Paper 23

Genetics and Schizophrenia: A Comprehensive Clinical Analysis

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ABSTRACT

Purpose: *Genetics is a significant risk factor for schizophrenia. In the last decade, molecular genetics research has yielded groundbreaking results, fueling hope for uncovering the basic causes of schizophrenia. However, because of the complexity of the subject of study, it is nearly hard for non-geneticists (e.g., many physicians and researchers) to grasp and appreciate the genetic results and their limitations. This study tries to aid such comprehension by offering a brief summary of some of the most important methodologies and results in schizophrenia genetics, from its historical beginnings to its current state, as well as addressing some of the limits and issues that this field of research faces. In short, schizophrenia's genetic architecture has been shown to be very complex, diverse, and polygenic. Numerous common genetic variations with minor individual effects and uncommon, highly penetrant genetic variants with bigger effects make up the illness risk. Despite recent improvements in molecular genetics, we still have a limited understanding of the etiopathogenesis of schizophrenia and genotype-environment interactions. Our understanding of the molecular genetics of schizophrenia is quickly evolving thanks to genome-wide research. These research revealed rare copy number changes (mostly deletions) linked to schizophrenia, as well as frequent SNPs linked to schizophrenia alleles. But yet, it is necessary to combine all novel research findings with the existing results to get a more precise and comprehensive idea about genetics of schizophrenia. So the main purpose of this paper is to amalgamate the newest research findings with the existing information and spread this information in society to understand the biological roots of schizophrenia.*

Design/Methodology/Approach: *Secondary data and information have been used to build the paper. All the information and new research findings have been taken from authentic journals/websites. Systematic clinical analysis has been done to create the paper more understandable to common population. More than fifteen articles have been systematically and thoroughly interpreted to derive the findings.*

Findings/Result: *The findings suggest polygenic inheritance and genetic overlap between schizophrenia, autism, and bipolar illness. As further genetic discoveries are made, it is expected that the use of a variety of systems biology approaches will lead to the identification of molecular pathways implicated in the pathophysiologies of schizophrenia, as well as the development of new therapeutics.*

Originality and value: *A novel approach has been taken to make the clinicians and people those who are in the field of providing care for schizophrenic patients to understand the genetic vulnerability of schizophrenia in a simplest and at most scientific way. The contents have been prepared and arranged such a way that even people those who are not belongs to the field, but interested to know more about schizophrenia and its genetic predispositions can make use of this article to enhance their knowledge.*

Paper Type: *Educational/Interpretive paper*

Keywords: Genetics of schizophrenia, Pre-molecular genetics, Molecular Genetics, Genome-wide association study (GWAS), Familial study

1.INTRODUCTION :

The goal of this chapter is to give the reader an overview of schizophrenia genetics, including its history, the present state of various genetic results, new advancements (which have been many since our last review), and current and future difficulties [1]. Schizophrenia is a life-threatening mental condition with a lifetime frequency of 4.0 per 1,000 and a morbidity risk of 7.2 per 1,000 people [2]. The beginning of the disease is usually in adolescence or early adulthood [3], with onset beyond the fifth decade of life and in childhood being extremely unusual [4]. Despite the fact that males and females have equal rates of schizophrenia, the males' course is generally more severe and begins sooner [5].When comparing patients with schizophrenia to the general population, the standardized mortality ratio (SMR; ratio of observed deaths to expected deaths) for all-cause mortality is high [6].With excess deaths primarily from suicide during the early stages of the disorder and later from cardiovascular complications. Schizophrenia usually has a long-term course, with varying patterns and cognitive impairment. Psychosis is its characteristic, with positive symptoms like hallucinations and delusions commonly accompanied by negative (deficit) symptoms like decreased emotions, speech, and interest, as well as disorganization signs like altered syntax and behaviour. In many cases, severe mood symptoms, including manic and major depressive episodes, are present. There are no diagnostic laboratory tests for schizophrenia; instead, clinical observation and self-report are used to make the diagnosis. The relevance of genetic variables in schizophrenia has been reliably demonstrated in ongoing epidemiological studies over the last century employing the clinical phenotype, but with varying ascertainment and assessment methods.

2.RELATED WORKS:

Many approaches were introduced to rule out the genetic factors to manifest schizophrenia and many other psychological distresses. Due to the immense development in genetic science nowadays it is easy to understand the genes that are contributes to develop schizophrenia and other psychopathologies. A lot of monozygotic, dizygotic, and adopted child studies have been done in the hope that by analyzing genotype and phenotype causes to develop schizophrenia can be obtained. Among more than 98% of the studies emphasized the strong relationship between genetic vulnerability and the development of schizophrenia. Rest of the studies upholds the view that only genetic components does not exert power to develop schizophrenia but the combination of some other factors also affects to develop the disease.

Recent molecular brain imaging studies have combined genetic analysis with multimodal neuroimaging to better understand the pathophysiological architecture of the illness [7]. Early-onset disturbance in the temporolimbic-prefrontal brain networks is hypothesised to be connected to schizophrenia [8]. In the nervous system, contingency alleles covering multiple genes across the 10q24.32 schizophrenia-related locus are linked to increased articulation of both BORCS7 and a previously uncharacterized, human-specific arsenite methyltransferase (AS3MT) isoform (AS3MT (d2d3)), which lacks arsenite methyltransferase activity and is more abundant in people with schizophrenia than BORCS7 and AS3MT(d2d3) signals [9]. Adult human neurons and astrocytes express both AS3MT (d2d3) and BORCS7, and their expression is increased during neuronal differentiation in human stem cells [10]. The VNTR genotype predicts promoter activity and DNA methylation inside the AS3MT gene in luciferase experiments [11]. Table 1 contains some data pertaining to this relevant topic area.

Table 1: Review of journals/articles deals with the topic genetics and its connection to develop schizophrenia.

S. No.	Title of the paper	Focus area/Findings	Reference
1	*"Molecular brain imaging and the neurobiology and genetics of schizophrenia"*	Schizophrenia is thought to be linked to early-onset disruption in the temporolimbic-prefrontal neural networks. Prefrontal dysfunction and elevation of presynaptic striatal DA activity have been linked to schizophrenia, according to brain imaging studies. Recent molecular brain imaging investigations have merged genetic analyses with multimodal neuroimaging to improve our understanding of the disorder's pathophysiological architecture.	Heinz A, Romero B, et al. (2003). [12]
2	*"The effect of a genetic variant at the*	The [18F]-DOPA PET scans were used to assess striatal dopamine production capability and the SNP	D'Ambrosio E, et al. (2019).

	schizophrenia associated AS3MT/BORCS7 locus on striatal dopamine function: A PET imaging study"	rs7085104 was genotyped. A strong link has been discovered between the rs7085104 genotype and striatal Kicer. The findings suggest that altered dopaminergic activity may be involved in the process mediating the 10q24.32 risk locus for schizophrenia. Future research is needed to determine the neurological process involved in this link.	[13]
3	*"A human-specific AS3MT isoform and BORCS7 are molecular risk factors in the 10q24.32 schizophrenia-associated locus"*	In the human brain, risk alleles spanning multiple genes across the 10q24.32 schizophrenia-related locus are associated with an increase in the expression of both BLOC-1 related complex subunit 7 (BORCS7) and a previously uncharacterized, human-specific arsenite methyltransferase (AS3MT) isoform (AS3MT(d2d3)), which lacks arsenite methyltransferase activity and is more abundant in people with schizophrenia than in BORCS7 and AS3MT(d2d3) signals appear to be mostly independent, according to conditional expression analyses. In both Caucasians and African Americans, GWAS risk SNPs in this area are connected to a variable number tandem repeat (VNTR) polymorphism in the first exon of AS3MT that is associated with the expression of AS3MT(d2d3). In luciferase tests, the VNTR genotype predicts promoter activity, as well as DNA methylation inside the AS3MT gene. Both AS3MT (d2d3) and BORCS7 are expressed in adult human neurons and astrocytes, and their expression is elevated during neuronal differentiation in human stem cells. Our findings reveal a mechanistic basis for the well-known 10q24.32 locus connection, which includes an unique and evolutionarily recent protein involved in early brain development and associated with psychiatric disorder risk.	Li M, et al. (2016). [14]
4	*"Cellular Models in Schizophrenia Research"*	Numerous loci have been discovered in schizophrenia genome-wide association studies (GWAS), however they do not directly identify mechanisms that are disrupted in the condition. As a result, in the post-GWAS age, the creation of cellular models harboring SZ-associated variants has become a priority. The use of cutting-edge CRISPR/Cas9 gene-editing techniques, as well as newly discovered technology for developing brain organoids in vitro, has opened up new avenues for the development of these models. Cellular models, in general, are used to investigate specific biological processes. They can fill in the gaps between findings from pathomorphological, electrophysiological, and behavioral research and schizophrenia-related phenotypic traits (like as transcriptional dysregulation, oxidative stress, and synaptic dysregulation).	Abashkin DA, et al. (2021).[15]
5	*"Expression of ZNF804A in human brain and alterations in*	ZNF804AE3E4 (ZNF804AE3E4), a truncated ZNF804A transcript with missing exons 1 and 2 and projected to produce a protein lacking the zinc finger	Tao R, Cousijn H, et al. (2014).

	schizophrenia, bipolar disorder, and major depressive disorder: a novel transcript fetally regulated by the psychosis risk variant rs1344706"	domain, was shown to be abundant and developmentally regulated. In the embryonic brain, rs1344706 impacted the expression of ZNF804AE3E4 mRNA. ZNF804AE3E4, a new splice variation, is influenced by rs1344706. Only the foetal brain and this isoform are affected. It might be a component of the process via which ZNF804A allelic variation influences psychosis risk. ZNF804A is translated in the human brain, where it may have activities other than that of a transcription factor.	[16]

Source: Compiled by the author.

3.OBJECTIVES:

This article is prepared to through light in the area of schizophrenia and its genetic vulnerability. It studies the genetic variables and non genetic variables which cause to produce schizophrenia and other psychological illness. The main objectives of this article are:

(1) To analyze the genetic variables that causes to manifest schizophrenia
(2) To understand some specific genes that are related with schizophrenia and other psychological illness
(3) To analyze whether schizophrenia is purely genetic or not
(4) To estimate non genetic factors

4.METHODOLOGY:

This paper is based in the secondary clinical data which have been published from various parts of the whole globe. Systematic clinical analysis has been done in each and every paper to make the content more precise and understandable. In order to obtain clinical data, we have relied on multiple scientific and authorized journals and various websites.

5. GENETIC TRANSMISSION MODELS:

Mental illness (along with many other human diseases and qualities) has long been known to run in families. Following Mendel's discovery of the principles of monogenic transmission of phenotypic characteristics, several of the first authors to describe schizophrenia thought that the disease or its milder variations had a hereditary foundation of risk [17]. The monogenic model of schizophrenia was appealing for several reasons, including its simplicity, the possibility of uncovering a related, simple pathophysiological mechanism, and the fact that it fit into existing theoretical choices (i.e., recessive, dominant, with varying penetrance). However, because the purely monogenic hypothesis did not suit the empirical facts, it was swiftly abandoned. Nonetheless, until recently, the concept that one or a few unique genes were etiologically required but not sufficient for the onset of schizophrenia persisted. For example, believed in a monogenic essential gene whose activity was influenced by polygenic circumstances [18]. Holzman suggested the "latent trait hypothesis," in which a dominant gene causes a latent trait, a hypothetical neurological deficiency with pleiotropic symptoms (schizophrenia, schizotypy and eye-movement disorder) [19]. Risch and Baron proposed the "mixed model," suggesting that the genetic substrate was produced by a single gene, a few oligogenes, and a polygenic-multifactorial background [20]. All of these models have been attempted to match the known epidemiological data on schizophrenia, with varied degrees of success. It's worth noting that Gottesman and Shields offered a polygenic explanation for schizophrenia in this setting [21]. As we'll see, molecular genetics research shows that schizophrenia is best explained by a complicated, polygenic model.

6. PRE MOLECULAR GENETICS AND ITS LINK WITH SCHIZOPHRENIA:

All of these models have been attempted to suit the avalanche with varied degrees of success. Family studies in the early part of the twentieth century revealed that relatives of patients with schizophrenia had a greater prevalence of schizophrenia than the general population [22], [23], [24] [25]. Monozygotic (MZ) twins had a higher concordance rate (both twins suffering from schizophrenia) than dizygotic (DZ) twins, according to twin studies [26], [27], [28]. These early twin studies were subsequently chastised for a variety of methodological flaws [29], [30]. Improved twin [31], [32] and adoption studies investigations were more important in evaluating the family clustering and concordance rates for schizophrenia starting in the 1960s [33], [34], [35], [36]. The results helped to debunk the psychoanalytical model of schizophrenic causation, which claimed that schizophrenogenic upbringing was either a

necessary or sufficient reason for developing schizophrenia, by revealing a major genetic component in the genesis of the condition. The underlying premise of the twin research is that while MZ twins (who share 100% of their genes) and DZ twins (who share 50% of their genes) share the same environment, higher concordance rates in MZ twins over DZ twins are most likely due to genetic similarities. According to estimates based on European twin studies from 1963 to 1987, MZ twins have a higher concordance rate (48%) than DZ twins (17%), and similar concordance rates were reported in European and Japanese twin studies from 1992 to 1999—41 percent –65 percent for MZ vs. 0 percent –28 percent for DZ twins [37]. According to a meta-analysis of twin studies, genetic vulnerability to schizophrenia is 81 percent (95 percent CI, 73 percent –90 percent), whereas shared environmental effects are 11 percent (95 percent CI, 3 percent –19 percent) [38]. Finally, a few studies of children of discordant MZ twins found a similar risk of schizophrenia spectrum disorders in the affected and unaffected MZ twins, implying that unaffected MZ twins carry silent (non-expressed) schizophrenia susceptibility genes. In the case of discordant DZ twins, however, the risk was larger in the afflicted DZ twin's offspring than in the unaffected DZ twin's children [39], [40].

Schizophrenia spectrum illnesses are more common in adopted-away children of mothers with schizophrenia than in their control adoptees, according to adoption research [41], [42]. Children of healthy parents who were adopted by a household where one of the parents subsequently had schizophrenia did not have an elevated risk of getting schizophrenia, according to a cross-fostering research. Other research indicated that children of women with schizophrenia had the same chance of getting the condition whether they were reared by their original moms or adoptive parents who had no history of mental illness [43], [44]. In a Finnish adoption study, it was discovered that severely dysfunctional rearing environments (adoptive families were assessed and classified on a scale ranging from "1. healthy" to "5. Severely disturbed") predicted schizophrenia spectrum disorders in adopted-away children of mothers with schizophrenia, but not in their genetically undisposed controls [45]. Interestingly, the Danish High-Risk research identified an elevated risk of schizophrenia among children of mothers with schizophrenia that were exposed to unstable parenting or reared in public childcare institutions [46], [47], [48].

7. OVERVIEW ON MOLECULAR GENETICS OF SCHIZOPHRENIA:

In molecular genetic studies on schizophrenia, the Human Genome Project, it was crucial. The Human Genome Project was an international scientific project aimed at determining the sequence of the three billion base pairs that make up the human genome and mapping all of its genes. Some experts, though definitely not all, anticipated that the availability of DNA would disclose the biological origins of the condition within a very short amount of time during the dawn of molecular genetics in the early 1980s as twin and adoption studies jointly showed [49]. The first DNA-based approach was "linkage analysis," which intended to find genomic areas in samples from afflicted extended or nuclear families, as well as sibling pairings, without pointing to a specific allelic mutation. Estimates of linkage between the disease and genomic loci were determined by analyzing the degree of co-segregation of genetic markers and established phenotypic features (schizophrenia spectrum diagnosis). Linkage analysis is based on the finding that genetic markers that are physically near together on the same chromosome are more likely to be inherited together, i.e. they remain "linked" during meiosis. Numerous schizophrenia linkage studies have been carried out, however good results have often proven difficult to duplicate in future investigations [50]. In summary, meta-analyses reveal that schizophrenia susceptibility loci may be found in numerous chromosomal regions [51], [52], [53]. These loci may not carry risk in and of themselves, but they may harbor variations that do. These findings also demonstrated that the linkage design's power was insufficient to address genomic loci with minor effects; the sample size required to identify linkage was simply unattainable [54]. As a result, alternative DNA-based methodologies were needed to pinpoint the genes that might be implicated in the etiology of schizophrenia. The "candidate gene" strategy was used in the following wave of molecular genetics research in schizophrenia, which used a case-control study design to see if putative susceptibility genes were linked to the condition. The candidate gene technique, unlike linkage analysis, can discover genes with minor impact alleles if the sample size is large enough. Candidate genes are generally chosen based on their location or functioning (genes coding strategies in proteins related to dopamine/serotonin neurotransmission). Despite the discovery of certain genes with minor impact alleles the general findings of candidate gene research have been unsatisfactory [55], [56]. DISC1, DTNBP1, NRG1, and COMT are some of the most commonly mentioned candidate genes; however their possible pathogenetic role in schizophrenia is still being contested. The lack of important discoveries might be due to a variety of factors, including difficulty in repeating favorable findings, statistical power limitations, and a lack of understanding of the genes thought to be implicated in the pathophysiology of schizophrenia (that noticeably makes it complicated to select significant candidate genes for testing).

In disparity to the hypothesis, driven by candidate gene approach, which can merely test only some genetic markers in delimited genomic loci in each revise, genome-wide association studies (GWAS), which often use a case-control study design, look for associations between common genomic variants or loci and the disorder purely empirically. The International Hap-Map Project and the 1000 Genomes Project have made it promising to identify and map millions of common single nucleotide polymorphisms (SNPs), which have aided the GWAS technique. Linkage disequilibrium, or a non-random connection of alleles at two or more loci, provides the basis for GWAS. Recent technology breakthroughs, such as microarrays and chips, have made it feasible to scan a million SNPs across the genome swiftly and cheaply. The GWAS technique is based on the idea that if particular allele variations are discovered more often in patients than in controls, the allele variants might indicate a genetic link. Most GWAS use a strict threshold of significance to reduce the probability of Type I errors (means, false positives errors). GWAS for schizophrenia have been reported since past few decades. Overall, the studies have failed to support the findings from linkage and candidate gene studies, but the GWAS have identified a large number of new susceptibility loci with only minor individual effects-and many of these genomic loci have been replicated in subsequent GWAS and have reached meta-analytic genome-wide significance [57], [58]. The GWAS technique is based on the idea that if certain allele variations are discovered more often in patients than in their controls, then the allele variant is more important. One seminal study successfully identified 128 independent schizophrenia associations, spanning 108 risk loci of genome-wide significance, 83 of which were novel findings, by combining available schizophrenia GWAS samples into a single analysis. The dopamine receptor D2, many genes involved in glutamatergic neurotransmission and synaptic plasticity, and tissues with central immune activities, for example, all showed relationships. These findings, according to the authors, give some genetic evidence for the theorized linkages between schizophrenia and dopamine and immunological deregulation.

8. GENOME-WIDE ASSOCIATION STUDY (GWAS) AND HISTOCOMPATIBILITY:

The rationale behind the GWAS advance is that if explicit allele variants are found more repeatedly in patients than in controls, then the allele one seminal study found that if specific allele variants are found more frequently in patients than in controls, then the allele is active. One seminal study found that if unambiguous allele variants are furthermore associated between schizophrenia and genetic markers have been discovered throughout the extended. Major Histocompatibility Complex (MHC) locus on chromosome 6 (25–34 Mb), implicating the MHC locus as the most powerful of the >100 genome-wide significance [59], [60], [61]. The MHC locus is known to have genes that operate in the immune system, and attempts to relate it to schizophrenia date back to the decade [62]. The GWAS technique is based on the idea that if certain allele variations are discovered more often in patients than in controls, the allele variants are more likely to be associated with disease. The Schizophrenia Working Group of the Psychiatric Research Society published a landmark that paved the way. According to a recent research numerous common, structurally different alleles of complement component 4 (C4) impact the expression of C4A and C4B in the brain and are related with schizophrenia in proportion to their effect on C4A expression [63]. Finally, several GWAS have discovered shared genetic risk loci in schizophrenia and bipolar; these findings are discussed [64], [65], [66], [67].

The "common-disease common-variations" concept, which claims that schizophrenia is mostly caused by common genetic variants, is the basis for GWAS (SNPs). Large-scale GWAS researches have revealed more than hundred risk loci, as we've shown.

However, it is worth noting that a landmark research indicated that a significant polygenic component of schizophrenia risk is present in hundreds of common alleles with just a little effect that do not reach significance individually [68]. As sample sizes rise, the prediction accuracy of polygenic risk scores is anticipated to improve much more [69]. Despite this, there is a growing recognition that common variations only account for a small percentage of the heritability of schizophrenia, which refers to the amount of variance across people that can be explained by genetic variables. Individually, most of these frequent alleles impose fairly minor risk but they have been projected to account for between a quarter and half of the diversity in genetic liability when added together [70]. In other words, common genetic variations appear to account for just a part of the variation in genetic risk. The "common-disease rare-variants" hypothesis indicates that exceedingly penetrant, atypical genetic variants, such as copy number variations (CNVs), solitary nucleotide variants (SNVs), and small insertions and deletions (indels), contribute to the genetic component of schizophrenia [71].

To begin with, there is now solid confirmation that uncommon, de novo or hereditary CNVs, means, structural genomic abnormalities that largely consist of duplication or deletion, are associated with a high risk of schizophrenia. CNVs can be one kilobase (kb) or quite a lot of megabase (Mb) pairs in size. In comparison to controls, people with schizophrenia had higher amounts of uncommon CNVs, according to several studies. For

example, there have been strong links discovered linking schizophrenia and uncommon, substantial CNVs, such as deletions on chromosomes like 1q21.1, 3q29, 15q13.3, and 22q11.2, and particularly, duplications on chromosomes such as 16p11.2 and 16p13.11- the odds ratios for these CNVs vary from 2 to 60 [72]. Furthermore, NRXN1 deletions have been strongly associated to schizophrenia [73].

Next, exome sequencing, a scheme that identifies DNA variations inside the 1% protein-coding sections or genes of the genome, has enabled single-base resolution scans of genes for mutations those were previously undetectable, such as SNVs and indels. Exome sequencing is justified by the fact that mutations in these sequences are more likely to have serious repercussions than differences in the remaining ninety nine percent of the genome. Exome sequencing has now been utilized in several researches to investigate SNVs and indwells in schizophrenia. Some studies have found that individuals with schizophrenia had a little higher exome-wide level of uncommon and/or de novo SNVs than controls, although this finding has not been reproduced in bigger investigation [74]. De novo SNVs and indels were found to be significantly enriched in glutamatergic postsynaptic proteins, including the ARC (activity-regulated cytoskeleton-associated protein) and N-methyl-D-aspartate receptor (NMDAR) postsynaptic protein complexes, which have previously been linked to schizophrenia in CNV studies by [75], [76]. Finally, it has been used to exome sequencing to investigate rare SNVs and indwells in schizophrenia and discovered a polygenic burden of very odd disruptive variants spread across many genes in a set of 2546 genes previously implicated in schizophrenia by GWAS, CNV, and de novo SNV studied [77], [78].

9. FINDINGS:

In conclusion, pre-molecular and molecular genetics research studies have proven beyond a shadow of a doubt that genetics is a significant risk factor for schizophrenia. In contrast to the preliminary monogenic and oligogenic models of genetic diffusion, there is now compelling support that the genetic architecture of schizophrenia is very complex, heterogeneous, and polygenic-the disease risk is constituted by plentiful common genetic variants with only minor individual effects and rare, highly penetrant genetic variants with larger effects.

10. CONCLUSIONS:

Genetics is a substantial risk factor for schizophrenia, according to pre-molecular and molecular genetics research. Many of the findings from schizophrenia genome-wide association studies have been reproduced, and some of them have gained meta-analytic genome-wide significance. On a variety of levels, the strong connections between schizophrenia and the >100 susceptibility loci, the discovered CNVs and SNVs, appear promising. Furthermore, the relevance of the hundreds of common alleles with just a minor impact, which do not individually attain significance but collectively comprise a significant polygenic component of schizophrenia risk, should not be overlooked. These findings should, hopefully, pave the path for really unique, practical therapeutic information. However, we should not overlook the following points: I associations between common (SNPs) or uncommon (CNVs, SNVs) genetic variants and schizophrenia are statistical facts, not necessarily indexes of causal pathways; and (ii) many of the discovered associations are non-specific to schizophrenia, but rather indicate a genetic vulnerability to a variety of mental disorders. Overall, the intricacies of schizophrenia's etiopathogenesis and genotype environment interplay are still largely unknown, thus care is still advised when making judgments regarding the amount of the genetic contribution to the disorder's etiology.

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