In pursuit of Novel Class of Drug that Affects the Core Symptoms of Autism Spectrum Disease

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Abstract

The research of autism is still in progress. We had a deal with the 9 type of experiment results and gene expression data showing how much it is affected by autism. Through t-SNE and NMF, 3 high ranking result group and 3 low ranking result group had a pattern in OFT, NORT, and Social test. We decided to analyze these 3 phenotypes to find significant gene list. Those gene list is visualized in volcano plot based on p-value which is less than 0.05 and absolute value of fold change which is larger than 1 at the same time. Using these genes, we obtained drug lists of each phenotype through connectivity map and common functions through GeneMANIA. It is said that vasopressin can affect the common functions of each phenotype. As a result, we found out that FG-7142 drug related to vasopressin and benproperine through connectivity map which affects on central nerve system and has not been used as a autism drug.

Introduction

Autism is referred to as Autism Spectrum Disorder or ASD and is a developmental disability that can cause a range of mild to severe social, communication and behavioral challenges. Most people with autism look like other people but their behavior, social skills and communication are markedly different than people without the disorder.

Unfortunately, few drugs on the market today effectively relieve symptoms of autism and none of the options most often prescribed by practitioners work well for every individual. Hence, we came up with the idea that if we analyze existing drugs, thanks to recent advances in big data analysis, and mix up with the advantages of them it might be possible to find new combination treatment of autisms' core symptoms.

Connectivity map: a set of gene expression signatures for defined cellular states that would be used to link any genetic, chemical or other perturbations of gene expression to actions on normal or pathological processes.

NMF: a powerful tool for data reduction and exploration that has seen popular use in analyzing high-throughput genomic data.

OFT (DM): Distance moved

NORT: Time spent around the novel object

Social test: Time spent around the stranger chamber

Result

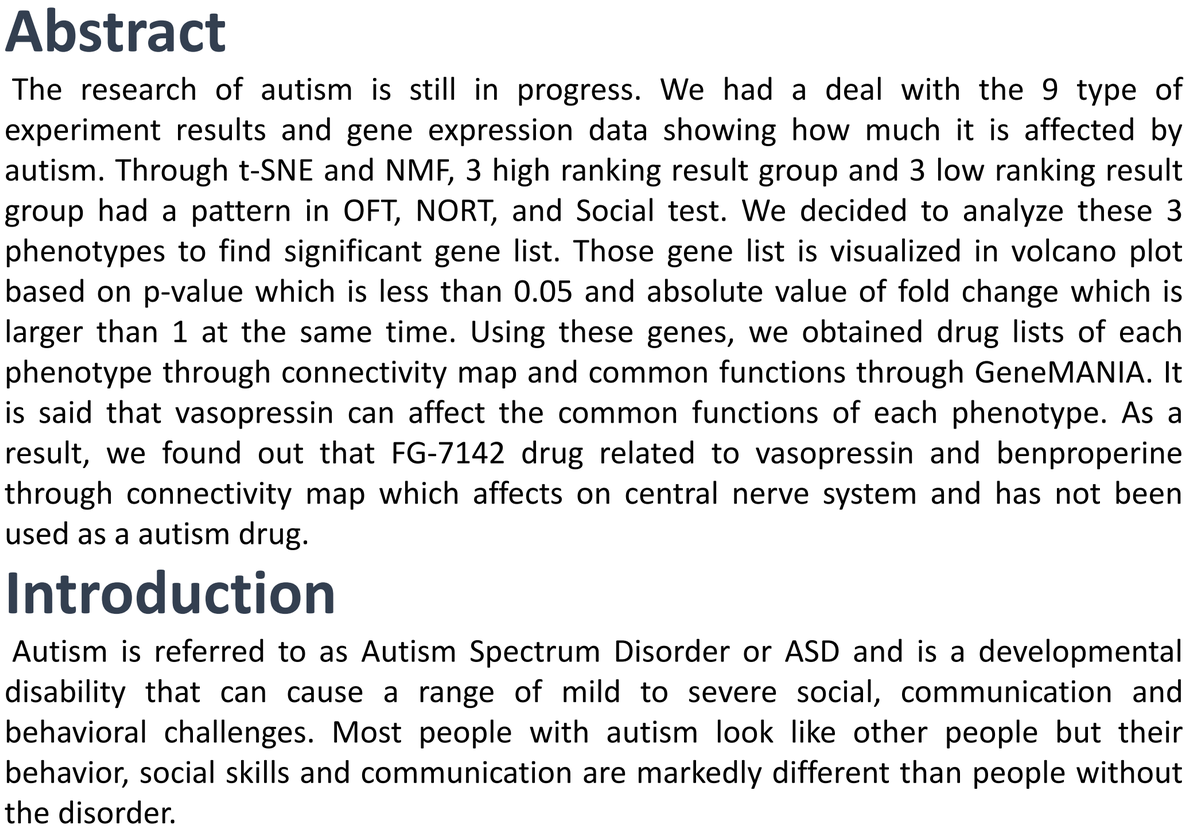
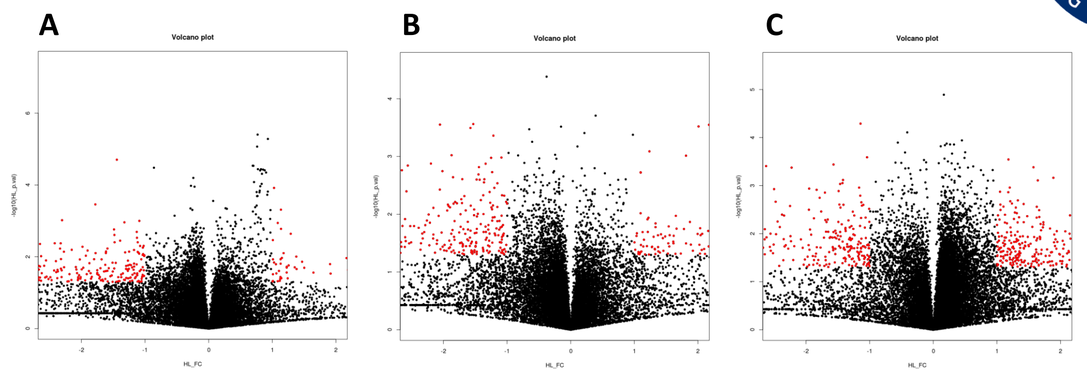
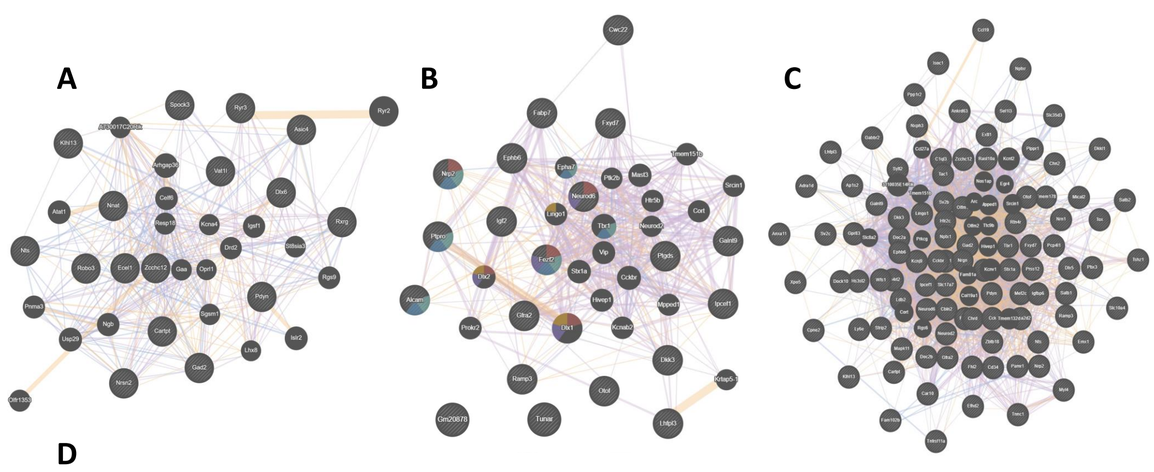


Figure 1A-B. The acquirement of the fact that OFT, NORT and Social test results from 9 phenotypes(FST, OFT, EPM, Y Maze, Social test, NORT, CA edge, RS_FST, RS_TST) are significant by t-SNE and NMF A) t-SNE of OFT, NORT and Social test using 101 genes out of variance 15. Each phenotype, 3 dots in green indicate that it made high ranking results into top 3 out of 20 samples and as opposed to in red it made 3 low ranking results from the bottom. B) NMF of OFT, NORT and Social test using same 20 sample. It indicates 3 high ranking results are grouped together as well as 3 low ranking results. (nrun = 15)



Figures 2A-C. The performance of acquiring significant genes through volcano plots of OFT, NORT and Social test. A) The volcano plot of OFT. 344 genes are obtained. B) The volcano plot of NORT. 353 genes are obtained. C) The volcano plot of Social test. 532 genes are obtained. (Each test, all significant genes are colored in red which p-value is less than 0.05 and absolute value of fold change is larger than 1. X-axis indicates log-scaled fold change between high ranking group and low ranking group. Y-axis indicates log-scaled p-value.)



D

	FDR		
	OFT	**NORT**	**Social test**
Neuropeptide Hormone Activity	0.02594223509	-	0.0003699372759
Axon Development	-	0.02052162281	0.01471822266

Figure 3A-D. The GeneMANIA results for generating hypotheses about functions of gene lists from volcano plot. The number of each test's gene list was reduced due to the amount of gene expression which should be larger than 10 for significance. A) The GeneMANIA result of OFT entering 17 genes. B) The GeneMANIA result of NORT entering 25 genes. C) The GeneMANIA result of Social test entering 101 genes. D) Two common functions of OFT, NORT, and Social test based on FDR are neuropeptide hormone activity and axon development.

A

Rank	Score	Type	ID	Name	Description
2	98.52	cp	BRD-K54256913	MK-1775	WEE1 kinase inhibitor
3	97.18	cp	BRD-K91623615	ABT-751	Tubulin inhibitor
4	95.21	cp	BRD-K35687265	ON-01910	PLK inhibitor
5	94.26	cp	BRD-K32828673	cheldonine	Tubulin inhibitor
7	92.22	cp	BRD-K59753975	vindesine	Tubulin inhibitor
9	90.41	cp	BRD-K02965346	SU-11274	Hepatocyte growth factor receptor inhibitor
12	90.1	cp	BRD-K12539581	nocodazole	Tubulin inhibitor
13	88.78	cp	BRD-K71823332	epothilone-a	Microtubule stabilizing agent
15	86.62	cp	BRD-K48427617	U-0124	MEK inhibitor
16	85.16	cp	BRD-K56334280	amonafide	Topoisomerase inhibitor
18	84.42	cp	BRD-K77687382	mebendazole	Tubulin inhibitor
22	82.95	cp	BRD-K90382497	GW-843682X	PLK inhibitor
25	81.26	cp	BRD-K17349619	HLI-373	MDM inhibitor
28	80.73	cp	BRD-K83376179	TCS-359	FLT3 inhibitor
33	77.77	cp	BRD-K26997899	SA-792574	Microtubule inhibitor
34	77.56	cp	BRD-K64451768	GANT-58	GLI antagonist
35	77.43	cp	BRD-K33226500	indinavir	HIV protease inhibitor
37	76.43	cp	BRD-A62182663	YK-4279	Apoptosis stimulant
41	73.75	cp	BRD-K40227168	vinburnine	Adrenergic receptor antagonist
43	71.25	cp	BRD-K08640512	RS-100329	Adrenergic receptor antagonist

B

Rank	Score	Type	ID	Name	Description
12	65.9	cp	BRD-K26521938	dinoprostone	Prostanoid receptor agonist
13	61.32	cp	BRD-K05464208	JX-401	p38 MAPK inhibitor
18	54.25	cp	BRD-A42423104	benproperine	Antitussive
29	37.72	cp	BRD-K48427617	U-0124	MEK inhibitor
30	33.67	cp	BRD-K05350981	oligomycin-c	ATPase inhibitor
31	33.27	cp	BRD-A17065207	brefeldin-a	Protein synthesis inhibitor
36	28.03	cp	BRD-K33553600	isoliquiritigenin	Guanylate cyclase activator
37	27.31	cp	BRD-K93258693	GW-9662	PPAR receptor antagonist
41	24.1	cp	BRD-K08556791	ethoprop	Acetylcholinesterase inhibitor
42	23.76	cp	BRD-K64857848	XMD-885	Leucine rich repeat kinase inhibitor
44	22.12	cp	BRD-A27554692	altrenogest	Progestogen hormone
50	20.83	cp	BRD-K84134924	pancuronium	Acetylcholine receptor antagonist
51	20.83	cp	BRD-K17086609	BRL-54443	Serotonin receptor agonist
53	19.63	cp	BRD-A71157293	fursultiamine	Vitamin B
63	17.72	cp	BRD-U86922168	QL-XI-47	BTK inhibitor
67	17.2	cp	BRD-K92446736	zatebradine	HCN channel blocker
71	15.88	cp	BRD-A55416093	colforsin	Adenylyl cyclase activator
74	15.19	cp	BRD-U94646492	quinine	Hemozoin biocrystallization inhibitor
76	14.88	cp	BRD-A26002865	verrucarin-a	Protein synthesis inhibitor
78	14.65	cp	BRD-K42831637	tetrahydrocannabinol-7-oic-acid	Anti-inflammatory

C

Rank	Score	Type	ID	Name	Description
8	69.63	cp	BRD-K76872913	benzanthrone	Aromatic hydrocarbon derivative
10	68.35	cp	BRD-K74402642	NSC-632839	Ubiquitin specific protease inhibitor
11	67.08	cp	BRD-K79659596	MLN-2238	Proteasome inhibitor
15	65.32	cp	BRD-K63784565	BRD-K63784565	Topoisomerase inhibitor
17	62.32	cp	BRD-A11007541	BCI-hydrochloride	Protein phosphatase inhibitor
18	61.59	cp	BRD-K12787491	U-0126	MEK inhibitor
21	58.79	cp	BRD-K62890442	3-methyl-GABA	GABA aminotransferase activator
26	51.29	cp	BRD-K64835161	BRD-K64835161	-666
29	48.87	cp	BRD-K61951118	PD-73-M2	GABA benzodiazepine site receptor inverse agonist
32	44.53	cp	BRD-K41859756	NVP-AUY922	HSP inhibitor
34	44.18	cp	BRD-K15935639	z-leu3-VS	Proteasome inhibitor
35	41.65	cp	BRD-A24817035	laudanosine	Central nervous system agent
36	41.4	cp	BRD-K20669427	WR-216174	PFMRK inhibitor
39	39.34	cp	BRD-A64228451	terreic-acid	BTK inhibitor
40	39.13	cp	BRD-K26863634	BIX-01338	Histone lysine methyltransferase inhibitor
45	36.04	cp	BRD-K44094599	tacrolimus	Calcineurin inhibitor
51	33.56	cp	BRD-K81916719	tricladendazole	Microtubule inhibitor
52	33.47	cp	BRD-K94270326	ecopipam	Dopamine receptor antagonist
54	33.01	cp	BRD-K09668667	benzo(a)pyrene	Carcinogen
60	31.52	cp	BRD-A54490543	pirlindole	Monoamine oxidase inhibitor

Figure 4A-C. The lists of potential drugs for OFT, NORT, and Social test executed from connectivity map. Each list is ranked based on the amount of gene expression difference between high ranking group and low ranking group. A) The list of potential drugs for OFT.
B) The list of potential drugs for NORT. C) The list of potential drugs for Social test. (MEK inhibitor in red is common compound out of 3 test's drug list which is too broad to use. Benproperine and FG-714 in yellow are potential drug to apply to autism's symptom relief.

Conclusion

We searched high-ranked drugs out of connectivity map results and found out that drug list of OFT was too broad to apply to. In case of NORT, it is possible to use benproperine as autism drug. It is a drug acting on the central and peripheral nerve system as a double-acting release. It is on the market and approved in the Ministry of Health and Welfare as a prescription for cold, chronic bronchitis, upper respiratory infections, and pulmonary tuberculosis. We also figured out that vasopressin is related to relieving the symptom of autism by GeneMANIA result of Social test. One of the compounds affecting this neurotransmitter is GABA receptor. FG-7142 is in the drug list of Social test. FG-7142 (ZK-31906) is a drug which acts as a partial inverse agonist at the benzodiazepine allosteric site of the GABAA receptor. It has anorectic, anxiogenic and pro-convulsant effects. It also increases release of acetylcholine and noradrenaline, and improves memory retention in animal studies. In summary, it is able to suggest benproperine and FG-714 as affective drugs to relieve the core symptoms of autism spectrum disease.

Reference

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