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microRNA as biomarkers of impulsiveness – preliminary study of forensic schizophrenia patients

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Abstract

Introduction:

Impulsivity is a key feature observed in forensic patients with schizophrenia and is frequently associated with aggression and violent behavior. Understanding its biological underpinnings is crucial for improving risk assessment and developing targeted interventions. Genetic factors, particularly microRNAs (miRNAs), have emerged as promising candidates for explaining the molecular basis of impulsivity. miRNAs are small, non-coding RNAs that regulate gene expression post-transcriptionally, influencing neurodevelopment, synaptic plasticity, and neuroinflammation, processes often disrupted in schizophrenia. This preliminary study investigates the contribution of miRNAs to impulsivity in forensic patients with schizophrenia, focusing on whether altered expression profiles may underlie behavioral dysregulation.

Patients and Methods:

The study included 14 forensic patients diagnosed with schizophrenia who had committed impulsive and/or violent acts, and 3 healthy controls. Impulsivity and aggression were assessed using standardized psychological tools - Impulsiveness-Venturesomeness-Empathy (IVE) and Buss–Perry Aggression Questionnaire (BPAQ). Sociodemographic and clinical data were collected to control for potential confounders, and the study groups were homogeneous with respect to age, gender, and disease severity. Peripheral blood samples were obtained, and expression profiling of 177 miRNAs was performed using miRCURY LNA miRNA Focus PCR Panels (Qiagen). Differentially expressed (DE) miRNAs were identified via real-time PCR. Target prediction for DE miRNAs was carried out using the multimiR R package with gene lists derived from DisGeNET for psychotic disorders and schizophrenia, as well as GWAS associations for schizophrenia and aggression. Additional aggression- and impulse control–related genes were included from curated resources.

Results

17 DE miRNAs were identified in forensic patients compared with controls, including 16 upregulated and 1 downregulated. Among these, hsa-miR-424-5p, hsa-miR-20b-5p, and hsa-let-7g-5p regulated the largest number of schizophrenia- and aggression-associated targets. Target prediction highlighted *QKI* and *SOBP*, implicated in neurodevelopment and psychosis, as common regulatory nodes. Gene enrichment and network analyses revealed significant associations with neurodevelopmental pathways, impulse control, aggression, and psychotic disorders. *ARID1A* emerged as a central hub gene, reinforcing the link between miRNA dysregulation, and disrupted cortical development.

Conclusion

These findings suggest that dysregulated miRNAs, particularly hsa-miR-424-5p, may contribute to the molecular basis of impulsivity and aggression in schizophrenia. The identification of key targets such as *QKI*, *SOBP*, and *ARID1A* genes underscores the role of miRNA regulatory networks in neurodevelopmental dysfunction. This preliminary evidence supports the potential of miRNAs as biomarkers and therapeutic targets in forensic schizophrenia populations, offering new opportunities for early identification and intervention.

Introduction

Schizophrenia is a severe psychiatric disorder characterized by disturbances in cognition, perception, and behavior, with a heritability estimated at nearly 80% and a complex polygenic architecture shaped by both common and rare genetic variants (1–3). Beyond psychotic symptoms, a subset of patients, particularly those in forensic settings, display heightened impulsivity and aggression, which are major contributors to violent behavior and criminal offenses (4–6). Understanding the biological determinants of such behaviors remains a critical challenge, as current clinical and sociodemographic predictors are limited in their explanatory power.

Recent advances in psychiatric genetics highlight the importance of post-transcriptional regulation by microRNAs (miRNAs), small non-coding RNAs that fine-tune gene expression and influence neuronal development, synaptic plasticity, and immune function (7, 8). Dysregulation of specific miRNAs, such as miR-137, miR-132, miR-34a, and miR-181, has been repeatedly implicated in schizophrenia, converging on pathways relevant to dopamine signaling, neurodevelopment, and inflammatory processes (9–12). Notably, miR-137 is a well-established schizophrenia risk locus from genome-wide association studies (GWAS) and regulates genes like *CACNA1C* and *ZNF804A*, underscoring the role of miRNAs as genetic modifiers of disease onset and severity (1, 2, 13–15).

Emerging evidence further suggests that miRNAs may serve as biomarkers of behavioral phenotypes within schizophrenia. Studies have shown associations between altered miRNA expression and impulse control, aggression, and violence-related traits, as well as enrichment of miRNA-regulated genes in pathways linked to psychotic disorders, mood instability, and neurodevelopmental syndromes (16–18). For instance, dysregulated miRNAs such as miR-424-5p and miR-20b-5p have been predicted to target schizophrenia- and aggression-related genes, while hub genes like *QKI* and *ARID1A*, critical for myelination and cortical development, emerge as convergence points of miRNA regulation (1). Moreover, structural variants such as the 1q21.1 deletion, associated with impulsivity and dopaminergic dysregulation, highlight the interplay between genetic risk and miRNA-mediated modulation of neurobehavioral outcomes (15).

Despite these advances, limited research has addressed miRNA dysregulation specifically in forensic schizophrenia populations, where impulsivity and aggression have direct societal and legal implications. This represents a critical gap, as identifying molecular biomarkers of these behavioral dimensions could improve risk stratification, forensic assessments, and personalized therapeutic strategies.

Here, we present a preliminary study examining the expression of candidate miRNAs in forensic patients with schizophrenia, with a focus on their potential role as biomarkers of impulsivity and aggressive behavior. By integrating psychiatric, psychological, and molecular data. This project aims to uncover novel mechanistic insights and lay the groundwork for future biomarker-driven approaches in high-risk populations and to provide a foundation for designing a methodologically robust study with appropriately sized study and control groups.

Materials and Methods

Study population

The study included 14 forensic male patients, aged between 22 and 55 (M = 33,86; SD = 9,42) who had committed impulsive and/or violent acts, and 3 healthy controls without psychiatric or neurological disorders. All 14 patients were diagnosed with schizophrenia. Eight of them (57.1%) were found to be addicted to drugs, while one person (7.1%) was addicted to alcohol.

Six patients (42.9% of the sample) were found to have also somatic diseases, including three diagnosed with diabetes, two with obesity, and isolated cases of psoriasis, Gilbert's syndrome, and gallstones. All of them were recruited from the Forensic Psychiatry Clinic at Institute of Psychiatry and Neurology in Warsaw, where they had been treated for a period ranging from 20 to 63 months (M = 31.86; SD = 11.84). Patients included in the study have committed the most serious violent crimes, mainly against human life and health. For all sociodemographic features see Fig. 1. Prior to their current hospitalization, the patients had committed violent offenses, including acts of homicide (Article 148 of the Polish Penal Code; n = 11, 78.6%) and bodily harm (Article 157 of the Polish Penal Code; n = 4, 28.6%). During hospitalization in the forensic psychiatry ward, aggressive behavior was observed in only one case. Most patients were stable, and an unstable mental state was observed in 4 out of 14 cases (28.6%). All patients were receiving antipsychotic pharmacotherapy in accordance with clinical guidelines. Treatment regimens were individualized and included both typical and atypical antipsychotics. Therapeutic interventions also encompassed psychoeducation and structured behavioral programs aimed at reducing impulsivity and enhancing emotional regulation.

(art. 148) – murder; (art. 156) – serious bodily injury; (art. 157) – bodily harm; (art. 190) – threat; (art. 207) – family abuse; (art. 223) - assault on a public official; (art. 224) - influencing official acts; (art. 278) – theft; (art. 288) - destruction of goods.

Clinical and psychological assessments

Diagnosis of schizophrenia was confirmed according to ICD-10/DSM-5 criteria using structured psychiatric interviews.

Impulsivity and aggression were assessed using standardized psychiatric and psychological tools - Impulsiveness-Venturesomeness-Empathy (IVE) and Buss–Perry Aggression Questionnaire (BPAQ).

IVE, by H.J. Eysenck and S.B.G Eysenck, is used to test impulsiveness, venturesomeness, and empathy. It consists of 54 items in the form of Yes/No questions. All scales have been normalized to Polish conditions. Theoretical assumptions of the IVE questionnaire were based on Eysenck's personality theory. The development of the questionnaire was preceded by a study on psychoticism, the fourth personality trail. In the opinion of the questionnaire's authors, psychoticism was the second nature of extraversion. Impulsiveness was considered an important element of extraversion because it acts as a regulatory function in human functioning. This means that the intensity of this trait determines whether a person will take specific (e.g., criminal) actions (19).

The Buss–Perry Aggression Questionnaire (BPAQ) is a validated self-report tool designed to measure trait aggression across four domains: physical aggression, verbal aggression, anger, and hostility. It comprises 29 items rated on a Likert scale and is widely used in forensic and clinical populations. Prior research has demonstrated significant correlations between impulsivity and all BPAQ subscales, supporting its relevance in assessing behavioral dysregulation in schizophrenia(20, 21).

Sociodemographic and clinical data were collected to account for confounding variables.

Sample collection and RNA extraction

Peripheral blood samples were obtained from all participants using EDTA tubes. Total RNA, including small RNAs, was isolated using the miRNeasy Serum/Plasma Kit (Qiagen) according to the manufacturer’s instructions. RNA quality and concentration were assessed with a NanoDrop spectrophotometer and Bioanalyzer 2100 (Agilent Technologies).

miRNA expression profiling

Expression profiling of 177 microRNAs was performed using the miRCURY LNA miRNA Focus PCR Panels (Qiagen). Reverse transcription and cDNA synthesis were carried out with the miRCURY LNA RT Kit. Quantitative real-time PCR (qPCR) was performed on a LightCycler 480 System (Roche) under standard cycling conditions. Ct values were normalized to suitable endogenous controls, and relative expression levels were calculated using the ΔΔCt method.

Differential expression analysis

Group comparisons between forensic patients and controls were performed using a t-test with false discovery rate (FDR) correction to adjust for multiple testing. Differentially expressed (DE) miRNAs were defined as those meeting statistical significance after correction and showing a minimum fold-change threshold ($p < 0.05$).

Target prediction and functional annotation

Putative gene targets of DE miRNAs were identified using the multimiR R package (22). The multiMiR R package integrates information from multiple databases to predict and validate miRNA–target interactions. It combines predicted targets from established algorithms (e.g., TargetScan, miRanda, PicTar, DIANA-microT, PITA) and experimentally validated interactions from curated databases (e.g., miRTarBase, TarBase, miRecords). Each predicted interaction is supported by confidence scores based on the number and quality of databases reporting it. The package allows querying by miRNA, gene, or interaction type and provides a unified framework for retrieving, filtering, and integrating miRNA-target relationships for downstream functional or network analyses. For our analysis we used top 20% of both validated and predicted miRNA-target interactions.

Target lists were cross-referenced with disease-relevant databases: DisGeNET for psychotic disorders (89 genes) and schizophrenia (119 genes), as well as GWAS catalogs for schizophrenia (68 genes) and aggressive behavior (34 genes). Additionally, a curated set of 8 genes linked to aggression and impulse control was included.

MiRNA-gene interactions were aggregated using our wizbionet R package (https://github.com/wizbionet/wizbionet/blob/master/.vignette_wizbionet.md) (23). In effect, we obtained information on how many genes from each list are regulated by a given miRNA and stacked the list of those genes. In the next step, we used our R function from wizbionet based on a machine learning algorithm OneR, which divided each numerical column with the number of targets into four clusters. In this context, OneR performs non-arbitrary numeric classification based on Jenks natural breaks optimization, which divides continuous numeric values (here, the number of regulated genes per miRNA) into four clusters that minimize within-cluster variance and maximize between-cluster separation. This method allows an objective distinction of miRNAs with particularly high regulatory counts without imposing arbitrary cut-offs. If the data distribution yielded clusters that were too small for robust comparison, the algorithm automatically applied k-means clustering (k = 4) as a fallback. Top targets were selected by aggregation of target-miRNA interactions. For further analysis, we selected targets regulated by all differentially expressed (DE) miRNAs.

Enrichment analysis

Gene enrichment analyses were performed using EnrichR, focusing on phenotypes implicated in neurodevelopment, synaptic function, and psychiatric disorders (24). We performed analysis of genes regulated by all DE miRNAs. This analysis employed Fisher's exact test with the Benjamini and Hochberg correction, using a precomputed background as the reference for each term within each gene set library. In all analyses, Benjamini-Hochberg (BH) corrected p-value cutoff was set as lower than 0.05.

Interaction network construction

Gene-gene interaction networks were constructed using StringApp and visualized in Cytoscape, enabling identification of hub genes regulated by all DE miRNAs (25, 26). Nodes were ordered using circular layout based on decreasing degree of connections.

Statistical analysis

All analyses were conducted in R (version X.X). Continuous variables were compared using t-tests or Mann–Whitney U tests, as appropriate. Categorical variables were analyzed with chi-square tests. A significance threshold of $p < 0.05$ (FDR-adjusted) was applied for all enrichment and expression analyses.

Results

Psychiatric and psychological tests

Owing to the specific characteristics of the study population, psychiatric and psychological assessments were completed for only 10 patients, as the remaining participants were transferred to other facilities by court order. The results obtained in the study group using the IVE questionnaire indicate significant diversity across all three measured dimensions (Table 1.). In the impulsivity scale, raw scores ranged from 1 to 15 points (M = 5.2; SD = 4.25), which translated to sten scores ranging from 1 to 9. Analysis of the sten score distribution showed that 3 individuals obtained very low results (sten 1–2), 2 individuals low results (sten 3–4), 2 individuals average results (sten 5–6), 2 individuals high results (sten 7–8), and 1 person a very high result (sten 9). In the risk-taking scale, raw scores ranged from 0 to 12 points (M = 6.5; SD = 3.92), corresponding to sten scores from 1 to 8. The distribution revealed that 2 individuals obtained very low results (sten 1–2), 3 individuals low results (sten 3–4), 2 individuals average results (sten 5–6), and 3 individuals high results (sten 7–8). In the empathy scale, raw scores ranged from 4 to 16 points (M = 11.0; SD = 4.49), translating to sten scores from 2 to 8. The score distribution showed that 2 individuals obtained low results (sten 2–3), 3 individuals average results (sten 4–5), 3 individuals high results (sten 6–7), and 2 individuals very high results (sten 8).

Table 1
Buss-Perry Aggression Questionnaire (BPAQ) – Results

ID		Physical Aggression (PA)	Verbal Aggression (VA)	Anger (A)	Hostility (H)	Total
P1		15	10	12	18	55
P2		25	16	15	22	78
P3		11	10	9	26	56
P4		23	15	10	10	58
P5		9	10	11	8	38
P6		25	14	15	13	67
P7		11	12	7	9	39
P8		26	18	16	19	79
P9		20	15	23	21	79
P10		24	14	23	25	86
	M	**18.9**	**13.4**	**14.1**	**17.1**	**63.5**
	SD	**6.73**	**2.84**	**5.52**	**7.08**	**6.73**

In the BPAQ (the physical aggression scale), raw scores ranged from 9 to 26 points (M = 18.9; SD = 6.72), see Table 2. Distribution analysis indicated that 2 individuals obtained low results (< 14 pts), 4 individuals average results (14–20 pts), and 4 individuals high results (> 20 pts). In the verbal aggression scale, raw scores ranged from 10 to 18 points (M = 13.4; SD = 2.80), with 2 individuals obtaining low results (< 12 pts), 5 individuals average results (12–15 pts), and 3 individuals high results (> 15 pts). In the anger scale, raw scores ranged from 7 to 23 points (M = 14.1; SD = 5.49). Score distribution revealed that 2 individuals obtained low results (< 10 pts), 5 individuals average results (10–18 pts), and 3 individuals high results (> 18 pts). In the hostility scale, raw scores ranged from 8 to 26 points (M = 17.1; SD = 6.96). Distribution analysis indicated that 3 individuals obtained low results (< 14 pts), 3 individuals average results (14–20 pts), and 4 individuals high results (> 20 pts). The total aggression score in the study group ranged from 38 to 86 points (M = 63.5; SD = 15.39). The score distribution showed that 2 individuals obtained low results (< 55 pts), 4 individuals average results (55–70 pts), and 4 individuals high results (> 70 pts).

Table 2
Impulsiveness-Venturesomeness-Empathy (IVE) – Results

		Raw Scores			Sten Scores		
		I	**R**	**E**	**I**	**R**	**E**
ID		Impulsivity	Risk-taking	Empathy	Impulsivity	Risk-taking	Empathy
P1		3	6	5	4	5	2
P2		2	4	15	3	4	7
P3		1	0	16	1	1	8
P4		6	12	9	6	8	4
P5		1	2	10	1	1	5
P6		7	10	16	5	5	8
P7		3	9	8	4	7	3
P8		15	7	13	9	6	6
P9		4	11	4	5	8	2
P10		10	4	14	6	2	7
	M	5,2	6,5	11	4,4	4,6	5,2
	SD	4,49	3,92	4,32	2,47	2,58	2,36

These results reflect the patients' status at a specific moment in the therapeutic process during their stay in the forensic psychiatry ward, undergoing regular pharmacotherapy and systematic therapeutic interventions. The observed diversity in results may stem from differential responses to treatment, the influence of the structured therapeutic environment, and individual psychological characteristics of the study participants.

Genetic - Differentially expressed miRNAs

Expression profiling of 177 miRNAs identified 17 differentially expressed (DE) miRNAs in forensic patients with schizophrenia compared to controls (FDR-corrected $p < 0.05$). Of these, 16 miRNAs were upregulated (hsa-miR-424-5p; hsa-miR-20b-5p; hsa-let-7g-5p; hsa-miR-18a-5p; hsa-miR-106b-5p; hsa-miR-19a-3p; hsa-miR-19b-3p; hsa-miR-106a-5p; hsa-miR-93-5p; hsa-miR-7-5p; hsa-miR-29c-3p; hsa-miR-125b-5p; hsa-miR-141-3p; hsa-miR-144-3p; hsa-miR-140-3p; hsa-miR-1) and 1 was downregulated (hsa-miR-126-5p). A volcano plot (Fig. 2.) illustrated the distribution of DE miRNAs, highlighting those with both statistical significance and strong fold-changes.

Target prediction and prioritization

Target prediction using the multimiR R package revealed that DE miRNAs collectively regulated numerous genes implicated in psychiatric disorders. To prioritize biologically relevant interactions, we cross-referenced predicted targets with gene lists obtained from DisGeNET (89 genes for psychotic disorders; 119 genes for schizophrenia), GWAS data (68 genes for schizophrenia; 34 genes for aggressive behavior), and curated aggression/impulse-control genes (8 genes). DE miRNAs were ranked by the number of disease-associated targets using the wizbionet R package, and clustering via the OneR algorithm identified three key candidates: hsa-miR-424-5p; hsa-miR-20b-5p; hsa-let-7g-5p. These miRNAs regulated the largest number of genes linked to schizophrenia, psychosis, and aggression (Table 3.).

Table 3

Differentially expressed (DE) miRNAs were ranked based on number of disease-related targets using wizbionet R package. Numbers of targets were divided into four clusters using the OneR algorithm. Three top miRNAs regulating highest number of disease related targets were hsa-miR-424-5p, hsa-miR-20b-5p, hsa-let-7g-5p.

mature mirna id	FDR	log2 fold change	Psychotic Disorders DisgeNet (89)	Schizophrenia DisgeNet (119)	Schizophrenia GWAS (68)	aggressive behavior GWAS (34)	Aggresion and impulse control (8)	Cluster 1 COUNT	Cluster1 2 COUNT
hsa-miR-424-5p	0.048	-2.13	62	81	31	15	7	4	5
hsa-miR-20b-5p	0.048	-2.67	61	81	36	14	3	4	4
hsa-let-7g-5p	0.048	-1.70	57	79	30	13	5	3	5
hsa-miR-18a-5p	0.036	-3.52	51	78	34	12	4	2	5
hsa-miR-106b-5p	0.036	-4.02	52	73	34	13	2	2	4
hsa-miR-19a-3p	0.048	-3.27	57	69	29	15	3	2	4
hsa-miR-19b-3p	0.036	-4.07	56	69	29	14	3	2	4
hsa-miR-106a-5p	0.043	-2.43	48	71	31	13	3	1	4
hsa-miR-93-5p	0.048	-2.61	46	74	31	12	4	0	5
hsa-miR-7-5p	0.006	-3.54	51	70	29	11	3	0	4
hsa-miR-29c-3p	0.048	-4.14	43	62	29	7	1	0	3
hsa-miR-125b-5p	0.048	-2.74	11	29	13	3	5	0	1
hsa-miR-126-5p	0.031	2.01	28	41	13	7	1	0	0
hsa-miR-141-3p	0.036	-3.67	24	35	17	4	3	0	0
hsa-miR-144-3p	0.036	-4.22	20	30	7	4	0	0	0

mature mirna id	FDR	log2 fold change	Psychotic Disorders DisgeNet (89)	Schizophrenia DisgeNet (119)	Schizophrenia GWAS (68)	aggressive behavior GWAS (34)	Aggresion and impulse control (8)	Cluster 1 COUNT	Cluster1 2 COUNT
hsa-miR-140-3p	0.043	-3.74	18	20	10	2	1	0	0
hsa-miR-1	0.046	-4.55	no data	no data	no data	no data	no data		

Disease-relevant gene targets

Across all DE miRNAs, 100 unique genes were identified (Supplementary Table 1). Two genes overlapped with schizophrenia-associated databases:

- *QKI* (Quaking homolog, KH domain RNA-binding protein): Strongly implicated in schizophrenia through roles in alternative splicing, mRNA stability, myelination, and glial function. Reduced *QKI* expression has been reported in the prefrontal cortex of patients with schizophrenia (27, 28)
- *SOBP* (Sine oculis-binding protein homolog): Implicated in neurodevelopment and has been found in GWAS located near loci associated with early-onset psychosis and cognitive deficits (GWAS meta-analyses (e.g., PGC data) have occasionally identified *SOBP*-adjacent loci with borderline significance, but replication is limited)(29).

Network and enrichment analyses

Enrichment analysis of the 100 target genes (EnrichR, GSEA) revealed significant associations with neurodevelopmental processes, synaptic plasticity, impulse control, aggression, and psychotic disorders (p-adj < 0.05; Table 4.).

Table 4
Enrichment analysis of all 100 targets performed in EnrichR database. In the table are showed top 20 ontological terms

Jensen DISEASES Curated 2025	Overlap	Adjusted P-value	Genes
Autosomal Dominant Intellectual Developmental Disorder	4/18	2.081E-04	*ADNP; ARID1A; ARID2; SOX11;*
Coffin-Siris Syndrome	3/10	5.599E-04	*ARID1A; ARID2; SOX11;*
Intellectual Disability	4/31	5.599E-04	*ADNP; ARID1A; ARID2; SOX11;*
Specific Developmental Disorder	4/33	5.599E-04	*ADNP; ARID1A; ARID2; SOX11;*
Developmental Disorder of Mental Health	5/68	5.599E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2;*
Disease of Mental Health	5/135	1.192E-02	*ADNP; ARID1A; ARID2; SOX11; CHD2;*
Congenital Nervous System Abnormality	4/92	2.046E-02	*CNOT1; CDK6; WDFY3; PAFAH1B1*
Autosomal Dominant Disease	8/444	2.648E-02	*ADNP; ARID2; ARID1A; SOX11; DICER1; TGFBR1; PAFAH1B1; SPRED1*
Organ System Cancer	5/204	4.902E-02	*ARID1A; CDK6; PPP2R1B; TET2; TGFBR1*
Syndrome	8/545	7.269E-02	*ARID1A; ARID2; SOX11; SPRED1; CNOT1; DICER1; TGFBR1; PAFAH1B1*
Tauopathy	2/26	7.269E-02	*ADAM10; RALGPS2*
Alzheimer's Disease	2/26	7.269E-02	*ADAM10; RALGPS2*
Neurodegenerative Disease	7/463	7.269E-02	*UNC80; DST; WNK1; ADAM10; LRP12; YWHAG; RALGPS2*
Central Nervous System Disease	10/874	7.269E-02	*UNC80; DST; WNK1; ADAM10; RORA; CHD2; LRP12; YWHAG; TNRC6A; RALGPS2*
Biliary Tract Cancer	2/34	7.269E-02	*ARID1A; CDK6;*
Bile Duct Carcinoma	2/34	7.269E-02	*ARID1A; CDK6;*
Cholangiocarcinoma	2/34	7.269E-02	*ARID1A; CDK6;*
Bile Duct Cancer	2/34	7.269E-02	*ARID1A; CDK6;*
Hepatobiliary System Cancer	2/34	7.269E-02	*ARID1A; CDK6;*
Adenocarcinoma	2/34	7.269E-02	*ARID1A; CDK6;*

A gene-gene interaction network constructed with STRING (Table 5.; Fig. 3.) and visualized in Cytoscape (Fig. 4.) identified *ARID1A* as a central hub gene. *ARID1A*, a key regulator of neural stem/progenitor cell proliferation and cortical development, was highly connected within the network and linked to phenotypes such as Coffin-Siris syndrome, characterized by neurodevelopmental delay and brain anomalies.

Table 5
Enrichment analysis of 76 interacting targets based on gene-gene interaction network. In the table are showed top 20 ontological terms

Monarch phenotypes	Overlap	Adjusted P-value	Genes
Autistic behavior	13/460	1.400E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; TAOK1; RORA; NONO; WDFY3; YWHAG; SON; MED13; TET3*
Abnormal corpus callosum morphology	16/784	1.400E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; CDK6; TAOK1; CNOT1; CCDC47; RORA; NONO; WDFY3; YWHAG; SON; PAFAH1B1; MED13*
Abnormal cerebral white matter morphology	17/914	1.400E-04	*ADNP; ARID1A ARID2; SOX11; CHD2; CDK6; TAOK1; CNOT1; CCDC47; RORA; NONO; WDFY3; YWHAG; SON; PAFAH1B1; MED13; TET3*
Abnormal cerebral subcortex morphology	17/999	2.400E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; CDK6; TAOK1; CNOT1; CCDC47; RORA; NONO; WDFY3; YWHAG; SON; PAFAH1B1; MED13; TET3*
Abnormal hair pattern	10/290	2.800E-04	*ADNP; ARID1A; ARID2 SOX11; CHD2; MAPK1; NR3C1; WDFY3; SPRED1; MED13*
Hematological measurement	37/4592	3.000E-04	*ARID1A; ARID2; CHD2; CDK6; TAOK1; CNOT1; APPBP2; GLCCI1; NUFIP2; NR3C1; CANX; RORA; CPEB3; WDFY3; SIK2; PPP2R1B; TNPO1; LARP1; WNK1; TMEM189-UBE2V1; QKI; RC3H1; MCL1; ZNF618; TNRC6A; PAFAH1B1; MED13; ARHGEF12; USP47; INO80D; TET3; MAP3K2; CREB1; CHD9; TET2; BAZ2A; PEAK1*
Wide mouth	8/163	3.000E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; MAPK1; NONO; MED13*
Abnormality of skull size	19/1333	3.000E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; MAPK1; CCDC47; TAOK1; CDK6; NONO; WDFY3; SPRED1; YWHAG; CNOT1; SON; PAFAH1B1; MED13; TET3; DICER1*
Abnormality of the forehead	16/926	3.000E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; CDK6; CNOT1; MAPK1; CCDC47; NONO; WDFY3; YWHAG; SON; MED13; TET3; DICER1*
Language impairment	15/809	3.000E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; CNOT1; MAPK1; CCDC47; RORA; NONO; WDFY3; YWHAG; PAFAH1B1; MED13; TET3*
Sex hormone-binding globulin measurement	13/625	4.100E-04	*ADNP; ARID1A; ARID2; CHD2; NR3C1; RORA; CDK6; KPNB1; TNPO1; TNRC6A; QSER1; CREB1; DICER1*
Thin vermilion border	10/338	4.100E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; CDK6; NONO; WDFY3; SON; MED13*
Abnormality of the philtrum	12/535	4.100E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; CNOT1; MAPK1; NONO; WDFY3; SON; MED13; TET3*
Hyperactivity	11/423	4.100E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; MAPK1; WDFY3; SPRED1; YWHAG; MED13; TET3*
Gastroesophageal reflux	10/331	4.100E-04	*ADNP; ARID2; CHD2; MAPK1; CCDC47; TAOK1; NONO; YWHAG; WNK1; SON;*
Abnormality of mouth size	10/337	4.100E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; MAPK1; NONO; WDFY3; SON; MED13*
Thin upper lip vermilion	9/269	4.500E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; CDK6; NONO; WDFY3; MED13*
Aplasia/Hypoplasia of the cerebrum	18/1300	4.500E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; CDK6; TAOK1; MAPK1; CCDC47; RORA; NONO; WDFY3; YWHAG; CNOT1; SON; PAFAH1B1; MED13; TET3*
Delayed speech and language development	14/790	5.100E-04	*ADNP; ARID1A; ARID2; SOX11; CHD2; CNOT1; MAPK1; CCDC47; RORA; NONO; WDFY3; YWHAG; MED13; TET3*
Joint laxity	8/200	5.100E-04	*ADNP; ARID1A ARID2; SOX11; MAPK1; CCDC47; NONO; TGFBR1*

Discussion

This preliminary study explored the expression of circulating miRNAs in forensic male patients with schizophrenia who had committed impulsive or violent acts. The results revealed a distinct miRNA expression profile in this population, with 17

differentially expressed miRNAs identified, 16 upregulated and one downregulated compared to healthy controls. Among these, hsa-miR-424-5p, hsa-miR-20b-5p, and hsa-let-7g-5p emerged as key regulatory molecules targeting multiple schizophrenia- and aggression-associated genes, notably *QKI*, *SOBP*, and *ARID1A*. These findings support a growing body of evidence implicating non-coding RNAs in the pathophysiology of schizophrenia and, more specifically, in behavioral dysregulation linked to impulsivity and aggression (17, 30–34).

The results from IVE and BPAQ questionnaires should be interpreted within the context of the specific clinical and environmental conditions of the studied group. The study participants were patients of a forensic psychiatry ward, undergoing regular pharmacotherapy and systematic therapeutic interventions. It is important to emphasize that these elements (pharmacological treatment and the environment) may influence the severity of the studied psychological traits (35, 36) and additionally they can modulate the expression of multiple target genes.

The IVE questionnaire results showed variation in the levels of impulsivity, risk-taking tendencies, and empathy among the participants. This diversity may stem from differential responses to pharmacotherapy, particularly to antipsychotic medications, which are known to reduce, among other things, impulsivity (37). This could explain why some individuals exhibited good impulse control while others were characterized by high impulsivity. The structured environment of forensic detention and the patients' therapeutic engagement may also contribute to the development of self-regulation skills, even among patients who initially displayed high impulsivity (38, 39).

The BPAQ results also demonstrated heterogeneity in aggression levels, which may reflect both the effectiveness of therapeutic interventions (40) and the complex nature of aggression in individuals with mental disorders (41). The closed environment of the patients' detention, which has clearly defined rules, may suppress the expression of physical aggression, while verbal aggression or hostility might be more acceptable forms of emotional expression (42). Furthermore, pharmacotherapy likely contributes to the reduction of anger and hostility (40), which is reflected in the variation of scores on the BPAQ subscales. Participation in individual and group therapy may also foster the development of empathy and social skills, partially explaining the variation in these areas (43).

Disturbances in cognitive processes within the domain of social cognition, including difficulties in recognizing the intentions, emotions, and mental states of others, represent a significant limitation in the functioning of some patients with schizophrenia (44). These deficits can limit the expression of empathy and social competencies (45). The presented results should be interpreted within the context of the patients' stay in a specific environment and at a specific point in their treatment. The severity of these traits may differ from pre-treatment levels or from profiles observed in less restrictive conditions, indicating a dynamic nature of the observed psychological processes (46).

Recent genomic and transcriptomic research underscores the polygenic and regulatory complexity of schizophrenia (2). Variants within non-coding regions and transcriptional regulators contribute substantially to disease risk (1, 18). The present results align with this framework, demonstrating altered miRNA activity that may affect gene networks involved in neurodevelopment and cortical maturation (47, 48). Notably, miR-424-5p and miR-20b-5p are components of the miR-16/15 family, known to regulate cell-cycle control, synaptic plasticity, and glial differentiation (27, 28, 34). These molecular functions resonate with neuropathological observations of glial and myelination deficits in schizophrenia, where decreased expression of *QKI*, an RNA-binding protein essential for oligodendrocyte function, disrupts neuronal connectivity and information processing. The identification of *QKI* as a shared target of miR-424-5p and miR-20b-5p strengthens the hypothesis that aberrant miRNA regulation contributes to white-matter and network abnormalities reported in schizophrenia (12, 18, 49, 50).

The observed enrichment of miRNA target genes in neurodevelopmental and synaptic pathways corroborates prior findings that implicate regulatory RNAs in early brain development and cognitive control mechanisms (5, 50, 51). Dysregulation of miRNAs such as miR-137, miR-132, and miR-34a described in earlier schizophrenia studies has been linked to altered dendritic morphology, neurotransmission, and immune signaling (13, 14, 34). The current data extend these insights by identifying miR-424-5p and miR-20b-5p as potential contributors to behavioral disinhibition, implicating shared molecular substrates between psychosis and impulsive-aggressive behavior (52). This is further supported by network analyses highlighting *ARID1A* (a chromatin-remodeling gene crucial for cortical development) as a central hub. Mutations or dysregulation of *ARID1A* have been associated with

neurodevelopmental syndromes characterized by cognitive deficits and social-behavioral disturbances, suggesting a possible mechanistic bridge between genetic vulnerability and maladaptive behavior (28, 53).

The inclusion of forensic schizophrenia patients provides a unique clinical dimension. Epidemiological and clinical research consistently demonstrates higher rates of impulsive and violent behavior among individuals with schizophrenia, particularly when comorbid with substance use or poor impulse control (54). Studies within the EU-VIORMED consortium have detailed neuropsychological differences between forensic and non-forensic schizophrenia populations, highlighting deficits in decision-making, risk evaluation, and executive function that may predispose to aggression (55–59). The current findings offer a molecular correlate to these behavioral observations, suggesting that specific miRNA dysregulation could underlie the impaired regulation of frontostriatal and limbic circuits governing impulse control. Monarch phenotype enrichment (Table 5) yielded terms like 'Autistic behavior' and 'Hyperactivity' among the most significant, indicating that the target genes of DE miRNAs are associated with neurodevelopmental and behavioral phenotypes relevant to impulse control.

Interestingly, neuropathological evidence points to overlapping mechanisms between impulsive violence and neurodegenerative processes. A study of "suicide killers" revealed Alzheimer-like changes in cortical regions, including neuroinflammation and tau pathology (60). Although distinct from schizophrenia, such convergence supports the notion that dysregulated molecular pathways, potentially involving miRNAs, may broadly influence aggression-related neurobiology through mechanisms of neuronal stress and synaptic instability (2, 11, 30, 31, 51, 61, 62).

From a translational perspective, these results contribute to an expanding effort to establish blood-based molecular biomarkers for psychiatric phenotypes. Peripheral miRNAs, stable and readily quantifiable, have been proposed as proxies for central nervous system processes, with studies in mood and psychotic disorders reporting diagnostic and prognostic potential. Nevertheless, replication and mechanistic validation remain critical challenges. The current data, though preliminary, highlight candidate miRNAs that warrant testing in larger, well-characterized forensic and clinical cohorts (12, 18, 50, 63, 64).

Methodologically, this work demonstrates the feasibility of integrating psychological assessment tools (IVE, BPAQ) with molecular profiling to explore the biological basis of behavioral traits. However, limitations must be acknowledged. In the control group, no psychological testing was conducted, which limits the possibility of direct comparison of behavioral profiles. In future studies, is it planned to include such measurements in order to better understand the specificity of impulsivity and aggression in the clinical population. The small sample size restricts statistical power and generalizability, and confounding variables such as medication, substance use, and chronic hospitalization may influence miRNA expression. Moreover, the cross-sectional design precludes causal inference. Despite these constraints, the convergent bioinformatic evidence (linking differentially expressed miRNAs to neurodevelopmental and behavioral gene networks) provides a coherent biological signal consistent with recent psychiatric genetics and biomarker research (1, 2, 5, 12, 19–21, 51, 63, 65).

Future directions should include replication in larger multi-center cohorts, longitudinal tracking of miRNA dynamics, and integration with other omics layers such as methylation, transcriptomics, and proteomics. Functional studies assessing how miR-424-5p and miR-20b-5p modulate neuronal differentiation and synaptic function could clarify mechanistic pathways linking gene regulation to behavior. Such translational efforts are essential for determining whether miRNAs may serve not only as biomarkers but also as therapeutic targets in the management of impulsivity and aggression in schizophrenia.

Conclusions

This preliminary study provides molecular evidence that dysregulated miRNAs contribute to the biological underpinnings of impulsivity and aggression in forensic patients with schizophrenia. Among the 17 differentially expressed miRNAs identified, hsa-miR-424-5p, hsa-miR-20b-5p, and hsa-let-7g-5p emerged as key regulators of neurodevelopmental and synaptic genes such as *QKI*, *SOBP*, and *ARID1A*, previously associated with schizophrenia and behavioral dysregulation. Gene network and enrichment analyses revealed convergence on pathways involved in neurodevelopment, dopamine signaling, calcium regulation, and neuroinflammation, processes central to the pathophysiology of schizophrenia. The findings suggest that circulating miRNAs may serve as accessible biomarkers for behavioral and neurobiological risk in high-risk forensic populations. Integrating these molecular patterns with clinical and neurocognitive data offers a promising step toward precision psychiatry approaches in forensic mental health.

Limitations

Several limitations should be acknowledged.

First, the sample size was small and limited to a single forensic center, reducing the statistical power and generalizability of the findings. The cross-sectional design prevents causal inference regarding the relationship between miRNA expression and impulsive-aggressive behaviors.

Second, all participants were receiving antipsychotic pharmacotherapy and participating in structured rehabilitation programs, which may have influenced both miRNA levels and behavioral measures. Medication type, duration, and dose (known to affect neurotransmission and inflammatory signaling) were not stratified in this analysis.

Third, environmental and clinical factors unique to forensic inpatient settings (e.g., restricted autonomy, institutional structure, and therapeutic engagement) could have moderated impulsivity and aggression scores. Studies by Gosek et al. (66, 67) and Slamanig et al. (56) emphasize that these contextual factors substantially shape behavioral expression and treatment response in such populations.

Finally, this study was restricted to peripheral blood miRNA profiling in the limited panel of 177 various miRNAs. Although peripheral miRNAs are correlated with central processes, direct validation through postmortem brain tissue or cerebrospinal fluid analyses would strengthen biological inference.

Future Directions

Future research should build upon these preliminary results through multi-site, longitudinal studies incorporating larger cohorts of forensic and non-forensic schizophrenia patients. This would enable replication of the observed miRNA signatures and clarify whether expression patterns fluctuate with treatment, symptom dynamics, or behavioral stabilization.

Integrating multimodal methodologies including neuroimaging, transcriptomic, and proteomic data, could reveal how miRNA regulation influences neural circuit function and behavioral outcomes. Combining molecular profiles with clinical variables such as treatment resistance, minor physical anomalies, and neurocognitive performance (68–70) will further illuminate the developmental and mechanistic pathways underlying aggression in schizophrenia.

Moreover, exploring functional consequences of dysregulated miRNAs, particularly miR-424-5p, miR-20b-5p and hsa-let-7g-5p, in neuronal and glial models could identify therapeutic targets for modulation of impulse control and emotional regulation.

Ultimately, longitudinal validation of miRNA-based biomarkers, combined with clinical, behavioral, and neurobiological indicators, may lead to personalized risk assessment and rehabilitation strategies in forensic psychiatry enhancing early identification, treatment optimization, and violence prevention.

Declarations

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Competing interests

The authors report no competing interests.

Author contribution

All authors contributed to the study conception and design. Janusz Heitzman initiated a research program investigating the biological determinants of aggression in schizophrenia. For molecular testing: material preparation, data collection and primary analysis were performed by Filip Tomczuk, Ewelina Elert-Dobkowska and Anna Sulek. Advanced bioinformatic analysis was performed by Zofia Wicik. Psychiatric and psychological evaluation was performed by Przemysław Cynkier, Grzegorz Kudlak, Inga

Markiewicz and Janusz Heitzman. The first draft of the manuscript was written by Filip Tomczuk and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability

Anonymized data from this study will be shared only by request from a qualified investigator.

Ethics approval and informed consent

All participants provided written informed consent prior to the collection of biological samples, in accordance with the principles outlined in the Declaration of Helsinki. The study protocol was reviewed and approved by the institutional Bioethics Committee of the Institute of Psychiatry and Neurology in Warsaw (ref. no. 31/2023).

Clinical trial number: not applicable.

References

1. Chick SL, Holmans P, Cameron D, Grozeva D, Sims R, Williams J, et al. Whole-exome sequencing analysis identifies risk genes for schizophrenia. Nat Commun. 2025 Aug 2;16(1):7102.
2. Owen MJ, Legge SE, Rees E, Walters JTR, O'Donovan MC. Genomic findings in schizophrenia and their implications. Mol Psychiatry. 2023 Sep 18;28(9):3638–47.
3. Trifu S, Kohn B, Vlasie A, Patrichi BE. Genetics of schizophrenia (Review). Exp Ther Med. 2020 Jul 7;
4. Refaat N, Fahmy M, El-Leithy W, Hassan H, El Moez KA. Correlation between aggressive behavior and sociodemographic characteristics in patients with schizophrenia at a psychiatry outpatient clinic. Middle East Current Psychiatry. 2017 Jan;24(1):30–5.
5. Han S, Li Y, Gao J. Peripheral blood MicroRNAs as biomarkers of schizophrenia: expectations from a meta-analysis that combines deep learning methods. The World Journal of Biological Psychiatry. 2024 Jan 2;25(1):65–81.
6. Fazel S, Gulati G, Linsell L, Geddes JR, Grann M. Schizophrenia and Violence: Systematic Review and Meta-Analysis. PLoS Med. 2009 Aug 11;6(8):e1000120.
7. Zhan N, Sham PC, So HC, Lui SSY. The genetic basis of onset age in schizophrenia: evidence and models. Front Genet. 2023 Jun 27;14.
8. Miyano T, Mikkaichi T, Nakamura K, Yoshigae Y, Abernathy K, Ogura Y, et al. Circulating microRNA Profiles Identify a Patient Subgroup with High Inflammation and Severe Symptoms in Schizophrenia Experiencing Acute Psychosis. Int J Mol Sci. 2024 Apr 12;25(8):4291.
9. Talukdar U, Bharali A, Kakoty SD, Choudhury C, Talukdar R, Das PP. Downregulation of NOTCH1 and NOTCH4 signalling influences the modulation of schizophrenia onset. Psychiatr Genet. 2025 Oct 22;35(5):128–35.
10. Ilieva MS. Non-Coding RNAs in Neurological and Neuropsychiatric Disorders: Unraveling the Hidden Players in Disease Pathogenesis. Cells. 2024 Jun 19;13(12):1063.
11. Merikangas AK, Shelly M, Knighton A, Kotler N, Tanenbaum N, Almasy L. What genes are differentially expressed in individuals with schizophrenia? A systematic review. Mol Psychiatry. 2022 Mar 28;27(3):1373–83.
12. Shboul M, Bani Domi A, Abu Zahra A, Khasawneh AG, Darweesh R. Plasma miRNAs as potential biomarkers for schizophrenia in a Jordanian cohort. Noncoding RNA Res. 2024 Jun;9(2):350–8.
13. Sabaie H, Moghaddam MM, Moghaddam MM, Ahangar NK, Asadi MR, Hussen BM, et al. Bioinformatics analysis of long non-coding RNA-associated competing endogenous RNA network in schizophrenia. Sci Rep. 2021 Dec 24;11(1):24413.
14. Mahmoudi E, Cairns MJ. MiR-137: an important player in neural development and neoplastic transformation. Mol Psychiatry. 2017 Jan 13;22(1):44–55.
15. Guo X, Guo J, Liu X, Hu T. A review on the relationship between the distal 1q21.1 microdeletion and schizophrenia. Front Genet. 2025 Jul 28;16.
16. Chen F, Zou L, Dai Y, Sun J, Chen C, Zhang Y, et al. Prognostic plasma exosomal microRNA biomarkers in patients with substance use disorders presenting comorbid with anxiety and depression. Sci Rep. 2021 Mar 18;11(1):6271.

17. Waltes R, Chiocchetti AG, Freitag CM. The neurobiological basis of human aggression: A review on genetic and epigenetic mechanisms. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2016 Jul 22;171(5):650–75.
18. You X, Wang J, Wei W, Zhang Y, Yin H, Zhao C, et al. Deciphering the Molecular Landscape of Schizophrenia: A Multi-Brain-Region Bioinformatics Analysis Identifies Key Hub Genes and miRNA Regulatory Networks [Internet]. Vol. 02, Journalnsmb.com. 2025 Jul. Available from: https://www.xiantao.love/
19. Eysenck SBG, Pearson PR, Easting G, Allsopp JF. Age norms for impulsiveness, venturesomeness and empathy in adults. Pers Individ Dif. 1985 Jan 1;6(5):613–9.
20. Aranowska E, Rytel J. Struktura czynnikowa kwestionariusza agresji Bussa i Perry'ego (BPQA) w populacji polskiej. Stud Psychol (Bratisl). 2012;(12/2):135–51.
21. Buss AH, Perry M. The Aggression Questionnaire. J Pers Soc Psychol. 1992 Sep;63(3):452–9.
22. Ru Y, Kechris KJ, Tabakoff B, Hoffman P, Radcliffe RA, Bowler R, et al. The multiMiR R package and database: integration of microRNA–target interactions along with their disease and drug associations. Nucleic Acids Res. 2014 Sep 29;42(17):e133–e133.
23. Wicik Z, Jales Neto LH, Guzman LEF, Pavão R, Takayama L, Caparbo VF, et al. The crosstalk between bone metabolism, lncRNAs, microRNAs and mRNAs in coronary artery calcification. Genomics. 2021 Jan;113(1):503–13.
24. Chen EY, Tan CM, Kou Y, Duan Q, Wang Z, Meirelles GV, et al. Enrichr: interactive and collaborative HTML5 gene list enrichment analysis tool. BMC Bioinformatics. 2013 Dec 15;14(1):128.
25. Doncheva NT, Morris JH, Gorodkin J, Jensen LJ. Cytoscape StringApp: Network Analysis and Visualization of Proteomics Data. J Proteome Res. 2019 Feb 1;18(2):623–32.
26. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res. 2003 Nov;13(11):2498–504.
27. Åberg K, Saetre P, Lindholm E, Ekholm B, Pettersson U, Adolfsson R, et al. Human QKI, a new candidate gene for schizophrenia involved in myelination. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics. 2006 Jan 5;141B(1):84–90.
28. Bernstein HG, Nussbaumer M, Vasilevska V, Dobrowolny H, Nickl-Jockschat T, Guest PC, et al. Glial cell deficits are a key feature of schizophrenia: implications for neuronal circuit maintenance and histological differentiation from classical neurodegeneration. Mol Psychiatry. 2025 Mar 5;30(3):1102–16.
29. Birk E, Har-Zahav A, Manzini CM, Pasmanik-Chor M, Kornreich L, Walsh CA, et al. SOBP Is Mutated in Syndromic and Nonsyndromic Intellectual Disability and Is Highly Expressed in the Brain Limbic System. The American Journal of Human Genetics. 2010 Nov;87(5):694–700.
30. Balcioglu YH, Kirlioglu Balcioglu SS, Oncu F, Turkcan A, Yorulmaz AC. Impulsive and aggressive traits and increased peripheral inflammatory status as psychobiological substrates of homicide behavior in schizophrenia. Eur J Psychiatry. 2022 Jul;36(3):207–14.
31. Hoptman MJ. Impulsivity and aggression in schizophrenia: a neural circuitry perspective with implications for treatment. CNS Spectr. 2015 Jun 22;20(3):280–6.
32. Wong N, Lee T. Genetic and neural relationships underpinning impulsivity. Int J Psychol Res (Medellin). 2013 Oct 30;6:80–93.
33. Uddin N, Hussain M, Rauf I, Zaidi SF. Identification of key pathways and genes responsible for aggressive behavior. Comput Biol Chem. 2020 Oct;88:107349.
34. Portugal R, Rodrigues B, Leitão RA, Silva M, Pinheiro PS, Carvalho AL. Shaping the synapse through neuronal activity-regulated miRNAs. Trends Neurosci. 2025 Sep;48(9):679–90.
35. Pharoah F, Mari J, Rathbone J, Wong W. Family intervention for schizophrenia. In: Pharoah F, editor. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2006.
36. Roder V. Integrated Psychological Therapy (IPT) for Schizophrenia: Is It Effective? Schizophr Bull. 2006 Aug 18;32(Supplement 1):S81–93.
37. Goozée R, Handley R, Kempton MJ, Dazzan P. A systematic review and meta-analysis of the effects of antipsychotic medications on regional cerebral blood flow (rCBF) in schizophrenia: Association with response to treatment. Neurosci Biobehav Rev. 2014 Jun;43:118–36.

38. Hodge MAR, Siciliano D, Withey P, Moss B, Moore G, Judd G, et al. A Randomized Controlled Trial of Cognitive Remediation in Schizophrenia. Schizophr Bull. 2010 Mar 1;36(2):419–27.
39. Kukla M, Bell MD, Lysaker PH. A randomized controlled trial examining a cognitive behavioral therapy intervention enhanced with cognitive remediation to improve work and neurocognition outcomes among persons with schizophrenia spectrum disorders. Schizophr Res. 2018 Jul;197:400–6.
40. Swanson JW, Swartz MS, Elbogen EB. Effectiveness of Atypical Antipsychotic Medications in Reducing Violent Behavior Among Persons With Schizophrenia in Community-Based Treatment. Schizophr Bull. 2004 Jan 1;30(1):3–20.
41. Siever LJ. Neurobiology of Aggression and Violence. American Journal of Psychiatry. 2008 Apr;165(4):429–42.
42. Patrick CJ. Psychophysiological correlates of aggression and violence: an integrative review. Philosophical Transactions of the Royal Society B: Biological Sciences. 2008 Aug 12;363(1503):2543–55.
43. Kingston DA, Olver ME, McDonald J, Cameron C. A randomised controlled trial of a cognitive skills programme for offenders with mental illness. Criminal Behaviour and Mental Health. 2018 Aug 6;28(4):369–82.
44. Yeo H, Yoon S, Lee J, Kurtz MM, Choi K. A meta-analysis of the effects of social-cognitive training in schizophrenia: The role of treatment characteristics and study quality. British Journal of Clinical Psychology. 2022 Mar 21;61(1):37–57.
45. Green MF, Horan WP, Lee J. Social cognition in schizophrenia. Nat Rev Neurosci. 2015 Oct 16;16(10):620–31.
46. Janković M, Masthoff E, Spreen M, de Looff P, Bogaerts S. A Latent Class Analysis of Forensic Psychiatric Patients in Relation to Risk and Protective Factors. Front Psychol. 2021 Jul 20;12.
47. Li T, Qi X, Jiang H, Ren B, Zhang Y, Zhou Y, et al. Alterations of plasma neuron-derived exosomal microRNAs in patients with bipolar disorder. 2024.
48. Ma L, Huo Y, Tang Q, Wang X, Wang W, Wu D, et al. Human Breast Milk Exosomal miRNAs are Influenced by Premature Delivery and Affect Neurodevelopment. Mol Nutr Food Res. 2024 May 21;68(9).
49. Prodan-Bărbulescu C, Alin CD, Faur IF, Bujor GC, Şeclăman EP, Enătescu V, et al. Identification of Specific Plasma miRNAs as Potential Biomarkers for Major Depressive Disorder. Biomedicines. 2024 Sep 24;12(10):2165.
50. Barnett MM, Reay WR, Geaghan MP, Kiltschewskij DJ, Green MJ, Weidenhofer J, et al. miRNA cargo in circulating vesicles from neurons is altered in individuals with schizophrenia and associated with severe disease. Sci Adv. 2023 Dec;9(48).
51. Adly NM, Khalifa D, Abdel-Ghany S, Sabit H. MicroRNAs as biomarkers and molecular mediators of cognitive dysfunction in schizophrenia. J Neural Transm. 2025 Aug 8;
52. Li J, Cheng Y, Lu W. The diagnostic significance of miR-20b-5p in schizophrenia and its impact on the symptoms of schizophrenia. Psychiatr Genet. 2025 Jun 8;35(3):51–7.
53. Liu X, Dai S, Liu P, Liu C. Arid1a regulates neural stem/progenitor cell proliferation and differentiation during cortical development. Cell Prolif. 2021 Nov 25;54(11).
54. Heitzman J, Gosek P, Lechowicz W, Wardeński R, Stępień T. Elevated hydroxylactam of hemopyrrole level in urine in perpetrators of extremely violent acts diagnosed with psychosis. Psychiatr Pol. 2017 Jun 18;51(3):413–23.
55. de Girolamo G, Iozzino L, Ferrari C, Gosek P, Heitzman J, Salize HJ, et al. A multinational case–control study comparing forensic and non-forensic patients with schizophrenia spectrum disorders: the EU-VIORMED project. Psychol Med. 2023 Apr 13;53(5):1814–24.
56. Slamanig R, Reisegger A, Winkler H, de Girolamo G, Carrà G, Crocamo C, et al. A Systematic Review of Non-pharmacological Strategies to Reduce the Risk of Violence in Patients With Schizophrenia Spectrum Disorders in Forensic Settings. Front Psychiatry. 2021 May 10;12.
57. Iozzino L, Harvey PD, Canessa N, Gosek P, Heitzman J, Macis A, et al. Neurocognition and social cognition in patients with schizophrenia spectrum disorders with and without a history of violence: results of a multinational European study. Transl Psychiatry. 2021 Dec 8;11(1):620.
58. Oberndorfer R, Alexandrowicz RW, Unger A, Koch M, Markiewicz I, Gosek P, et al. Needs of forensic psychiatric patients with schizophrenia in five European countries. Soc Psychiatry Psychiatr Epidemiol. 2023 Jan 15;58(1):53–63.
59. Iozzino L, Canessa N, Rucci P, Iommi M, Dvorak A, Heitzman J, et al. Decision-making and risk-taking in forensic and non-forensic patients with schizophrenia spectrum disorders: A multicenter European study. Schizophr Res Cogn. 2022 Sep;29:100257.

60. Stępień T, Heitzman J, Wierzba-Bobrowicz T, Gosek P, Krajewski P, Chrzczonowicz-Stępień A, et al. Neuropathological Changes in the Brains of Suicide Killers. Biomolecules. 2021 Nov 11;11(11):1674.
61. Gangachannaiah S, Shenoy S, Upadhya D, Stanly EAR, Gudi N, Lakshmi Chandrashekar P, et al. Potential of extracellular vesicle cargo as molecular signals in Schizophrenia: a scoping review. Schizophrenia. 2025 Feb 12;11(1):17.
62. Miyano T, Mikkaichi T, Nakamura K, Yoshigae Y, Abernathy K, Ogura Y, et al. Circulating microRNA Profiles Identify a Patient Subgroup with High Inflammation and Severe Symptoms in Schizophrenia Experiencing Acute Psychosis. Int J Mol Sci. 2024 Apr 12;25(8):4291.
63. Du X, Hu W, Li X, Gao Y, Li J, Hu X, et al. CircRNA-miRNA-mRNA networks in plasma extracellular vesicles as biomarkers for first-onset schizophrenia. BMC Psychiatry. 2025 Jul 9;25(1):688.
64. Huang H, Luo J, Qi Y, Wu Y, Qi J, Yan X, et al. Comprehensive analysis of circRNA expression profile and circRNA-miRNA-mRNA network susceptibility to very early-onset schizophrenia. Schizophrenia. 2023 Oct 10;9(1):70.
65. Ma J, Shang S, Wang J, Zhang T, Nie F, Song X, et al. Identification of miR-22-3p, miR-92a-3p, and miR-137 in peripheral blood as biomarker for schizophrenia. Psychiatry Res. 2018 Jul;265:70–6.
66. Gosek P, Kotowska J, Rowińska-Garbień E, Bartczak D, Heitzman J. Treatment resistance and prolonged length of stay among schizophrenia inpatients in forensic institutions. Psychiatry Res. 2021 Apr;298:113771.
67. Gosek P, Kotowska J, Rowińska-Garbień E, Bartczak D, Heitzman J. Factors Influencing Length of Stay of Forensic Patients: Impact of Clinical and Psychosocial Variables in Medium Secure Setting. Front Psychiatry. 2020 Aug 14;11.
68. Sut E, Akgül Ö, Bora E. Minor physical anomalies in schizophrenia and first-degree relatives in comparison to healthy controls: A systematic review and meta-analysis. European Neuropsychopharmacology. 2024 Sep;86:55–64.
69. Uğurpala C, Berberoğlu E, Özkan U, Genç SA, Tanrıverdi NÇ, İnhanlı D, et al. Minor physical anomalies may be related to treatment resistance in patients with schizophrenia. Asian J Psychiatr. 2023 Oct;88:103729.
70. Bora E. Minor physical anomalies in bipolar disorder in comparison to healthy controls and schizophrenia: A systematic review and meta-analysis. European Neuropsychopharmacology. 2022 Dec;65:4–11.

Figures

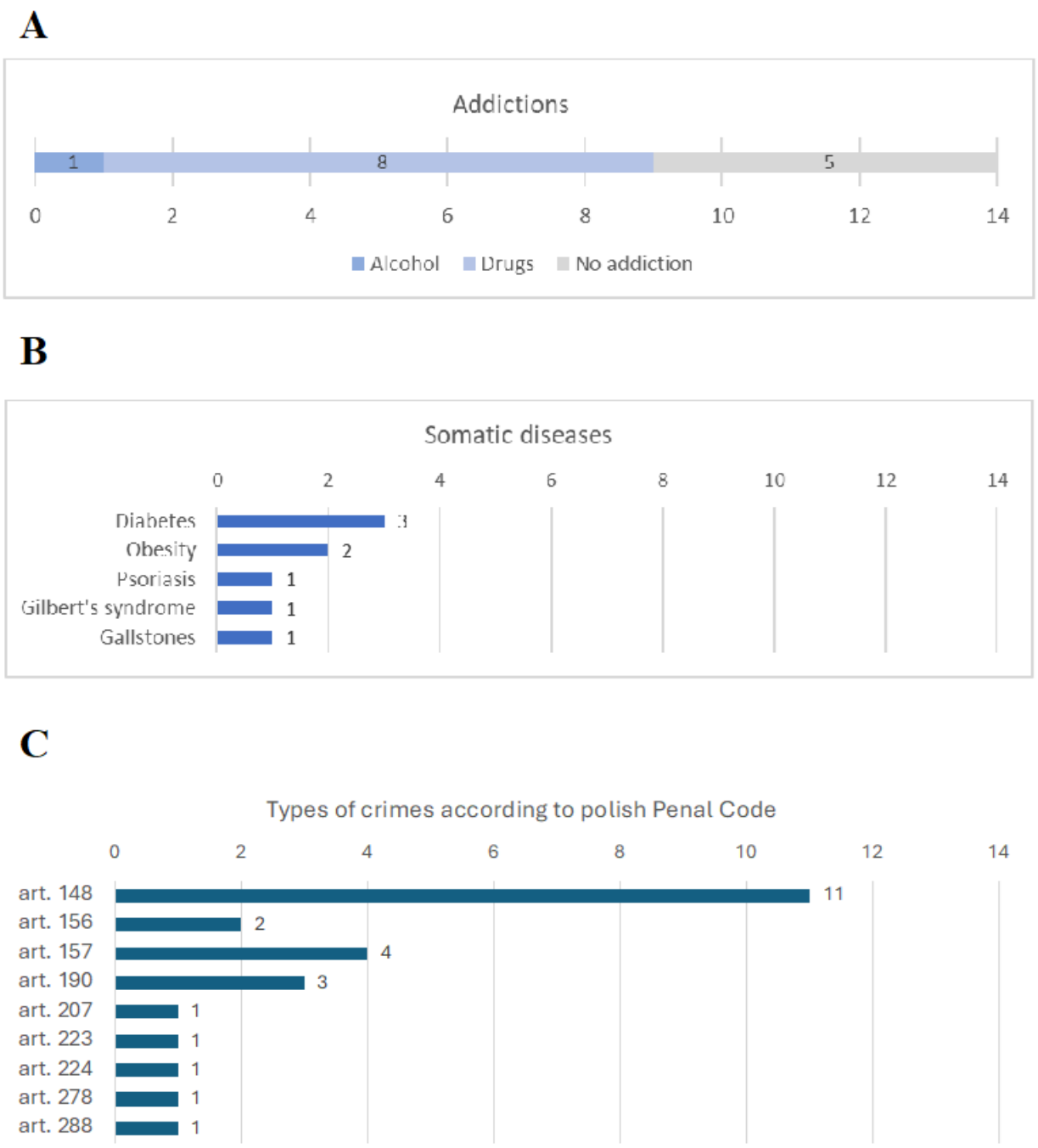


Figure 1

The sociodemographic features of studied population. A) Addictions among patients; B) Somatic diseases of patients; C) The types of crimes committed by the patients according to polish Penal Code.

[i](art. 148) – murder; (art. 156) – serious bodily injury; (art. 157) – bodily harm; (art. 190) – threat; (art. 207) – family abuse; (art. 223) - assault on a public official; (art. 224) - influencing official acts; (art. 278) – theft; (art. 288) - destruction of goods.

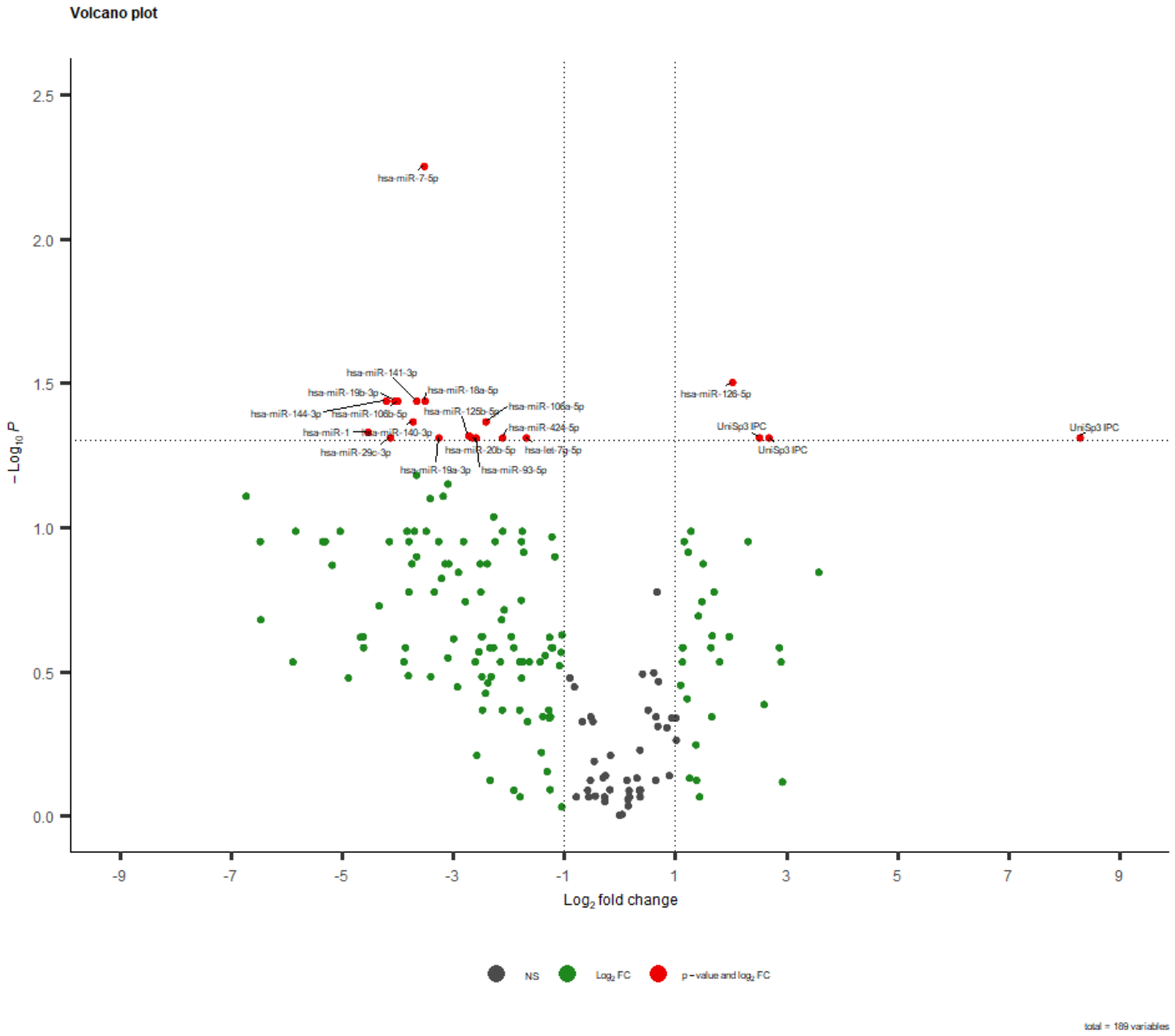


Figure 2

Volcano plot of miRNA expression differences between forensic schizophrenia patients (n=14) and controls (n=3). The –log10 p-value is plotted against log2 fold change for each miRNA. Points above the horizontal line (FDR<0.05) are considered significantly DE; red points indicate those with largest fold changes. Notably, 16 miRNAs show higher expression and 1 (hsa-miR-126-5p) lower expression in patients vs controls.

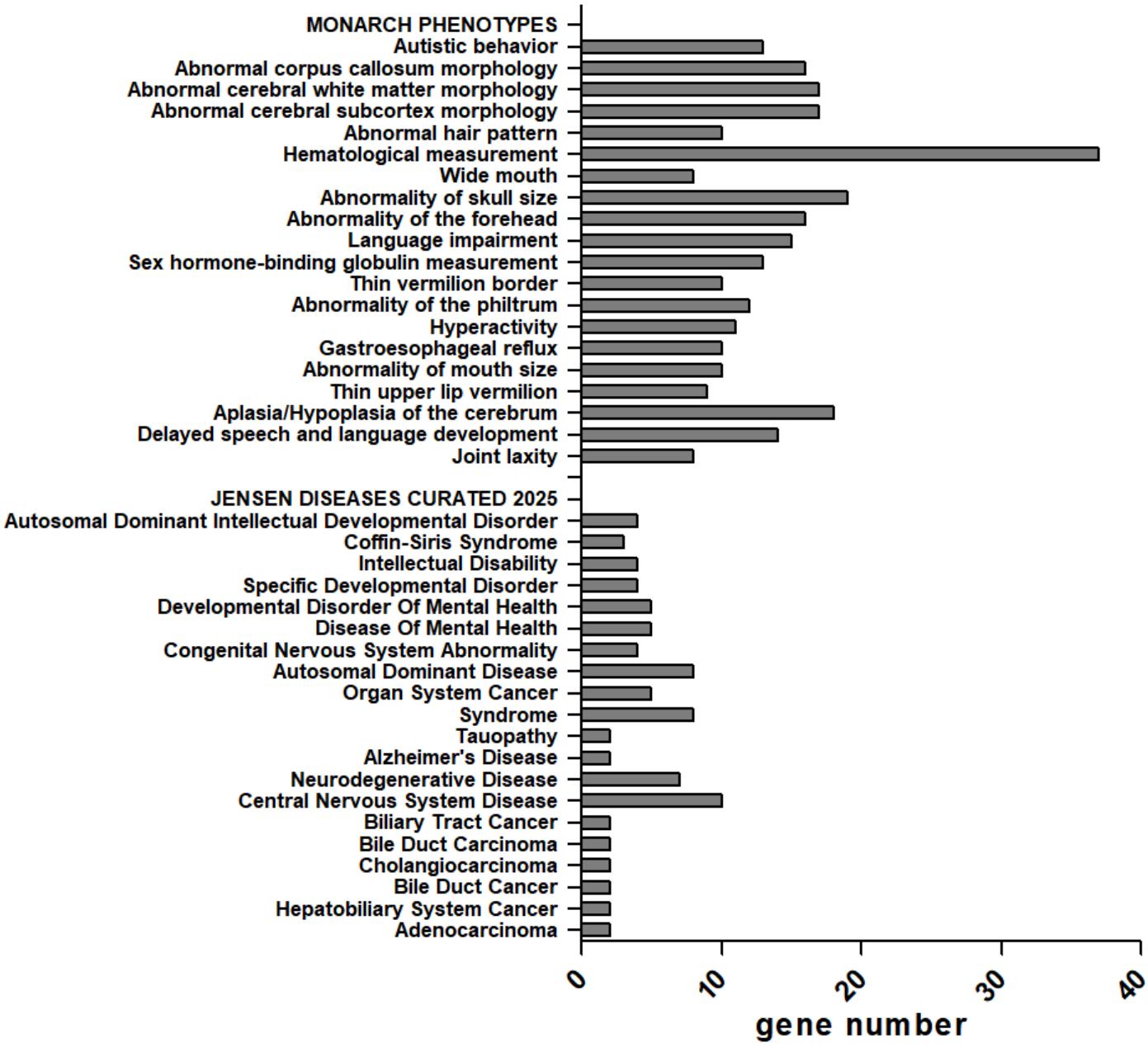


Figure 3

Enriched phenotypes from Monarch database and Jensen database. Most significant are on top of the graph.

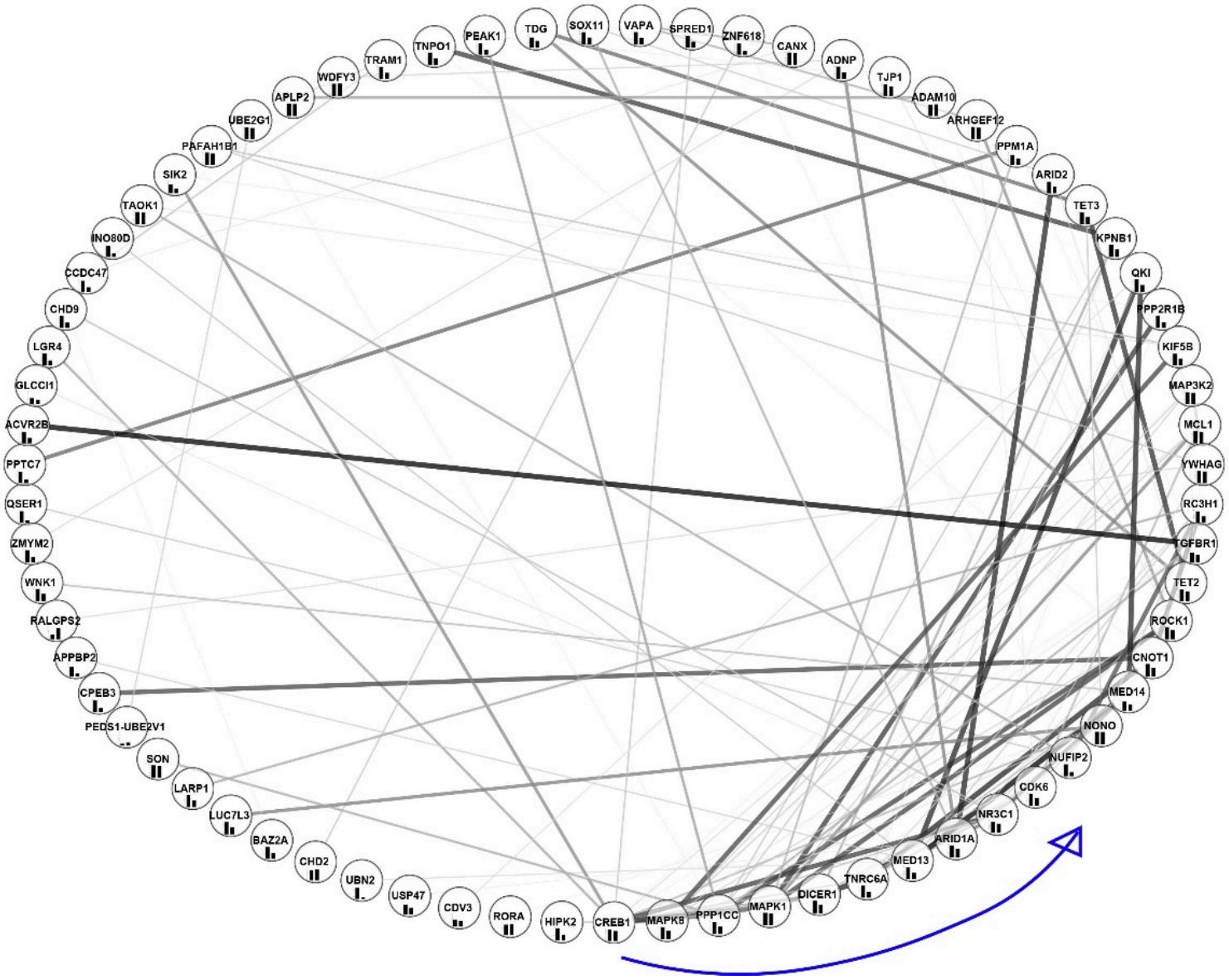


Figure 4

Interaction network between targets regulated by all DE miRNAs. Interactions were retrieved from String database. Visualization was made in Cytoscape software. Bars below gene symbols reflect tissue expression confidence for nervous system and blood on scale 0-5.