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Methylome-Wide Association Studies of Psychiatric Disorders

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Abstract

Neuroepigenetics underscores the significance of the methylome in both normal and pathological brain function, influencing neurobiological processes and psychiatric well-being. This study systematically examines methylome-wide association studies (MWAS) across various psychiatric disorders that utilize array-based and sequencing approaches on blood or brain tissue samples. The findings provide valuable insights into the early stages of neuropathogenesis in psychiatric disorders, revealing altered epigenetic mechanisms. The methylome emerges as a pivotal factor in the development and treatment of psychiatric conditions, potentially offering avenues for identifying therapeutic targets and informing treatment strategies.

Keywords: *Methylome-Wide Association Study; Psychiatric Disorders; CpG Island; Microarray; Sequencing*

Introduction

Over the last decade, there has been significant advancement in our comprehension of the epigenome, with a particular focus on DNA methylation-a widespread modification occurring throughout the genome. DNA methylation, a conserved epigenetic modification, shapes the methylome, which represents all-encompassing changes in methylation across the genome. Its primary role lies in serving as a stable and heritable mechanism for silencing in heterochromatic and repetitive regions [1].

DNA methylation is crucial for mammalian gene regulation, genome stability, and development [1]. Neuroepigenetics highlights its role in normal and pathological brain function, with variability impacting neurobiological functioning, psychiatric well-being, and exhibiting cell-type specificity and dynamic changes in gene regulatory elements during various developmental stages [1]. Diverse modifications significantly influence brain development, function, and aging.

The focal point of research lies in the modifications of CpG sites within gene promoters, playing a pivotal role in gene regulation during mammalian development and diseases. CpG-SNPs, where CpGs are influenced by SNPs, showcase variations in methylation levels extending beyond sequence changes, potentially marking disease hotspots [2]. The cumulative alterations in DNA methylation across CpGs within genes may carry biological significance. Additionally, the less-explored realm of non-CpG DNA methylation at mCpHs (where H = A, T, or C) could also contribute to gene regulation, especially in neurons [3].

Roles of methylome in psychiatric diseases

Comprehending the intricate factors that contribute to psychiatric disorders, incorporating both genetic and non-genetic influences, is essential for unraveling their biological mechanisms and formulating effective preventive and therapeutic strategies. While disorders like autism spectrum disorder (ASD) have a robust genetic foundation, the increasing prevalence implies the role of environmental influences [4]. Conditions such as ASD and Attention-deficit/hyperactivity disorder (ADHD) often arise from complex genetics interacting with the perinatal environment, indicating an epigenetic influence [5]. The pathophysiological complexity emerges from shared genetic and environmental risk factors, propelled by intricate gene-environment interactions. These interactions result from the interplay between genetic predisposition and environmental impact, mediated through dynamic changes in the epigenome and transcriptome. DNA methylation, influenced by both genetic variation and the environment, serves as the foundation for heritable phenotypic diversity and disorders, potentially contributing to pathogenesis [6]. As the primary epigenetic mark, DNA methylation disrupts gene expression regulation during development and disease. Recent research on the brain DNA methylome has linked abnormal methylation to crucial gene expression irregularities in psychiatric diseases. Despite unveiling genetic risk loci, transcriptome-wide association studies (TWAS) often neglect essential DNA methylation and enhancer-promoter interactions central to psychiatric genetics. Methylome-wide association studies (MWAS) complement GWAS, revealing correlations with psychiatric disorders. The integration of DNA methylation and transcriptomics enhances our understanding of epigenetic changes and their implications.

Roles of methylome in treatment on psychiatric diseases

The limited understanding of underlying pathomechanisms impedes effective treatment for psychiatric disorders. Recent advancements highlight the significance of genetics, environment, and DNA methylation. However, a substantial proportion of patients, including 30 - 50% with major depressive disorder (MDD), fail to achieve remission with standard treatments [7]. For example, electroconvulsive therapy (ECT), a potent antidepressant for severe, treatment-resistant depression, is effective, but ECT remission rates barely exceed 50% in large-scale studies [7]. Recent research suggests that epigenetic mechanisms mediate treatment response, although investigations into ECT effects and DNA methylation predominantly employ candidate approaches. Methylome-wide association studies could deepen our understanding of the pathomechanism of treatment response.

Objectives of methylome-wide association studies (MWAS)

Ongoing methylome-wide studies on psychiatric disorders aim to elucidate the role of DNA methylation in mammalian development, tissue maturation, and its regulatory processes [1]. These studies investigate shared epigenetic risk factors, e.g. between schizophrenia and bipolar disorder [8], identify gender-specific differentially methylated regions in schizophrenia [9], and explore altered methylation patterns in relation to schizophrenia symptoms and early trauma [10]. Additionally, the studies seek to establish links between altered methylation and metabolic syndrome in schizophrenia patients on atypical antipsychotics [11], examine brain and blood methylation changes in major depressive disorder (MDD) [12], and identify significant MDD-associated methylation sites through methylome-wide association studies (MWAS) [13]. They aim to predict electroconvulsive therapy (ECT) response, understand its mechanism, and optimize long-term MDD treatment strategies using ECT response indicators [7,14]. Further investigations delve into smoking-related transcriptomic consequences through DNA methylation and transcriptomics analysis [15], assess the epigenetic impact of traumatic stress on post-traumatic stress disorder (PTSD) by studying genome-wide blood DNA methylation changes [16], and evaluate mCpHs

in the human postmortem orbital frontal cortex (OFC) in the context of opioid use disorder [3]. Additionally, the studies explore DNA methylation and transcription variations in neuropathologically defined groups, including controls, Alzheimer's disease (AD), pure dementia with Lewy bodies (DLB), DLB with concomitant AD (DLBAD), and Parkinson's disease dementia (PDD) [17]. They aim to identify novel DNA methylation biomarkers for Alzheimer's disease (AD) by analyzing blood DNA methylome profiles in Chinese patients with mild cognitive impairment (MCI) and AD [18].

Materials and Methods

Numerous studies have employed methylome-wide association studies (MWAS), an epigenetic research approach, to investigate the links between psychiatric disorders and DNA methylation patterns across the entire genome. MWAS analyzes CpG sites and other non-CpG epigenetic markers, elucidating the potential impact of DNA methylation on gene expression and biological processes. Researchers leverage MWAS to reveal epigenetic signatures, identify differentially methylated regions, and establish potential connections between epigenetic variations and psychiatric disorders or related traits. The studied psychiatric disorders and traits encompass schizophrenia, sex differences in schizophrenia, response to medications like risperidone or haloperidol in schizophrenia, bipolar disorder, major depressive disorder, response to electroconvulsive therapy (ECT) in depression, Alzheimer's disease, smoking, alcohol dependence, opioid use disorder, autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), and post-traumatic stress disorder (PTSD).

Materials - Blood/brain tissues

Psychiatric disorders, being brain-related conditions, necessitate the examination of optimal brain tissues/cells such as the BA10 cortex, hippocampus, OFC, neurons, and glia. However, the challenge of acquiring brain tissues often leads studies to resort to peripheral tissues as alternatives. These alternatives encompass whole blood samples containing granulocytes, T cells, B cells, and monocytes, along with whole cord blood, neonatal blood, placental tissue, and sperm samples. Acknowledging the cell-specific nature of methylation patterns, most studies delve into changes at the level of specific cell types. Encouragingly, many studies report robust correlations in methylation patterns across tissues, particularly between brain and blood samples [2,12,19-21].

Methods - Array/sequencing technologies

Two main methods, array-based and sequencing approaches, are utilized to profile genome-wide methylation alterations. Commonly employed arrays include (1) Agilent Human DNA Methylation Microarray, (2) Illumina HumanMethylation450K BeadChip, (3) Infinium Methylation EPIC BeadChip array, and (4) Illumina Infinium 850k array. The mouse genome contains approximately 22 million CpGs, while the human genome harbors around 28 million autosomal CpGs [19,21]. Methylation arrays often cover only a limited fraction of CpGs, lacking representation of the most variable structurally and epigenetically regions in the human genome.

Sequencing methodologies comprise: (1) whole-genome bisulfite sequencing for detecting genome-wide differentially methylated regions (DMRs); (2) methyl-CpG binding domain (MBD) protein capture followed by next-generation sequencing (MBD-seq) to identify common CpG-SNPs; and (3) reduced representation oxidative bisulfite sequencing for assessing mCpHs. Whole-genome sequencing provides nearly comprehensive coverage of all DNA methylation information across the genome.

Methods - Data/statistical analyses

The central analysis of MWAS involves comparing DNA methylation patterns between individuals with and without the condition of interest. MWAS data are frequently integrated with GWAS or transcriptome-wide data to uncover causal associations. Environmental factors, such as lifestyle choices (smoking, alcohol, exercise, diet), are taken into account as controls.

Subsequent analyses for disease-related methylation alterations encompass gene ontology analysis, pathway analysis, and Mendelian randomization (MR). These approaches contribute to a deeper understanding of potential causal effects within the intricate landscape of epigenetic modifications and their role in disease development.

Methods - Systematic review

A systematic literature search was conducted using the PubMed database to identify papers published up to October 2023, with the search terms "methylome[tiab]". The present study reviewed, extracted, summarized, and discussed the positive findings between methylation landscapes and psychiatric disorders.

Results

MWAS of schizophrenia

Methylome-wide association studies (MWAS) have identified thousands of differentially methylated regions (DMRs) associated with schizophrenia, and treatment induces substantial methylation changes [22]. These changes exhibit a remarkable 94% similarity between blood and brain tissues, surpassing the expected 46.2% overlap by chance ($p < 10^{-8}$) [2].

DMRs linked to schizophrenia primarily localize within gene promoters' 3'-UTRs and 5'-UTRs, displaying abnormal methylation patterns at transcription start sites, CpG islands (CGIs), adjacent regions, and CGI-sparse promoters [22]. Investigations reveal correlations between methylation markers and schizophrenia across various cell types, featuring significant associations in monocytes, natural killer cells, and B cells within whole blood ($p<5\times10^{-8}$) [23]. Research unveils the widespread distribution of DMRs across diverse genomic elements, notably introns, with pronounced enrichment for regulatory components such as enhancers and binding sites specific to transcription factors like Pol3 [6]. Certain intronic DMRs intersect with intragenic miRNAs, including hsa-mir-7-3, targeting differentially expressed genes in major psychosis, mediating changes in DNA methylation and gene expression [6]. These unconventional promoter methylation profiles highlight escalated epigenetic alterations in genes associated with psychiatric disorders and neurodevelopment.

MWAS integrates with genome-wide association studies (GWAS) or transcriptome-wide differential studies (TWDS) to discern differentially methylated genes related to schizophrenia. Differentially methylated CpG sites near genes SDCCAG8, CREB1, ATXN7, ENC1, IL1RAP, FAM63B, IR, TBC1D22A, and BDNF demonstrate replicability [24]. Numerous differentially methylated positions (DMPs) and regions (DMRs) associate with antipsychotic response [25]. The most noteworthy DMPs at CYP46A1, SPATS2, and ATP6V1E1, and the salient DMR on PTPRN2, linked to schizophrenia or antipsychotic response, may enrich synaptic function, neurotransmission, and transcriptional disparities [25]. Aberrant promoter methylation patterns can perturb gene transcription, with hypermethylation of promoter CGIs linked to gene repression and hypomethylation of CGI 3'-shores correlated with heightened gene expression [22].

MWAS of bipolar disorder

Methylome-wide association studies (MWAS) revealed numerous differentially methylated regions (DMRs) associated with bipolar disorder, primarily located within gene promoters' 3'-UTRs and 5'-UTRs [22]. These DMRs exhibit abnormal methylation patterns, including transcription start sites, CpG islands (CGIs), adjacent regions, and CGI-sparse promoters [22].

The integration of MWAS and transcriptome-wide gene expression data unveiled alterations in over 45 genes for bipolar disorder [26]. Hypermethylation of some promoter CGIs represses gene expression, while hypomethylation of CGI 3'-shores increases gene expression [22]. For instance, CpG sites in FAM63B and IR were significantly hypomethylated [8], whereas CpG sites in TBC1D22A were hypermethylated in bipolar disorder [8], distinguishing it from schizophrenia. Notably, genes MED1, HSPA1L, GTF2A1, and TAF15, enriched in the glucocorticoid receptor (GR) pathway, may be modulated by DNA methylation, potentially contributing to the reported role of stress response in bipolar disorder risk [26].

MWAS of depression

Widespread associations were identified between Polygenic Risk Scores (PRS) derived from genetic risk variants for depression and CpG methylation in genes associated with immune responses and neural development [13].

In a blood MWAS (with over 25,000 markers), multiple loci with p-values < 5×10^{-8} were detected for MDD [19]. Another MWAS involving 970,414 common CpG-SNPs revealed 27 suggestively significant ($p<10^{-5}$) associations of CpG-SNPs with MDD. Some loci overlapped between MWAS and GWAS, including genes such as ROBO2, ASIC2, and DCC [27].

Cell type-specific analyses on blood samples identified methylome-wide significant associations in T cells, monocytes, and whole blood between methylation and MDD, supporting findings from a previous methylation study on MDD. Significant methylation sites were located near genes implicated in p75 neurotrophin receptor/nerve growth factor signaling and innate immune toll-like receptor signaling in MDD. Results from neurons, glia, bulk brain, T cells, monocytes, and whole blood were enriched for genes supported by genome-wide association studies for MDD [12].

In an ECT response MWAS, differentially methylated CpG sites were identified, with the most prominent site in FKBP5 [14]. Another MWAS (involving 1,476,812 single CpG sites) revealed eight novel candidate genes for ECT response, including RNF175, RNF213, TBC1D14, TMC5, WSCD1, AC018685.2, AC098617.1, and CLCN3P1. Changes in methylation of two CpG sites at AQP10 and TRERF1 were observed during the treatment course [7].

Methylation changes also demonstrate a high degree of similarity between blood and brain (BA10) tissues in the MDD MWAS, encompassing eQTL signals, CpG islands and shores, exons, and active chromatin states like genic enhancers and active transcription start sites [19].

MWAS of Alzheimer's disease

MWAS unveiled significant alterations in the methylome profiles of blood leukocytes in MCI and AD, with 2,582 and 20,829 differentially methylated CpG sites in AD and MCI compared with cognitively healthy controls (CHCs) [18]. Among these, 441 differentially methylated positions (DMPs) overlapped in AD versus CHCs, MCI versus CHCs, and AD versus MCI. Notably, 6 and 5 DMPs were continuously hypermethylated and hypomethylated in MCI and AD, respectively, including FLNC cg20186636 and AFAP1 cg06758191. The overlapping genes were primarily associated with neurotransmitter-related processes, such as transport, GABAergic synaptic transmission, signal release from synapses, neurotransmitter secretion, the regulation of neurotransmitter levels, and responses to oxidative stress [17,18]. Tissue expression enrichment analysis identified potentially cerebral cortex-enriched genes associated with MCI and AD, including SYT7, SYN3, and KCNT1 [18].

The integration of methylation and GWAS results revealed six loci associated with AD [28]. Another MWAS identified 152 methylated sites corresponding to 113 genes epigenetically associated with AD [29]. Among these, 10 genes showed significant methylation changes in both brain-specific and blood-based analyses. Additionally, 22 and 79 methylation changes had group-specific associations with AD, respectively, suggesting a potential role for such epigenetic modifications in the heterogeneous nature of AD. Aberrant methylation patterns of promoters deregulate several genes fundamental to the development of neurodegenerative disorders, and common epigenetic signatures for some dementia-associated pathologies have been identified [30]. Furthermore, BRCA1 expression was significantly up-regulated in AD brains, consistent with its hypomethylation [31].

MWAS of substance dependence

An MWAS on alcohol dependence revealed significant overlap in methylation patterns between the brain and blood [21]. The top brain result was a CpG located in the intron of Ttc39b, while in blood, it was within Espnl [21]. Analyses implicated pathways associated with

inflammation and neuronal differentiation, including CXCR4, IL-7, and Wnt signaling [21]. Pathway analyses of the shared genes focused on MAPKinase signaling, a central player in both acute and chronic responses to alcohol, and glutamate receptor pathways known to regulate neuroplastic changes associated with addictive behavior [21]. Additionally, combining another MWAS with GWAS data on alcohol dependence identified a consistent methylation change in an intronic region of CNTN4 [32].

In opioid use disorder, one MWAS identified 2,352 differentially methylated genome-wide significant mCpHs, mapped to 2,081 genes [3]. Gene ontology (GO) analysis revealed enrichment in nervous system development, and KEGG analysis highlighted pathways related to axon guidance and glutamatergic synapses [3]. Drug interaction analysis identified 3,420 interactions with 15 opioid-related drugs, including lofexidine and tizanidine, used for treating opioid use disorder symptoms [3].

Another MWAS identified 10,381 differentially methylated CpGs due to tobacco smoke exposure, with 557 at DMRs overrepresented in regulatory regions, including enhancers [33]. Notably, one CpG in the promoter of SLC7A8 was replicated across two different array platforms [33]. In smokers, one MWAS identified two sets of genes, with 49 genes featuring hypomethylated CpG sites in their body region and 33 genes with hypomethylated CpG sites in their promoter region, which were differentially expressed [15].

MWAS of autism spectrum disorder (ASD)

Among the 134 ASD-associated DMRs in placental samples, a noteworthy cluster at 22q13.33 is a consistently replicated 118-kilobase hypomethylated segment. Within this genomic locus, NHIP, a nuclear peptide-encoding transcript with prominent expression in the brain, exhibits increased expression after neuronal differentiation or hypoxia but reduced levels in both ASD placenta and brain tissues. NHIP's overexpression is associated with heightened cellular proliferation and disruptions in gene expression related to synapses and neurogenesis. This substantial overlap with established ASD risk genes and NHIP-associated genes in the ASD brain underscores its relevance. Additionally, a common structural variant disrupting NHIP's proximity to a fetal brain enhancer correlates with NHIP expression, methylation levels, and ASD risk, providing compelling evidence for a shared genetic influence [5].

Gene ontology, functional, and pathway analyses of genes associated with ASD-related DMRs revealed enrichment in genes linked to neurological functions and neurodevelopmental processes affected in ASD. These identified genes also significantly overlap with known ASD risk genes [4].

MWAS of ADHD

Methylome-wide significant associations were detected for ODD and headstrong, implying a genetically influenced DNA methylation pattern. Overlap analysis revealed biological correlations among ODD, headstrong, and ADHD [34].

DNA methylation at birth distinguished ADHD trajectories across various genomic locations, encompassing SKI (involved in neural tube development), ZNF544 (previously associated with ADHD), ST3GAL3 (linked to intellectual disability), and PEX2 (related to peroxisomal processes). Nevertheless, none of these associations with ADHD persisted beyond age 7 [35].

MWAS of PTSD

In the initial cohort of male Dutch military servicemen, changes in DNA methylation at 17 genomic positions and 12 regions were significantly linked to PTSD symptoms during deployment to a combat zone. Evidence of mediation through longitudinal DNA methylation changes between combat trauma and PTSD symptoms was observed. Bioinformatic analyses revealed pathway enrichment relevant to PTSD symptoms. Subsequent targeted analyses in an independent cohort of male US marines replicated the association between decreased DNA methylation and PTSD symptoms at genomic regions in ZFP57, RNF39, and HIST1H2APS2 [16].

Discussion

Methylome-wide studies identify genes linked to schizophrenia susceptibility, potential methylation-based biomarkers for early detection. Findings hint at associations of DNA methylation with metabolic syndrome and sex in schizophrenia. Differential DNA methylation is associated with the pathophysiology of psychosis and early trauma. DMP- and DMR-overlapping genes related to antipsychotic response involve synaptic function and neurotransmitters, emphasizing DNA methylation's role. Hypomethylation in FAM63B and IR on chromosome 16 supports DNA methylation's involvement in antipsychotic response, serving as potential common epigenetic risk factors for schizophrenia and bipolar disorder.

Methylome-wide studies indicate consistent MDD-methylation associations in human brain and blood at a cell type-specific level. Methylated loci related to vital biological functions establish the causal effect of methylation on MDD, with variations associating with immune responses, shedding light on the immune-brain interaction in MDD susceptibility. Associations involve closely interconnected biological pathways, offering potential therapeutic targets. Additionally, findings identify epigenetic changes tied to ECT response and propose at least ten risk genes associated with either ECT response or its mechanism.

The findings indicate the usefulness of peripheral measures for identifying risk biomarkers within high-risk populations. They also underscore the potential involvement of stress and DNA methylation in the risk for bipolar disorder in youth.

Methylome-wide association studies suggest DNA integrity deterioration as a pivotal factor in AD pathogenesis. Potential biomarkers for MCI and AD are identified, emphasizing epigenetically dysregulated gene networks contributing to underlying pathological processes leading to cognitive impairment and AD progression. Compelling evidence implicates at least four genes (AIM2, C16orf80, DGUOK, and ST14) in AD pathogenesis, transcriptionally associated with the condition.

Maternal tobacco smoke exposure induces DNA methylation changes in cord blood, including a consistently responsive differentially methylated CpG in SLC7A8 across cord blood and adults. Smoking-related gene sets associated with processes like bone formation, metal ion transport, cell death, peptidyl-serine phosphorylation, and cerebral cortex development were uncovered, linking specific epigenetic-transcriptomic pathways to smoking-related conditions such as osteoporosis, atherosclerosis, and cognitive impairment. These alterations are correlated with maternal cigarette smoking's prenatal risk exposures.

The findings show methylation changes in both brain and blood following acute alcohol administration, suggesting the potential use of blood DNA methylation as biomarkers for alcohol use. The study also identified CNTN4 as a risk factor for regular alcohol use. Additionally, the findings indicate mCpHs' involvement in opioid use disorder within cortical neurons, revealing significant biological pathways and drug targets associated with the disorder.

The findings introduce a novel ASD risk gene responsive to the environment, providing insights into the epigenetic profile of ADHD symptoms. Emphasizing DNA methylation variability in genes associated with neurodevelopmental processes pivotal for cortical circuit maturation, a proposed mechanism suggests altered methylation of ASD risk genes introduces epigenetic modifications into the sperm methylome, potentially enabling transgenerational inheritance of ASD. Additionally, findings identify three new genomic regions where longitudinal decreases in DNA methylation during exposure to combat trauma indicate vulnerability to PTSD.

In summary, methylome-wide studies establish connections between DNA methylation and metabolic syndrome, sex, and identify genes associated with schizophrenia susceptibility. They also reveal the impact of maternal tobacco smoke and alcohol exposure on DNA methylation. Affective disorders underscore the role of stress and DNA methylation in youth risk, with depression studies implicating immune responses as potential targets. The link between opioid use disorder and mCpHs is identified, and ASD risk genes responsive to environmental factors are characterized. In Alzheimer's disease, the findings demonstrate DNA integrity deterioration, specific gene

involvement, biomarker potential, and epigenetic dysregulation contributing to cognitive impairment. The epigenetic landscape of ADHD highlights DNA methylation in neurodevelopment, and longitudinal changes indicate vulnerability to PTSD. DNA methylation alterations in genes related to synaptic function and neurotransmission are linked to antipsychotic response, supported by shared risk factors for schizophrenia and bipolar disorder. CpG-SNP methylation serves as biomarkers for environmental insults. These studies contribute to understanding relevant loci, suggesting the role of methylation in genetic associations and establishing a foundation for investigating psychiatric mechanisms. Methylome studies shed light on psychiatric mechanisms, revealing connections between blood and brain methylation, and showing that DNA methylation changes indirectly influence expression via miRNA, uncovering mechanisms in psychosis.

Significance

Methylome-wide association studies offer insights into the neuropathogenesis of psychiatric disorders by uncovering altered epigenetic mechanisms in their early stages. These findings improve our understanding of the pathophysiology of psychiatric diseases, potentially identifying therapeutic targets and guiding treatment decisions. This knowledge unravels the etiopathology and progression of psychiatric disorders, informing the design of effective therapies to address this global public health challenge. Moreover, DNA methylation signatures hold promise as biomarkers for future psychosis and treatment response.

Conclusion

Methylome-wide association studies (MWAS) have significantly advanced our understanding of the epigenetic mechanisms underlying psychiatric disorders. By analyzing DNA methylation patterns across the genome, MWAS reveal critical insights into the role of the methylome in disease pathogenesis and treatment responses. These studies underscore the importance of DNA methylation in gene regulation and highlight potential therapeutic targets. The integration of methylome data with genetic and transcriptomic information offers a comprehensive view of the epigenetic changes contributing to psychiatric conditions. This knowledge paves the way for the development of more effective, personalized therapeutic strategies, addressing the complex interplay between genetics, environment, and epigenetics in psychiatric disorders.

Authors Contribution

#Qiao Mao, Zhixiong Luo and Xiaoping Wang: These authors contributed equally.

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