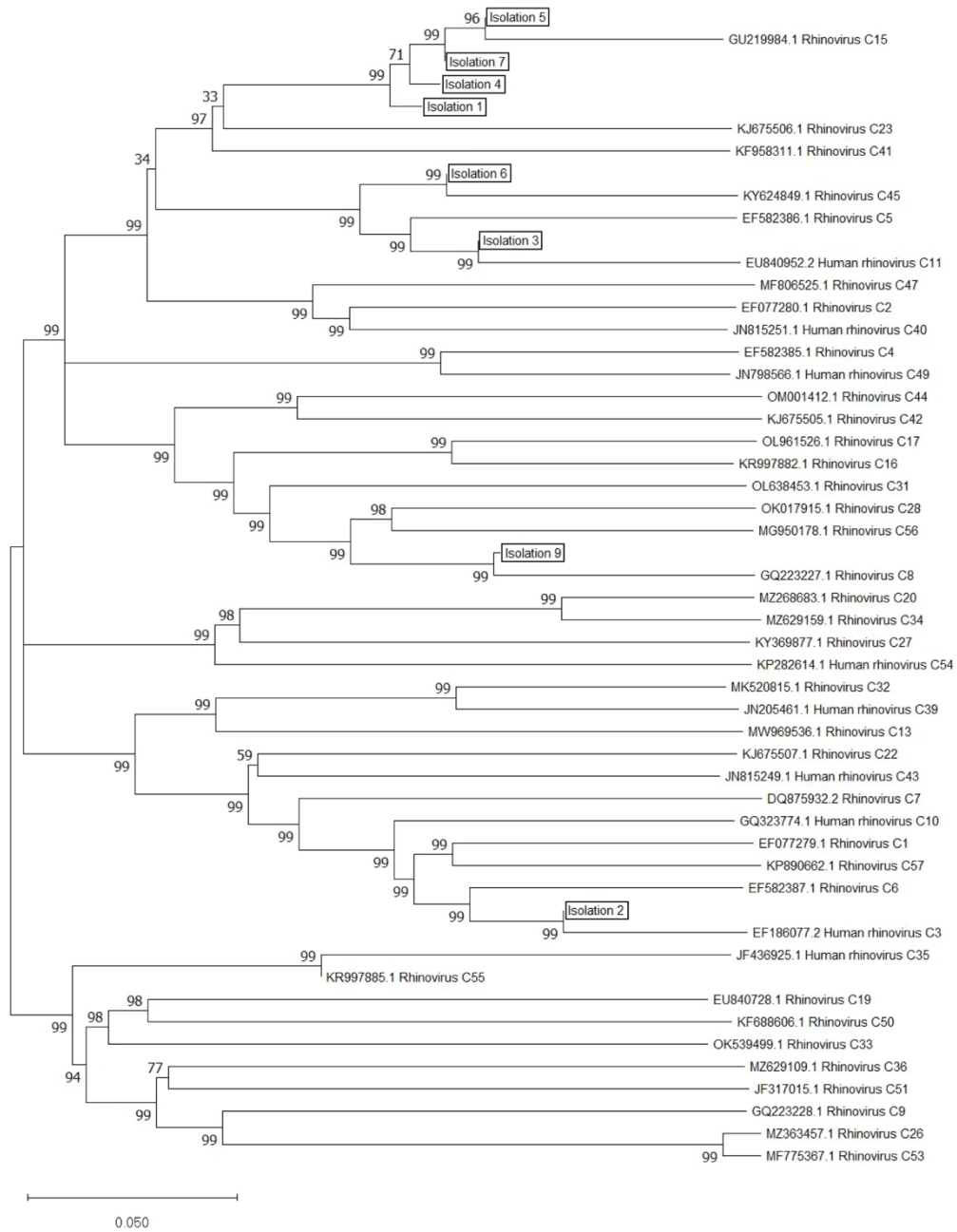


Supplementary Figure 1. Phylogenetic analysis of 8 isolated HRV-C and 43 HRV-C reference subtypes based on the 5' UTR (372bp, position nt 179-551).

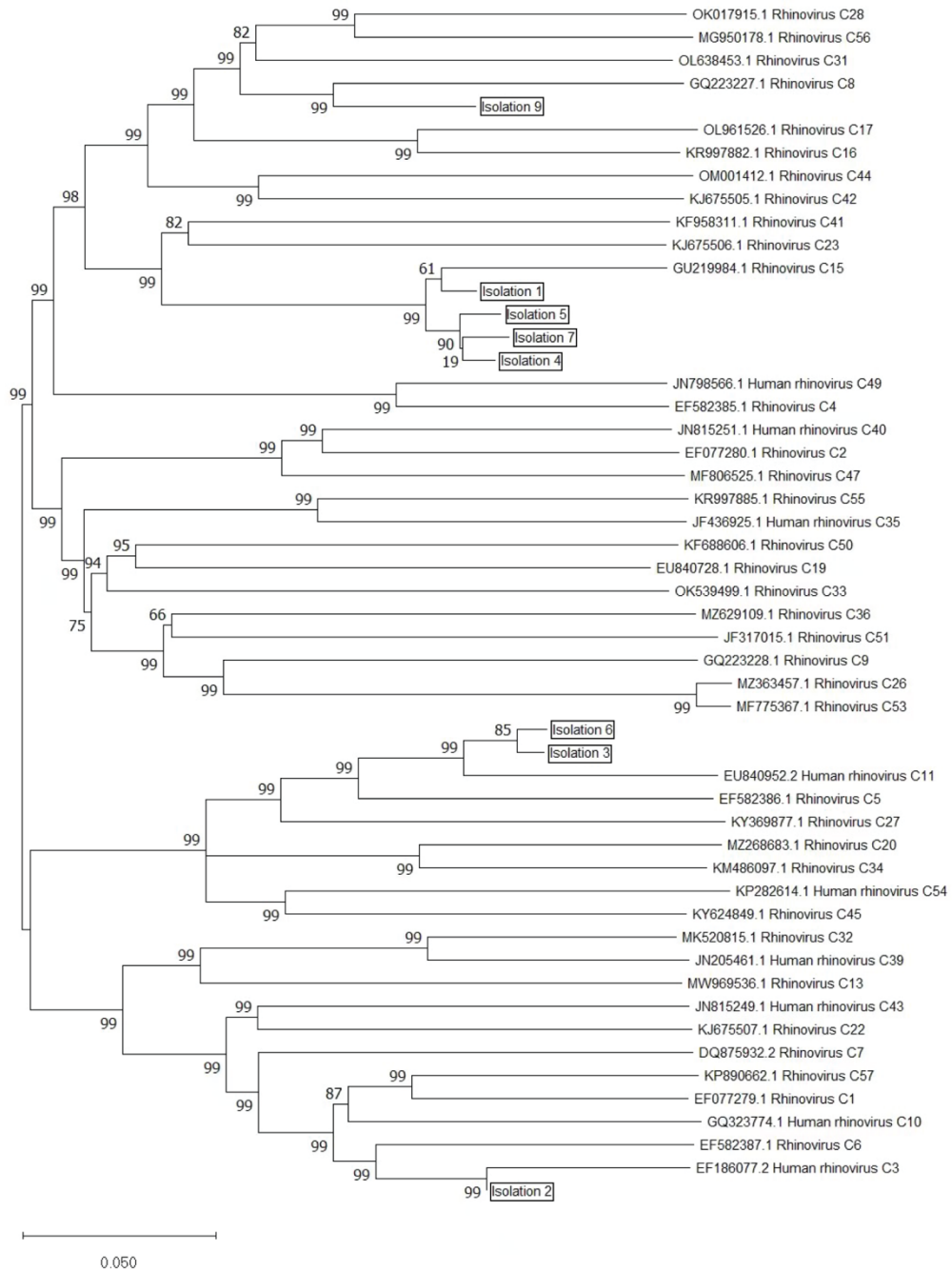
5' UTR



The phylogenetic tree was constructed using the neighbor-joining method and p-distance model with bootstrap replicated from 1,000 trees using MEGA 10.2.3. Genetic distance is represented by the scale bar.

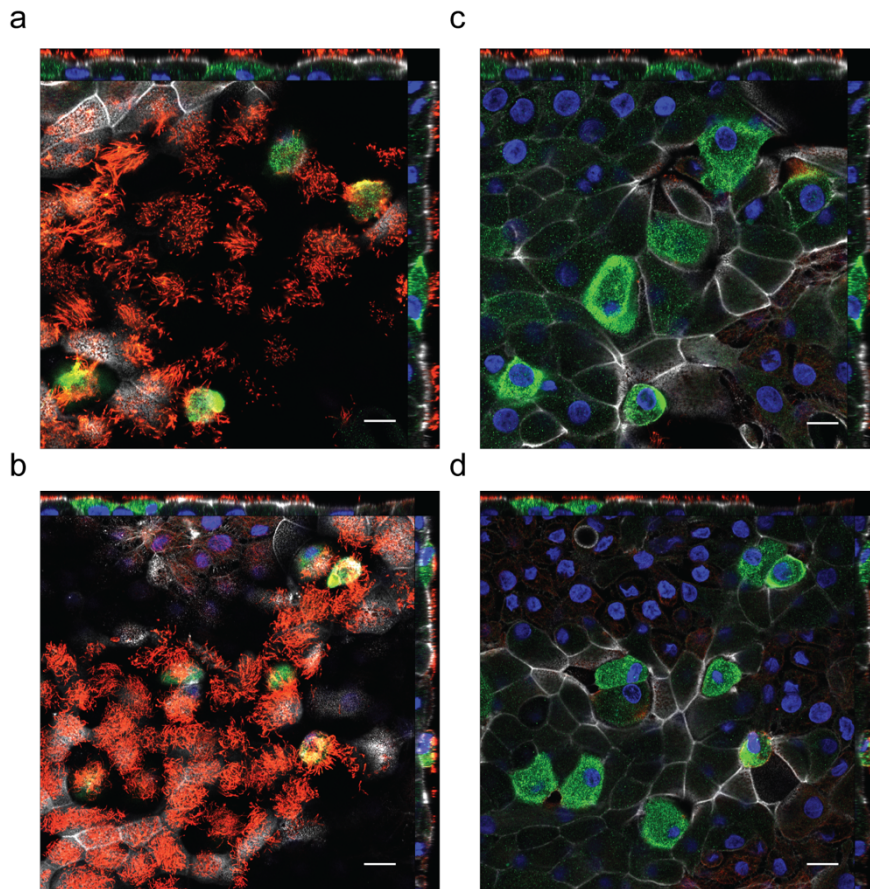
Supplementary Figure 2. Phylogenetic analysis of 8 isolated HRV-C and 43 HRV-C reference subtypes based on the VP4/VP2 gene (540bp, position nt 547-1087).

VP4/VP2



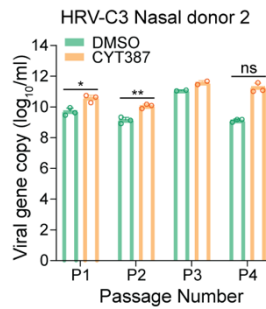
The phylogenetic tree was constructed using the neighbor-joining method and p-distance model with bootstrap replicated from 1,000 trees using MEGA 10.2.3. Genetic distance is represented by the scale bar.

Supplementary Figure 3. Orthogonal views of human airway organoid with HRV-C infection.



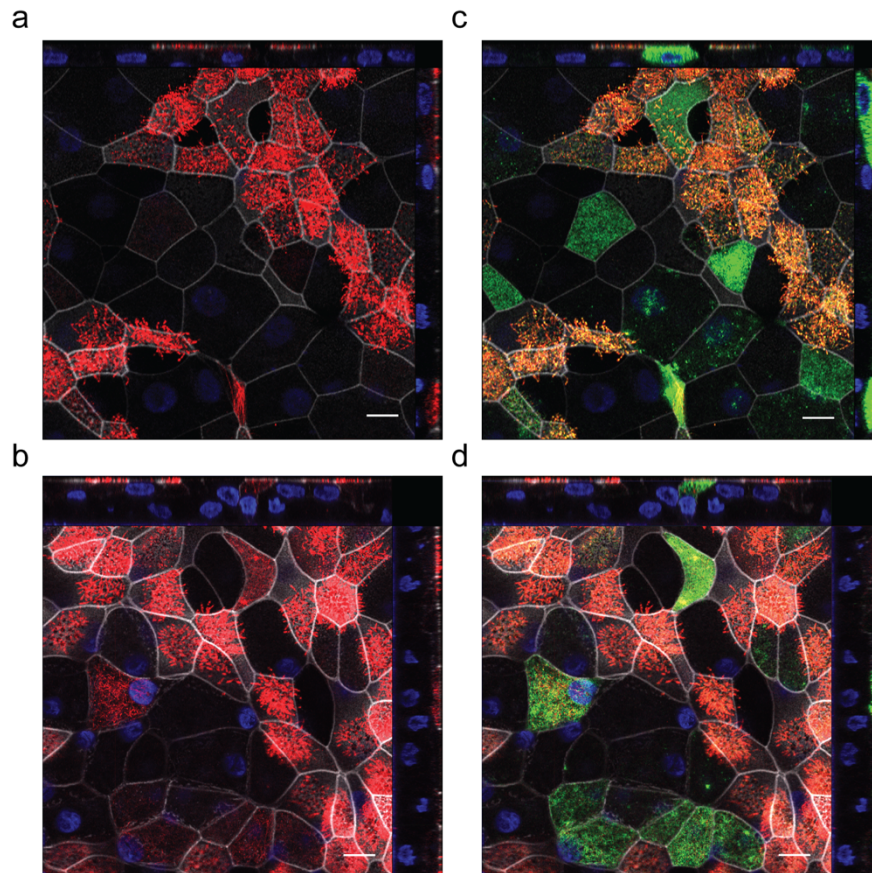
(a-d) Orthogonal views of human airway organoid with HRV-C infection. Airway organoids were fixed and double-stained with an α -VP3 (green) and α -ACCTUB (red). Upper layers (a, b) and lower layers (c, d) of orthogonal views of confocal images with en face and cross-section are shown. Nuclei and actin filaments were counterstained with DAPI (blue) and Phalloidin-647 (white), respectively. The experiment was performed three times independently with similar results. Scale bar, 10 μ m.

Supplementary Figure 4. Human nasal organoid sustained serial HRV-C propagation.



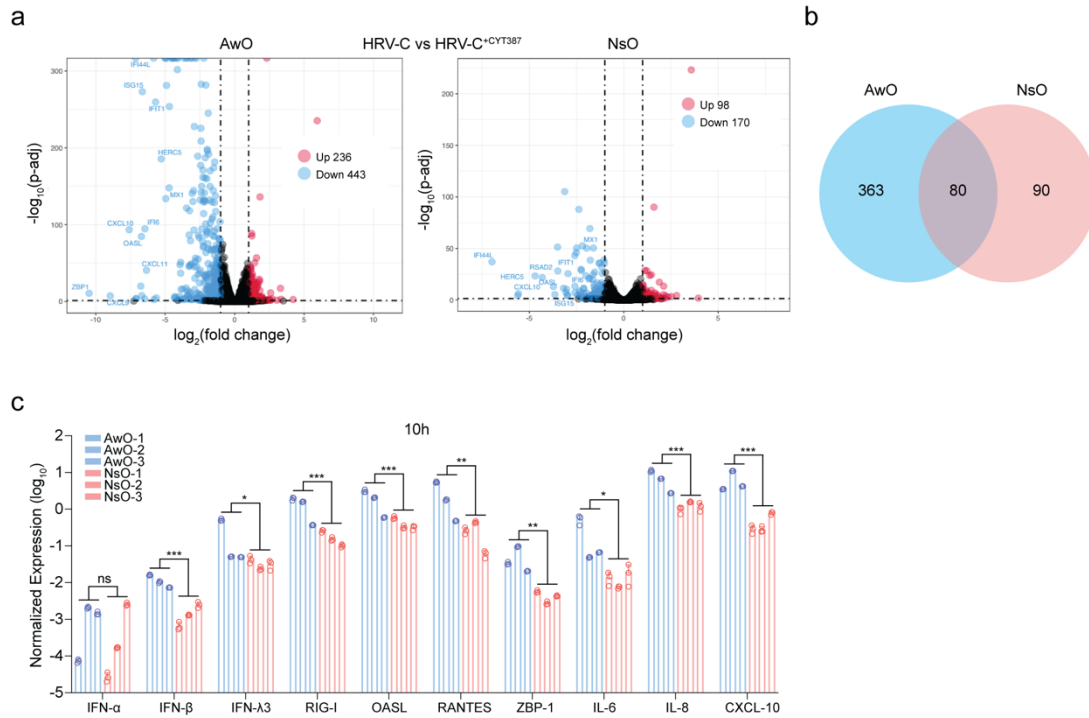
Nasal organoids pre-treated with CYT387 or DMSO were inoculated with HRV-C3 at 100 viral gene copy/cell and incubated in the presence of CYT387 or DMSO respectively. CYT387- and DMSO-treated media were brought forward as inoculum to the next round of infection, during which CYT387 and DMSO treatment continued. Culture media were harvested at 96 h.p.i. to detect viral replication (P1, P2, and P4, n=3; P3, n=2). Data represent mean and SD of the indicated number (n) of biological replicates from a representative experiment. Statistical significance (in P1, P2, and P4) was determined using a two-tailed Student's t-test. * $P < 0.05$, ** $P < 0.01$. *ns* not significant. Source data are provided as a Source Data file.

Supplementary Figure 5. Orthogonal views of human nasal organoid with HRV-C infection.



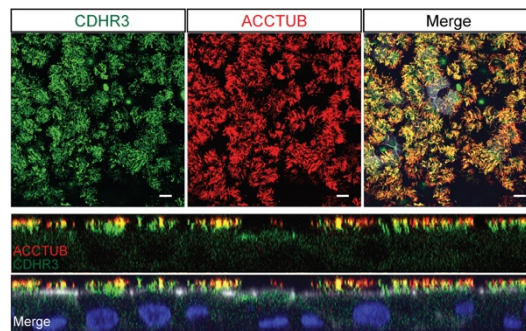
(a-d) Orthogonal views of human nasal organoid with HRV-C infection. Nasal organoids were fixed and double-stained with an α -VP3 (green) and α -ACCTUB (red). Orthogonal views of confocal images with en face and cross-section are shown. Nuclei and actin filaments were counterstained with DAPI (blue) and Phalloidin-647 (white), respectively. (a, b) Three channels are shown: α -ACCTUB (red), DAPI (blue), and Phalloidin-647 (white). (c, d) Four channels are shown: α -VP3 (green), α -ACCTUB (red), DAPI (blue), and Phalloidin-647 (white). The experiment was repeated three times independently with similar results. Scale bar, 10 μ m.

Supplementary Figure 6. Host transcriptional response in human airway and nasal organoids.



HRV-C3 infected airway (AwO) organoids and nasal organoids (NsO) treated with CYT387 (HRV-C^{+CYT387}) or DMSO (HRV-C) were applied to RNA sequencing analysis. (a) Volcano plot shows DEGs in the HRV-C-infected airway and nasal organoids with CYT387 treatment compared with HRV-C-infected organoids. DEGs with a $\log_2(\text{fold change}) > 1$ and < -1 are shown in red and blue respectively. (b) Venn diagram shows the numbers of unique and common downregulated DEGs in the infected airway and nasal organoids. (c) Three lines of airway and nasal organoids were treated with 10 $\mu\text{g/ml}$ Poly(I:C) or mock-treated. At 10 h post-treatment, organoids were harvested for RT-qPCR ($n=3$). Results showed the GAPDH normalized expression level of innate immune molecules in the airway and nasal organoids. Data represent mean and SD of the indicated number (n) of biological replicates from a representative experiment. Statistical significance (in c) was determined using a two-tailed Student's t-test. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. *ns* not significant. Source data are provided as a Source Data file for Supplementary Figure 6c.

Supplementary Figure 7. High CDHR3 expression on the apical surface of the airway organoids.



Airway organoids were fixed and double-stained with an α -CDHR3 (green) and α -ACCTUB (red). Confocal images of en face (top) and cross-section (bottom) are shown. Nuclei and actin filaments were counterstained with DAPI (blue) and Phalloidin-647 (white), respectively. The experiment was performed three times independently with similar results. Scale bar, 10 μ m.

Supplementary Table 1. Antibody list.

Name	Supplier	Cat. no.	Lot no.	Dilution (IF)	Dilution (Flow)
Mouse IgG	abcam	ab91353	GR3327311-3	1:100	1:100
Rabbit IgG	abcam	ab172730	GR3284310-8	1:100	1:100
Rhinovirus VP3	Invitrogen	MA5-18249	YD3903932	1:100	1:100
CDHR3	abcam	ab121337	1016309-2	1:100	1:100
CDHR3	Sigma-Aldrich	HPA011218	000006575	1:100	-
TUBULIN	abcam	ab179509	GR252919-6	1:100	1:1000
TUBULIN	Sigma-Aldrich	T7941	088M4793	1:100	-
Goat anti-Mouse 488	invitrogen	A-11001	2090562	1:200	1:300
Goat anti-Mouse 594	invitrogen	A-11005	1750828	1:200	-
Goat anti-Rabbit 488	invitrogen	A-11034	1885241	1:200	1:300
Goat anti-Rabbit 594	invitrogen	A-11037	1608397	1:200	1:300

Supplementary Table 2. Primer sequences for qPCR analysis

Gene	Sequence
IFN- α	F 5'-AGAATCACTCTCTATCTGAAAGAGAAGAAATA-3' R 5'-TCATGATTTCTGCTCTGACAACCT-3'
IFN- β	F 5'-CTTGGATTCTACAAAGAAGCAGC-3' R 5'-TCCTCCTTCTGGAAGTCTGCA-3'
IFN- λ 3	F 5'-TCGAGGCCTCTGTCACCTTC-3' R 5'-AGGTTGCATGACTGGCGGAA-3'
RIG-I	F 5'-AGAGCACTTGTGGACGCTTT-3' R 5'-GCCACGTCCAGTCAATATGC-3'
OASL	F 5'-AAACCATGTGGCAAAGCCAG-3' R 5'-GCTCTGTAGGCAGGCACAAT-3'
RANTES	F 5'-TCATTGCTACTGCCCTCTGC-3' R 5'-TACTCCTTGATGTGGGCACG-3'
ZBP1	F 5'-GCAAACCTCCGAAGCCATCCAGA-3' R 5'-CCAAGTTGAGGAATCACCTGGTG-3'
IL-6	F 5'-AGACAGCCACTCACCTCTTCAG-3' R 5'-TTCTGCCAGTGCCTCTTTGCTG-3'
IL-8	F 5'-GAGAGTGATTGAGAGTGGACCAC-3' R 5'-CACAACCCTCTGCACCCAGTTT-3'
IP-10	F 5'-GAAATTATTCCTGCAAGCCAATTT-3' R 5'-TCACCCTTCTTTTTCATTGTAGCA-3'
HRV-C 5' UTR	F1 5'-AGCCYGCGTGGCKGCC-3' F2 5'-AGCCYGCGTGGTGCCC-3' R 5'-GAAACACGGACACCCAAAGTAGT-3' Probe 5' HEX-TCCGGCCCCTGAATGYGGCTAA-IABkFQ 3'

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HRV-C_P1 1201 CATCAGTTAGCATACATTGGAGGTGACAACACCCGAGTCAAATATAAGCACACACACCCAGGTGAATTAGGCCATAAAAT
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