Psychiatr. Pol. 2026; 60(3): 453–472
PL ISSN 0033-2674 (PRINT), ISSN 2391-5854 (ONLINE)
www.psychiatriapolska.pl
DOI: https://doi.org/10.12740/PP/OnlineFirst/208424

What do the GWAS studies say about language in schizophrenia?

Przemysław Zakowicz[1,2], Bartłomiej Sporniak[3], Maksymilian Grabarczyk[1], Maria Skibińska[1], Joanna Pawlak[1]

[1] Chair of Psychiatry, Department of Genetics in Psychiatry, Poznan University of Medical Sciences
[2] Department of Neuroengineering and Space Medicine, University of Zielona Gora
[3] Wroclaw Medical University

Summary

Aim. Schizophrenia links with altered language structure and may be evolutionary consequence of language development. High heritability of the disease led to recent endeavour in explaining the genetic background. Genome-Wide Association Studies (GWAS) indicate schizophrenia as highly polygenic disease with many receptor and synaptic plasticity pathways engaged.

Material and methods. Here we present a systematic review on the topic of schizophrenia GWAS findings and its potential relevance to language skills. We used GWAS catalogue data to identify all significant associations in schizophrenia (including selected endophenotypes) and studied its relevance in the context of language phenotypes associations.

Results. Among genes involved in language evolution, *FOXP1* and *ROBO2* were indicated by GWAS as associated with schizophrenia. Evidence on schizophrenia linked SNPs was found for association with intelligence, educational attainment, cognitive abilities, and language processing brain structures imaging results.

Conclusions. The review discusses hypotheses of language alterations in schizophrenia as a consequence of impaired synaptic plasticity and neural network formation.

Key words: genetics, schizophrenia, language

Introduction

Genome-wide association studies (GWAS) are often used to study the molecular basis of schizophrenia [1]. The core benefit of GWAS is that it enables a wide platform examination of single-nucleotide polymorphisms (SNPs) genetic variants in affected and control subjects, as well as searching for biological associations without hypoth-

esised target. Stringent statistical rules are employed to find evidence of associations between clinical phenotypes and SNPs in studied individuals.

At the time of writing (April 2023), the GWAS catalogue (https://www.ebi.ac.uk/gwas/home) featured over 471,482 associations across near six thousand research papers. Horwitz et al. [2] found that 6,632 SNPs were associated with psychiatric symptoms, with 1,109 reaching the genome-wide statistical significance (as at 2017).

The main challenge of GWAS in schizophrenia is the sample size required to empower reaching the genome-wide significance and phenotypic heterogeneity of the studied population. Hence, the most reliable data usually comes from multi-centred collaborations. The largest study to date [3] revealed 287 valid, independent loci in the sample size of 76,755 patients and 243,649 healthy controls. Most reliable findings indicated molecular pathways crucial for schizophrenia, like GABA-ergic, dopaminergic and glutamatergic signalling (*GRIN2A*), calcium signalling (*CACNA1C*), as well as major histocompatibility complex (*MHC* [4] and *FOXP1* [3]) associations. Overall, it is estimated that current data can explain over 30% of schizophrenia heritability, although gaps exist in understanding the realm of epigenetic and evolutionary aspects in populations of different ancestry [5].

It is hypothesized that the first-rank symptoms of schizophrenia such as thought steering, auditory verbal hallucinations (AVH) and formal thought disorders (FTDs) can have a common background of language disturbance. This phenomenon is complex and can be explained by connectomics, molecular biology, as well as societal and cultural factors [6].

Language disturbance is recognised in many psychometric scales [7], such as the *Positive and Negative Symptoms Scale* (PANSS) [8], *Scale for the Assessment of Positive/Negative Symptoms* (SAPS, SANS), *Brief Psychiatric Rating Scale* (BPRS), *Thought and Language Index* (TLI) [9] or the *Operational Criteria Checklist for Psychotic Illness and Affective Illness* (OPCRIT) [10]. The presence of language disturbance symptoms affects the general prognosis of schizophrenic patients. Formal thought disorders (FTDs) are associated with poor social, occupational and neurocognitive functioning, as well as with a higher relapse rate [7]. FTDs are also linked with the phenomenological concept of the self, which may coincide with negative symptoms severity and cognitive deficits [11]. Auditory verbal hallucinations (AVH), seen in 60–70% [12] of patients, may not respond entirely to pharmacological management [12] and could be a risk factor for suicide and violent behaviour [13].

The language symptoms of schizophrenia can also be studied in an evolutionary context. Schizophrenia can be dated back to the language ability formation in our ancestors [14]. In this approach, Crow [15] recognises schizophrenia as the evolutionary consequence of language invention (the price that Homo sapiens pay for language. The language of the human species could have spawned as a genetic mutation, or co-evolved with social skills, shared intentionality or reasoning abilities [16]. Following Enard's approach [16] (2016), human speech may be an elaborated form of vocalisation, which is observed in other species, like birds or mice. Hence, translational genetic studies may reveal specific genetic variants that occurred in human evolution resulting in human language acquisition. The main restriction of translational studies

between human and other species relies on similarity between animals' vocalisations and human language which is not obvious.

Until today, translational studies have identified putative language-related genes such as *FOXP1* and *FOXP2, CNTNAP2, ROBO1* and *ROBO2, KIAA0319, GNPTAB, GNPTG, SRPX2, ATP2C2, DCDC2, CMIP, DYX1C1, TSC1, NFXL1*, and *NAGPA* [16–18]. However the biology of human language may significantly differ from this known in other species.

Linguistic assessment can also be a valuable clinical tool in schizophrenia diagnosis and screening for at-risk mental states. Quantitative analysis of speech samples can distinguish individuals with schizophrenia from healthy controls by assessing linguistic abilities [19]. This observations are reflected in functional brain imaging results, which show aberrant connectivity in auditory and language brain networks [20].

In this review, we present the data from GWAS studies, available in the GWAS catalogue (as at February 2023). The study aim was to seek for common genes proven in GWAS as significant for schizophrenia and involved in language ability formation.

1. Materials and Methods

We searched the GWAS catalogue (https://www.ebi.ac.uk/gwas/) using the query 'schizophrenia' (131 articles, number of associations obtained: $n = 6953$). Then, we scanned each title and abstract for eligibility. We excluded studies conducted on mixed-diagnosis populations (e.g. schizophrenia + bipolar disorder or autism) and non-schizophrenia populations (38 publications, $n = 2326$ associations), studies assessing associations between SNPs and the drug response, eye-movement dysfunctions, aggression and violence, smoking behaviour, diabetes risk, interaction with cytomegalovirus infection, alcohol dependence or niacin metabolism (endophenotypes non-assessed for eligibility, 22 publications, $n = 431$); as not connected with language skills.

The following endophenotypes were included to the analysis: treatment-resistance [21, 22], neuroimaging studies [23–26], age at onset [27–29], neurocognitive functions [30, 31], neurophysiology of brain cortex [32], and schizophrenia symptomatology [33–35]. Next, we made a list of each SNP indicated in a GWAS study and we assessed the association significance according to the GWAS threshold. We removed all non-significant associations and duplications ($p > 10^{-8}$; $n = 2512$).

Overall, 1684 associations localised in 748 genes and 476 intergenic regions were found as significant (see supplementary materials). Each of the listed SNPs was subsequently searched using the GWAS catalogue to find if it is associated with language symptoms in the database. Then each gene was scanned if it is linked with language abilities [30].

Moreover, the list of genes perceived as evolutionarily involved in language development (the genes mentioned above, see: [17]) was compared to SNPs and genes significant in GWAS for schizophrenia and its selected endophenotypes. A detailed process of data selection is available in the diagram (Figure 1). Detailed list of genes included in analysis (significantly associated to schizophrenia) is attached in a supplementary file. We used *Annotation, Visualisation and Integrated Discovery Clas-*

sification System (DAVID 6.8) [36] to identify biological pathways associated with selected genes.

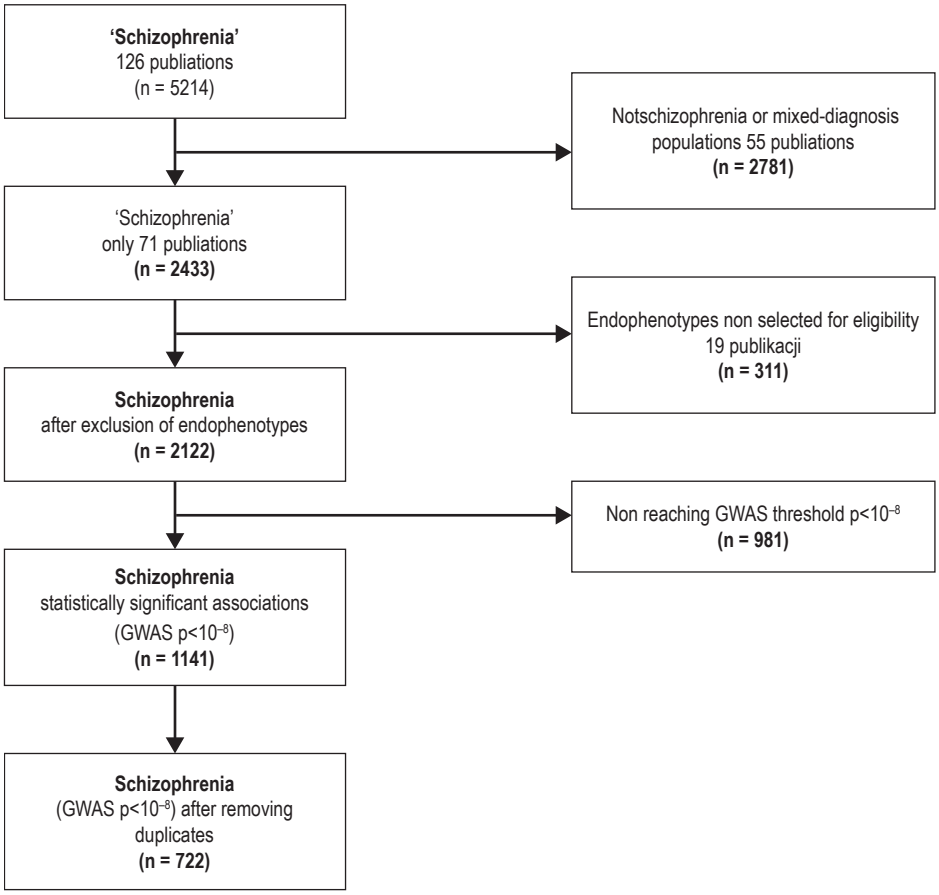

Figure 1. **The process of data selection in the GWAS catalogue**

2. Results

Among the genes influencing the acquisition of language skills in the light of the evolutionary approach, only the *FOXP1* and *ROBO2* genes are indicated as being associated with schizophrenia [30].

We did not find any significant GWAS results in schizophrenia on majority of putative language genes (see *Introduction* and [17]): *FOXP2, CNTNAP2, ROBO1, KIAA0319, GNPTAB, GNPTG, SRPX2, DCDC2, CMIP, DYX1C1, ATP2C2*, and *NAGPA*. Comparing abovementioned list to genes associated with schizophrenia diagnosis, *FOXP1* and *ROBO2* genes only are involved. Study by Lam et al. [30] (2019) revealed

association of two SNPs, in *FOXP1* (rs62244881, 3p12.3) and *ROBO2* (rs3849490, 3p12.3), with schizophrenia.

We did not find any direct associations between GWAS-significant SNPs for schizophrenia and selected endophenotypes and direct language traits in GWAS catalogue. Evidence of selected SNPs associations was found for intelligence, educational attainment and cognitive abilities. Several SNPs were also associated with brain volume imaging, including language functional connectivity. Below, SNPs significantly associated with schizophrenia and its selected endophenotypes are enumerated in the context of traits indirectly linked to language skills. Four, independent studies [37–40] showed 9 SNPs found in schizophrenia studies as related to intelligence. The SNPs are located in 9 gene areas: *SEPTIN3* [39]*, LINC00461* [40]*, CALN1, PRKD1, CARMIL1-CMAHP, RPS19BD1-CACNA1I, OR2U2D-OR14J1, PTPNR2* [38], and *RAI1* [37]. Educational attainment was associated with 19 gene areas [30–41]: *DPYD, NFIA, CORO1C, VWA52B, BCL11B-SETD3, ZSWIM6, GGNBP1*[41], *PALS2, BNIP3L, GLCCI1* [39], *TAOK2, TCF4, EP300-AS1, ZEB2, ATP2A2, FURIN* [30], *CEP57-MTMR2* [42], *KCNG2-CTDP1* [43]*, PCGEM1-SLC44A3P1* [39–42]. Regarding the association with cognitive abilities two independent studies [37, 39] and a meta-analysis [30] indicated 25 SNPs, located in 21 identified genes (2 SNPs for *TSNARE1*, 3 SNPs did not map to the genome). For rs13107325 (*SLC9A8*, 4q24) significant associations were obtained in brain imaging: volumetrics of subcortical nuclei, cerebellum and brain stem, as well as cortical thickness in general, including temporal lobe [44–47]. For rs160593 (*LIN28B*, 6q21) association was found for cortical surface area [48]; rs245201 (*CCDC192*, 5q23.2) was associated with functional imaging of dorsolateral prefrontal cortex (dlPFC) [49]. Particular significance for language was found for rs4702 (*FURIN*, 15q26.1), rs62266110 (*HSPE1P19-RNU6448P,* 3q11.2) and rs35124509 (*EPHA3,* 3p11.1), which were associated with resting-state functional connectivity of brain language areas [50].

Out of 748 genes associated with schizophrenia, 263 genes were found to be associated with educational attainment as well, 193 with cognitive ability, 133 with intelligence, and 342 with brain imaging data. Associations with more specific language traits were observed for 24 genes. These genes, including their chromosomal location, function and evidenced association with language are presented in Table 1.

Table 1. **Loci identified in schizophrenia GWAS studies, associated with language features, based on GWAS Catalogue (https://www.ebi.ac.uk/gwas/home; retrieved: April 2023)**

Gene	Chromosomal location	Function	Language parameter	Citation
ACTG1P22	2p16.1	Actin gamma-1 pseudogene 22	Language network functional connectivity	Mekki Y et al., 2022 [50]
AXDND1	1q25.2	Axonemal dynein light chain domain containing 1	Stuttering	Shaw DM et al., 2021 [53]
CACNA1C	12p13.33	Calcium voltage-gated channel Subunit 1 c	Short-term verbal memory	Gialluisi A et al., 2019 [96]

table continued on the next page

CALN1	7q11.22	Calneuron 1	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
ETF1	5q31.2	Eukaryotic translation termination Factor 1	Verbal test score	Greenwood TA et al., 2019 [97]
FOXO3	6q21	Forkhead box O3	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
LINC01435	10q25.1	Long intergenic non-protein Coding rna 1435	Cognitive language assessment	Homann J et al., 2022 [58]
LINC02404	12q21.33	Long intergenic non-protein Coding rna 2404	Stuttering	Shaw DM et al., 2021 [53]
LPP	3q28	LIM domain containing preferred translocation partner in lipoma	Verbal memory	Arpawong TE et al., 2017 [98]
MAGI2	7q21.11	Membrane-associated guanylate kinase, WW and PDZ domain containing 2	Reading ability	Davis OS et al., 2014 [56]
MIR124-2HG	8q12.3	MIR124-2 host gene	Verbal memory	Debette S et al., 2014 [100]
PHACTR3	20q13.32	Phosphatase and actin regulator 3	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
SGCZ	8p22	Sarcoglycan zeta	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
TCF20	22q13.2	Transcription factor 20	Language ability	Homann J et al., 2022 [58]
LCORL	4p15.31	Ligand-dependent nuclear receptor corepressor	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
NEGR1	1p31.1	Neuronal growth regulator 1	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
SEPTIN3	22q13.2	Septin 3	Verbal numerical reasoning	de la Fuente J et al., 2020 [52]
ARL14EP-DT	11p14.1	ARL14EP divergent transcript	Dyslexia	Doust C et al., 2022 [54]

table continued on the next page

ITIH1	3p21.1	Inter-alpha-trypsin inhibitor heavy chain H1	Verbal learning	Lahti J et al., 2022 [59]
GLI3	7p14.1	Zinc finger protein GLI3	Verbal functions in elderly	Deters KD et al., 2017 [57]

2.1. Verbal memory

Verbal memory comprises encoding, storage and retrieval of the verbal material, including immediate or delayed recall. A literature review revealed three genes sharing a potential common impact on schizophrenia and verbal memory. A study by Gialluisi et al. [96] encompassed GWAS of children population with developmental dyslexia (DD) and indicated two potential candidate genes: *MIR924HG* and *NKAIN3*; *CACNA1C*, rs11062222 SNP did not obtain the GWAS *p* threshold ($p > 10^{-6}$). Further two studies assessed the genetic associations of age-related verbal memory decline in the elderly-adult population.

In the work by Arpawong et al. [98], genome-wide significance was obtained for *TOMM40* and *APOE* SNPs and delayed verbal recall testing, another *APOE* SNP was also identified by Debette et al. as associated with the delayed recall [100]. To sum up, SNPs identified in schizophrenia cohorts did not meet the GWAS statistical threshold in studies on verbal memory.

2.2. Verbal numerical reasoning

Verbal numerical reasoning (VNR) has been recently indicated as strongly related to schizophrenia genetic background. A combined analysis by Smeland et al. [51] (2017) indicated two loci associated with VNR and schizophrenia: *TCF20* (22q13.2) and SLC39A8 (4q24).

Furthermore, the analysis by de la Funete et al. [52] (2021) identified 7 loci associated both with schizophrenia and VNR: *LCORL* (4p15.31)*, NEGR1* (1p31.1), *CALN1* (7q11.22), *FOXO3* (6q21), *PHACTR3* (20q13.22), and *SGCZ* (8p22), *SEPTIN3* (22q13.2*)*, all of SNPs meet the threshold of GWAS significance ($p < 10^{-8}$).

2.3. Stuttering

We found one GWAS by Shaw et al. [53] (2021) showing potential shared genetic evidence on schizophrenia and stuttering, with two loci: *AXDND1* (1q25.2) and *LINC02404* (12q21.33). The second one met the GWAS threshold of significance at rs115024493.

2.4. Dyslexia

Dyslexia is pervasive neurodevelopmental disorder with reading and linguistic disturbances. In two independent GWAS studies [54, 55] three of genes significant for schizophrenia were found: *EPHA4, ARL14EP-DT, HTT*. *ARL14EP-DT* gene (11p14.1) SNPs met the statistical threshold in GWAS study that assessed 51,800 subjects with dyslexia and over one million healthy controls [54].

2.5. Other findings

ACTG1P22 identified in schizophrenia GWAS was significantly linked with language functional disconnectivity in the study by Mekki et al. [50]. Two other genes were linked with reading ability in children (*MAGI2*) [56] and two with language ability (*TCF20, GLI3*) in individuals with Alzheimer's disease [57, 58]. *GLI3* SNP (rs3801203) met statistical threshold for GWAS significance. For verbal learning, study by Lahti et al. [59] identified two genes previously found as significant for schizophrenia (*ITIH1, PRKAG2*). For *ITIH1* (3p21.1), three SNPs met GWAS statistical significance (rs2239551, rs2286798, rs678).

Pathway analysis by *Database for Annotation, Visualisation and Integrated Discovery Classification System* (DAVID 6.8) [36] revealed engagement of significant genes in two categories with potential impact on central nervous system: nerve growth factors response and cellular homeostasis (for details see supplementary data: DAVID).

3. Discussion

Despite strong suggestions of the genetic background of language ability in humans, current evidence stemming from GWAS studies did not show any clear genetic architecture of language. From the analysis of the literature we performed, the linguistic background of schizophrenia appears to be complex and polygenic. Out of 14 identified genes, 10 are known as protein-coding and may be functionally classified as: calcium signalling molecules (*CACNA1C, CALN1*), transcription factors (*ETF1, FOXO3, TCF20*) and cytoskeleton-cell adhesion molecules (*AXDND1, LPP, SGCZ, PHACTR3*, and *MAGI2*). Engagement of these three groups of biological factors suggests the common denominator of language disturbances as the consequence of synaptic plasticity and neural network formation impairment.

3.1. Transcription factors and language

The role of transcription factors in language disturbances is exerted by the family of forkhead box/winged-helix (FOX) proteins [60]. The FOX family of proteins contains a highly conserved DNA-binding domain (forkhead domain) and serves as transcription factors in processes of cell differentiation, expression of genes and metabolic coordination [60]. In the human genome, 17 classes of fox proteins (fox: A to Q) were classified with localisation proneness to centromeric and telomeric parts of chromosomes [61].

Until today, the main candidate gene for linguistic skills and disturbances is seen in *FOXP2*. The transcription factor *FOXP2* interacts with multiple gene promoters, including *CNTNAP2* or *DISC1* and has been linked with developmental speech apraxia (DAS) and speech-language disorder (*SPCH1*) [62], moreover, rs10447760 SNP was associated in genetic studies on the Chinese population with schizophrenia [63]. *FOXP2* expression change is therefore suggested as the evolutionary switch in modern human development leading to language exuberance. However, we did not find direct evidence in GWAS studies for an association of *FOXP2* with schizophrenia.

Another important gene is *FOXO3*. It appears that in schizophrenia, mutations in this gene cause disruption of the forkhead box protein pathway. The *FOXO3* gene encodes the Fox-O3 transcription factor, expressed ubiquitously and related to the processes of ageing [64]. Due to its structure, it is involved in the cell's response to oxidative stress, apoptosis, cell cycle regulation, as well as in the response to insulin and insulin-like growth factor 1 (*IGF-1*). Studies on *PC12* (pheochromocytoma-derived) cells revealed the impact of clozapine treatment on the phosphorylation status of Fox-O3 proteins and potential corticosteroids stress response [65], hence atypical neuroleptic action may promote defence mechanisms in neural cells, by inhibiting the impact of ageing and stress. Another analysis connects *FOXO3* with brain volume. A study by Smeland et al. [66], on a large group of patients (n = 82,315), identified a polymorphism within *FOXO3* (rs10457180) associated with smaller brain volume. This suggests a similar process to that seen in dementia, which leads to a systematic reduction in brain volume. Among schizophrenia patients, the expression of Fox-O3 mRNA was also recently found to be altered and related to olanzapine treatment [67].

Another significant gene found in schizophrenia GWAS studies was *FOXP1*, engaged in brain development [68]. The *FOXP1* encodes forkhead box protein 1 transcription factor; mutations in this gene was identified as the cause of *FOXP1* syndrome (*FOXP1S*) linked with intellectual disability and language delay combined with autism spectrum [68].

The abovementioned evidence suggests possible impairments in molecular DNA repair mechanisms, which may be related to brain aging processes [69].

3.2. Calcium signalling and language

The role of calcium ions is stressed by their engagement in the action of G protein-coupled receptors (*GPCR*) crucial for the central nervous system and serves as a therapeutic target in schizophrenia [70]. Calcium signalling also provides excitatory-inhibitory balance in neural networks due to GABA/glutamate interaction and generating the proper oscillatory rhythm [71]. Here we put forward two potential genes, encoding calcium-related proteins as playing the role in schizophrenia and language.

The first gene – *CACNA1C*, encoding calcium voltage-gated channel subunit alpha1 (Cav1.2), has been recognised in genetic association studies as related to schizophrenia, major depressive disorder and autism [72].

The Cav1.2 forms a pore through which calcium flows into the cell and initiates further signalling cascades regulating gene expression – these involve cAMP response

element binding protein (CREB) and Ca2+/calmodulin-dependent protein kinase (CaMKII). This pathway is believed to be essential for maintaining long-term neural plasticity mechanisms. This pathway is believed to be essential for maintaining long-term neural plasticity mechanisms. A recent study by Rodan et al. [73] described the *CACNA1C* variant as determining neurodevelopmental delay phenotype combined with expressive language dysfunctions. Hence, language decline seems to be the trait depending on global disruption of brain development, impacting motoric ability, epileptogenesis and autism traits. The broader clinical picture of *CACNA1C*-derived genetic syndrome is recognised as the autosomal dominant Timothy Syndrome defined by QT interval prolongation and subsequent cardiac dysrhythmias, syndactyly and facial dysmorphic features [74].

The second finding, *CALN1* is a protein-coding gene localised on 7q11.22, widely expressed in the central nervous system; the encoded product, calneuron 1 protein, is thought to be engaged in learning processes [75]. The detailed, molecular role of calneuron 1 is not fully understood. It is believed that the protein regulates vesicular transport as a part of the trans-Golgi network [76].

3.3. Neural cells adhesion and language

Here, we identified five genes taking part both in schizophrenia and language disturbances which may be collectively classified as cell adhesion/cytoskeleton. Engagement of this gene group suggests common background based on intracellular and intercellular mechanisms of connection shaping and plasticity in neural networks. The key role in the disruption of these cellular mechanisms is played by the *DISC1* protein, which occurs in rare cases of hereditary mental illnesses [77]. The Disc1 protein serves as a metabolic hub, integrating cell membrane signalling, second messengers and cytoskeleton in processes of neuronal migration and neurogenesis (particularly in embryonal development) and synaptic plasticity (also in adulthood). It has been suggested that mutation of the *DISC1* gene causes impaired cAMP signalling and increased activity of phosphodiesterase 4 [78], impaired neuronal branching due to dynein motor complex interaction [79] and aggregation of Disc1 protein multimers among neural cells [77], which results in the occurrence of psychiatric symptoms.

A similar association with the cytoskeleton is seen for *AXDND1* and *SGCZ* gene indicated in the review, encoding axonemal dynein light chain and zeta-sarcoglycan domain. *AXDND1* has been recently recognised as crucial for cytoskeleton motility in sperm cells [80], the *AXDND1* mRNA is expressed in the brain [81], however, the putative role in neuronal cytoskeleton has not been confirmed. In the case of zeta-sarcoglycan, the molecule is engaged in the dystrophin-associated complex, clinically linked with muscular dystrophies [82].

Another mentioned gene, *PHACTR3*, plays similar cellular roles and was combined with the functioning of the central nervous system, including the prefrontal cortex structure [83]. Protein phosphatase and actin regulator 3 (phactr) molecules share a unique structure containing two motifs: G-acting binding protein and phosphatase-binding domain [84]; for the phactr3 (scapinin), studies on animal models confirm

its impact on axonal and dendritic length [84]. The impact of scapinin on neural cell morphogenesis may be associated with its forced activity near the cell membrane [85]. Cell membrane activity also links with the *MAGI2* gene product (membrane-associated guanylate kinase), engaged in AMPA receptors (*AMPAR*) synaptic trafficking and recently linked with neurodevelopmental disorder and epilepsy [86].

In summary, indicated genes take part in neurodevelopment, cell and connection shaping, as well as migration. The potential implication to language processing may be explained by a global impairment of neural network shaping on the interhemispheric level, organisation of language centres in the brain, and finally local anatomic changes due to impaired connectivity [87].

4. Summing-up previous GWAS data and recent genome mapping in the context of language

Recent results by Trubetskoy et al. [3] strongly underline the role of pre – and postsynaptic molecular pathways, previously identified as common in neurodevelopmental disorders including autism-spectrum disorder (ASD) [88]. These pathways include excitatory-inhibitory balance in neural networks. Genetic studies indicate schizophrenia as having high overlap with neurodevelopmental speech disorders and autism due to glutamatergic system impairment [89].

The common phenomenon, linking glutamate alterations in neurodevelopment with language features is disconnectivity. Altered functional connections were found in schizophrenia patients including language brain centres (e.g. Broca's area) and linked with synaptic plasticity deficits. These features may also progress with the course of the illness [90, 91].

Language disturbances, may be therefore a consequence of GABA – glutamate disequilibrium. Hence, overactive and prone to degeneration cortical neurons with concurrent GABA-interneuron hypofunction lead to diminished ability to form neural connections [92]. Disconnectivity seems to be a shared mechanism involved in general cognitive decline in schizophrenia. From this point of view, language symptoms reflect only neural associational alterations and do not emerge as an isolated pathology. GWAS studies show the association of schizophrenia diagnosis with major histocompatibility complex (MHC) genes and immunological factors (e.g. CD4) [3, 4, 93].

Chronic mild inflammation linked to schizophrenia is proposed as causal pathology for negative symptoms. Meta-analysis by Dunleavy et al. [94] (2022) suggests proinflammatory cytokines to be dysregulated in schizophrenia with an impact on negative symptoms spectrum. Regarding language, negative formal thought disorders (nFTD) may be a consequence of inflammatory neurodegeneration. Immunological approach should be interpreted having in mind restrictions due to MHC high linkage-disequilibrium [3]. In addition, other hypotheses should be considered, including disturbances of dopamine neurotransmission in the prefrontal cortex (PFC) [99].

5. Conclusion remarks and limitations

Based on the analysis of available GWAS studies, we have proposed several observations regarding the potential biological basis of language impairments in schizophrenia.

First, the polygenic structure of schizophrenia suggests that language impairments may arise from the interaction of multiple molecular pathways rather than a single genetic variant.

We identified several key mechanisms potentially linked to these impairments, including calcium signalling, morphogenesis and cell adhesion, and gene expression regulation (transcription factors) (Figure 2). Their influence on the central nervous system may be significant, but a full explanation requires further research.

Synaptic plasticity alterations may play a role in the language impairments observed in schizophrenia. However, the complexity of this process indicates that language-related symptoms of the disorder may result from the interplay of multiple factors, both biological and environmental. It is also important to consider other possible explanations, including psychological and social factors, which may impact language development and its impairments in schizophrenia.

Our study is not without limitations:

– We did not conduct our own raw data analyses, relying solely on available GWAS study findings.

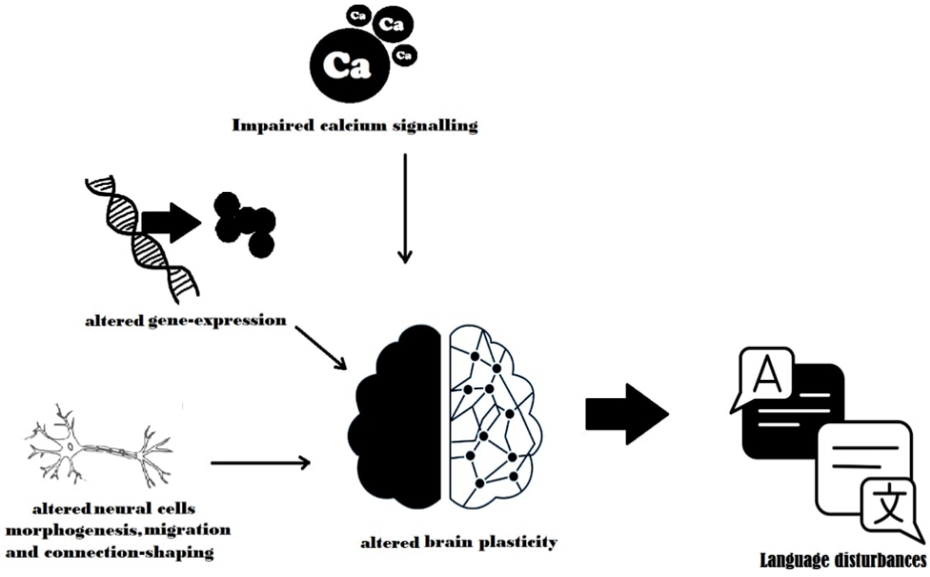

Figure 2. **Suggested mechanism of language impairment in schizophrenia**

- The gene regions identified as potentially associated with language and schizophrenia require further investigation to confirm their actual role.
- There is a lack of large genetic studies specifically focused on language, and the limited number of associations exceeding the GWAS significance threshold reduces the overall scientific value of the analysis.
- GWAS findings are based on correlations, meaning they do not establish a causal relationship. Despite genetic predispositions, the phenotypic expression of language-related traits in schizophrenia may be shaped by additional factors, such as environment and individual experiences [95].

In summary, the genetic determinants of language impairments in schizophrenia should be complemented with psychological and social perspectives to better reflect the multidimensional nature of the disorder

References

1. Kanazawa T, Bousman CA, Liu C, Everall IP. *Schizophrenia genetics in the genome-wide era: a review of Japanese studies*. NPJ Schizophr. 2017; 3(1): 27. Doi: 10.1038/s41537-017-0028-2.
2. Horwitz T, Lam K, Chen Y, Xia Y, Liu C. *A decade in psychiatric GWAS research*. Mol. Psychiatry 2019; 24(3): 378–389. Doi: 10.1038/s41380-018-0055-z.
3. Trubetskoy V, Pardiñas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB et al.; Schizophrenia Working Group of the Psychiatric Genomics Consortium. *Mapping genomic loci implicates genes and synaptic biology in schizophrenia*. Nature 2022; 604(7906): 502–508. Doi: 10.1038/s41586-022-04434-5.
4. Schizophrenia Working Group of the Psychiatric Genomics Consortium. *Biological insights from 108 schizophrenia-associated genetic loci*. Nature 2014; 511(7510): 421–427. Doi: 10.1038/nature13595.
5. Bergen SE, Petryshen TL. *Genome-wide association studies (GWAS) of schizophrenia: Does bigger lead to better results?* Curr. Opin. Psychiatry 2012; 25(2): 76–82. Doi: 10.1097/YCO.0b013e32835035dd.
6. Hugdahl K, Sommer IE. *Auditory verbal hallucinations in schizophrenia from a levels of explanation perspective*. Schizophr. Bull. 2018; 44(2): 234–241. Doi: 10.1093/schbul/sbx142.
7. Oeztuerk OF, Pigoni A, Antonucci LA, Koutsouleris N. *Association between formal thought disorders, neurocognition and functioning in the early stages of psychosis: A systematic review of the last half-century studies*. Eur. Arch. Psychiatry Clin. Neurosci. 2022; 272(3): 381–393. Doi: 10.1007/s00406-021-01295-3.
8. Kay SR, Fiszbein A, Opler LA. *The positive and negative syndrome scale (PANSS) for schizophrenia*. Schizophr. Bull. 1987; 13(2): 261–276. Doi: 10.1093/schbul/13.2.261.
9. Liddle PF, Ngan ETC, Caissie SL, Anderson CM, Bates AT, Quested DJ et al. *Thought and Language Index: An instrument for assessing thought and language in schizophrenia*. Br. J. Psychiatry 2002; 181(4): 326–330. Doi: 10.1192/bjp.181.4.326.
10. McGuffin P, Farmer A, Harvey I. *A polydiagnostic application of operational criteria in studies of psychotic illness: Development and reliability of the OPCRIT system*. Arch. Gen. Psychiatry 1991; 48(8): 764–770. Doi: 10.1001/archpsyc.1991.01810320088015.

11. Nordgaard J, Gravesen-Jensen M, Buch-Pedersen M, Parnas J. *Formal thought disorder and self-disorder: An empirical study*. Front. Psychiatry 2021; 12: 640921. Doi: 10.3389/fpsyt.2021.640921.
12. Craig TK, Rus-Calafell M, Ward T, Leff JP, Huckvale M, Howarth E et al. *AVATAR therapy for auditory verbal hallucinations in people with psychosis: A single-blind, randomised controlled trial*. Lancet Psychiatry 2018; 5(1): 31–40. Doi: 10.1016/S2215-0366(17)30427-3.
13. Hor K, Taylor M. *Review: Suicide and schizophrenia: A systematic review of rates and risk factors*. J. Psychopharmacol. 2010; 24(4_suppl): 81–90. Doi: 10.1177/1359786810385490.
14. Crow TJ. *Schizophrenia as the price that homo sapiens pays for language: A resolution of the central paradox in the origin of the species*. Brain Res. Brain Res. Rev. 2000; 31(2–3): 118–129. Doi: 10.1016/s0165-0173(99)00029-6.
15. Crow TJ. *Is schizophrenia the price that Homo sapiens pays for language?* Schizophr. Res. 1997; 28(2–3): 127–141. Doi: 10.1016/S0920-9964(97)00110-2.
16. Enard W. *The molecular basis of human brain evolution*. Curr. Biol. 2016; 26(20): R1109–R1117. Doi: 10.1016/j.cub.2016.09.030.
17. Mozzi A, Forni D, Clerici M, Pozzoli U, Mascheretti S, Guerini FR et al. *The evolutionary history of genes involved in spoken and written language: Beyond FOXP2*. Sci. Rep. 2016; 6: 22157. Doi: 10.1038/srep22157.
18. Konopka G, Roberts TF. *Insights into the neural and genetic basis of vocal communication*. *Cell* 2016; 164(6): 1269–1276. Doi: 10.1016/j.cell.2016.02.039.
19. Voppel AE, Boer de JN, Brederoo SG, Schnack HG, Sommer I. *Quantified language connectedness in schizophrenia-spectrum disorders*. Psychiatry Res. 2021; 304: 114130. Doi: 10.1016/j.psychres.2021.114130.
20. Liemburg EJ, Vercammen A, Ter Horst GJ, Curcic-Blake B, Knegtering H, Aleman A. *Abnormal connectivity between attentional, language and auditory networks in schizophrenia*. Schizophr. Res. 2012; 135(1–3): 15–22. Doi: 10.1016/j.schres.2011.12.003.
21. Li J, Meltzer HY. *A genetic locus in 7p12.2 associated with treatment resistant schizophrenia*. Schizophr. Res. 2014; 159(2–3): 333–339. Doi: 10.1016/j.schres.2014.08.018.
22. Liou YJ, Wang HH, Lee MTM, Wang SC, Chiang HL, Chen CC et al. *Genome-wide association study of treatment refractory schizophrenia in Han Chinese*. PLoS One 2012; 7(3): e33598. Doi: 10.1371/journal.pone.0033598.
23. Bi X, Feng L, Wang S, Lin Z, Li T, Zhao B et al. *Common genetic variants have associations with human cortical brain regions and risk of schizophrenia*. Genet. Epidemiol. 2019; 43(5): 548–558. Doi: 10.1002/gepi.22203.
24. Luo Q, Chen Q, Wang W, Desrivières S, Burke Quinlan E, Jia T et al.; IMAGEN consortium. *Association of a schizophrenia-risk nonsynonymous variant with putamen volume in adolescents: A voxelwise and genome-wide association study*. JAMA Psychiatry 2019; 76(4): 435–445. Doi: 10.1001/jamapsychiatry.2018.4126.
25. Nakahara S, Turner JA, Calhoun VD, Lim KO, Mueller B, Bustillo JR et al. *Dentate gyrus volume deficit in schizophrenia*. Psychol. Med. 2020; 50(8): 1267–1277. Doi: 10.1017/S0033291719001144.
26. Wolthusen RPF, Hass J, Walton E, Turner JA, Rössner V, Sponheim SR et al. *Genetic underpinnings of left superior temporal gyrus thickness in patients with schizophrenia*. World J. Biol. Psychiatry 2015; 1–11. Online ahead of print.
27. Bakken TE, Bloss CS, Roddey JC, Joyner AH, Rimol LM, Djurovic S et al. *Association of genetic variants on 15q12 with cortical thickness and cognition in schizophrenia*. Arch. Gen. Psychiatry 2011; 68(8): 781–790. Doi: 10.1001/archgenpsychiatry.2011.81.

28. Hass J, Walton E, Kirsten H, Liu J, Priebe L, Wolf C et al. *A genome-wide association study suggests novel loci associated with a schizophrenia-related brain-based phenotype*. PLoS One 2013; 8(6): e64872. Doi: 10.1371/journal.pone.0064872.

29. Wang KS, Liu X, Zhang Q, Aragam N, Pan Y. *Genome-wide association analysis of age at onset in schizophrenia in a European-American sample*. Am. J. Med. Genet. B Neuropsychiatr. Genet. 2011; 156B(6): 671–680. Doi: 10.1002/ajmg.b.31209.

30. Lam M, Hill WD, Trampush JW, Yu J, Knowles E, Davies G et al. *Pleiotropic meta-analysis of cognition, education, and schizophrenia differentiates roles of early neurodevelopmental and adult synaptic pathways*. Am. J. Hum. Genet. 2019; 105(2): 334–350. Doi: 10.1016/j.ajhg.2019.06.012.

31. McClay JL, Adkins DE, Aberg K, Bukszár J, Khachane AN, Keefe RSE et al. *Genome-wide pharmacogenomic study of neurocognition as an indicator of antipsychotic treatment response in schizophrenia*. Neuropsychopharmacology 2011; 36(3): 616–626. Doi: 10.1038/npp.2010.193.

32. Konte B, Leicht G, Giegling I, Pogarell O, Karch S, Hartmann AM et al. *A genome-wide association study of early gamma-band response in a schizophrenia case-control sample*. World J. Biol. Psychiatry 2018; 19(8): 602–609. Doi: 10.1080/15622975.2017.1366054.

33. Fanous AH, Zhou B, Aggen SH, Bergen SE, Amdur RL, Duan J et al.; Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. *Genome-wide association study of clinical dimensions of schizophrenia: Polygenic effect on disorganized symptoms*. Am. J. Psychiatry 2012; 169(12): 1309–1317. Doi: 10.1176/appi.ajp.2012.12020218.

34. Shin W, Kweon H, Kang R, Kim D, Kim K, Kang M et al. *Scn2a haploinsufficiency in mice suppresses hippocampal neuronal excitability, excitatory synaptic drive, and long-term potentiation, and spatial learning and memory*. Front. Mol. Neurosci. 2019; 12: 145. Doi: 10.3389/fnmol.2019.00145.

35. Wang KS, Zhang Q, Liu X, Wu L, Zeng M. *PKNOX2 is associated with formal thought disorder in schizophrenia: A meta-analysis of two genome-wide association studies*. J. Mol. Neurosci. 2012; 48(1): 265–272. Doi: 10.1007/s12031-012-9787-4.

36. Sherman BT, Hao M, Qiu J, Jiao X, Baseler MW, Lane HC et al. *DAVID: A web server for functional enrichment analysis and functional annotation of gene lists (2021 update)*. Nucleic Acids Res. 2022; 50(W1): W216–W221. Doi: 10.1093/nar/gkac194.

37. Davies G, Lam M, Harris SE, Trampush JW, Luciano M, Hill WD et al. *Study of 300,486 individuals identifies 148 independent genetic loci influencing general cognitive function*. Nat. Commun. 2018; 9(1): 2098. Doi: 10.1038/s41467-018-04362-x.

38. Hill WD, Marioni RE, Maghzian O, Ritchie SJ, Hagenaars SP, McIntosh AM et al. *A combined analysis of genetically correlated traits identifies 187 loci and a role for neurogenesis and myelination in intelligence*. Mol. Psychiatry. 2019; 24(2): 169–181. Doi: 10.1038/s41380-017-0001-5.

39. Lee JJ, Wedow R, Okbay A, Kong E, Maghzian O, Zacher M et al. *Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals*. Nat. Genet. 2018; 50(8): 1112–1121. Doi: 10.1038/s41588-018-0147-3.

40. Savage JE, Jansen PR, Stringer S, Watanabe K, Bryois J, Leeuw de CA et al. *Genome-wide association meta-analysis in 269,867 individuals identifies new genetic and functional links to intelligence*. Nat. Genet. 2018; 50(7): 912–919. Doi: 10.1038/s41588-018-0152-6.

41. Okbay A, Wu Y, Wang N, Jayashankar H, Bennett M, Nehzati SM et al. *Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals*. Nat. Genet. 2022; 54(4): 437–449. Doi: 10.1038/s41588-022-01016-z.

42. Demange PA, Malanchini M, Mallard TT, Biroli P, Cox SR, Grotzinger AD et al. *Investigating the genetic architecture of noncognitive skills using GWAS-by-subtraction*. Nat. Genet. 2021; 53(1): 35–44. Doi: 10.1038/s41588-020-00754-2.

43. Kichaev G, Bhatia G, Loh PR, Gazal S, Burch K, Freund MK et al. *Leveraging polygenic functional enrichment to improve GWAS power*. Am. J. Hum. Genet. 2019; 104(1): 65–75. Doi: 10.1016/j.ajhg.2018.11.008.

44. Smith SM, Douaud G, Chen W, Hanayik T, Alfaro-Almagro F, Sharp K et al. *An expanded set of genome-wide association studies of brain imaging phenotypes in UK Biobank*. Nat. Neurosci. 2021; 24(5): 737–745. Doi: 10.1038/s41593-021-00826-4.

45. Elvsåshagen T, Shadrin A, Frei O, Meer van der D, Bahrami S, Kumar VJ et al. *The genetic architecture of the human thalamus and its overlap with ten common brain disorders*. Nat. Commun. 2021; 12(1): 2909. Doi: 10.1038/s41467-021-23175-z.

46. Satizabal CL, Adams HHH, Hibar DP, White CC, Knol MJ, Stein JL et al. *Genetic architecture of subcortical brain structures in 38,851 individuals*. Nat. Genet. 2019; 51(11): 1624–1636. Doi: 10.1038/s41588-019-0511-y.

47. Meer van der D, Frei O, Kaufmann T, Shadrin AA, Devor A, Smeland OB et al. *Understanding the genetic determinants of the brain with MOSTest*. Nat. Commun. 2020; 11(1): 3512. Doi: 10.1038/s41467-020-17368-1.

48. Shadrin AA, Kaufmann T, Meer van der D, Palmer CE, Makowski C, Loughnan R et al. *Vertex-wise multivariate genome-wide association study identifies 780 unique genetic loci associated with cortical morphology*. Neuroimage 2021; 244: 118603. Doi: 10.1016/j.neuroimage.2021.118603.

49. Potkin SG, Turner JA, Guffanti G, Lakatos A, Fallon JH, Nguyen DD et al.; FBIRN. *A genome-wide association study of schizophrenia using brain activation as a quantitative phenotype*. Schizophr. Bull. 2009; 35(1): 96–108. Doi: 10.1093/schbul/sbn155.

50. Mekki Y, Guillemot V, Lemaître H, Carrión-Castillo A, Forkel S, Frouin V et al. *The genetic architecture of language functional connectivity*. Neuroimage 2022; 249: 118795. Doi: 10.1016/j.neuroimage.2021.118795.

51. Smeland OB, Frei O, Kauppi K, Hill WD, Li W, Wang Y et al.; NeuroCHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Cognitive Working Group. *Identification of genetic loci jointly influencing schizophrenia risk and the cognitive traits of verbal-numerical reasoning, reaction time, and general cognitive function*. JAMA Psychiatry 2017; 74(10): 1065–1075. Doi: 10.1001/jamapsychiatry.2017.1986.

52. Fuente de la J, Davies G, Grotzinger AD, Tucker-Drob EM, Deary IJ. *A general dimension of genetic sharing across diverse cognitive traits inferred from molecular data*. Nat. Hum. Behav. 2021; 5(1): 49–58. Doi: 10.1038/s41562-020-00936-2.

53. Shaw DM, Polikowsky HP, Pruett DG, Chen HH, Petty LE, Viljoen KZ et al. *Phenome risk classification enables phenotypic imputation and gene discovery in developmental stuttering*. Am. J. Hum. Genet. 2021; 108(12): 2271–2283. Doi: 10.1016/j.ajhg.2021.11.004.

54. Doust C, Fontanillas P, Eising E, Gordon SD, Wang Z, Alagöz G et al.; 23andMe Research Team; Quantitative Trait Working Group of the GenLang Consortium. *Discovery of 42 genome-wide significant loci associated with dyslexia*. Nat. Genet. 2022; 54(11): 1621–1629. Doi: 10.1038/s41588-022-01192-y.

55. Gialluisi A, Newbury DF, Wilcutt EG, Olson RK, DeFries JC, Brandler WM et al. *Genome-wide screening for DNA variants associated with reading and language traits*. Genes Brain Behav. 2014; 13(7): 686–701. Doi: 10.1111/gbb.12158.

56. Davis OSP, Band G, Pirinen M, Haworth CMA, Meaburn EL, Kovas Y et al. *The correlation between reading and mathematics ability at age twelve has a substantial genetic component*. Nat. Commun. 2014; 5(1): 4204. Doi: 10.1038/ncomms5204.

57. Deters KD, Nho K, Risacher SL, Kim S, Ramanan VK, Crane PK et al.; Alzheimer's Disease Neuroimaging Initiative. *Genome-wide association study of language performance in Alzheimer's disease*. Brain Lang. 2017; 172: 22–29. Doi: 10.1016/j.bandl.2017.04.008.

58. Homann J, Osburg T, Ohlei O, Dobricic V, Deecke L, Bos I et al. *Genome-wide association study of Alzheimer's disease brain imaging biomarkers and neuropsychological phenotypes in the European medical information framework for Alzheimer's disease multimodal biomarker discovery dataset*. Front. Aging Neurosci. 2022; 14: 840651. Doi: 10.3389/fnagi.2022.840651.

59. Lahti J, Tuominen S, Yang Q, Pergola G, Ahmad S, Amin N et al. *Genome-wide meta-analyses reveal novel loci for verbal short-term memory and learning*. Mol. Psychiatry. 2022; 27(11): 4419–4431. Doi: 10.1038/s41380-022-01710-8.

60. Hoed den J, Devaraju K, Fisher SE. *Molecular networks of the FOXP2 transcription factor in the brain*. EMBO Rep. 2021; 22(8): e52803. Doi: 10.15252/embr.202152803.

61. Lehmann OJ, Sowden JC, Carlsson P, Jordan T, Bhattacharya SS. *Fox's in development and disease*. Trends Genet. 2003; 19(6): 339–344. Doi: 10.1016/S0168-9525(03)00111-2.

62. Akter M, Khan SF, Sajib AA, Rima FS. *A comprehensive in silico analysis of the deleterious nonsynonymous SNPs of human FOXP2 protein*. PLoS One 2022; 17(8): e0272625. Doi: 10.1371/journal.pone.0272625.

63. Li T, Zeng Z, Zhao Q, Wang T, Huang K, Li J et al. *FoxP2 is significantly associated with schizophrenia and major depression in the Chinese Han population*. World J. Biol. Psychiatry 2013; 14(2): 146–150. Doi: 10.3109/15622975.2011.615860.

64. Morris BJ, Willcox DC, Donlon TA, Willcox BJ. *FOXO3 – A major gene for human longevity*. Gerontology 2015; 61(6): 515. Doi: 10.1159/000375235.

65. Zeng Z, Wang X, Bhardwaj SK, Zhou X, Little PJ, Quirion R et al. *The atypical antipsychotic agent, clozapine, protects against corticosterone-induced death of PC12 cells by regulating the Akt/FoxO3a signaling pathway*. Mol. Neurobiol. 2017; 54(5): 3395–3406. Doi: 10.1007/s12035-016-9904-4.

66. Smeland OB, Wang Y, Frei O, Li W, Hibar DP, Franke B et al. *Genetic overlap between schizophrenia and volumes of hippocampus, putamen, and intracranial volume indicates shared molecular genetic mechanisms*. Schizophr. Bull. 2018; 44(4): 854–864. Doi: 10.1093/schbul/sbx148.

67. Gu S, Cui F, Yin J, Fang C, Liu L. *Altered mRNA expression levels of autophagy – and apoptosis – related genes in the FOXO pathway in schizophrenia patients treated with olanzapine*. Neurosci. Lett. 2021; 746: 135669. Doi: 10.1016/j.neulet.2021.135669.

68. Lozano R, Gbekie C, Siper PM, Srivastava S, Saland JM, Sethuram S et al. *FOXP1 syndrome: A review of the literature and practice parameters for medical assessment and monitoring*. J. Neurodev. Disord. 2021; 13(1): 18. Doi: 10.1186/s11689-021-09358-1.

69. Papanastasiou E, Gaughran F, Smith S. *Schizophrenia as segmental progeria*. J. R. Soc. Med. 2011; 104(11): 475–484. Doi: 10.1258/jrsm.2011.110051.

70. Boczek T, Mackiewicz J, Sobolczyk M, Wawrzyniak J, Lisek M, Ferenc B et al. *The role of G Protein-Coupled Receptors (GPCRs) and calcium signaling in schizophrenia. Focus on GPCRs activated by neurotransmitters and chemokines*. Cells 2021; 10(5): 1228. Doi: 10.3390/cells10051228.

71. Berridge MJ. *Dysregulation of neural calcium signaling in Alzheimer disease, bipolar disorder and schizophrenia*. Prion 2013; 7(1): 2–13. Doi: 10.4161/pri.21767.

72. Moon AL, Haan N, Wilkinson LS, Thomas KL, Hall J. *CACNA1C: Association with psychiatric disorders, behavior, and neurogenesis*. Schizophr. Bull. 2018; 44(5): 958–965. Doi: 10.1093/schbul/sby096.

73. Rodan LH, Spillmann RC, Kurata HT, Lamothe SM, Maghera J, Jamra RA et al. *Phenotypic expansion of CACNA1C-associated disorders to include isolated neurological manifestations*. Genet. Med. 2021; 23(10): 1922–1932. Doi: 10.1038/s41436-021-01232-8.

74. Baurand A, Falcon-Eicher S, Laurent G, Villain E, Bonnet C, Thauvin-Robinet C et al. *Incomplete Timothy syndrome secondary to a mosaic mutation of the CACNA1C gene diagnosed using next-generation sequencing*. Am. J. Med. Genet. A. 2017; 173(2): 531–536. Doi: 10.1002/ajmg.a.38045.

75. Wu YQ, Lin X, Liu CM, Jamrich M, Shaffer LG. *Identification of a human brain-specific gene, calneuron 1, a new member of the calmodulin superfamily*. Mol. Genet. Metab. 2001; 72(4): 343–350. Doi: 10.1006/mgme.2001.3160.

76. McCue HV, Haynes LP, Burgoyne RD. *The diversity of calcium sensor proteins in the regulation of neuronal function*. Cold Spring Harb. Perspect. Biol. 2010; 2(8): a004085. Doi: 10.1101/cshperspect.a004085.

77. Tropea D, Hardingham N, Millar K, Fox K. *Mechanisms underlying the role of DISC1 in synaptic plasticity*. J. Physiol. 2018; 596(14): 2747–2771. Doi: 10.1113/JP274330.

78. Millar JK, Pickard BS, Mackie S, James R, Christie S, Buchanan SR et al. *DISC1 and PDE4B are interacting genetic factors in schizophrenia that regulate cAMP signaling*. Science 2005; 310(5751): 1187–1191. Doi: 10.1126/science.1112915.

79. Kamiya A, Kubo K, Tomoda T, Takaki M, Youn R, Ozeki Y et al. *A schizophrenia-associated mutation of DISC1 perturbs cerebral cortex development*. Nat. Cell Biol. 2005; 7(12): 1167–1178. Doi: 10.1038/ncb1328.

80. Ma Q, Cao C, Zhuang C, Luo X, Li X, Wan H et al. *AXDND1, a novel testis-enriched gene, is required for spermiogenesis and male fertility*. Cell Death Discov. 2021; 7: 348. Doi: 10.1038/s41420-021-00738-z.

81. Hiradate Y, Harima R, Yanai R, Hara K, Nagasawa K, Osada M et al. *Loss of Axdnd1 causes sterility due to impaired spermatid differentiation in mice*. Reprod. Med. Biol. 2022; 21(1): e12452. Doi: 10.1002/rmb2.12452.

82. Waite AJ, Carlisle FA, Chan YM, Blake DJ. *Myoclonus dystonia and muscular dystrophy: ε-sarcoglycan is part of the dystrophin-associated protein complex in brain*. Mov. Disord. 2016; 31(11): 1694–1703. Doi: 10.1002/mds.26738.

83. Schneider E, El Hajj N, Müller F, Navarro B, Haaf T. *Epigenetic dysregulation in the prefrontal cortex of suicide completers*. Cytogenet. Genome Res. 2015; 146(1): 19–27. Doi: 10.1159/000435778.

84. Miyata T, Kikuchi K, Ihara D, Kaito M, Ishibashi Y, Hakamata T et al. *Neuron-enriched phosphatase and actin regulator 3 (Phactr3)/ nuclear scaffold-associated PP1-inhibiting protein (Scapinin) regulates dendritic morphology via its protein phosphatase 1-binding domain*. Biochem. Biophys. Res. Commun. 2020; 528(2): 322–329. Doi: 10.1016/j.bbrc.2020.05.006.

85. Itoh A, Uchiyama A, Taniguchi S, Sagara J. *Phactr3/scapinin, a member of protein phosphatase 1 and actin regulator (phactr) family, interacts with the plasma membrane via basic and hydrophobic residues in the N-terminus*. PLoS One 2014; 9(11): e113289. Doi: 10.1371/journal.pone.0113289.

86. Heyne HO, Artomov M, Battke F, Bianchini C, Smith DR, Liebmann N et al. *Targeted gene sequencing in 6994 individuals with neurodevelopmental disorder with epilepsy*. Genet. Med. 2019; 21(11): 2496–2503. Doi: 10.1038/s41436-019-0531-0.

87. Poeppel D. *The neuroanatomic and neurophysiological infrastructure for speech and language*. Curr. Opin. Neurobiol. 2014; 28: 142–149. Doi: 10.1016/j.conb.2014.07.005.

88. Nisar S, Bhat AA, Masoodi T, Hashem S, Akhtar S, Ali TA et al. *Genetics of glutamate and its receptors in autism spectrum disorder*. Mol. Psychiatry 2022; 27(5): 2380–2392. Doi: 10.1038s41380-022-01506-w.

89. Chang X, Zhao W, Kang J, Xiang S, Xie C, Corona-Hernández et al. *Language abnormalities in schizophrenia: Binding core symptoms through contemporary empirical evidence*. Schizophrenia (Heidelb.). 2022; 8(1): 95. Doi: 10.1038/s41537-022-00308-x.

90. Benetti S, Pettersson-Yeo W, Allen P, Catani M, Williams S, Barsaglini A et al. *Auditory verbal hallucinations and brain dysconnectivity in the perisylvian language network: A multimodal investigation*. Schizophr. Bull. 2015; 41(1): 192–200. Doi: 10.1093/schbul/sbt172.

91. Du J, Palaniyappan L, Liu Z, Cheng W, Gong W, Zhu M et al. *The genetic determinants of language network dysconnectivity in drug-naïve early stage schizophrenia*. NPJ Schizophr. 2021; 7(1): 18. Doi: 10.1038/s41537-021-00141-8.

92. Nelson EA, Kraguljac NV, Maximo JO, Briend F, Armstrong W, Ver Hoef LW et al. *Hippocampal dysconnectivity and altered glutamatergic modulation of the default mode network – A combined resting state connectivity and magnetic resonance spectroscopy study in schizophrenia*. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 2022; 7(1): 108–118. Doi: 10.1016/j.bpsc.2020.04.014.

93. Kelly DL, Li X, Kilday C, Feldman S, Clark S, Liu F et al. *Increased circulating regulatory T cells in medicated people with schizophrenia*. Psychiatry Res. 2018; 269: 517–523. Doi: 10.1016/j.psychres.2018.09.006.

94. Dunleavy C, Elsworthy RJ, Upthegrove R, Wood SJ, Aldred S. *Inflammation in first-episode psychosis: The contribution of inflammatory biomarkers to the emergence of negative symptoms, a systematic review and meta-analysis*. Acta Psychiatr. Scand. 2022; 146(1): 6–20. Doi:10.1111/acps.13416.

95. Bowden J, Holmes MV. *Meta-analysis and Mendelian randomization: A review*. Res. Synth. Methods 2019; 10(4): 486–496. Doi: 10.1002/jrsm.1346.

96. Gialluisi A, Andlauer TFM, Mirza-Schreiber N, Moll K, Becker J, Hoffmann P et al. *Genome-wide association scan identifies new variants associated with a cognitive predictor of dyslexia*. Transl. Psychiatry 2019; 9(1): 77. Doi: 10.1038/s41398-019-0402-0.

97. Greenwood TA, Lazzeroni LC, Maihofer AX, Swerdlow NR, Calkins ME, Freedman R et al. *Genome-wide Association of Endophenotypes for Schizophrenia from the Consortium on the Genetics of Schizophrenia (COGS) Study*. JAMA Psychiatry 2019; 76(12): 1274–1284. Doi: 10.1001/jamapsychiatry.2019.2850.

98. Arpawong TE, Pendleton N, Mekli K, McArdle JJ, Gatz M, Armoskus C et al. *Genetic variants specific to aging-related verbal memory: Insights from GWASs in a population-based cohort*. PLoS One 2017; 12(8): e0182448. Doi: 10.1371/journal.pone.0182448.

99. Samochowiec J, Szulc A, Bieńkowski P, Dudek D, Gałecki P, Heitzman J et al. *Polish Psychiatric Association consensus statement on non-pharmacological methods in the treatment of negative symptoms of schizophrenia*. Psychiatr. Pol. 2021; 55(4): 719–742. https://doi.org/10.12740/PP/OnlineFirst/135527.

100. Debette S, Ibrahim Verbaas CA, Bressler J, Schuur M, et al. *Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium. Genome-wide studies of verbal declarative memory in nondemented older people: the Cohorts for Heart and Aging Research in Genomic Epidemiology consortium.* Biol Psychiatry. 2015 Apr 15;77(8):749-63. doi: 10.1016/j.biopsych.2014.08.027.

Corresponding author: Przemysław Zakowicz
e-mail: przemek@zakowicz.eu