**Supplementary Information**

**SARS-CoV-2 strategically mimics proteolytic activation**

**of human ENaC**

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**Supplementary Tables**

**Supplementary file 1a.** SARS-CoV-2 variants in the RRARSVAS 8-mer peptide from 10,987 spike (S) protein sequences of the GISAID database. The specific variations are highlighted in **Red**.

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| --- | --- | --- |
| **Variation in the mimicked**  **8-mer of interest (RRARSVAS)** | **Number of occurrences in the**  **SARS-CoV-2 S-protein sequences** | **Strain Information (GISAID)** |
| **RRARSVAS** | **10,976** | - |
| R**P**ARSVAS | 1 | HCOV-19/NETHERLANDS/ZUIDHOLLAND\_37/2020|EPI\_ISL\_422909|2020-03-17 |
| **Q**RARSVAS | 1 | HCOV-19/HANGZHOU/ZJU-01/2020|EPI\_ISL\_415709|2020-01-25 |
| R**Q**ARSVAS | 1 | HCOV-19/ENGLAND/CAMB-73800/2020|EPI\_ISL\_425243|2020-04-01 |
| RRAR**G**VAS | 1 | HCOV-19/RUSSIA/KRASNODAR-63401/2020|EPI\_ISL\_428867|2020-03-11 |
| RRARSV**V**S | 2 | HCOV-19/ENGLAND/20104035803/2020|EPI\_ISL\_417238|2020-03-0  HCOV-19/WALES/PHWC-2658D/2020|EPI\_ISL\_422346|2020-03-26 |
| RRARSVA**I** | 3 | HCOV-19/ENGLAND/20140007302/2020|EPI\_ISL\_421925|2020-03-28  HCOV-19/ENGLAND/20140005304/2020|EPI\_ISL\_423380|2020-03-29  'HCOV-19/FRANCE/ARA12265/2020|EPI\_ISL\_419186|2020-03-22 |
| RR**V**RSVAS | 2 | HCOV-19/BRAZIL/RJ-872/2020|EPI\_ISL\_427304|2020-03-26  HCOV-19/SPAIN/VALENCIA98/2020|EPI\_ISL\_425222|2020-03-17 |
| **[RQ][RQP][AV][R][SG][V][AV][IS]** | **10,987** |  |

**Supplementary file 1b.** Protease cleavage propensities for FURIN and the other proteases identified as similar from the vector space analysis conducted. Similarity (FURIN) ranges from 0 to 1. Highlighted green are amino acids occurring in greater than 10% of the cleaved substrates at that position (compiled from MEROPS).

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Protease** | **Cleavage substrates** | **Similarity (FURIN)** | **P4** | **P3** | **P2** | **P1** | **P1'** | **P2'** | **P3'** | **P4'** |
| **MIMICKED PEPTIDE** | | | **R** | **R** | **A** | **R** | **S** | **V** | **A** | **S** |
| **FURIN** | 208 | 1.00 | R(158)  I(8)  K(7)  F(7)  Others(26) | K(34)  S(27)  R(26)  T(18)  Others(97) | K(88)  R(68)  P(9)  A(8)  Others(34) | R(203)  K(4)  L(1) | S(57)  A(23)  D(22)  E(20)  Others(86) | V(46)  A(34)  L(31)  I(15)  Others(76) | S(30)  G(21)  D(18)  E(16)  Others(113) | S(19)  G(19)  A(17)  E(16)  Others(129) |
| **PCSK5** | 129 | 0.992 | R(97)  K(8)  I(6)  V(4)  Others(12) | K(23)  S(16)  R(13)  Q(10)  Others(62) | K(59)  R(41)  P(8)  S(4)  Others(12) | R(125)  K(4) | S(37)  A(11)  D(11)  F(9)  Others(58) | V(25)  A(24)  L(22)  I(12)  Others(43) | S(15)  G(15)  D(15)  E(13)  Others(62) | E(15)  L(13)  P(12)  G(11)  Others(71) |
| **PCSK4** | 103 | 0.99 | R(77)  K(8)  V(4)  I(2)  Others(7) | K(18)  R(12)  S(11)  Q(10)  Others(45) | K(49)  R(32)  P(6)  A(3)  Others(7) | R(100)  K(3) | S(31)  E(9)  D(9)  A(9)  Others(37) | V(25)  A(19)  L(15)  T(10)  Others(26) | S(13)  G(12)  D(12)  E(11)  Others(47) | E(13)  P(11)  L(11)  S(8)  Others(52) |
| **PCSK6** | 105 | 0.99 | R(85)  K(7)  V(4)  I(2)  Others(7) | K(19)  S(12)  R(12)  Q(10)  Others(45) | K(53)  S(36)  R(6)  Q(3)  Others(7) | R(102)  K(3) | S(33)  A(10)  E(9)  D(9)  Others(41) | V(29)  A(20)  L(15)  T(10)  Others(28) | G(15)  S(14)  D(13)  E(11)  Others(49) | E(13)  L(12)  P(11)  S(10)  Others(46) |
| **PCSK7** | 117 | 0.989 | R(85)  K(9)  I(5)  V(4)  Others(8) | K(23)  S(13)  R(12)  Q(11)  Others(50) | K(54)  R(38)  P(7)  A(3)  Others(8) | R(112)  K(4) | S(34)  E(11)  D(10)  A(10)  Others(44) | V(25)  L(22)  A(20)  T(11)  Others(31) | D(14)  S(13)  G(13)  E(13)  Others(52) | E(15)  P(11)  L(11)  A(10)  Others(60) |
| **PCSK2** | 205 | 0.941 | R(86)  K(13)  V(11)  I(11)  Others(8) | Q(27)  S(22)  K(20)  E(19)  Others(109) | K(123)  R(44)  P(9)  A(6)  Others(9) | R(192)  K(11)  S(1)  F(1) | S(43)  Y(25)  A(20)  G(15)  Others(93) | V(27)  G(23)  L(22)  A(22)  Others(102) | G(31)  E(27)  S(17)  Q(17)  Others(103) | E(31)  D(27)  F(17)  S(17)  Others(117) |
| **PLG** | 126 |  | P(18)  A(16)  R(13)  S(8)  Others(52) | R(17)  S(12)  Q(11)  G(10)  Others(70) | L(15)  S(13)  P(12)  A(11)  Others(72) | R(65)  K(57)  Others(3) | S(23)  A(20)  G(11)  R(10)  Others(51) | R(13)  V(12)  S(12)  K(8)  Others(70) | S(13)  P(11)  A(9)  Q(8)  Others(74) | G(12)  P(11)  L(11)  A(9)  Others(72) |

**Supplementary file 1c.** **List of single-cell studies analyzed and incorporated into the nferX resource (**[**https://academia.nferx.com/**](https://academia.nferx.com/))

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| --- | --- | --- | --- |
| **Study ID** | **Organism** | **Study Title** | **Pubmed ID (PMID)** |
| study1 | Mus musculus | A single-cell survey of the small intestinal epithelium | PMID: 29144463 |
| study2 | Mus musculus | Single-cell transcriptomics of 20 mouse organs creates a Tabula Muris. | PMID:30283141 |
| study3 | Homo sapiens | Intra- and Inter-cellular Rewiring of the Human Colon during Ulcerative Colitis | PMID:31348891 |
| study4 | Homo sapiens | Immune Cell Atlas: Blood Mononuclear Cells (2 donors, 2 sites) | <https://singlecell.broadinstitute.org/single_cell/study/SCP345/ica-blood-mononuclear-cells-2-donors-2-sites> |
| study5 | Homo sapiens | Spleen - Ischaemic sensitivity of human tissue by single cell RNA seq | <https://data.humancellatlas.org/explore/projects/c4077b3c-5c98-4d26-a614-246d12c2e5d7> |
| study6 | Homo sapiens | Esophagus - Ischaemic sensitivity of human tissue by single cell RNA seq | <https://data.humancellatlas.org/explore/projects/c4077b3c-5c98-4d26-a614-246d12c2e5d7> |
| study7 | Homo sapiens | A cellular census of human lungs identifies novel cell states in health and in asthma. | PMID: 31209336 |
| study8 | Mus musculus | A revised airway epithelial hierarchy includes CFTR-expressing ionocytes | PMID: 30069044 |
| study9 | Homo sapiens | Fetal Kidney - Spatiotemporal immune zonation of the human kidney | PMID: 31604275 |
| study10 | Homo sapiens | Mature Kidney - Spatiotemporal immune zonation of the human kidney | PMID: 31604275 |
| study11 | Homo sapiens | Identification of grade and origin specific cell populations in serous epithelial ovarian cancer by single cell RNA-seq | PMID: 30383866 |
| study12 | Homo sapiens | A human liver cell atlas reveals heterogeneity and epithelial progenitors. | PMID:31292543 |
| study13 | Homo sapiens | Human Pancreas scRNA-seq (Integration of 3 Datasets) | PMID:27345837,PMID:27667667,PMID:27693023 |
| study14 | Homo sapiens | Census Of Immune Cells | <https://data.humancellatlas.org/explore/projects/cc95ff89-2e68-4a08-a234-480eca21ce79> |
| study15 | Mus musculus | Mapping the Mouse Cell Atlas by Microwell-Seq. | PMID:29474909 |
| study16 | Homo sapiens | Transcriptome Landscape of Human Folliculogenesis Reveals Oocyte and Granulosa Cell Interactions. | PMID: 30472193 |
| study17 | Homo sapiens | A Cellular Anatomy of the Normal Adult Human Prostate and Prostatic Urethra. | PMID: 30566875 |
| study18 | Homo sapiens | Single-cell reconstruction of the early maternalâ€“fetal interface in humans | PMID: 30429548 |
| study19 | Homo sapiens | Single-cell transcriptome analysis reveals differential nutrient absorption functions in human intestine | PMID: 31753849 |
| study20 | Homo sapiens | Single-Cell Transcriptomic Analysis of Primary and Metastatic Tumor Ecosystems in Head and Neck Cancer | PMID: 29198524 |
| study22 | Homo sapiens | Single-cell reconstruction of the adult human heart during heart failure and recovery reveals the cellular landscape underlying cardiac function | PMID:31915373 |
| study23 | Mus musculus | Single cell analysis reveals immune cell-adipocyte crosstalk regulating the transcription of thermogenic adipocytes | PMID: 31644425 |
| study24 | Mus musculus | An atlas of the aging lung mapped by single cell transcriptomics and deep tissue proteomics | PMID: 30814501 |
| study25 | Homo sapiens | The adult human testis transcriptional cell atlas | PMID: 30315278 |
| study26 | Homo sapiens | Single-cell reconstruction of follicular remodeling in the human adult ovary | PMID: 31320652 |
| study27 | Homo sapiens | Single-cell analysis of olfactory neurogenesis and differentiation in adult humans | PMID: 32066986 |
| study28 | Homo sapiens | Single-Cell Transcriptomic Map of the Human and Mouse Bladders | PMID: 31462402 |
| study29 | Mus musculus | Single cell analysis reveals immune cell-adipocyte crosstalk regulating the transcription of thermogenic adipocytes | PMID: 31644425 |
| study30 | Homo sapiens | Single-cell analysis of human adipose tissue identifies depot- and disease-specific cell types | PMID: 32066997 |
| study31 | Homo sapiens | Adipose tissue - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study32 | Homo sapiens | Adrenal gland - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study33 | Homo sapiens | Artery - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study34 | Homo sapiens | Ascending colon - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study35 | Homo sapiens | Bladder - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study36 | Homo sapiens | Bone marrow - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study37 | Homo sapiens | Cerebellum - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study38 | Homo sapiens | Cervix - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study39 | Homo sapiens | Small intestine duodenum - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study40 | Homo sapiens | Appendix - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study41 | Homo sapiens | Esophagus - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study42 | Homo sapiens | Fallopian tube - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study43 | Homo sapiens | Gallbladder - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study44 | Homo sapiens | Heart - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study45 | Homo sapiens | Small intestine ileum - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study46 | Homo sapiens | Small intestine jejunum - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study47 | Homo sapiens | Kidney - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study48 | Homo sapiens | Liver - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study49 | Homo sapiens | Lung - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study50 | Homo sapiens | Muscle - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study51 | Homo sapiens | Omental adipose tissue - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study52 | Homo sapiens | Pancreas - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study53 | Homo sapiens | Peripheral blood - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study54 | Homo sapiens | Lung pleura - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study55 | Homo sapiens | Prostate - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study56 | Homo sapiens | Rectum - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study57 | Homo sapiens | Sigmoid colon - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study58 | Homo sapiens | Spleen - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study59 | Homo sapiens | Stomach - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study60 | Homo sapiens | Brain temporal lobe - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study61 | Homo sapiens | Thyroid - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study62 | Homo sapiens | Trachea - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study63 | Homo sapiens | Transverse colon - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study64 | Homo sapiens | Ureter - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study65 | Homo sapiens | Uterus - Construction of a human cell landscape at single-cell level | <https://www.nature.com/articles/s41586-020-2157-4> |
| study66 | Homo sapiens | SARS-CoV-2 receptor ACE2 and TMPRSS2 are predominantly expressed in a transient secretory cell type in subsegmental bronchial branches | <https://doi.org/10.15252/embj.20105114> |
| study67 | Homo sapiens | SARS-CoV-2 receptor ACE2 and TMPRSS2 are predominantly expressed in a transient secretory cell type in subsegmental bronchial branches | <https://doi.org/10.15252/embj.20105114> |
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