REVIEW ARTICLE

Potential gene targets for schizophrenia detection through molecular techniques: A review

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Singh N, Mishra DK., Bhange K, et al. Potential gene targets for schizophrenia detection through molecular techniques: A review. J Clin Psychiatry Neurosci. 2023;6(1), 75-8.

ABSTRACT

Schizophrenia is a chronic idiopathic neuropsychiatric illness. The exact cause of this disease is unknown but scientists believed that the environmental, genetic and societal factors are cumulatively responsible for Schizophrenia. Due to their polygenic architecture, there are several gene and their interaction is responsible for the development and progression of Schizophrenia such as *α-7 nicotinic receptor gene*, Tryptophan Hydroxylase (TPH) and *D2 Dopamine Receptor Gene* (DRD2) etc. The new gene targets have still been investigated through linkage statistics and Logarithmic Odd Ratios (LOD). The Molecular Techniques such as Reverse Transcriptase Polymerase Chain Reaction RT-PCR, quantitative PCR, Restriction Fragment Length Polymorphism are taking advantage over conventional methods in predicting the Schizophrenia disease. Moreover, nucleotide and protein Microarray, whole genome sequencing, DNA barcoding, Next generation sequencing are also trying to unfold the causes of Schizophrenia. The molecular techniques will open the door of preventative psychiatry.

Key Words: *Schizophrenia; Psychiatry; Molecular techniques; RT-PCR; Gene Targets*

INTRODUCTION

Schizophrenia is a chronic idiopathic neuropsychiatric illness which affects the patient's social and professional life [1]. The lifetime morbid risk of Schizophrenic patients is roughly 1% [2]. The disease is characterised by positive symptoms such as lack of insight, hallucinations, delusions, thought disorders, etc. and negative symptoms including demotivated and disorganized behaviour, reduced emotional behaviour, anhedonia etc. [3]. The processes driving the development, relapse, symptomatology, and management of Schizophrenia (SZ) have eluded researchers for many years [4]. Schizophrenia patients have anomalies in brain glutamatergic metabolism, mitochondrial metabolism and redox balance (NAD^+/NADH ratio) [5].

Schizophrenia is thought to be caused by a number of variables including genetic, environmental, and societal influences. Infact gene-environment interactions and epigenetic alterations may be a part of the overall risk, according to recent studies [6,7].The detail of these factors are shown in Table 1.

TABLE 1
Details of schizophrenia factors

Factors responsible for schizophrenia	Types	Reference
Environmental	Drug abuse, viral exposure	[3]
adverse gestational events	Perinatal hypoxia, maternal infection, obstetric complications	[8]
Genetic	Mutation in genes involved in neuron development	[9]
Societal atmosphere	Migration, persecution, isolation, urban life style physical abuse, ethnic minorities	[10] [11]

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Received: 20-January-2023, Manuscript No. PULJCPN-23-6073; Editor assigned: 23- January-2023, Pre QC No. PULJCPN-23-6073 (PQ); Reviewed: 24-January-2023, QC No.PULJCPN-23-6073(Q); Revised: 25-January-2023, Manuscript No.PULJCPN-23-6073(R); Published:10-February-2023, doi:10.37532/puljcpn.2023.6(1).75-8.

LITERATURE REVIEW

Genetic discernment of Schizophrenia

Two methods i.e. Linkage statistics and Logarithm of the Odds Ratio (LOD) score are popularly used to determine the gene involved in any disease [8]. Schizophrenia very rarely exhibits traditional Mendelian inheritance patterns and majority of schizophrenia cases are still sporadic in the general population. There are several hypothesis such as missense and nonsense mutation in *D5 dopamine receptor* gene play crucial role in the development of schizophrenia [9].Our knowledge of the molecular genetics of schizophrenia is rapidly evolving due to genome-wide research [10-13]. However, finding the genes and DNA markers for Schizophrenia is still a challenging task as multiple genes associated with this disorder and phenotype is only minimally impacted by each gene.

Linkage based molecular genetic studies suggested that there are various locus on chromosomes which can be utilized as DNA markers for detection of Schizophrenia (Table 2). For instance, The role of 22q11.2 deletion is found to be clinically relevant for Schizophrenia. Further, quantitative Reverse Transcriptase Polymerase Chain Reaction (RTPCR) and Western Blot analysis based data suggested that altered expression of CAP2 mRNA and *Cyclase-Associated Protein* 2 levels are also associated with Schizophrenia [14]. Moreover, mutation in genes involved in neuronal metabolism and brain development also play crucial role in the development of Schizophrenia. For instance, SETD1A, a histone methyl transferase gene is linked to the schizophrenia as its mutation leads to its loss of function which further reduced the neuronal development [15].

Though mutation of multiple genes are involved in the development and progression of Schizophrenia but not all population exhibit similar gene mutation. For example mutation in gene *NRG 1* is most prevalent in Icelandic and Scottish population [16]. Similarly, deletion mutation in *α-7 nicotinic receptor* gene is widely seen in US population as shown in Table 2.

TABLE 2
Described some important gene and their functions and mutation associated with schizophrenia disease

Location of gene	Gene associated	Type of mutation	Function	References
15q13–q15	*α-7 nicotinic receptor gene*	Deletion	neuronal death/survival and synaptic plasticity.	[9], [1],
11p15	*tryptophan hydroxylase (TPH) and*	Point mutation	TPH maintains the serotonergic functions by limiting biosynthesis of 5-HT	[9], [16]
11q23	*D2 dopamine receptor gene (DRD2)*		DRD2 participate in neuronal signaling and inhibits adenylyl cyclase activity	[9]
22q11	*catechol-O-methyl transferase (COMT)*	Deletion	metabolizing various catecholamine neurotransmitters, such as epinephrine and dopamine	[2]
8p22–p21	*neuregulin 1 (NRG1)*		participates in glutamatergic signaling by regulating the N-methyl-D-aspartate (NMDA) receptor	[3]
6p22.3	*dysbindin (DTNBP1)*		Neuronal development,	[7]

Conventional Vs molecular diagnostic tools

The conventional methods to evaluate Schizophrenia is Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT) and Magnetic Resonance (MR) Spectroscopy, Computed Tomography (CT). Some biochemical markers such as *C- Reactive protein* responsible for inflammation have also been correlated with schizophrenia [17]. The conventional methods are not only indefinite but also diagnose disease at very late stage. Apart from that the conventional methods are not predictive in nature. As we are gradually shifted in the direction of preventative psychiatry, it is essential to adopt more sensitive predictive diagnostic techniques. Molecular techniques such as multiplex immunoassay [18]. Polymerase Chain Reaction And Restriction Fragment Length Polymorphism (PCR–RFLP) methods [19], RT PCR and Western Blot methods are widely used to decipher specific mutation involved in Schizophrenia disease. PCR RFLP based methods are helpful in the detection of single nucleotide polymorphism. Further, RT PCR predict the gene expression of disease related genes through evaluation of m RNA levels [20]. Moreover, nucleotide and protein Microarray, whole genome sequencing, DNA barcoding, Next generation sequencing can also unfold the causes of schizophrenia [21-23]. The molecular techniques are able to detect Single Nucleotide Polymorphism (SNPs), Copy Number Variations (CNVs), upregulation and downregulation of gene expressions, tissue specific gene expression, epigenetics etc. There are several studies available where Schizophrenia have been associated with different genes and proteins on the basis of molecular techniques in Table 3.

TABLE 3
Schizophrenia association with different genes and proteins on the basis of molecular techniques

RT-PCR	RT-PCR	RT-PCR
Sequencing-based-typing (PCR-SBT)	major histocompatibility complex class I polypeptide-related sequence A (MICA) polymorphisms	[20]
direct sequencing of the promoter region	5' regulatory region of GABRB3 (gamma-aminobutyric acid type A receptor beta 3, subunit gene).	[21]
PCR–RFLP	DRD2 gene polymorphisms	[19]

Whole genome sequencing	Whole genome	[22]
RT PCR	*CAP2, DLG1* and *ADAM10* Genes	[13]
Western Blot	*CAP2, DLG1* and *ADAM10* protein	[13]
mRNA expression arrays	GSE93987 and GSE38485	[23]
Solexa sequencing, TaqMan Low Density Array and qRT-PCR	mi RNA	[24]
real-time PCR analysis	*catechol-O-methyltransferase* gene expression level	[25]
Q-RT-PCR	SNPs and CNVs of cell cycle related genes	[26]

The molecular methods are more specific and sensitive. Further, it opens the option for genetic counselling and preventive medicine [24]. However, the molecular techniques are expensive and required trained and expertise personal [25]. The gene targets have been investigated which could be potentially utilized for molecular diagnosis of Schizophrenia [26].

CONCLUSION

Since there is no primary preventive or cure for schizophrenia, and the basic pathophysiological mechanisms underlying it are still unclear. Therefore, understanding the Molecular genetics of schizophrenia can help the modern health system to diagnose the disease in its early phase. However, the diagnosis should be appropriately sensitive, specific and inexpensive. Research should also be navigating to find new genetic markers in order to prevent progression of this devastated mental disease. Such studies will surely open the path for prediction, counselling and potential therapeutic targets for Schizophrenia.

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