www.mednet.gr/archives
ARCHIVES OF HELLENIC MEDICINE: ISSN 11-05-3992

REVIEW
ΑΝΑΣΚΟΠΗΣΗ

Schizophrenia
Genetic profiling and association to depressive and immune disorders and environmental factors

ARCHIVES OF HELLENIC MEDICINE 2026, 43(1):10–17
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2026, 43(1):10–17

D. Ioannou,
D. Kavvadas,
T. Papamitsou

"Histologistas" Research Group, Faculty of Health Sciences, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece

Schizophrenia is an intricate mental disorder characterized by severely impaired thinking, delusional thoughts, hallucinations and poor emotional responsiveness, and typically arises in late adolescence or early adulthood. Although the cause of this disorder cannot be determined yet, the genetic background is not completely unclear. Provided that there are no distinct pathology or diagnostic standards for schizophrenia, it is challenging to link gene mutations to specific physiological or biochemical alterations linked to the illness. However, plenty of genes are clearly linked to schizophrenia. The disorder seems to have a similar genetic background with depressive disorders, since a gene overlap is observed, and with immune disorders, as well. Epidemiological evidence shows that there is an increased incidence of immune disorders to people suffering from schizophrenia and to their relatives. Finally, schizophrenia is, also, related to environmental factors, smoking and substance use; alcohol and drugs.

Σχιζοφρένεια: Γενετικό προφίλ και σύνδεση με καταθλιπτικές διαταραχές και διαταραχές του ανοσοποιητικού, καθώς και περιβαλλοντικούς παράγοντες

Περίληψη στο τέλος του άρθρου

Key words

Depressive
Genetics
Immune
Schizophrenia
Smoking
Substances

Submitted 4.10.2024
Accepted 19.10.2024

1. INTRODUCTION

Schizophrenia (SCZ) is identified as a neurodevelopmental disorder, which includes disability of growth and development of the brain, and is frequently linked to cognitive, neurological, or psychiatric dysfunction. "Neurodevelopmental disorder" is a general term that can encompass a wide range of disease classifications, such as bipolar disorder (BP), autism, SCZ, intellectual disability (ID), developmental delay (DD), etc. to different degrees.[1]

SCZ is an intricate mental disorder, the severe symptoms of which include delusional thoughts, hallucinations, severely impaired thinking, and poor emotional responsiveness,[2] and that typically arises in late adolescence or early adulthood.[3] It is estimated that 1% of people globally suffer from SCZ, this invalidating mental illness.[4] SCZ affects males 1.4 times more than females,[5] but in a different age of onset; 20–28 years for the firsts and 26–32 for the second ones.[6] Both genetic and environmental factors affect the risk of developing schizophrenia,[4] which involves both developmental and degenerative features.[7] SCZ seems to be among the top ten global causes of long-term disability, characterized by a complex set of symptoms including hallucinations, delusions, restlessness, apathy, alogia, and cognitive impairment.[8]

As far as the cause of the disorder is concerned, the etiology of SCZ has not been identified yet, despite the large number of investigations on the biological foundations of the disorder.[9] However, the increased risk of developing SCZ is confirmed for susceptible people exposed to certain environmental factors;[4] hence, the age at illness onset in SCZ is influenced by a combination of both genetic and environmental factors. Additionally, the variety of SCZ symptoms and outcomes seen can be explained by the amalgamation of genetic and environmental backgrounds in the vascular-inflammatory theory of SCZ.[8]

An elevated genetic susceptibility to schizophrenia has been linked to an early age at illness onset, which has

been considered a key risk factor for SCZ.[10] Research has also shown that a course of illness, a positive family history of psychosis, and a higher risk of illness in siblings are associated with an early age at illness onset.[11] The aforementioned risk differentiates between males and females, being consistently proved raised for males[12] and concerning the mean age at onset, being later for females, despite the equal peak age at onset for both sexes.[13] Additionally, SCZ is hereditary to a remarkable extent; the heritability of SCZ is around 60 to 80%.[14,15] This explains the risk of suffering from SCZ between relatives of those with SCZ and differs according to the relation among them, as well (tab. 1).[16]

2. GENETICS BEHIND SCHIZOPHRENIA

Linking gene mutations to specific physiological or biochemical alterations related to SCZ seen to be challenging provided the absence of distinct pathologies or diagnostic standards.[1] Consequently, the genetic architecture is intricate, with thousands of independent common genetic variants accounting for between 23% and 50% of the variance.[17,18] This suggests a polygenic model in which a variety of genetic variants affect the risk of the disease.[17,19]

Research has consistently proved the relation between SCZ and several genes including: genes of the major histocompatibility complex (MHC) region on chromosome 6p21.3–22.1,[20–23] the zinc finger protein gene *ZNF804A* on chromosome 2q32.1,[24] neuregulin1 (*NRG1*) on chromosome 8,[22] and transcription factor 4 (*TCF4*) on chromosome 18q21.1.[22,25] Other genes that influence SCZ are the following: a negative regulator of the Wnt signaling pathway (NRX1),[26] a potassium channel (KCNH2),[27] and many other brain-expressed proteins, such as dysbindin.[28] Additionally, the most researched candidate genes are *GRIN1, GPM6A, SEPTIN4, TPH1, TPH2, CACNA1C, CACNB2*, and *BCL9*,[30] and three of the best-supported regions are 6p24–22, 1q21–22, and 13q32–34, where individual studies have attained genome-wide significance.[32] Some genomic "hotspots" in sizable patient cohorts with the disease carry multiple structural variants that are strongly related to the illness. For instance, when comparing SCZ patients to controls, deletions at four different loci (1q21.1,[33] 15q11.2, 15q13.3,[34] and 22q11.12[35]) show a significant over-presentation.

Table 1. Risk of relatives of those with schizophrenia.

Relation	Risk (%)
Identical twins	57.70
Parents	4.40
Brothers and sisters	8.50
Children	8.20
Uncles and aunts (second-degree relatives)	2.00
Nephews and nieces (second-degree relatives)	2.20
Grandchildren	2.80
Half-brothers and sisters	3.20
Third-degree relatives (first cousin)	2.90
Risk of offspring of 0–2 schizophrenic parents	
Neither parents schizophrenic	8.20
One parent schizophrenic	13.80
Both parents schizophrenic	36.60
General population	0.86

Figure 1 depicts the links between the genes as mentioned above, not only concerning SCZ but also in different other symptoms.[36]

Pertaining to the etiopathogenesis of SCZ, over fifty-seven have been found and confirmed by the Genome-Wide Association Studies (GWAS) carried out in the last few years.[37] Immunology, neuroendocrinology, and neurodevelopment constitute the fields to which most of the genes are associated.[38] In addition to this, neurodevelopment, neurotransmission, and neuroplasticity-related genes may play significant roles in the development of the illness. These could indicate the molecular pathways altered in SCZ, even though they only slightly increase the risk for the SCZ.[39] The precise molecular pathways whose disruption results in the disorder are not completely concrete, though.[2] Another likely reason for this is that SCZ is not generated by a single genetic factor, but a combination of them. A more plausible theory presents SCZ as the "product" of a variety of both common and uncommon alterations.[2]

Other genes reported that single nucleotide polymorphisms (SNPs) that seem to be mostly related to this disorder are the below: *ADORA2A, BCL9L, CASP2, CDH4, CEBPA, COPG, DAXX, DTNBP1, FLOT1, FOLH1, FUBP3, GABBR1, GTF2IRD1, HIST1H1E, HRAS, KCNQ1, MAPK1, MEF2A, MYLK, NFASC, NMB, PICALM, PIK3C2A, PPFIA3, PRX, SLC2A4, SMAD3, SNX22, STX1B, TRAF2, TRIM39, TUBA8, VARS, ZFP36L1*.[2]

Several genes (e.g., *GRM3, GRIN2A, SRR, GRIA1*) involved in synaptic plasticity and glutamatergic neurotransmission, as well as DRD2; the target of all effective anti-psychotic drugs, have concrete significant associations with the etiopathology and the therapy of SCZ according to major hypotheses. Moreover, correlations at the voltage-gated calcium channel subunit-encoding sites CACNA1C, CACNB2, and CACNA1A expand on earlier discoveries linking the protein family to SCZ and other mental illnesses.[3]

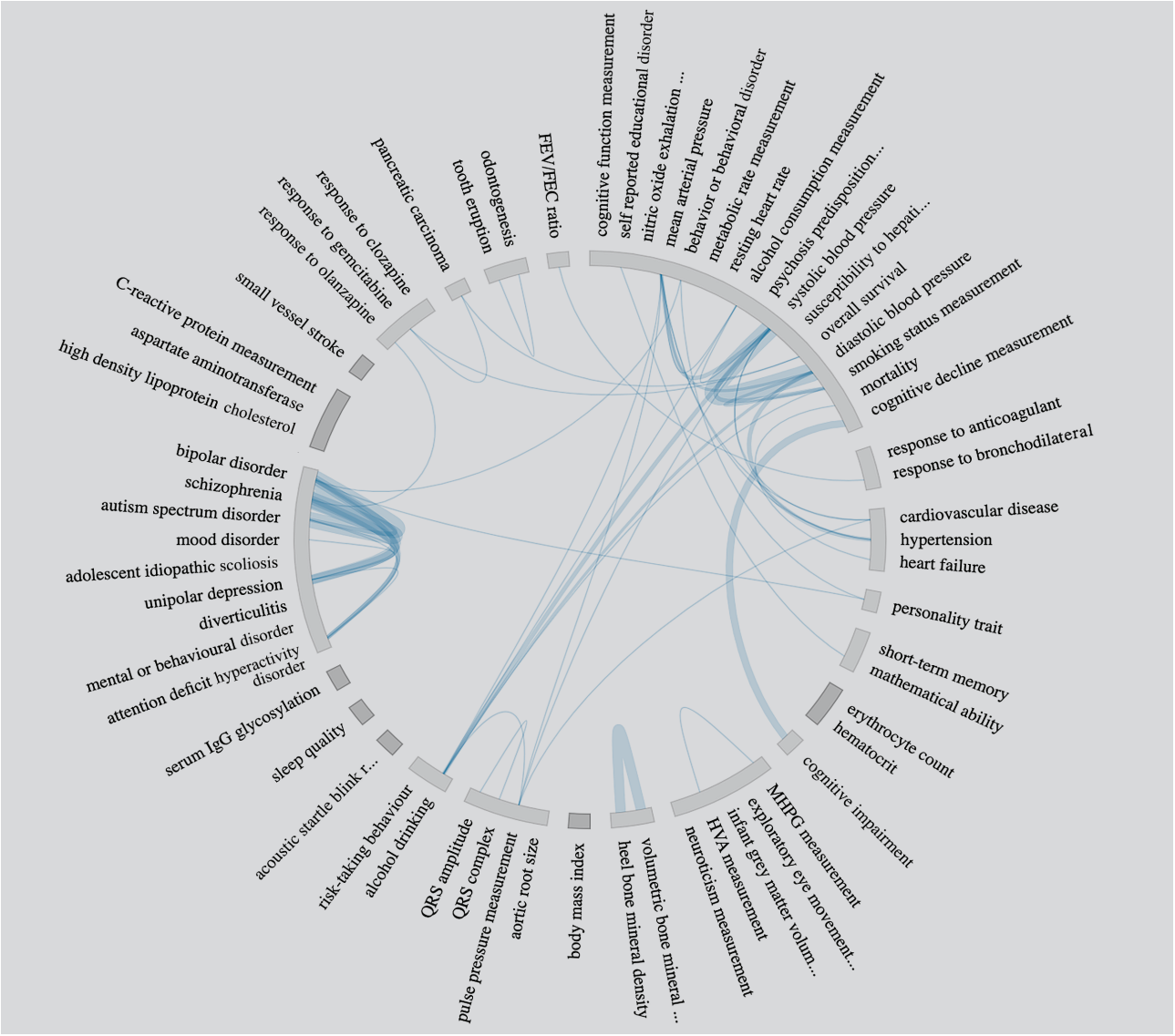

Figure 1. Visualization of the genes that seem to relate with schizophrenia (SCZ): *NRG1, TCF4, NRX1, KCNH2, GRIN1, GPM6A, SEPTIN4, TPH1, TPH2, CACNA1C, CACNB2*, and *BCL9*.

Furthermore, of the over 100 chromosomal locations on the genomic "skyline" of SCZ that are known to carry a hereditary risk for the disorder, the gene known as C4; complement component 4, is by far the tallest tower. SCZ is a disorder that influences approximately 1% of the population and is up to 90% heritable; nevertheless, understanding how particular genes contribute to risk has been confirmed to come by until recently.[40] Research in "DISGENET" concerning genes that are relative to SCZ showed, also, that they are about 4,064, most of them being protein-coding.

A Manhattan plot of the SCHizophrenia Exome Meta-Analysis (SCHEMA) findings declared genes substantially linked to the risk of the disorder. These seem to be the following: *SETD1A, CUL1, XPO7, TRIO, SP4, RB1CC1, HERC1, GRIN2A, CACNA1G, GRIA3*.[29] *GRIN2A* and *GRIA3*, two of the ten aforementioned genes identified in the SCHEMA study, provide evidence that synapse plays a significant role in the mechanistic foundation of SCZ. The function of these genes is the encoding of a portion of the glutamate receptor, namely the cellular antenna neighboring neurons. Although prior pharmacological research has contributed to the investigation of the influence of glutamate signaling on SCZ, the SCHEMA study offers the first conclusive genetic proof of this. Regarding GRIN2A activity in the brain, the peak appears during adolescence, coinciding with the onset of symptoms in individuals with the disorder.[29]

Nonetheless, none of the SCHEMA genes have previously been linked to a brain ailment or neuron-specific function.

Finally, some additional schizophrenia candidate genes are the following: *AKT1, APOE, COMT, DAOA (G72), DISC1, DTNBO1, ERBB4, GABRB2, GRIN2B, HTR2A, IL1B, NOTCH4, NRG1, NRXN1, PDE48, PRODH, RELN, RGS4*.[30]

All the genes that seem to be linked to schizophrenia are summarized in table 2.

2.1. Genes overlapping with depressive disorders

More and more research is pointing to shared genetic risk factors for both depression and SCZ.[30]

A comprehensive associative investigation encompassing five primary psychiatric disorders revealed that single-nucleotide variations (SNVs) in chromosomal loci 3p21 and 10q24, along with the *CACNA1C* and *CACNB2* genes that encode calcium subunits, are predominantly linked to SCZ, depression, BP, attention deficit hyperactivity disorder (ADHD), and autism spectrum disorders (ASDs).[41] Nevertheless, *GRIN1, GPM6A, SEPTIN4, TPH1, TPH2, CACNA1C, CACNB2*, and *BCL9* are the most researched candidate genes of SCZ and depression comorbidity (overlap).[30] In more detail, the localization and the function of these genes are described in table 3.[42]

2.2. Rare genetic variation

According to research, the genes released by the ultra-rare variants were found to have the several functions,[43] including the movement of charged particles into and out of cells and synaptic functioning (*CACNA1G, GRIN2A*, and *GRIA3*), the control of transcription – the copying of instructions coded in DNA that are used to make proteins (SP4, RB1CC1, and SETD1A), the movement and growth of neurons during development (TRIO), the movement of substances into and out of the nucleus of cells (XP07), and the modification of proteins by adding ubiquitin, which helps tell the cell where the protein should go (CUL1 and HERC1).

Current research on the molecular genetics of SCZ, concentrating on positional and functional candidate genes suggested to be related to SCZ, seems to generate upcoming findings of great interest. These include neuregulin (NRG-1, 8p12-21), dysbindin (DTNBP1, 6p22.3), G72 (13q34), D-amino acid oxidase (DAAO, 12q24), proline dehydrogenase (PRODH-2, 22q11.21), catechol-O-methyltransferase (COMT, 22q11.21), regulator of G protein signaling (RSG-4), 5HT2A and dopamine D3 receptor (DRD3). Examining the new genome scan project in the context of earlier scans, chromosomes 1q, 2q, 5q, 6p, 8p, 10p, 13q, 15q, and 22q are, also, among the regions associated with the disorder.[16]

Table 2. Genes associated to schizophrenia.

Genes associated to schizophrenia				
ZNF804A	*DTNBO1*	*SETD1A*	*NMB*	*COPG*
KCNH2	*HTR2A*	*SP4*	*PRX*	*FOLH1*
TPH1	*PDE48*	*CACNA1G*	*STX1B*	*HIST1H1E*
BCL9	*NRG1*	*COMT*	*VARS*	*MEF2A*
CASP2	*GRIN1*	*ERBB4*	*CUL1*	*PICALM*
DAXX	*TPH2*	*IL1B*	*RB1CC1*	*SLC2A4*
FUBP3	*CACNA1I*	*PRODH*	*GRIA3*	*TRAF2*
HRAS	*CDH4*	*TCF4*	*DAOA (G72)*	*ZFP36L1*
MYLK	*DTNBP1*	*GPM6A*	*GABRB2*	*XPO7*
PIK3C2A	*GABBR1*	*CACNA1C*	*NOTCH4*	*HERC1*
SMAD3	*KCNQ1*	*ADORA2A*	*RELN*	*AKT1*
TRIM39	*NFASC*	*CEBPA*	*NRX1*	*DISC1*
C4	*PPFIA3*	*FLOT1*	*SEPTIN4*	*GRIN2B*
TRIO	*SNX22*	*GTF2IRD1*	*CACNB2*	*NRXN1*
GRIN2A	*TUBA8*	*MAPK1*	*BCL9L*	*RGS4*
APOE				

Table 3. Description of the genes overlapping both schizophrenia and depression.

Genes	Localization on chromosome	Function
GRIN1	9q34.3	Encodes a critical subunit, a member of the glutamate receptor channel superfamily
GPM6A	4q34.2	Encodes a neuronal membrane glycoprotein M6-A
SEPTIN4	17q22	Encodes different isoforms of the protein septin 4 with alternative splicing
TPH1	11p15.1	Encodes an enzyme, member of the aromatic amino-acids hydroxylase family, tryptophan hydroxylase type 1 (TPH1)
TPH2	12q21.1	Encodes an enzyme, member of the family of pterin-dependent aromatic amino-acid hydroxylases, tryptophan hydroxylase type 2 (TPH2)
CACNA1C	12p13.33	Encodes the α-1 subunit of the potential-dependent calcium channel
CACNB2	10p12.31	Encodes a subunit of the potential-dependent calcium channel protein, which is a member of the superfamily of potential-dependent calcium channel
BCL9	1q21.1	Unknown

3. LINKS BETWEEN SCHIZOPHRENIA AND DEPRESSIVE AND IMMUNE DISORDERS

3.1. Depressive disorders

When considering depressive disorders, individuals

with SCZ are more likely to experience them than people in general.[44] The co-occurrence of depression and SCZ raises the possibility that the pathophysiology and or genetic predispositions coincide of these mental illnesses coincide.[31] Additionally, patients suffering from both SCZ and depressive disorders have a higher risk of suicide.[45,46]

Regarding depression, the molecular mechanisms linking SCZ and depression seem to be polygenic.[31] A substantial portion of the worldwide disease burden is attributed to these two socially relevant mental disorders; depression and SCZ.[47–49] That explains the fact that patients suffering from depression may have a high risk of developing SCZ and psychotic disorders as well.[50–55] Nevertheless, it is still unknown if depression symptoms are indicative of comorbidity, SCZ, or the non-connectedness of epiphenomena.[56] Negative symptoms of SCZ, such as anhedonia, abulia, alogia, amotivation, volitional states, and social isolation, partially overlap with depressive symptoms,[57] which are suggested to be part of the SCZ syndrome complex.[58–61] This is verified by the high prevalence of depressive symptoms in SCZ and the link between depression and other manifestations of SCZ.[62] Alternately, depressive disorders in individuals with SCZ may be provoked in part by an adverse reaction to antipsychotics (APs),[63] secondary to other comorbid conditions, such as substance of abuse or an unclear reaction to the consequences of the disorder.[64]

It is evident that there is some overlap in the presentation of both mental illnesses, regardless of the status of depressive symptoms as major or comorbid with SCZ, a fact that is declared by the increasing evidence of common genetic risk factors for both SCZ and depression.[31]

3.2. Immune disorders

Immune system disorders are more common in SCZ patients and their parents than in population controls and their parents. This statement could be explained by the genetic overlap in the pathogenesis of both kinds of disorders. In particular, there are multiple significant genetic similarities between SCZ and immune disorders, which adds to the growing body of evidence suggesting the immune system may be involved in the genesis of SCZ.[68]

Epidemiological research confirms the raised frequency of immune system abnormalities among patients suffering from SCZ and their relatives. Provided that the immunological condition was identified prior to the onset of SCZ, the elevated risk is not solely a result of the mental illness. Moreover, parents of SCZ patients had a higher incidence rate ratio (IRR) than parents of comparison subjects.[65,66]

A noteworthy exception, as far as immune disorders are concerned, is rheumatoid arthritis (RA), which has been reported to be higher in parents of participants with SCZ than in parents of controls.[67] Additional epidemiological investigations have proved the protective role of SCZ against RA.[66] This divergence implies that RA risk may be augmented by both genetic and other family-related factors, in contrast with environmental and disease-related factors that may shield SCZ patients from developing the condition (RA).

Research into the shared genetics between SCZ and auto-immune diseases has been carried out through the usage of targeted techniques, focusing on the significance of specific gene variants or locations that might be related to the chance of developing both types of conditions. The outcomes strengthen the growing and convergent body of proof indicating that immunological elements are influential in the origin of SCZ.[65]

4. LINKS BETWEEN SCHIZOPHRENIA AND ENVIRONMENTAL FACTORS

4.1. Environmental factors

Numerous studies substantiate the link between SCZ and environmental variables including birth in winter or early spring, urban birth, paternal age, famine, and nutritional and perinatal complications.[68] Analysis of twin pairs with SCZ reveals both genetics and environment contribute to the risk of developing the disorder. These studies consistently demonstrate a raised concordance in monozygotic (MZ, B50%) than dizygotic (DZ, B17%) twins. As a consequence, while SCZ appears to be heavily influenced by genetics, it is not solely determined by genetic factors.[69]

4.2. Cigarette smoking

Observational studies have effectively demonstrated the strong correlation between smoking cigarettes and SCZ. The cause-and-effect relationship is still unknown, though.[15,70] In earlier studies, about 80% of participants with SCZ reported that they are currently smoking,[71] confirming that patients suffering from SCZ smoke more than the general population, even though most recent estimates suggest that the prevalence of smoking in in-patients is nearer 60%.[72] In comparison to the general population, individuals with SCZ are more likely to be heavy smokers, starting earlier in life, smoking more cigarettes per day, and consuming larger quantities of smoke overall.[73]

4.3. Substances: alcohol and drugs

Evidence shows that comorbidity between SCZ and

substance abuse exists and it could be attributed to common underlying risk factors such as a shared genetic background.[74] Previous investigations into the lives of adolescents and young adults have indicated a correlation between mental health conditions –specifically SCZ, depression and anxiety disorders– and substance use.[75] To be more precise, it has been established that cannabis use[76] and cigarette smoking[77] are linked to a propensity for psychosis. There have also been reports of a high comorbidity rate between alcoholism-alcohol dependence and psychiatric problems in general.[78] Factors are pertinent for both SCZ and substance use provided that they follow a heritability pattern/schema. It should also be noted that heritability concerning substance use varies from 11% to 84% for substance use.[74,79]

Recent research has demonstrated that there is a genetic overlap between substance use, especially cannabis use and SCZ Polygenic Risk Score (PRS). Cannabis use patterns during adolescence are also linked to genetic vulnerability to SCZ.[74]

5. CONCLUSIONS

SCZ constitutes a complicated neurodevelopmental condition that is impacted by both genetic and environmental features, characterized by severe cognitive and emotional impairments and is associated with a significant risk of comorbid conditions, such as depression and immune disorders. Understanding the genetic underpinnings and shared risk factors can not only contribute to the formation of more effective and successful treatment plans for the patients suffering from this disorder but it can also enhance their outcomes.

ΠΕΡΙΛΗΨΗ

Σχιζοφρένεια: Γενετικό προφίλ και σύνδεση με καταθλιπτικές διαταραχές και διαταραχές του ανοσοποιητικού, καθώς και περιβαλλοντικούς παράγοντες

Δ. ΙΩΑΝΝΟΥ, Δ. ΚΑΒΒΑΔΑΣ, Θ. ΠΑΠΑΜΗΤΣΟΥ

Ερευνητική Ομάδα "Histologistas", Σχολή Επιστημών Υγείας, Τμήμα Ιατρικής, Αριστοτέλειο Πανεπιστήμιο Θεσσαλονίκης, Θεσσαλονίκη

Αρχεία Ελληνικής Ιατρικής 2026, 43(1):10–17

Η σχιζοφρένεια είναι μια σύνθετη ψυχική διαταραχή που χαρακτηρίζεται από σοβαρή διαταραχή της σκέψης, παραληρητικές σκέψεις, ψευδαισθήσεις και κακή συναισθηματική ανταπόκριση, ενώ συνήθως εμφανίζεται στα τέλη της εφηβείας ή στην πρώιμη ενήλικη ζωή. Παρ' όλο που η αιτία της διαταραχής αυτής δεν μπορεί να προσδιοριστεί ακόμη, το γενετικό υπόβαθρο δεν είναι εντελώς ασαφές. Με την προϋπόθεση ότι η σχιζοφρένεια δεν έχει διακριτική παθολογία ή διαγνωστικά κριτήρια, είναι δύσκολη η συσχέτιση των γονιδιακών μεταβολών με διακριτές φυσιολογικές ή βιοχημικές αλλαγές που σχετίζονται με τη νόσο. Ωστόσο, πολλά γονίδια συνδέονται σαφώς με τη σχιζοφρένεια. Η διαταραχή φαίνεται να έχει παρόμοιο γενετικό υπόβαθρο με καταθλιπτικές διαταραχές, αφού παρατηρείται γονιδιακή επικάλυψη, καθώς και με διαταραχές του ανοσοποιητικού. Επιδημιολογικά στοιχεία δείχνουν ότι υπάρχει αυξημένη συχνότητα διαταραχών του ανοσοποιητικού σε άτομα που πάσχουν από σχιζοφρένεια και στους συγγενείς τους. Τέλος, η σχιζοφρένεια σχετίζεται επίσης με περιβαλλοντικούς παράγοντες, το κάπνισμα και τη χρήση ουσιών: οινόπνευμα και ναρκωτικά.

Λέξεις ευρετηρίου: Γενετική, Ουσίες, Κάπνισμα, Καταθλιπτικός, Σχιζοφρένεια

References

1. SINGH S, KUMAR A, AGARWAL S, PHADKE SR, JAISWAL Y. Genetic insight of schizophrenia: Past and future perspectives. *Gene* 2014, 535:97–100
2. CRISAFULLI C, DRAGO A, CALABRÒ M, SPINA E, SERRETTI A. A molecular pathway analysis informs the genetic background at risk for schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2015, 59:21–30
3. SADA-FUENTE E, ARANDA S, PAPIOL S, HEILBRONNER U, MOLTÓ MD, AGUILAR EJ ET AL. Correction: Common genetic variants contribute to heritability of age at onset of schizophrenia. *Transl Psychiatry* 2023, 13:369
4. VAN OS J, KENIS G, RUTTEN BP. The environment and schizophrenia. *Nature* 2010, 468:203–212
5. PICCHIONI MM, MURRAY RM. Schizophrenia. *Br Med J* 2007, 335:91–95
6. CASTLE D, WESSELY S, DER G, MURRAY RM. The incidence of operationally defined schizophrenia in Camberwell, 1965–84. *Br J Psychiatry* 1991, 159:790–794
7. HANSON DR, GOTTESMAN II. Theories of schizophrenia: A genetic-inflammatory-vascular synthesis. *BMC Med Genet* 2005, 6:7
8. BEERS MH, BERKOW R. Psychiatric emergencies. In: Porter RE (ed) *The Merck manual of diagnosis and therapy.* 20th ed. Merck Re-

search Laboratories, Whitehouse Station, New Jersey, NJ, 2018
9. O'CONNELL G, LAWRIE SM, McINTOSH AM, HALL J. Schizophrenia risk genes: Implications for future drug development and discovery. *Biochem Pharmacol* 2011, 81:1367–1373
10. HILKER R, HELENIUS D, FAGERLUND B, SKYTTHE A, CHRISTENSEN K, WERGE TM ET AL. Is an early age at illness onset in schizophrenia associated with increased genetic susceptibility? Analysis of data from the nationwide Danish Twin Register. *EBioMedicine* 2017, 18:320–326
11. BYRNE M, AGERBO E, MORTENSEN PB. Family history of psychiatric disorders and age at first contact in schizophrenia: An epidemiological study. *Br J Psychiatry Suppl* 2002, 43:s19–s25
12. ALEMAN A, KAHN RS, SELTEN JP. Sex differences in the risk of schizophrenia: Evidence from meta-analysis. *Arch Gen Psychiatry* 2003, 60:565–571
13. VAN DER WERF M, HANSSEN M, KÖHLER S, VERKAAIK M, VERHEY FR; RISE INVESTIGATORS ET AL. Systematic review and collaborative recalculation of 133,693 incident cases of schizophrenia. *Psychol Med* 2014, 44:9–16
14. SULLIVAN PF. The genetics of schizophrenia. *PLoS Med* 2005, 2:e212
15. BURMEISTER M, McINNIS MG, ZÖLLNER S. Psychiatric genetics: Progress amid controversy. *Nat Rev Genet* 2008, 9:527–540
16. SALLEH MR. The genetics of schizophrenia. *Malays J Med Sci* 2004, 11:3–11
17. LEE SH, DeCANDIA TR, RIPKE S, YANG J; SCHIZOPHRENIA PSYCHIATRIC GENOME-WIDE ASSOCIATION STUDY CONSORTIUM (PGC-SCZ); INTERNATIONAL SCHIZOPHRENIA CONSORTIUM (ISC) ET AL. Estimating the proportion of variation in susceptibility to schizophrenia captured by common SNPs. *Nat Genet* 2012, 44:247–250
18. RIPKE S, O'DUSHLAINE C, CHAMBERT K, MORAN JL, KÄHLER AK, AKTERIN S ET AL. Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nat Genet* 2013, 45:1150–1159
19. INTERNATIONAL SCHIZOPHRENIA CONSORTIUM; PURCELL SM, WRAY NR, STONE JL, VISSCHER PM, O'DONOVAN MC ET AL. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 2009, 460:748–752
20. LI T, LI Z, CHEN P, ZHAO Q, WANG T, HUANG K ET AL. Common variants in major histocompatibility complex region and *TCF4* gene are significantly associated with schizophrenia in Han Chinese. *Biol Psychiatry* 2010, 68:671–673
21. SHI J, LEVINSON DF, DUAN J, SANDERS AR, ZHENG Y, PE'ER I ET AL. Common variants on chromosome 6p22.1 are associated with schizophrenia. *Nature* 2009, 460:753–757
22. STEFANSSON H, OPHOFF RA, STEINBERG S, ANDREASSEN OA, CICHON S, RUJESCU D ET AL. Common variants conferring risk of schizophrenia. *Nature* 2009, 460:744–747
23. WRIGHT P, DONALDSON PT, UNDERHILL JA, CHOUDHURI K, DOHERTY DG, MURRAY RM. Genetic association of the *HLA DRB1* gene locus on chromosome 6p21.3 with schizophrenia. *Am J Psychiatry* 1996, 153:1530–1533
24. HILL MJ, BRAY NJ. Evidence that schizophrenia risk variation in the *ZNF804A* gene exerts its effects during fetal brain development. *Am J Psychiatry* 2012, 169:1301–1308
25. BLAKE DJ, FORREST M, CHAPMAN RM, TINSLEY CL, O'DONOVAN MC, OWEN MJ. *TCF4*, schizophrenia, and Pitt-Hopkins Syndrome. *Schizophr Bull* 2010, 36:443–447
26. RUJESCU D, INGASON A, CIVHON S, PIETILÄINEN OPH, BARNES MR, TOULOPOULOU T ET AL. Disruption of the neurexin 1 gene is associated with schizophrenia. *Hum Mol Genet* 2009, 18:988–996
27. HUFFAKER SJ, CHEN J, NICODEMUS KK, SAMBATARO F, YANG F, MATTAY V ET AL. A primate-specific, brain isoform of KCNH2 affects cortical physiology, cognition, neuronal repolarization and risk of schizophrenia. *Nat Med* 2009, 15:509–518
28. STRAUB RE, JIANG Y, McLEAN CJ, MA Y, WEBB BT, MYAKISHEV MV ET AL. Genetic variation in the 6p22.3 gene *DTNBP1,* the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. *Am J Hum Genet* 2002, 71:337–348
29. ULRICH T. Two large studies reveal genes and genome regions that influence schizophrenia risk. Broad Institute, Cambridge, MA, 2022. Available at: https://www.broadinstitute.org/news/two-large-studies-reveal-genes-and-genome-regions-influence-schizophrenia-risk
30. TIWARI AK, ZAI CC, MÜLLER DJ, KENNEDY JL. Genetics in schizophrenia: Where are we and what next? *Dialogues Clin Neurosci* 2010, 12:289–303
31. SHNAYDER NA, NOVITSKY MA, NEZNANOV NG, LIMANKIN OV, ASADULLIN AR, PETROV AV ET AL. Genetic predisposition to schizophrenia and depressive disorder comorbidity. *Genes (Basel)* 2022, 13:457
32. BRZUSTOWICZ LM, HODGKINSON KA, CHOW EW, HONER WG, BASSETT AS. Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21-q22. *Science* 2000, 288:678–682
33. INTERNATIONAL SCHIZOPHRENIA CONSORTIUM. Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature* 2008, 455:237–241
34. STEFANSSON H, RUJESCU D, CICHON S, PIETILÄINEN OPH, INGASON A, STEINBERG S ET AL. Large recurrent microdeletions associated with schizophrenia. *Nature* 2008, 455:232–236
35. KARAYIORGOU M, MORRIS MA, MORROW B, SHPRINTZEN RJ, GOLDBERG R, BORROW J ET AL. Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. *Proc Natl Acad Sci U S A* 1995, 92:7612–7616
36. GePhEx. Available at: https://gephex.ega-archive.org (accessed 22.9.2024)
37. ALLEN NC, BAGADE S, McQUEEN MB, IOANNIDIS JPA, KAVVOURA FK, KHOURY MJ ET AL. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: The SzGene database. *Nat Genet* 2008, 40:827–834
38. HOSÁK L, SILHAN P, HOSÁKOVÁ J. Genome-wide association studies in schizophrenia, and potential etiological and functional implications of their results. *Acta Medica (Hradec Kralove)* 2012, 55:3–11
39. ARNOLD SE, TALBOT K, HAHN CG. Neurodevelopment, neuroplasticity, and new genes for schizophrenia. *Prog Brain Res* 2005, 147:319–345
40. NATIONAL INSTITUTES OF HEALTH. Schizophrenia's strongest known genetic risk deconstructed. NIH, Bethesda, Maryland, 2016. Available at: https://www.nih.gov/news-events/news-releases/schizophrenias-strongest-known-genetic-risk-deconstructed
41. CROSS-DISORDER GROUP OF THE PSYCHIATRIC GENOMICS CONSORTIUM. Identification of risk loci with shared effects on five major psychiatric disorders: A genome-wide analysis. *Lancet* 2013, 381:1371–1379
42. FAGERBERG L, HALLSTRÖM BM, OKSVOLD P, KAMPF C, DJUREINOVIC D, ODEBERG J ET AL. Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. *Mol Cell Proteomics* 2014, 13:397–406
43. NATIONAL INSTITUTES OF HEALTH. Rare genetic variation in 10 genes substantially raise the risk for schizophrenia. NIH, Bethesda, Maryland, 2022. Available at: https://www.nimh.nih.gov/news/science-news/2022/rare-genetic-variation-in-10-genes-substantially-raise-the-risk-for-schizophrenia
44. BUCKLEY PF, MILLER BJ, LEHRER DS, CASTLE DJ. Psychiatric comor-

bidities and schizophrenia. *Schizophr Bull* 2009, 35:383–402
45. UPTHEGROVE R, BIRCHWOOD M, ROSS K, BRUNETT K, McCOLLUM R, JONES L. The evolution of depression and suicidality in first episode psychosis. *Acta Psychiatr Scand* 2010, 122:211–218
46. ANDRIOPOULOS I, ELLUL J, SKOKOU M, BERATIS S. Suicidality in the "prodromal" phase of schizophrenia. *Compr Psychiatry* 2011, 52:479–485
47. EKMAN M, GRANSTROM O, OMEROV S, JACOB J, LANDEN M. The societal cost of schizophrenia in Sweden. *J Ment Health Policy Econ* 2013, 16:13–25
48. WORLD HEALTH ORGANIZATION. The global burden of disease: 2004 update. WHO, Geneva, 2008
49. WHITEFORD HA, DEGENHARDT L, REHM J, BAXTER AJ, FERRARI AJ, ERSKINE HE ET AL. Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *Lancet* 2013, 382:1575–1586
50. JOHNSON J, HORWATH E, WEISSMAN MM. The validity of major depression with psychotic features based on a community study. *Arch Gen Psychiatry* 1991, 48:1075–1081
51. OHAYON MM, SCHATZBERG AF. Prevalence of depressive episodes with psychotic features in the general population. *Am J Psychiatry* 2002, 159:1855–1861
52. HÄFNER H, MAURER K, TRENDLER G, AN DER HEIDEN W, SCHMIDT M, KÖNNECKE R. Schizophrenia and depression: Challenging the paradigm of two separate diseases – a controlled study of schizophrenia, depression and healthy controls. *Schizophr Res* 2005, 77:11–24
53. HÄFNER H, LÖFFLER W, MAURER K, HAMBRECHT M, AN DER HEIDEN W. Depression, negative symptoms, social stagnation and social decline in the early course of schizophrenia. *Acta Psychiatr Scand* 1999, 100:105–118
54. YUNG AR, PHILLIPS LJ, YUEN HP, FRANCEY SM, McFARLANE CA, HALLGREN M ET AL. Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. *Schizophr Res* 2003, 60:21–32
55. SCHOTHORST PF, EMCK C, VAN ENGELAND H. Characteristics of early psychosis. *Compr Psychiatry* 2006, 47:438–442
56. MÖLLER HJ. Occurrence and treatment of depressive comorbidity/cosyndromality in schizophrenic psychoses: Conceptual and treatment issues. *World J Biol Psychiatry* 2005, 6:247–263
57. SIRIS SG, ADAN F, COHEN M, MANDELI J, ARONSON A, CASEY E. Postpsychotic depression and negative symptoms: An investigation of syndromal overlap. *Am J Psychiatry* 1988, 145:1532–1537
58. BIRCHWOOD M, IQBAL Z, CHADWICK P, TROWER P. Cognitive approach to depression and suicidal thinking in psychosis. 1. Ontogeny of post-psychotic depression. *Br J Psychiatry* 2000, 177:516–521
59. JOHNSON DA. Studies of depressive symptoms in schizophrenia. *Br J Psychiatry* 1981, 139:89–101
60. AN DER HEIDEN W, KÖNNECKE R, MAURER K, ROPETER D, HÄFNER H. Depression in the long-term course of schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 2005, 255:174–184
61. CHIAPPELLI J, KOCHUNOV P, DeRISO K, THANGAVELU K, SAMPATH H, MUELLERKLEIN F ET AL. Testing trait depression as a potential clinical domain in schizophrenia. *Schizophr Res* 2014, 159:243–248
62. GOZDZIK-ZELAZNY A, BORECKI L, POKORSKI M. Depressive symptoms in schizophrenic patients. *Eur J Med Res* 2011, 16:549–552
63. NASYROVA RF, SCHNAIDER NA, MIRONOV K, SHIPULIN GA, DRIBNOKHODOVA OP, GOLOSOV EA ET AL. Pharmacogenetics of schizophrenia in real clinical practice: A clinical case. *Neurol Neuropsychiatry Psychosom* 2018, 10:88–93
64. TURKINGTON A, MULHOLLAND CC, RUSHE TM, ANDERSON R, McCAUL R, BARRETT SL ET AL. Impact of persistent substance misuse on 1-year outcome in first-episode psychosis. *Br J Psychiatry* 2009, 195:242–248
65. STRINGER S, KAHN RS, DE WITTE LD, OPHOFF RA, DERKS EM. Genetic liability for schizophrenia predicts risk of immune disorders. *Schizophr Res* 2014, 159:347–352
66. CHEN SJ, CHAO YL, CHEN CY, CHANG CM, WU EC, WU CS ET AL. Prevalence of autoimmune diseases in in-patients with schizophrenia: Nationwide population-based study. *Br J Psychiatry* 2012, 200:374–380
67. EATON WW, BYRNE M, EWALD H, MORS O, CHEN CY, AGERBO E ET AL. Association of schizophrenia and autoimmune diseases: Linkage of Danish national registers. *Am J Psychiatry* 2006, 163:521–528
68. ABDOLMALEKY HM, THIAGALINGAM S. Can the schizophrenia epigenome provide clues for the molecular basis of pathogenesis? *Epigenomics* 2011, 3:679–683
69. CARDNO AG, GOTTESMAN II. Twin studies of schizophrenia: From bow-and-arrow concordances to star wars Mx and functional genomics. *Am J Med Genet* 2000, 97:12–17
70. CHEN J, CHEN R, XIANG S, LI N, GAO C, WU C ET AL. Cigarette smoking and schizophrenia: Mendelian randomisation study. *Br J Psychiatry* 2021, 218:98–103
71. DALACK GW, HEALY DJ, MEADOR-WOODRUFF JH. Nicotine dependence in schizophrenia: Clinical phenomena and laboratory findings. *Am J Psychiatry* 1998, 155:1490–1501
72. DE LEON J, DIAZ FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res* 2005, 76:135–157
73. OHI K, SHIMADA T, KUWATA A, KATAOKA Y, OKUBO H, KIMURA K ET AL. Smoking rates and number of cigarettes smoked per day in schizophrenia: A large cohort meta-analysis in a Japanese population. *Int J Neuropsychopharmacol* 2019, 22:19–27
74. HIEMSTRA M, NELEMANS SA, BRANJE S, VAN EIJK KR, HOTTENGA JJ, VINKERS CH ET AL. Genetic vulnerability to schizophrenia is associated with cannabis use patterns during adolescence. *Drug Alcohol Depend* 2018, 190:143–150
75. SCHUBART CD, VAN GASTEL WA, BREETVELT EJ, BEETZ SL, OPHOFF RA, SOMMER IEC ET AL. Cannabis use at a young age is associated with psychotic experiences. *Psychol Med* 2011, 41:1301–1310
76. ARSENEAULT L, CANNON M, POULTON R, MURRAY R, CASPI A, MOFFITT TE. Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. *Br Med J* 2002, 325:1212–1213
77. McGRATH JJ, ALATI R, CLAVARINO A, WILLIAMS GM, BOR W, NAJMAN JM ET AL. Age at first tobacco use and risk of subsequent psychosis-related outcomes: A birth cohort study. *Aust N Z J Psychiatry* 2016, 50:577–583
78. KESSLER RC, McGONAGLE KA, ZHAO S, NELSON CB, HUGHES M, ESHLEMAN S ET AL. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994, 51:8–19
79. GOLDMAN D, OROSZI G, DUCCI F. The genetics of addictions: Uncovering the genes. *Nat Rev Genet* 2005, 6:521–532

Corresponding author:

D. Kavvadas, "Histologistas" Research Group, School of Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece
e-mail: kavvadas@auth.gr