NURR1 Network: Modeling Cellular Lithium Response

McEachin RC, McInnis MG, Keller BJ, Prossin AR, Bai Y, Carlson NT, Zandi P, Chen H

University of Michigan Medical School

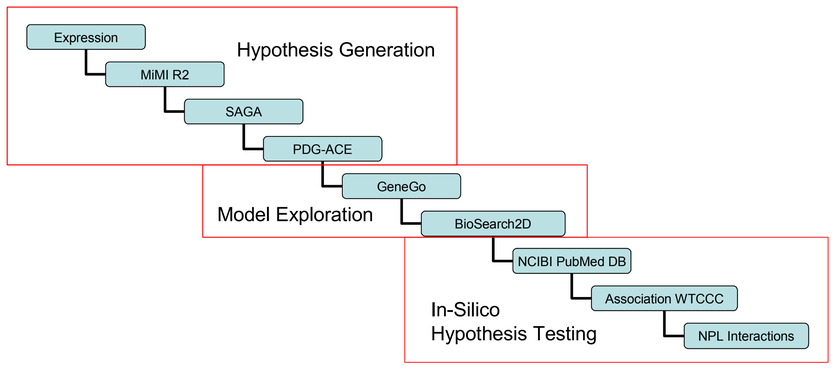
NURR1 Analysis

Focuses on a driving biological question – genetic influences on lithium response in Bipolar Disorder (BD)
Addresses all three specific aims of this Driving Biological Project (Core 3D)
Demonstrates an integrated biomedical informatics analysis using NCIBI-developed and external tools
- MiMI, SAGA, PDG-ACE, Local PubMed database, SNP Function Portal, BioSearch2D
Is strengthened by collaboration across the NCIBI and with external experts
- NCIBI Sub-contractors, T2DM DBP, UM Depression Center, the Johns Hopkins Univ., Univ. Colorado
Poses a novel, statistically significant, biologically plausible hypothesis on lithium response in BD

Background

Bipolar Disorder (BD) is characterized by mania and depression.
Familiality suggests genetic influence(s) - Relative Risk of ~ 4 to 7 for 1st degree relatives
Lithium is effective in treating mania and is the most effective treatment for suicide prevention in BD
Approximately 70% of BD patients respond to Li treatment (~ 30% non-responders)
Comorbidities may be significant - especially substance abuse

Analysis Flow



Brain Expression

GENE	Brain Expression	Temporal Regulation
FOS	523	Yes
NURR1	134	Yes
RGC32	58	Yes
HIG2	57	Yes
DUSP1	53	Yes
AHNAK	52	No
ADM	41	No
FOSB	34	Yes
STC2	22	Yes
IL8	13	No

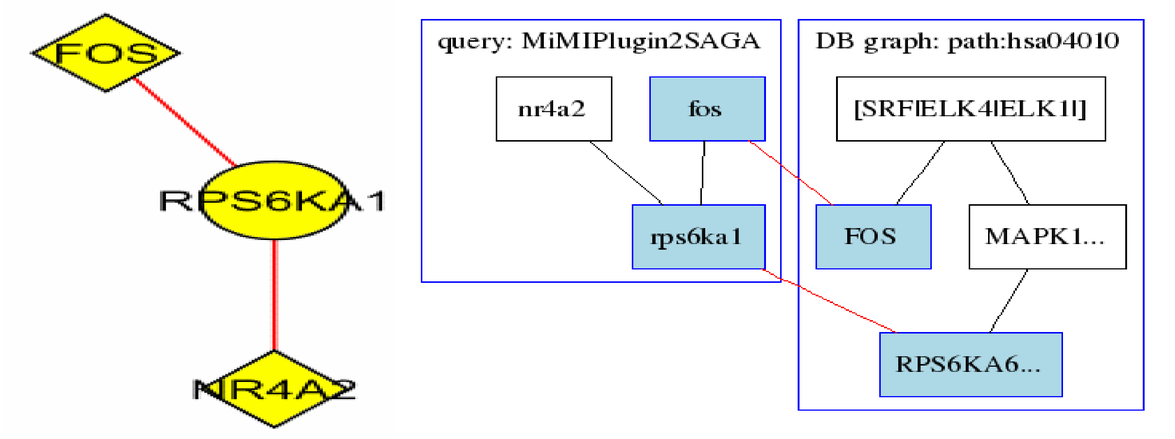
Expression Analysis

Lymphoblast Cell Lines - 14 pairs (Li treated and untreated) - therapeutic dose for 8 days
~22,000 transcripts – select genes that showed FDR < 0.05 AND fold change > +/- 30%
Based on brain expression, prioritize FOS and NURR1 for follow-up

FOS and NURR1: Roles in BD?

Cellular oncogene c-fos dimerizes with proteins of the JUN family, forming the TF complex AP-1
- The literature provides general support for FOS in BD
Orphan nuclear receptor NURR1 (a.k.a. Nuclear receptor subfamily 4, group A, member 2 (NR4A2))
- The literature provides specific support for NURR1 in BD
What else do FOS and NURR1 have in common?

Exploring FOS and NURR1 Interactions in MiMI and SAGA



- MiMI - not a direct interaction
- SAGA - hsa04010 MAPK signaling, consistent with TFs in differential expression
- No compelling link between FOS and NURR1 found with MiMi or SAGA

FOS and NURR1 in PDG-ACE

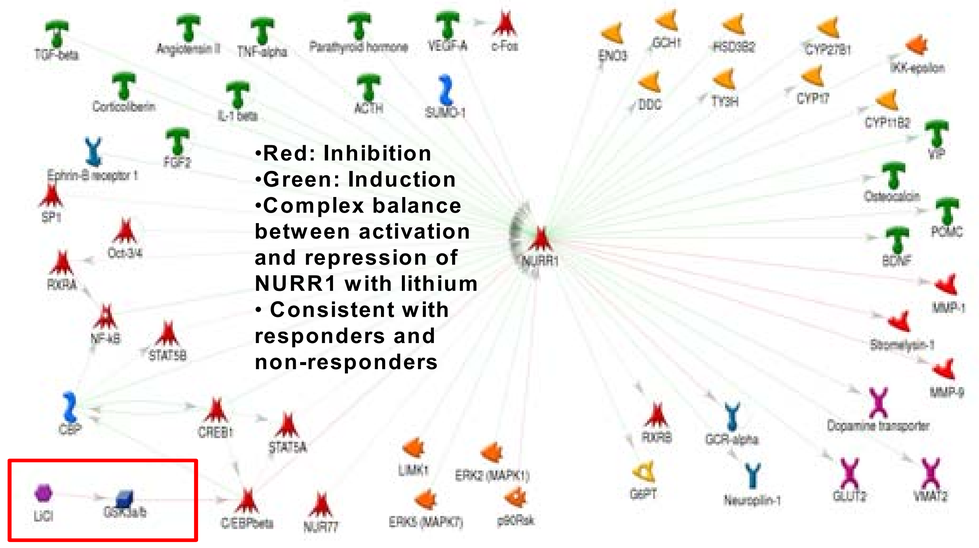
- Common over-represented keyword is "cocaine" (corrected p-value 0.006) in the context of dopamine signaling
- NURR1 - "Decreased expression of the transcription factor NURR1 in dopamine neurons of cocaine abusers"
- FOS - "Fos produced in [dopamine] D1 receptor-expressing neurons integrates mechanisms to facilitate both the acquisition and extinction of cocaine-induced persistent changes in brains of Drd-1-Cre transgenic mice."
- Cocaine can induce mania in humans and is used to induce experimental mania in animal models

Hypothesis:

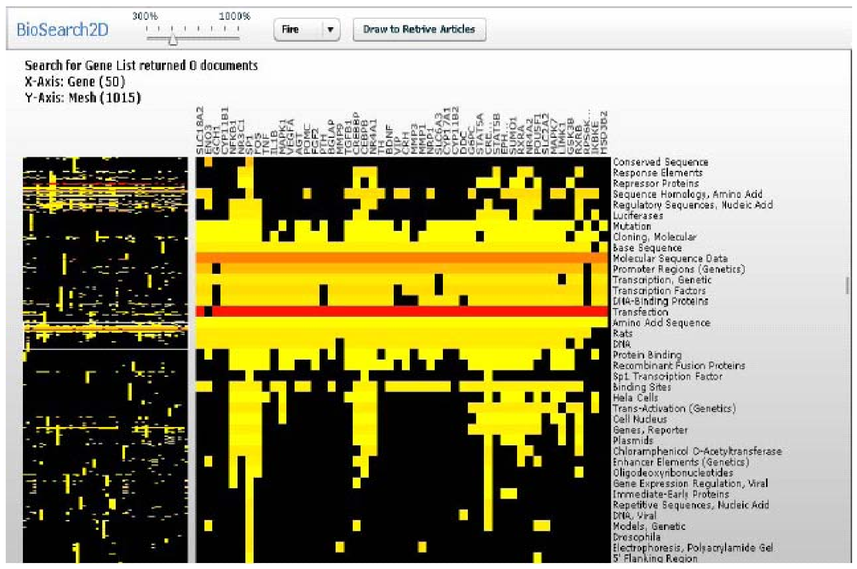
FOS and NURR1 transduce lithium signal via dopamine signaling

NURR1 is primarily expressed in brain and the published evidence is specific
Prioritize NURR1 for exploratory work

NURR1 Network, FOS, & Lithium



NURR1 Network in BioSearch2D



Strongest Signals are for Regulation of Gene Expression

Model Consistent With Lithium's Impact on Dopamine Signaling Via NURR1 Network

In-Silico Hypothesis Testing

Local NCIBI PubMed Database

- Publications tagged for MeSH annotation, as well as the genes that occur in the text
- High positive predictive value for gene/publication pairs returned from queries
- Co-occurrence may indicate a relationship - Not always a positive relationship
- Count provides a quantitative measure of research relating to the relationship

Disease	NURR1 Network Hits	Genome Hits	NURR1 Network Expected	HypGeom P-value	Significant	Fold Enrichment
Lithium	**22**	**1140**	**3**	**4.5414E-14**	**SIG**	**6.96**
Cocaine	**18**	**970**	**3**	**3.64223E-11**	**SIG**	**6.69**
Bipolar Disorder	**27**	**1759**	**5**	**3.76356E-15**	**SIG**	**5.54**
Parkinson Disease	**33**	**2266**	**6**	**1.14361E-18**	**SIG**	**5.25**
Dopamine	**30**	**2073**	**6**	**1.81036E-16**	**SIG**	**5.22**
Psoriasis	31	2218	6	1.01495E-16	SIG	5.04
Coronary Disease	32	2641	7	1.39429E-15	SIG	4.37
Lupus Erythematosus, Systemic	33	2788	8	6.43919E-16	SIG	4.27
Cystic Fibrosis	25	2183	6	4.80768E-11	SIG	4.13
Multiple Sclerosis	27	2385	7	6.09313E-12	SIG	4.08
Schizophrenia	**28**	**2728**	**8**	**2.01608E-11**	**SIG**	**3.70**
Breast Neoplasms	47	6489	18	1.51093E-18	SIG	2.61
Diabetes Mellitus, Type 2	38	3265	9	3.57025E-19	SIG	4.20
Abetalipoproteinemia	3	143	0	0.006627021		7.57
Tuberculosis, Lymph Node	5	271	1	0.000799132		6.65
Retinitis Pigmentosa	12	1054	3	1.85245E-05		4.11
Streptococcal Infections	12	1206	3	6.69059E-05		3.59
Urologic Diseases	5	574	2	0.016023966		3.14
Depressive Disorder, Major	20	1239	3	2.5287E-11	SIG	5.82

Enrichment for Lithium, Cocaine, BD, Parkinson's Disease, and Dopamine -related genes
Nominally significant replication in WTCCC association analysis via **SNP Function Portal**
Non-Parametric Linkage Interactions analysis yields 13 matches – p-value > 0.01
14 NURR1 network genes are therapeutic drug targets for related diseases
10 NURR1 network genes are differentially expressed - corrected for 50 hypothesis tests

NCIBI Impact

Analysis suggests a role for the NURR1 network in cellular responses to lithium treatment
- Comorbid substance abuse
Collaborations across NCIBI
- MiMI, SAGA, PDG-ACE, local NCIBI PubMed database, BioSearch2D, SNP Function Portal
An opportunity to answer a compelling biological question using resources unique to NCIBI
- PDG-ACE provided the essential link to dopamine signaling in hypothesis generation

Acknowledgements

This work was supported by the National Institutes of Health: Grant #U54 DA021519
and the Prechter Bipolar Genetics Fund