

ACE2 Netlas: In-silico functional characterization and drug-gene interactions of *ACE2* gene network to understand its potential involvement in COVID-19 susceptibility

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Running Title: Characterization of *ACE2*- gene network

Abstract

Angiotensin-converting enzyme-2 (*ACE2*) receptor has been identified as the key adhesion molecule for the transmission of the SARS-CoV-2. However, there is no evidence that human genetic variation in *ACE2* is singularly responsible for COVID-19 susceptibility. Therefore, we performed a multi-level characterization of genes that interact with *ACE2* (*ACE2*-gene network) for their over-represented biological properties in the context of COVID-19.

The phenome-wide association of 51 genes including *ACE2* with 4,756 traits categorized into 26 phenotype categories, showed enrichment of immunological, respiratory, environmental, skeletal, dermatological, and metabolic domains ($p < 4e-4$). Transcriptomic regulation of *ACE2*-gene network was enriched for tissue-specificity in kidney, small intestine, and colon ($p < 4.7e-4$). Leveraging the drug-gene interaction database we identified 47 drugs, including dexamethasone and spironolactone, among others.

Considering genetic variants within ± 10 kb of *ACE2*-network genes we characterized functional consequences (among others) using miRNA binding-site targets. MiRNAs affected by *ACE2*-network variants revealed statistical over-representation of inflammation, aging, diabetes, and heart conditions. With respect to variants mapped to the *ACE2*-network, we observed COVID-19 related associations in *RORA*, *SLC12A6* and *SLC6A19* genes.

Overall, functional characterization of *ACE2*-gene network highlights several potential mechanisms in COVID-19 susceptibility. The data can also be accessed at <https://gpwhiz.github.io/ACE2Netlas/>

Keywords: *ACE2*, COVID-19, miRNA, immune response, network

2 **1 Introduction**

4 SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) is the causative agent
6 responsible for recent global spread of COVID-19 (coronavirus disease 2019) [1,2].
Millions of people have been infected with the virus, which caused global lockdowns and
heavily restricted interpersonal contact. These measures were taken to reduce viral
spread through respiratory droplet exchange between persons.

8 SARS-CoV-2 is capable of entering the host cells via ACE2 (angiotensin converting
enzyme 2) [3]. ACE2 is found on many different cell types, which normally helps regulate
10 blood pressure and inflammation through cleavage of angiotensin II (ANG II) [4]. The virus
occupies cell-surface of *ACE2* leading to accumulation of angiotensin (ANGII),
12 inflammation, and cell death [3]. In the lungs, SARS-CoV-2 mediated ANGII accumulation
leads to alveolar cell death and a reduction in oxygen uptake [5].

14 Although ACE2 is the cellular entry point, there is little evidence that genetic variation in
ACE2 is singularly responsible for COVID-19 susceptibility. Indeed, *ACE2* failed to
16 associate with COVID-19 informative phenotype definitions from large genome-wide
studies [6–8] . However, due to the functional role of ACE2 in SARS-CoV-2 infection, we
18 hypothesize that genes interacting with ACE2 activity are enriched for molecular
pathways relevant for COVID-19 susceptibility. Accordingly, we employed a top-down
20 approach to analyze tissue-specific transcriptomic regulation, drug-gene interactions, and
variant prioritization using genetic variants within the ACE2 gene-gene connectome and
22 protein-protein interaction networks. With this approach we identified several biological
processes and functional effects of ACE2-gene network relevant for the vast symptoms
24 observed following SARS-CoV-2 infection.

26 **2 Results**

A study overview is presented in [Supplementary file1 Figure S1](#).

28 2.1 The ACE2 gene connectome

A total of 60 ACE2-interacting genes were identified from different network databases
30 (Supplementary file2 Table S1; Figure 1).

2.2 Tissue-specific transcriptomic regulation

32 Using differential expression data of 54 tissues (GTEx-v8), the genes in the ACE2-gene
network were enriched for upregulated expression in small intestine ($p=1.07 \times 10^{-16}$), colon
34 ($p=7.60 \times 10^{-13}$), kidney ($p=1.93 \times 10^{-8}$), and liver ($p=4.63 \times 10^{-4}$) (Figure 2; Supplementary
file2 Table S2). No tissue-specific enrichment was observed for down-regulated
36 expression.

2.3 Gene-Drug Interaction and Over-represented Biological Functions

38 Out of 61 genes, 29 had information about their drug-gene interaction in the drug-gene
interaction database (DGIdb)[9]. This assessment resulted in 238 unique drug-gene
40 observations (Supplementary file2 Table S3). Some of the notable drugs observed via this
approach were spironolactone, dexamethasone, metformin, and hydrocortisone. To
42 understand the role of these drugs in affecting biological processes, we performed drug-
set enrichment analysis. DSEA [10] found gene-ontology mapping for 47 drugs and tested
44 against REACTOME gene ontology database. Although the results did not survive
Bonferroni correction, the strongest enrichments were observed for platelet sensitization
46 by low-density lipoprotein cholesterol ($p=0.003$), IL-7 signaling ($p=0.004$),
glycerophospholipid biosynthesis ($p=0.005$), and viral messenger RNA synthesis
48 ($p=0.011$) (Figure 3; Supplementary file2 Table S4).

2.4 Over-representation of phenotypic domains within ACE2 gene network

50 A phenome-wide association study (PheWAS) was performed for 51 genes leveraging
data from the GWASAtlas [11]. The GWASAtlas categorized traits into 26 phenotype
52 domains (Supplementary file1 Figures S2-S52; Supplementary file2 Table S5). Each
domain was tested for enrichment of significant traits versus non-significant traits
54 (Supplementary file2 Table S6). Six domains were significant: 'Immunological'
($p=7.62 \times 10^{-25}$), 'Respiratory' ($p=1.30 \times 10^{-8}$), 'Skeletal' (2.94×10^{-8}), 'Dermatological'
56 ($p=7.91 \times 10^{-8}$), 'Environmental' ($p=2.21 \times 10^{-7}$), and 'Metabolic' (4.33×10^{-4}) (Supplementary

file2 Table S7). *SLC44A4* had the highest number of associated traits across the
58 significant domains ($n_{\text{total}} = 173$) followed by *APOA1* had highest number of traits
associations, mostly metabolic ($n_{\text{total}} = 100$; metabolic = 71) (Figure 4). *SLC44A4*, *APOA1*,
60 and *RORA* showed associations across all six enriched domains.

2.5 Characterization of SNPs

62 We extracted all 957,222 SNPs in the ACE2-network and annotated for allele frequency
(Supplementary file3), nearby genes and coordinates (Supplementary file4), Combined
64 Annotation Dependent Depletion (CADD) [12] and DeepSEA [13] scores. There were
98,529 SNPs with CADD score >10 , which corresponds to the top 10% pathogenic
66 variants across the human genome (Supplementary file5). To identify their regulatory
consequences, variants were annotated with DeepSEA which provides functional
68 probability of the SNPs in serving as gene expression, disease and chromatin regulating
variants. There were 12,095 SNPs within the ACE2-gene network which had $>50\%$
70 functional probability (DeepSEA functional score > 0.5) (Supplementary file6). The
miRNAs altered by the SNPs were analyzed for over-represented miRNA-family, biological
72 functions, and diseases considering false discovery rate multiple testing correction (FDR
 $p < 0.05$). There were 4 miRNA clusters that were enriched, miR-302b, miR-181d
74 ($p = 0.0079$), miR-17, and 106a ($p = 0.00298$). We found 65 biological functions that were
significant and the top five significant biological processes were cell death ($p = 1.5 \times 10^{-20}$),
76 inflammation ($p = 2.57 \times 10^{-20}$), cell cycle ($p = 2.09 \times 10^{-18}$), apoptosis ($p = 4.15 \times 10^{-18}$), and
immune response ($p = 3.17 \times 10^{-17}$) (Figure 5). We observed a total of 152 significant
78 diseases of which the most significant were diabetes mellitus type 2 ($p = 1.55 \times 10^{-22}$),
hepatitis c virus infection ($p = 5.56 \times 10^{-21}$), atherosclerosis ($p = 3.08 \times 10^{-19}$), heart failure
80 ($p = 4.22 \times 10^{-19}$), and Alzheimer's disease ($p = 1.35 \times 10^{-17}$) (Supplementary file2 Table S8).

2.6 Neanderthal LA introgression within ACE2 network SNPs

82 Due to the Neanderthal introgression observed in 3p21 locus as risk to COVID-19 [14],
we compared mean probability of Neanderthal LA between the ACE2-network SNP set
84 (mean = 0.032) and 1,000 randomly selected SNP sets with comparable genomic features
(range of Neanderthal LA means = 0.027-0.036). The ACE2-network SNPs did not show

86 evidence of Neanderthal LA introgression significantly different from those expected by
chance ($p=0.663$) ([Supplementary file1 Figure 55](#)).

88 2.7 Annotation of network SNPs using the COVID-19 GWAS

We tested ACE2-network SNPs with respect to six COVID-19-related phenotypes (Freeze
90 3) released by the COVID-19 Host Genetics Initiative [15]. To identify independent
variants, the variants were pruned for linkage disequilibrium ($LD < 0.1$ within 250kb
92 genomic size) and clumped for p -value < 0.01 . Variants surviving multiple testing were
annotated for eQTLs, and mQTLs. Three genes – *RORA*, *SLC12A6*, and *SLC6A19* –
94 showed associations with multiple COVID-19 phenotypes ([Supplementary file2 Tables
S9-S14](#); [Supplementary file6 Figures S56-S61](#)). *RORA* SNPs were associated with
96 COVID-19 positive status (rs17303202, $p=2.35E-5$), laboratory-confirmed positive
COVID-19 status (rs4774377, $p=8.25E-5$), hospitalized COVID-19 (rs17303202, $p=2.76E-$
98 05), and COVID-19 with very severe respiratory symptoms (rs341419, $p=8.13E-4$). The
SNPs in *RORA* gene are also associated with gene expression of *RORA* gene
100 (rs12912196; $p=3.9E-5$) and trans-mQTL (cg00930615 in *ANXA2*). *SLC12A6* associations
were observed with respect to COVID-19 (rs145719616, $p=1.19E-4$), hospitalized COVID-
102 19 (rs192235418, $p=4.42E-4$), COVID-19 with very severe respiratory (rs2705343,
 $p=1.86E-3$), and. *SLC6A19* SNPs were associated with severe COVID-19 phenotype
104 definitions, i.e. COVID-19 with very severe respiratory confirmed (rs76067074, $p=2.65E-$
3) and hospitalized COVID-19(rs76067074, $p=2.52E-4$).

106 3 Discussion

ACE2 is expressed in several tissues and plays a key role in host-entry of SARS-CoV-2
108 [16]. However, the genomic profile of *ACE2* is limited in explaining the vast symptomology
observed for COVID-19. Understanding *ACE2* associated molecular networks presents
110 several functional insights between genetic targets based on gene expression, topology,
and protein and signaling relationships [17]. Due to the well-characterized role of *ACE2* in
112 SARS-CoV-2 infection, we generated novel information regarding the molecular and
phenotypic characteristics of ACE gene network in the context of their potential

114 involvement in COVID-19 susceptibility. Our PheWAS-based analysis showed that genetic
variation within ACE2 gene network is associated with immunity, respiratory, and
116 metabolic traits. This is in line with known epidemiology of COVID-19 and its comorbidities
[18,19].

118 The expression of ACE2-network genes was enriched for regulatory mechanisms related
to small intestine, colon, kidney, and liver. It is hypothesized that furin, a serine protease
120 present in lungs but also highly expressed in small intestine, presents S-spike for
attachment of the ACE2 receptor [20]. Patients with kidney disease have higher risk for
122 COVID-19 severe symptoms [21]. Additionally, the inflammation and cytokine storm from
COVID-19 is observed to damage kidney tissues [22]. Lastly, modest increase in liver
124 enzymes has been associated with COVID-19, and returning to baseline during the
recovery phase [23].

126 Understanding the genes that interact with ACE2 receptor has potential to understand
drug-targets and molecular processes that might play a role in susceptibility and
128 treatment response of COVID-19. The drug-gene interaction analysis within ACE2
network identified dexamethasone, reported to lower mortality in COVID-19 cases
130 requiring mechanical ventilation [24]. Drugs – spironolactone and hydrocortisone target
the androgen system. The androgen receptor has been associated with severe
132 symptomology of COVID-19 [25]. Spironolactone is a diuretic and alleviates respiratory
symptoms by reducing fluid from the lungs [26]. The use of spironolactone is currently
134 being tested for acute respiratory distress syndrome in COVID-19 patients [27].
Hydrocortisone is currently under clinical trials for treating COVID-19 related hypoxia
136 symptoms [28]. Among the other compounds identified, metformin, a known drug for
treating diabetes, can also affect respiratory outcomes [29]. A recent study reported
138 protective effects of metformin in women with diabetes and obesity who were admitted
with COVID-19 diagnosis [30]. Lastly, melatonin has been hypothesized to improve
140 general immunity and lower oxidative stress generated from SARS-CoV-2 infection [31].

142 The miRNA target sites altered by ACE2-network SNPs identified miR-302b and miR-181d
144 as over-represented miRNA clusters. The downregulated expression of miR-302b has
146 been observed to reduce survival rates in chronic obstructive pulmonary disease (COPD)
148 patients [32]. A meta-analysis showed that COPD diagnosis increased susceptibility to
150 COVID-19 [33]. The miRNA-181 cluster has been associated with regulation of TNF-alpha
152 [34], T-cell aging [35] and emphysema [36]. miRNA-17 and 106 belong to same miRNA
154 family, miRNA-17 is upregulated in bronchoalveolar stem cells to lower SARS-CoV
156 replication [37]. An *in silico* study of miRNA targets for SARS-CoV-2 genomic sequence
158 found miRNA-17 as one of the targets with experimental evidence of its upregulation in
160 H7N9 Influenza virus infection [38]. The top over-represented diseases in miRNA-ACE2-
network-SNPs were diabetes, hepatitis C viral infection, heart failure and Alzheimer's
disease. COVID-19 in individuals with diabetes has been reported to require
hospitalization than non-diabetic individuals [39]. Furthermore, SARS-CoV-2 infection
contributes in the development of ketosis in diabetic individuals resulting in longer length
of hospitalization stay [40]. Triglyceride and glucose index was associated with severity of
COVID-19 [41]. While there are limited studies about hepatitis C in COVID-19 patients
[42], heart failure was reported by multiple studies as being associated with COVID-19
severity [43,44]. Alzheimer's disease is another condition associated with COVID-19
susceptibility [45], including *APOE4* carrier status with increased risk of severe COVID-
19 [46].

162 In contrast to specific enrichment of Neanderthal LA in a COVID-19 risk locus on
164 chromosome 3 [47], there is no evidence of increased Neanderthal LA in the ACE2
166 network investigated here. This suggests that, although some loci conferring risk for
168 COVID-19 severity, such as the one identified on chromosome 3, may have originated
from Neanderthal admixture events, this mechanism did not shape the genetic
architecture of the ACE2 network responsible for entry of SARS-CoV-2 into host cellular
machinery.

168 Lastly, among ACE2-network-SNPs, potential COVID-19 risk alleles were observed in
RORA gene with respect to multiple COVID-19 phenotypes. *RORA* protein product is

170 involved in immune response, cancer and metabolism [48]. *RORA* plays a role in the
activation of T helper cells during lung inflammation by regulating tumor necrosis factor
172 and interleukins [49,50], and its protein product showed multiple regulatory functions in
human epithelial cell cultures inoculated with SARS-CoV-1 [51]. The hypothesis-free
174 approach of genome-wide association of hospitalized COVID-19 vs the population
highlighted *SLC6A20* with genome-wide significance on chromosome 3 locus. The
176 *SLC12* (*SLC12A6*) class is responsible for inorganic ions such as sodium and chloride
while the *SLC6* class (*SLC6A19*, identified via network approach and *SLC6A20*, identified
178 via genome-wide approach) are responsible for transport of amino acids such as
glutamate and glycine which are important neurotransmitter activity [52]. *SLC6A19*
180 (among other *SLC*-class genes) serves similar function to *SLC6A20*, both are expressed
in the intestinal tissue and contingent upon *ACE2* expression [53]. Multiple studies report
182 more than 10% of the COVID-19 confirmed patients exhibit gastrointestinal symptoms[54–
56]

184 Although we provided a wide range of information highlighting the molecular and
phenotypic characteristics of *ACE2* gene network and their putative implications with
186 COVID-19 risk, the findings reported have to be considered exploratory. We used
appropriate computational methods and statistical approaches to generate reliable
188 evidence useful to open new directions in COVID-19 research. We also highlighted when
the results reported did not survive stringent multiple testing correction. This limitation is
190 particularly relevant with respect to the *ACE2* network genetic associations. Due to the
limited statistical power of the genome-wide data available to date, none of the risk alleles
192 identified as functionally relevant survive genome-wide testing correction. Further
analyses will be needed to validate our current findings.

194 **4 Conclusion**

ACE2 is one of the few molecular targets recognized to play a key role in the COVID-19
196 pathogenesis. We conducted a comprehensive analysis leveraging multiple resources
(e.g., drug-gene interactions, tissue-specific transcriptomic profile, and phenome-wide

198 and genome-wide datasets) to expand our understanding of the genomic characteristics
of the host *ACE2* gene network. Overall, our findings highlight the potential mechanisms
200 linking *ACE2* systems biology to COVID-19 susceptibility.

5 Methods

202 5.1 Gene network collection

Information regarding *ACE2* gene network was mined from GeneMANIA [57], Stringdb
204 [58], APID [59], GeneNetwork [60], Biogrid[61] and FunctionalNet [62]. Immediate genes
connections that were available in each databank with their default settings result in 61
206 unique genes (60 genes plus *ACE2*) ([Supplementary file1 Figure 1](#); [Supplementary file2 Table S1](#)). The genomic coordinates for the genes were annotated using biomaRt [63],
208 ensemble GRCh37/hg19. The analysis and visualization were performed in R 3.6.

5.2 2.2 Tissue-specific transcriptomic regulation

210 The tissue specificity was tested for 60 *ACE2*-interacting genes in FUMA [64]. The input
genes were tested for pre-calculated tissue-specific differentially expressed genes from
212 the GTEx v8 [65]. We also considered the t-statistic sign for up and down-regulated genes
against protein coding genes as background. Enrichments were performed using
214 hypergeometric tests and significant enrichments were defined according to Bonferroni
corrected p-value ≤ 0.05 .

216 5.3 Phenome-wide analysis of *ACE2* gene network

A phenome-wide association study (PheWAS) was performed for 51 of 60 genes that
218 were present in GWASAtlas [11] using all traits available per gene. Statistical significance
was determined by applying a Bonferroni multiple-testing correction accounting for the
220 number of GWAS traits (4,765 traits) available in the GWASAtlas ($p < 1.05 \times 10^{-5}$). Each trait
was grouped into a domain ([Supplementary file2 Table S5](#)) which was tested for
222 enrichment using one-sided Fisher's exact test for high proportion of significant traits
versus all others tested. A significant domain enrichment was defined considering a
224 Bonferroni-corrected threshold accounting for the number of domains tested (p-value $<$
0.0019; $0.05/26$).

226 **5.4 Gene-Drug Interactions and Biological Functions**

Information on drugs that interact with ACE2 network genes were extracted from The
228 Drug-Gene Interaction database (DGIdb) [9] followed by drug-set enrichment for over
represented biological functions using DSEA (Drug-Set Enrichment Analysis) [10].

230 **5.5 Characterization of SNPs**

Single nucleotide polymorphism (SNPs) were extracted based on the genomic
232 coordinates of the genes ($\pm 10\text{kb}$) for GrCh37; dbSNP153 from the UCSC browser [66]
using bigbed utilities [67], and referred to as 'ACE2-network SNPs.' ACE2-network SNPs
234 were annotated for global allele frequency, Combined Annotation-Dependent Depletion
(CADD) score [12], deep learning based algorithm framework (DeepSEA) [13], and target
236 miRNAs using SNPnexus [68]. DeepSEA is a deep learning-based algorithmic framework
for predicting the chromatin effects of sequence alterations with single nucleotide
238 sensitivity [13]. The identified miRNAs were tested for over-represented miRNA clusters,
functions, and diseases using TAM 2.0 [69].

240 **5.6 Neanderthal introgression**

Motivated by evidence of a chromosome 3 COVID-19 risk locus enriched of Neanderthal
242 local ancestry (LA) [47], we compared the distribution of probability of Neanderthal LA in
our COVID-19 ACE2-network SNP set and 1,000 randomly sampled SNP sets comprised
244 on SNPs across the genome with comparable genomic features. ACE2-network SNPs
were mapped using previously-defined Neanderthal LA data [70,71]. A total of 6,822 LD-
246 independent pairwise SNPs ($r^2=0.1$ and $p=0.1$ in 250kb window size) were used as
standard input for SNPsnap [72]. In SNPsnap, 1,249/6,822 independent ACE2 network
248 SNPs could be matched based on the following genomic features relative to the input
SNP list: minor allele frequency within 2%, gene density within 50%, nearest gene within
250 50%, and number of linkage disequilibrium groups within 50%. SNPsnap was instructed
to exclude the ACE2-network SNP list from the pool of eligible feature-matched SNPs.
252 Non-parametric Wilcoxon rank sum tests were used to compare the Neanderthal LA of
our ACE2 network SNP list to that of all 1,000 random SNP sets and multiple testing
254 correction was applied to adjust for a false discovery rate of 5%.

5.7 Association statistics of ACE2 network SNPs from the COVID-19 Host Genetics Initiative (HGI)

256
258 The ACE2-network SNPs were extracted from association statistics released by the
260 COVID-19 HGI [15] for six phenotypes describing COVID-19 susceptibility. These
262 phenotypes were A2_V2 (very severe respiratory confirmed COVID-19 cases [N=536] vs.
264 population[N=329391]), B1_V2 (hospitalized COVID-19 cases [N=928] vs. not hospitalized
266 COVID-19 cases [N=2028]), B2_V2 (hospitalized COVID-19 cases [N=3199] vs.
268 population [N=897488]), C1_V2 (COVID-19 cases [N=3523] vs. lab/self-reported negative
270 [N=36634]), C2_V2 (COVID-19 cases [N=6696] vs. population [N=1073072]), and D1_V2
(predicted COVID-19 cases from self-reported symptoms [N=1865] vs. predicted or self-
reported non-COVID-19 cases [N=29174]). The SNPs of the ACE2 network were
extracted and pruned for LD and p-value using plink1.9. The multiple testing correction
was applied using Bonferroni p-value < 0.05. These significant SNPs were annotated
further for pathogenicity using Combined Annotation Dependent Depletion (CADD) score
and their role as quantitative trait loci (QTL) for gene expression using GTE_x, and
methylation using QTLbase [73].

6 Author Contribution

272 G.A.P conceptualized the study design, analyzed, and drafted the manuscript. F.R.W.
contributed to analysis, and manuscript writing. Authors, A.G., F.D.A. and R.P. contributed
274 to result interpretation, manuscript drafting and revision. R.P. supervised the study and
finalized the manuscript.

7 Competing Interests

The authors have no competing interests.

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9 Data Availability

284 The data presented is available in supplementary files and also on
<https://gpwhiz.github.io/ACE2Netlas/>

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Figures and Supplementary file Legends

Figures

Figure 1: The ACE2-gene network. The genes that connect with ACE2 were extracted from six different gene-network databases and compiled together in one network.

Figure 2: Tissues enriched based on ACE2-network gene expression for GTEx tissues. The genes from the ACE2-network show over-representation of tissues (x-axis) and $-\log_{10}$ p-value (y-axis). The red bars are significant enrichments.

Figure 3: Drug-set enrichment analysis. LEFT: The similarity of drugs based on pathways identified. RIGHT: Biological Processes identified based on drugs that interact with genes from the ACE2-network

Figure 4: Domain distribution of PheWAS of ACE2-network genes. The ACE2 gene network associations are grouped based on domains (y-axis) and gene names (x-axis). The size of the data points reflects number of phenotypes surviving multiple testing correction.

Figure 5: Enrichment of biological functions based on miRNA:SNP annotation. Using miRNAs annotation, over-represented biological processes are shown on y-axis and $-\log_{10}$ pvalue on x-axis.

Supplementary files

Supplementary file1: File containing figures S1-S60

Supplementary file2: Tables S1:S14. Tabular details of the list of genes, tissue enrichment, gene-drug interaction, drug-set enrichment, PheWAS of all genes, Significant traits of PheWAS, domain enrichment, miRNA enrichment, SNPs from the network for six COVID-19 phenotypes from COVID-19 Host Genetics Initiative – Freeze3

Supplementary file3: Text file of all the SNPs within ± 10 kb of the genes and their genomic coordinates and allele frequency.

- Column Headers:
 - Variation ID: <dbsnp rs#>
 - dbSNP: link to dbSNP, if known
 - Chromosome: Variant mapped chromosome location
 - Position: Variant start position on chromosome
 - REF Allele: Reference allele
 - ALT Allele (IUPAC): Observed allele
 - Minor Allele: Minor allele observed in global population, if known

- Minor Allele Frequency: Minor allele frequency observed in global population, if known
- Contig: Variant mapped contig location
- contigPosition: Variant start position on contig
- Band: SNP cytogenetic location

Supplementary file4: Text file of SNPs with their overlapping and nearest gene annotation using Ensembl GRCh37.

- Column Headers:
 - Variation ID: <dbsnp rs#>
 - Chromosome: Variant mapped chromosome location
 - Position: Variant start position on chromosome
 - Overlapped Gene: Name of the gene (HGNC system) to which the variant is overlapped
 - Type: Gene type, e.g., protein coding, miRNA, non coding, Pseudogene, snoRNA, lincRNA etc.
 - Annotation: Summary of whether the variant overlapped with the coding, intronic or untranslated regions of the various transcript isoforms of the gene, as annotated from Ensembl gene system.
 - Nearest Upstream Gene: If variant is not overlapped with any gene, then the gene whose end position is nearest to the variant on the left (considering the alignment of genes on the positive strand as left-to-right)
 - Type of Nearest Upstream Gene: Gene type, e.g., protein coding, miRNA, non coding, Pseudogene, snoRNA, lincRNA etc.
 - Distance to Nearest Upstream Gene: distance from the end position of the nearest upstream gene.
 - Nearest Downstream Gene: If variant is not overlapped with any gene, then the gene whose start position is nearest to the variant on the right (considering the alignment of genes on the positive strand as left-to-right)
 - Type of Nearest Downstream Gene: Gene type, e.g., protein coding, miRNA, non coding, Pseudogene, snoRNA, lincRNA etc.
 - Distance to Nearest Downstream Gene: distance from the start position of the nearest downstream gene.

Supplementary file5: Text file of all the SNPs with CADD (Combined Annotation Dependent Depletion) scores >10

- Column Headers:

- Variation ID: <dbsnp rs#>
- Chromosome: Chromosome name
- Position: Variant start position on chromosome
- Variant: <reference allele,"/",observed allele> as reported in the tool's genome-wide score
- PHRED: PHRED-like ($-10 \cdot \log_{10}(\text{rank}/\text{total})$) scaled CADD-score ranking a variant relative to all possible substitutions of the human genome. A score ≥ 10 indicates that it is predicted to be in the 10% most deleterious substitutions that you can do to the human genome, a score ≥ 20 indicates the 1% most deleterious and so on.

Supplementary file6: Text file of all the SNPs with DeepSEA (deep learning based algorithm framework) functional scores > 0.5 , which represents atleast 50% probability to have regulatory effect

- Column Headers:
 - Variation ID: <dbsnp rs#>
 - Chromosome: Chromosome name
 - Position: Variant start position in the chromosome
 - Variant: <reference allele,"/",observed allele> as reported in the tool's genome-wide score
 - eQTL Probability: The probability of the variant being a eQTL variant given by functional variant prioritization classifier.
 - GWAS Probability: The probability of the variant being a trait-associated (GWAS) variant given by functional variant prioritization classifier.
 - HGMD Probability: The probability of the variant being a inherited disease-associated (HGMD) variant given by functional variant prioritization classifier.
 - Functional Significance Score: A measure in the range [0-1] depicting the significance of magnitude of predicted chromatin effect and evolutionary conservation. Lower score indicates higher likelihood of functional significance of the variant.

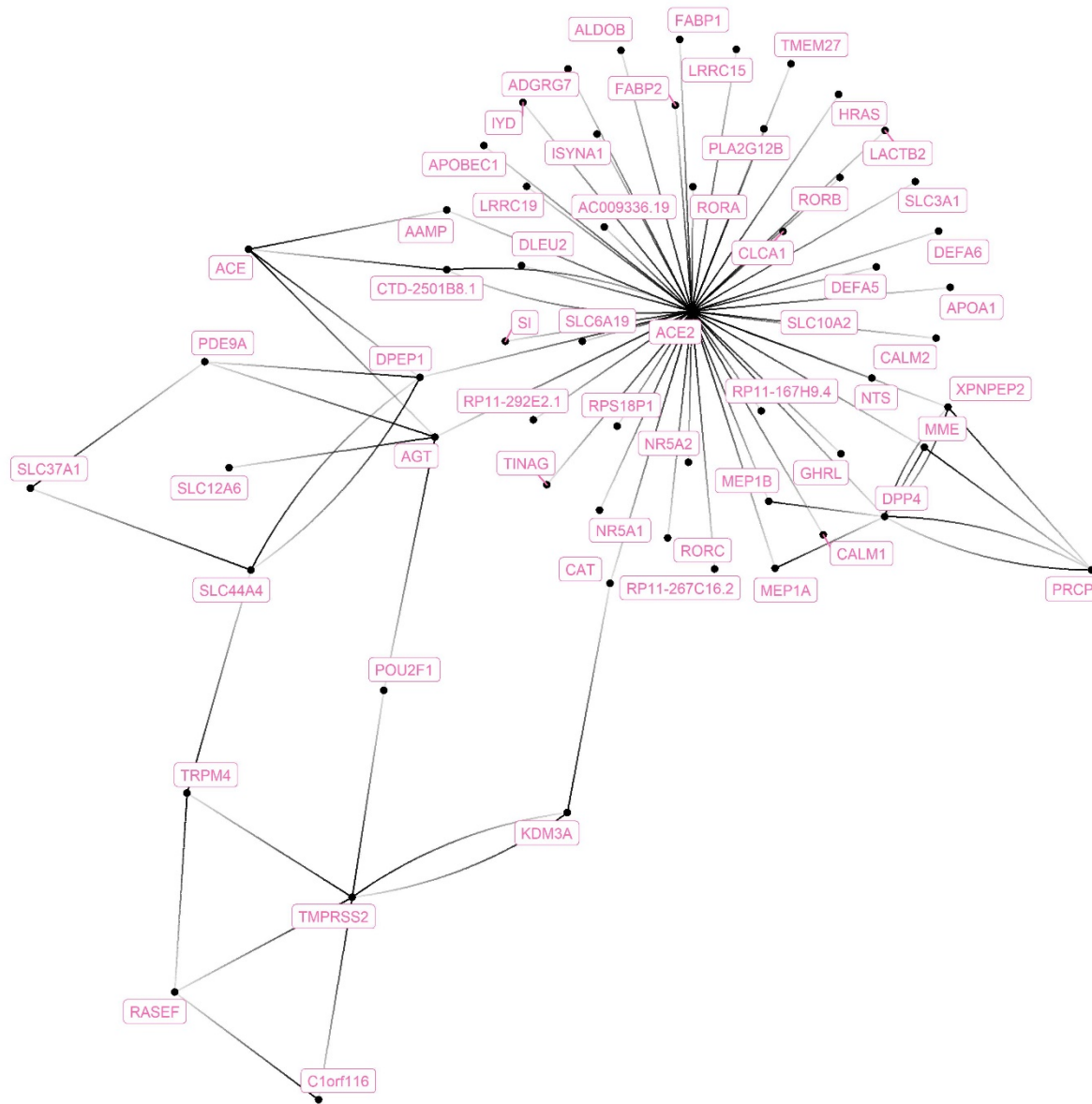


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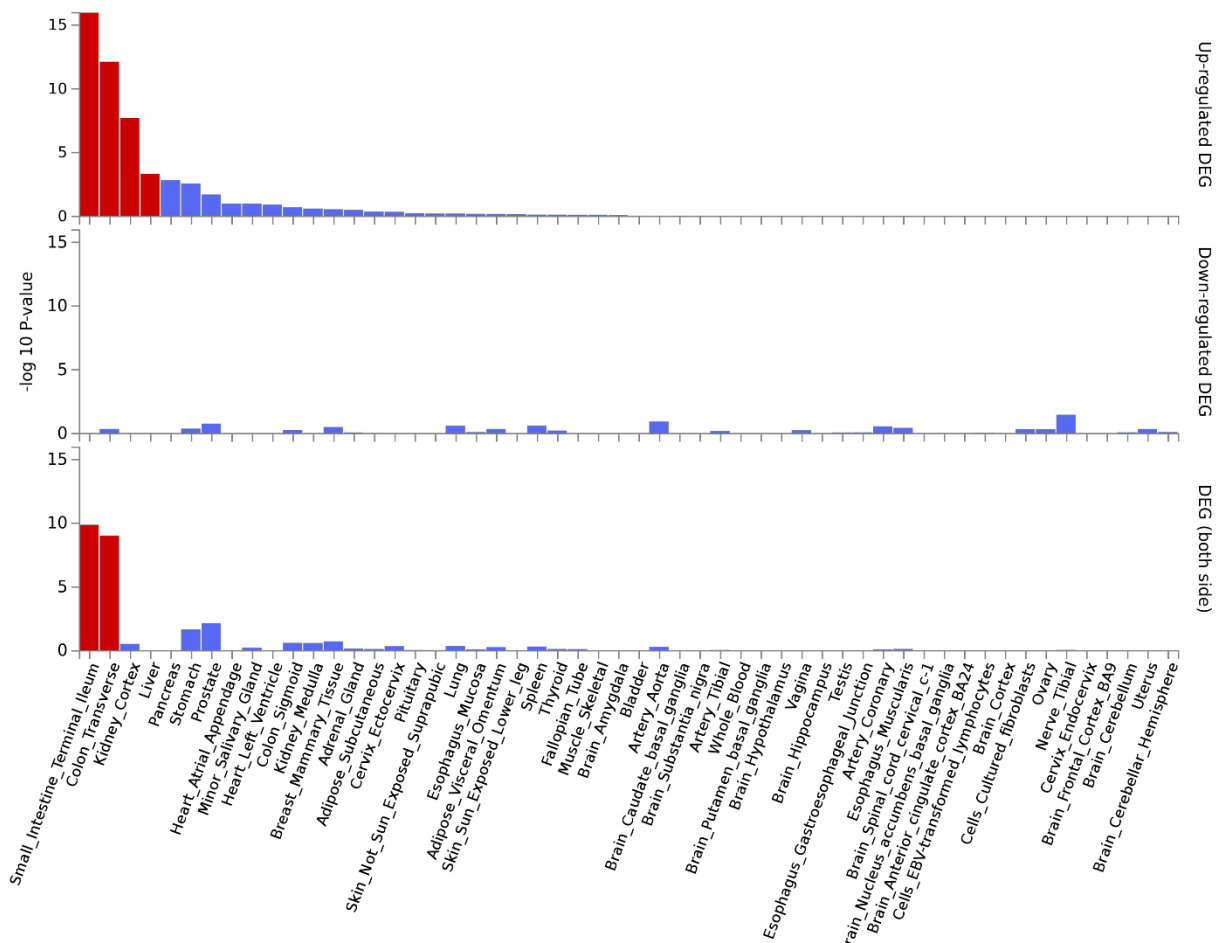


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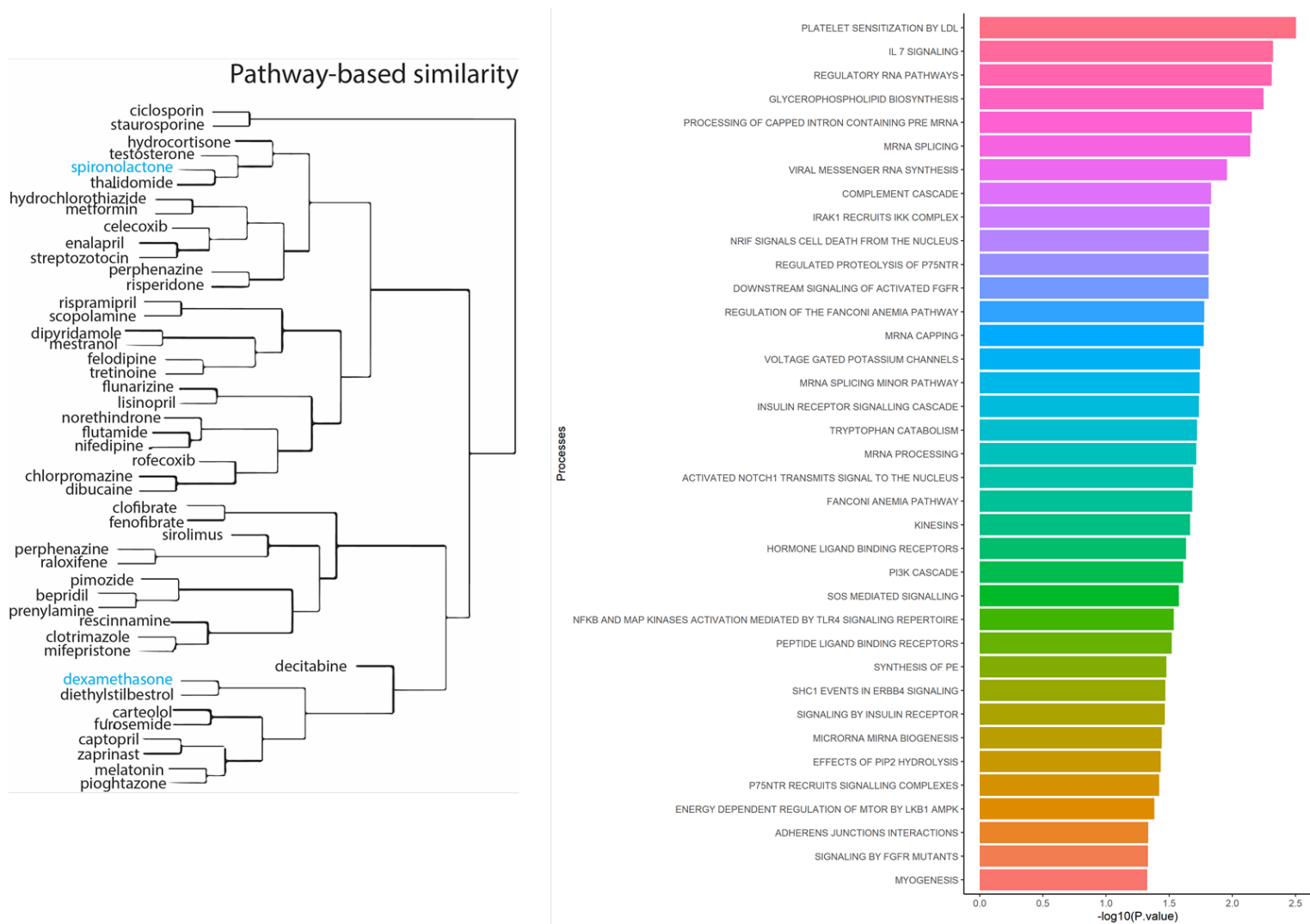


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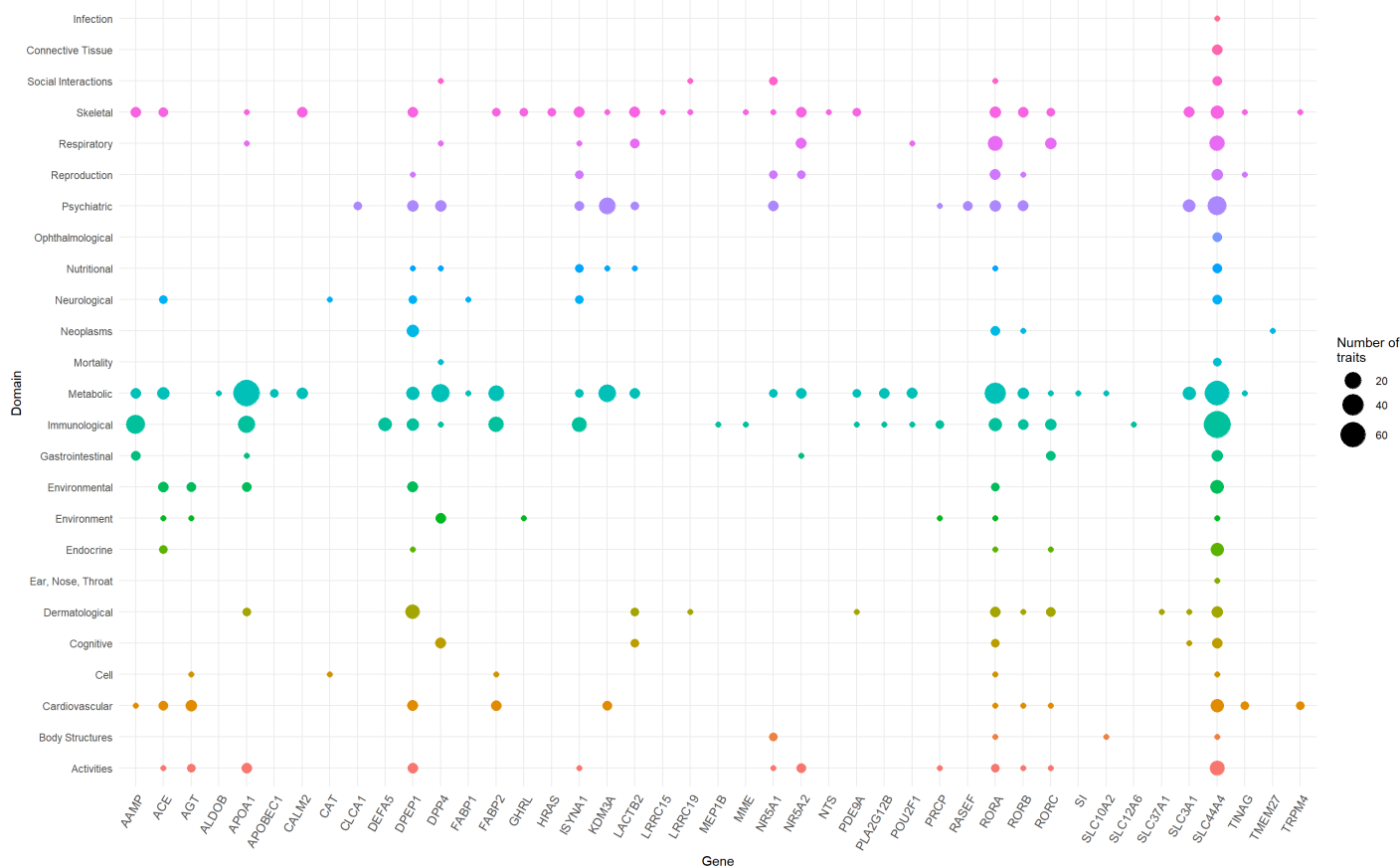


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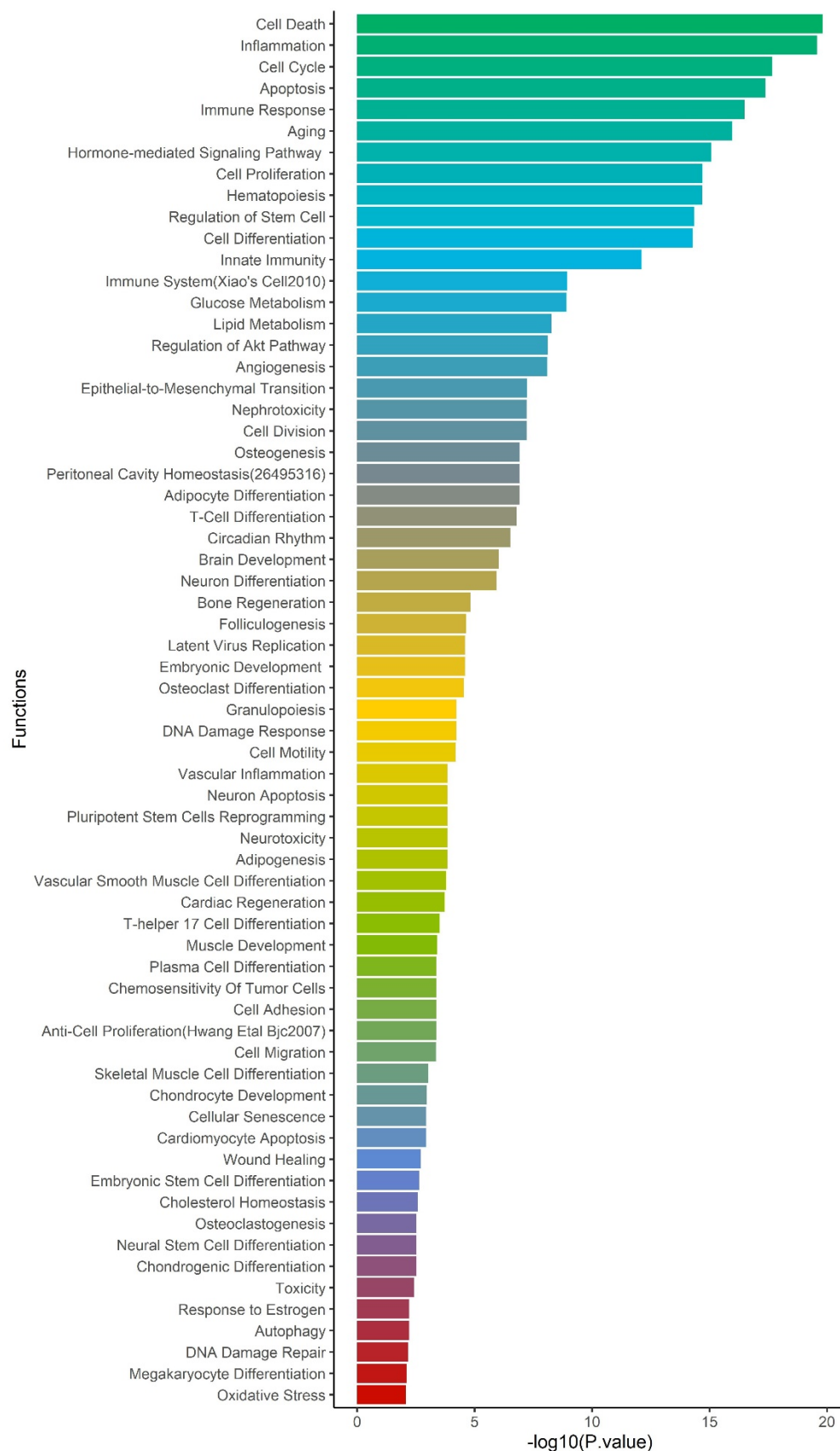


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