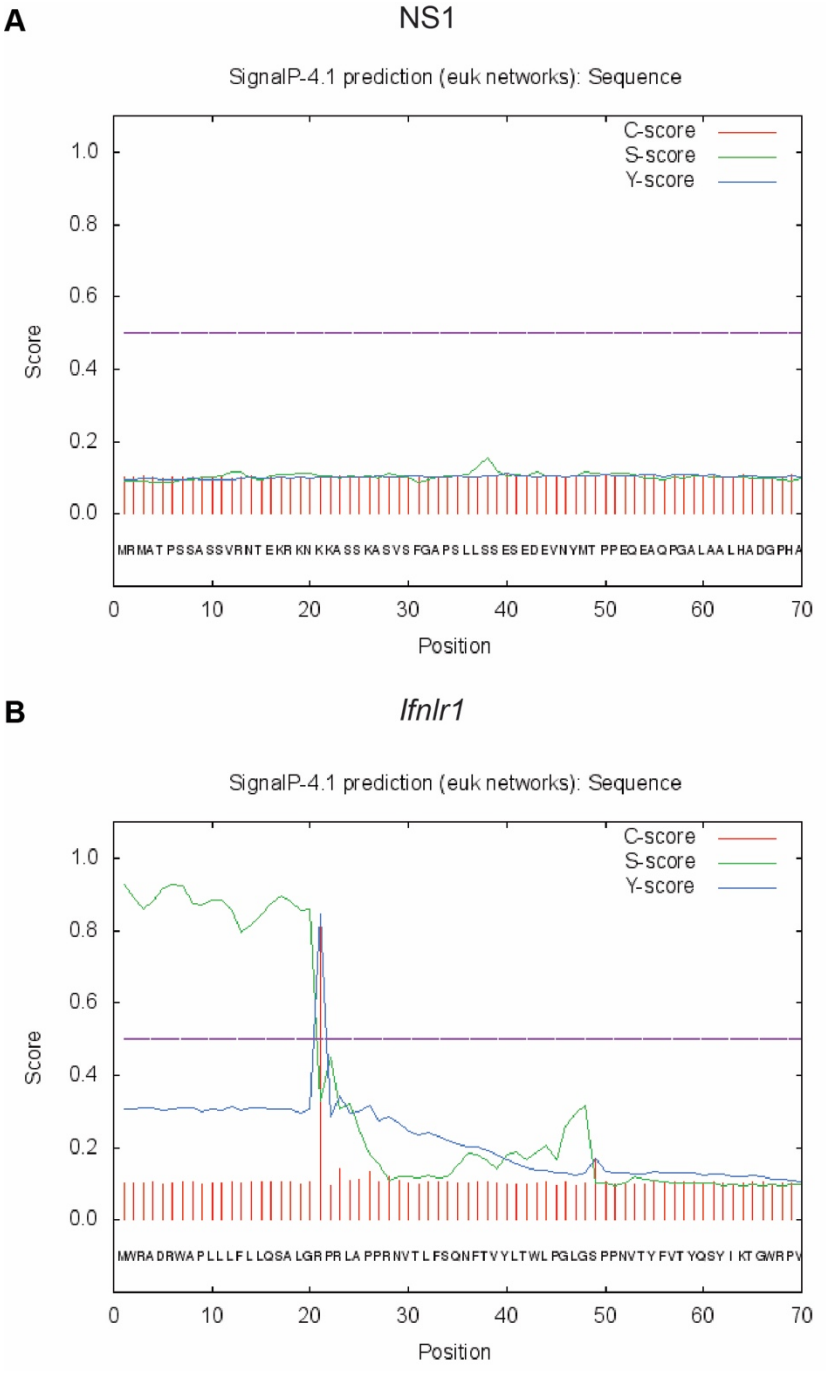

Figure S2. Signal peptide prediction of NS1. Related to Figure 2.

(**A**) Signal peptide sequence of NS1 was predicted by SignalP. None of the peptide sequences in NS1 was scored as a potential signal peptide. Blue dashed bar is a score-threshold to be predicted as a signal peptide. (**B**) The same algorithm was applied to *Ifnlr1* sequences as a positive control. Signal peptide prediction of Ifnlr1 provided a single peptide sequence at the N-terminal site of *Ifnlr1*. C-score (raw cleavage site score), S-score (signal peptide score) and Y-score (combined cleavage site score).

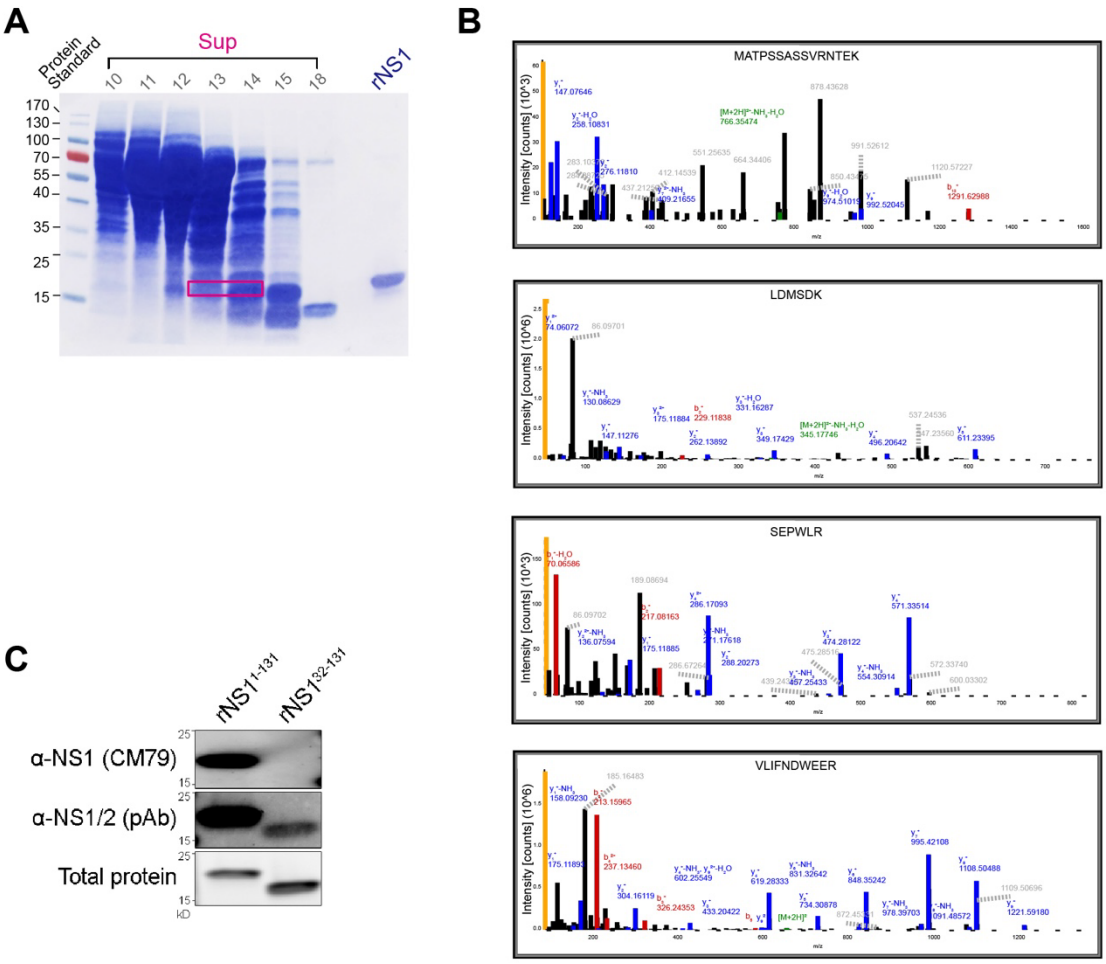

Figure S3. Protein identification of secreted NS1 by LC-MS/MS. Related to Figure 3.

(**A**) The corresponding fractions from the size exclusion chromatography were collected in sequence as numbers indicated on the elution axis then determined by Coomassie blue stain after SDS-PAGE. Gel bands were sliced as indicated by the red rectangle and subjected to LC-MS/MS protein identification. (**B)** LC-MS/MS with secreted NS1. Peptide mapping in raw fragmentation spectrum is shown. The peptide sequences are labeled on the top of each panel. Representative fragments of each peptide shown as colored peaks with corresponding colored annotation and m/z digits in each panel while theoretical fragments that are not found in the spectrum shown as black peaks and grey annotation and m/z digits. (**C**) Epitope mapping of anti-NS1 monoclonal antibody, CM79. The full-length protein of NS1, rNS1$^{1\text{-}131}$, and the N-terminally truncated protein of NS1, rNS1$^{32\text{-}131}$ were used to determine the epitope of CM79. Rabbit polyclonal anti-NS1/2 (α-NS1/2 pAb) detected both proteins. CM79 only detected rNS1$^{1\text{-}131}$ but failed to detect rNS1$^{32\text{-}131}$, indicating the epitope of CM79 exists between 1 to 31 amino acids in NS1 protein.

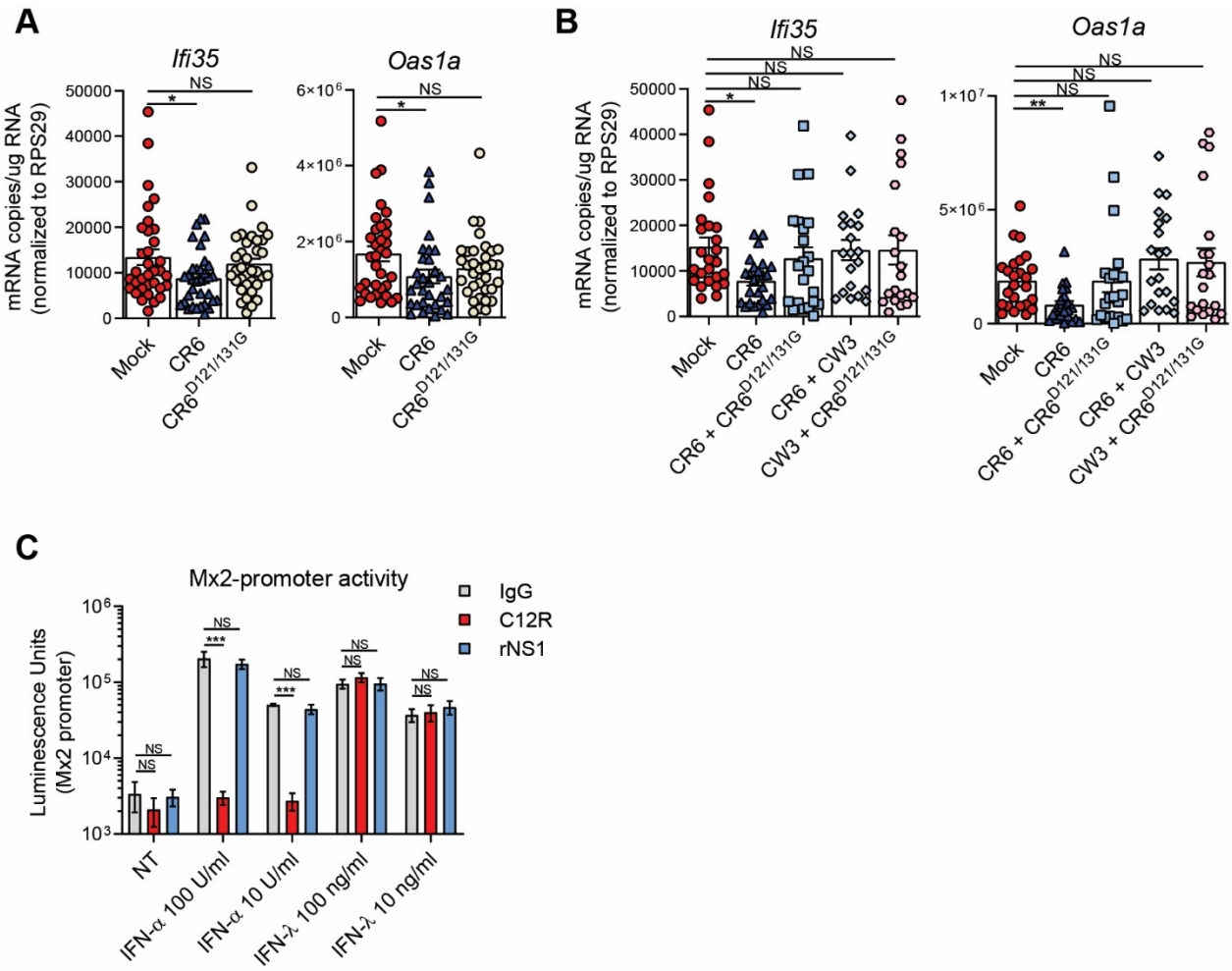

Figure S4. ISG induction with infection of different MNoV strains, and ISG induction with NS1-treatment in the mouse IEC line. Related Figure 5.

(**A**) Wild-type mice were infected with 10^6 PFU of CR6 or CR6$^{D121/131G}$, and the expression of *Ifi35* and *Oas1a* mRNA in ileum was analyzed at 3 dpi by qRT-PCR (n = 34-35 mice per group, combined from four independent experiments). Shown are means ± SEM. NS, not significant; *P < 0.05, determined by one-way ANOVA followed by Tukey's multiple comparison. (**B**) Wild-type mice were singly- or co-infected with 10^6 PFU of CR6, CR6$^{D121/131G}$, CW3, and the expression of *Ifi35* and *Oas1a* mRNA in ileum was analyzed at 3 dpi by qRT-PCR (n = 20-23 mice per group, combined from three independent experiments). Shown are means ± SEM. NS, not significant; *P < 0.05, **P < 0.01, determined by determined by Brown-Forsythe and Welch ANOVA test followed by Games-Howell's multiple comparisons test. (C) Mx2LUC-IEC cells, mouse IEC line encoding the Mx2-reporter construct, were pre-treated with IgG, C12R or rNS1 (100 ng/ml) for 30 minutes, then treated with IFN-α or IFN-λ. After 12 hours, Mx2-promoter activity was quantified by detecting luminescence (n = 4 per group, representative data from two independent experiments). Shown are means ± SD. NT, no treatment; NS, not significant; ***P < 0.001, determined by unpaired t-test.

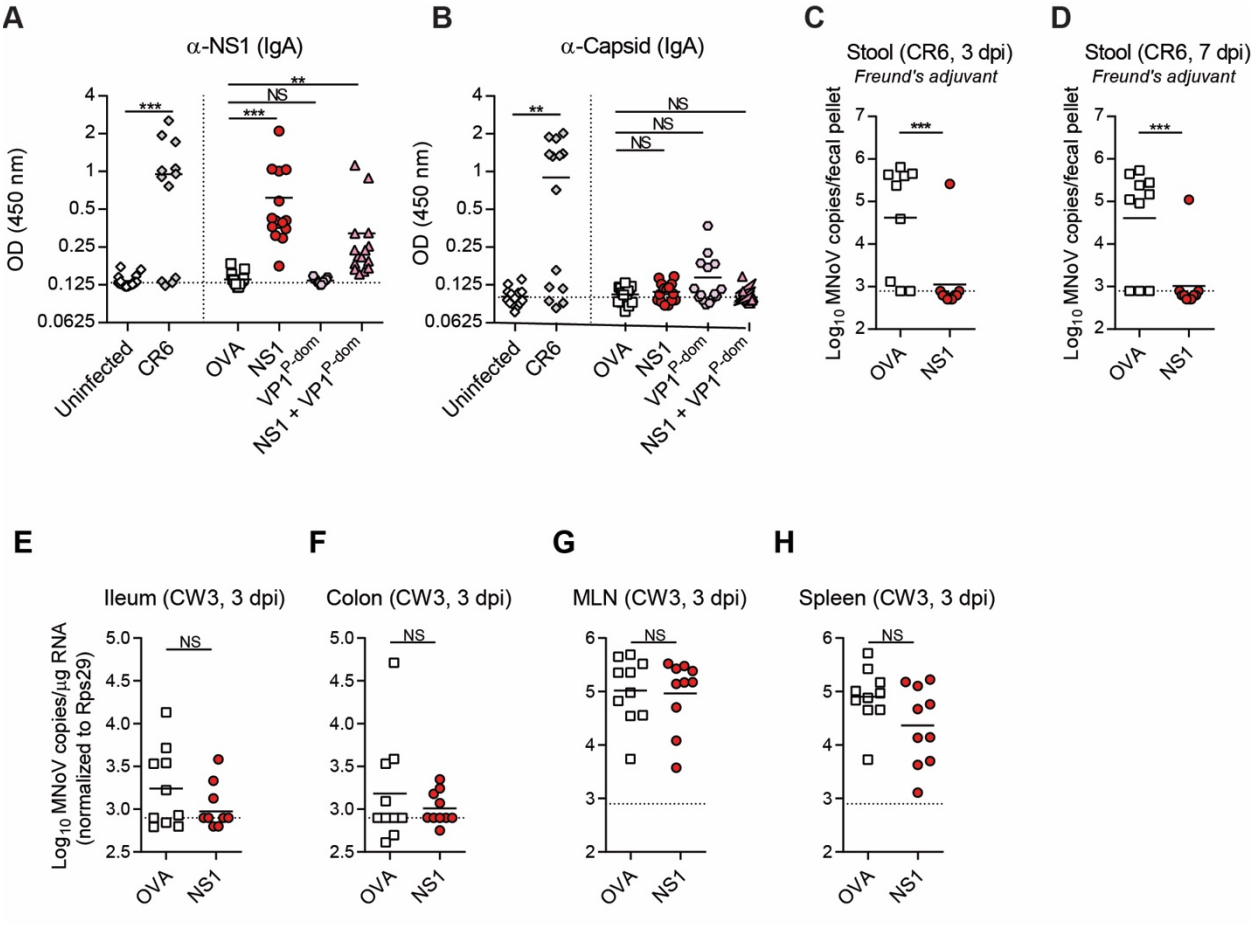

Figure S5. Serum IgA levels of anti-NS1 and anti-capsid, NS1-immunization with Freund's adjuvant protected the mice from CR6-infection, and NS1-immunization did not protect the mice from CW3-infection. Related to Figure 6.

(**A-B**) Serum IgA levels of Figure 6. Concentration of α-NS1 IgA (**A**) and α-capsid IgA (**B**) in the serum was measured by ELISA. Optical density (OD) value was detected at 450 nm. N = 14-15 per group, combined from three independent experiments. Shown are means ± SEM. NS, not significant; *P < 0.05; **P < 0.01; ***P < 0.001, determined by Mann-Whitney test for infection group and Kruskal-Wallis test for immunized group. (**C-H**) Wild-type mice were immunized subcutaneously three times with Ovalbumin (OVA) or recombinant NS1 (NS1) in Freund's adjuvant (**C-D**) or in Poly I:C (**E-H**). The immunized mice were infected with 10^6 PFU of CR6 or CW3 perorally. MNoV genome copies in stool at 3 dpi (**C**) and at 7 dpi (**D**) was quantified by qRT-PCR. N = 10 per group, combined from two independent experiments. (**E-H**) MNoV genome copies in the tissues at 3 dpi is quantified by qRT-PCR. N = 10 per group, combined from two independent experiments. NS = not significant, ***P<0.001, analyzed by Mann-Whitney test (**C-H**).

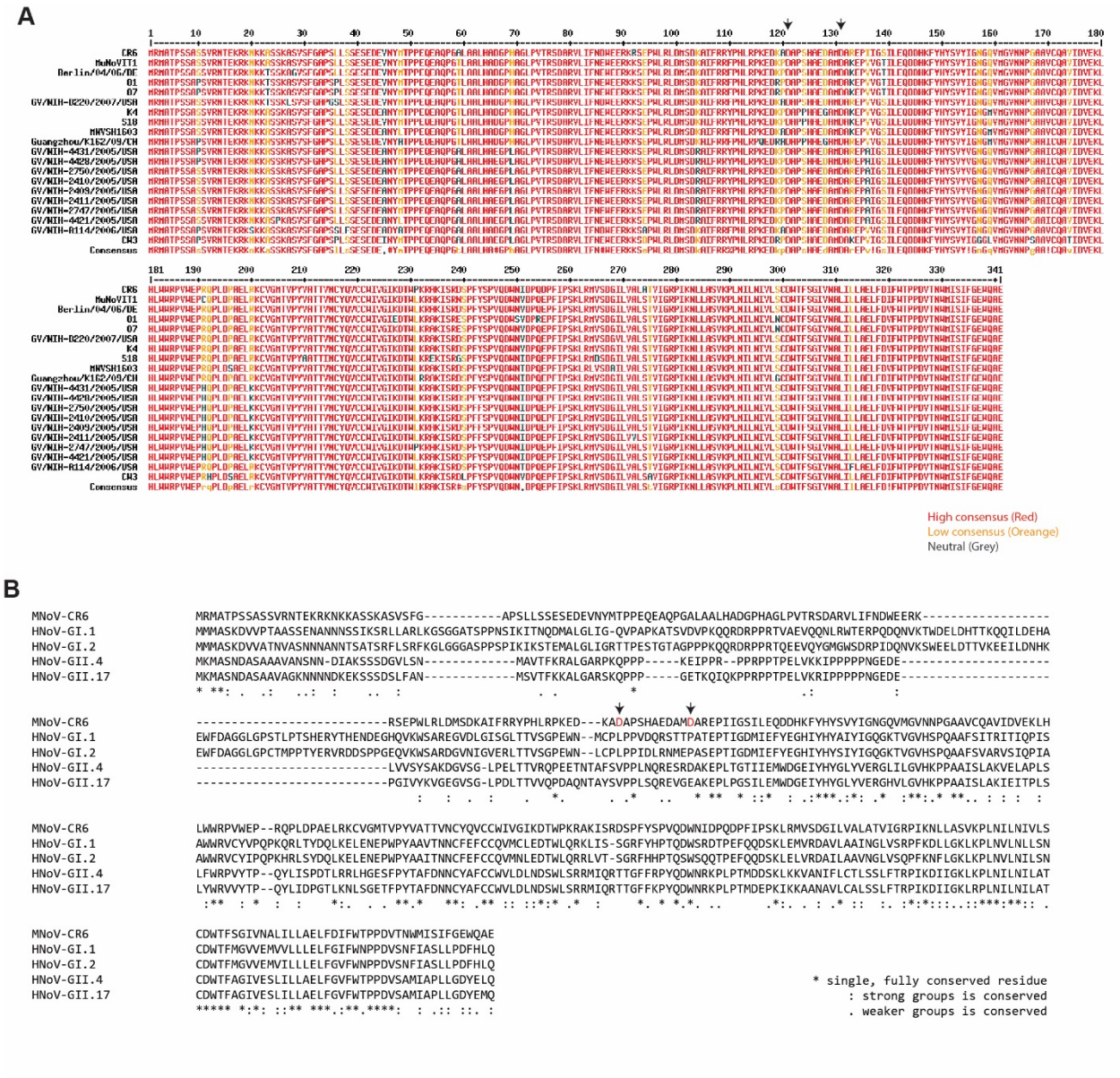

Figure S6. NS1/2 sequence conservation between murine and human noroviruses. Related to Figure 6.

(A) Nucleotide sequence alignment of the NS1/2 region of 20 different MNoV strains. The amino acid sequences are analyzed by Multalin (http://multalin.toulouse.inra.fr/multalin/multalin.html) (B) Nucleotide sequence alignment of the NS1/2 region of murine and human noroviruses; MNoV (CR6 strain), HNoV-GI.1, HNoV-GI.2, HNoV-GII.4 and HNoV-GII.17. The sequence conservation was analyzed by CLUSTALW. (A-B) The NS1-cleavage sites by Casp3 (D121 and D131) were indicated by arrow.

Table S1. Gene list of Interferon lambda response. Related to Figure 1.

MITD1	SASS6	IFIT2	OGFR
STAT2	TOR1AIP1	MLKL	CMPK2
AW011738	LGALS3BP	PHF11B	OASL1
PLAC8	APOL9B	GM4951	ADAR
GCA	LY6E	OAS3	HERC6
RP24-328P2.5	TRIM34A	IFIH1	BATF2
CLEC2H	RNF213	IFIT3	BST2
COX18	SP110	DTX3L	RSAD2
ISG20	ZNFX1	APOL9A	IL18BP
AGRN	MME	HSH2D	SLC28A2
TOMM40	MX2	TOR3A	KIFC2
ZCCHC2	TRIM6	CAAA01077340.1	PARP12
VAT1	SP100	OAS1B	IFI35
SAMD9L	TRIM25	SPATS2L	LYPD8
CASP3	1700030C10RIK	UBE2L6	H2-T24
SLFN9	DDX60	IRGM1	GBP3
GBP9	PHF11A	DHX58	IFIT1
NT5C3	IFI27L2B	DDX58	IFI27L2A
IFI204	TRIM30A	IFITM3	UBA7
FBXW17	PHF11D	SLFN5	LY6A
RBM43	PARP11	GBP7	NLRC5
MNDA	OAS2	SLFN4	SLFN2
IFIT3B	CUBN	RTP4	IIGP1
NAMPT	SAMHD1	IFI47	STAT1
MX1	IFI44	ISG15	GM5431
SHISA5	GMPPB	C2	GM14446
CNP	TLR3	IRF7	PSMB9
SLFN1	EHD4	XAF1	GM12250
ACADL	MOCOS	USP18	IGTP
CRYBB3	MNDAL	EPSTI1	ZBP1
PML	OAS1A	EIF2AK2	XIST
PLS1	DIO1	TRIM12A	
HELZ2	OASL2	IFT172	