**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|2020-03-0HCOV-19/WALES/PHWC-2658D/2020|EPI\_ISL\_422346|2020-03-26 |
| RRARSVA**I** | 3 | HCOV-19/ENGLAND/20140007302/2020|EPI\_ISL\_421925|2020-03-28HCOV-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|2020-03-26HCOV-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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