

SAP97 regulates behavior and expression of schizophrenia risk enriched gene sets in mouse hippocampus

Preetika Gupta , Ogul E. Uner, Soumyashant Nayak, Gregory R. Grant, Robert G. Kalb

Published: July 11, 2018 • <https://doi.org/10.1371/journal.pone.0200477>

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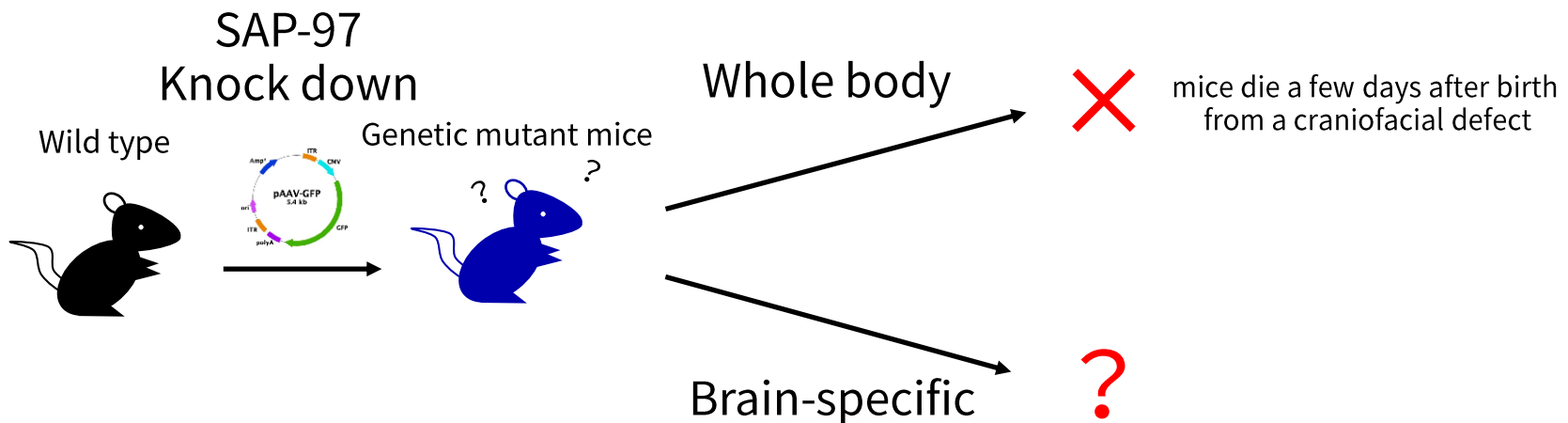
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Hikaru KOIZUMI

- Discs-large (Dlg) family has been implicated to be involved in autism spectrum disorders (ASD) or Schizophrenia (SCZ).
- PSD-95, PSD-93, and SAP102 : Knockout mice have been generated and studied
- SAP97 null knockout mice die a few days after birth from a craniofacial defect

Purpose

To investigate behavioral and transcriptomic characterization of brain-specific SAP97 Knock out mice.

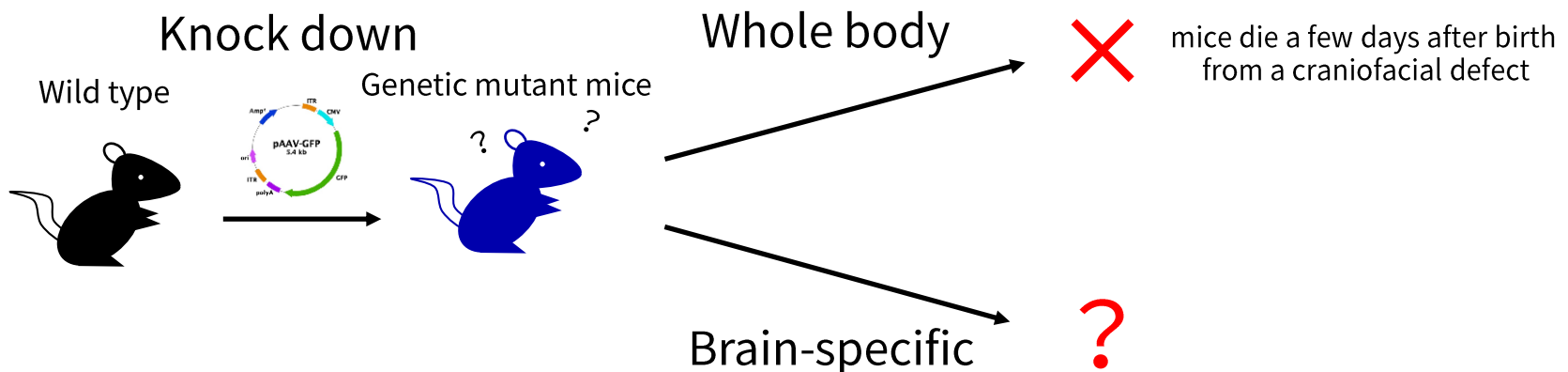


- Discs-large (Dlg) family has been implicated to be involved in autism spectrum disorders (ASD) or Schizophrenia (SCZ).
- PSD-95, PSD-93, and SAP102 : Knockout mice have been generated and studied
- SAP97 null knockout mice die a few days after birth from a craniofacial defect

Purpose

My Project

Analyze raw data using R and Bioconductor



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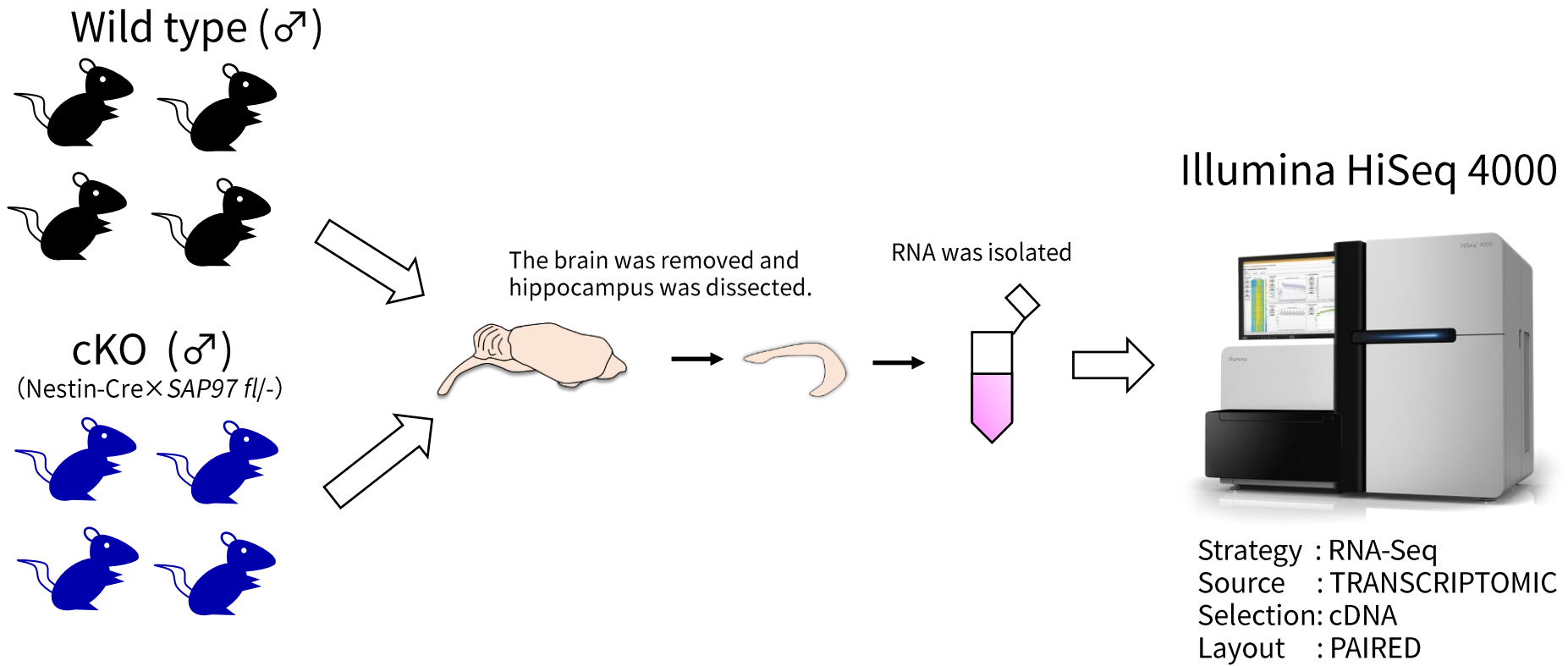
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Result – Get SRA data

1. Design



2. Accession

- BioProject : PRJNA481012
- GSE : GSE117067
 - Ctrl1 : SRR7519452
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 - cKO3 : SRR7519458
 - cKO4 : SRR7519459

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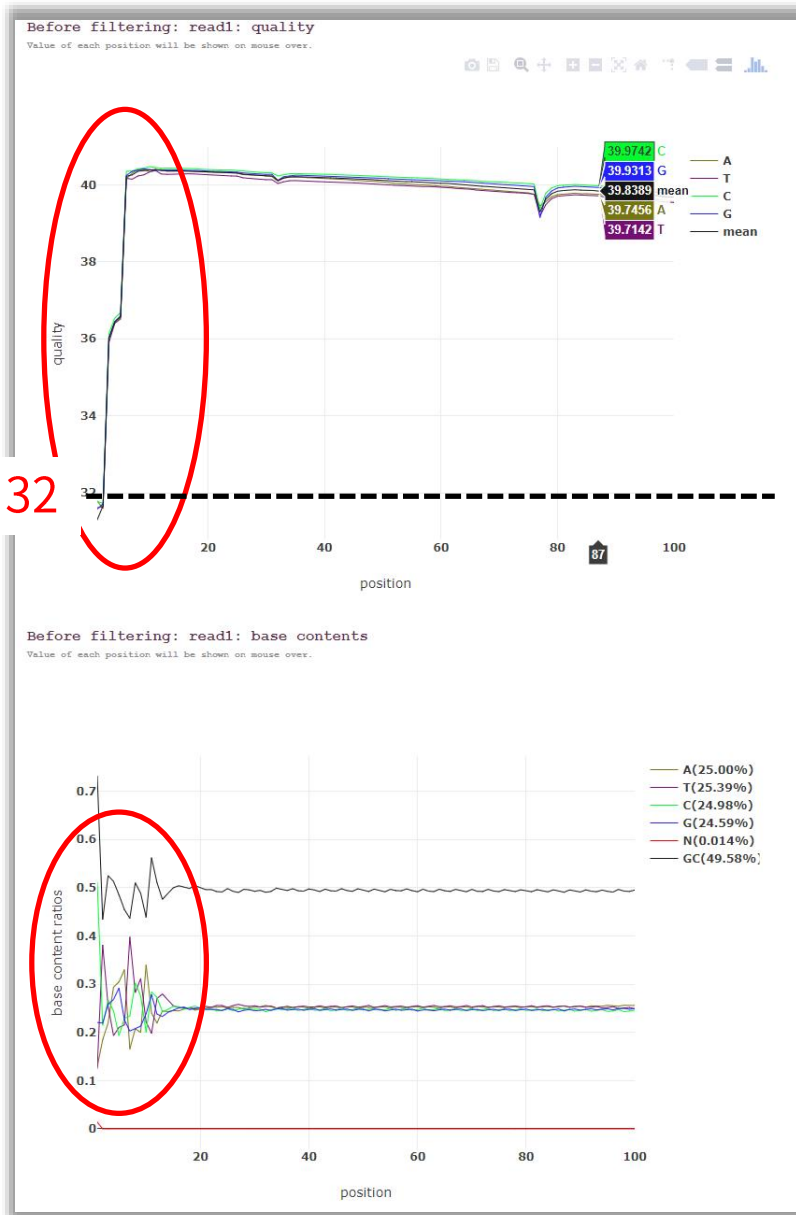
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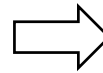
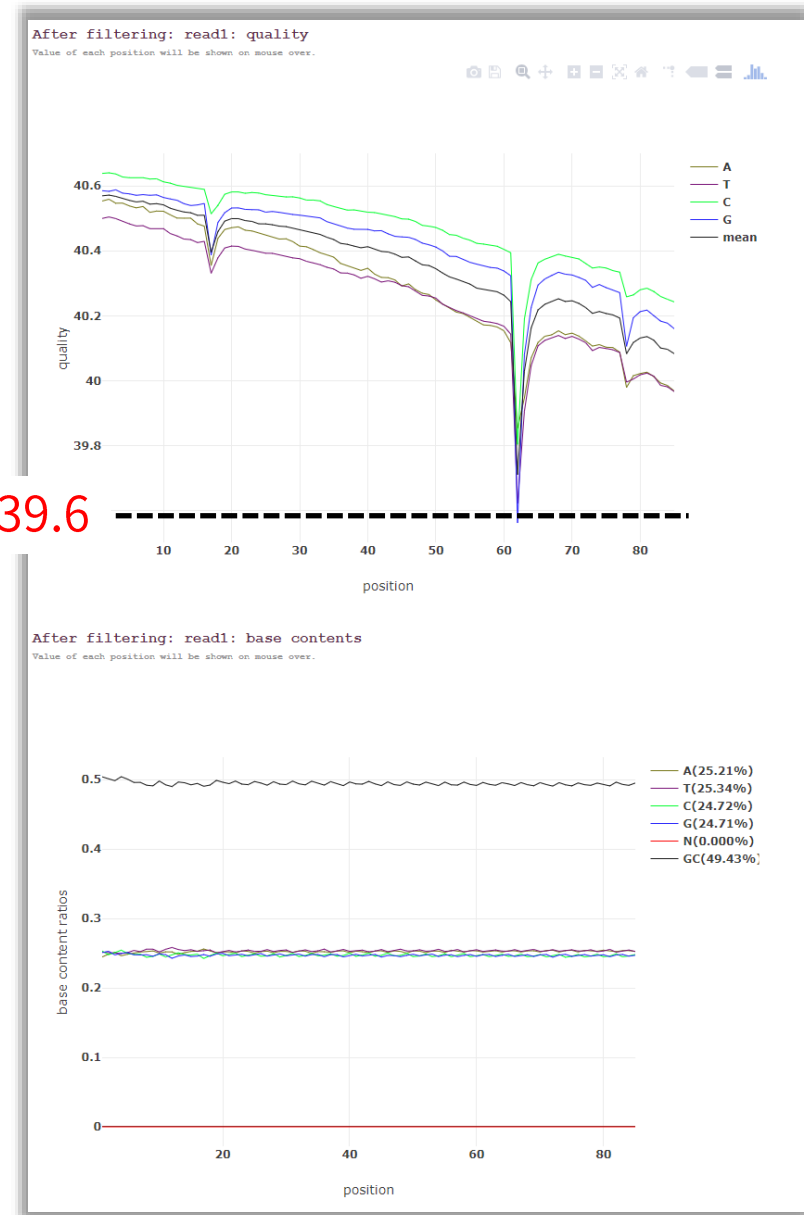
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Before



After



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Mapping

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Get DEG list

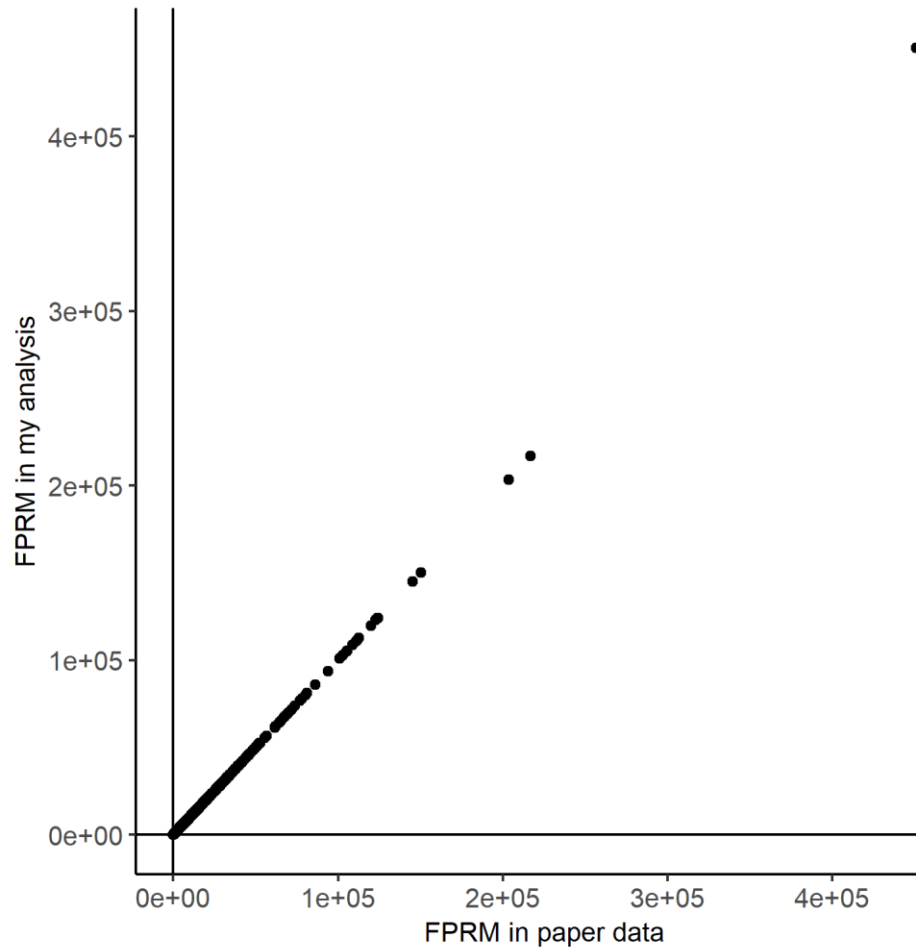
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Enrichment
Analysis:clusterProfiler package
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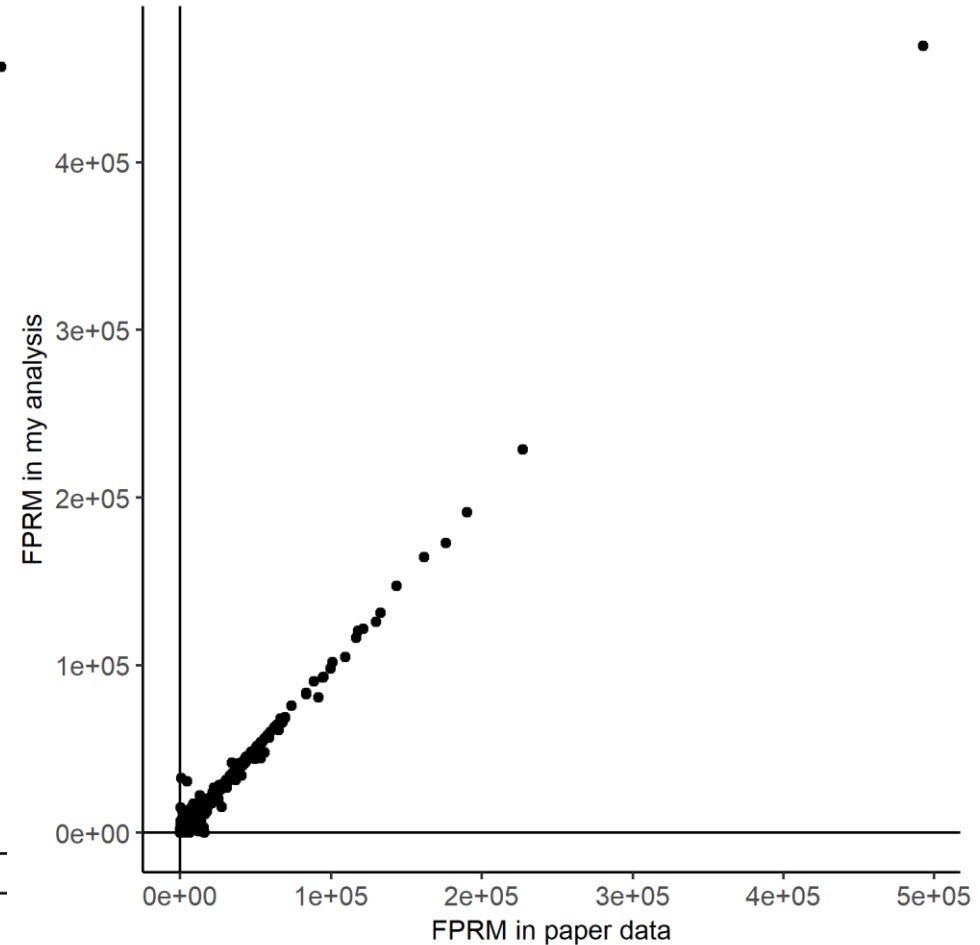
Result – Mapping result

My Analyzed data vs Paper supplement data
(FPKM)

Wild-type mice



KO mice



Windows subsystem on Linux

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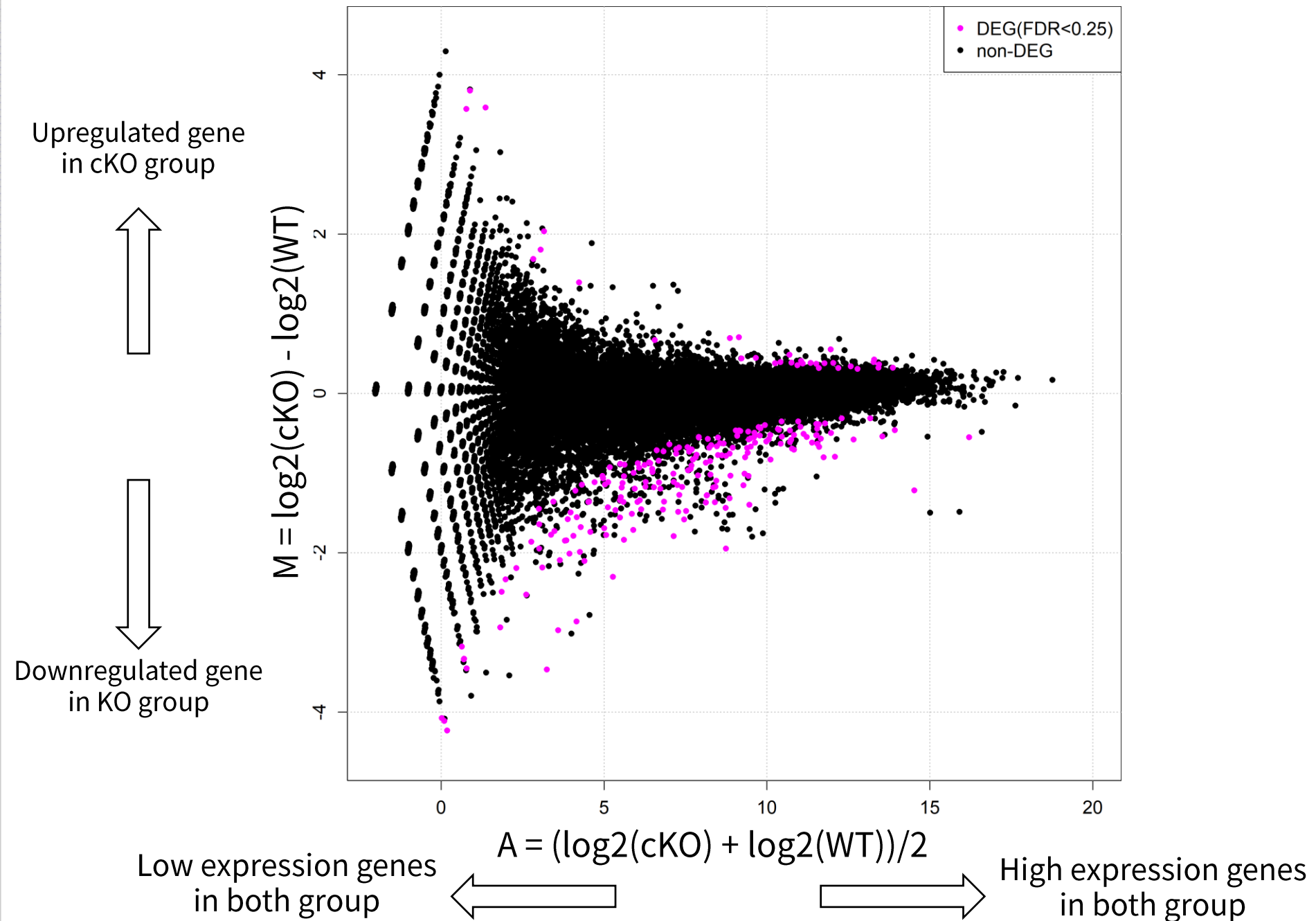
Enrichment
Analysis:clusterProfiler package
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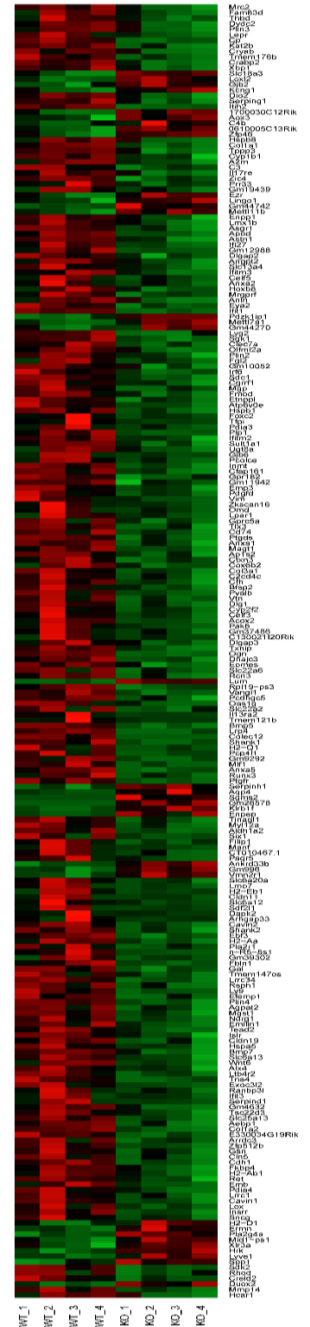
Result - Differential Expression Genes

12

gene_id	WT_1	WT_2	WT_3	WT_4	KO_1	KO_2	KO_3	KO_4	a.value	m.value	p.value	q.value
ENSMUSG00000029304	643.3372211	880.4783615	1075.439636	757.4899797	175.2393638	332.9545722	261.0727027	100.3101791	8.738508492	-1.948677645	7.61E-12	2.33E-07
ENSMUSG00000022770	4251.576797	4746.883902	4102.710417	4902.972251	2513.114807	3289.037896	2324.986037	2198.464759	11.73498991	-0.802102853	3.67E-10	3.91E-06
ENSMUSG00000021390	671.0929101	995.9671152	569.1230418	681.5437187	316.0386214	346.7865129	315.5485028	194.3509721	8.853138816	-1.314980531	3.83E-10	3.91E-06
ENSMUSG00000015090	33691.4414	47335.58276	24138.9335	38349.90285	15123.25839	20844.73461	15250.14051	10509.58106	14.52224071	-1.217219901	7.46E-10	5.70E-06
ENSMUSG00000026728	1929.020389	2398.612577	2466.844016	2519.048708	1599.439049	1300.202424	1542.795774	1261.191523	10.83138803	-0.707447327	8.15E-09	4.98E-05
ENSMUSG00000023224	467.8816153	466.8904316	382.6362047	433.9786342	245.1325205	213.4070849	247.7107139	158.8244503	8.26548156	-1.017601077	1.36E-08	6.95E-05
ENSMUSG00000037254	214.1153155	190.5070894	142.0391972	189.3724949	71.91904527	93.85959751	76.06055117	44.93060107	6.843689028	-1.359879526	1.87E-08	8.17E-05
ENSMUSG00000019970	3953.20314	4407.327224	3682.390343	3606.954239	2575.917354	2530.25715	2747.43045	2714.644223	11.65065614	-0.566414741	2.92E-08	0.000105576
ENSMUSG00000029661	986.3182357	1286.169624	874.4590031	799.901528	510.523927	566.1215723	522.1454053	327.0529799	9.428880215	-1.035210345	3.40E-08	0.000105576
ENSMUSG00000033227	87.23216557	63.17333535	39.61637472	57.20627451	13.16827589	22.72390255	19.52906044	16.71836319	5.061209386	-1.776979652	3.45E-08	0.000105576
ENSMUSG00000031431	3447.653089	3002.707596	3144.187399	3635.557376	2550.593746	2000.691421	2126.611897	1942.464823	11.38253483	-0.618004221	7.93E-08	0.000214553
ENSMUSG00000024650	311.2602272	362.2595949	202.9131388	335.3471264	107.3720957	157.0913264	90.45038517	50.15508956	7.452467845	-1.580888686	8.42E-08	0.000214553
ENSMUSG00000013584	403.4487658	594.2241857	299.538443	477.3764976	189.420584	233.1670001	192.2070685	118.07344	8.155339029	-1.275858571	1.36E-07	0.000319266
ENSMUSG00000030218	771.2116456	1119.352536	689.904672	1019.84979	454.8119905	524.6257503	500.5606543	309.289719	9.309539439	-1.008738886	1.70E-07	0.000370858
ENSMUSG00000030109	102.1012847	130.2950042	47.34639906	88.76835699	30.38832899	36.55584324	22.61259629	13.58367009	5.607015163	-1.837097774	2.81E-07	0.000571755
ENSMUSG00000057836	23.79059061	30.59958431	55.0764234	65.09679513	14.18122019	10.8679534	5.13922643	10.44897699	4.396171311	-2.102871863	5.79E-07	0.00110587
ENSMUSG00000022548	4853.280485	6379.519787	5474.789736	6208.853414	4422.514812	3082.546781	3428.891874	2284.146371	12.08716136	-0.793868361	7.68E-07	0.00138198
ENSMUSG00000030108	528.3493665	529.0766836	376.8386864	530.6375118	232.9771889	297.3867247	222.0145818	114.9387469	8.350328903	-1.179825846	1.07E-06	0.00182019
ENSMUSG00000105843	382.631999	477.7483486	487.9577862	438.9102096	284.6373482	142.2713899	182.9564609	82.54691824	8.119505781	-1.368037238	1.16E-06	0.001868529
ENSMUSG00000079293	22.799316	30.59958431	32.85260343	37.47997295	10.129443	3.951983053	12.33414343	9.404079293	4.056874019	-1.788389465	1.30E-06	0.001991153
ENSMUSG00000022766	199.2461964	204.3262565	118.8491242	218.9619473	83.06143256	98.79957632	51.3922643	36.57141947	6.804977407	-1.458197674	1.57E-06	0.002181377

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Bioconductor

Get DEG list

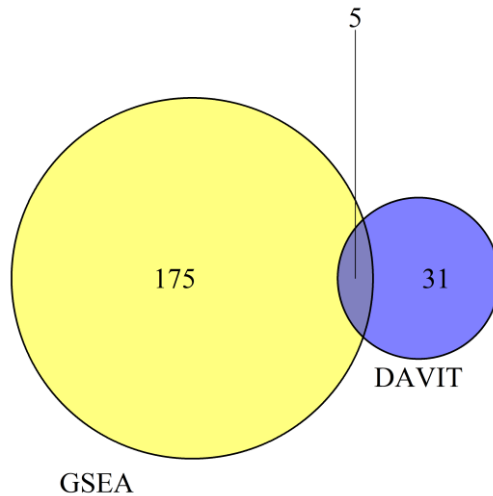
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Enrichment
Analysis:clusterProfiler package
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Web tool: DAVIT Functional Annotation Chart

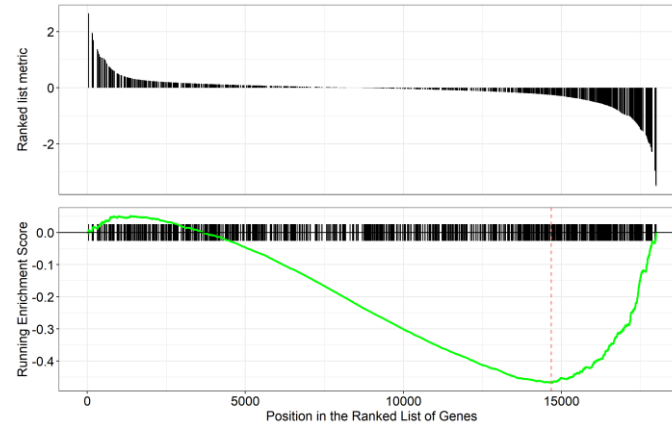
Bioconductor: Gene set enrichment analysis (GSEA) by *clusterProfiler*
: Over-representation analysis (ORA) by *clusterProfiler*

A

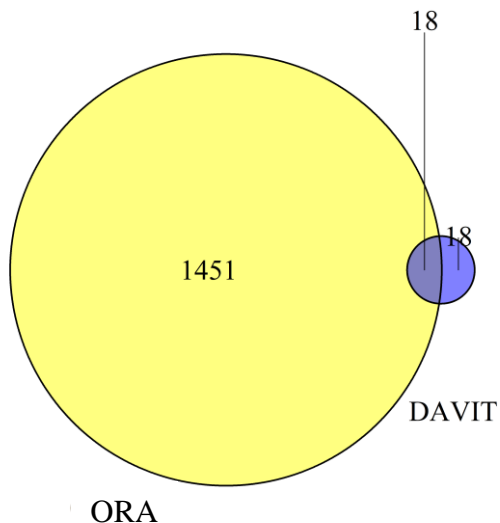


B

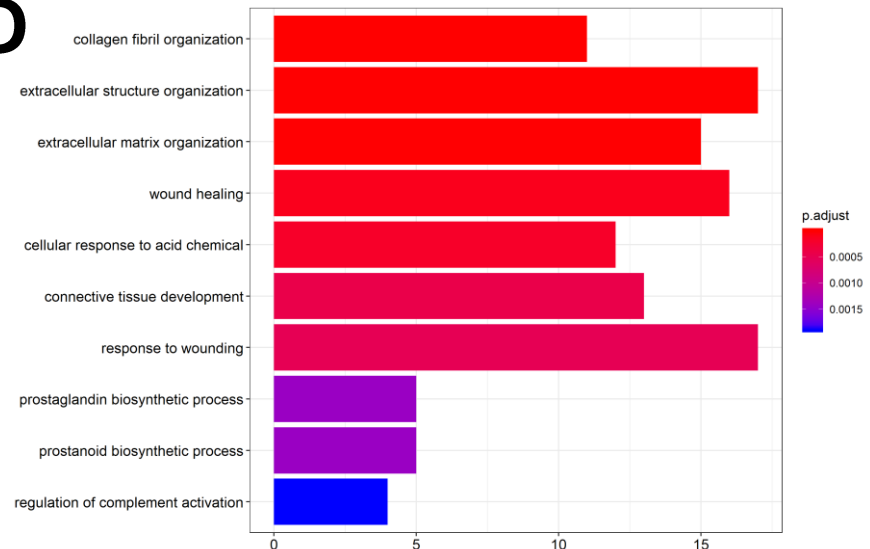
【SKELETAL_SYSTEM_DEVELOPMENT】
enrichmentScore = -0.45, q.value = 0.32



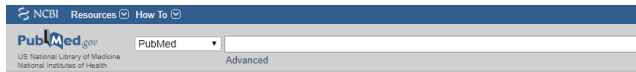
C



D



Larger vocabulary than GO term



Format: Abstract + Send to +

Int J Neuropsychopharmacol. 2015 May;18(7):pyu114.

Neuregulin 1 Prevents Phencyclidine-Induced Behavioral Impairments and Disruptions to GABAergic Signaling in Mice.

Eppel M, Srikari P, Jenner A, Karl T, Huang XF, Frank E.

Abstract

BACKGROUND: Substantial evidence from human post-mortem and genetic studies has linked the neurotrophic factor neuregulin 1 (NRG1) to the pathophysiology of schizophrenia. Genetic animal models and in vitro experiments have suggested that altered NRG1 signaling, rather than protein changes, contributes to the symptomatology of schizophrenia. However, little is known about the effect of NRG1 on schizophrenia-relevant behavior and neurotransmission (particularly GABAergic and glutamatergic) in adult animals.

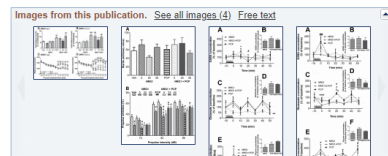
METHOD: To address this question, we treated adult mice with the extracellular signaling domain of NRG1 and assessed spontaneous locomotor activity and acoustic startle response, as well as extracellular GABA, glutamate, and glycine levels in the prefrontal cortex and hippocampus via microdialysis. Furthermore, we asked whether the effect of NRG1 would differ under schizophrenia-relevant impairments in mice and therefore co-treated mice with NRG1 and phencyclidine (PCP) (3 mg/kg).

RESULTS: Acute intraventricular- or systemically-injected NRG1 did not affect spontaneous behavior, but prevented PCP-induced hyperlocomotion and deficits of prepulse inhibition. NRG1 retrodialysis (10 nM) reduced extracellular glutamate and glycine levels in the prefrontal cortex and hippocampus, and prevented PCP-induced increase in extracellular GABA levels in the hippocampus.

CONCLUSION: With these results, we provide the first compelling in vivo evidence for the involvement of NRG1 signaling in schizophrenia-relevant behavior and neurotransmission in the adult nervous system, which highlight its treatment potential. Furthermore, the ability of NRG1 treatment to alter GABA, glutamate, and glycine levels in the presence of PCP also suggests that NRG1 signaling has the potential to alter disrupted neurotransmission in patients with schizophrenia.

PMID: 26478928 PMCID: PMC4540095

(Indexed for MEDLINE) Free PMC Article

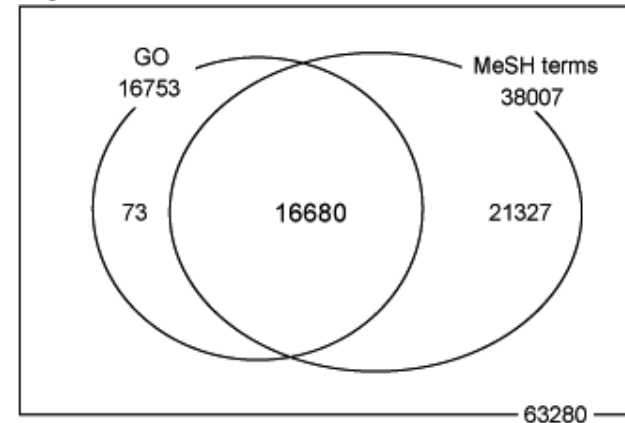


Publication type, MeSH terms, Substances, Grant support

Publication type
Research Support, Non-U.S. Gov't

MeSH terms
Animals
Behavior, Animal/drug effects*
Excitatory Amino Acid Antagonists/administration & dosage
Excitatory Amino Acid Antagonists/pharmacology
Glutamic Acid/analysis
Glutamic Acid/metabolism
Glycine/analysis
Glycine/metabolism
Hippocampus/drug effects
Hippocampus/metabolism*
Humans
Injections, Intraventricular
Locomotion/drug effects
Male
Mice
Mice, Inbred C57BL
Microdialysis
Motor Activity/drug effects
Neuregulin-1/administration & dosage
Neuregulin-1/pharmacology*
Phencyclidine/administration & dosage
Phencyclidine/pharmacology*
Prefrontal Cortex/drug effects
Prefrontal Cortex/metabolism*
Pretreatment/drug effects
Reflex, Startle/drug effects
Signal Transduction/drug effects*
Treatment Outcome
gamma-Aminobutyric Acid/analysis
gamma-Aminobutyric Acid/metabolism*

MeSH Term



(Nakazato et al., 2008)

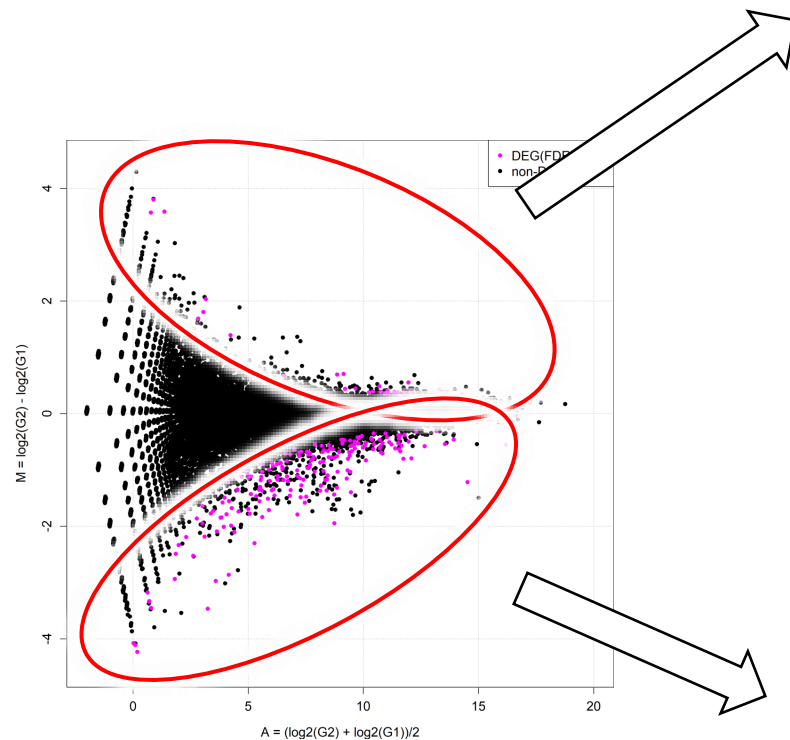
More categories than GO term

GO term

biological process
cellular component
molecular function

MeSH Term

A Anatomy
B Organisms
C Diseases
D Chemicals and Drugs
E Analytical, Diagnostic and Therapeutic Techniques and Equipment
F Psychiatry and Psychology
G Phenomena and Processes
H Disciplines and Occupations
I Anthropology, Education, Sociology and Social Phenomena
J Technology and Food and Beverages
K Humanities
L Information Science
M Persons
N Health Care
V Publication Type
Z Geographical Locations



Enrich Term

[1] "Child Development Disorders, Pervasive"	"Vocalization, Animal"
[3] "Stereotyped Behavior"	"Self-Injurious Behavior"
[5] "Grooming"	"Maze Learning"
[7] "Behavior, Animal"	"Creutzfeldt-Jakob Syndrome"
[9] "Lewy Body Disease"	"Obsessive Disorder"
[11] "Cognition"	"Schizophrenia"
[13] "Mental Disorders"	"Depression"
[15] "Compulsive Behavior"	"Psychomotor Agitation"
[17] "Touch Perception"	"Retention (Psychology)"
[19] "Thermosensing"	

Enrich Term

[1] "Chemotaxis"	"Behavior, Animal"	"Maze Learning"
[4] "Sensation"	"Alzheimer Disease"	"Auditory Threshold"
[7] "Psychomotor Performance"	"Electroshock"	"Sleep"
[10] "Reaction Time"	"Pain"	"Sexual Behavior, Animal"
[13] "Hearing"	"Stress, Psychological"	"Grooming"
[16] "Motor Skills Disorders"	"Auditory Perception"	"Motor Activity"
[19] "Nociception"	"Piloerection"	"Touch"
[22] "Exploratory Behavior"	"Extinction, Psychological"	"Touch Perception"
[25] "Conditioning, Classical"	"Anxiety"	"Vision, Ocular"
[28] "Food Preferences"	"Intellectual Disability"	"Visual Acuity"
[31] "Functional Laterality"	"Feeding Behavior"	"Cognition Disorders"
[34] "Homosexuality, Male"	"Heterosexuality"	"Food Deprivation"
[37] "Executive Function"	"Choice Behavior"	"Sucking Behavior"
[40] "Pain Threshold"	"Cognition"	"Suicide"
[43] "Spatial Processing"	"Depression"	"Conditioning, Operant"
[46] "Arousal"	"Fear"	"Learning"
[49] "Transsexualism"	"Avoidance Learning"	"Alcohol Drinking"
[52] "Attention"	"Orientation"	"Pattern Recognition, Visual"
[55] "Mental Disorders"	"Proprioception"	"Sleep Deprivation"
[58] "Vocalization, Animal"	"Electroconvulsive Therapy"	"Phantom Limb"
[61] "Mating Preference, Animal"	"Recognition (Psychology)"	"Neuropsychological Tests"
[64] "Tourette Syndrome"	"Pitch Perception"	"Spatial Navigation"
[67] "Inhibition (Psychology)"	"Freezing Reaction, Cataleptic"	"Paternal Behavior"
[70] "Retention (Psychology)"	"Wakefulness"	"Emotions"
[73] "Critical Period (Psychology)"	"Thermosensing"	"Memory Disorders"
[76] "Appetite"	"Conditioning (Psychology)"	"Memory, Episodic"
[79] "Psychomotor Disorders"	"Reflex, Startle"	"Time Perception"
[82] "Cocaine-Related Disorders"	"Space Perception"	"Erectile Dysfunction"
[85] "Psychoacoustics"	"Spatial Memory"	

Get ASD-related gene list

nature
International journal of science

Article | Published: 29 October 2014

Synaptic, transcriptional and chromatin genes disrupted in autism

Silvia De Rueters, Xin He [...] Joseph D. Buxbaum

Nature **515**, 209–215 (13 November 2014) | Download Citation

Corrected online 12 November 2014



Hypergeometric Test

	ASD-related gene	not ASD-related gene	Total
non-DEG	87	28450	28537
DEG	1	2107	2108
Total	88	30557	30645

Get schizophrenia-related gene list

SZDB: A Database for Schizophrenia Genetic Research

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Gene score result

Show / Hide columns

Show 10 entries

Search: [] Select all Deselect all Print Save

Gene	Entrez Id	CFR	CNV	Differential Expression	GWAS	Linkage & Association	Sherlock	Pascal	Score
PGBD1	84547	no	no	yes	yes	yes	no	yes	4
DOC2A	8448	no	yes	yes	yes	no	no	yes	4
DRD2	1813	yes	no	no	yes	yes	no	yes	4
MAGI2	9863	no	yes	yes	yes	yes	no	no	4
SNAP91	9892	no	no	yes	yes	no	no	yes	3
HIST1H2BJ	8970	no	no	no	yes	yes	no	yes	3
TCF4	6505	yes	no	no	yes	yes	no	no	3
RTN4R	65078	no	yes	yes	no	yes	no	no	3
SLC1A2	6506	yes	no	yes	no	yes	no	no	3
ZSCAN31	64288	no	no	no	yes	no	yes	yes	3

Showing 1 to 10 of 2,752 entries

Previous 1 2 3 4 5 ... 276 Next



	SZ-related gene	not SZ-related gene	Total
non-DEG	194	28343	28537
DEG	40 ***	2068	2108
Total	234	30411	30645

*** P < 0.001

Conclusion

Loss of SAP97 contributes to enrichment of SCZ related genes in the male animals.

1. De Rubeis S, He X, Goldberg AP, et al. Synaptic, transcriptional, and chromatin genes disrupted in autism. *Nature*. 2014;515(7526):209-215. doi:10.1038/nature13772.
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