MOLECULAR GENETIC STUDY OF BIPOLAR AFFECTIVE DISORDER: A LINKAGE BASED APPROACH

PhD Synopsis

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October 2010

Synopsis

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Date of registration : 12.04.05
Progress reports submitted : Ten
Topic : **MOLECULAR GENETIC STUDY OF BIPOLAR AFFECTIVE DISORDER: A LINKAGE BASED APPROACH**

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Introduction

Bipolar affective disorder (BPAD) and schizophrenia (SCZ) are the most severe psychiatric disorders with approximately 1% prevalence, each worldwide, occurring at approximately the same rate across the globe. They profoundly affect thought, perception, emotion, and behavior, and their symptoms cause significant social and/or occupational dysfunction. The World Health Organization ranks both disorders among the top 10 leading causes of the global burden of disease for the 15-to-44 age group. It is generally accepted that the inheritance of psychiatric disorders is complex. Although the causes for these remain unknown, evidence from family, twin and adoption studies clearly demonstrates that it aggregates in families, with the clustering being largely attributable to genetic factors (McGuffin *et al.,* 2002). There might be multiple genetic factors involved and environmental factors contribute to the development of these disorders and it is possible that gene-gene interactions also play a role (Thapar *et al.,* 2007; van Os *et al.,* 2008). It has not yet been possible to identify any genetic variant that confers a direct functional effect which is consistently associated with disease across populations. Recently, specific genes or loci have been implicated in both disorders and, crucially, replicated. Current evidence supports *NRG1, DTNBP1, DISC1, DAOA (G72), DAO,* and *RGS4* as schizophrenia susceptibility loci. For bipolar disorder the strongest evidence supports *DISC1, DAOA (G72)* and *BDNF*.

In this thesis, I have carried out a whole genome based analysis by using linkage based approach in two families with multiple members affected with BPAD. In addition to this I have studied Single nucleotide polymorphisms (SNPs) from *TSNAX* and *DISC1*, which are candidate genes for both BPAD and SCZ. As these genes are implicated in both disorders, I have included samples from both BPAD and SCZ in this analysis. This is an attempt to replicate the positive association findings of these candidate genes for schizophrenia and

BPAD in the south Indian population using case-control and family-based association analysis methods.

The thesis has been portioned as introduction, review of literature, genome scan analysis in family 319, genome scan analysis in family 2717, case-control study for *TSNAX/DISC1*, conclusions, appendices and finally references.

Chapter 1: Introduction

This chapter gives a general overview of the phenotype of BPAD and SCZ, diagnosis criteria and proposed theories for these disorders. The basic strategies used to map genes viz linkage and association studies have been discussed. Some of the genes implicated in the disorders- *BDNF* (Brain derived neurotrophic factor)*, DAO* (d-amino-acid oxidase) and *DAOA* (d-amino-acid oxidase activator)*, DISC1* (disrupted in schizophrenia gene 1), *COMT* (catechol-o-methyl transferase), *DTNBP1* (dystrobrevin binding protein 1), *NRG1* (neuregulin 1), *RGS4* (Regulator of G-protein signalling 4), along with other genes are discussed. BPAD and SCZ are regarded as separate disease entities according to most diagnostic classification schemes despite their overlap in symptoms such as psychosis. The concept of SZ and BP as distinct entities was further distinguished from the work of Benedict Augustin Morel and Emil Kraepelin (Morel 1857; Kraepelin, 1919), the so-called ‘‘Kraepelinian dichotomy’’. However, the distinction between these 2 disorders has received renewed consideration since the 1980s and this concept has been challenged (Greene, 2007). The overlap between these two disorders is discussed in terms of phenomenology, pharmacology, familial aggregation, genetics and common endophenotypes. In addition to these the data on the genome-wide association studies (GWAS), chromosomal abnormalities and copy number variations (CNVs) have been presented.

Chapter 2: Review of literature

In this chapter, I provide literature on the genetic epidemiology (family, twin and adoption studies) of BPAD and SCZ. While the twin and adoption literature leave little doubt that genes are important, they also point to the

importance of environmental factors, since the concordance for schizophrenia in MZ twins is typically around 50% and heritability estimates are less than 100% (Shih *et al.,* 2004). Systematic genome screens have been, and are being, conducted on a variety of sample sets, ranging from large densely affected pedigrees in genetic isolates to large numbers of affected sib pairs. A review of linkage studies reported for BPAD, SCZ and for a combined phenotype of these, which reached genome wide significance level, is given. Large families with high density of members affected have identified several susceptibility loci for BPAD (Blackwood *et al.,* 2001). Linkage studies reported for BPAD in these kinds of families have been discussed along with the advantages and drawbacks.

The chapter also reviews *DISC1*, a candidate gene for both SCZ and BPAD. This includes association studies reported using SNPs from the *DISC1* and *TSNAX*, and the interacting genes.

Objectives and scope of the study

In this thesis, I have attempted to identify disease loci for bipolar affective disorder in two large pedigrees from South India comprising multiple affected members using linkage mapping strategy.

In addition, I have attempted to replicate associations with Single nucleotide polymorphisms previously reported in other populations for a candidate region harboring Translin Associated Factor X (*TSNAX*) , Disrupted in Schizophrenia gene 1(*DISC1*), using samples from south India. A population based case-control design was used in order to test the association for BPAD. As this gene is also reported to be a candidate gene for schizophrenia, I have extended the study using schizophrenia as a phenotype, and also combining both as a broader phenotype.

Thus the aims of our study are:

i) To identify susceptibility loci for bipolar affective disorder using whole genome linkage analysis,

ii) To validate previously reported association between SNPs in *TSNAX/DISC1* gene and bipolar affective disorder and schizophrenia.

Chapter 3: Genome wide linkage analysis reveals a putative locus for BPAD at chromosome 6pter-p24.3

In this chapter, I present a genome-wide linkage analysis carried out on a 3 generation family (family 319) with 9 affected members with BPAD. Another 11 relatively smaller families, which had major phenotype of BPAD with psychotic symptoms, similar to family 319 phenotype were analysed for fine mapping markers.

These 12 families consisted of 97 genotyped individuals. 48 could be assigned a diagnosis; among these 45 were BPAD, 2 Schizophrenia, and 1 Psychosis NOS (not otherwise specified). Subjects were recruited through the clinical services of the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore. Ethical approval for molecular genetic studies was obtained from the Institute Ethics Committee. Written informed consent was obtained from all participating subjects before collecting the blood samples.

Genomic DNA was isolated from whole blood of all participating subjects using modified salting-out method (Miller *et al.,* 1988). In the first stage of the study family 319 with 19 individuals available was used for the genome scan. These were genotyped with 381 autosomal microsatellite markers from ABI PRISM® Linkage Mapping Set version 2.5 MD10 (Applied Biosystems) divided into 27 different panels covering the 22 autosomes. These markers provide an average resolution of 10 cM across the human genome. Positive regions were followed up by including additional markers.

Two-point LOD scores were calculated using the MLINK program from the LINKAGE package5.2 (Lathrop *et al.,* 1984). Equal allele frequencies were used for the markers typed as population-specific allele frequencies were not available. As the inheritance model was not known LOD score calculation was done for both dominant and recessive models with different penetrances of 90%, 80%, 70%, and 60% at different recombination fractions. LOD score calculation was done separately for each family and positive scores were added for respective markers and theta (Ɵ) values across families. Two diagnostic models were used. The first

model consisted of individuals diagnosed with BPAD; all others were coded as unaffected. The second model included other diagnosis namely, Schizophrenia and Psychosis NOS (Not Otherwise Specified) in the affection status; all others were coded as unaffected. GENEHUNTER v2.1 (Kruglyak *et al.,* 1996) was used for multipoint analysis. Haplotypes were assigned manually based on genotyping data and were inferred when possible, while a minimum number of intermarker recombination events was maintained. These haplotypes were also confirmed with those generated using MaxProb in GENEHUNTER.

Evidence of linkage was observed at 6pter-24.3 with parametric two-point LOD score of 1.23 (Θ = 0.1). Haplotype analysis revealed shared haplotype in 8 affected individuals. The lower boundary was defined by D6S1640 and the upper boundary extended till p-ter with a critical region of 7.35 Mb. Other regions of the genome were excluded for linkage as there was no haplotype sharing found in the affected individuals.

Analysis of 11 additional families with 3 or more affected members, for 6 markers on chromosome 6p region, further strengthened the evidence of linkage to the same chromosomal region with 3 families showing concordance for the disease haplotype. Combined analysis of all 12 families did not give positive LOD scores in the region.

Conditional on the positive two-point LOD scores in 3 of the 11 additional families, a combined LOD score of 2.19 was obtained based on 4 families (family 319, family 583, family 580 and family 298) for D6S1591 (Θ = 0.1) in the 6p25.1 region, under a dominant model with 60% penetrance for the dominant genotypes and a phenocopy rate 1%. When SCZ and Psychosis NOS were included in the phenotype classification, 2-point LOD score of 2.94 was obtained for D6S1591 (Θ = 0.1), under the same model. Multipoint analysis assuming locus heterogeneity gave a HLOD of 0.71 (α = 0.83) and a NPL score of 2.2 (p = 0.021) with BPAD as phenotype (Figure 3.4a). Under broad phenotype HLOD of 1.19 (α = 1) and NPL score of 2.52 (p = 0.019) was obtained. Other families did not show evidence of linkage to chromosome 6p region.

Sequence analysis of *NRN1* (Neuritin 1), a gene which is expressed in postmitotic-differentiating neurons of the developmental nervous system and neuronal structures associated with plasticity in the adults and lies within this region revealed no potentially pathogenic coding mutation. Further analysis of positional candidate genes from this region shall help to identify the gene responsible for the disorder in these families.

Chapter 4: A whole genome based analysis of a large multiplex pedigree for BPAD from South India.

This chapter describes similar kind of work as the previous one. With an aim to identify locus for BPAD, a whole genome-based linkage analysis was conducted in a large 3-generation south Indian family, Family 2717, with multiple members affected with the disorder.

Family 2717 was identified through the proband using the clinical services of NIMHANS. The family members were invited to participate in the study and assessed by means of the Diagnostic Interview for Genetic Studies (DIGS) and Family Interview for Genetic Studies (FIGS). Total individuals sampled were 62, of whom 19 were diagnosed as BPAD and one with depression. The study was approved by the institute ethics committee. After complete description of the study to the subjects, written informed consent was obtained. 10ml of venous blood was drawn from each participant.

Genomic DNA was isolated from whole blood of all participating subjects using modified salting-out method (Millers *et al.,* 1988). The initial genome scan was performed with 381 highly polymorphic fluorescent markers (ABI PRISM® Linkage Mapping Set version 2.5 MD10) that have an average spacing of 10cM covering 22 autosomes. The part of the pedigree used in the initial genetic screen contained 24 most informative individuals with available DNA samples, including 14 affected individuals.

Two-point LOD scores were calculated between each marker and the disease by use of the SuperLink v 1.5 program and multipoint analysis using SimWalk v2.91 of the easyLINKAGE package, version 5.02 (Lindner and

Hoffmann, 2005). Haplotype analysis was done manually and also confirmed using SimWalk v2.91 program. Data was analysed for both dominant and recessive models under different penetrance values from 50% to 95%, phenocopy values of 1%, 5% and 10% at different recombination values (Θ) from 0 to 0.5. Data was analysed under two setups (a) using only affected individuals (affecteds-only analysis) and (b) using both affected and unaffected individuals (full pedigree analysis).

A two-point LOD score of 2.63 (Θ = 0.05) was obtained at 95% penetrance, 10% phenocopy under full pedigree analysis at D1S207. Fine mapping of the region did not improve the results with multipoint analysis showing negative scores. Z_{max} 3.19 (Θ = 0) was observed, in a part of the family at 95% penetrance, 5% phenocopy for the marker D1S207 on 1p31.1. Fine mapping using additional markers and members from the family $Z_{max\ =}$ 3.71 (Θ = 0) was obtained for marker D1S410 at 1p32.1. Haplotype analysis revealed sharing in 7 of 10 affected members. A region 15Mb below this region showed haplotype sharing in 8 affected individuals, with a $Z_{max\ =}$ 2.59 (Θ = 0) and multipoint score of 2.62. The critical region was defined by markers D1S207 and D1S435, (1p31.1-22.1), a 9.01Mb region.

Further work on mutational analysis of the locus identified in this study shall help find the gene responsible for the clinical phenotype and enhance our understanding of molecular basis of BPAD.

Chapter 5: An association study of TSNAX/DISC1 locus for schizophrenia and bipolar affective disorder in the South Indian Population.

Two genes in the chromosome 1q42 region- *DISC1* and *TSNAX* represent good candidate genes based on positional and functional considerations. The gene *DISC1* was first identified in a large Scottish family with a balanced translocation t [1, 11] [q42.2, q14.3] segregating with major mental illness including SCZ, BPAD and recurrent major depression (St Clair *et al.,* 1996; Millar

et al., 2000; Blackwood *et al.,* 2001). The Translin- Associated Factor X (*TSNAX)* gene is located adjacent to the *DISC1* towards the 5' region.

Several linkage studies have observed linkage near 1q42, which harbors *DISC1*, to SCZ (Hovatta *et al*., 1999; Ekelund *et al.*, 2001, 2004; Hwu *et al*., 2003) and BPAD (Curtis *et al.,* 2003; Detera-Wadleigh *et al.,* 1999; Macgregor *et al.,* 2004). Several population-based and family-based association studies have supported the role of the *DISC1/TSNAX* locus in SCZ and/or BPAD in Caucasian (Hennah *et al.,* 2003; Hodgkinson *et al.,* 2004; Thomson *et al.,* 2005; Callicott *et al.,* 2005; Zhang *et al.,* 2006; Schosser *et al.,* 2010; Rastogi *et al.,* 2009; Lepagnol-Bestel *et al.,* 2010) and Asian (Liu *et al.,* 2006; Chen *et al.,* 2007; Qu *et al.,* 2007) populations. The *DISC1* gene is expressed in neurons and glia and is translated to a protein that has an impact on neurodevelopmental and neurochemical processes thought to be involved in the pathophysiology of BPAD and SCZ including neurite outgrowth, neuronal migration, synaptogenesis and glutametergic transmission (reviewed by Chubb *et al.,* 2008).

This study was performed to assess the possible involvement of *TSNAX/DISC1* locus in the etiology of BPAD and SCZ in the southern Indian population. Seven SNPs from *TSNAX/DISC1* region in 1252 individuals (419 BPAD patients, 408 SCZ patients and 425 controls) were genotyped. All patients were recruited from the inpatient and outpatient services of NIMHANS, evaluated using the Diagnostic Interview for Genetic Studies (DIGS). Patients were diagnosed by at least two experienced psychiatrists using DSM-IV criteria. Control subjects were recruited by a standardized semi-structured interview with psychiatrists from healthy volunteers and hospital staff who had no family history of axis I disorders, in first degree relatives.

The study was approved by the Institute ethics committee. All participants gave written informed consent after a complete description of the study.

Association between disease and genotype/allele frequencies was tested by Chi-square test. A nominal ($p < 0.05$) association was observed for rs766288 within *TSNAX* for BPAD and also for BPAD and SCZ combined, and rs821616 in

DISC1 for BPAD, SCZ and also BPAD and SCZ combined, but after corrections for multiple tests, these results were non-significant. However, significant genotypic and allelic association was observed with BPAD as well as the pooled phenotype of BPAD or SCZ within the female subjects for the SNP rs766288. Two locus analysis of rs766288 and rs821616 showed the allelic combination of C-A as a risk combination, whereas A-A and A-T as a protective combination in female cases compared to control females. Significant genotypic association was also seen in SCZ males and in pooled male cases for rs766288. No positive association was detected for other SNPs studied.

Our results provide further evidence for sex-dependent effects of the *TSNAX/DISC1* locus in the etiology of SCZ and BPAD, and also suggest involvement of the locus for psychosis in our population, which warrants replication.

Conclusions

BPAD and SCZ are relatively common psychiatric disorders affecting tens of millions of individuals around the world. Neither disorder has an objective biological marker thus far that can be used to make diagnoses or to guide treatment. Genetic epidemiological studies have indicated genetic basis for both the disorders. Genetic studies have identified and implicated several loci and genes in etiology of these disorders. In this thesis I have attempted to identify BPAD susceptibility loci with the help of two large families with multiple members affected. I have also attempted to validate the association of a candidate locus with both disorders in our Indian sample set.

Both the disorders are phenotypically and genetically complex. In order to understand the genetic contribution to the pathophysiology of these disorders, several linkage and association studies have been carried out over the years, although no single gene has yet been identified. The number of susceptibility loci, the disease risk conferred by each locus, the extent of genetic heterogeneity, and the degree of interaction among loci all remain unknown. Results from linkage studies have been encouraging and large family studies have suggested that alleles of larger effect may be operating in families with a high density of illness.

Since I was able to work with two such BPAD families with samples for several multiple affected individuals, we hoped to be able to identify such a locus of large effect. The case control study on the combined sample was an effort towards understanding the role of this candidate gene in our population.

The present study has identified two loci for BPAD at chromosome 6pter-24.3 and chromosome 1p31.1-22.1 using linkage based approach. The results suggest a possible susceptibility locus for psychosis at chromosome 6p, and a locus for BPAD at chromosome 1p. Potential susceptibility genes within the region identified in this study and specific susceptibility alleles remain to be identified. These studies represent the initial studies for BPAD from an Indian population in families with multiple members having the illness. Further continuation of this work would lead to better understanding of the disorder.

The case-control study, has found significant allelic association with the intronic SNP rs766288 in *TSNAX,* supported by genotypic associations and a two marker haplotype analysis. Our results in the Indian population also provide evidence for sex-dependent effects of variations in the *TSNAX/DISC1* locus and susceptibility to psychosis. Further replication, in larger and more diverse samples, using dense markers, may be necessary to understand the role of these genes in the pathophysiology of these disorders.

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