American Impact Review

Review Article

Brain-centred transcriptomic convergence in autism spectrum disorder: synaptic, immune-glial and mitochondrial-transcriptional axes.

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OPEN ACCESS

Citation:
Ruslan Kurmashev (2026). Brain-centred transcriptomic convergence in autism spectrum disorder: synaptic, immune-glial and mitochondrial-transcriptional axes.. *Am. Impact Rev.*
10.66308/air.e2026029

Received: January 20, 2026
Accepted: February 2, 2026
Published: February 5, 2026

DOI:
10.66308/air.e2026029

ISSN: 3071-124X

Abstract

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition in which transcriptomic findings vary across cohorts, brain regions, developmental stages, and analytical platforms. This narrative review synthesises human ASD transcriptomic evidence with primary emphasis on post-mortem cerebral cortex and examines whether recurrent biological programs emerge despite substantial heterogeneity between studies. Across cortical datasets, the most reproducible pattern is not a single universal molecular signature but partial convergence at the level of synaptic and neuronal programs, immune-glial activation, and mitochondrial-transcriptional regulation. Bulk RNA-seq has defined broad tissue-level shifts, whereas single-cell and single-nucleus approaches refine these signals at cell-type resolution and long-read transcriptomics extends interpretation to isoform structure and splicing complexity. Peripheral blood transcriptomic studies are discussed only as secondary contextual observations because immune-cell composition and clinical-state effects limit direct inference about central nervous system mechanisms. Overall, current evidence supports a brain-centred model of transcriptomic convergence in ASD that is mechanistically informative but constrained by regional specificity, cohort heterogeneity, and methodological variation.

Keywords: autism spectrum disorder, cortical transcriptomics, RNA sequencing, synaptic dysfunction, immune-glial activation, mitochondrial-transcriptional dysregulation, alternative splicing, isoform dysregulation, single-nucleus RNA-seq, long-read RNA-seq

1. Introduction

Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition whose marked clinical and biological variability has complicated efforts to define consistent molecular features across affected individuals (American Psychiatric Association, 2013; Lord et al., 2020). Although ASD is diagnosed behaviourally, increasing evidence suggests that its underlying biology involves disrupted developmental programs rather than a single uniform pathogenic pathway. This heterogeneity makes transcriptomic analysis particularly relevant, because it enables investigation of convergent gene-expression patterns and regulatory programs that may not be evident at the level of individual

genes alone (Wang, Gerstein & Snyder, 2009).

This review focuses primarily on transcriptomic convergence in human ASD brain tissue, particularly post-mortem cerebral cortex, where mechanistic interpretation is strongest. Peripheral transcriptomic findings are considered only in a secondary contextual role, because variation in tissue composition, immune-cell distribution, and clinical state makes direct comparison with central nervous system molecular changes inherently limited.

Transcriptomic studies of post-mortem cerebral cortex indicate that ASD is characterised less by a single universal set of dysregulated genes than by recurrent disturbance of broader biological programs. Across cortical datasets, the most reproducible signals involve relative downregulation of neuronal and synaptic pathways alongside upregulation of glial and immune-related programs, supporting a program-level framework of partial molecular convergence despite substantial heterogeneity between studies (Voineagu et al., 2011; Parikshak et al., 2016; Gandal et al., 2022).

Scope and source selection

The literature discussed in this narrative review spans foundational and recent studies published between 2009 and 2025. Searches were conducted primarily in PubMed and Google Scholar and were last updated in September 2025. Search terms combined ASD-related concepts (“autism spectrum disorder”, autism, ASD) with transcriptomic terms (“transcriptomics”, “RNA-seq”, “RNA sequencing”, “single-cell RNA-seq”, “single-nucleus RNA-seq”, “long-read RNA-seq”, “splicing”, “isoform”) and tissue-related terms (“brain”, “cortex”, “cortical”, “post-mortem”, “blood”, “peripheral”). Additional papers were identified through reference-list screening of key human ASD transcriptomic studies. Priority was given to peer-reviewed human transcriptomic studies using post-mortem brain tissue, particularly cerebral cortex, together with key bulk RNA-seq, single-cell or single-nucleus RNA-seq, and long-read transcriptomic studies that informed mechanistic interpretation. Peripheral blood studies were included only when they provided relevant contextual comparison or recurrent immune-related observations and were not treated as equivalent evidence of central nervous system mechanisms. Studies focused primarily on non-transcriptomic biomarkers, clinically oriented screening panels, or non-human data without direct relevance to the mechanistic framework of this review were not treated as core evidence. The review was designed as a concept-driven narrative synthesis organised around three focal axes: synaptic dysfunction, immune-glial activation, and mitochondrial-transcriptional dysregulation, rather than as an exhaustive systematic survey of all published ASD transcriptomic findings.

Convergent transcriptomic axes in ASD To organise recurrent transcriptomic patterns reported in ASD, this review focuses on three partially interacting axes: synaptic dysfunction, immune-glial activation, and mitochondrial-transcriptional dysregulation. These axes are derived primarily from human post-mortem cortical studies, where transcriptomic convergence is most consistently observed at the level of biological programs rather than individual genes. Selected peripheral studies are discussed only as secondary contextual observations, mainly for immune-related signals, and are not treated as equivalent evidence of central nervous system mechanisms.

Cross-axis integration and cross-talk (Fig. 1)

Available evidence supports partial coordination across synaptic, immune-glial, and mitochondrial-transcriptional programs in ASD rather than wholly isolated pathway changes. In post-mortem cortex, downregulation of mitochondrial-related transcripts has been reported alongside downregulation

of synaptic gene programs, consistent with a coupled "energy-synapse" pattern at the level of cortical transcriptomic organisation (Schwede et al., 2018). Peripheral blood transcriptome studies reporting myeloid-lineage shifts and immune-related co-expression signals are considered here only as secondary cross-tissue context for immune-related dysregulation, because they remain substantially more vulnerable than brain-based data to immune-cell composition effects and clinical-state confounding (Li et al., 2023; Tomaiuolo et al., 2023).

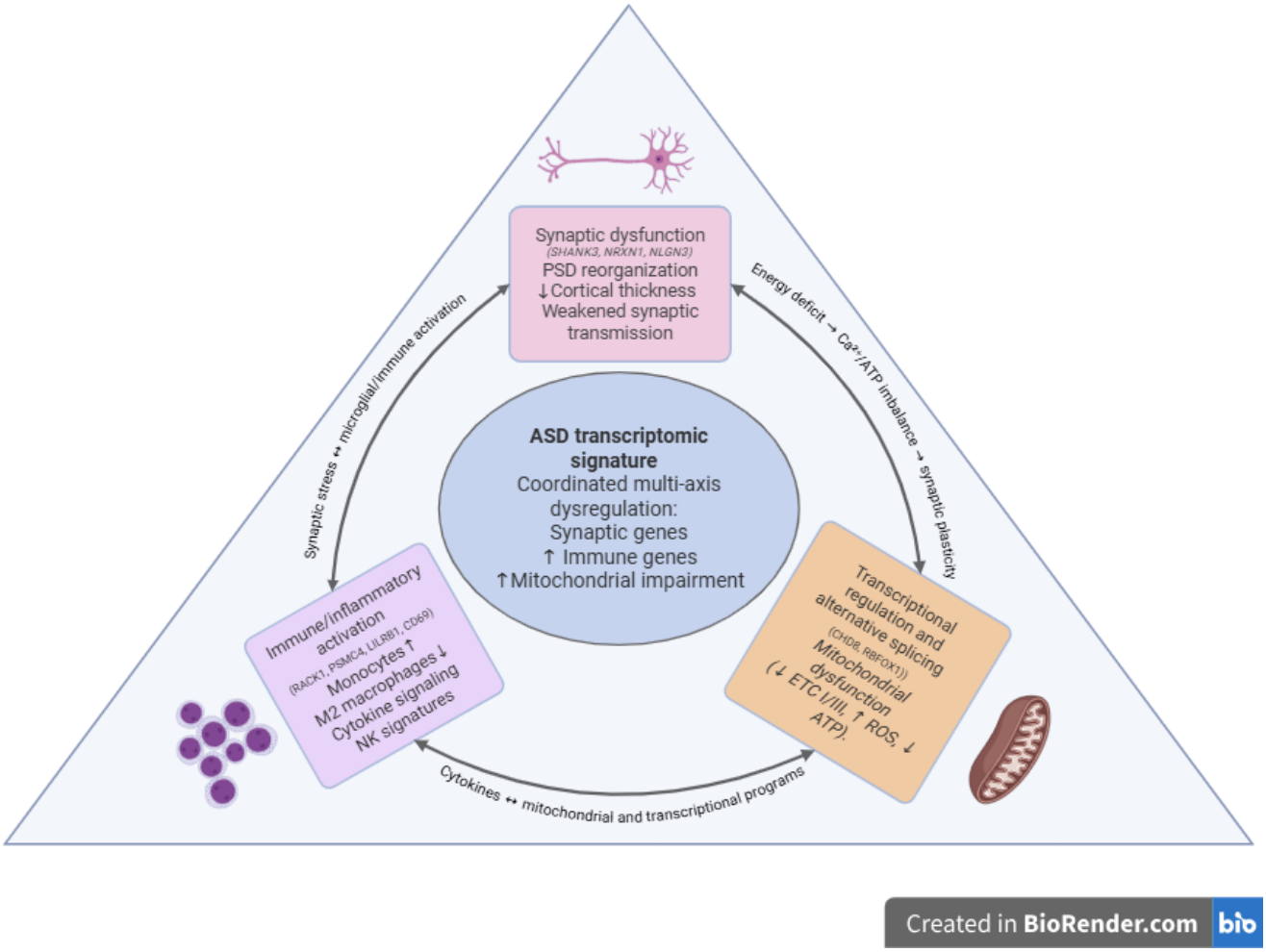

Figure 1. Conceptual summary of three partially interconnected transcriptomic axes in ASD, interpreted primarily from human post-mortem cortical studies and supplemented by secondary peripheral context. (1) Co-reduction of synaptic and mitochondrial-related gene-expression programs in post-mortem cortex, consistent with an "energy-synapse" pattern of cortical transcriptomic dysregulation (Schwede et al., 2018). (2) Peripheral blood transcriptome studies reporting myeloid-lineage shifts and immune-related hub transcripts are shown only as contextual support for immune-related dysregulation and not as direct equivalents of central nervous system molecular changes (Li et al., 2023). (3) A reduced blood co-expression module ("midnight blue") with RACK1 reported as a hub gene is included as a peripheral contextual observation and remains vulnerable to cell-composition and clinical-state confounding (Tomaiuolo et al., 2023). Arrows indicate putative relationships among immune-related signalling, synaptic stress, and mitochondrial-transcriptional dysregulation and are intended as a conceptual summary rather than a causal model.

Axis 1. Synaptic dysfunction Synaptic dysfunction represents one of the most recurrent program-level findings in ASD and is supported most consistently by human cortical transcriptomic studies. Synapse-related pathways involving the NRXN-NLGN adhesion system and SHANK-family scaffold proteins are biologically relevant to ASD because they contribute to synapse formation, organisation, and functional stability (Bourgeron, 2015). Across post-mortem cortical transcriptomic datasets, neuronal and synaptic gene-expression programs are commonly reported as relatively downregulated, often in parallel with upregulation of glial and immune-related modules (Voineagu et al., 2011; Parikshak et al., 2016). Integrative analyses linking cortical morphometry to transcriptomic reference maps further suggest that genes associated with cortical-thickness differences in children with ASD overlap with transcriptionally downregulated ASD gene sets and are enriched for synaptic transmission-related pathways (Romero-Garcia et al., 2019). These observations support synaptic dysfunction as a central axis of transcriptomic convergence in ASD, although interpretation remains constrained by developmental stage, regional specificity, tissue heterogeneity, and cell-type composition effects in bulk post-mortem data.

Axis 2. Immune-glial activation

Immune-glial activation represents a recurrent component of ASD cortical transcriptomic organisation and is most consistently observed in human brain-centred studies alongside relative downregulation of neuronal and synaptic programs. Across post-mortem cortical datasets, upregulation of glial and immune-related gene-expression modules repeatedly accompanies synaptic downregulation, supporting immune-glial dysregulation as one axis of partial transcriptomic convergence rather than an isolated inflammatory signal (Gandal et al., 2022).

Peripheral blood transcriptome studies may provide contextual support for immune-related dysregulation in ASD, but their interpretation remains constrained by immune-cell composition effects and clinical-state confounding; accordingly, they are not used here to infer central nervous system mechanisms. In a sex- and age-matched discordant sibling cohort comprising 27 pairs, differential-expression and co-expression analyses identified immune-related transcripts, including EGR1 and IGKV3D-15, and a downregulated WGCNA module ("midnight blue") with RACK1 reported as a hub gene (Tomaiuolo et al., 2023).

In a separate peripheral-blood analysis, integrative re-analysis of six GEO transcriptome datasets using immune-cell deconvolution (CIBERSORT) suggested a myeloid-lineage shift in ASD, including increased monocytes and non-classical monocytes; flow-cytometry validation further reported higher proportions of these cell populations in an independent paediatric cohort comprising 30 ASD cases and 30 controls (Li et al., 2023). Adult blood RNA-seq studies have likewise reported co-expression modules enriched for natural killer (NK) cell signalling together with qPCR-supported changes in selected transcripts (Horiuchi et al., 2021). However, because these findings derive from adult peripheral blood, their comparability with paediatric ASD cohorts remains limited by differences in age, medication exposure, and comorbidity structure.

Axis 3. Mitochondrial-transcriptional dysregulation

Mitochondrial-transcriptional dysregulation is best interpreted in ASD within a broader cortical transcriptomic framework that includes both gene-level and isoform-level disturbance. Cortex-wide RNA-seq studies have reported broad gene-expression dysregulation across ASD cerebral cortex (Gandal et al., 2022), while complementary isoform-level analyses have identified transcriptome-

wide isoform dysregulation, including differential transcript usage and altered isoform-network structure, supporting an additional role for splicing- and isoform-level regulation (Gandal et al., 2018).

Mitochondrial-related transcriptional alterations have also been reported in human post-mortem cortex. In a multi-dataset analysis, genes associated with mitochondrial function were reported as downregulated in ASD cerebral cortex and were strongly correlated with downregulation of synaptic transmission-related genes, supporting an "energy-synapse" pattern of cortical transcriptomic dysregulation; however, this evidence should still be interpreted within the broader constraints of post-mortem regional heterogeneity and cross-dataset variation (Schwede et al., 2018).

Regional qPCR-array profiling across the anterior cingulate gyrus (ACG), motor cortex (MC), and thalamus (THL) reported reduced expression of MTX2, NEFL, and SLC25A27 in ASD cases; however, none of the nominal expression P-values remained significant after multimarker testing with conventional Bonferroni correction, and these findings should therefore be interpreted cautiously pending independent replication (Anitha et al., 2012).

Beyond transcriptomic studies, a narrative synthesis of ASD brain-tissue literature published predominantly since 2010 reported findings consistent with mitochondrial dysfunction in 11 of 13 reviewed studies (85%) and identified electron transport chain complex I deficiency as the most frequently described abnormality across brain-tissue studies (Rossignol and Frye, 2014). These observations support consideration of mitochondrial biology within mechanistic models of ASD, but they should be interpreted cautiously because the underlying evidence is limited by small sample sizes, heterogeneous methods, and cross-study confounding.

Transcriptomic approaches relevant to ASD

Transcriptomic approaches have become central to mechanistic ASD research because they enable analysis of recurrent biological programs and isoform-level dysregulation, with the strongest interpretive value arising from human brain tissue rather than peripheral samples. The core technology is RNA sequencing (RNA-seq), which enables quantitative measurement of coding and non-coding RNAs and, with appropriate library design and analytical workflows, supports detection of alternative splicing events and isoform diversity (Conesa et al., 2016).

With advances in sequencing platforms, three complementary transcriptomic approaches have become especially relevant to mechanistic ASD research. Bulk RNA-seq estimates average expression across mixed cell populations and remains a robust method for identifying tissue-level gene-expression programs in human post-mortem cortex. In ASD cortical studies, bulk RNA-seq has reported recurrent synaptic and immune-related module-level alterations together with transcriptomic signals consistent with altered splicing regulation (Parikshak et al., 2016). Its main limitation is sensitivity to cellular heterogeneity and shifts in cell-type composition across samples.

To address the limitations of bulk tissue averaging, single-cell and single-nucleus RNA-seq (sc/snRNA-seq) provide cell-type-resolved expression profiles and therefore offer greater mechanistic resolution in ASD brain research. In ASD cortical tissue, snRNA-seq has identified cell-type-specific dysregulation, including signals in upper-layer excitatory neurons and microglia; some analyses have additionally reported associations between dysregulation in projection-neuron populations and clinical measures, although interpretation remains constrained by sample size, tissue availability, and cohort heterogeneity (Velmeshev et al., 2019). Despite this higher biological

resolution, sc/snRNA-seq remains technically demanding, financially costly, and strongly dependent on tissue handling and quality-control standards.

A third relevant approach is long-read RNA-seq, including PacBio and Oxford Nanopore platforms, which can capture full-length transcripts and improve structural characterisation of isoforms, including previously unannotated transcript variants. In the context of ASD, its main value lies in refining transcript structure and splicing interpretation rather than replacing short-read expression profiling. However, expression quantification with long reads remains challenging because of throughput constraints, platform-specific error profiles, and variability across computational pipelines (Pardo-Palacios et al., 2024).

Collectively, these approaches should be regarded as complementary rather than interchangeable: bulk RNA-seq is most useful for tissue-level program discovery, sc/snRNA-seq resolves the cell-type architecture of transcriptomic dysregulation, and long-read RNA-seq strengthens isoform and transcript-structure inference.

RNA sequencing (RNA-seq) is a core tool for mechanistic ASD research because it enables detection of recurrent gene-expression programs and transcript-level dysregulation, with the strongest interpretive value arising from human cortical and other central nervous system tissue. Across cortical datasets, the most consistently reported findings include relative downregulation of neuronal and synaptic gene programs, transcriptomic signals consistent with altered splicing regulation, attenuation of typical cortical gene-expression patterning, and upregulation of glial and immune-related modules (Parikshak et al., 2016; Gandal et al., 2022). Single-cell and single-nucleus approaches further refine these observations by assigning dysregulation to specific cell populations, including upper-layer excitatory neurons, selected interneuron subtypes, astrocytes, and microglia (Velmeshev et al., 2019). Peripheral RNA-seq studies, including blood and saliva, are discussed in this review only as secondary contextual comparison because their signals remain strongly influenced by immune-cell composition and clinical-state confounding.

The choice of transcriptomic platform in ASD research should be determined by the mechanistic question being asked rather than by expectations of near-term clinical screening utility. Bulk RNA-seq provides robust tissue-level differential-expression and pathway-level analyses but remains sensitive to cellular heterogeneity and shifts in cell-type composition. sc/snRNA-seq offers cell-type-resolved signatures and can be integrated with bulk datasets to assign tissue-level signals to specific cell populations, although its routine use at scale is still limited by cost, technical complexity, and tissue-quality constraints. Long-read RNA-seq improves isoform-level structural resolution and is best used as a targeted follow-up to short-read findings in order to validate transcript structures and refine splicing or isoform-level hypotheses. Summary selection criteria are provided in Table 1.

Table 1. Comparison of transcriptomic technologies for mechanistic ASD research

Method	Material	Cell res.	Cost	Complexity	Feasibility in CNS studies	Mechanistic use case	Notes / Key sources
Bulk RNA-seq	T/B	-	↑	↑	△	Tissue-level modules, DE genes; pathway enrichment.	Requires cell-composition adjustment, best-practice workflow: Conesa et al. (2016); classic overview: Wang, Gerstein & Snyder (2009).
sc/snRNA-seq	T/Org	++	↑↑	↑↑	△	Cell-type attribution; cell-state changes; reference for deconvolution	Sensitive to nuclei/tissue quality, ASD cortical cell-type signals reported in Velmeshev et al. (2019); integration with bulk (incl. Orgo-Seq) can prioritise cell-type drivers (Lim et al., 2022).
Long-read RNA-seq (PacBio/ONT)	T/Org	+	↑↑	↑	△	Isoform discovery and validation; complex splicing; transcript structure refinement	Best as targeted follow-up to short-read findings; trade-off between read accuracy/length and depth for transcript identification vs quantification; pipeline-dependent variability (Pardo-Palacios et al., 2024).

Legend. Material: *B = blood; T = tissue; Org = cerebral organoids. Cell res. = relative cell-type resolution (− / + / ++). Cost and complexity are shown as relative burden (↑ / ↑↑). Feasibility in CNS studies: △ = limited or conditional feasibility.*

Illustrative transcriptomic signals in ASD: cortical examples and peripheral context

Rather than being interpreted as diagnostic markers, transcriptomic findings in ASD are better understood as cortical molecular signals that are tissue-dependent, cell-type-sensitive, and mechanistically informative at the level of biological programs. The examples below are presented as illustrative observations from human cortical transcriptomic studies, with particular emphasis on alternative splicing and isoform-level regulation within synaptic, immune-glial, and mitochondrial-transcriptional frameworks.

Synaptic splicing and isoform-related signals

GRIN1 (NR1). In human post-mortem ASD cortex, Voineagu et al. reported dysregulated splicing of A2BP1/RBFOX1-dependent alternative exons in the context of reduced A2BP1 expression, with GRIN1 identified among the experimentally confirmed differentially spliced targets (Voineagu et al., 2011). RT-PCR validation supported a high proportion of tested differential-splicing events involving predicted A2BP1 targets (~85%), and the affected gene set was enriched for synaptic and synaptogenesis-related categories, consistent with synaptic transcriptomic dysregulation at the splicing level rather than with a standalone diagnostic marker (Voineagu et al., 2011).

CAMK2G; NRCAM. In the same human post-mortem cortical dataset, CAMK2G and NRCAM were listed among the top predicted A2BP1/RBFOX1-dependent differential-splicing events together with GRIN1, and the broader differential-splicing gene set was enriched for synaptic and synaptogenesis-related functions (Voineagu et al., 2011). These observations are consistent with synaptic transcriptomic dysregulation at the splicing level, although they should be interpreted as pathway-level support rather than as standalone ASD-specific markers.

SHANK3. SHANK3 shows complex transcriptional regulation with multiple isoforms that differ in domain composition and are therefore likely to differ functionally (Wang et al., 2014). In human post-mortem cortex, cDNA-capture and long-read RNA-seq profiling has further identified region-specific differences in SHANK3 transcript and isoform patterns in ASD, reinforcing the importance of isoform-aware analysis for synaptic genes; however, these transcriptomic observations should be interpreted as mechanistic context rather than as direct evidence of causality or ASD specificity (Lu et al., 2024; Wang et al., 2014).

ANK2 (DTU / isoform modules). In a large cross-disorder cortical RNA-seq analysis, Gandal et al. reported transcriptome-wide isoform-level dysregulation and identified ANK2 isoforms with disorder-associated differential transcript usage, including ANK2-013 in ASD (FDR < 0.05), while isoform-level network structure placed these signals within distinct co-expression modules, including neuronal and synaptic isoform modules such as isoM18 (Gandal et al., 2018). These findings support isoform-specific transcriptomic convergence at the network level, but they should not be interpreted as direct evidence of in vivo protein interaction or ASD-specific causality.

Peripheral immune-inflammatory signals (contextual, non-specific)

IL-6 / TNF-α signalling. Reviews of immune dysregulation in ASD indicate that pro-inflammatory cytokines including IL-6 and TNF-α may be elevated in peripheral blood and have also been reported in post-mortem brain tissue in some cohorts; however, these findings are heterogeneous across biological matrices, study designs, and clinical subgroups and are not specific to ASD (Erbescu et al., 2022). In the present review, they are interpreted only as contextual support for the immune-glial axis and not as transcriptomic markers or as direct evidence of ASD-specific central mechanisms.

NMUR1, HMGB3, PTPRN2 (peripheral transcriptome context). In a whole-blood RNA-seq study of discordant sibling pairs, transcriptional differences between affected and unaffected siblings were generally small, and deconvolution analyses indicated that the observed signal was driven largely by variation in peripheral immune-cell composition, particularly NK-cell-related components (Filosi et al., 2020). NMUR1, HMGB3, and PTPRN2 were highlighted as exploratory candidate transcripts, but their interpretation should remain cautious given the peripheral tissue context, compositional confounding, and the trend-level statistical threshold used in that study.

Regulators of splicing and transcriptional control (mechanistic evidence)

RBFOX1 (A2BP1). RBFOX1 is a neuronal splicing regulator with clear relevance to ASD-related transcriptomic frameworks because RBFOX1-dependent differential splicing has been implicated in human post-mortem ASD cortex (Voineagu et al., 2011). Supportive functional evidence from a preclinical model further showed that in vivo knockdown of the nuclear Rbfox1 isoform (Rbfox1-iso1) by in utero electroporation disrupted radial migration and terminal translocation during corticogenesis, reduced axon extension and dendritic arborisation, and altered membrane and synaptic properties in affected neurons (Hamada et al., 2016). Together, these findings support the biological plausibility of RBFOX1-linked splicing dysregulation in cortical circuit development, while not establishing ASD specificity or direct human causal inference.

POU3F2. Integrative genetic-regulatory analyses have implicated POU3F2 as a candidate transcriptional regulator in ASD through convergent evidence from developmental brain expression, fetal-brain chromatin contacts near risk loci, enrichment of downstream target sets among ASD-associated genes, and enrichment of ASD heritability near inferred POU3F2 binding sites (Huang et al., 2021). However, this signal should be interpreted cautiously: in stratified LDSC, SNPs near inferred POU3F2 binding sites explained approximately 11.7% of ASD heritability but with only marginal statistical support ($p \approx 0.054$), so the finding is better treated as plausible integrative regulatory evidence than as a validated transcriptomic mechanism.

Table 2. Axes and illustrative transcriptomic signals in ASD: study context, methods, key effects.

Axis	Gene / signal	Context / level	Method	Key effect	Statistical summary	Source
Synaptic axis: splicing/isoform regulation (RBFOX1/A2BP1)	GRIN1 (NR1)	Primary human CNS: postmortem cortex (frontal and temporal), H	RNA-seq; RBFOX1/A2BP1 motif analysis; RT-PCR validation	GRIN1 among top RBFOX1/A2BP1-dependent differential splicing (DS) targets; DS set enriched for synaptic/synaptogenesis categories	Motif enrichment in DS set (p=1.09×10^-7); RT-PCR confirmed ~85% of tested DS events	Voineagu et al., 2011
Synaptic axis: splicing/isoform regulation (RBFOX1/A2BP1)	CAMK2G (CaMKIIγ)	Primary human CNS: postmortem cortex, H	RNA-seq; RBFOX1/A2BP1 motif analysis; RT-PCR validation	CAMK2G listed among top predicted RBFOX1/A2BP1-dependent DS targets in the same dataset	See GRIN1 row	Voineagu et al., 2011
Synaptic axis: splicing/isoform regulation (RBFOX1/A2BP1)	NRCAM	Primary human CNS: postmortem cortex, H	RNA-seq; RBFOX1/A2BP1 motif analysis; RT-PCR validation	NRCAM listed among top predicted RBFOX1/A2BP1-dependent DS targets; synaptogenesis-related functional context	See GRIN1 row	Voineagu et al., 2011
Transcriptional/isoform axis: differential transcript usage (DTU)	ANK2 (DTU; ASD-associated isoform ANK2-013)	Primary human CNS: postmortem cortical tissue, H	Bulk RNA-seq; isoform-level DTU; co-expression network analysis	Disorder-associated DTU reported for ANK2 isoforms (e.g., ANK2-013 in ASD; FDR<0.05); isoform-level signals map to distinct co-expression modules	DTU FDR < 0.05	Gandal et al., 2018
Synapse	SHANK3	Primary human CNS: postmortem cortex, H	cDNA-capture + long-read RNA-seq	Region-specific differences in SHANK3 transcript/isoform patterns reported in ASD cortex	NR	Lu et al., 2024
Immune axis (peripheral context only)	NMUR1, HMGB3, PTPRN2	Contextual peripheral evidence: whole blood (discordant siblings), paediatric	RNA-seq; immune-cell deconvolution (xCell/CIBERSORT); co-expression (WGCNA)	Reduced NK-cell-related signature reported; overall signal strongly influenced by immune cell composition; candidate transcripts highlighted at exploratory threshold	FDR < 0.25 (exploratory / trend-level threshold)	Filosi et al., 2020
Splicing regulator (functional evidence; preclinical)	RBFOX1 (nuclear isoform, iso1)	Supportive preclinical evidence: mouse, Paed	In utero electroporation (shRNA knockdown); migration assays; neuronal morphometry; electrophysiology	Defects in radial migration and terminal translocation; reduced axonal growth and dendritic arborisation	NR	Hamada et al., 2016
Transcriptional regulation	POU3F2	Integrative regulatory evidence: brain-integrative, H	TITANS; fetal-brain Hi-C; developmental/spatiotemporal brain expression; TFBS-LDSC	Candidate transcriptional regulator: target sets enriched for ASD genes/LoF-DNMs; inferred TFBS annotations capture a portion of ASD heritability	TFBS $h^2 \approx 11.7\%$ ($p \approx 0.054$); target enrichment ≈ 2.1-2.68× ($p \leq 0.012$)	Huang et al., 2021

2. Conclusion

Overall synthesis Taken together, current evidence supports a brain-centred model of partial transcriptomic convergence in ASD rather than a single uniform molecular signature. Across human post-mortem cortical datasets, the most recurrent findings include relative downregulation of neuronal and synaptic gene programs, upregulation of immune-glial modules, altered transcript-level regulation including splicing and isoform signals, and mitochondrial-related transcriptional disturbance that appears linked to broader cortical program-level dysregulation (Parikshak et al., 2016; Velmeshev et al., 2019; Schwede et al., 2018; Gandal et al., 2022). Together, these observations support a mechanistic framework in which synaptic and immune-glial programs emerge as the most reproducible axes of ASD cortical transcriptomic dysregulation, while mitochondrial-transcriptional signals appear as a linked but currently less consolidated layer of evidence; peripheral transcriptomes remain secondary contextual evidence rather than direct indicators of central nervous system mechanisms.

Key limitations and priorities Interpretation of ASD transcriptomic findings remains limited by regional and tissue specificity, developmental-stage effects, cohort heterogeneity, and technical variation across studies, as well as by the sensitivity of bulk datasets to shifts in cell-type composition. Single-nucleus approaches improve cellular attribution but remain constrained by sample availability, cost, and incomplete cross-cohort standardisation (Velmeshev et al., 2019). Future brain-focused work should therefore prioritise replication across independent cohorts and cortical regions, joint modelling of cell-type composition and transcript-level regulation, isoform- and splicing-aware analyses implemented through transparent analytical pipelines, and integration of bulk and single-nucleus evidence to distinguish shared from cell-type-specific transcriptomic programs (Parikshak et al., 2016; Gandal et al., 2022). Peripheral transcriptomes may offer useful contextual comparison across tissues, but they should remain secondary to brain-based evidence because inference about central nervous system mechanisms is strongly limited by cell-composition effects and state-related confounding.

Declarations

Acknowledgments: The author thanks Professor Roy D. Sleator (Department of Biological Sciences, Munster Technological University, Cork, Ireland) for academic supervision and for constructive comments on earlier drafts of this manuscript.

Conflict of interest

The author declares no conflicts of interest.

Funding

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Ethical approval

This article is a narrative review and does not involve human participants, personal data, or new experimental procedures. Ethical approval was therefore not required.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this manuscript, the author used ChatGPT solely for language-related assistance, including translation, grammatical correction, and refinement of academic English. All AI-assisted edits were carefully reviewed and verified by the author. The study design, literature interpretation, synthesis of evidence, and all scientific conclusions were performed independently by the author, who takes full responsibility for the content of this manuscript.

Informed consent

Not applicable.

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