Multi-functional abnormality and bipolar disorder

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Background

Bipolar disorder (BD) is a chronic, severe psychiatric disorder with an estimated lifetime risk of about 1% (Ryan et al., 2006). Previously called manic depression, BD is one of the most challenging psychiatric disorders to manage. Patients are characterized by **alternating episodes of mania and depression**, accompanied by changes in activity associated with characteristic cognitive, physical, and behavioral symptoms (Anderson, Haddad, & Scott, 2012).

Motivations

Despite extensive research efforts, the underlying pathophysiology of BD remains unknown (Ryan et al., 2006). BD is a multi-system disorder, with symptoms likely caused by different diseases.

To explore these causes, we obtained functional analysis of genomic profile of BD cohorts using multiple sets of gene expression microarray data.

The purpose was to identify biological functions (as defined by Gene Ontology, or GO) associated with BD, to find relations among the functions, and to use these relations to construct a function association map for BD (BDFAM), thereby gaining insight to the systems property of BD.

Result 3- Used top 40% GO functions as key words to search databases

Verification by text-mining (We mention three examples)

Purine catabolism

Several reports implicates cAMP signaling plays a central role in the psychobiology of mood disorders due to mediating responses of a number of monoaminergics (e.g., dopamine).

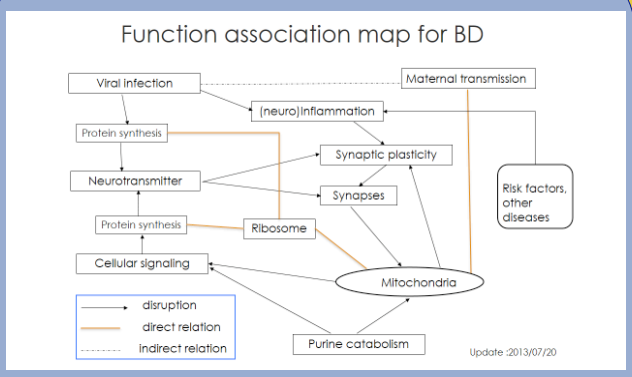
Multi-organism processes (virus infection)

Several reports suggest Borna disease virus (BDV) causes several changes in brain functions resulting in mood, behavior, cognitive and neurologic disturbances including movement impairment.

Mitochondrial dysfunction

Several reports implicates defective energy metabolism of mitochondrial dysfunction merges into the pathophysiology of bipolar disorder, such as alterations of mitochondria size, decrease in phosphocreatine and ATP ect.

Result 4 - Found relations among functions



A prominent interaction was “disruption”: if one function were disturbed, it might directly or indirectly affect other functions.

Proposed Approaches

1. We selected 12 sets of gene expression microarray data.
2. We used WABE (Weighing Arrays By Error, Chen et al.), *t-test* and MAQCm (*Shi et al*. 2006) to obtain differentially expressed genes between patients and healthy control, with which we then identify over-represented GO functions on bipolar affective disorder.
3. We ranked GO functions yielded by WABE by –log(p) value, then used the top 40% terms as key words to search the databases MEDLINE, PUBMED, and PsycINFO (1900-2013) for verification and annotation of our GO function results, and for the construction of BDFAM.

Result 1:Three Protocols for Bipolar Collection

WABE yielded vastly more over-represented GO functions than *t-test* and MAQCm FDR=0.5 was used to call differentially expressed genes, when a smaller value FDR=0.05 was used, only yielded GO functions.

Contrast	WABE	TTest	MAQCM	WABE	TTest	MAQCM	WABE	TTest	MAQCM
SklarA	450	0	0	479	0	0	258	0	0
AltarA	558	0	0	514	0	0	430	0	0
SklarB	205	0	0	229	0	0	202	0	0
Laeng	2966	0	0	2348	0	0	395	0	0
GSE12654	48	0	0	78	0	0	83	0	0
GSE12649	690	0	0	603	0	0	383	0	0
GSE5388	996	0	0	925	0	0	144	0	0
GSE5389	407	0	0	367	0	0	134	0	0
Feinberg	809	13	0	855	21	0	233	0	0
Chen	1181	0	0	937	0	0	429	0	0
Dobrin	213	0	0	197	0	0	111	0	0
Probeset									
Gene									
Function									

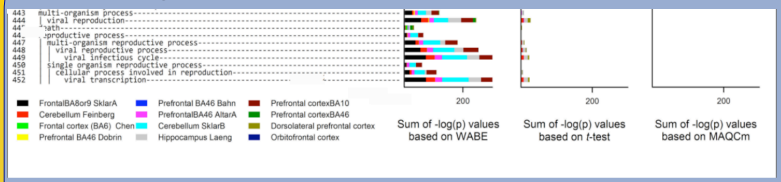
Contrast	WABE	Ttest	MAQCM	WABE	Ttest	MAQCM	WABE	Ttest	MAQCM
SklarA	859	0	0	879	0	0	358	0	0
AltarA	1239	199	0	1121	211	0	574	29	0
SklarB	429	0	0	504	0	0	248	0	0
Laeng	7891	2926	0	5560	2272	0	497	206	0
GSE12654	109	0	0	148	0	0	126	0	0
GSE12649	1727	0	0	1484	0	0	555	0	0
GSE5388	4067	7691	1	3482	6228	1	204	109	0
GSE5389	1317	215	0	1140	214	0	361	11	0
Feinberg	2030	2986	0	2026	2813	0	318	109	0
Chen	3304	5	0	2459	4	0	773	3	0
Dobrin	721	0	0	618	0	0	347	0	0
Bahn	2633	2061	2	2312	1884	2	224	68	0
Probeset									
Gene									
Function									

The prominent GO functions found by WABE were: mitochondrial dysfunction, purine catabolism, synaptic plasticity, neurotransmitter, cellular component organization, cell signaling, establishment of protein ocalization, multi-organism processes, inflammation, and others.

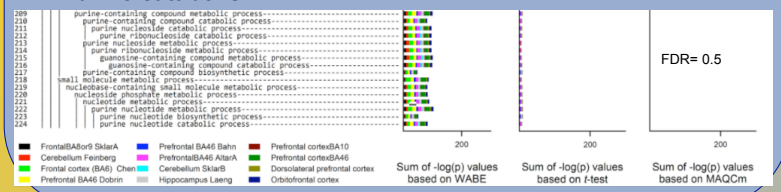
Result 2: Prominent GO functions found

(**we mention two examples**)

A. Multi-organism processes



B. Purine catabolism



References

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Summary: **Our results suggest multi-functional abnormality as a cause of BD.**