IBRO Neuroscience Reports 17 (2024) 311–319

Contents lists available at ScienceDirect

IBRO Neuroscience Reports

journal homepage: www.sciencedirect.com/journal/IBRO-Neuroscience-Reports

Research paper

Immune signature of gene expression pattern shared by autism spectrum disorder and Huntington's disease

Huanhuan Liu [a], Qiuyu Bai [b], Xueying Wang [c], Yunlei Jin [d], Xingda Ju [a,e,*], Chang Lu [a,e,*]

[a] School of Psychology, Northeast Normal University, Changchun, China
[b] Yancheng College of Mechatronic Technology, Yancheng, China
[c] Datong Normal College, Datong, China
[d] Children' s Hospital of Changchun, Changchun, China
[e] Jilin Provincial Key Laboratory of Cognitive Neuroscience and Brain Development, Changchun, China

ARTICLE INFO

Keywords:
Autism spectrum disorder
Huntington's disease
Gene expression
Pathway
Immunity

ABSTRACT

Autism spectrum disorder (ASD) and Huntington's disease (HD) are complex neurological conditions with unclear causes and limited treatments, affecting individuals, families, and society. Despite ASD and HD representing two opposing stages of neuronal development and degeneration, they share similar clinical-pathological features in motor function. In this study, we leveraged transcriptomic data from the prefrontal cortex available in public databases to identify shared transcriptional characteristics of ASD and HD. Differential expression analysis revealed that the majority of differentially expressed genes (DEGs) were up-regulated in ASD carriers, whereas most DEGs were down-regulated in HD carriers. Among the DEGs shared between both diseases, three out of seven protein-coding genes were related to the immune system. Furthermore, we identified two enriched pathways shared between ASD and HD DEGs. The gene interaction network analysis unveiled four hub genes shared by both diseases, all of which are associated with immune functions. The findings suggest a shared gene expression pattern in the prefrontal cortex of people with ASD and HD, closely linked to the immune system. These findings will contribute to exploring the biological mechanisms underlying the shared phenotypes of these two diseases from an immunological perspective.

1. Introduction

Autism spectrum disorder (ASD) is the archetype of neurodevelopmental disorders (Kim and Leventhal, 2015). Huntington's disease (HD) is a common model of neurodegeneration (Ross and Tabrizi, 2011). ASD and HD are two severe mental disorders that reflect abnormalities in the development and decline of the nervous system, respectively. The pathogenesis of two diseases is complex, early screening is arduous, and treatment methods are limited, which causes severe adverse effects on patients, families, and society (Ellison, 2017; Romero, 2017). There is commonality in the mechanisms that play a role in neurodevelopmental and neurodegenerative diseases (Thibaut, 2018). The shared pathogenic mechanisms of ASD and HD warrant attention and in-depth investigation. One common pathological feature of ASD and HD is motor dysfunction. ASD patients exhibit motor impairments characterized by muscle tone abnormalities, rigidity, and pyramidal signs (Bell et al., 2019; Cook, 2016). Chorea and dyskinesia are the hallmark features of HD patients (Snowden, 2017). Exploring these shared pathological characteristics of both diseases is pivotal for uncovering common pathogenic mechanisms. Prior research has often neglected the commonalities between these two complex disorders from a transcriptomic perspective. Investigating the shared transcriptional patterns of these two diseases can help identify common genes and pathways, key for prevention and treatment.

Transcriptomics entails the complete set of transcripts within specific cell types or tissues under defined developmental stages or physiological conditions. Transcriptomic analysis serves as a powerful tool for uncovering an organism's gene expression levels, structural variations and the discovery of novel genes. (Qi et al., 2011). Transcriptomic analysis is a quintessential approach for exploring the pathogenic mechanisms of diseases (Chen et al., 2023). Transcriptomic analysis has revealed dysregulation of genes associated with innate immune responses and neuronal activity dependence in ASD. The discovery that the M2 activation gene module in microglial cells negatively correlates

* Corresponding authors at: School of Psychology, Northeast Normal University, Changchun, China.
E-mail addresses: juxd513@nenu.edu.cn (X. Ju), luc816@nenu.edu.cn (C. Lu).

https://doi.org/10.1016/j.ibneur.2024.09.004
Received 12 August 2024; Received in revised form 25 September 2024; Accepted 25 September 2024
Available online 29 September 2024

with neuronal gene modules provides important insights into the pathways and candidate genes involved in the interplay between innate immunity and neuronal activity in ASD pathogenesis (Gupta et al., 2014b). The combined analysis of transcriptome-wide association studies and mRNA expression profiling identifies candidate genes associated with ASD. A group of candidate genes, namely MUTYH, ARHGAP27, GCA, CCDC14, and MED15, demonstrated associations with transcriptomic changes in ASD. These findings may provide new clues to unravel the pathogenesis of ASD (Huang et al., 2019). Analysis of the transcriptome in neural progenitor cells with MBD5-related neurodevelopmental disorders, a form of ASD, identified connections to crucial high-risk ASD genes that play a significant role in these disorders (Mullegama et al., 2021). One study performed a transcriptome analysis of total peripheral blood RNA from 91 HD patients and 33 controls and identified 167 genes significantly associated with clinical total motor scores in HD patients. Five of these genes (PROK2, ZNF238, AQP9, CYSTM1, and ANXA3) provide a portfolio of candidate biomarkers for HD (Mastrokolias et al., 2015). RNA-Seq of whole blood in subjects with HD also identified repeat variants associated with the expression of MSH3 and DHFR genes (Flower et al., 2019). Transcriptome analysis of HD patients' blood revealed dysregulated immune functions and inflammatory responses, including the induction of interferon-responsive genes IFITM3, IFI6, and IRF7, compared to controls (Andrade-Navarro et al., 2020). The systematic approach based on genomics and big data analysis will contribute significantly to more effective biomarkers and treatment development for diseases (Park, 2020). Transcriptome analysis uses different tissues for the in-depth study of diseases to discover the pathogenic mechanism of diseases.

The brain is a critical tissue for studying neurodevelopmental disorders and neurodegenerative diseases. The cerebral cortex, being the most developed part of the brain, governs all bodily processes and regulates the balance between the organism and its surrounding environment. The cerebral cortex serves as the foundation for advanced neurological activities (Akre, 2023). ASD is believed to result from various functional disturbances during the development of the cerebral cortex (Fukuda and Yanagi, 2017). The heterogeneity of clinical symptoms in HD is also related to changes in the degree of cell loss in the corresponding functional areas of the cerebral cortex (Thu et al., 2010). The prefrontal cortex plays a crucial role in the entire cerebral cortex. Most of the higher and more complex motor, cognitive, and expressive behavioral functions are believed to reside primarily in the prefrontal cortex (Leisman et al., 2023). Activation of the right prefrontal cortex is the basis for successfully updating verbal working memory in adolescents with ASD (Yeung et al., 2019). Prefrontal cortex activity in HD individuals reflects cognitive and neuropsychiatric disorders (Gray et al., 2013). Focusing on the role of the prefrontal cortex in both of these diseases will be more conducive to exploring the shared pathogenic factors of ASD and HD.

This study integrated transcriptomic data from the prefrontal cortex of human ASD and HD patients sourced from the Gene Expression Omnibus (GEO) public database (https://www.ncbi.nlm.nih.gov/geo/). Through differential expression analysis, pathway enrichment analysis, as well as hub gene and module analysis, we investigated dysregulated genes in ASD and HD. The study aimed to identify shared pathogenic genes and pathways shared between these two diseases, providing new evidence for their pathogenic mechanisms.

2. Materials and methods

2.1. Data collection and processing

The data was downloaded from the GEO database (accessed on 1 February 2023). Data that met the following criteria were included in this study: sequencing samples had human ASD and HD patients, sequencing tissue was prefrontal cortex, and data type was double-ended sequencing RNA-Seq. After the screening, two ASD datasets (PRJNA316853 and GSE198951) and one HD dataset (GSE64810) were included in this study, with a total of 110 individuals. Data from all diseased samples in the two ASD datasets were combined into the diseased group by batch correction, and data from all normal samples were combined into the normal group by batch correction. Finally, there were 41 samples in the ASD group and 69 samples in the HD group. The basic information about the samples included in this study is in Table 1.

Data were downloaded using Sratoolkit (version: Sratoolkit.2.11.0-ubuntu64). After the 110 data are converted from the original ".sra" file to a ".fastq" file. First, the ".fastq" file was quality-controlled using the fastp software for 110 pairs. (Fastp download URL: http://opengene.org/fastp/fastp) (Chen et al., 2018). Each data has its corresponding quality control report. Whether the quality control is qualified is judged by Q20 value and Q30 value. Q20 and Q30 represent the percentage of a certain base quality value in the total number of bases, which is similar to the qualified rate of products. Different quality standards will produce different pass rates. The higher the pass rate, the more qualified the data. Generally speaking, the base of Q20 should be above 95 % at best and not less than 90 % at worst; Q30 requires at best more than 85 % and at worst not less than 80 %. The data quality control results adopted in this study are as follows: the average Q20 of all data is 98.11 %, among which the lowest value is 94.55 %; The mean value of Q30 of all data was 94.72 %, and the lowest value was 90.03 %. The quality control results of all data were in line with the standards. The data after quality control can be sequentially matched in the next step. Secondly, HISAT2 software (version HISAT2–2.2.1) was used to sequence the alignment of the ".fastq" files after quality control. (Ngwa et al., 2017). The reference genome was the human reference genome on the HISAT2 website. In general, the one-time alignment ratio of HISAT2 should be more than 60 %. The average one-time alignment ratio of the data used in this study is 91.61 %. The lowest value is 83.35 %. The results of the sequence alignment of all data were qualified. FeatureCounts (subread-1.6.0-Linux-x86_64) was used as a counting tool (Liao et al., 2014). After the quantification of the expression, an expression matrix file is obtained, which is the basis of downstream analysis and the last step of preprocessing (Supplementary Material 1).

2.2. Identification of differentially expressed genes

To mitigate the potential impact of batch effects, we initially obtained a normalized expression matrix and filtered out lowly expressed genes before conducting the DEG analysis. Any confounding factors were predicted and removed to ensure the robustness and accuracy of the results (Jeng et al., 2021). The processed data satisfy the conditions for analysis. DESeq2 (version 1.32.0) was used for DEGs analysis (Love et al., 2014). We were using the difference of gene screening threshold differences in genetic screening, screening criteria for *p*-value-adjusted (padj) < 0.05 and $|\log2FoldChange| >= 1$. For DEGs, if a gene has log2Foldchange>0, this indicates that the expression of this gene is up-regulated in the diseased group compared to the control group, and conversely down-regulated. The regulatory profiles of differential genes of two diseases were shown as volcano plot. The overlap of co-upregulated and co-downregulated DEGs of two diseases was shown as a Venn diagram. The 50 genes with the most significant differences in the two diseases are shown as a heat map in order of padj value.

Table 1
Basic information of samples.

		Disease group	Normal group
ASD	***n***	22	19
	Age (M±SD)	15.32±4.90	15.11±5.09
	Gender (M: F)	8:3	11:8
HD	***n***	20	49
	Age (M±SD)	58.25±10.37	68.35±15.83

Note. The data information for HD's original program did not include gender.

2.3. Pathway enrichment analysis of significant DEGs

To further elucidate the pathways associated with DEGs, the DEGs of the two diseases were imported into the DAVID database (https://david.ncifcrf.gov/tools.jsp) separately for pathway enrichment analysis (Sherman et al., 2022). The DEGs of ASD obtained from differential expression analysis were all entered into the DAVID database, leaving the genes that could be annotated to do KEGG Pathway analysis. The enriched pathways were thresholded with *p*-value less than 0.05 and sorted according to the *p*-value from smallest to largest, and the top 10 items were selected for visualization. The enriched genes were annotated according to the locations of genes in the displayed pathways in the Kegg database (https://www.genome.jp/kegg/) (Kanehisa and Goto, 2000). The process of pathway enrichment analysis of DEGs for HD was the same as for ASD. Information on the input DEGs for the two groups is provided in Supplementary Material 2.

2.4. Hub genes and module analysis

Using R (version 4.1.0) filtered out poorly linked genes. The correlation of gene expression was calculated using cycles. Correlation coefficients between DEGs shared by ASD and HD were calculated using R. Data with a correlation greater than 0.5 or less than −0.5 were selected to draw the genes interaction network. Cytoscape (version 3.8.2) displayed the genes interaction network based on the selected data (Muetze et al., 2016). The Degree algorithm was used to screen hub genes by the cytoHubba plug-in of Cytoscape. The most significant gene clustering module was obtained by using the MCODE tool in Cytoscape.

3. Results

3.1. Identification of shared DEGs for ASD and HD

Through differentially expressed gene analysis, we obtained the results of abnormally expressed genes in two diseases, ASD and HD. There were 835 DEGs in ASD carriers (n=22) compared to healthy controls (n=19), of which 822 were up-regulated and 13 were down-regulated (Fig. 1A). There were 919 DEGs in HD carriers (n=20) compared to healthy controls (n=49), of which 317 were up-regulated and 602 were down-regulated. The most significant down-regulation was in the HOX family genes. (Fig. 1B). According to the differential gene situation of ASD and HD, a total of 63 DEGs were found between the two diseases (Fig. 2). Among the 63 DEGs, 21 DEGs were up-down-regulated consistency. Among the 21 DEGs, 7 were protein-coding gene (GPR183, SLC4A1, ESRP2, CEACAM8, C1QTNF8, MUC6, PBOV1), while the rest were pseudogenes (RPL7AP60, LOC100418874, LOC100418723, LOC100419562, LOC100421094, RN7SL471P), lincRNA (GSN-AS1, RAI1-AS1, CELF2-AS2, LINC02688, PPP1R13B-DT, LCMT1-AS2), miRNA (MIR3151), and SRP RNA (RN7SL3). Meanwhile, clustering analyses of the most significant 50 DEGs in two diseases were performed, and the results were displayed as heatmaps (Supplementary Material 3).

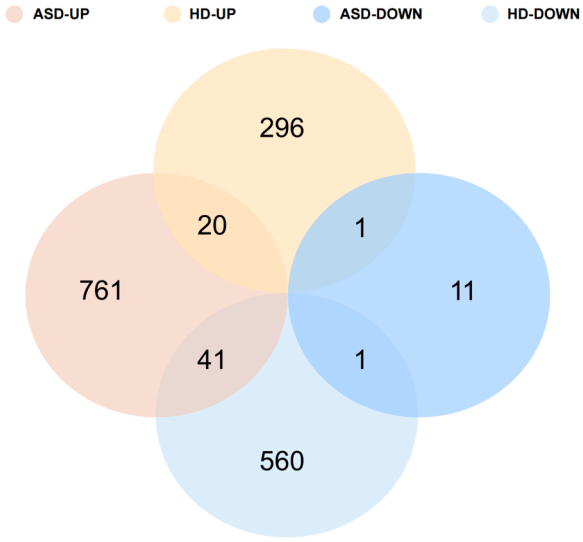

Fig. 2. The Venn diagram indicates an overlap of ASD and HD co-regulated DEGs.

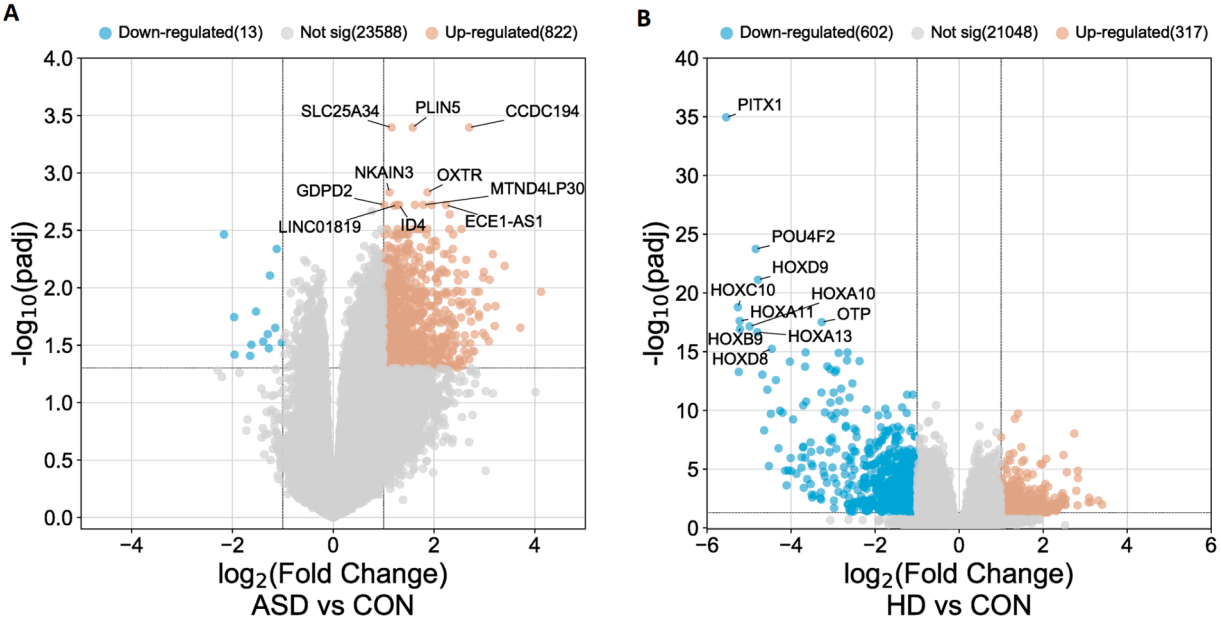

Fig. 1. Identification of gene expression profiles in ASD and HD (A)The volcano map showed the DEGs between ASD and the control group. Up-regulated genes are marked in light red; Down-regulated genes are kept in light blue. The threshold was set to padj < 0.05 and |log2FoldChange| > = 1. The top 10 DEGs are annotated with their respective positions. (B) The volcano map showed the DEGs between HD and the control group.

3.2. Pathway enrichment analysis results of ASD and HD DEGs

To clarify the pathways of DEGs in ASD and HD, "DAVID "was used for pathway enrichment analysis. The pathway enrichment analysis results showed that 9 pathways were significant in ASD (Fig. 3A), and 29 pathways were significant in HD (Fig. 3B). The two diseases shared two pathways: neuroactive ligand-receptor interaction (hsa04080) and signaling pathways regulating the pluripotency of stem cells (hsa04550). ASD and HD shared one differential gene, FPR2, in the neuroactive ligand-receptor interaction pathway. One differential gene, FZD2, in the signaling pathways regulating the pluripotency of stem cells. Kegg database was used to search pathways and annotate the locations of genes in pathways. In the neuroactive ligand-receptor interaction pathway, ASD and HD share the same homologous genes: FPRL, P2RY, GRIN, and GRI. In the signaling pathways regulating pluripotency of stem cells, ASD and HD share the same homologous genes: Activin, Wnt, Frizzled, and ID (Fig. 3C, D). FPR2 belongs to a member of the FPRL family, and FZD2 belongs to a member of the Frizzled family.

3.3. Identification hub genes and module

We used Cytoscape to create more detailed network diagrams to visualize gene interactions. This helps to better explain the relationships between shared DEGs in ASD and HD and identify key hub genes. The hub genes of ASD and HD were identified based on the 63 DEGs shared by the two diseases. The Degree algorithm revealed that SLC7A2, NFE2, EMP3, and MSX1 were the same hub genes for ASD and HD (Fig. 4A, B). MCODE was used to obtain the most significant gene cluster modules for each disease. There were 26 genes in the most significant module of ASD, of which the hub gene MSX1 scored the highest in the module. There are 23 genes in the most significant module of HD. The four hub genes SLC7A2, NFE2, EMP3, and MSX1 were all in the HD and scored in the top 10 (Fig. 4C, D).

4. Discussion

This study is the first to comprehensively compare gene expression in the prefrontal cortex of patients with ASD and HD using mRNA-Seq. Only one previous study based on family and case-control association study focused on the effect of HD gene CA duplication size on the risk of ASD (Piras et al., 2020). We comprehensively analyzed gene expression in the prefrontal cortex of both diseases and found some common factors.

We examined DEGs in ASD and healthy controls and found 835 significant DEGs, more than 98 % up-regulated. This result suggests that the cause of cortical abnormalities in ASD patients is not "insufficient" gene expression but a "disorder" caused by gene overexpression. A previous study has confirmed a similar idea. Oligodendrocyte lineage markers in the cerebellum of ASD patients are up-regulated through network analysis of gene expression in cerebellum tissues (Zeidan-Chulia et al., 2016). In addition, we also examined DEGs in HD and healthy controls and found 919 significant DEGs, more than 65 % of which were down-regulated. This result suggests that the abnormalities in the cerebral cortex of HD patients are due to "insufficient" gene expression. RNA sequencing was used to analyze HD gene-carrying blood studies also demonstrate this idea, and 60 genes were found to be differentially expressed in HD and healthy controls, with 21 up-regulated and 39 down-regulated (Colpo et al., 2020). Notably, the majority of the most significantly down-regulated in HD compared to CON were HOX family genes. The HOX family genes that have been found to be associated with HD are HOXA5, HOXA10, HOXA11, HOXA13, HOXB9, HOXC6, HOXC10, HOXD8, HOXD9, and HOXD10 (Labadorf et al., 2015). We found that the expression of the genes HOXA10, HOXA11, HOXA13, HOXB9, HOXC10, HOXD8, and HOXD9 was downregulated in HD compared to CON. This finding is consistent with what was found in previous study results. Our study did not find HOX family genes in DEGs in ASD compared to CON. However, these

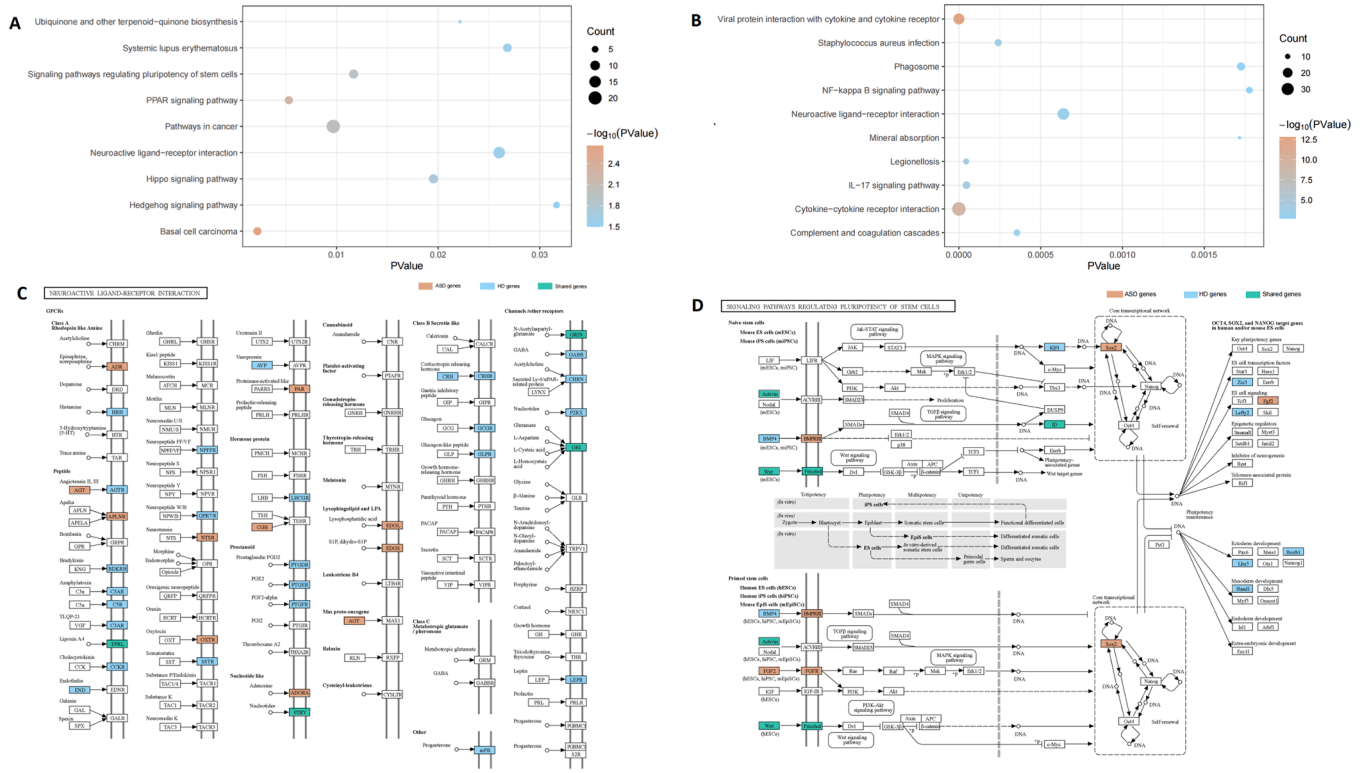

Fig. 3. Results of pathway enrichment analysis (A) Visualization of enrichment analysis of differential gene pathways in ASD. The top 10 items were visualized in order of *p*-value. (B) Visualization of enrichment analysis of differential gene pathways in HD. (C) Mapping of DEGs enriched in neuroactive ligand-receptor interaction. (D) Mapping of DEGs enriched in signaling pathways regulating pluripotency of stem cells. Gene names follow the presentation in the Kegg database.

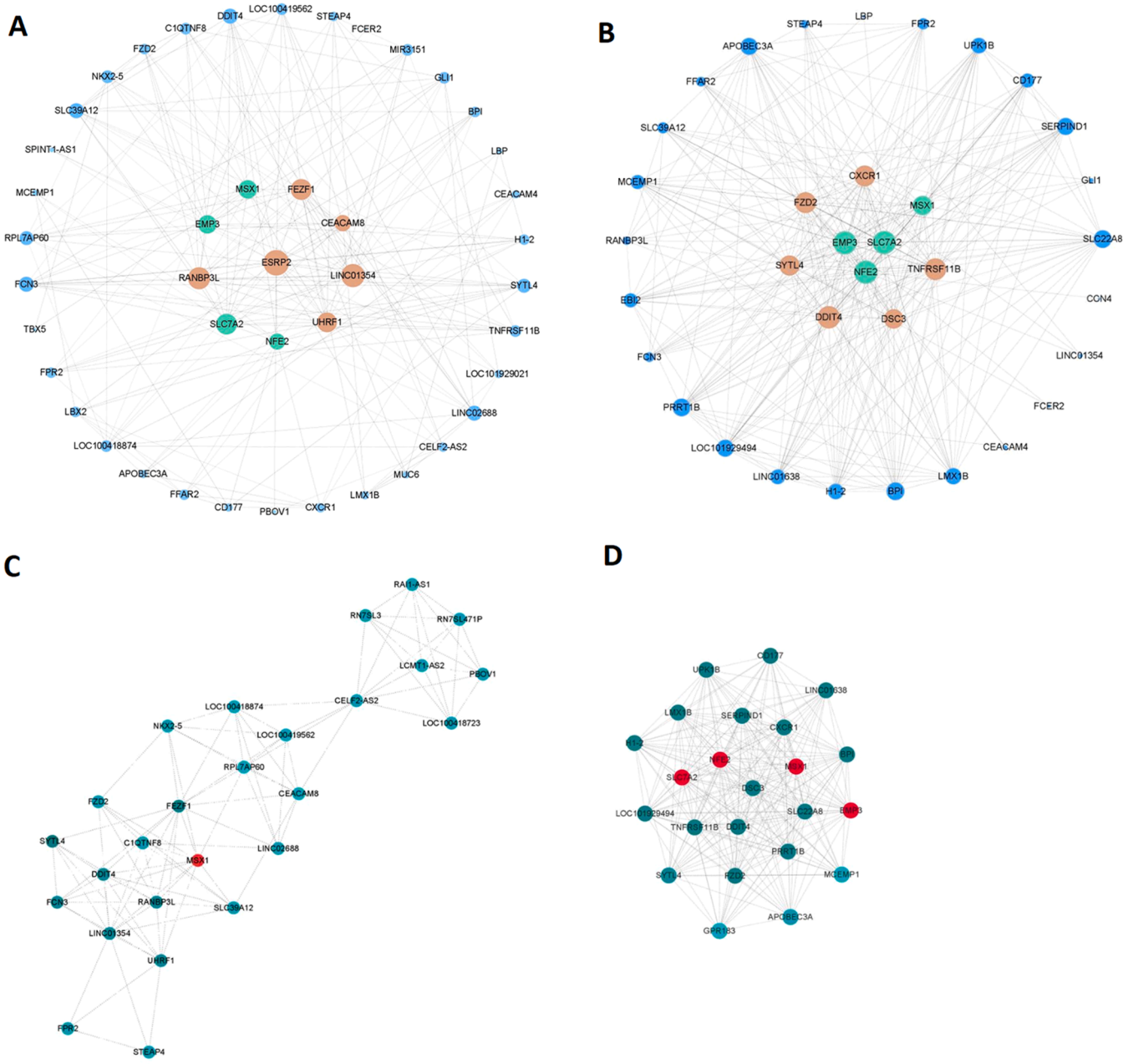

Fig. 4. Shared DEGs genes network diagrams and significant modules (A) Shared DEGs genes network diagrams from ASD. (B) Shared DEGs genes network diagrams from HD. (C) The differential genes clustering module from ASD. (D) The differential genes clustering module from HD. Based on 63 DEGs shared by ASD and HD.

genes were found in the Psymukb database (HOXA1, HOXA7, HOXA9, HOXB3, HOXB4, HOXB7, HOXB9, HOXB13, HOXC, HOXC6, HOXC8, HOXC12, HOXC14, HOXD1, HOXD3, HOXD4, HOXD8, HOXD9, HOXD10, HOXD11, HOXD13) the primary phenotype is ASD (Lin et al., 2019). The connection of HOX family genes in ASD and HD can be determined more in future studies. In summary, most of the DEGs in ASD are up-regulated, while most of the DEGs in HD are down-regulated.

Exploring the commonalities of gene expression in ASD and HD can help to find pathogenic genes and pathways in both diseases. We identified 63 DEGs shared by ASD and HD carriers, with 21 DEGs showing consistent regulatory trends (20 co-upregulated and 1 co-downregulated). Of the 21 DEGs with consistent regulatory trends, 7 were protein-coding genes: GPR183, SLC4A1, ESRP2, CEACAM8, C1QTNF8, MUC6, and PBOV1. GPR183 (G protein-coupled receptor, 183) is a protein-encoded gene regulating B-cell migration and response. It is a member of the class A family of seven transmembrane G protein-coupled receptors (Chen et al., 2022; Katritch et al., 2013). GPR183 was co-downregulated in DEGs in ASD and HD. Deficiency in GPR183 has been associated with increased susceptibility to intestinal bacterial infections, indicating its role in immune responses and inflammation. The downregulation of GPR183 may impair immune function, potentially contributing to neuroinflammation observed in both ASD and HD (Chu et al., 2018). SLC4A1, a solute carrier family member, functions as a structural protein or a transporter mediating the exchange of electrically neutral anions on the cell membrane (Nettuwakul et al., 2010). While its direct link to ASD and HD is less clear, alterations in SLC4A1 may affect cellular homeostasis and ion balance, which could influence neuronal activity and immune responses. ESRP2, epithelial splicing regulatory protein 2, is an epithelial cell-type-specific splicing regulator (Ishii et al., 2014). Dysregulation of splicing factors like ESRP2 can lead to aberrant gene expression, which may affect cellular functions and contribute to the disease phenotypes. CEACAM8 (CEA cell adhesion molecule 8) is a

carcinoembryonic antigen gene family member that acts mainly through plasma membrane cell adhesion molecules involved in heterogeneous cell-cell adhesion (Kuroki et al., 2001). Many gene upregulations in drug-resistant animals appear to be associated with host resistance and adaptive immune regulation, particularly CEACAM8 (Mackintosh et al., 2016). Its involvement in immune cell adhesion and activation might influence neuroinflammation and contribute to disease pathogenesis in both ASD and HD. C1QTNF8 (C1q and TNF related 8) may function as a ligand for RXFP1 (Klonisch et al., 2017). MUC6 (Mucin 6, Oligomeric Mucus/Gel-Forming) is a member of the mucin family that provides a mechanism to regulate the composition of the protective mucus layer associated with acid secretion or the presence of bacteria and toxic agents in the lumen and plays an essential role in cytoprotection of the epithelial surface (Nordman et al., 2002). In addition, MUC6 was found to be a variant gene in multiple sclerosis and involved in immunity (Alkhateeb et al., 2021). MUC6's involvement in immunity and its association with multiple sclerosis suggest it may play a role in neuroimmune interactions, impacting the pathology of both ASD and HD. PBOV1 is a protein of unknown function that is up-regulated in certain cancers (Xue et al., 2018). Its role in cancer suggests it might be involved in cell proliferation, potentially affecting neuroinflammatory processes. In summary, the shared immune-related genes GPR183, CEACAM8, and MUC6 highlight the involvement of immune dysregulation in both ASD and HD. Their consistent regulatory trends suggest that immune system disturbances might play a significant role in the phenotypic similarities between these disorders. Further research into these genes could provide deeper insights into their contributions to disease mechanisms and identify potential therapeutic targets.

Exploring the commonality of the KEGG pathway in DEGs of ASD and HD carriers will help to understand the mechanisms of nervous system abnormalities caused by DEGs. By KEGG pathway enrichment analysis, two pathways shared in DEGs of ASD and HD carriers were identified: neuroactive ligand-receptor interaction (hsa04080) and signaling pathways regulating pluripotency of stem cells (hsa04550). In the neuroactive ligand-receptor interaction pathway , FPRL, P2RY, GRIN, and GRI were contained by both homologous genes of ASD and HD carriers. In the signaling pathways regulating pluripotency of stem cells, Activin, Wnt, Frizzled, and ID were contained by both homologous genes of ASD and HD carriers. The homologous gene FPRL includes FPR1 (formyl peptide receptor 1), FPR2 (formyl peptide receptor 2) and other genes. The pathways enriched by FPR1 in the Kegg database are related to the immune system, and some studies have proved the role of FPR1 in immunity (Osei-Owusu et al., 2019; Vacchelli et al., 2020). FPR2 responds to infection by immune cells and suppresses the immune system under certain conditions (Braun et al., 2001; Zhang et al., 2019). The homologous gene P2RY includes P2RY1 (Purinergic Receptor P2Y1), P2RY8 (P2Y Receptor Family Member 8) and other genes, belonging to the G protein coupled receptor family. P2RY1 receptors are oncogenic through the activation of ERK signaling (Hua et al., 2023). P2RY8 is aberrantly expressed in diseases such as B-lymphocytic leukemia (Fang et al., 2022). The homologous gene GRI contains the GRIN family of genes. GRIN includes GRIN2C (Glutamate Ionotropic Receptor NMDA Type Subunit 2 C) and GRIN3B (Glutamate Ionotropic Receptor NMDA Type Subunit 3B), which belongs to the N-methyl-D-aspartate (NMDA) receptor. Variations in this gene are thought to be associated with schizophrenia (Hornig et al., 2017). Activin refers to activin, which contains genes such as INHBB (Inhibin Subunit Beta B) and INHBC (Inhibin Subunit Beta B). Wnt Family contains WNT6 (Wnt Family Member 6), WNT16 (Wnt Family Member 16), WNT7B (Wnt Family Member 7B) and other genes. These proteins are involved in several processes of tumorigenesis (Wang et al., 2019). Frizzled is a family of G protein-coupled receptor proteins that can act as receptors in the Wnt signaling pathway and other signaling pathways. The Frizzled family contains genes such as FZD2 (Frizzled Class Receptor 2) (Malbon, 2004). The ID family contains ID3 (Inhibitor Of DNA Binding 3), ID4 (Inhibitor Of DNA Binding 4) and other genes. ID proteins have been implicated in regulating gene expression and cell cycle progression. ID3 is known to be a tumor promoter; in contrast, ID4 has become a tumor suppressor (Sharma et al., 2015). Among the eight homologous genes, only FPR2, the gene contained in FPRL, has been implicated in immunity. FPR2 is one of the subtypes of formyl peptide receptors (He et al., 2013). Novel FPR2 agonists are protective in behavioral, anti-inflammatory, and neurological aspects (Cristiano et al., 2022). Clarifying the mechanism of the role of FPR2 in ASD and HD will contribute to the in-depth study of related pathways.

Exploring the genes interaction network of DEGs in ASD and HD carriers can help understand the combined mechanism of multiple genes. Genes interaction network identified ten hub genes and one significant gene clustering module in ASD. Similarly, we identified ten hub genes and one significant gene clustering module in HD. SLC7A2, NFE2, EMP3, and MSX1 were shared hub genes for both diseases, and they all play essential roles in the immune system. SLC7A2 from the solute carrier family mediates the immunopathogenesis of adherence and the killing of bacteria (Singh et al., 2016). SLC7A2 drugs up-regulate CXCL1 through the PI3K/Akt/NF-k kappa B pathway to recruit myeloid-derived suppressor cells (MDSCs) and exert tumor immunosuppressive effects (Xia et al., 2021). SLC7A2 may act as a tumor suppressor to regulate drug sensitivity, immune infiltration, and survival in non-small-cell lung cancer (Jiang et al., 2023). NFE2 plays a role in the Parkinson disease pathway (hsa05012) involved in neurodegenerative diseases. NFE2 is involved in hematopoietic functions of immunity, as well as transcriptional regulation (Wang et al., 2023). In identifying the potential immune/diagnostic gene-immune cell subtype network in the extracellular immune response to respiratory syncytial virus infection, NFE2 was identified as a gene related to diagnostic immunity (Wang and Liu, 2022). NFE2 regulates tumor immunity and affects immunotherapy, which is expected to become a marker of immunotherapy (Feng et al., 2023). Epithelial membrane protein 3 (EMP3) plays a crucial role in the immune regulation of glioblastoma (Chen et al., 2021). EMP3 may also be a candidate biomarker for renal clear cell carcinoma associated with immune infiltration (Lv et al., 2021). EMP3 plays a vital role in the TGF-beta signaling pathway (hsa04350). MSX1 is an essential component of RLR-mediated signaling and plays a role in innate immunity to RNA viruses (Chen et al., 2016). MSX1 plays an essential role in cleft lip and cleft palate (hsa00516). The above studies show that SLC7A2, NFE2, EMP3, and MSX1 are inextricably linked to immunity.

Immunity is one of the common links between neurodegenerative and neuropsychiatric diseases (Novellino et al., 2020). The view of neural-immune interactions suggests that immunity is involved in the response in the nervous system (Schiller et al., 2021). Exploring the immunological commonalities between the two diseases can further elucidate the pathogenesis of the diseases. Immunity is one of the keys to the pathogenesis of ASD (Tomaiuolo et al., 2023). Transcriptome analysis revealed dysregulation of immune response genes and neuronal activity-dependent genes in ASD (Gupta et al., 2014a). The whole-blood RNA-Seq transcriptomics analysis of HD showed that the transcription of peripheral cells in HD was disrupted. The mechanism was similar to that in the brain. Upregulation of immune-related genes in HD was also found (Moss et al., 2017). Some immune-related genes were found to play essential roles in ASD and HD. Common genetic variants identified in HLA and KIR immune genes in ASD (Torres et al., 2016). Toll-like receptors (TLRS) are central players in the innate immune response. They are expressed in glial cells and neurons. Their excessive activation produces proinflammatory molecules, neuroinflammation, and nerve damage associated with HD (Martinez-Gopar et al., 2023). Exploring the transcriptional commonalities between ASD and HD from the immune perspective will help study the neuro-immune interaction mechanism of these diseases.

This study also contains some limitations: Our study did not compare brain transcriptional changes in patients at different ages, for example, patients' brain transcriptional changes during adolescence and adulthood. The reason for this is that post-mortem brain samples are valuable

and scarce resources, and conducting longitudinal autopsy studies requires sustained financial support and a long timeframe. In general, longitudinal autopsy studies span a period of approximately 20–30 years, beginning with the assessment and continuing until the subject's death (Harrison, 2011; McCullumsmith and Meador-Woodruff, 2011). The data used in this study do not fulfill the conditions for a longitudinal study. Therefore, this study failed to reflect brain transcriptional changes in patients of different ages.

In our study, although hub genes shared with ASD and HD were explored and potentially involved in immunity, the underlying molecular mechanisms have not been fully elucidated. In the future, we will further validate the role of the above hub genes in ASD and HD through biological experiments and other methods.

5. Conclusions

In this study, we performed transcriptomic analysis based on RNA-seq data from the GEO database of the prefrontal cortex to explore the DEGs and KEGG pathways shared by ASD and HD. Most DEGs of ASD carriers were up-regulated (822 of 835), and most DEGs of HD carriers were down-regulated (602 of 919). A total of 63 DEGs were shared by the two diseases. Among them, three of seven protein-coding genes (GPR183, CEACAM8, and MUC6) with same regulatory trend were related to immunity. Two KEGG pathways (neuroactive ligand-receptor interaction (hsa04080) and signaling pathways regulating pluripotency of stem cells (hsa04550)) were simultaneously enriched in both diseases. In addition, we identified four hub genes (SLC7A2, NFE2, EMP3, and MSX1) that play key roles in two diseases through gene interaction network analysis, and all of them are immune-related. In conclusion, ASD and HD have commonalities in gene expression of prefrontal lobe, and these commonalities may result in similar disease phenotypes through immune ways. Exploring the commonalities between the two diseases from an immune perspective will bring new clues to the field of basic pathological research and clinical diagnosis of neuropsychiatric diseases.

Ethics approval

This study was a transcriptome data analysis study. The Ethics Committee of the School of Psychology, Northeast Normal University, has confirmed that ethical approval was granted.

Consent to participate

Not applicable.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by HL, QB, XW and YJ. The first draft of the manuscript was written by HL, XJ and CL. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Supplementary Material

Supplementary Material 1: Gene expression matrices for ASD and HD.

Supplementary Material 2: KEGG pathway enrichment analysis input data.

Supplementary Material 3: The cluster heatmap of top 50 DEGs.

Funding

This work was supported by the Natural Science Foundation of Jilin Province [grant numbers 20220101296J] and the National Natural Science Foundation of China [grant number 62302089].

CRediT authorship contribution statement

Xueying Wang: Writing – original draft, Formal analysis. **Qiuyu Bai:** Writing – original draft, Methodology, Conceptualization. **Huanhuan Liu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Chang Lu:** Writing – review & editing, Writing – original draft, Software, Formal analysis. **Xingda Ju:** Writing – review & editing, Funding acquisition, Formal analysis. **Yunlei Jin:** Writing – review & editing, Software, Methodology.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data Availability

All data were obtained from the Gene Expression Omnibus (GEO), a public database accessible at https://www.ncbi.nlm.nih.gov/geo/ (accessed on 1 February 2023).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ibneur.2024.09.004.

References

Akre, K., 2023. "cerebral cortex". Encyclopedia Britannica.

Alkhateeb, A.M., Salman, D.S., Al-Hayk, K.A., 2021. Exome sequencing analysis of familial cases of multiple sclerosis and a monozygotic discordant twin. Arab. J. Sci. Eng. 46, 5421–5427. https://doi.org/10.1007/s13369-020-05242-7.

Andrade-Navarro, M.A., Mühlenberg, K., Spruth, E.J., Mah, N., González-López, A., Andreani, T., Russ, J., Huska, M.R., Muro, E.M., Fontaine, J.F., Amstislavskiy, V., Soldatov, A., Nietfeld, W., Wanker, E.E., Priller, J., 2020. RNA sequencing of human peripheral blood cells indicates upregulation of immune-related genes in Huntington's disease. Front. Neurol. 11. https://doi.org/10.3389/fneur.2020.573560.

Bell, L., Wittkowski, A., Hare, D.J., 2019. Movement disorders and syndromic autism: a systematic review. J. Autism Dev. Disord. 49, 54–67. https://doi.org/10.1007/s10803-018-3658-y.

Braun, M.C., Wang, J.M., Lahey, E., Rabin, R.L., Kelsall, B.L., 2001. Activation of the formyl peptide receptor by the HIV-derived peptide T-20 suppresses interleukin-12 p70 production by human monocytes. Blood 97, 3531–3536. https://doi.org/10.1182/blood.V97.11.3531.

Chen, Y., Dai, J., Tang, L., Mikhailova, T., Liang, Q., Li, M., Zhou, J., Kopp, R.F., Weickert, C., Chen, C., Liu, C., 2023. Neuroimmune transcriptome changes in patient brains of psychiatric and neurological disorders. Mol. Psychiatry 28, 710–721. https://doi.org/10.1038/s41380-022-01854-7.

Chen, L., Hu, M., Xu, Z., Liu, Y., Shu, H., 2016. MSX1 modulates RLR-mediated innate antiviral signaling by facilitating assembly of TBK1-associated complexes. J. Immunol. 197, 199–207. https://doi.org/10.4049/jimmunol.1600039.

Chen, H., Huang, W., Li, X., 2022. Structures of oxysterol sensor EBI2/GPR183, a key regulator of the immune response. Structure 30, 1016–1024.e5. https://doi.org/10.1016/j.str.2022.04.006.

Chen, Q., Jin, J., Huang, X., Wu, F., Huang, H., Zhan, R., 2021. EMP3 mediates glioblastoma-associated macrophage infiltration to drive T cell exclusion. J. Exp. Clin. Cancer Res. 40, 160. https://doi.org/10.1186/s13046-021-01954-2.

Chen, S., Zhou, Y., Chen, Y., Gu, J., 2018. fastp: an ultra-fast all-in-one FASTQ preprocessor. Bioinformatics 34, 884–890. https://doi.org/10.1093/bioinformatics/bty560.

Chu, C., Moriyama, S., Li, Z., Zhou, L., Flamar, A.-L., Klose, C.S.N., Moeller, J.B., Putzel, G.G., Withers, D.R., Sonnenberg, G.F., Artis, D., 2018. Anti-microbial functions of group 3 innate lymphoid cells in gut-associated lymphoid tissues are regulated by G-protein-coupled receptor 183. Cell Rep. 23, 3750–3758. https://doi.org/10.1016/j.celrep.2018.05.099.

Colpo, G.D., Rocha, N.P., Furr Stimming, E., Teixeira, A.L., 2020. Gene expression profiling in Huntington's disease: does comorbidity with depressive symptoms matter? Int. J. Mol. Sci. 21, 8474. https://doi.org/10.3390/ijms21228474.

Cook, J., 2016. From movement kinematics to social cognition: the case of autism. Philos. Trans. R. Soc. Lond. B Biol. Sci. 371, 20150372. https://doi.org/10.1098/rstb.2015.0372.

Cristiano, C., Volpicelli, F., Crispino, M., Lacivita, E., Russo, R., Leopoldo, M., Calignano, A., Perrone-Capano, C., 2022. Behavioral, anti-inflammatory, and neuroprotective effects of a novel FPR2 agonist in two mouse models of autism. Pharmaceuticals 15, 161. https://doi.org/10.3390/ph15020161.

Ellison, M., 2017. The impact of Huntington disease on young people. Handb. Clin. Neurol. 144, 179–182. https://doi.org/10.1016/B978-0-12-801893-4.00015-8.

Fang, Y., Wang, M., Hu, S., Wang, T., Liu, Y., Xiao, J., Cai, Y., Wang, Y., Qiu, H., Tang, X., Chen, S., Wu, D., Xu, Y., Liu, T., 2022. Recurrent novel P2RY8/IGH translocations in B-lymphoblastic leukemia/lymphoma. Front. Oncol. 12, 896858. https://doi.org/10.3389/fonc.2022.896858.

Feng, H.-M., Zhao, Y., Yan, W.-J., Li, B., 2023. Genomic and immunogenomic analysis of three prognostic signature genes in LUAD. Bmc Bioinforma. 24, 19. https://doi.org/10.1186/s12859-023-05137-y.

Flower, M., Lomeikaite, V., Ciosi, M., Cumming, S., Morales, F., Lo, K., Hensman Moss, D., Jones, L., Holmans, P., Monckton, D.G., Tabrizi, S.J., Investigators, T.-H., Consortium, O., 2019. MSH3 modifies somatic instability and disease severity in Huntington's and myotonic dystrophy type 1. Brain 142, 1876–1886. https://doi.org/10.1093/brain/awz115.

Fukuda, T., Yanagi, S., 2017. Psychiatric behaviors associated with cytoskeletal defects in radial neuronal migration. Cell. Mol. Life Sci. 74, 3533–3552. https://doi.org/10.1007/s00018-017-2539-4.

Gray, M.A., Egan, G.F., Ando, A., Churchyard, A., Chua, P., Stout, J.C., Georgiou-Karistianis, N., 2013. Prefrontal activity in Huntington's disease reflects cognitive and neuropsychiatric disturbances: the IMAGE-HD study. Exp. Neurol. 239, 218–228. https://doi.org/10.1016/j.expneurol.2012.10.020.

Gupta, S., Ellis, S.E., Ashar, F.N., Moes, A., Bader, J.S., Zhan, J., West, A.B., Arking, D.E., 2014a. Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. Nat. Commun. 5, 5748. https://doi.org/10.1038/ncomms6748.

Gupta, S., Ellis, S.E., Ashar, F.N., Moes, A., Bader, J.S., Zhan, J.N., West, A.B., Arking, D. E., 2014b. Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. Nat. Commun. 5. https://doi.org/10.1038/ncomms6748.

Harrison, P.J., 2011. Using our brains: the findings, flaws, and future of postmortem studies of psychiatric disorders. Biol. Psychiatry 69, 102–103. https://doi.org/10.1016/j.biopsych.2010.09.008.

He, H.-Q., Liao, D., Wang, Z.-G., Wang, Z.-L., Zhou, H.-C., Wang, M.-W., Ye, R.D., 2013. Functional Characterization of Three Mouse Formyl Peptide Receptors. Mol. Pharmacol. 83, 389–398. https://doi.org/10.1124/mol.112.081315.

Hornig, T., Gruening, B., Kundu, K., Houwaart, T., Backofen, R., Biber, K., Normann, C., 2017. GRIN3B missense mutation as an inherited risk factor for schizophrenia: whole-exome sequencing in a family with a familiar history of psychotic disorders. Genet. Res. 99, e1. https://doi.org/10.1017/s0016672316000148.

Hua, Y., Liu, Y., Li, L., Liu, G., 2023. Activation of hypermethylated P2RY1 mitigates gastric cancer by promoting apoptosis and inhibiting proliferation. Open Life Sci. 18, 20220078. https://doi.org/10.1515/biol-2022-0078.

Huang, H.M., Cheng, S.Q., Ding, M., Wen, Y., Ma, M., Zhang, L., Li, P., Cheng, B.L., Liang, X., Liu, L., Du, Y.A., Zhao, Y., Kafle, O.P., Han, B., Zhang, F., 2019. Integrative analysis of transcriptome-wide association study and mRNA expression profiles identifies candidate genes associated with autism spectrum disorders. Autism Res. 12, 33–38. https://doi.org/10.1002/aur.2048.

Ishii, H., Saitoh, M., Sakamoto, K., Kondo, T., Katoh, R., Tanaka, S., Motizuki, M., Masuyama, K., Miyazawa, K., 2014. Epithelial splicing regulatory proteins 1 (ESRP1) and 2 (ESRP2) suppress cancer cell motility via different mechanisms. J. Biol. Chem. 289, 27386–27399. https://doi.org/10.1074/jbc.M114.589432.

Jeng, S.L., Chi, Y.C., Ma, M.C., Chan, S.H., Sun, H.S., 2021. Gene expression analysis of combined RNA-seq experiments using a receiver operating characteristic calibrated procedure. Comput. Biol. Chem. 93. https://doi.org/10.1016/j.compbiolchem.2021.107515.

Jiang, S., Zou, J., Dong, J., Shi, H., Chen, J., Li, Y., Duan, X., Li, W., 2023. Lower SLC7A2 expression is associated with enhanced multidrug resistance, less immune infiltrates and worse prognosis of NSCLC. Cell Commun. Signal. 21, 9. https://doi.org/10.1186/s12964-022-01023-x.

Kanehisa, M., Goto, S., 2000. KEGG: kyoto encyclopedia of genes and genomes. Nucleic Acids Res. 28, 27–30. https://doi.org/10.1093/nar/28.1.27.

Katritch, V., Cherezov, V., Stevens, R.C., 2013. Structure-Function of the G Protein-Coupled Receptor Superfamily. In Annual Review of Pharmacology and Toxicology. Annual Review of Pharmacology and Toxicology, Vol. 53, P.A. Insel, ed, pp. 531-556.

Kim, Y.S., Leventhal, B.L., 2015. Genetic epidemiology and insights into interactive genetic and environmental effects in autism spectrum disorders. Biol. Psychiatry 77, 66–74. https://doi.org/10.1016/j.biopsych.2014.11.001.

Klonisch, T., Glogowska, A., Thanasupawat, T., Burg, M., Krcek, J., Pitz, M., Jaggupilli, A., Chelikani, P., Wong, G.W., Hombach-Klonisch, S., 2017. Structural commonality of C1q TNF-related proteins and their potential to activate relaxin/insulin-like family peptide receptor 1 signalling pathways in cancer cells. Br. J. Pharmacol. 174, 1025–1033. https://doi.org/10.1111/bph.13559.

Kuroki, M., Abe, H., Imakiirei, T., Liao, S.X., Uchida, H., Yamauchi, Y., Oikawa, S., Kuroki, M., 2001. Identification and comparison of residues critical for cell-adhesion activities of two neutrophil CD66 antigens, CEACAM6 and CEACAM8. J. Leukoc. Biol. 70, 543–550. https://doi.org/10.1189/jlb.70.4.543.

Labadorf, A., Hoss, A.G., Lagomarsino, V., Latourelle, J.C., Hadzi, T.C., Bregu, J., MacDonald, M.E., Gusella, J.F., Chen, J.F., Akbarian, S., Weng, Z.P., Myers, R.H., 2015. RNA sequence analysis of human huntington disease brain reveals an extensive increase in inflammatory and developmental gene expression. Plos One 10. https://doi.org/10.1371/journal.pone.0143563.

Leisman, G., Melillo, R., Melillo, T., 2023. Prefrontal functional connectivities in autism spectrum disorders: A connectopathic disorder affecting movement, interoception, and cognition. Brain Res. Bull. 198, 65–76. https://doi.org/10.1016/j.brainresbull.2023.04.004.

Liao, Y., Smyth, G.K., Shi, W., 2014. featureCounts: an efficient general purpose program for assigning sequence reads to genomic features. Bioinformatics 30, 923–930. https://doi.org/10.1093/bioinformatics/btt656.

Lin, G.N., Guo, S., Tan, X., Wang, W., Qian, W., Song, W., Wang, J., Yu, S., Wang, Z., Cui, D., Wang, H., 2019. PsyMuKB: An Integrative De Novo Variant Knowledge Base for Developmental Disorders. Genom. Proteom. Bioinforma. 17, 453–464. https://doi.org/10.1016/j.gpb.2019.10.002.

Love, M.I., Huber, W., Anders, S., 2014. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biol. 15, 550. https://doi.org/10.1186/s13059-014-0550-8.

Lv, Q., Xiao, W., Xiong, Z., Shi, J., Miao, D., Meng, X., Yuan, H., Yang, H., Zhang, X., 2021. Identification of candidate biomarker EMP3 and its prognostic potential in clear cell renal cell carcinoma. Front. Biosci. -Landmark 26, 1176–1190. https://doi.org/10.52586/5018.

Mackintosh, C.G., Griffin, J.F.T., Scott, I.C., O'Brien, R., Stanton, J.L., MacLean, P., Brauning, R., 2016. SOLiD SAGE sequencing shows differential gene expression in jejunal lymph node samples of resistant and susceptible red deer (Cervus elaphus) challenged with Mycobacterium avium subsp paratuberculosis. Vet. Immunol. Immunopathol. 169, 102–110. https://doi.org/10.1016/j.vetimm.2015.10.009.

Malbon, C.C., 2004. Frizzleds: New members of the superfamily of G-protein-coupled receptors. Front. Biosci. -Landmark 9, 1048–1058. https://doi.org/10.2741/1308.

Martinez-Gopar, P.E., Perez-Rodriguez, M.J., Angeles-Lopez, Q.D., Tristan-Lopez, L., Gonzalez-Espinosa, C., Perez-Severiano, F., 2023. Toll-like receptor 4 plays a significant role in the biochemical and neurological alterations observed in two distinct mice models of Huntington's disease. Mol. Neurobiol. 60, 2678–2690. https://doi.org/10.1007/s12035-023-03234-w.

Mastrokolias, A., Ariyurek, Y., Goeman, J.J., van Duijn, E., Roos, R.A.C., van der Mast, R. C., van Ommen, G.B., den Dunnen, J.T., t Hoen, P.A.C., van Roon-Mom, W.M.C., 2015. Huntington's disease biomarker progression profile identified by transcriptome sequencing in peripheral blood. Eur. J. Hum. Genet. 23, 1349–1356. https://doi.org/10.1038/ejhg.2014.281.

McCullumsmith, R.E., Meador-Woodruff, J.H., 2011. Novel Approaches to the Study of Postmortem Brain in Psychiatric Illness: Old Limitations and New Challenges. Biol. Psychiatry 69, 127–133. https://doi.org/10.1016/j.biopsych.2010.09.035.

Moss, D.J.H., Flower, M.D., Lo, K.K., Miller, J.R.C., van Ommen, G.-J.B., t Hoen, P.A.C., Stone, T.C., Guinee, A., Langbehn, D.R., Jones, L., Plagnol, V., van Roon-Mom, W.M. C., Holmans, P., Tabrizi, S.J., 2017. Huntington's disease blood and brain show a common gene expression pattern and share an immune signature with Alzheimer's disease. Sci. Rep. 7, 44849. https://doi.org/10.1038/srep44849.

Muetze, T., Goenawan, I.H., Wiencko, H.L., Bernal-Llinares, M., Bryan, K., Lynn, D.J., 2016. Contextual Hub Analysis Tool (CHAT): A Cytoscape app for identifying contextually relevant hubs in biological networks. F1000Research 5, 1745. https://doi.org/10.12688/f1000research.9118.2.

Mullegama, S.V., Klein, S.D., Williams, S.R., Innis, J.W., Probst, F.J., Haldeman-Englert, C., Martinez-Agosto, J.A., Yang, Y., Tian, Y.C., Elsea, S.H., Ezashi, T., 2021. Transcriptome analysis of MBD5-associated neurodevelopmental disorder (MAND) neural progenitor cells reveals dysregulation of autism-associated genes. Sci. Rep. 11. https://doi.org/10.1038/s41598-021-90798-z.

Nettuwakul, C., Sawasdee, N., Yenchitsomanus, P.-t, 2010. Rapid detection of solute carrier family 4, member 1 (SLC4A1) mutations and polymorphisms by high-resolution melting analysis. Clin. Biochem. 43, 497–504. https://doi.org/10.1016/j.clinbiochem.2009.12.010.

Ngwa, J., Wojciechowski, R., Zack, D.J., Beaty, T., Ruczinski, I., 2017. Differential Expression Analysis of Gene and Transcript Abundance for Single Cell RNA-Seq Data using STAR and HISAT Aligners. Invest. Ophthalmol. Vis. Sci. 58, 1850.

Nordman, H., Davies, J.R., Lindell, G., de Bolos, C., Real, F., Carlstedt, I., 2002. Gastric MUC5AC and MUC6 are large oligomeric mucins that differ in size, glycosylation and tissue distribution. Biochem. J. 364, 191–200. https://doi.org/10.1042/bj3640191.

Novellino, F., Sacca, V., Donato, A., Zaffino, P., Spadea, M.F., Vismara, M., Arcidiacono, B., Malara, N., Presta, I., Donato, G., 2020. Innate immunity: a common denominator between neurodegenerative and neuropsychiatric diseases. Int. J. Mol. Sci. 21, 1115. https://doi.org/10.3390/ijms21031115.

Osei-Owusu, P., Charlton, T.M., Kim, H.K., Missiakas, D., Schneewind, O., 2019. FPR1 is the plague receptor on host immune cells. Nature 574, 57–62. https://doi.org/10.1038/s41586-019-1570-z.

Park, D.I., 2020. Genomics, transcriptomics, proteomics and big data analysis in the discovery of new diagnostic markers and targets for therapy development. Autism 173, 61–90.

Piras, I.S., Picinelli, C., Iennaco, R., Baccarin, M., Castronovo, P., Tomaiuolo, P., Cucinotta, F., Ricciardello, A., Turriziani, L., Nanetti, L., Mariotti, C., Gellera, C., Lintas, C., Sacco, R., Zuccato, C., Cattaneo, E., Persico, A.M., 2020. Huntingtin geneCAGrepeat size affects autism risk: family-based and case-control association study. Am. J. Med. Genet. Part B-Neuropsychiatr. Genet. 183, 341–351. https://doi.org/10.1002/ajmg.b.32806.

Qi, Y., Liu, Y., Rong, W., 2011. RNA-Seq and its applications: a new technology for transcriptomics. Hereditas 33, 1191–1202.

Romero, N.L., 2017. A pilot study examining a computer-based intervention to improve recognition and understanding of emotions in young children with communication and social deficits. Res Dev. Disabil. 65, 35–45. https://doi.org/10.1016/j.ridd.2017.04.007.

Ross, C.A., Tabrizi, S.J., 2011. Huntington's disease: from molecular pathogenesis to clinical treatment. Lancet Neurol. 10, 83–98. https://doi.org/10.1016/S1474-4422(10)70245-3.

Schiller, M., Ben-Shaanan, T.L., Rolls, A., 2021. Neuronal regulation of immunity: why, how and where? Nat. Rev. Immunol. 21, 20–36. https://doi.org/10.1038/s41577-020-0387-1.

Sharma, P., Chinaranagari, S., Chaudhary, J., 2015. Inhibitor of differentiation 4 (ID4) acts as an inhibitor of ID-1,-2 and-3 and promotes basic helix loop helix (bHLH) E47 DNA binding and transcriptional activity. Biochimie 112, 139–150. https://doi.org/10.1016/j.biochi.2015.03.006.

Sherman, B.T., Hao, M., Qiu, J., Jiao, X., Baseler, M.W., Lane, H.C., Imamichi, T., Chang, W., 2022. DAVID: a web server for functional enrichment analysis and functional annotation of gene lists (2021 update). Nucleic Acids Res. 50, W216–W221. https://doi.org/10.1093/nar/gkac194.

Snowden, J.S., 2017. The neuropsychology of Huntington's disease. Arch. Clin. Neuropsychol. 32, 876–887. https://doi.org/10.1093/arclin/acx086.

The L-arginine transporter solute carrier family 7 member 2 mediates the immunopathogenesis of attaching and effacing bacteria. Plos Pathog. 12, e1005984, 10.1371/journal.ppat.1005984..

Thibaut, F., 2018. Psychiatric disorders: neurodevelopmental disorders, neurodegenerative disorders, or both? Dialog-. Clin. Neurosci. 20, 251–252.

Thu, D.C.V., Oorschot, D.E., Tippett, L.J., Nana, A.L., Hogg, V.M., Synek, B.J., Luthi-Carter, R., Waldvogel, H.J., Faull, R.L.M., 2010. Cell loss in the motor and cingulate cortex correlates with symptomatology in Huntington's disease. Brain 133, 1094–1110. https://doi.org/10.1093/brain/awq047.

Tomaiuolo, P., Piras, I.S., Sain, S.B., Picinelli, C., Baccarin, M., Castronovo, P., Morelli, M.J., Lazarevic, D., Scattoni, M.L., Tonon, G., Persico, A.M., 2023. RNA sequencing of blood from sex- and age-matched discordant siblings supports immune and transcriptional dysregulation in autism spectrum disorder. Sci. Rep. 13, 807. https://doi.org/10.1038/s41598-023-27378-w.

Torres, A.R., Sweeten, T.L., Johnson, R.C., Odell, D., Westover, J.B., Bray-Ward, P., Ward, D.C., Davies, C.J., Thomas, A.J., Croen, L.A., Benson, M., 2016. Common genetic variants found in HLA and KIR immune genes in autism spectrum disorder. Front. Neurosci. 10, 463. https://doi.org/10.3389/fnins.2016.00463.

Vacchelli, E., Le Naour, J., Kroemer, G., 2020. The ambiguous role of FPR1 in immunity and inflammation. OncoImmunology 9, 1760061. https://doi.org/10.1080/2162402X.2020.1760061.

Wang, X., Bajpai, A.K., Gu, Q., Ashbrook, D.G., Starlard-Davenport, A., Lu, L., 2023. Weighted gene co-expression network analysis identifies key hub genes and pathways in acute myeloid leukemia. Front. Genet. 14, 1009462. https://doi.org/10.3389/fgene.2023.1009462.

Wang, F.-W., Cao, C.-H., Han, K., Zhao, Y.-X., Cai, M.-Y., Xiang, Z.-C., Zhang, J.-X., Chen, J.-W., Zhong, L.-P., Huang, Y., Zhou, S.-F., Jin, X.-H., Guan, X.-Y., Xu, R.-H., Xie, D., 2019. APC-activated long noncoding RNA inhibits colorectal carcinoma pathogenesis through reduction of exosome production. J. Clin. Investig. 129, 727–743. https://doi.org/10.1172/jci122478.

Wang, B., Liu, H., 2022. Identification of potential immune/diagnosis related gene-immunocyte subtype networks in extracellular immune response to respiratory syncytial virus infection. Virus Res. 321, 198906. https://doi.org/10.1016/j.virusres.2022.198906.

Xia, S., Wu, J., Zhou, W., Zhang, M., Zhao, K., Liu, J., Tian, D., Liao, J., 2021. SLC7A2 deficiency promotes hepatocellular carcinoma progression by enhancing recruitment of myeloid-derived suppressors cells. Cell Death Dis. 12, 570. https://doi.org/10.1038/s41419-021-03853-y.

Xue, C., Zhong, Z., Ye, S., Wang, Y., Ye, Q., 2018. Association between the overexpression of PBOV1 and the prognosis of patients with hepatocellular carcinoma. Oncol. Lett. 16, 3401–3407. https://doi.org/10.3892/ol.2018.9013.

Yeung, M.K., Lee, T.L., Chan, A.S., 2019. Right-lateralized frontal activation underlies successful updating of verbal working memory in adolescents with high-functioning autism spectrum disorder. Biol. Psychol. 148, 107743. https://doi.org/10.1016/j.biopsycho.2019.107743.

Zeidan-Chulia, F., de Oliveira, B.-H.N., Casanova, M.F., Casanova, E.L., Noda, M., Salmina, A.B., Verkhratsky, A., 2016. Up-regulation of oligodendrocyte lineage markers in the cerebellum of autistic patients: evidence from network analysis of gene expression. Mol. Neurobiol. 53, 4019–4025. https://doi.org/10.1007/s12035-015-9351-7.

Zhang, H., Wang, D., Gong, P., Lin, A., Zhang, Y., Ye, R.D., Yu, Y., 2019. Formyl peptide receptor 2 deficiency improves cognition and attenuates tau hyperphosphorylation and astrogliosis in a mouse model of Alzheimer's disease. J. Alzheimers Dis. 67, 169–179. https://doi.org/10.3233/jad-180823.