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Hunting for molecules in schizophrenia through omics technologies

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Abstract

Schizophrenia is a complex mental disorder that affects 1% of the population worldwide with ~80% heritability rate. This mental disorder has dramatic impacts not only on the patients but also on the society as well. Unfortunately our knowledge about the molecular mechanisms underlying the disease is limited. To understand the pathological mechanisms that lead to disease phenotype we need to use genomics, transcriptomics, epigenomics, proteomics, metabolomics like approaches with newly developed technologies. These approaches will also help scientist to find out new diagnostic tools that can be used as biomarkers in a complex disease like schizophrenia or personalized therapy strategies. It is possible to map the molecular changings in disease and healthy state with the help of the OMICS based technologies. This review sheds light on these OMICS based approaches to hunt the biomarkers that can be used as diagnostic tools for schizophrenia and other mental disorders or to figure out the candidate molecules for new treatment options.

Keywords: Schizophrenia, OMICS, biomarker, genomics, proteomics, metabolomics

Introduction

Schizophrenia is complex and debilitating disorder with both positive and negative symptoms and cognitive disturbances as well [1]. It affects 1% of the worldwide population and it imposes domestic and global burden of morbidity and mortality [2]. This disorder has ~80% heritability rate and this shows the importance of genetics in the aetiology of the disease [1]. Eventhough several reports can be found on the databases related with the candidate molecules for schizophrenia, the molecular architecture of the disease can not be established well. The advancements in the technology that is used in research area open new doors for the scientist to understand more of the molecules and their interactions that are responsible for the disease phenotypes. It is not enough to find out the candidate molecules in complex disease, their interactions with other molecules and the consequences of these interactions should be understood well in order to get a molecular profile for the disease at the systems level. To understand these relations OMICS technologies are employed. Especially when we think about the etymology of the word OMICS which is derived from Sanskrit "OM" meaning completeness and fullness which fullfills the term OMICS well [3]. In the present review the efforts to find out candidate molecules for schizophrenia and interactions in different areas of OMICS are discussed.

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Genomics-Epigenomics

The neurobiology leading to schizophrenia is poorly understood and as a result of this there is no objective measurement or a lab test that supports clinical diagnosis. The research in the molecular genetics area has increased our understanding the mechanisms of schizophrenia in recent years and let us see more of the molecular architecture of the disease and find therapeutic targets.

The first study that focuses on the molecular markers of schizophrenia was published in Nature in 1988 [4]. In that 31 years we expanded our knowledge a lot with the advancements in the techniques. During that period many genome-wide association studies were performed and many genes were found to be candidates. But schizophrenia is a complex disease and there are no singular causal schizophrenia genes but many. So maybe it is the accumulation and interaction of the variants that leads to disease state [2]. So not only the genes and their interactions but also the epigenetic conditions are responsible for the pathology underlying the disease.

Genetic structure of complex disorders are characterized by

genome-wide association studies (GWAS). When a search is run for the keywords GWAS in schizophrenia more than 16000 published reports are found in the networks. The latest GWAS study published in this year in Nature Neuroscience reported that more than 100 schizophrenia loci have been identified. But still there is a big question mark on the biology of the disease. So by using multi-omics data and gene networks Wang et al tried to figure out the risk genes in GWAS loci [5]. With their method they predicted 104 network derived risk genes.

Here we only gave the examples of genomic marker studies for schizophrenia but as mentioned earlier there are thousands of GWAS or individual SNP studies to find the available biomarkers for schizophrenia including our group's reports [1,6]. In a large study which includes 36989 cases and 113075 individuals in 108 loci 128 common variants were reported to be accounting for a modest disease risk [7]. The genes involved were related with glutamatergic neurotransmission, synaptic plasticity, voltage gated calcium channels and dopamine receptor (DRD2).

On the other side application of epigenetic data for diagnosis is comparing to genomics is a new and promising area. The studies on that subject focusing on DNA methylation and histone modification patterns or from time to time on small non-coding RNAs. For each, different technological approaches like next generation sequencing (NGS), microarrays, ChIP-Chip/ChIP-Seq, qPCR, RNA Seq are used to analyze the difference between the healthy and the disease states [8].

Related with epigenomics in different studies more than one thousand differentially methylated regions were identified. Some of these regions were also overlapping with the genomics data as well [7, 9].

Still genomics and epigenomics based studies are the hot topics in mental disease research in order to find right type of biomarker for diagnosis and better treatment targets.

Transcriptomics

When molecular architecture studies are considered DNA data is not the only material that can be used, RNA and protein levels which is derived from that DNA should be taken into account as well. In the last decades transcriptomics and proteomics studies are taking leading roles in OMICS innovations in neuroscience.

Transcriptome can be defined as the full set of mRNA molecules expressed by an organism or it is also possible to define the term as mRNA transcripts produced in a particular cell or tissue type. Belgard et al stated that "understanding the concept of a transcriptome is key to understanding modern biology" [10]. We know that not all the RNAs are expressed in all cell types or not every gene is expressed at the same level, so the amounts are different in different cells in different times. So in transcriptomics studies gene activity of the biological system is tried to be solved, how the genes are expressed, in what conditions they are expressed and when they are expressed, in what conditions they are silenced are the questions that need to be answered.

One handicap of these transcriptomics research in mental disorders is to get the right type of tissue to analyze. So mainly blood transcriptomics is on the table or post mortem brain samples are also used in some of the studies. So inflammation related genes' or immune response related genes' expression profiles are examined mainly from blood samples. For example in a study done by Gardiner et al in 2013, 114 cases of schizophrenia or schizoaffective disorder vs 80 healthy controls were reported. Their results pointed 6 genes (EIF2C2, EVL, DEFA4, S100A12, PI3 and MEF2D) that showed validated expression changes. On the other side by using post mortem prefrontal cortex samples of 45 schizophrenia subjects vs 46 healthy controls, two genes (NOTCH 2 and MT1X) turned out to be associated with schizophrenia. Also in another study by Perez-Santiago et al the expressions of BAG3, C4B, EGR1, MT1X, NEUROD6, SST and S100A8 were found to be altered in schizophrenia. These results were from a meta analysis conducted on data from microarray studies of dorsolateral prefrontal cortex of 107 patients and 118 healthy individuals [9].

When RNA is taken into account we need to talk about small noncoding RNAs which take part in regulation of gene expression or gene silencing. In Pubmed there are 337 miRNA and schizophrenia papers are reported and in PubMed Central 3749 reports are found with the same keywords. So many miRNA target related with schizophrenia are shown as biomarkers for the disease and the researches are stilll going on [11].

Proteomics

As it is mentioned previously in the text it is not enough to work on DNA in order to figure out the molecular events in particular systems both RNA and proteins and other metabolic products should be characterized both in normal and disease states. If the proteins are the focus of research we need to talk about proteomics studies. As can be understood from the term proteomics it is the large scale analysis of proteins expressed in a given biological system [12]. The current research in the area is going on three main subejcts which are protein expression states both in qualitative and quantitative levels, posttranslational modifications and protein-protein interactions. The techniques that are used in the proteomics area are mainly Two Dimensional Gel Electrophoresis (2DGE) and Mass Spectrometry (MS) bu also yeast two hybrid studies are employed for interaction mappings or individual blotting studies are also used for proteins.

In the case neuroproteomics it is difficult to get the samples as much as needed. Most of the time just like the situation with mRNAs the sampling is done from post mortem tissue. This brings the ethical and technical concerns. Since the inaccesibility of the central nervous system tissue in order to find a way scientists use blood associated cellular and molecular markers in the diseases of brain. And for their convenience antibody based assays are used a lot for identifying the blood based biomarkers [13]. As an example for this type of research in schizophrenia and depression subjects BDNF levels turned out to be reduced. For another example to that our group's report in which we studied the levels of some inflammatory factors in patients with treatment resistant schizophrenia. In that study we checked the effect of electroconvulsive therapy on some inflammatory factors like IL-4, TGF-β, MPO and NF-κB and we have seen that the anti-inflammatory response such as the levels of IL-4 and TGF-β was increasing but this did not affect the levels of MPO and NF-κB activation [14].

Metabolomics

Metabolomics is the comprehensive analysis of metabolites in a biological specimen [15]. It is thought that disease, drugs, or toxins cause perturbations in the concentrations and fluxes of endogenous metabolites involved in key cellular pathways [16]. Previously small number of metabolites were used to diagnose complex metabolic diseases or certain monogenic diseases but current metabolomics technologies have the capability to test huge number of metabolites. So this gives us the ability to characterize the metabolite profile both in normal and disease states.

In literature there are several reports found to figure out metabolic signature of schizophrenia. In these studies comparison of healthy and patient subjects or pre-post treatment metabolic profiles are checked. In a study performed with 122 schizophrenia patients pre- and post treatment serum samples were analyzed and 14 water soluble metabolites were identified which include amino acids, carnitines, polar lipids and an organic acid. In that study it is revealed that the amino acids and lysophosphatidylcholines (LysoPC) were increased, on the contrary the four carnitines-oleoylcarnitine, L-palmitoylcarnitine, linoleyl carnitine, and L-acetylcarnitine- were decreased post-treatment [17]. A case control study from the same group showed that four amino acids and derivatives (cysteine, GABA, glutamine and sarcosine) were higher in patients comparing to healthy subjects on the opposite seven other amino acids and derivatives (arginine, L-ornithine, threonine, taurine, tryptophan, methylcysteine, and kynurenine) were lower in schizophrenia subjects [18]. Previous studies have also shown that abnormal lipid metabolism was also seen in schizophrenia patients. In the light of that Yang et al investigated the serum fatty acid patterns in 110 schizophrenia patients and 109 normal controls. In that study it is reported that monounsaturated fatty acids and ω-6 polyunsaturated fatty acids were significantly increased in schizophrenia patients [19]. It is possible to increase the examples to the metabolomics studies in schizophrenia and when one searches in PubMed there are 49 reports that are published from different parts of the world. They serve good information to point out new candidate biomarkers for schizophrenia. But of course these data should be evaluated with bioinformatic tools as well to interpret the right type of biomarkers for the diagnosis of mentioned disease.

Cellomics-Connectomics

It is known that nervous system has most significant cellular diversity [20]. How this diversity has an impact on the cause of mental disorders is a problem to be solved. To find a way out the cell types and their functions should be clarified in the first place. OMICS approaches are good tools to characterize these cells at the molecular level in detail. Each cell type has its own expression profile to do its normal function. But single cell profiling won't help us to understand the complex events that are happening in our brains, we need to understand how these diverse cells are communicating with each other and how this communication is disrupted in the case of disease. So cellomics and connectomics studies are aiming to understand the cellular and molecular architecture of the brain both in normal and in unhealthy states. Different imaging techniques are used to characterize the cells and their connections in brain networks. This is the new rising area of this branch of science with the help of the advancements in technology [20].

Discussion and Conclusion

Here the summary of the impact of OMICS technologies in mental disorders like schizophrenia is discussed. The data obtained from these types of studies unlock new information to understand more about the underlying mechanisms that leads to schizophrenia. OMICS derived markers will be helpful for the precise diagnosis of the disease, for preventive medicine and target new therapy strategies against certain molecules that are playing roles in the molecular pathology of the disease.

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