

A systems biological study on the comorbidity of autism spectrum disorders and bipolar disorder

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Abstract:

Autism Spectrum Disorder (ASD) is a "spectrum" of disorders, characterized by varying degrees of symptoms ranging from mild to severe. Among Psychiatric disorders, Autism Spectrum Disorders have the strongest evidence for a genetic basis, yet the search for specific genes contributing to these often devastating developmental syndromes has proven extraordinarily difficult. Bipolar Disorder (BP) is a manic-depressive disorder whose symptoms are characterized by extremities in moods. It is also called as the "Mood disorder". BP, like, ASD also has a strong genetic basis and identification of the candidate genes still remains an ongoing effort. Literature studies point to the hypothesis that ASD and BP have good chances of comorbidity and that they may share common pathways for their manifestation. But this hypothesis has not been worked on in depth. Thus, the study focuses on identifying the chances of their comorbidity by identifying their common pathways and the genes involved in the pathways and also discuss the degree of chances of their comorbidity based on the genes involved in the common pathways. Networks for the genes are also constructed to represent their commonness or uniqueness for the disorders.

Keywords: Autism Spectrum Disorders, Bipolar Disorder, Comorbidity, Systems Biology, Gene Networks

Background:

Systems Biology involves the study of the interactions of biological systems and ultimately their functions. Understanding the structure of the system, such as gene regulatory and biochemical networks, dynamics of the system involving both quantitative and qualitative analysis and construction of theory/model with powerful prediction capability, control methods of the system and design methods of the system are the key milestones to the Systems Biological study [1]. Autism Spectrum Disorders (ASDs) are a group of related neuro-developmental disorders characterized by delayed or abnormal language development, deficits in social interaction and restricted, repetitive behaviors and interests (Valerie W.Hu. 2009) [2]. They are pervasive developmental disorders that include Autistic disorder, Asperger syndrome, Pervasive Developmental Disorder- Not Otherwise Specified (PDD-NOS) and the rare disorders that include Rett disorder

and Childhood Disintegrative Disorder (CDD). These conditions are complex, behaviorally-defined syndromes with variable, severity and highly diverse symptoms and etiologies [3]. The most recent survey data estimates that, more than 1 in 150 children in the US may have an ASD diagnosis. Most estimates are based on population and there has been little evidence of variation based on geographic region. This makes ASDs the third most common developmental disorders [4].

Bipolar disorder (BP) is another common psychiatric disorder categorized under the Mood Disorders. It is characterized by mood alterations, with recurrent depressive and manic episodes in lifetime. Extreme changes in energy, activity, sleep, and behavior go along with these changes in mood. An overly joyful or overexcited state is called a manic episode, and an extremely sad or hopeless state is called a depressive episode. Manic episode is characterized by elated mood, grandiosity, pressure

to keep talking, flight of ideas, hyperactivity and diminished need for sleep. Depressive episode is characterized by depressed mood, loss of interest, appetite loss, sleep disturbance, psychomotor retardation, feelings of worthlessness and suicidal ideation [5]. Zutshi A *et al.* (2011) [6] has indicated that diagnosis of BP changed from 2.5% in 2004 to 3.3% in 2008. There was a significant increase in the prevalence of BP in 2008. Carroll and Owen (2009) [7] showed with evidences that ASDs, schizophrenia and BP have a convergence on the specific processes involved in the development and regulation of synaptic transmission. It has been hypothesized that the neural systems responsible for the regulation of circadian rhythm, synthesis of neurotransmitters such as dopamine and GABA can play a significant role in the etiology of disorders. Also, Rudan Igor (2010) [8] has indicated that although psychiatric disorders are highly heritable, identifying their genetic basis has so far been challenging, with most discoveries failing to be replicated. A few studies have elucidated the comorbidity of the two psychiatric disorders and their relation, but a clear insight into the concept has not been established as yet.

DeLong R (1994) [9] suggested that the pattern of affective and cognitive symptoms showed notable similarities across an entire group with ASD, with a family history of BPAD or major depression. Munesue T *et al.* (2008) [10] has emphasized BP as a comorbidity in high functioning ASD. He also speculated that the major comorbid mood disorder in patients with high functioning ASD is BP and also referred that both may share certain common vulnerability genes. Depression is the main psychiatric co-morbidity reported in individuals with ASD. It is considerably clear that lacunae pertaining to the comorbidity of ASD and BP exist at the genomic level. Thus, we have made an attempt to discover, understand, and interpret the relevance of comorbidity of the two disorders, carrying out *in silico* studies at the genomic level, contributing to the research that has progressed rapidly over the past few years due to the advancement of Bioinformatics applications.

Methodology:

Dataset Collection:

A rigorous search for genes associated with autism spectrum disorders and bipolar disorder performed manually from 8 sources viz., PubMed, Reactome [11], Genetic Association database [12], Huge Navigator [13], ENSEMBL [14], Cytoscape [15] and Sequence Retrieval System [16]. Around 714 genes and 675 genes were collected for BP and ASD respectively. The collected genes were then validated using the databases-GENECARDS [17] and UNIPROTkb.

Analysis:

A bottom-up approach (exploring the pathways involved in the disorders from the list of genes that were collected, rather than the usual *pathways to gene* approach) was employed to build the further methodology of the experiment. GeneGO Pathway maps (METACORE, GeneGo, Inc.) and CONSENSUSPATH database [18] was used for identifying the pathways to which the genes were associated. MetaCore (Thomson Reuter Inc) provides highly extensive grounds for analyzing pathways, building networks, analyzing expression profiles and many more. GeneGo Pathway Maps facility was chosen since it supports extensive analysis of pathways for gene lists imported

by the user with an additional facility of Enrichment analysis. Pathways were ranked based on the P-Values and the enriched pathways were then listed with their Log P Values. Such efficient and extensive pathway analysis feature is considered the crux of the study. Consensuspath Database [18] offers an extensive integration of pathways from various manually curated pathway databases. Therefore, it could be considered to be a central hub of pathways. With regard to the study taken up, this database was observed to be very useful and efficient. Thus, it was chosen for the study. NAViGaTor [19] provides an efficient representation of the networks. It was chosen as the visualization tool for the study to depict the common and unique genes involved in the chosen pathways. The gene lists were submitted to the two tools individually and their corresponding pathways were recorded. An enrichment analysis was performed by the two tools and statistically significant pathways were noted. The common pathways involved in both the disorders, as recorded by the two tools were individually shortlisted. As many as 33 pathways were recorded from metacore and 60 pathways from consensuspath database. A manual comparative study of the common pathways listed by both the tools was carried out and they were consolidated using knowledge from literature. Four pathways were identified to be common to both the disorders and are strongly associated with the basic etiology of the disorders.

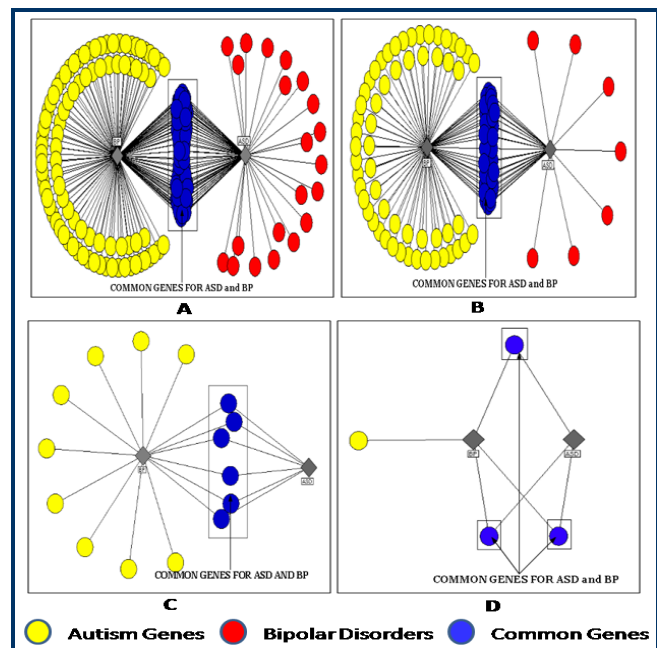


Figure 1: Networks for the chosen 4 pathways showing genes which are associated with ASDs or BP or common for both. (A) Network for Neuroactive Ligand Receptor Interaction Pathway (B) Synaptic Transmission (C) Circadian Rhythm Pathway (D) Catecholamine Biosynthesis

Network Construction:

The genes involved in these four pathways were then identified and a network for each of the 4 pathways was constructed using the tool NAViGaTOR [19] (Figure 2). Finally, the common genes associated with the two disorders were keyed out.

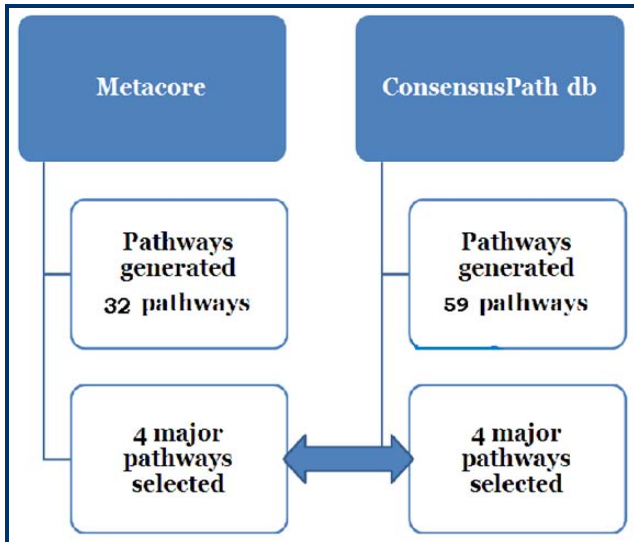


Figure 2: Methodology employed is depicted.

Results:

The initial data collection yielded around 675 genes for Autism Spectrum Disorder and 713 genes for Bipolar Disorder. The pathways associated with the genes have been recorded from both the consensuspath database and Metacore. A brief study on the pathways revealed that they are being regulated by 4 primary pathways and those pathways are indispensable for the other pathways to function properly. They are: Neuroactive Ligand Receptor Interaction Pathway (**Figure 1A**); Circadian Rhythm Pathway (**Figure 1B**); Synaptic Transmission (**Figure 1C**); Catecholamine Biosynthesis (**Figure 1D**); Thus, those 4 pathways were selected and networks were constructed using NaViGaTOR.

Discussion:

Autism Spectrum Disorders and Bipolar disorder continue to prove a great challenge to the medical community due to their heterogeneity and gaps, in diagnosis. The chances of comorbidity of the disorders are also considerably strong with validated literature support [9, 10, 20]. ASDs and BP have also been shown to implicate a few common symptoms viz., sleep deprivation, depression, anxiety and social-behavioral problems. This similarity between the 2 disorders could be due to disturbances in their common pathways that may involve commonalities and uniqueness in the contributing genes. Taking into account the gaps in diagnosing the disorders and perplexities in identifying the chances of their co-morbidity and unclear and polygenic factors, they have been chosen as case studies for the work. Out of the 50-60 common pathways (as on April 28, 2011) that were recorded from the 2 methods, 4 major pathways were chosen since they were found to mediate the other pathways. Moreover, 70% of those pathways were observed to be derived from any one of the above mentioned four pathways namely, Neuroactive Ligand receptor interaction pathway, Circadian rhythm pathway, Synaptic transmission and Catecholamine biosynthesis.

The Synaptic transmission pathway was observed to be extremely significant as it is the pathway through which the neurotransmitters- dopamine, serotonin, acetylcholine, Gamma

Amino Butyric Acid, Glutamate, Substance P are synthesized and released to perform the highly important function of transmitting signals from a neuron to the target cells. Thus, any disturbances in the pathway can lead to a constellation of complexities in the system. The Neuroactive Ligand receptor interaction pathway was ranked as the pathway with the highest score (involving the greatest number of genes implicated in the two disorders) for both ASD and BP by the ConsensusPath database. The pathway utilizes the neurotransmitters glutamate, dopamine, serotonin, nor-adrenaline as its starters and regulates certain crucial pathways that maintain mood and regulate stress such as, Long-term potentiation, Long-term depression, GnRH (Gonadotrophin Releasing Hormone) signaling and synthesis of Gap junction. The Circadian Rhythm pathway, is a key pathway to maintain the biological clock in our body and the CLOCK genes holds strong implications to be a factor for the disorders [21, 22]. Catecholamines are the “flight-fight” hormones that are released in response to stress. They include dopamine, epinephrine, and nor-epinephrine. The end product of this pathway nor-epinephrine mediates the synthesis of the corticosteroid- Cortisol by activating the Corticotropin-Releasing hormone (CRH) along-with Adrenocorticotrophic hormone (ACTH) in the pituitary gland. Cortisol is very important to regulate and handle stress and has innumerable functions in the body including mediating other hormones such as insulin, thyroxine, etc.

In addition, cortisol content in the plasma might also play a pivotal role by influencing the production of Serotonin, which is the precursor for Melatonin, a hormone synthesized in the pineal gland. Both serotonin and melatonin are very significant to maintain an individual's appetite, muscle movements, bone formation, memory, circadian rhythm cycle and many other activities. Cortisol content is observed to increase up to 2-3 folds in the morning and decrease gradually with the day's progress. During the night hours, cortisol content drops down and the synthesis of serotonin and melatonin takes place. This process is a routine in our body and only when it occurs normally, our body can maintain its balance and handle stresses throughout the day. Elevated cortisol level hinders the synthesis of serotonin and thus decreases the serotonin and melatonin levels. This undesirable process can lead to implications such as stresses, depressions, abnormal mental states which are the symptoms of ASD and BP. Based on a careful study of the four pathways and subsequent examination of the other pathways involved in the list, the above mentioned 4 pathways were selected for further analysis. The chances of comorbidity of ASD and BP can be speculated by the genes involved in the pathways. Although, the 4 pathways were observed to be associated with both the disorders, the fate of the disorders can be determined by the genes that get involved. While scrutinizing the list of genes involved in each pathway that are implicated as candidates for both the disorders separately, certain common and unique features were observed. As represented by the 4 networks, both disorders have their own unique genes and share common genes too. This can lead us to the speculation that when a disruption occurs in the genes common to both the disorders in a pathway, the chances of comorbidity of ASD and BP can be considerably high. However, when there is a mutation in the genes associated with only one

disorder, the susceptibility rate of a person with any of the ASDs to BP can be considerably low. Thus, though certain pathways have been observed to be similar to both ASD and BP, the chances of their co-occurrence in an individual can depend on the nature of the genes which get disrupted. The results obtained indicate that, any disturbance in the Circadian rhythm pathway (**Figure 1C**), the chances of comorbidity of BP and ASD in a person can be higher as ASD shares all its genes with BP (**Table 1, see Supplementary material**). But, a person can be diagnosed with BP only, in his later life if there is any disruption in the genes unique to BP in the pathway. However, disturbances in the Neuroactive Ligand Receptor Interaction, Synaptic Transmission and Catecholamine Biosynthesis pathways (**Figure 1A, 1B & 1D**) could increase susceptibility to any of the ASDs, if the genes identified as unique for ASD are disrupted, or might be affected by BP alone, if the genes identified as unique for BP are disrupted. However, commonalities among the genes of the 2 disorders raise a speculation that the chances of co-morbidity of ASD and BP can be higher if disruptions occur in those genes.

Conclusion:

A systems biology study of Autism Spectrum Disorders (ASD) and Bipolar Disorder (BP) proved to yield important insight on the genetic basis of comorbidity between the two disorders. The networks constructed for the selected 4 pathways leads to a hypothesis that the comorbidity of ASD and BP can be correlated to the genes involved in the pathways common to the two disorders and a further examination can pave way to the identification of the specific genes that contribute to comorbidity. Such knowledge would help in devising a novel management technique or developing therapeutics.

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Supplementary material:

Table 1: List of Genes Associated With Both ASD & BP Involved In the Selected Pathways

Pathway	Genes common for ASD and BP
Neuroactive Ligand Receptor Pathway	AVPR1A, HTR1E, HTR1D, HTR1B, HTR1A, CNR1, HTR7, VIPR1, ADRA2A, LHCGR, GABRB3, GABRB1, OPRK1, GRIN2A, ADRA1B, GABRA6, GABRA5, GABRA4, GABRA3, ADRB2, GABRA2, GRIA3, GABRA1, PRLR, GRM8, GRM7, ADORA2A, OXTR, DRD5, DRD4, DRD3, DRD2, DRD1, GRIK3, GRIK2, MCHR1, PRL, CRHR1, LEP, NPY5R, CHRM5, CHRM4, LEPR, CHRNA4, OPRD1, HTR5A, GABRG3, GABRG1, NPY2R, HTR2C, HTR2A, GRID2, GRID1, OPRM1, HCRTR2, HCRTR1
Synaptic Transmission	SLC1A1, SNAP25, GRIK3, GRIK2, GABRB3, GABRB1, GABRA6, GABRA5, GABRA4, GRIP1, GABRA3, GABRA2, GABRA1, GABRG3, COMT, DDC, GAD2, GAD1, DLG1, GRIA3, GRIN2A, MAOA, CHRNA4, SLC6A3, SLC6A1, TH, SLC1A3, SLC1A2
Circadian Rhythm Pathway	CLOCK, NPAS2, PER1, PER2, KC1E, BHE41
Catecholamine Biosynthesis	DDC, TY3H, DOPO