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Analysis of genetic overlap between inborn errors of immunity and neurodevelopmental disorders

Dr. Ines Serra[1], Mr. Mick de Koning[1], Prof. Dr. Peter J. van der Spek[2], Dr. Virgil A. S. H. Dalm[3], Dr. Aleksandra Badura[1]
[1]Department of Neuroscience, Erasmus MC, Rotterdam, Netherlands, [2]Department of Pathology and Clinical Bioinformatics, Erasmus MC, Rotterdam, Netherlands, [3]Division of Allergy and Clinical Immunology, Department of Internal Medicine, and Department of Immunology, Erasmus MC, Rotterdam, Netherlands

Objective: Inborn errors of immunity (IEI), formerly known as primary immune deficiencies (PID), are a group of genetic disorders that affect the immune system, leading to increased susceptibility to infections, autoimmunity, allergy, and cancer. So far, 449 IEI-causing genes have been identified with more likely to be discovered with the rapid adoption of whole genome sequencing in clinical practice. Patients with IEI often present with neurological symptoms such as cognitive impairments, neurodevelopmental delay and even seizures. These clinical features could be indicative of an increased risk of neurodevelopmental disorders (NDDs) in IEI patient population. However, to date, no exhaustive study has been done on the genetic overlap between NDDs and IEIs.

Design and Method: Publicly available NDD and IEI variant databases were used to identify risk genes belonging to the two groups of diseases and gene ontology, machine learning, and protein-network clustering analysis was employed to analyse gene function and group prediction.

Results: Our analysis shows that one-third of IEI-causing genes were also linked to NDD symptomatology (Figure 1). These genes were primarily involved in immune development and DNA repair pathways. In contrast, genes causing exclusively IEIs were enriched in immune response functions (Figure 2). Additionally, while IEI genes were enriched in immune cells, genes associated with both IEIs and NDDs presented a clear signature of expression in distinct brain cells (Figure 3). Functional connectivity analysis revealed that NDD-risk genes integrated immune-related networks, including those involved in DNA repair, highlighting immune-NDD interactions (Figure 4).

Conclusion: Altogether, this work demonstrates a molecular and protein-network level overlap between NDD and IEI-causing genes. Our analysis strongly suggests that NDD phenotypes in IEI patients could be underreported in both IEI patients and in NDD-related databases.

Figure 1

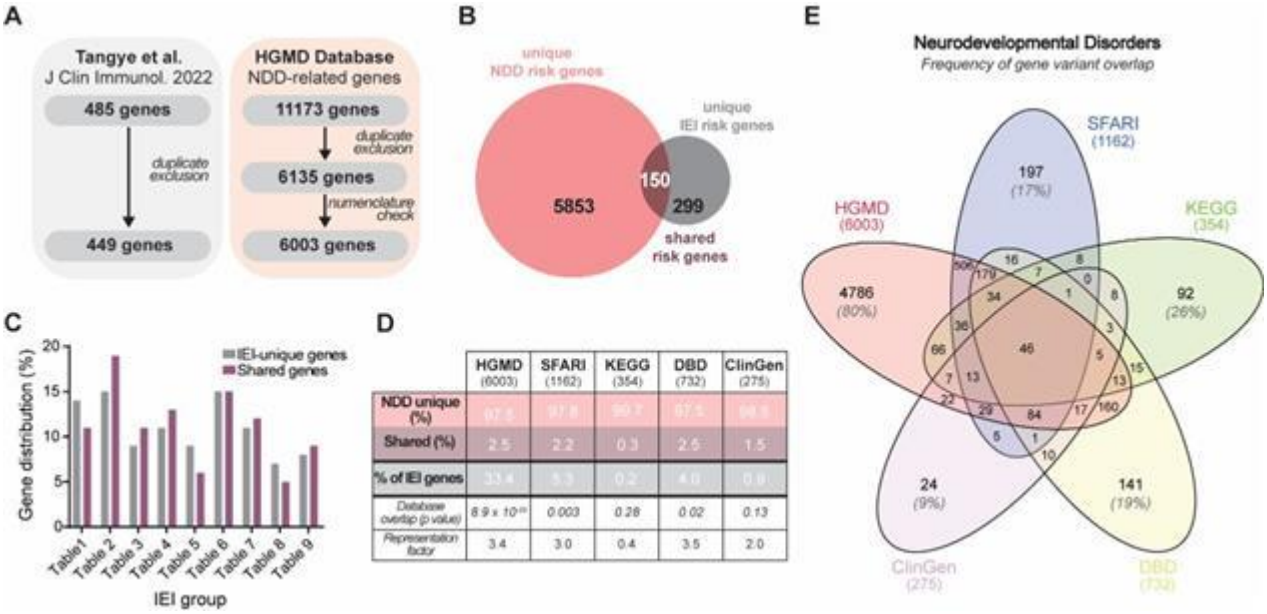

A
Tangye et al.
J Clin Immunol. 2022
485 genes
duplicate exclusion
449 genes
HGMD Database
NDD-related genes
11173 genes
duplicate exclusion
6135 genes
nomenclature check
6003 genes
B
unique NDD risk genes
unique IEI risk genes
5853
150
299
shared risk genes
E
Neurodevelopmental Disorders
Frequency of gene variant overlap
HGMD (6003)
SFARI (1162)
KEGG (354)
DBD (732)
ClinGen (275)
4786 (80%)
197 (17%)
92 (26%)
24 (9%)
141 (19%)
46
C
IEI-unique genes
Shared genes
Gene distribution (%)
Table1
Table 2
Table 3
Table 4
Table 5
Table 6
Table 7
Table 8
Table 9
IEI group
D
HGMD (6003)
SFARI (1162)
KEGG (354)
DBD (732)
ClinGen (275)
NDD unique (%)
97.6
97.8
99.7
97.5
98.5
Shared (%)
2.5
2.2
0.3
2.5
1.5
% of IEI genes
33.4
5.3
0.2
4.0
0.8
Database overlap (p value)
8.9 x 10-25
0.003
0.28
0.02
0.13
Representation factor
3.4
3.0
0.4
3.5
2.0

Figure 2

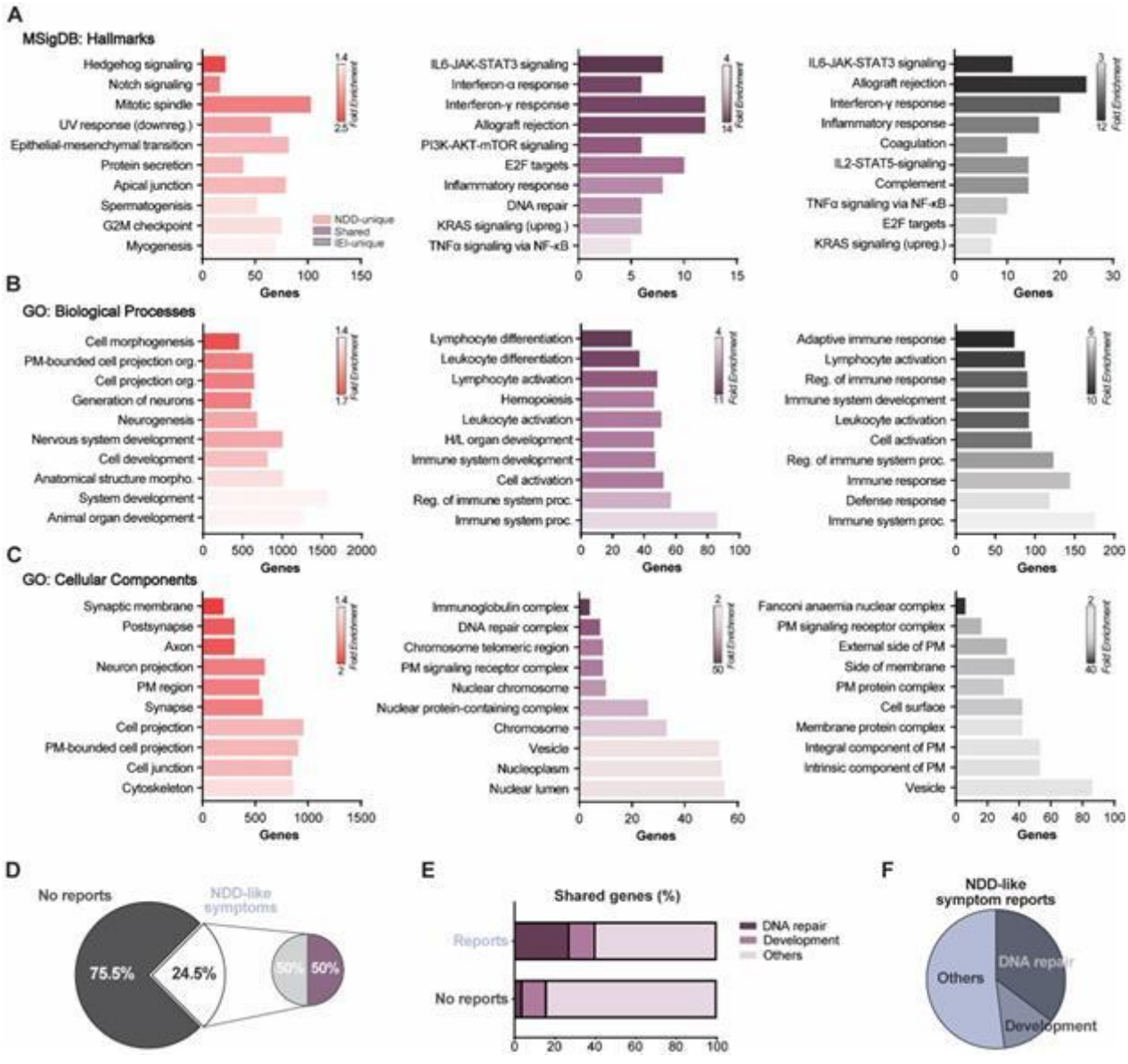

A
MSigDB: Hallmarks
Hedgehog signaling
Notch signaling
Mitotic spindle
UV response (downreg.)
Epithelial-mesenchymal transition
Protein secretion
Apical junction
Spermatogenisis
G2M checkpoint
Myogenesis
NDD-unique
Shared
IEI-unique
Genes
IL6-JAK-STAT3 signaling
Interferon-α response
Interferon-γ response
Allograft rejection
PI3K-AKT-mTOR signaling
E2F targets
Inflammatory response
DNA repair
KRAS signaling (upreg.)
TNFα signaling via NF-κB
Genes
IL6-JAK-STAT3 signaling
Allograft rejection
Interferon-γ response
Inflammatory response
Coagulation
IL2-STAT5-signaling
Complement
TNFα signaling via NF-κB
E2F targets
KRAS signaling (upreg.)
Genes
Fold Enrichment
B
GO: Biological Processes
Cell morphogenesis
PM-bounded cell projection org.
Cell projection org.
Generation of neurons
Neurogenesis
Nervous system development
Cell development
Anatomical structure morpho.
System development
Animal organ development
Genes
Lymphocyte differentiation
Leukocyte differentiation
Lymphocyte activation
Hemopoiesis
Leukocyte activation
H/L organ development
Immune system development
Cell activation
Reg. of immune system proc.
Immune system proc.
Genes
Adaptive immune response
Lymphocyte activation
Reg. of immune response
Immune system development
Leukocyte activation
Cell activation
Reg. of immune system proc.
Immune response
Defense response
Immune system proc.
Genes
Fold Enrichment
C
GO: Cellular Components
Synaptic membrane
Postsynapse
Axon
Neuron projection
PM region
Synapse
Cell projection
PM-bounded cell projection
Cell junction
Cytoskeleton
Genes
Immunoglobulin complex
DNA repair complex
Chromosome telomeric region
PM signaling receptor complex
Nuclear chromosome
Nuclear protein-containing complex
Chromosome
Vesicle
Nucleoplasm
Nuclear lumen
Genes
Fanconi anaemia nuclear complex
PM signaling receptor complex
External side of PM
Side of membrane
PM protein complex
Cell surface
Membrane protein complex
Integral component of PM
Intrinsic component of PM
Vesicle
Genes
Fold Enrichment
D
No reports
NDD-like symptoms
75.5%
24.5%
50%
50%
E
Shared genes (%)
Reports
No reports
DNA repair
Development
Others
F
NDD-like symptom reports
Others
DNA repair
Development

Figure 3

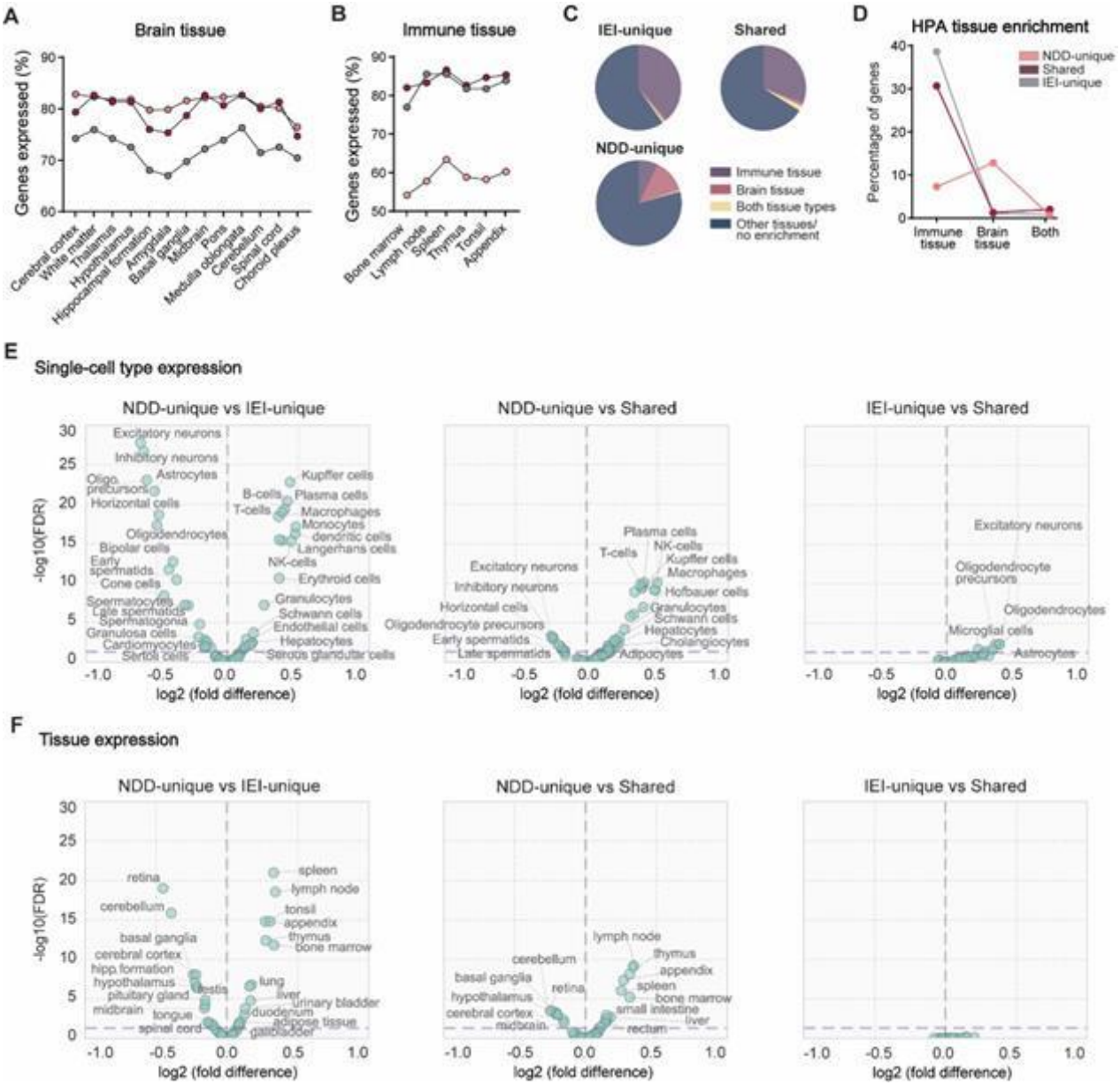
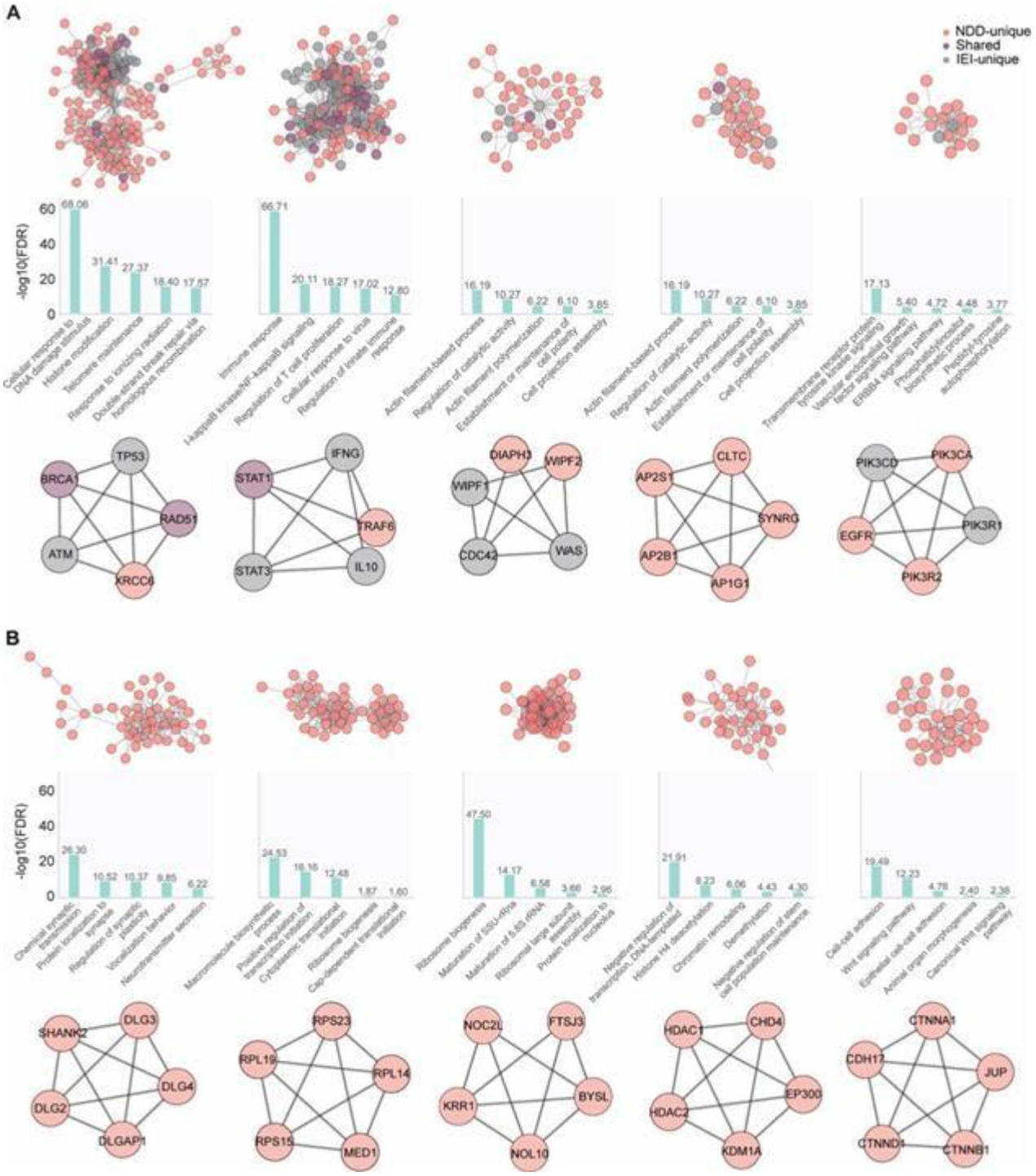


Figure 4


A
NDD-unique
Shared
IEI-unique
-log10(FDR)
68.06
31.41
27.37
18.40
17.57
Cellular response to DNA damage stimulus
Histone modification
Telomere maintenance
Response to ionizing radiation
Double-strand break repair via homologous recombination
66.71
20.11
18.27
17.02
12.80
Immune response
I-kappaB kinase/NF-kappaB signaling
Regulation of T cell proliferation
Cellular response to virus
Regulation of innate immune response
16.19
10.27
6.22
6.10
3.85
Actin filament-based process
Regulation of catalytic activity
Actin filament polymerization
Establishment or maintenance of cell polarity
Cell projection assembly
16.19
10.27
6.22
6.10
3.85
Actin filament-based process
Regulation of catalytic activity
Actin filament polymerization
Establishment or maintenance of cell polarity
Cell projection assembly
17.13
5.40
4.72
4.48
3.77
Transmembrane receptor protein tyrosine kinase signaling
Vascular endothelial growth factor signaling pathway
ERBB4 signaling pathway
Phosphatidylinositol biosynthetic process
Peptidyl-tyrosine autophosphorylation
TP53
BRCA1
RAD51
ATM
KRCC6
IFNG
STAT1
TRAF6
STAT3
IL10
DIAPH3
WIPF2
WIPF1
CDC42
WAS
CLTC
AP2S1
SYNRG
AP2B1
AP1G1
PIK3CD
PIK3CA
EGFR
PIK3R1
PIK3R2
B
-log10(FDR)
26.30
10.52
10.37
9.85
6.22
Chemical synaptic transmission
Protein localization to synapse
Regulation of synaptic plasticity
Vocalization behavior
Neurotransmitter secretion
24.53
18.16
12.48
1.87
1.60
Macromolecule biosynthetic process
Positive regulation of transcription initiation
Cytoplasmic translational initiation
Ribosome biogenesis
Cap-dependent translational initiation
47.50
14.17
6.58
3.66
2.96
Ribosome biogenesis
Maturation of SSU-rRNA
Maturation of 5.8S rRNA
Ribosomal large subunit assembly
Protein localization to nucleolus
21.91
8.23
6.06
4.43
4.30
Negative regulation of transcription, DNA-templated
Histone H4 deacetylation
Chromatin remodeling
Demethylation
Negative regulation of stem cell population maintenance
19.49
12.23
4.78
2.40
2.36
Cell-cell adhesion
Wnt signaling pathway
Epithelial cell-cell adhesion
Animal organ morphogenesis
Canonical Wnt signaling pathway
SHANK2
DLG3
DLG4
DLG2
DLGAP1
RPS23
RPL19
RPL14
RPS15
MED1
NOC2L
FTSJ3
KRR1
BYSL
NOL10
HDAC1
CHD4
EP300
HDAC2
KDM1A
CTNNA1
CDH17
JUP
CTNND1
CTNNB1