JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م /١٤٤٦هـ
العدد الثالث والعشرون
(748)- (731)

استكشاف الشبكات الوظيفية ومسارات KEGG للجينات والبروتينات المرتبطة بمرض طيف التوحد: دراسة معلوماتية بايولوجية

د.منى عبد الرحيم عبد الرضا
جامعة واسط /كلية العلوم
mrhida@uowasit.edu.iq

المستخلص:

اضطراب طيف التوحد (ASD) هو خلل في النمو العصبي للدماغ ينشأ نتيجة عدة اسباب جينية وبيئية. هذه الدراسة تركز على استخدام أدوات المعلوماتية الحيوية (Bioinformatics)مثل (ENRICHRو STRING) لتحديد الشبكات الوظيفية بالإضافة إلى مسارات KEGG المرتبطة بثمانية جينات لها علاقة بوظائف الدماغ و لها أدوار أساسية في اضطراب طيف التوحد. هذه الجينات تتمثل ب SLC6A4, ITGB3, DISC1, AVPR1a, SHANK3, RPL10, RELN, DYX1c1. اقترحت المعلومات الوظيفية الجينية GO تحليلا للمكونات الخلوية والوظائف الجزيئية والعمليات البيولوجية بالإضافة إلى المستقبلات التي تشبه مستقبلاتASD . باستخدام تحليل مسار KEGG، اكتشفنا مسارات متعددة ترتبط بشكل كبير باضطراب طيف التوحد، بما في ذلك دورة الحويصلة المشبكية والمشبك الجلوتاماتي المعروف بدوره الأساسي في التشابك العصبي، والنقل العصبي، بالإضافة إلى تفاعل مستقبلات ECM التي تلعب دورًا رئيسيًا في النمو العصبي، والنقل العصبي، والمرونة التشابكية. حدد تحليل STRING شبكة معقدة من التفاعلات بين الجينات المختارة. تعمق هذه النتائج فهمنا للآليات الجزيئية التي تسبب اضطراب طيف التوحد وتقترح أهدافًا مستقبلية للتطوير العلاجي.

الكلمات المفتاحية: التوحد،KEGG، علم الوجود الجيني ،الاثراء ،السلسلة.

Exploring Functional Networks and KEGG Pathways of Autism-Associated Genes and Proteins: A Bioinformatics Study

Muna A. Abdal Rhida[1]*
Department of Biology/ Wasit University/ Kut, Iraq.
mrhida@uowasit.edu.iq

JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م /١٤٤٦هـ

Abstract

Autism Spectrum Disorder (ASD) is a neuro-developmental disorder of the brain which arises due to numerous genetic and environmental interplay. In our study, we utilized bioinformatics tools Enrichr and STRING) to find the functional networks as well as KEGG pathways associated with eight brain related genes (RELN, SLC6A4, ITGB3, AVPR1a, DISC1, SHANK3, RPL10, DYX1c1) that have essential roles in ASD. GO enrichment analyses suggested cellular components, molecular functions and biological processes in addition to those included that were associated with ASD like receptor binding. Using KEGG pathway enrichment analysis, we detected multiple pathways to be highly associated with ASD including the synaptic vesicle cycle and glutamatergic synapse known for the essential roles in neurodevelopment (synaptic function), neurotransmission, as well as ECM-receptor interaction that plays a key role in neurodevelopment, neurotransmission, and synaptic plasticity. STRING analysis identified an intricate network of interactions among the chosen genes. These results expand our understanding of the molecular mechanisms causes the ASD disorder and propose potential targets for future investigation and therapeutic development.

Keywords: Autism; KEGG; Gene Ontology, ENRICHR; STRING

Introduction

Autism Spectrum Disorder (ASD), the complex neurodevelopmental condition with social interaction difficulties, communication, and repetitive behaviors is a hall mark for ASD (Khalifeh et al., 2016; Lord et al., 2020; Muammar & Alnusayri, 2021). Previous years have shown increased incidence and currently, in the United States of America (USA), 1 out of 44 children are reported to be born with ASD (Walensky et al., 2021) .

The pathophysiology of ASD is complex and the exact etiology of ASD continues to remain unknown. Nevertheless, there is evidence from the literature supporting this conjecture of a gene-environment interaction. Environmental factors include also early exposure to certain chemicals, advanced parental age and complications at pregnancy or during delivery

JOBS مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م/١٤٤٦هـ

(Park et al., 2016; Sauer et al., n.d.), (Karimi et al., 2017; Modabbernia et al., 2017).

Unlike the environmental factors, however, there are multiple genes on which genetic factors represent and alteration in these genes could increase an individual probability of ASD (Genovese & Butler, 2023; Rylaarsdam & Guemez-Gamboa, 2019a, 2019b). However, there is no one cause and the genetic and environmental contributions to disorder remain to be elucidated. The diagnosis and intervention of children with ASD needs to be done as soon as possible, when difficulties are beginning to manifest themselves progressively. Early intervention programs, including speech, occupational, and behavioral therapy can benefit children with ASD by teaching them necessary skills for better communication and interaction in social contexts. Most of these therapies are successful in helping autistic people in realizing their potentials as early as start (Geschwind, 2009; Okoye et al., 2023). The proliferation of genetic studies revealed dozens of genes and pathways influencing ASD development, while pointing to the extensive regulatory network underlying the disorder. The reelin gene (RELN), Solute Carrier Family 6 Member 4 (SLC6A4), integrin beta 3 (ITGB3), arginine vasopressin receptor 1A (AVPR1a), disrupted schizophrenia 1 (DISC1), SH3 and multiple ankyrin repeat domains (SHANK3). However, genes such as ribosomal protein L10 (RPL10), and dyslexia candidate gene (DYX1C1) are among the brain-related genes that play key roles in the occurrence of the ASD (Lopes Cardoso & Almeida, 2019). They could be contributing factors to the other observed behavioural profile. They function in all aspects of signal transduction and a variety of brain functions including but not limited to synaptic transmission, and brain development Instantaneous compensation may be a way for these streamlined muscle genes to temper the otherwise extreme potential for overloading experienced by metabolic tissues. Each and every one of these genes is necessary for normal brain growth and function. ASD's complexity depends on the interactions between these genes and the larger molecular networks in which they contribute (Sauer et al., n.d.).

JOBS مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م/١٤٤٦هـ

Bioinformatics is very helpful to analyze the functional networks and paths related with the genes responsible for disease pathology (Tang et al., 2023; Wei et al., 2022). Bioinformatics approaches are used to achieve an understanding of the underlying molecular mechanisms of ASD which is fueled by various genomic and proteomic data (Talli et al., 2022; Tang et al., 2023). In particular, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways are key information about the data on these genes and their protein products in the cell biochemical pathways and signaling networks. Here, we systematically investigated the functional networks and KEGG pathways associated with a set of genes (AVPR1a, DISC1, DYX1C1, ITGB3, SLC6A4, RELN, RPL10 and SHANK3) previously implicated in ASD. To better understand the molecular pathways behind ASD, we will investigate the interactions between these genes and the proteins they encode through bioinformatics techniques. We seek for discovering putative biological processes and signaling cascades that contribute to the pathophysiology of ASD by aligning these genes to certain KEGG pathways. Comprehending these pathways provide an insight into novel ideas for therapy targets and ASD intervention techniques.

Methodologies

1. Gene Assortment

In this study, 8 genes related to autism spectrum disorder (ASD): RELN, SLC6A4, ITGB3, AVPR1a, DISC1, SHANK3, RPL10, and DYX1C were designated. By reviewing the literature, these genes were formerly selected as brain-related that have vital role on the prevalence of Autism (Lopes Cardoso & Almeida, 2019; Yonan et al., n.d.).

2. Functional Enrichment Analysis

Enrichr database server (https://maayanlab.cloud/Enrichr/) was used to achieve the functional enrichment analysis, we retrieved enriched terms into Gene Ontology (GO) categories such as Cellular Component (CC), Molecular Function (MF), and Biological Process (BP). The KEGG (Kyoto Encyclopedia of Genes and Genomes) via Enrichr tool was applied to conduct pathway enrichment analysis. This tool allows to crosslink genes data with diverse databases such as Gene Ontology or Reactome.

JOBS مجلة العلوم الأساسية Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م/١٤٤٦هـ

3. Network Analysis of Protein-Protein Interaction (PPI)

The network of protein-protein interaction (PPI) was shaped by STRING database v.11 (https://string-db.org/) (Abdal Rhida, 2024). The selected genes group was uploaded to the STRING database. Interaction sources included databases, experimental data, gene fusion, co-expression, co-occurrence, and neighborhood.

Results and Discussion

While studying the intricate links between genetics and autism, our research group conducted an extensive investigation of the functional networks and pathways associated with eight genes tied to this neurodevelopmental condition. Using bioinformatics tools such as Enrichr and the STRING database, we performed an in-depth functional enrichment analysis of RELN, SLC6A4, ITGB3, AVPR1a, DISC1, SHANK3, RPL10, and DYX1C1 - eight genes previously implicated in autism spectrum disorder.

The Enrichr platform proved quite insightful for deciphering Gene Ontology terms and molecular pathways relevant to our selected gene set. An analysis of Gene Ontology annotations illuminated the cellular components, molecular functions, and biological processes attributable to these genes, helping to further elucidate their potential roles in neurodevelopment as well as any contributions to core symptoms of ASD. Cellular component categories that emerged as enriched provided clues about the subcellular locales where these gene products exert their influences including neuron projection (GO:0043005) especially for RELN, SHANK3, and SLC6A4, asymmetric synapse (GO:0032279), and postsynaptic density (GO:0014069) for both of DISC1 and SHANK3 (Table 1). These results come in agreement with what have been experimentally evidenced by (Jossin, 2020; Kirkpatrick et al., 2006; Tao-Cheng et al., 2016; Wang et al., 2024). These terms propose that the selected genes are largely associated with synaptic structures, highlighting their roles in neuronal wiring and signaling, which are vital processes often disrupted in ASD (Figure 1).

JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م/١٤٤٦هـ

Table1. The top 10 GO Cellular Component with significant p-values and q-values

term	p-value	q-value	overlap genes
Glutamatergic Synapse (GO:0098978)	0.000414	0.009577	[ITGB3, DISC1]
Cell Projection Membrane (GO:0031253)	0.000749	0.009577	[ITGB3, SHANK3]
Neuron Projection (GO:0043005)	0.001084	0.009577	[RELN, SHANK3, SLC6A4]
Asymmetric Synapse (GO:0032279)	0.001197	0.009577	[DISC1, SHANK3]
Postsynaptic Density (GO:0014069)	0.001539	0.009849	[DISC1, SHANK3]
Filopodium Membrane (GO:0031527)	0.004392	0.023425	[ITGB3]
Microvillus Membrane (GO:0031528)	0.005189	0.023721	[ITGB3]
Platelet Alpha Granule Membrane (GO:0031092)	0.006383	0.024243	[ITGB3]
GABA-ergic Synapse (GO:0098982)	0.007576	0.024243	[DISC1]
Smooth Endoplasmic Reticulum (GO:0005790)	0.007576	0.024243	[RPL10]

JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م/ ١٤٤٦هـ

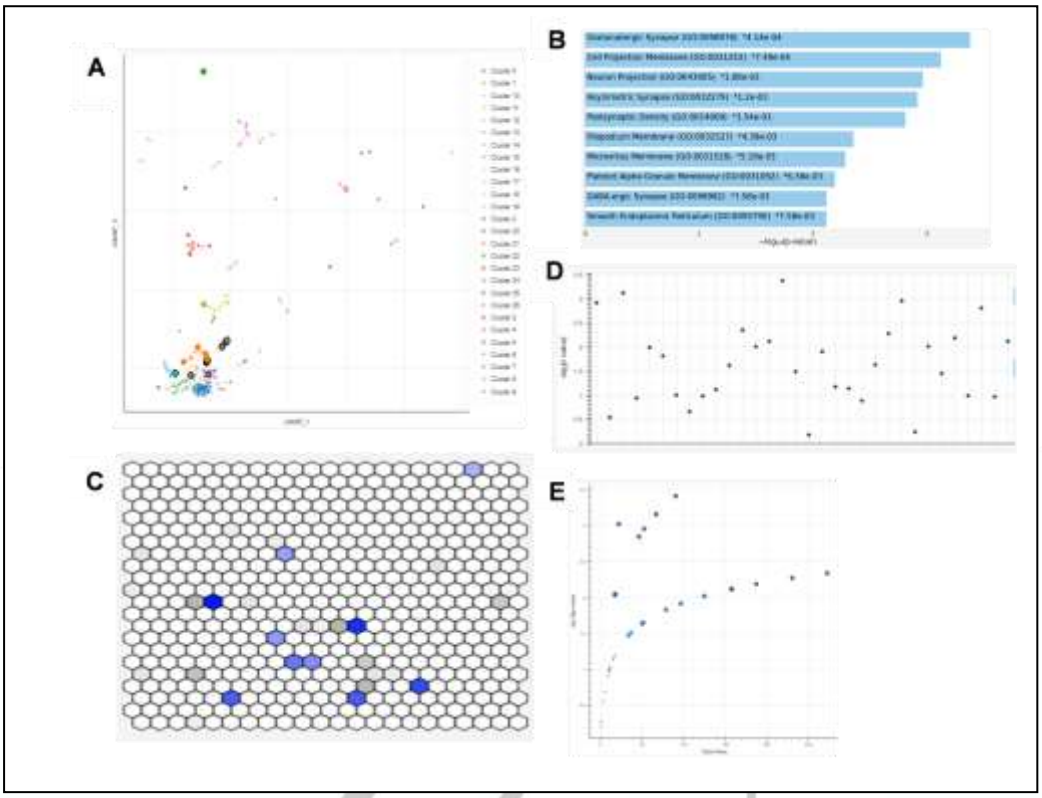


Figure 1. GO Cellular Component. **A.** Scatterplot of terms in the gene ontology Cellular Component gene set library. Points represent terms in the library. **B.** Bar chart of the top 10 enriched terms from GO Cellular Component gene set library. **C.** Hexagonal canvas plot of terms from GO Cellular Component gene set library. Each hexagon represents a single term. **D.** Manhattan plot of terms from GO Cellular Component gene set library..**E.** Volcano plot of terms from the GO Cellular Component gene set library. Each point denotes a single term.

Biological Processes (BP) revealed enrichment in processes like synaptic signaling (GO:1900273) and Synaptic Transmission, Glutamatergic (GO:0051968) specifically for both RELN and SHANK3, neurodevelopment (GO:0007420) for RELN, SHANK3, and SLC6A4. According to (Wang et al., 2024), RELN absence or damage in its signaling cascade causes neurodevelopmental defects which are linked with ataxia, intellectual

JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م/١٤٤٦هـ

disability, autism, and several psychiatric disorders. These results are consistent with what has been experimentally shown by (Arons et al., 2016; Huang et al., 2019; Joly-Amado et al., 2023; Murphy & Moya, 2011). RELN and SHANK3 have shown Biological Processes in Regulating Dendritic Spine Morphogenesis (GO:0061001) (Table 2). According to (Dansie & Ethell, 2011; Knuesel, 2010), mutations in RELN have been reported to be a more likely reason of autism and schizophrenia. Additionally, research has shown that mutations in SHANK3 related with autism make modifications to dendritic spine morphology via actin-dependent mechanism (Durand et al., 2012; Grabrucker et al., 2011; Roussignol et al., 2005) (Figure 2).

Table 2. The top 10 GO Biological Process with significant p-values and q-values

term	p-value	q-value	overlap genes
Positive Regulation of Signal Transduction (GO:0009967)	0.000002	0.000417	[RELN, ITGB3, DISC1, SHANK3]
Brain Morphogenesis (GO:0048854)	0.000008	0.000780	[SHANK3, SLC6A4]
Positive Regulation of Long-Term Synaptic Potentiation (GO:1900273)	0.000013	0.000860	[RELN, SHANK3]
Positive Regulation of Dendritic Spine Development (GO:0060999)	0.000029	0.000934	[RELN, SHANK3]
Brain Development (GO:0007420)	0.000032	0.000934	[RELN, SHANK3, SLC6A4]
Positive Regulation of Synaptic Transmission, Glutamatergic (GO:0051968)	0.000032	0.000934	[RELN, SHANK3]
Positive Regulation of Excitatory Postsynaptic Potential (GO:2000463)	0.000032	0.000934	[RELN, SHANK3]
Regulation Of AMPA Receptor Activity (GO:2000311)	0.000038	0.000976	[RELN, SHANK3]
Regulation Of Dendritic Spine Morphogenesis (GO:0061001)	0.000061	0.001194	[RELN, SHANK3]
Modulation Of Excitatory Postsynaptic Potential (GO:0098815)	0.000065	0.001194	[RELN, SHANK3]

JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م/١٤٤٦هـ

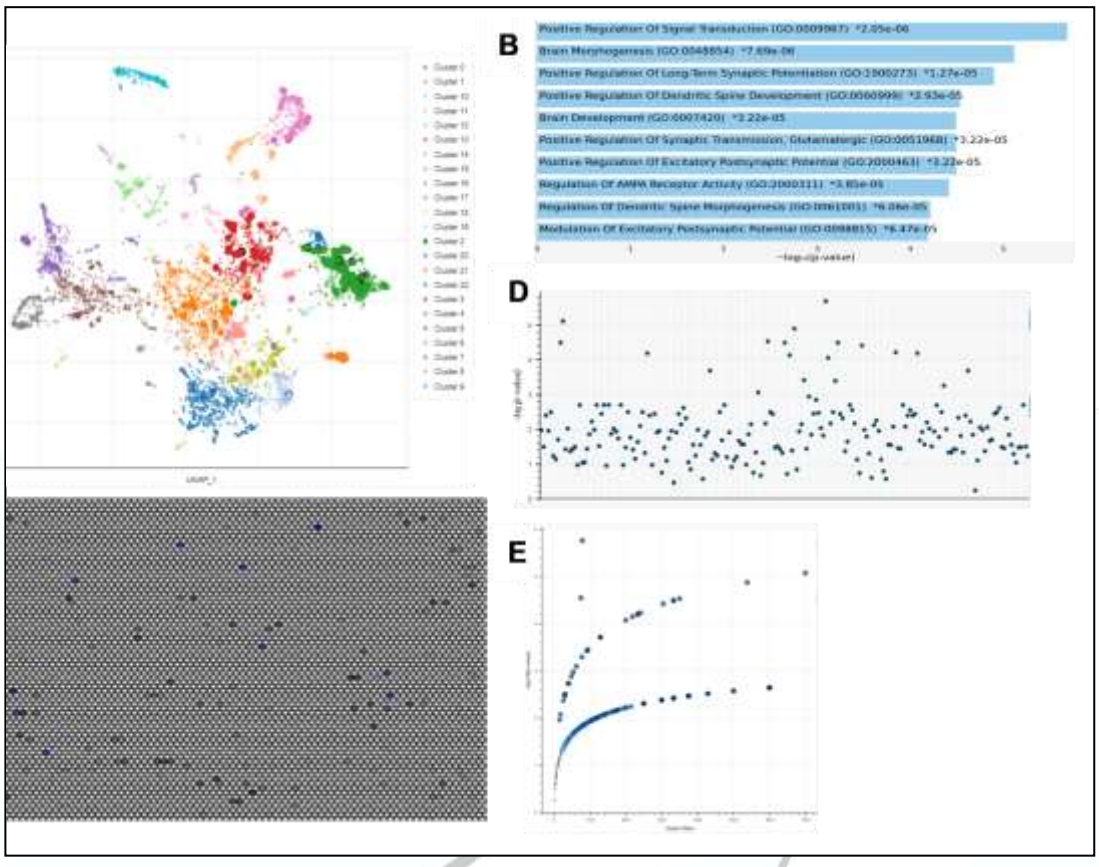


Figure 2. GO Biological Process. **A.** Scatterplot of terms in the gene ontology Biological Process gene set library. Points represent terms in the library. **B.** Bar chart of the top 10 enriched terms from GO Biological Process gene set library. **C.** Hexagonal canvas plot of terms from GO Biological Process gene set library. Each hexagon represents a single term. **D.** Manhattan plot of terms from GO Biological Process gene set library. **E.** Volcano plot of terms from the GO Biological Process gene set library. Each point denotes a single term.

Molecular Functions (MF) analysis showed significant terms such as receptor binding Platelet-Derived Growth Factor Receptor Binding (GO:0005161) for ITGB3 which has been involved in platelet disorder (Ross et al., 2021), ion channel activity Sodium: Chloride Symporter Activity (GO:0015378) for SLC6A4, and G-protein coupled receptor activity such as Glutamate Receptor Binding (GO:0035255) for SHANK3 (Table 3). These findings line up with what has been experimentally demonstrated by

JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م /١٤٤٦هـ

(Rylaarsdam & Guemez-Gamboa, 2019). These functions are suggestive of the genes' contribution in neurotransmission and signaling pathways, more supporting their importance to ASD (Figure 3).

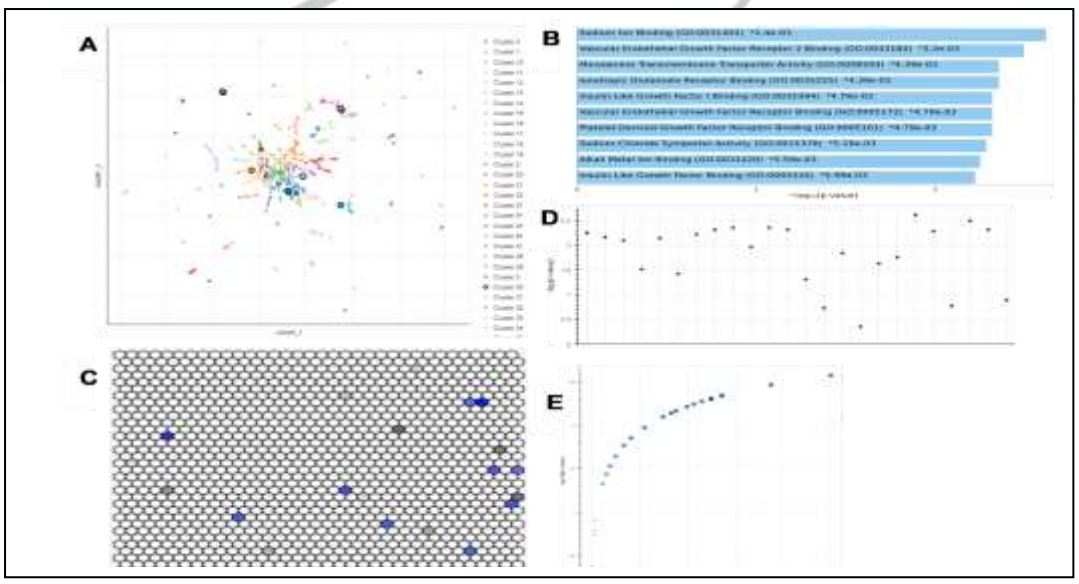
Table 3. The top 10 GO Molecular Function with significant p-values and q-values

term	p-value	q-value	overlap genes
Sodium Ion Binding (GO:0031402)	0.002398	0.014357	[SLC6A4]
Vascular Endothelial Growth Factor Receptor 2 Binding (GO:0043184)	0.003196	0.014357	[ITGB3]
Monoamine Transmembrane Transporter Activity (GO:0008504)	0.004392	0.014357	[SLC6A4]
Ionotropic Glutamate Receptor Binding (GO:0035255)	0.004392	0.014357	[SHANK3]
Insulin-Like Growth Factor I Binding (GO:0031994)	0.004791	0.014357	[ITGB3]
Vascular Endothelial Growth Factor Receptor Binding (GO:0005172)	0.004791	0.014357	[ITGB3]
Platelet-Derived Growth Factor Receptor Binding (GO:0005161)	0.004791	0.014357	[ITGB3]
Sodium: Chloride Symporter Activity (GO:0015378)	0.005189	0.014357	[SLC6A4]
Alkali Metal Ion Binding (GO:0031420)	0.005587	0.014357	[SLC6A4]
Insulin-Like Growth Factor Binding (GO:0005520)	0.005985	0.014357	[ITGB3]

JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م/١٤٤٦هـ

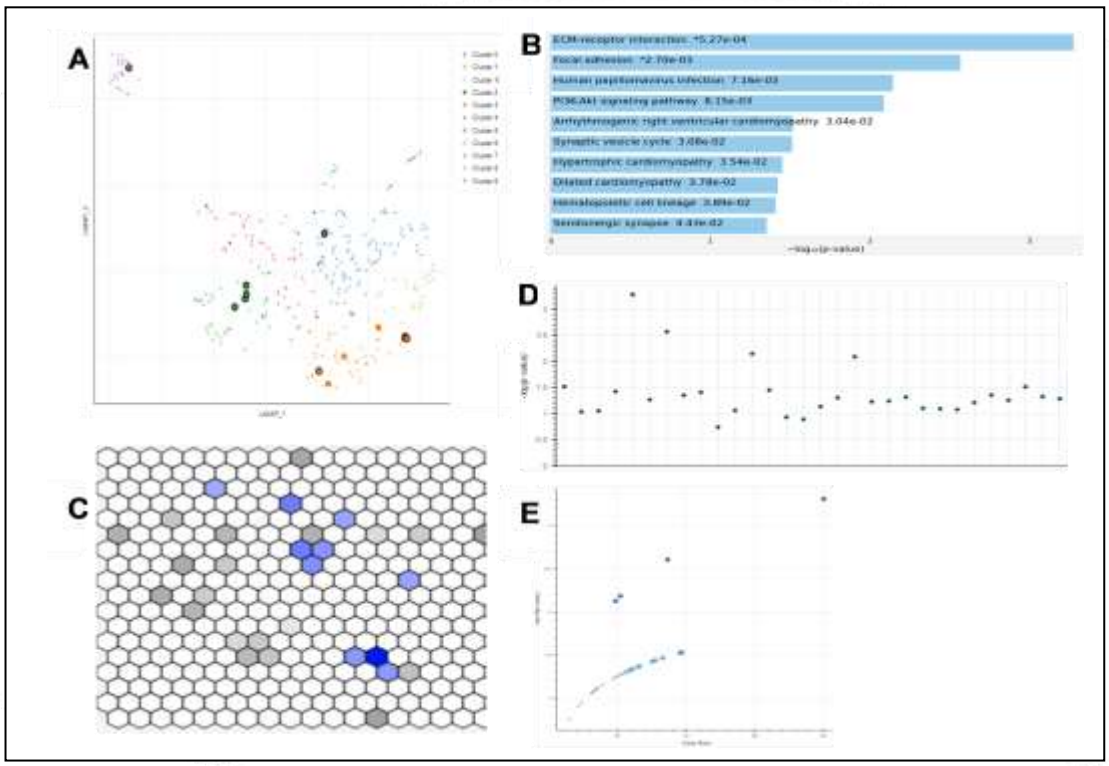
In KEGG pathway analysis, several pathways significantly associated with the selected genes were recognized. Particularly, pathways related to glutamatergic synapse, synaptic vesicle cycle, and ECM-receptor interaction were enriched (Table 4). These pathways are commonly involved in synaptic transmission and neuronal connection makes them vital for precise neurodevelopment and implicated in the ASD's pathophysiology. The significance of these pathways ($p < 0.05$) underlines the latent role of these genes in taking part in the ASD by disturbances of these important pathways (Figure 4).

The PPI network constructed by STRING database revealed clear insights into the interactions among the designated genes and their encoded proteins. The network analysis displayed a high degree of connectivity, especially among the proteins encoded by RELN, SLC6A4, ITGB3, and DISC1, and, which are well-documented for their roles in synaptic function and neurodevelopment (Figure 5). The STRING analysis revealed a network with eight nodes and eight edges, resulting in an average node degree of two and an average local clustering co-efficient of 0.562. The observed number of edges significantly exceeded the expected number (1edge), with a PPI enrichment p-value of 4.78e-07, verifying that the network has significantly more connections than expected by chance.



JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م/١٤٤٦هـ

Figure 3. GO Molecular Function. **A.** Scatterplot of terms in the gene ontology Molecular Function gene set library. Points represent terms in the library. **B.** Bar chart of the top 10 enriched terms from GO Molecular Function gene set library. **C.** Hexagonal canvas plot of terms from GO Molecular Function gene set library. Each hexagon represents a single term. **D.** Manhattan plot of terms from GO Molecular Function gene set library. **E.** Volcano plot of terms from the GO Molecular Function gene set library. Each point denotes a single term.



JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م /١٤٤٦هـ

Table 4. The top 10 KEGG Human with significant p-values

term	p-value	q-value	overlap genes
ECM-receptor interaction	0.000527	0.015804	[RELN, ITGB3]
Focal adhesion	0.002704	0.040562	[RELN, ITGB3]
Human papillomavirus infection	0.007158	0.061138	[RELN, ITGB3]
PI3K-Akt signaling pathway	0.008152	0.061138	[RELN, ITGB3]
Arrhythmogenic right ventricular cardiomyopathy	0.030393	0.092235	[ITGB3]
Synaptic vesicle cycle	0.030783	0.092235	[SLC6A4]
Hypertrophic cardiomyopathy	0.035444	0.092235	[ITGB3]
Dilated cardiomyopathy	0.037767	0.092235	[ITGB3]
Hematopoietic cell lineage	0.038927	0.092235	[ITGB3]
Serotonergic synapse	0.044324	0.092235	[SLC6A4]

Figure 4. KEGG Pathway Human Gene Set Library. **A.** Scatterplot of terms in the KEGG Pathway human gene set library. Points represent terms in the library. **B.** Bar chart of the top 10 enriched terms from KEGG Pathway human gene set library. **C.** Hexagonal canvas plot of terms from KEGG Pathway humen gene set library. Each hexagon represents a single term. **D.** Manhattan plot of terms from KEGG Pathway human gene set library. **E.** Volcano plot of terms from the KEGG Pathway human gene set library. Each point denotes a single term.

JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م/ ١٤٤٦هـ

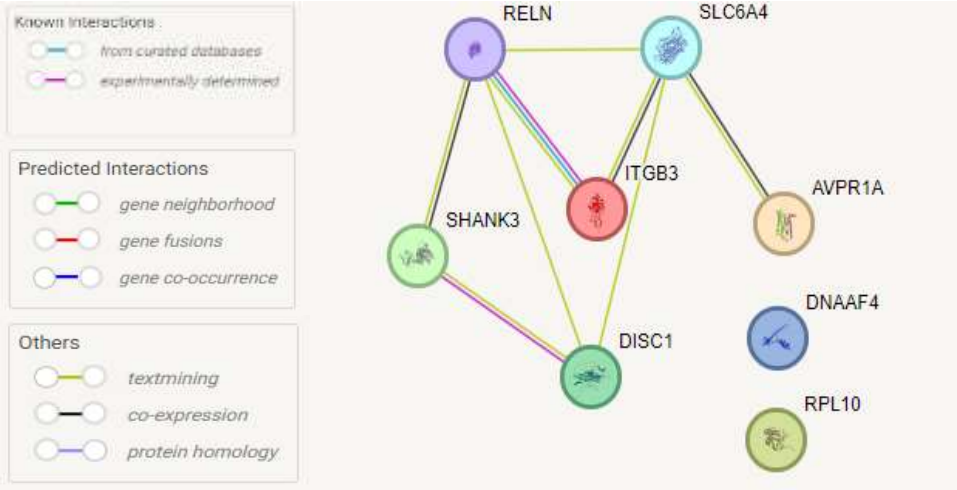


Figure 5. protein-protein interaction (PPI) network construct of brain-related genes involved in ASD.

Conclusion

In this study, bioinformatics tools such as Enrichr and STRING were employed to examine the functional network and KEGG pathways of genes and proteins linked with autism spectrum disorder (ASD), concentrating on RELN, SLC6A4, ITGB3, AVPR1a, DISC1, SHANK3, RPL10, and DYX1C1. Our analysis showed momentous insights into the molecular mechanisms causing ASD.

several pathways associated with ASD were identified through KEGG pathway enrichment analysis using Enrichr database. These pathways included glutamatergic synapse, synaptic vesicle cycle, and ECM-receptor interaction. These pathways are significant for neurotransmission, synaptic plasticity, and neurodevelopment, supporting the hypothesis that dysregulation in these parts subsidizes to the pathophysiology of ASD.

The functional enrichment analysis found a number of significant Gene Ontology (GO) terms and pathways linked with the selected gene set. The enriched GO terms in the Cellular Component category were also associated with neuron projection, asymmetric synapse and postsynaptic density as important factors in neuronal connecting and signaling pathways (both disrupted processes during ASD). Likewise, processes such as synaptic

signaling, neurodevelopment and regulation of neurotransmitter levels were all enriched in the category called biological process which are crucial for ASD condition. Similarly in the case of Molecular Functions analysis; some very important terms were found like receptor binding Factor, ion channel activity and G-protein coupled receptor activity; inferring their utilization in neurotransmission and signaling pathways of ASD. The protein-protein interaction analysis using STRING demonstrated a wide-ranging system underlying the selected genes, suggesting that these genes have an interrelated range of signaling pathways as well as biological processes. Two of these Key hubs, RELN and SLC6A4 are associated with synaptic function and neuronal signaling in regards to standard cognitive and social behaviors. In this study, we have verified the efficiency of bioinformatics tools like Enrichr and STRING in predicting wide range multi-faceted functional interactors as well as pathways related to autism. Results have yielded deeper insight to the underlying molecular mechanisms of the disease and contribute with suggestions for further study as well as potential therapies. More research is necessary to identify RELN and SLC6A4 in autism, which may serve as biomarkers or therapeutic targets.

References

1.Abdal Rhida, M. A. (2024). Bioinformatics Analysis in Predicting Transcription Factors of Robo3 Gene in Drosophila melanogaster. *Biomedical and Pharmacology Journal*, *17*(2), 725–734. https://doi.org/10.13005/bpj/2899

2.Arons, M. H., Lee, K., Thynne, C. J., Kim, S. A., Schob, C., Kindler, S., Montgomery, J. M., & Garner, C. C. (2016). Shank3 is part of a zinc-sensitive signaling system that regulates excitatory synaptic strength. *Journal of Neuroscience*, *36*(35), 9124–9134. https://doi.org/10.1523/JNEUROSCI.0116-16.2016

3.Dansie, L. E., & Ethell, I. M. (2011). Casting a net on dendritic spines: The extracellular matrix and its receptors. *Developmental Neurobiology*, *71*(11), 956–981. https://doi.org/10.1002/dneu.20963

4.Durand, C. M., Perroy, J., Loll, F., Perrais, D., Fagni, L., Bourgeron, T., Montcouquiol, M., & Sans, N. (2012). SHANK3 mutations identified in autism lead to modification of dendritic spine morphology via an actin-dependent mechanism. *Molecular Psychiatry*, *17*(1), 71–84. https://doi.org/10.1038/mp.2011.57

5.Geschwind, D. H. (2009). Advances in autism. In *Annual Review of Medicine* (Vol. 60, pp. 367–380). https://doi.org/10.1146/annurev.med.60.053107.121225

6.Grabrucker, A. M., Knight, M. J., Proepper, C., Bockmann, J., Joubert, M., Rowan, M., Nienhaus, G. U., Garner, C. C., Bowie, J. U., Kreutz, M. R., Gundelfinger, E. D., & Boeckers, T. M. (2011). Concerted action of zinc and ProSAP/Shank in synaptogenesis and synapse maturation. *EMBO Journal*, *30*(3), 569–581. https://doi.org/10.1038/emboj.2010.336

7.Huang, G., Chen, S., Chen, X., Zheng, J., Xu, Z., Doostparast Torshizi, A., Gong, S., Chen, Q., Ma, X., Yu, J., Zhou, L., Qiu, S., Wang, K., & Shi, L. (2019). Uncovering the functional link between SHANK3 deletions and deficiency in neurodevelopment using iPSC-derived human neurons. *Frontiers in Neuroanatomy*, *13*. https://doi.org/10.3389/fnana.2019.00023

8.Joly-Amado, A., Kulkarni, N., & Nash, K. R. (2023). Reelin Signaling in Neurodevelopmental Disorders and Neurodegenerative Diseases. In *Brain Sciences* (Vol. 13, Issue 10). Multidisciplinary Digital Publishing Institute (MDPI). https://doi.org/10.3390/brainsci13101479

9.Jossin, Y. (2020). Reelin functions, mechanisms of action and signaling pathways during brain development and maturation. In *Biomolecules* (Vol. 10, Issue 6, pp. 1–31). MDPI AG. https://doi.org/10.3390/BIOM10060964

10.Karimi, P., Kamali, E., Mousavi, S. M., & Karahmadi, M. (2017). Environmental factors influencing the risk of autism. In *Journal of Research in Medical Sciences* (Vol. 22 Issue 1). Isfahan University of Medical Sciences(IUMS). https://doi.org/10.4103/1735-1995.200272

11.Kirkpatrick, B., Xu, L., Cascella, N., Ozeki, Y., Sawa, A., & Roberts, R. C. (2006). DISC1 immunoreactivity at the light and ultrastructural level in the human neocortex. *Journal of Comparative Neurology*, *497*(3), 436–450. https://doi.org/10.1002/cne.21007

12.Knuesel, I. (2010). Reelin-mediated signaling in neuropsychiatric and neurodegenerative diseases. In *Progress in Neurobiology* (Vol. 91, Issue 4, pp. 257–274). Elsevier Ltd. https://doi.org/10.1016/j.pneurobio.2010.04.002

13.Lopes Cardoso, I., & Almeida, S. (2019). Issue 1 Citation: Cardoso IL, Almeida S (2019) Genes Involved in the Development of. *Cardoso and Almeida. Int Arch Commun Disord*, *2*, 11.

14.Modabbernia, A., Velthorst, E., & Reichenberg, A. (2017). Environmental risk factors for autism: an evidence-based review of systematic reviews and meta-analyses. In *Molecular Autism* (Vol. 8, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s13229-017-0121-4

15.Murphy, D. L., & Moya, P. R. (2011). Human serotonin transporter gene (SLC6A4) variants: Their contributions to understanding pharmacogenomic and other functional G × G and G × e differences in health and disease. In *Current Opinion in Pharmacology* (Vol. 11, Issue 1, pp. 3–10). Elsevier Ltd. https://doi.org/10.1016/j.coph.2011.02.008

16.Okoye, C., Obialo-Ibeawuchi, C. M., Obajeun, O. A., Sarwar, S., Tawfik, C., Waleed, M. S., Wasim, A. U., Mohamoud, I., Afolayan, A. Y., & Mbaezue, R. N. (2023). Early Diagnosis of Autism Spectrum Disorder: A Review and Analysis of the Risks and Benefits. *Cureus*. https://doi.org/10.7759/cureus.43226

17.Park, H. R., Lee, J. M., Moon, H. E., Lee, D. S., Kim, B. N., Kim, J., Kim, D. G., & Paek, S. H. (2016). A short review on the current understanding of autism spectrum disorders. In *Experimental Neurobiology* (Vol. 25, Issue 1, pp. 1–13). Korean Society for Neurodegenerative Disease. https://doi.org/10.5607/en.2016.25.1.1

18.Ross, J. E., Zhang, B. M., Lee, K., Mohan, S., Branchford, B. R., Bray, P., Dugan, S. N., Freson, K., Heller, P. G., Kahr, W. H. A., Lambert, M. P., Luchtman-Jones, L., Luo, M., Botero, J. P., Rondina, M. T., Ryan, G., Westbury, S., Bergmeier, W., & Di Paola, J. (2021). Specifications of the variant curation guidelines for ITGA2B/ITGB3: ClinGen Platelet Disorder Variant Curation Panel. *Blood Advances*, *5*(2), 414–431. https://doi.org/10.1182/bloodadvances.2020003712

19.Roussignol, G., Ango, F., Romorini, S., Tu, J. C., Sala, C., Worley, P. F., Bockaert, J., & Fagni, L. (2005). Shank expression is sufficient to induce functional dendritic spine synapses in aspiny neurons. *Journal of Neuroscience*, *25*(14), 3560–3570. https://doi.org/10.1523/JNEUROSCI.4354-04.2005

20.Rylaarsdam, L., & Guemez-Gamboa, A. (2019). Genetic Causes and Modifiers of Autism Spectrum Disorder. In *Frontiers in Cellular Neuroscience* (Vol. 13). Frontiers Media S.A. https://doi.org/10.3389/fncel.2019.00385

21.Sauer, A. K., Stanton, J. E., Hans, S., & Grabrucker, A. M. (n.d.). *Autism Spectrum Disorders: Etiology and Pathology*. https://doi.org/10.36255/exonpublications

22.Tao-Cheng, J. H., Toy, D., Winters, C. A., Reese, T. S., & Dosemeci, A. (2016). Zinc stabilizes SHANK3 at the postsynaptic density of hippocampal synapses. *PLoS ONE*, *11*(5). https://doi.org/10.1371/journal.pone.0153979

23.Walensky, R. P., Bunnell, R., Layden, J., Kent, C. K., Gottardy, A. J., Leahy, M. A., Martinroe, J. C., Spriggs, S. R., Yang, T., Doan, Q. M., King, P. H., Starr, T. M., Yang, M., Jones, T. F., Timothy Jones, C. F., Matthew Boulton, C. L., Carolyn Brooks, M., Jay Butler, M. C., Caine, V. A., … Yang, W. (2021). *Morbidity and Mortality Weekly Report Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years-Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2018 Surveillance Summaries Centers for Disease Control and Prevention MMWR Editorial and Production Staff (Serials) MMWR Editorial Board*.

24.Wang, Y. Z., Perez-Rosello, T., Smukowski, S. N., Surmeier, D. J., & Savas, J. N. (2024). Neuron type-specific proteomics reveals distinct Shank3 proteoforms in iPSNs and dSPNs lead to striatal synaptopathy in Shank3B–/– mice. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-024-02493-w

JOBS
مجلة العلوم الأساسية
Journal of Basic Science
Print -ISSN 2306-5249
Online-ISSN 2791-3279
العدد الثالث والعشرون
٢٠٢٤م /١٤٤٦هـ

25.Yonan, A. L., Palmer, A. A., Smith, K. C., Feldman, I., Lee, H. K., Yonan, J. M., Fischer, S. G., Pavlidis, P., & Gilliam, T. C. (n.d.). *Bioinformatic analysis of autism positional candidate genes using biological databases and computational gene network prediction*. https://doi.org/10.1046/j.1601-183X.2003.00041.x