Original Paper

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Evaluation of Whole Genome Association Study Data in Bipolar Disorders: Potential Novel SNPs and Genes

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ABSTRACT:

Evaluation of whole genome association study data in bipolar disorders: potential novel SNPs and genes

Objective: As a result of studies of multifactorial conditions, genetic, physiological and environmental factors, the overall heritability of bipolar disorders has been estimated to be up to 70%. In this study, an analysis of genome-wide association study data using data mining algorithms has revealed single-nucleotide polymorphisms that may be the basis for the molecular etiology of bipolar disorders.

Methods: The study was conducted as a case-control study, and data from the Whole Genome Association Study of Bipolar Disorder (dbGaP Study Accession: phs000017.v3.p1) were used. The goal of the project was to identify genes that make individuals more susceptible to bipolar disorders. The data set included 1767 controls and 653 bipolar disorder only cases. Genotyping data were generated by Affymetrix Affy 6.0. A total of 934,940 oligos were scanned.

Results: Various data mining approaches have identified 6 common SNPs which also have a statistically higher importance than others (rs10415145, rs10857580, rs11023096, rs4654814, rs4792189, rs7569781). rs10415145 is located on chromosome 19 at 19q13.11 and is related to ZNF507 (Zinc Finger Protein 507). While there are no publications reporting ZNF507 in bipolar disorders, a few publications exist studying other zinc finger protein genes. In addition, because it had the highest regulome score, DOCK10 was found to be a potentially related gene.

Conclusion: Zinc finger protein genes may play a role in the etiology of bipolar disorders. More detailed studies would help clarify this relation and describe its pathway.

Keywords: bipolar disorders, GWAS, ZNF507, DOCK10, zinc finger protein, chromosome 19

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INTRODUCTION

Bipolar disorder (BD) is a lifelong mental disorder characterized by significant elevation of mood and depression episodes. It affects 2-5% of the population[1] and has negative effects on quality of life, functioning and employment. It is responsible for the loss of more disability-adjusted life years than cancer or many major neurologic conditions[2-4]. The WHO reports that the loss of disability-adjusted life years due to BD results in a great burden globally[6]. The economic cost of the disorder is over $45 billion for the United States, and missed working days run up to around 50 days per year[5].

Several factors should be taken into account in the diagnosis of BD. Average onset of the disorder is at the age of 25. It is seen equally in males and females. A clear anamnesis of the patient's self-reported experiences should be performed and

information from family members and friends received. Psychiatric examination is critical to establish the diagnosis and decide on the treatment of the disorder. The most commonly used criteria for BD are found in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD-10). DSM criteria are mostly used in research studies in the USA, whereas ICD-10 criteria are commonly used in Europe[10].

BD has a heterogeneous etiology, affected by environmental and biological factors, especially genetics. Overall heritability of bipolar disorders is estimated up to 70%. Bipolar concordance rates are around 40% in monozygotic and 10% in dizygotic twins[6]. The risk of bipolar disorder is nearly tenfold greater in first-degree relatives of BD patients than in the general population[7]. Many chromosomal regions, candidate genes and polymorphisms have been suggested in the etiology of BD, but the study results are not consistent. The current genome-wide association study failed to find any particular locus for BD, which suggests that no single gene is responsible for the condition. Findings show that different genes from different families are implicated. The most implied locations are on chromosomes 6q, 8q and 21, and the most reported and justified genes are SLC6A4/5-HTT [serotonin transporter gene], BDNF [brain-derived neurotrophic factor], DAOA [D-amino acid oxidase activator], DTNBP1 [dysbindin], NRG1 [neuregulin 1] and DISC1. Genome-wide significant associations showed many common single nucleotide polymorphisms and variants within the genes CACNA1C, ODZ4, and NCAN[8].

ZNF (Zinc Finger Protein) family genes have been reported to be involved in many psychiatric conditions recently. The gene encoding Zinc Finger Protein 804A (ZNF804A) has been found to be a potential risk predictor in schizophrenia. Some Genome Wide Association Studies (GWAS) and their meta-analyses have supported these results. Although some work exists about functional and biological effects of ZNF, much remains unknown about its expression. Some epidemiologic evidence suggests a role of ZNF804A polymorphisms in both schizophrenia and BD, but functional links between these variants and biological states have not been clarified[9]. A relationship between DOCK (Dedicator of Cytokinesis) series genes and bipolar disorders has been shown in some publications. Kuramoto found a regulatory function of DOCK9 on dendrite growth, and Detera reported a relation between DOCK9 and bipolar disorders. There are some articles in the literature about the DOCK10 gene, reporting its relationship with some metabolic and hematologic conditions, but there are none about psychiatric disorders[10,11].

In this study, we aimed at identifying new potential SNPs and evaluating their pathway among a large genome-wide data set of bipolar disorder cases.

MATERIAL AND METHODS

The study was conducted as a case-control study. Data were obtained from the Whole Genome Association Study of Bipolar Disorder (dbGaP Study Accession: phs000017.v3.p1). The goal of the project was to identify genes that make individuals more susceptible to bipolar disorders. All required permissions for using the data were granted by NIH. Genotyping data were generated by Affymetrix Affy 6.0. A total of 934,940 oligos were scanned. Data were analyzed in 2013 and no part of the data has been used for any purposes other than this study.

In 1989, the National Institute of Mental Health (NIMH) launched a Genetics Initiative to collect family data for a linkage analysis of Alzheimer disease, schizophrenia, and bipolar disorders. The NIMH BP Genetics Initiative has been funded to create a national resource of demographic, clinical, and diagnostic data and to establish immortalized cell lines available to the scientific community. Such a resource will provide qualified

investigators with DNA and clinical/diagnostic information necessary for the identification of multiple disease susceptibility loci that contribute to the etiology of BD disorders[12].

Eventually data from 1767 controls and 653 Bipolar disorders only (BDO) groups were analyzed.

We used an Affymetrix Gene Console and PLINK for preprocessing steps (Filtering signals, background correction, data normalization) and quality checking. Univariate analysis was performed by PLINK. An R Bioconductor module was used to perform data mining modeling. To evaluate and visualize gene network and functional pathways, Genemania web based tools were used.

RESULTS

The statistics are based on 604 BDO patients and 1767 controls. Three hundred and thirty-nine of the cases (56.1%) and 1081 of the controls (61.2%) were European Caucasian, and the remaining subjects were African-American; 267 of the cases (44.2%) and 836 of the controls (47.3%) were male. Mean age of the patients was 42.1 and of the controls 49.9. The main sociodemographic features of the study group are presented in Table 1.

The prioritized SNPs were searched in electronic databases to find related genes and pathways. The mapped SNPs and related genes are reported in Table 2.

Table 1: Main descriptive statistics: ...

	Group		Frequency	Valid Percent
BDO			604	34.2
GRU			1767	65.6
Race	**BDO**	EA	339	56.1
		AA	265	43.9
	GRU	EA	1081	61.2
		AA	686	38.8
Smoking	**BDO**	Yes	171	30.3
		No	393	69.7
	GRU	Yes	891	50.4
		No	875	49.5
Previous daily smoking	**BDO**	No	119	23.6
		Yes	284	56.2
		Former	102	20.2
	GRU	Unknown	580	32.8
		Yes	839	47.5
		No	345	19.5
Sex: male. female. (African American participants)	**BDO**	male	267	44.2
		female	337	55.8
	GRU	male	836	47.3
		female	931	52.7
Marital status. (African American participants)	**BDO**	Married	168	27.9
		Single	42	7
		Divorced	128	21.2
		Widowed	17	2.8
		Separated	248	41.1
	GRU	Married	846	61
		Single	241	17.4
		Divorced	170	12.3
		Widowed	100	7.2
		Separated	29	2.1
Age	**BDO**	Mean		42.1
		Std. Deviation		11.5
	GRU	Mean		49.9
		Std. Deviation		16.5

BDO: Bipolar disorders only (cases), GRU: General research use, EA: European American, AA: African American

Table 2: Gene mapping results of SNPs.

UserID	Gene Symbol	Gene Name	Location	Entrez Gene ID	Regulome Score
rs10415145	ZNF507	zinc finger protein 507	19q13.11	22847	3a
rs10857580	ARHGAP22	Rho GTPase activating protein 22	10	58504	No data
rs11023096	KCNQ1	potassium voltage-gated channel, KQT-like subfamily, member 1	11	3784	No data
rs4654814	EPHB2	EPH receptor B2		2048	6
rs4792189	DNAH9	dynein, axonemal, heavy chain 9		1770	5
rs7569781	DOCK10	dedicator of cytokinesis 10	2q36.2	55619	1f

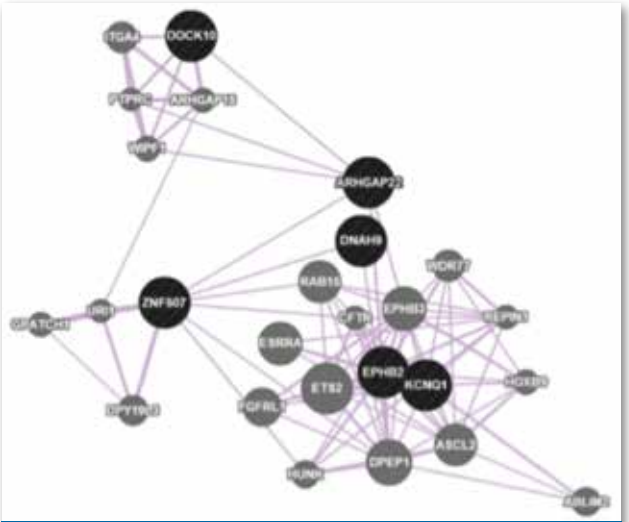

Figure 1: Genemania Network of selected SNPs

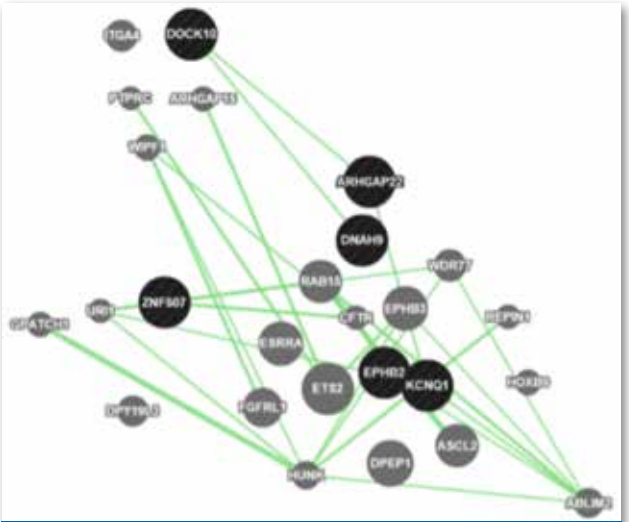

Figure 2: Genemania Interactions of selected SNPs

Using the Genemania web based tool, selected SNPs networks and interactions have been evaluated and visualized (Figure 1, 2).

DISCUSSION

In this study, we have analyzed BD GWAS data to show the association between the manifestation of disorders and genomic data. In addition to basic statistical data analysis, 3 data mining algorithms have been used to explore new potential SNPs. The common results of all of 3 algorithms show that the SNPs with the top 5 priorities according our data were rs7569781, rs2194124, rs9375098, rs4792189, and rs10857580.

rs10415145 is located on the 19th chromosome at 19q13.11 and is related to ZNF507 (Zinc Finger Protein 507). However there are no publications about ZNF507 in bipolar disorders, while a few publications discuss another zinc finger protein gene, ZNF 804A. Bergman et al. have found a relation between ZNF804A, schizophrenia, and bipolar disorders. Both disorders affect cortical thickness[13]. Schwab et al. have reported a significant association between zinc finger proteins and psychotic disorders[14]. Li et al. have evaluated zinc finger proteins in a large meta-analysis based on a Han Chinese population and found that ZNF 804A is related to the presence of psychotic disorders[15].

rs7569781 is located on the 2nd chromosome at location 2q36.2, related to the DOCK10 (dedicator of cytokinesis 10) gene. This gene encodes many of the dedicator of cytokinesis proteins. There are some articles in the literature about the DOCK10 gene reporting its relation with some metabolic and hematologic conditions, but there are no reports of an association with psychiatric disorders. A relation between DOCK series genes and bipolar disorders has been established in

some publications[10,11].

rs10857580 is located on the 10th chromosome, related to ARHGAP22 (Rho GTPase activating protein 22). Rho family small GTPases are describe as key regulators of morphological changes in neurons. They are involved in axon and dendrite outgrowth through cytoskeletal reorganization. Kuramoto et al. have described their important roles in both neurological and psychiatric disorders (10).

rs11023096 is located on the 11th chromosome, related to the KCNQ1 (potassium voltage-gated channel, KQT-like subfamily, member 1) gene. Potassium voltage-gated channels and related genes are known to be associated with bipolar disorders. The first gene suspected to be related to bipolar disorders is ANK3; other popular examples such as KCNQ2, KCNQ3 are also members of this group. Judy et al. reported that they have implicated ANK3 as a susceptibility gene for bipolar disorders. When they tested statistical interactions, the most significant interaction in the discovery GWAS was between SNPs in ANK3 and KCNQ2[16].

rs4654814 is located on the 1st chromosome and related to EPHB2 (EPH receptor B2) genes. EphB receptors and ephrinB ligands transduce bidirectional signals. This mediator produces contact-dependent axon guidance primarily by promoting growth cone repulsion[17]. These functions were closely related with the central neuronal system and its mediator. There is no publication about this family among psychiatric disease.

rs4792189 is located on the 17th chromosome and related to DNAH9 (dynein, axonemal, heavy chain 9). While there is some research about the relation between dynein, axonemal, heavy chain and psychological issues such as alcoholism or intellectual disabilities, there is no evidence regarding bipolar disorders[18,19].

Data mining has great advantages for analyzing high-dimensional GWAS data of complex psychiatric disorders. In this way, it is possible to extract complex relationships and correlations hidden in large data sets. These processes may also include computer modeling of learning processes. In our study, we prioritize the most important SNPs by using three algorithms. The SNPs or mapped genes should be confirmed by prospective studies.

In contrast to previous studies, we eliminated bipolar related disorder case data and exclusively analyzed bipolar disorders only patients' results. Given the complex disposition of bipolar disorders, this refinement helps to control confounders. In the end, the validity of the models was satisfactory.

Limitations of this Study

The data set included genotyping and phenotyping data. We tried to evaluate both of them. However significant the amount of work, we have not been able to find clues about treatment efficacy and adequate response to medical therapy. Because of the nature of retrospective data, it was impossible to describe response criteria well.

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