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Personalized Medicine in Bipolar Disorder

Parham Pooladgar[1], Bahar Naghavi Gargari[2*]

[1] School of Medicine, Shahid Beheshti University of Medical Sciences
[2] Basic Sciences Department, Shahid Beheshti University of Medical Sciences

**Corresponding author: Bahar Naghavi Gargari, Basic Sciences Department, Shahid Beheshti University of Medical Sciences. Email: bnaghavi@sbmu.ac.ir*

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Abstract

Bipolar Disorder (BD) is a cognitive and behavioral disease with mood fluctuation. The 6th global problem is in adults. Disease susceptibility is affected through genetic factors, the epigenetic process marked the disease phenotype. On the other hand, the importance of DNA methylation in some neurobiological and cognitive activities such as brain development processes and activity includes psychiatric diseases like BD. Numerous long intergenic noncoding RNAs were found that regulate gene expression of several diseases and are involved in the brain and cognitive development as well as psychiatric disorders such as BD.
Despite advances in neuropsychological or biological markers discoveries which predict personalized treatment efficacy, the clinical history and exhibition are careful and predictable markers for patient categorizing and treatment management. The aim of individualized medicine is to find vulnerability or preservative factors through genetic change.
Genetic, epigenetic factors, imaging, psychopathology and biomarkers can affect new treatments. Various studies such as family, twin, and adoption studies, linkage analysis indicated the association of HPA axis genes with vulnerability to BD. Personalized medicine applications in psychiatry focus on descriptive psychopathology and phenomenology via precise analysis and attention to each patient's impaired brain and mood processes.
The precision medicine studies concentrate on response to lithium, main treatment of BD, frequent mood diseases, antidepressant resistant prediction,risk and outcome assessment. Precision medicine is a hopeful way to develop new treatments based on individual genetic features. Personalized medicine in psychiatric disorder is in the infancy phases, but promising approaches were developed for complex diseases treatment with human genome sequencing.

INTRODUCTION

Bipolar Disorder (BD) is a cognitive and behavioral disease with mood swings from mania to depression or mixed conditions. Almost 1-4% of world population suffer from BD. Suicide is common in the bipolar patients with 14-59% suicidal ideation, 25 to 50 % suicide and attemption (1) .

Understanding of the mechanisms and neurobiology of BD is important in discovering of biomarkers and new treatments (2). The diagnosis of psychiatric or behavioral and cognitive diseases of the brain is difficult due to DSM-5 criteria. The patients with bipolar type I and II suffer from long term depression and could not recognize hypomanic or manic conditions which leads to having interval 5-10 years between the disease onset and diagnosis (3). Bipolar I with a mania phase, with or without major depression and BD II with frequent phases with one hypomania period without manic phase are categorized. The prevalence of BD is among ages from15 to 25. The 6th global problem is in adults. The patients suffer from social and clinical complaints and their family are affected by stress and distress (4). Increased risk of mortality is associated to conditions such as diabetes and cardiovascular disease in patients with bipolar disorder. Evidence indicated genetic and epigenetic factors in pathobiology of BD. Also, twin studies reported high heritability (70-80%).The offspring of BD patients have an increased risk of bipolar disorder. The familial aggregation and molecular genetic analyses reported inherited genes and inherited familial environment psychopathology. Genome wide

association studies (GWASs) recognized multiple loci showing heritability and 30 loci including encoding ion channels, neurotransmitter transporter and synaptic components (5).

The role of epigenetic modification in the pathogenesis of complex diseases like BD reported. DNA modification, histone modification and staining quality remodeling are epigenetic mechanisms suggested in bipolar disorder. In the present, symptomatic treatment is the only indicator for BD. Communication between body and environment as epigenetic mechanism includes DNA methylation and histone modification leads to pathological tag on the individual. It is important to BD which candidate genes do not exhibit powerful variation, but the epigenetic modification encountered heritable changes. Disease susceptibility is affected through genetic factors, the epigenetic process marked the disease phenotype. In point of genetic researches, BD is a polygenetic that is influenced via environmental factors. The methylation of COMT and PPIEL genes is an important epigenetic mechanism in biphasic disorders because these genes regulate the dopamine measure (6).

On the other hand, the importance of DNA methylation in some neurobiological and cognitive activities such as brain development processes and activity includes psychiatric diseases like BD. Reeline, Sox, and Foxp2 were observed in the postmortem brain and blood of patients. Epigenome wide studies indicated 12000GC-rich such as CPG islands in prefrontal cortical brain tissue. Increasing methylation upstream of Sms gene and decline of methylation upstream of Ppiel were showed in BD. Using next-generation sequencing, Methyl-DNA immunoprecipitation and high-throughput sequencing (MeDIP-Seq), various patterns of aberrant DNA methylation and next transcriptional start sites (TSS), sequences as CpG island shores" as well as promoters without CGIs were observed (7).

The important function of intergenic non- coding RNAs (lincRNAs) in psychiatric and mental disorders was know. Due to RNA-seq-based transcriptome studies, numerous long intergenic non-coding RNAs (LincRNAs) were found that regulate gene expression of several diseases. Furthermore , LincRNAs are involved in the brain and cognitive development as well as psychiatric disorders such as BD. For example, lincRNA LINC00173 is variously expressed in bipolar disease. Differentially expressed lincRNAs (DELincRNAs (with some genes regulate various functions in different regions of the brain. lncRNAs, involve in brain development and modulate production and differentiation of pluripotent stem cells. Almost, 3600 LncRNAs are expressed in the various regions of the brain like subventricular zone, olfactory bulb, and dentate gyrus. Microarray and RNA-sequencing (RNA-seq, as high resolution and high throughput techniques and with differential detection are used to discover lncRNAs involved in the brain development and neuro/pscychiatric disorders. Brn1b, RMST, and TUNA lead to neural stem cell differentiation. The modulation of GABAergic neurons was performed by EVF2. Moreover, the association of GABA system was indicated in psychiatric disorders such as SCZ, MDD and BD. BDNF protein level is increased with brain-derived neurotrophic factor (BDNF) antisense RNA (BDNF-AS) and promotes outgrowth, differentiation, survival, and proliferation. The mechanism of antidepressants reaction) and electroconvulsive treatment changes BDNF levels. Also, several studies reported a feedforward and feedback loop between neurotrophin signaling and lncRNA expression in psychiatric disorders (8, 9).

Brain studies of bipolar patients indicated alternative splicing impairments and changed levels of circular RNAs (circRNAs) cNEBL and cEPHA3 in bipolar disorder (10).

Malat1 expression level as long non -coding RNA was decreased in peripheral mononuclear blood cells (pbmc) of BD patients (11).

Genome wide association study reports hundreds or thousands of common variants without great influence on the probable role in heredity psychiatric diseases. Powerful association in C4 variants at MHC locus was found through GWAS in schizophrenia. However, targeted NGS of the GWAS zone is applicable to determine rare and common variants in BD and AD. It is difficult to use GWAS results in psychiatric disorder heritability due to the paucity of common causal variants at personalized medicine, but rare copy number variants (CNVs) function in the etiology of neuropsychiatric disorders was discovered. The role of CNVs in autism (1q21, 17p12, NRXN1 (neurexin 1) and other CNV region like 1q21.1, NRXN1, 2q37, 3q29, 7q11.23, 15q11.2, 15q13.3, 16p11.2, 16p13.1, 17q12 and 22q11.2 association with schizophrenia , intellectual disability and neuropsychiatric/neurodevelopmental conditions (12).

Personalized medicine is interested in combing novel molecular profiling with clinical-pathological indexes leads to proper diagnosis, prognostic and curative approaches tailored to any individual. Despite advances in neuropsychological or biological markers discoveries which predict personalized treatment efficacy , the clinical history and exhibition are careful and predictable markers for patient categorizing and treatment management (13).

Genetic markers are provided a hopeful approach to improve tailored therapeutics and disease prognosis for a reason 20-95% variations in central nervous drug using and pharmacodynamics. The response of lithium as a mood stabilizer was interesting phenotype and the genes with more

replication implied in serotonergic (SLC6A4) and dopaminergic (DRD1) neurotransmission, synaptic plasticity (BDNF), and second messenger cascades (GSK3B). Pharmacogenetic results are very important in polypharmacy and provide some information about other mood stabilizers effects such as hyperammonaemia (CPS1 gene) and hepatic dysfunction (POLG gene), the effect of valproate and cutaneous hypersensitivity reactions (HLA-B*1502), the effect of lamotrigine or carbamazepine. Also, cytochrome (CYP) P450 gene polymorphisms prepare benefit data (14, 15).

The aim of individualized medicine is to find vulnerability or preservative factors through genetic change. Genetic, epigenetic factors, imaging, psychopathology and biomarkers can affect new treatments. Various studies such as family, twin, and adoption studies, linkage analysis ,the association of HPA axis genes with vulnerability to BD, as well as five SNPs (rs4713902,rs7757037, rs9296158, rs3800373 , rs9380525 , rs4713902 and four SNPs (rs1043805, rs3800373, rs9296158, and rs1360780) differential association with episodes of depression or suicide attempt in BD. The evidence of GWAS showed the susceptibility to bipolar disorder with FKBP5 SNPs. Bipolar disease pathogenesis is suggested to related to the dopaminergic, serotonergic, and noradrenergic systems. The positive and negative associations of the genes encoding 5-HTT, monoamineoxidase A (MAOA) and catechol-O-methyltransferase (COMT) with BD were reported. Also, the relationship of circadian rhythm genes were shown. The function of aryl hydrocarbon receptor nuclear translocator-like BmaL1 (ARNTL) and circadian locomotor output cycles kaput (CLOCK) genes in controling of the internal circadian clock in BD patients was indicated. Other genes such as are calcium channel, voltage-dependent, L type alpha1C subunit (CACNA1C), ankyrin 3 (ANK3), neurocan(NCAN) and odd Oz/ten-m homolog4 (ODZ4) candidate genes for BD. Some specific mechanisms such as DNA methylation alternative splicing, RNA editing, histone modification, and non-transcriptional gene silencing via microRNAs regulated neurogenesis, addiction, psychiatric diseases mechanism and chronic stress. BDNF is involved in the pathophysiology of some psychiatric disorders like bipolar illness. BDNF cross the blood –brain barrier and increase the level of BDNF in the serum of bipolar patients with pharmacologic treatment. Thus, this protein is a striking candidate for BD researches because the peripheral blood level of BDNF decrease in mania, depression and euthymia (16).

Stress is an environmental factor that leads to improper regulation of the HPA axis, a principal coordinator of the adaptive response to stress. Cortisol level rise and SNPs in gene coding corticotropin releasing hormone receptor 1 (CRHR1) were reported in the major depressive disease. The therapeutic response in BD is affected by genetic modification .Several candidate genes variation such as 5-HTTLPR, CLOCK, BDNF, X-box binding protein 1 (XBP1), glycogen-synthase kinase 3 beta (GSK3B), breakpoint cluster region (BCR), cAMP responsive element binding proteins 1to 3 (CREB 1, 2, and 3) and neurotrophic tyrosinekinase receptor, type 2 (NTRK2) were found in lithium response (16).

Personalized medicine substitute classic evidence-based process with person based phenotypic and biological features. The individualized medicine concentrates on a patients' features. Personalized medicine applications in psychiatry focus on descriptive psychopathology and phenomenology via precise analysis and attention to each patient's impaired brain and mood processes. The precision medicine studies concentrate on response to lithium , main treatment of BD , frequent mood diseases , antidepressant resistant prediction ,risk and outcome assessment (17).

Lithium is a first- line therapeutic approach of BD. Commonly, lithium alone or with other drugs is applied in 60% of patients with a chronic disorder, the response to this therapy persist heterogenous. The determination of molecular and genetic markers can predict mood balance mediators response and drug side effects. Lithium is very attractive drug in Pharmacogenetic studies in spite of slightly known mechanism and the heterogenous phenotype response which

made it difficult to use as a strong biomarker. Genome-wide studies with profound phenotyping, in silico analyses and machine learning with pharmacogenomics investigations could apply individualized therapy to BD. Besides, pharmacogenetics and pharmacogenomics investigate the safety and efficacy of valproate and carbamazepine (18).

The onset of sever psychiatric conditions is in childhood or early youth.

The personalized psychiatry can be preventive worth. Phenotypic information and neuroimaging with Omics data develop precision diagnosis in high-risk population. The importance of microbiome on disease recurrences risks in BD.

However, ethical issues, stigma, autonomy, clinician expertise ,fairness, validity and cost benefit are important concepts in precision psychiatry (19).

The discovery of proper biomarkers for mental and psychiatric disorders is very important. Although using biomarkers for diagnosis, prognosis, evaluation of responses to treatment and preventing drug side effects of neurological and psychiatric diseases has not proper results. So, personalized medicine or individual patient treatments based on the patient genotype and specific phenotype help tailor therapy to patients (20, 21). The prevention

and effective treatment of BD are very interesting medical researchers due to chronicity, disability and morbidity of bipolar illness. Lithium has been an effective drug for the acute treatment and debarment of frequent mania/hypomania and depression for more than half a century , the mechanism of lithium function in modulation of affective behavior was slightly known and lead to having no proper mood stabilizers without side effects (22). However, advances in the discovery of new drugs for mania, could not suggest appropriate treatment for acute BD. The polygenic and heterogeneous of bipolar illness convergence with other neuropsychiatric diseases that leads to little information about its true pathobiology (23).

Precision medicine is a hopeful way to develop new treatments based on individual genetic features. Personalized medicine in psychiatric disorder is in the infancy phases, but promising approaches were developed for complex diseases treatment with human genome sequencing. Dexamethasone suppression test with high specificity (96%) and moderate sensitivity (50-65%) could prognosticate next episodes of depression and mania as well as response to drugs. Although, common characteristics of serious psychiatric diseases are modified activity of the hypothalamus–pituitary–adrenal (HPA) axis which makes these findings not used in personal medicine-based therapy (19). The dosage of drugs such as carbamazepine, atomoxetine, selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCAs) could be regulated based on genetic data. Likewise, Clinical Pharmacogenetics Implementation Consortium (CPIC) administrated proper dosage of psychiatric treatments by using CYP2D6 (atomoxetine) and/or CYP2C19 (SSRIs and TCAs) genotyping as well carbamazepine based on HLA genotypes (19).

Personalized medicine in psychiatric disorders particularly in bipolar is great with focuses on psychopathology onset, genetic and epigenetic background , bipolar types ,biomarkers and imaging can modulate treatment especially proper treatment based on targeted bipolar patients ,but can be understood only by considering the temporal dynamics of mental diseases (13).

CONCLUSIONS

In the present, personalized medicine is a new approach in psychiatry. There is a great prediction about this approach using ,in spite of challenging ,will finally provide the best ,conventional and tailored treatment for mental disorders patients.

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