ISSN: ٢٦٧٦-٥٧٦٤
www.jocrisar.ir

مجله پژوهش های معاصر در علوم و تحقیقات
سال هشتم، شماره ۸۲، اردیبهشت ۱۴۰۵

Integrative Bioinformatics Prioritization of Schizophrenia-Associated Genes: Re-Evaluating the Role of SV۲A

Sasan Azizi[۱], **Fatemeh Bossaghzadeh**[۲]

[۱]MSc student of cellular and molecular biology,department of biology,faculty of Modern Sciences ,Azad university,Dezful , Iran

[۲]Associate professor, Department of Biology,Faculty of Modern Sciences,Azad university,Dezful,Iran

ABSTRACT

Synaptic vesicle protein ۲A (SV۲A) is a gene involved in neurotransmitter release and has been hypothesized to contribute to the pathophysiology of schizophrenia (SZP). However, direct evidence linking SV۲A to SZP remains limited. This bioinformatics study aimed to investigate the potential role of SV۲A in SZP by analyzing gene expression data and constructing protein-protein interaction networks. Candidate genes associated with SZP were extracted from NCBI, SWISS-Prot, and Disaesome databases based on in-vivo, in-vitro, and in-silico evidence. Using MATLAB and Gephi software, a communication network was built from expression data of SZP patients compared to healthy controls. Structural network parameters—including Maximum Neighborhood Component (MNC), degree, betweenness, closeness, and radiality—were calculated to identify key biomarkers. Results revealed that the five most frequent and significantly confirmed genes in the SZP network were Dopamine Receptor D ۲(DRD۲), DISC ۱Scaffold Protein (DISC۱), Catechol-O-Methyltransferase (COMT), ٥-Hydroxytryptamine Receptor ۲A (HTR۲A), and D-Amino Acid Oxidase (DAO). Notably, SV۲A did not appear among the top five genes or show high centrality in any of the network analyses. These findings suggest that, based on the bioinformatics methods and databases used, SV۲A does not play a major role in the pathogenesis of schizophrenia. While SV۲A remains a marker for synaptic density, its direct genetic involvement in SZP was not supported by this study. Further experimental research is needed to clarify whether SV۲A contributes indirectly or under specific conditions. This study highlights the utility of bioinformatics approaches in prioritizing candidate genes and understanding the complex genetic architecture of schizophrenia.

Keywords: Schizophrenia · SV۲A · Bioinformatics · DRD۲ · Gene network analysis

١. Introduction

More than ٤٥٠ million people worldwide suffer from psychiatric disorders, among which SZP is the most common (Đorđević, Đukić, Janković, Todorović , ٢٠١٦) Schizophrenia (SZP) is one of the most severe, poorly understood mental disorders affecting humanity. This debilitating mental disorder impairs the normal development and maturation of the brain, and it is marked by a series of neurotransmitter and neural circuit abnormalities in early adulthood (Tandon, Nasrallah, Akbarian, Carpenter, DeLisi, Gaebel, et al. ٢٠٢٤) SZP impacts ١ in ١٠٠ individuals globally and manifests equally in men and women, with a delayed onset in females(Khan, Rahman, Khan, Hossain, & Billah, ٢٠٢٢) .Although the overall prevalence of SZP is relatively low compared to other psychiatric disorders (such as depression or anxiety), SZP remains a significant cause of disability and burden of mental illness in Iran. (Farhang et al., ٢٠٢١)The progress of a mental disorder is usually determined by genetic factors related to developmental and maturational pathways that integrate into the proper functioning of the brain. The etiology of SZP is multifactorial and involves the diverse influence of predisposing genes that interact with numerous environmental variables (Prata, Costa-Neves, Cosme, & Vassos, ٢٠١٩)Synaptic vesicle glycoprotein SV٢A is a critical gene located at position ١q٢١,٢ and found in the nervous system. SV٢A is expressed primarily in synaptic vesicles of neurons throughout the brain and spinal cord and in secretory vesicles of endocrine cells. It is particularly abundant in gray matter brain regions, rich in synaptic connections, and vital in synaptic function and neurotransmitter release (Rossi, Arjmand, Bærentzen, Gjedde, & Landau, ٢٠٢٢)Research has shown that synaptic density is often reduced in people with SZP. SV٢A serves as a marker for synaptic density, and imaging studies using SV٢A-specific PET radiotracers have shown reduced SV٢A connectivity in the brains of SZP patients (Toyonaga, Fesharaki-Zadeh, Strittmatter, Carson, & Cai, ٢٠٢٢)The diagnosis of SZP mainly relies on symptom criteria, which may overlap with other mental disorders. On the other hand, understanding the spectrum of SZP and its complications is below average due to its inherent complexity in etiology and molecular and biological mechanisms of pathophysiology, diagnosis, prognosis, and treatment strategy (Khan, Rahman, Khan, Hossain, & Billah, ٢٠٢٢)So, investigating the genetic mechanisms and diagnostic criteria of SZP facilitates an accurate diagnosis. Recent advances in human genomics technologies have enabled extensive research on SZP. Therefore, the current situation necessitates elucidating the molecular mechanisms and biological processes underlying the initiation and progression of SZP, which will provide a definitive basis for identifying biomarkers and potential drug targets (Rahi, ٢٠٢٥)This study aimed to investigate the bioinformatics of the SV٢A gene in SZP patients.

٢. Material and method

This study's initial data were extracted from the NCBI, SWISS-Prot, and Disaesome bioinformatics databases. The data recorded in these databases are considered the gold standard, including all validated data on gene expression of healthy individuals and SZP patients.After reviewing the literature and searching the mentioned databases, genes involved in SZP that were suggested based on at least one of the in vivo, in vitro, and in silico methods were extracted and considered as candidate genes. Then, to compare the results in the two case and control groups and examine the research hypotheses, the expression data obtained from each group were standardized against the control group.Next, the communication network (CN) was drawn from the expression data of candidate genes in sick and healthy individuals separately using MATLAB software, and the structural parameters of the CNs of the expression data were compared.Advanced descriptive and analytical statistical methods and machine learning methods based on advanced bioinformatics algorithms were used to analyze data.

۳. Result

In this study, the genes involved in the disease were first identified using text mining data. Then, the target gene set in this disease was ranked using the Gene-Disease Association score index, which is defined as follows. N sources i is the number of specialized sources scoring the association of the desired gene with the target disease.

GDA = C+M+I+L

$$C \begin{cases} \text{٠,٦} & \text{N sources i} > \text{٢} \\ \text{٠,٥} & \text{N sources i} = \text{٢} \\ \text{٠,٣} & \text{N sources i} = \text{١} \\ \text{٠} & \text{Otherwise} \end{cases}$$

(CTD, UNIPROT, PSYGENET, CGL, GENOMICS, CLINGEN, ORPHANET)

$$M = \begin{cases} \text{٠,٢} & \text{N sources i} > \text{٠} \quad \text{if} \\ \text{٠} & \text{Otherwise} \end{cases}$$

J ϵ CTD, MGD, RGD Mouse or Rat Databases Included:

$$I = \begin{cases} \text{٠,١} & \text{N sources i} > \text{٠} \\ \text{٠} & \text{Otherwise} \end{cases}$$

K ϵ HPO, CLINVAR, GWASCAT, GWASDB

N pubs is the number of articles (text sources) confirming the association of a gene with a disease in the BEFREE and LHGDN databases.

$$L = \begin{cases} \text{۰,۱} & \text{N pubs} > \text{۹} \\ \text{N pubs } \text{۰,۰۱} & \text{N pubs} < \text{۹} \end{cases}$$

After calculating the GDA score, candidate genes in SZP were ranked (Table ۱).

In the next step, the expression levels of candidate genes sorted by Gene Entrez and Uniprot were extracted. Then, using the Gephi platform, a CN was drawn between the candidate genes. While determining the communication structure network between the candidate genes, the structural centrality criteria of the network were calculated to determine the essential genes. In this network, the weight of the edges was determined based on the expression level of the relevant genes (Fig ۱).

Network structural parameters

Maximum Neighborhood Component (MNC)

The MNC score for each vertex is defined as the value of the largest element connected to that vertex. Table ۲ and Figure ۲ show the highest scoring biomarkers and the CN between SZP genes based on the MNC score, respectively.

Degree

The number of edges connected to a vertex defines its degree. Based on this criterion, Table ۲ lists the most effective biomarkers of the SZP disease network in this study. Figure ۳ shows the CN between SZP genes based on degree scores.

Closeness

Closeness is defined in a connected network CN as the sum of the lengths of the shortest paths between a vertex and other vertices. Closeness is one of the most important criteria for determining biomarkers in biological networks, which determines the proximity of a gene to different genes. Based on closeness, the most important biomarkers of SZP are in Table ۳. Figure ٤ shows the CN of SZP based on the closeness score.

Radiality

Radiality identifies the vertex with the shortest distance to other vertices in its neighboring vertex set. The radiality score for the association network between SZP disease genes is shown in Table ٤. Figure ٥ shows the CN between SZP genes based on the radiality score.

Betweeneness

Betweenness measures the extent to which a vertex is in the path of other vertices. Based on this metric, a vertex with the highest betweenness score may have the highest impact on information transfer in a biological network compared to other vertices in the network, and removing it from the network will disrupt the entire network communication. The highest betweenness score criterion for the SZP disease network genes is shown in Table ٥. The CN of SZP based on betweenness is shown in Figure ٦.Based on the results of the analysis of the CN of candidate proteins in SZP and the calculation performed using the five components of MNC, degree, betweenness, closeness, and radiality, the five proteins Dopamine Receptor D٢ (DRD٢), DISC١ Scaffold Protein (DISC١), Catechol-O-Methyl transferase (COMT), ٥-Hydroxytryptamine Receptor ٢A (HTR٢A), and D-Amino Acid Oxidase (DAO) had the highest frequency and confirmation, respectively. Figures ٧-١١ show the increased expression levels of ٥ proteins in different body tissues based on three methods: RNA seq, Microarray, and SAG.

٤. Discussion

In this investigation, by studying SV٢A in SZP patients, the related genes DRD٢, DISC١, COMT, HTR٢A, and DAO were identified. These genes have a potential role in various neural signaling pathways and synaptic plasticity. Although the SV٢A gene was not implicated in this study, many studies have investigated its role in SZP patients. SV٢A is integral to regulating synaptic vesicles, which store and release neurotransmitters at synapses. As a result, SV٢A helps these vesicles function properly and ensures the efficient release of neurotransmitters (Mikkelsen, Kaad, Aripaka, & Finsen, ٢٠٢٣)In vivo imaging studies using PET radiotracers have provided evidence for reduced synaptic terminal density early in the course of SZP. These studies suggest that synaptic loss may be an early feature of the disorder (Onwordi et al., ٢٠٢٠)Overall, further genetic research and elucidation of the mechanisms by which SV٢A contributes to the onset or progression of SZP could unlock its potential in developing new treatments for this complex disorder.Disturbances in neurotransmitter systems, especially glutamate and dopamine, are thought to play a key role in SZP (Onwordi et al., ٢٠٢١& Kayaaltı, Güneş, & Erbaş, ٢٠٢١)In this study, the increased expression in the DRD٢ and COMT genes, which play a crucial role in dopamine signaling, confirms this hypothesis. Dysregulation of dopamine transmission contributes to the positive symptoms of SZP (hallucinations and delusions) (Saravani, Galavi, & Sargazi, ٢٠١٧)
Higher levels of dopamine, particularly in the prefrontal cortex, can lead to cognitive impairment and exacerbation of symptoms associated with SZP (Jiménez-Trejo, Jiménez-García, & Canul-Medina, ٢٠٢٤)Dysfunction of the serotonin system, like dopamine, has a causative role in the pathogenesis of SZP. The role of serotonin in SZP is intertwined with the dopamine and glutamate systems and affects the symptom profile and treatment outcomes (Mattina, Samaan, Hall, & Steiner, ٢٠٢٠)HTR٢A is a critical component of the serotonin signaling pathway. It functions primarily as a G protein-coupled receptor (GPCR) and plays a prominent role in various physiological and pathological processes, including mood regulation, cognition, and modulation of multiple neurotransmitter systems (Gill & Grace, ٢٠١٦)The co-expression of HTR٢A with DRD٢ and COMT in SZP patients in this study suggests a link between the dopamine-glutamate system and serotonin in these patients. Serotonin may modulate dopamine hyperactivity, particularly through ٥-HT٢A receptors (Gill & Grace, ٢٠١٦)

DISC١ and DAO proteins, like SV٢A, are involved in synaptic function and cell signaling pathways. Given their involvement in neurodevelopment, targeting the pathways affected by DISC١ and DAO could lead to new therapeutic strategies aimed at restoring balance in neurotransmitter systems and improving cognitive and emotional outcomes for patients with SZP (Watanabe et al., ٢٠٢٣&Tang et al., ٢٠٢٢).The complex and heterogeneous pathophysiology of SZP can be interpreted by examining extensive datasets to describe the genetic and proteomic basis, which can be extracted and evaluated by biological algorithms. In summary, bioinformatics and gene databases help to elucidate gene function, estimate gene prevalence in populations, distinguish disease subtypes, and identify genetic protections against disease. They enable the analysis of individual genetic profiles to tailor medical treatments to the patient's unique genetic makeup. They also foster global collaboration in understanding the genetic contribution to health and disease (Lowrance, ٢٠٠١& Bean & Hegde, ٢٠١٦& Basak, Bhattacharya, & Das, ٢٠٢٥)

٥. Conclusion

The present bioinformatics investigation was designed to evaluate the potential involvement of the synaptic vesicle glycoprotein ٢A (SV٢A) gene in the pathogenesis of schizophrenia (SZP) through the construction and analysis of gene expression networks derived from patient and healthy control data. Despite the growing interest in SV٢A as a synaptic density marker and its proposed role in neurotransmitter release, our integrated bioinformatics approach did not place SV٢A among the top five central genes in the schizophrenia-associated protein interaction network. Instead, five other genes—DRD٢, DISC١, COMT, HTR٢A, and DAO—consistently emerged as high-frequency, high-centrality nodes across multiple network topological parameters, including Maximum Neighborhood Component (MNC), degree, betweenness, closeness, and radiality.

The absence of SV٢A from the core network of schizophrenia-associated genes suggests that, at least under the analytical conditions and databases employed in this study (NCBI, SWISS-Prot, Disaesome), SV٢A may not serve as a primary driver in the molecular pathology of SZP. This finding does not entirely exclude a secondary or modulatory role for SV٢A, particularly given prior in vivo PET imaging studies that have reported reduced SV٢A-based synaptic density in schizophrenia patients. Rather, our results indicate that at the transcriptional and protein interaction levels, SV٢A does not exhibit the same degree of disease-specific connectivity as other well-established schizophrenia risk genes. This discrepancy highlights the importance of distinguishing between synaptic density changes (a downstream or compensatory phenomenon) and direct genetic etiological factors.In contrast, the five identified genes—DRD٢, DISC١, COMT, HTR٢A, and DAO—demonstrate strong and reproducible associations with schizophrenia pathophysiology. DRD٢ and COMT are central to dopaminergic signaling, which is classically linked to the positive symptoms of schizophrenia, including hallucinations and delusions. The elevated expression of these genes in patient datasets supports the dopamine dysregulation hypothesis. HTR٢A, a key serotonin receptor, further implicates the serotoninergic system, which modulates both dopaminergic and glutamatergic pathways, thereby influencing symptom expression and treatment response. The co-expression patterns observed among DRD٢, COMT, and HTR٢A in our network analysis suggest a functional crosstalk between monoamine systems in schizophrenia.DISC١ and DAO, like SV٢A, are involved in synaptic function and neurodevelopment. DISC١ has been extensively studied as a scaffold protein affecting neuronal migration, synaptic plasticity, and cyclic AMP signaling. Its high centrality in our network underscores its pleiotropic role in multiple signaling cascades relevant to SZP. DAO, which metabolizes D-serine (a co-agonist of NMDA receptors), directly impacts glutamatergic transmission. The presence of DAO among the top five genes reinforces the growing consensus that glutamatergic dysfunction is a core component of schizophrenia pathophysiology, complementing the monoamine-based models.

From a methodological perspective, our study demonstrates the power of bioinformatics and network-based approaches to prioritize candidate genes from large-scale expression data. The use of multiple centrality metrics (degree, betweenness, closeness, radiality, and MNC) provides a robust, multidimensional assessment of gene importance within a disease network. This approach reduces the risk of false positives associated with single-metric analyses and offers a more comprehensive view of the molecular architecture of schizophrenia.

Clinically, the identification of DRD٢, DISC١, COMT, HTR٢A, and DAO as central network hubs supports their potential as biomarkers for diagnosis, prognosis, or therapeutic targeting. For instance, DRD٢ remains the primary target of antipsychotic drugs, while COMT inhibitors and DAO modulators are under investigation as adjunctive treatments. The absence of SV٢A from the central network suggests that, despite its utility as a synaptic density imaging marker, therapeutic strategies directly targeting SV٢A in schizophrenia may not address core etiological mechanisms, unless further evidence establishes a causal link.In conclusion, while SV٢A is not among the principal genes in the schizophrenia gene interaction network based on our bioinformatics analysis, the robust presence of DRD٢, DISC١, COMT, HTR٢A, and DAO reaffirms their critical roles in disease pathogenesis. Future studies should integrate multi-omics data (genomics, transcriptomics, proteomics) and functional validation in animal models to clarify the precise contribution of SV٢A and other peripheral genes. Nevertheless, the current findings provide a clear, data-driven prioritization of schizophrenia-associated genes, offering valuable direction for biomarker discovery and targeted therapeutic development.

References

Basak, S., Bhattacharya, K., & Das, P. (٢٠٢٥). In silico drug discovery of two novel kojic acid metal complex against CALM protein for the treatment of Alzheimer’s disease. *Journal of Preventive, Diagnostic and Treatment Strategies in Medicine*, ٤(١), ٢٦-٣٥.

Bean, L. J., & Hegde, M. R. (٢٠١٦). Gene variant databases and sharing: Creating a global genomic variant database for personalized medicine. *Human Mutation*, ٣٧(٦), ٥٥٩-٥٦٣.

Đorđević, V., Đukić, D. S., Janković, L., & Todorović, L. (٢٠١٦). Schizophrenia and oral health: Review of the literature. *Balkan Journal of Dental Medicine*, ٢٠(١), ١٥-٢١.

Farhang, S., Ghaemmaghami, M., Shafiee-Kandjani, A. R., Noorazar, S. G., Veling, W., Malek, A., et al. (٢٠٢١). An observational cohort of first episode psychosis in Iran: The Azeri Recent Onset Acute Phase Psychosis Survey (ARAS Cohort) study protocol. *Frontiers in Psychiatry*, ١٢, ٦٢٧٩٦٠.

Gill, K., & Grace, A. (٢٠١٦). The role of neurotransmitters in schizophrenia. In *Schizophrenia and psychotic spectrum disorders* (pp. ١٥٣-١٥٤).

Jiménez-Trejo, F., Jiménez-García, K. L., & Canul-Medina, G. (٢٠٢٤). Serotonin and schizophrenia: What influences what? *Frontiers in Psychiatry*, ١٥, ١٤٥١٢٤٨.

Kayaaltı, A., Güneş, B., & Erbaş, O. (٢٠٢١). Synaptic vesicle protein ٢A: Basic facts and roles in schizophrenia. *Journal of Experimental and Basic Medical Sciences*, ٢(٣), ٣٥٨-٣٦٤.

Khan, U., Rahman, M. H., Khan, M. S., Hossain, M. S., & Billah, M. M. (٢٠٢٢). Bioinformatics and network-based approaches for determining pathways, signature molecules, and drug substances connected to genetic basis of schizophrenia etiology. *Brain Research*, ١٧٨٥, ١٤٧٨٨٩.

Lowrance, W. W. (٢٠٠١). The promise of human genetic databases. *BMJ*, ٣٢٢(٧٢٩٣), ١٠٠٩-١٠١٠.

Mattina, G. F., Samaan, Z., Hall, G. B., & Steiner, M. (٢٠٢٠). The association of HTR٢A polymorphisms with obsessive-compulsive disorder and its subtypes: A meta-analysis. *Journal of Affective Disorders*, ٢٧٥, ٢٧٨-٢٨٩.

Mikkelsen, J. D., Kaad, S., Aripaka, S. S., & Finsen, B. (٢٠٢٣). Synaptic vesicle glycoprotein ٢A (SV٢A) levels in the cerebral cortex in patients with Alzheimer's disease: A radioligand binding study in postmortem brains. *Neurobiology of Aging*, ١٢٩, ٥٠-٥٧.

Onwordi, E. C., Halff, E. F., Whitehurst, T., Mansur, A., Cotel, M.-C., Wells, L., et al. (٢٠٢٠). Synaptic density marker SV٢A is reduced in schizophrenia patients and unaffected by antipsychotics in rats. *Nature Communications*, ١١(١), ٢٤٦.

Onwordi, E. C., Whitehurst, T., Mansur, A., Statton, B., Berry, A., Quinlan, M., et al. (٢٠٢١). The relationship between synaptic density marker SV٢A, glutamate and N-acetyl aspartate levels in healthy volunteers and schizophrenia: A multimodal PET and magnetic resonance spectroscopy brain imaging study. *Translational Psychiatry*, ١١(١), ٣٩٣.

Prata, D. P., Costa-Neves, B., Cosme, G., & Vassos, E. (٢٠١٩). Unravelling the genetic basis of schizophrenia and bipolar disorder with GWAS: A systematic review. *Journal of Psychiatric Research*, ١١٤, ١٧٨-٢٠٧.

Rahi, A. A. (٢٠٢٥). Investigate the relationship between the presence of the CRISPR-Cas system and antimicrobial resistance in *Klebsiella pneumoniae*. *Journal of Preventive, Diagnostic and Treatment Strategies in Medicine*, ٤(١), ١-٨.

Rossi, R., Arjmand, S., Bærentzen, S. L., Gjedde, A., & Landau, A. M. (٢٠٢٢). Synaptic vesicle glycoprotein ٢A: Features and functions. *Frontiers in Neuroscience*, ١٦, ٨٦٤٥١٤.

Saravani, R., Galavi, H. R., & Sargazi, M. L. (٢٠١٧). Catechol-O-methyltransferase (COMT) gene (Val١٥٨Met) and brain-derived neurotropic factor (BDNF) (Val٦٦Met) genes polymorphism in schizophrenia: A case-control study. *Iranian Journal of Psychiatry*, ١٢(٤), ٢٦٥.

Stout, K. A., Dunn, A. R., Hoffman, C., & Miller, G. W. (٢٠١٩). The synaptic vesicle glycoprotein ٢: Structure, function, and disease relevance. *ACS Chemical Neuroscience*, ١٠(٩), ٣٩٢٧-٣٩٣٨.

Tandon, R., Nasrallah, H., Akbarian, S., Carpenter, W. T., Jr., DeLisi, L. E., Gaebel, W., et al. (٢٠٢٤). The schizophrenia syndrome, circa ٢٠٢٤: What we know and how that informs its nature. *Schizophrenia Research*, ٢٦٤, ١-٢٨.

Tang, H., Jensen, K., Houang, E., McRobb, F. M., Bhat, S., Svensson, M., et al. (٢٠٢٢). Discovery of a novel class of D-amino acid oxidase inhibitors using the Schrödinger computational platform. *Journal of Medicinal Chemistry*, ٦٥(٩), ٦٧٧٥-٦٨٠٢.

Toyonaga, T., Fesharaki-Zadeh, A., Strittmatter, S. M., Carson, R. E., & Cai, Z. (٢٠٢٢). PET imaging of synaptic density: Challenges and opportunities of synaptic vesicle glycoprotein ٢A PET in small animal imaging. *Frontiers in Neuroscience*, ١٦, ٧٨٧٤٠٤.

Watanabe, M., Khu, T. M., Warren, G., Shin, J., Stewart, C. E., Jr., & Roche, J. (٢٠٢٣). Evidence of Disrupted-in-Schizophrenia ١ (DISC١) as an arsenic binding protein and implications regarding its role as a translational activator. *bioRxiv*. Advance online publication.

Yan, Q., Wu, X., Zhou, P., Zhou, Y., Li, X., Liu, Z., et al. (٢٠٢٢). HERV-W envelope triggers abnormal dopaminergic neuron process through DRD٢/PP٢A/AKT١/GSK٣ for schizophrenia risk. *Viruses*, ١٤(١), ١٤٥.

Table ۱. Protein network connectivity score of schizophrenia

Gene	GDA score
DISC١	١
TNF	١
CHRNA٧	١
GRIN٢B	١
DRD٣	١
GABBR١	١
ZNF٨٠٤A	١
HTR٢A	١
ERBB٤	١
COMT	١

Table ۲. MNC and degree scores for the association network between SZP genes

Biomarkers
DRD٢
DISC١
COMT
HTR٢A
DAO
GRIN٢B
DTNBP١
SLC٦A٤

DAOA
GRM۳

Table ۳. Closeness score for the connection network between SZP genes

Biomarkers
DRD۲
DISC۱
COMT
HTR۲A
DAO
GRIN۲B
DTNBP۱
BDNF
SLC٦A٤
GRM۳

Table ٤. Radiality score for the connection network between SZP genes

Biomarkers
DRD۲
DISC۱
COMT
HTR۲A
GRIN۲B
DTNBP۱

BDNF
SLC٦A٤
DAO
GRM۳

Table ٥. Betweeness score for the connection network between SZP genes

Biomarkers
BDNF
SLC٦A٤
DRD۲
GRIN۲B
HTR۲A
GABRB۲
DRD۳
COMT
GRM۳
DISC۱

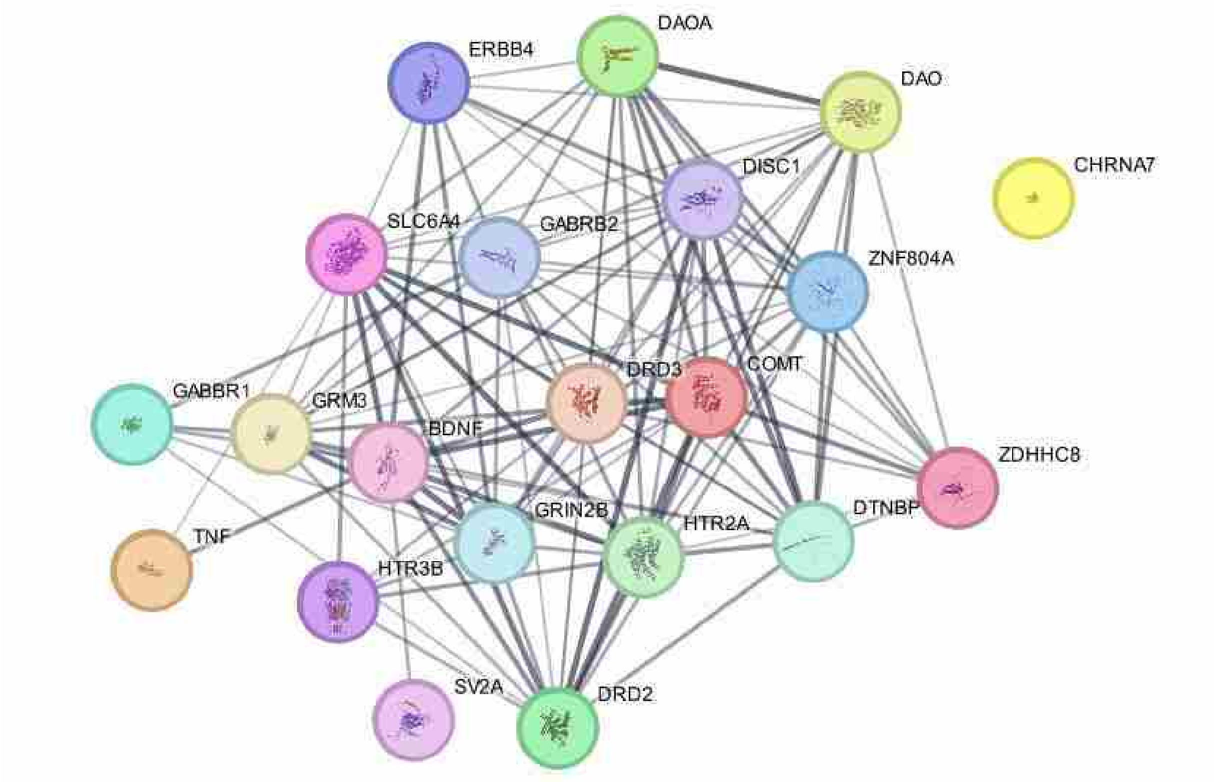

Figure ۱: Communication network between SZP genes. Each node (vertex) is a gene, and the connecting edge between them is a physical or functional relationship based on at least one type of in vivo, in vitro, or in silico study, and the genes calculated based on the GDA criterion.

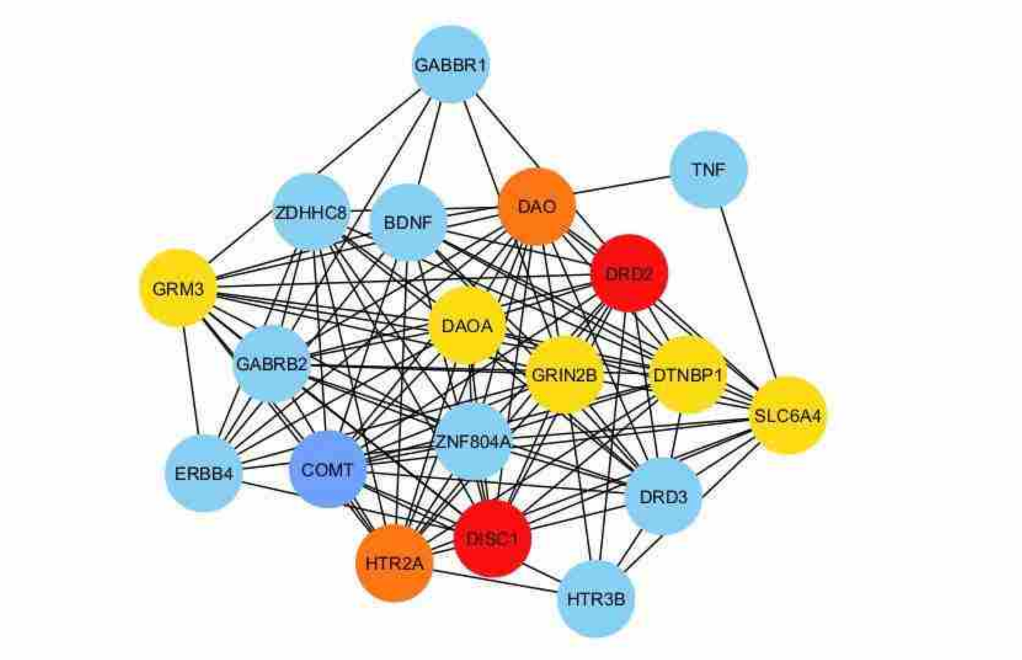

Fig ۲. The connection network between SZP genes based on the MNC score.

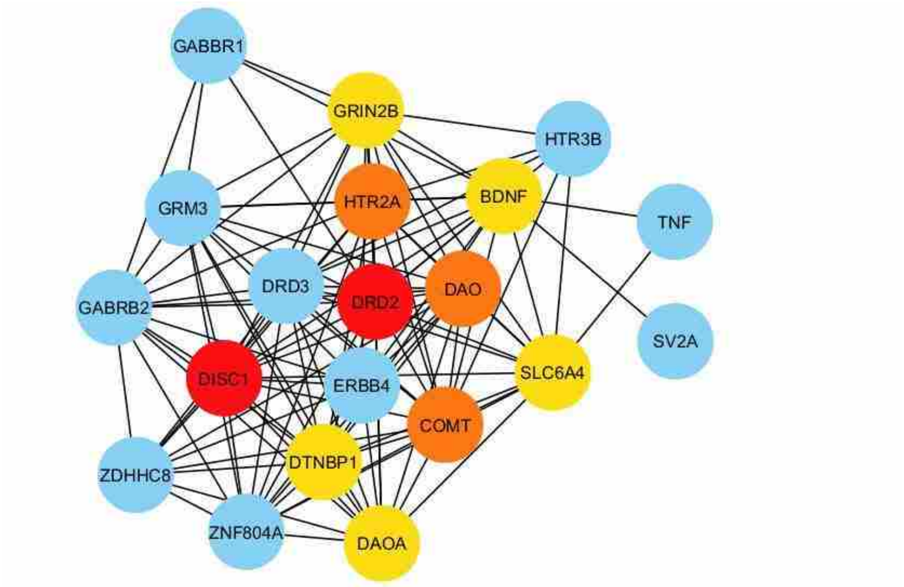

Fig ۳. The connection network between SZP genes based on degree scores.

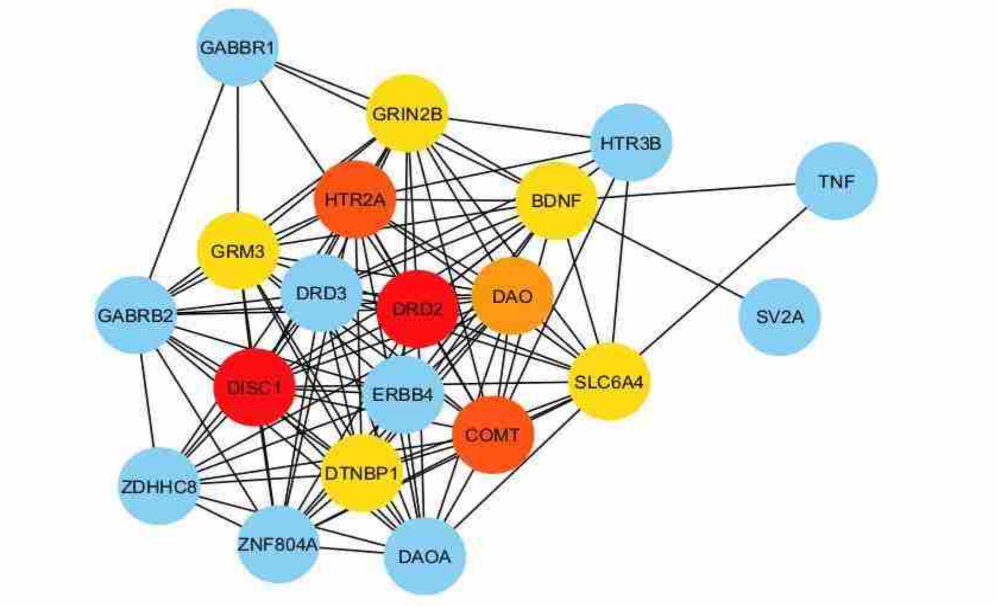

Figure ٤. SZP communication network based on closeness score.

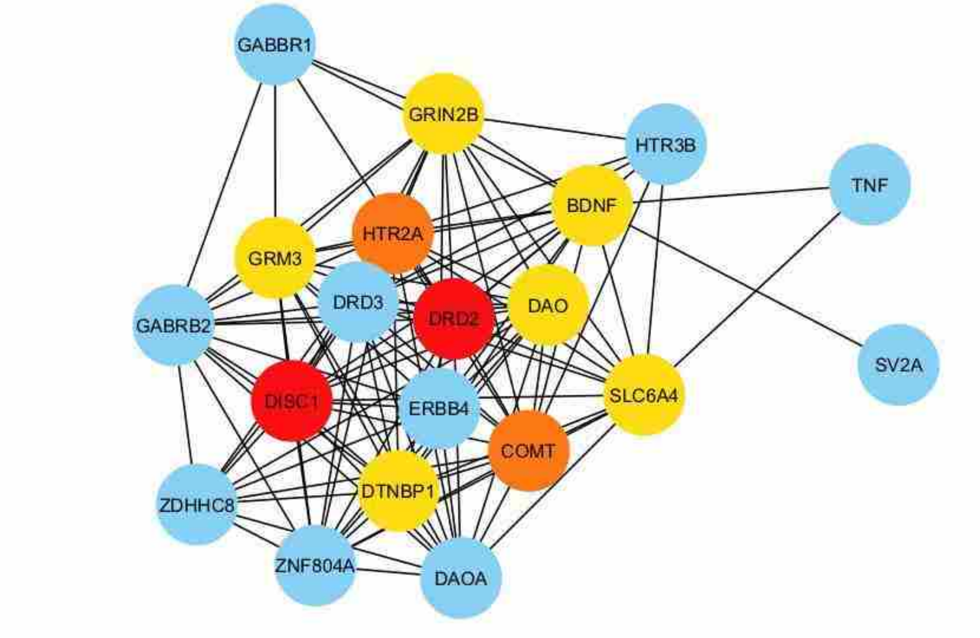

Figure ٥. Connection network between SZP genes based on radiality score.

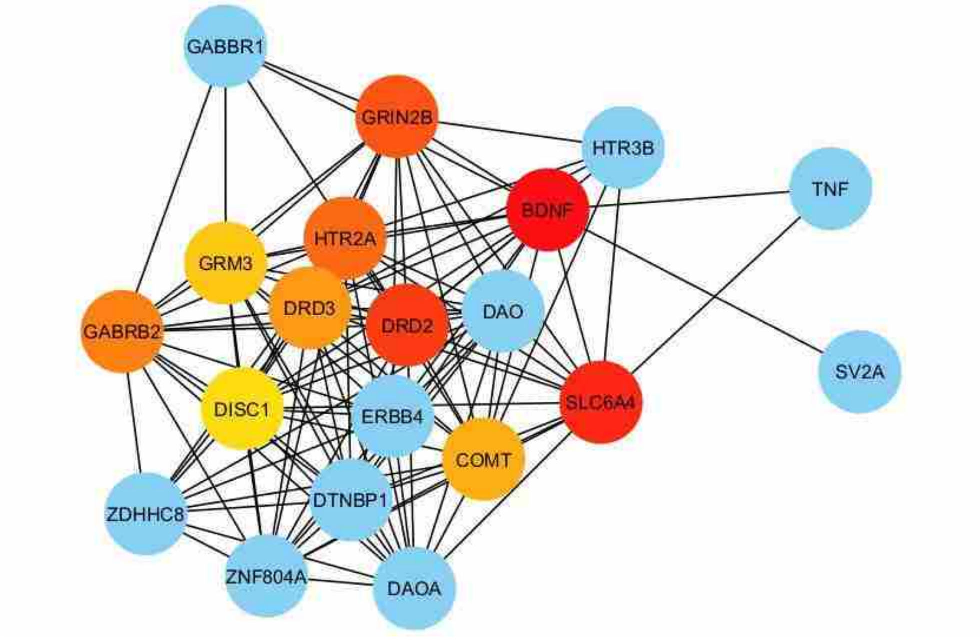

Figure ٦. The connection network between SZP genes based on betweenness

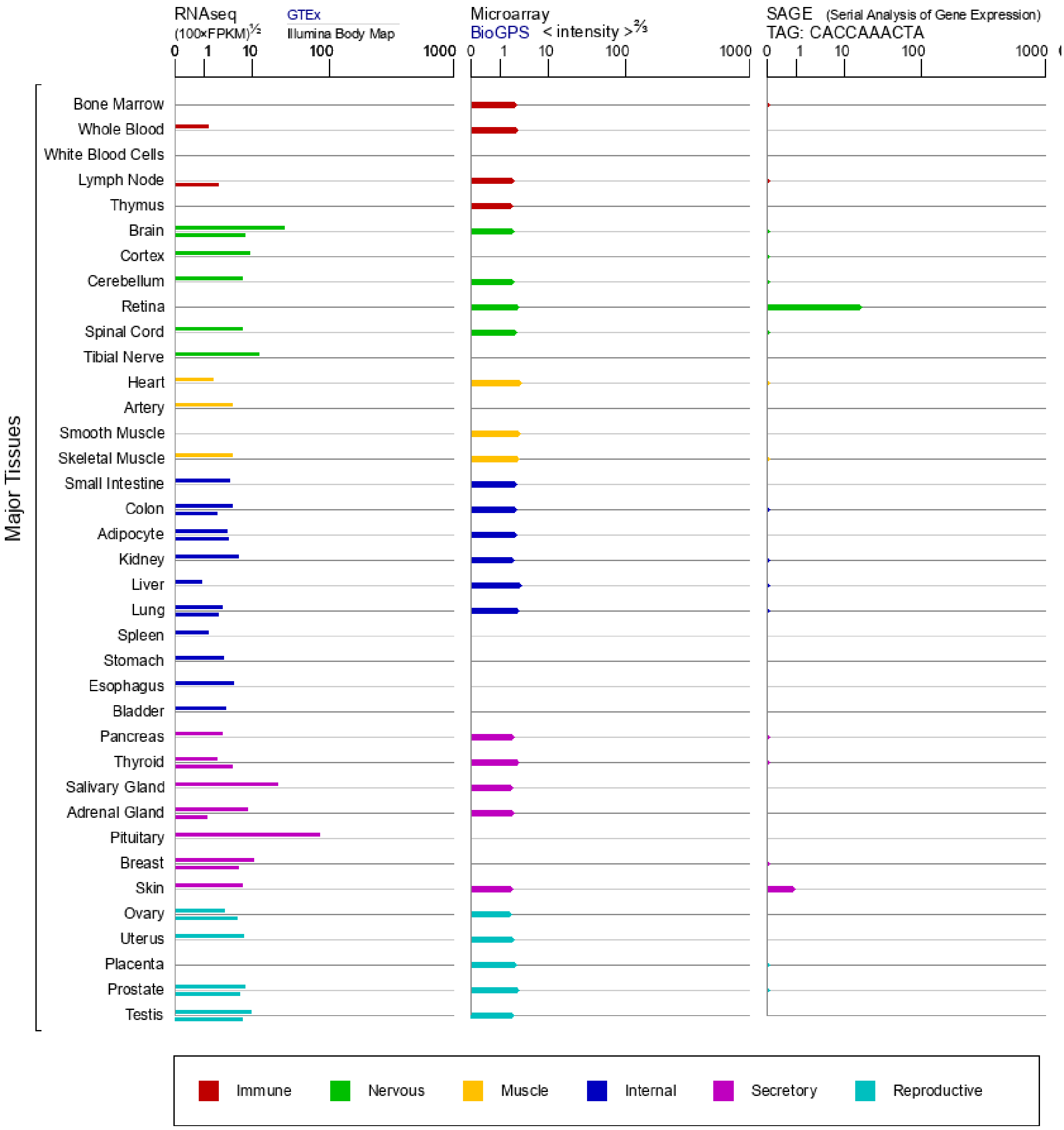

Figure ۷. Expression level of DRD۲ protein in different body tissues based on three methods: RNAseq, Microarray, and SAG

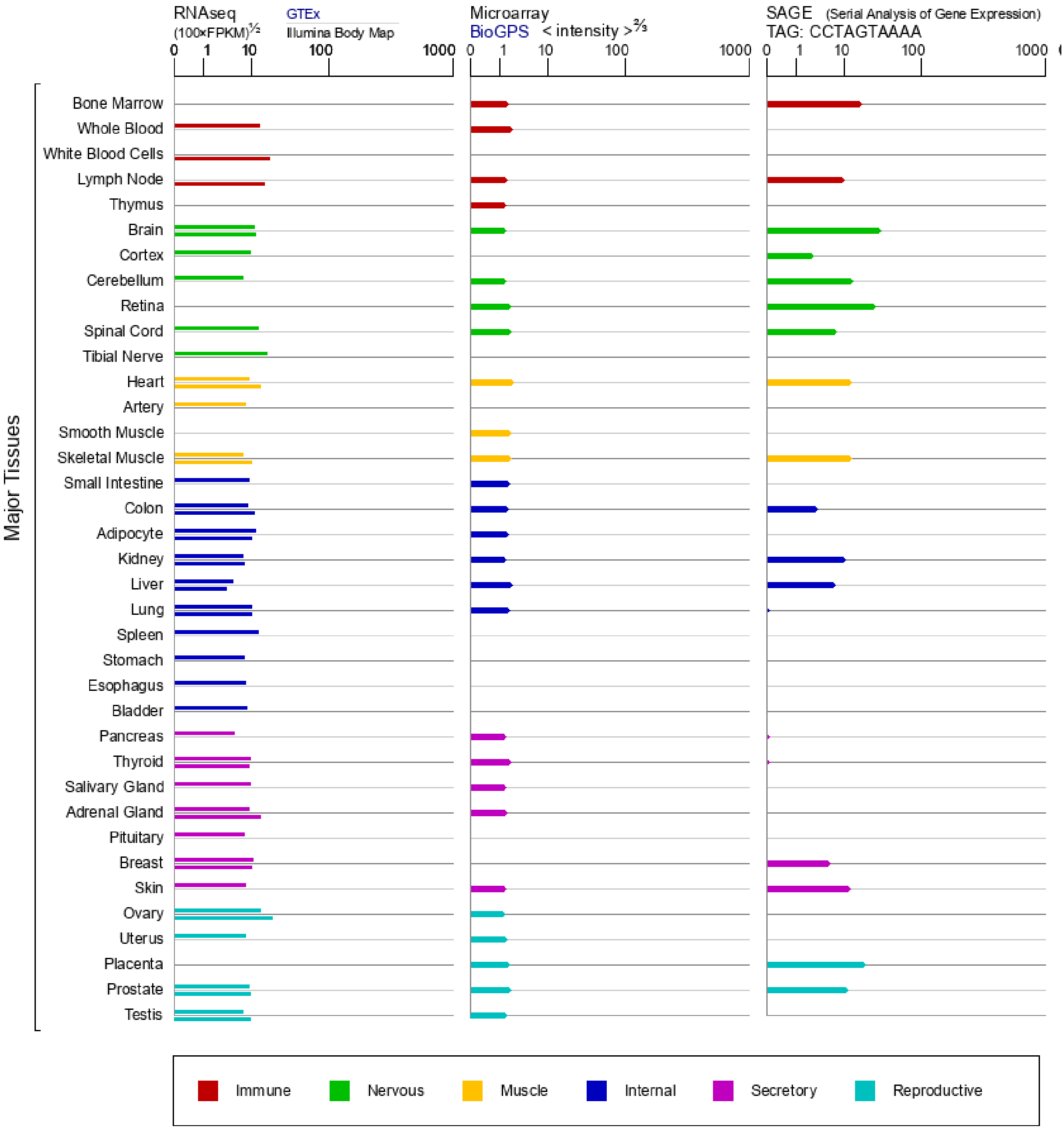

Figure ۸. Expression level of DISC۱ protein in different body tissues based on three methods: RNAseq, Microarray, and SAG

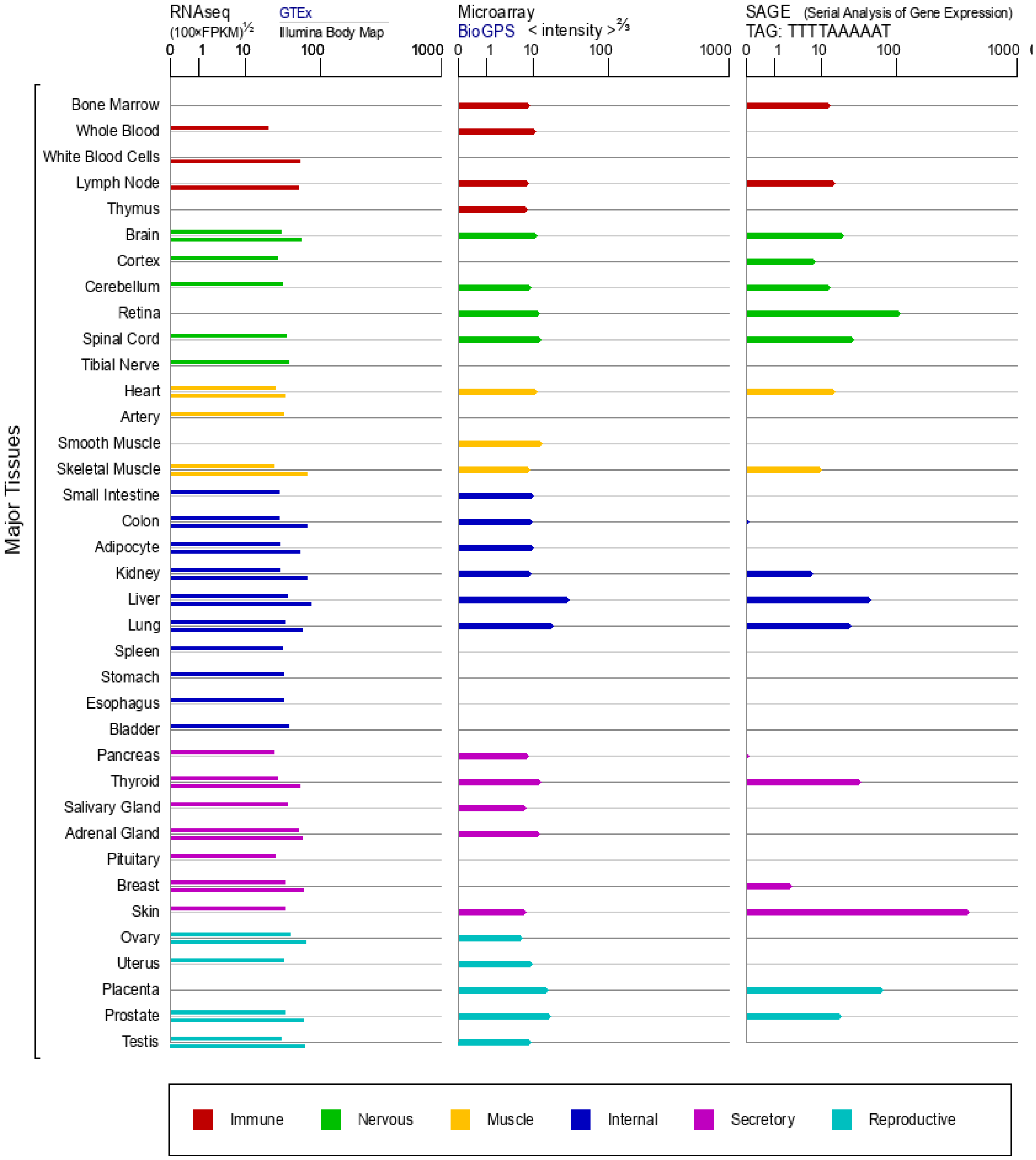

Figure ۹. Expression level of COMT protein in different body tissues based on three methods: RNAseq, Microarray, and SAG

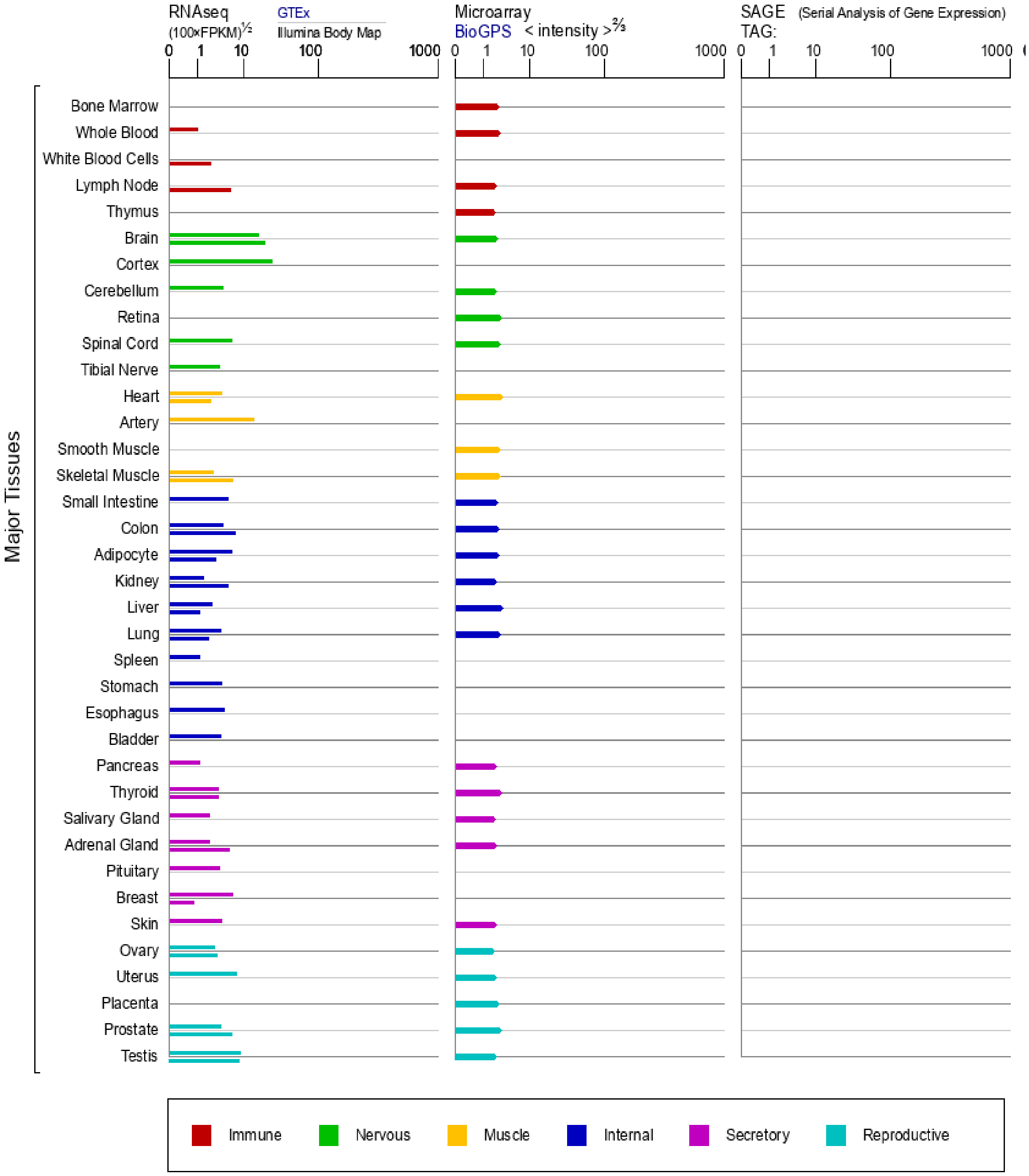

Figure ۱۰. Expression level of HTR۲A protein in different body tissues based on three methods: RNAseq, Microarray, and SAG

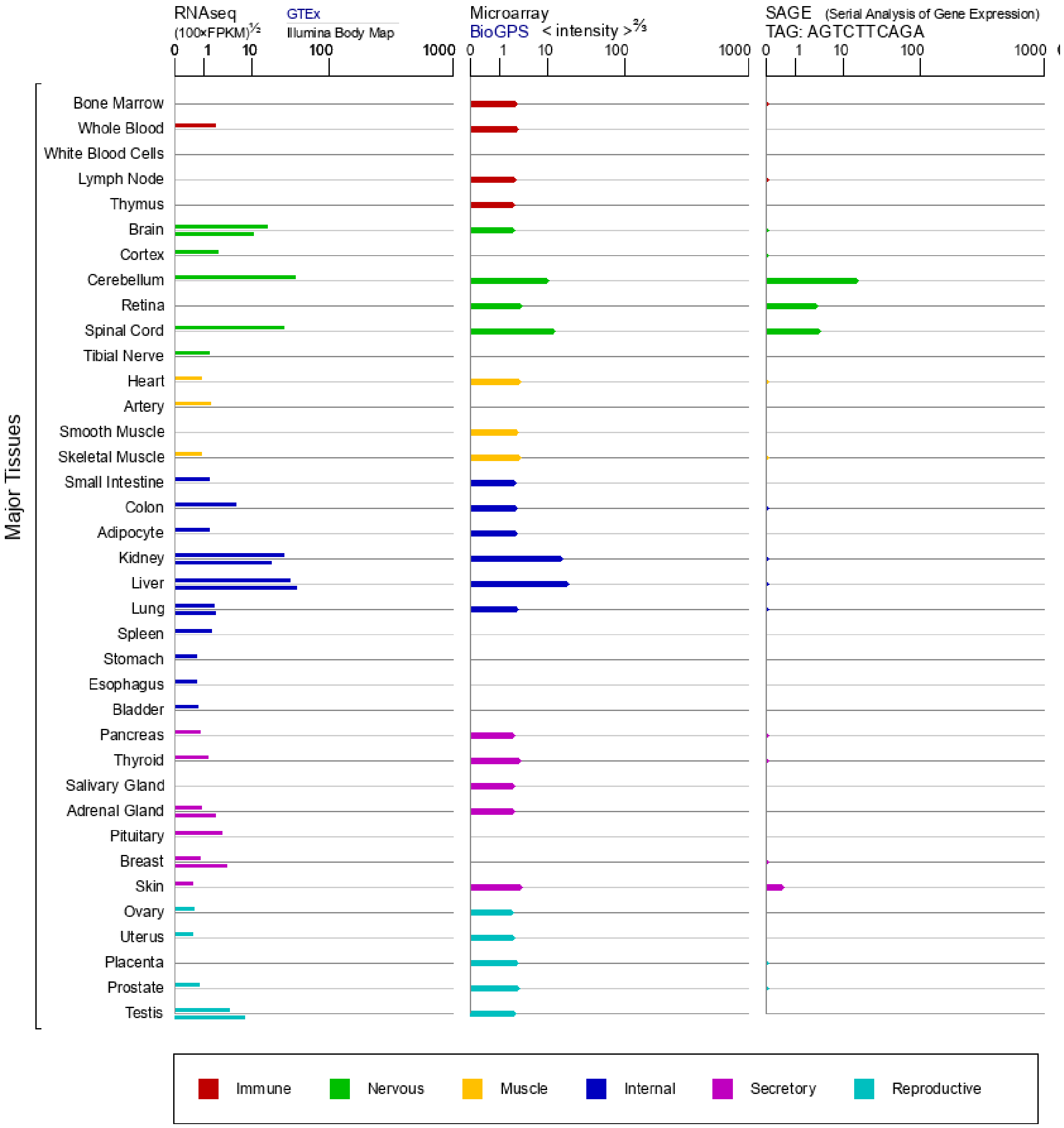

Figure ۱۱. Expression level of DAO protein in different body tissues based on three methods: RNAseq, Microarray, and SAG