

Supplemental table 1. Demographic and cannabis exposure characteristics of the fetal brain cohorts

Subject ID	Trimester	Postconception age (weeks)	Fetal sex	Assay modality	Maternal race	Maternal ethnicity	Group	Cannabis use route	Cannabis frequency	Amount at last sitting	Tobacco use last month
29111	1	7.6	F	Transcriptomic / Proteomic	Black or African American	Non-Hispanic	Control				NO
90001	1	10.3	F	Transcriptomic / Proteomic	White	Non-Hispanic	Control				NO
90007	1	10.9	M	Transcriptomic / Proteomic	NA†	Hispanic	Control				NO
90009	1	8.1	F	Transcriptomic / Proteomic	Black or African American	Non-Hispanic	Control				NO
90028	1	7.6	F	Transcriptomic / Proteomic	Asian	Non-Hispanic	Control				NO
90034	1	10.3	F	Transcriptomic / Proteomic	White	Non-Hispanic	Control				NO
28711	1	11.4	M	Transcriptomic / Proteomic	White	Non-Hispanic	Case	inhalation / ingestion	1-2 times per week	0.3-0.5 grams/marijuana plant	NO
28928	1	9.6	M	Transcriptomic / Proteomic	Black or African American	Non-Hispanic	Case	inhalation	2-3 times per month	3 grams marijuana plant	YES
28972	1	10.3	M	Proteomic	White	Non-Hispanic	Case	inhalation / ingestion	three or more times per day	1/2 gram marijuana plant	YES
29045	1	10.6	F	Proteomic	White	Non-Hispanic	Case	inhalation	three or more times per day	0.10 grams marijuana plant	NO
29050	1	8.1	M	Proteomic	Black or African American	Non-Hispanic	Case	inhalation	three or more times per day	1 gram marijuana plant	NO
29110	1	11.7	F	Transcriptomic	NA	Hispanic	Case	inhalation / ingestion	twice per day	2 grams marijuana plant	NO
29141	1	9.6	M	Transcriptomic / Proteomic	Asian	Non-Hispanic	Case	inhalation	three or more times per day	1 gram marijuana plant	NO
90004	1	10.6	F	Transcriptomic / Proteomic	White	Non-Hispanic	Case	inhalation / ingestion	three or more times per day	1 gram marijuana plant	NO
90006	1	8.4	F	Transcriptomic / Proteomic	White	Non-Hispanic	Case	ingestion	once per day	100 mg THC	YES
90020	1	10.6	F	Transcriptomic / Proteomic	White	Non-Hispanic	Case	inhalation / ingestion	three or more times per day	2 mg marijuana plant/100 mg THC	NO
90024	1	10.4	M	Transcriptomic / Proteomic	White	Non-Hispanic	Case	inhalation	twice per day	3 grams marijuana plant	NO
90025	1	8.1	M	Transcriptomic	Asian	Non-Hispanic	Case	NR‡	NR	NR	NR
90030	1	11.1	M	Transcriptomic / Proteomic	Black or African American	Non-Hispanic	Case	inhalation	three or more times per day	2 grams marijuana plant	YES
90032	1	7.7	F	Transcriptomic	Asian	Non-Hispanic	Case	inhalation	three or more times per day	not sure	YES
90033	1	8.9	F	Transcriptomic	American Indian / Alaska Native	Hispanic	Case	inhalation	1-2 times per week	0.5 grams	NO
90035	1	7.6	F	Transcriptomic / Proteomic	NA	Hispanic	Case	NR	NR	NR	NR
28726	2	17.9	F	Transcriptomic / Proteomic	Native Hawaiian / Pacific Islander	Non-Hispanic	Control				NO
28973	2	18.9	F	Transcriptomic / Proteomic	Asian	Non-Hispanic	Control				NO
29035	2	13.7	F	Transcriptomic / Proteomic	Asian	Non-Hispanic	Control				NO
29058	2	12.7	M	Proteomic	NA	Hispanic	Control				NO
90002	2	13.0	F	Transcriptomic / Proteomic	White	Non-Hispanic	Control				NO
90013	2	12.3	M	Transcriptomic / Proteomic	NA	Hispanic	Control				NO
90019	2	14.0	F	Transcriptomic / Proteomic	White	Non-Hispanic	Control				YES
90031	2	14.0	M	Transcriptomic / Proteomic	Black or African American	Non-Hispanic	Control				NO
90037	2	13.4	M	Transcriptomic / Proteomic	NA	Hispanic	Control				NO
28891	2	14.0	M	Transcriptomic	Black or African American	Non-Hispanic	Case	inhalation / other	once per month or less	NR	YES
28894	2	12.4	M	Proteomic	White	Non-Hispanic	Case	inhalation	three or more times per day	1-2 grams plant	YES
28983	2	15.4	M	Proteomic	White	Non-Hispanic	Case	inhalation / other	three or more times per day	NR	YES
28998	2	13.0	M	Proteomic	Black or African American	Non-Hispanic	Case	inhalation	three or more times per day	1 gram marijuana plant	NO
29069	2	15.7	M	Transcriptomic	Black or African American	Non-Hispanic	Case	inhalation	once per day	0.5 grams/plant	NO
90000	2	14.7	F	Proteomic	White	Non-Hispanic	Case	inhalation / ingestion	twice per day	1 gram marijuana plant	NO
90014	2	15.0	M	Transcriptomic / Proteomic	White	Hispanic	Case	inhalation	three or more times per day	not sure	NO
90016	2	14.4	M	Transcriptomic / Proteomic	Native Hawaiian / Pacific Islander	Non-Hispanic	Case	inhalation	twice per day	NR	NO
90018	2	14.7	M	Transcriptomic / Proteomic	White	Non-Hispanic	Case	inhalation	three or more times per day	0.5 mg THC oil	NO
90022	2	15.7	M	Proteomic	White	Non-Hispanic	Case	inhalation	three or more times per day	3 grams marijuana plant	YES
90023	2	12.4	M	Transcriptomic / Proteomic	Black or African American	Non-Hispanic	Case	inhalation	2-3 times per month	0.5 marijuana plant	NO
90038	2	13.0	M	Transcriptomic	NA	Hispanic	Case	inhalation	three or more times per day	NR	YES

† NA, not available. ‡ NR, not reported. THC-equivalent dose was estimated assuming 15% Δ9-THC by weight in cannabis plant material. Based on self-reported amount consumed at last sitting, the estimated THC-equivalent dose was 183 ± 145 mg per use in T1 participants (n = 13 of 15) and 161 ± 138 mg per use in T2 participants (n = 7 of 12).

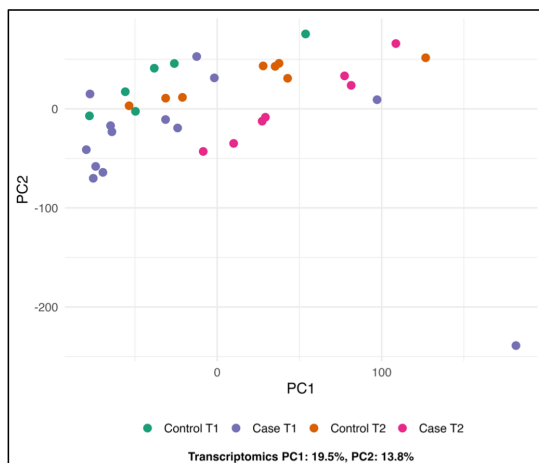
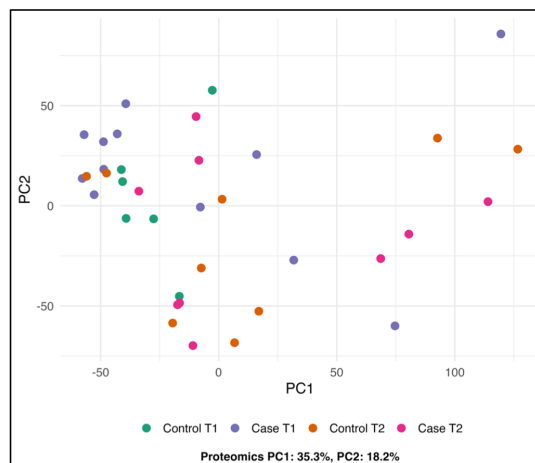
A**B**

Figure S1. Principal component analysis of fetal brain transcriptomic and proteomic data.

(A) Normalized transcriptomic data segregated primarily by trimester, with PC1 and PC2 explaining 19.5% and 13.8% of the variance, respectively. (B) Normalized proteomic data showed substantial overlap between trimesters though it remained a major source of variation, with PC1 and PC2 explaining 35.3% and 18.2% of the variance, respectively.

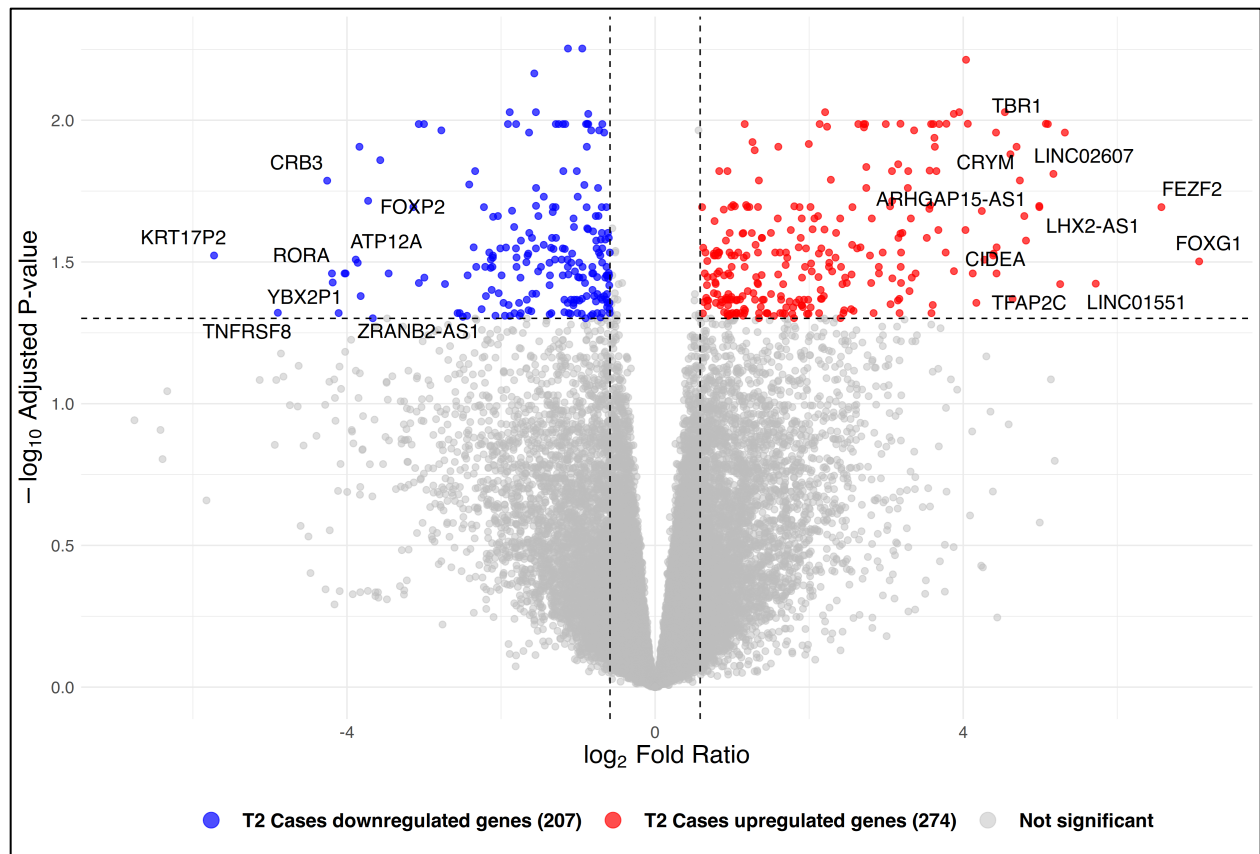


Figure S2. Transcriptomic alterations in T2 male fetal brains associated with prenatal cannabis exposure. Transcriptomic comparison of T2 Cases vs. Controls showing genes associated with prenatal cannabis exposure. Volcano plot showing quantified genes plotted by $\log_2$ fold ratio and Benjamini-Hochberg adjusted P value. Dashed vertical lines indicate the fold-ratio threshold ($|\log_2 \text{FR}| \geq 0.58$), and the horizontal dashed line indicates the adjusted P-value cutoff (adjusted $P \leq 0.05$). A total of 481 DEGs were identified. Selected DEGs are labeled. Significantly downregulated and upregulated genes are shown in blue and red, respectively.

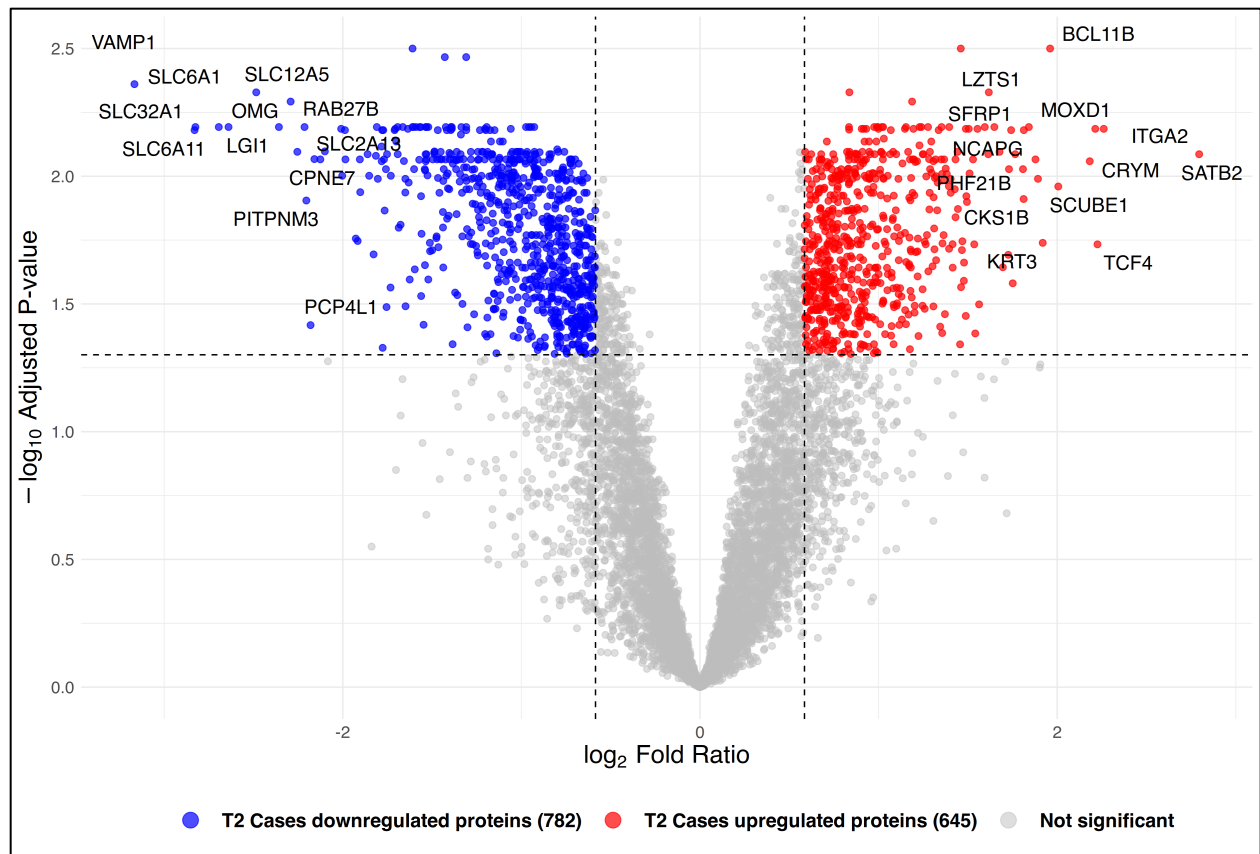


Figure S3. Proteomic alterations in T2 male fetal brains associated with prenatal cannabis exposure. Proteomic comparison of T2 Cases vs. Controls showing proteins associated with prenatal cannabis exposure. Volcano plot showing quantified proteins plotted by $\log_2$ fold ratio and Benjamini-Hochberg adjusted P value. Dashed vertical lines indicate the fold-ratio threshold ($|\log_2 \text{FR}| \geq 0.58$), and the horizontal dashed line indicates the adjusted P-value cutoff (adjusted $P \leq 0.05$). A total of >1,400 DEPs were identified. Significantly downregulated (blue) and upregulated (red) proteins are highlighted, with selected proteins labeled.

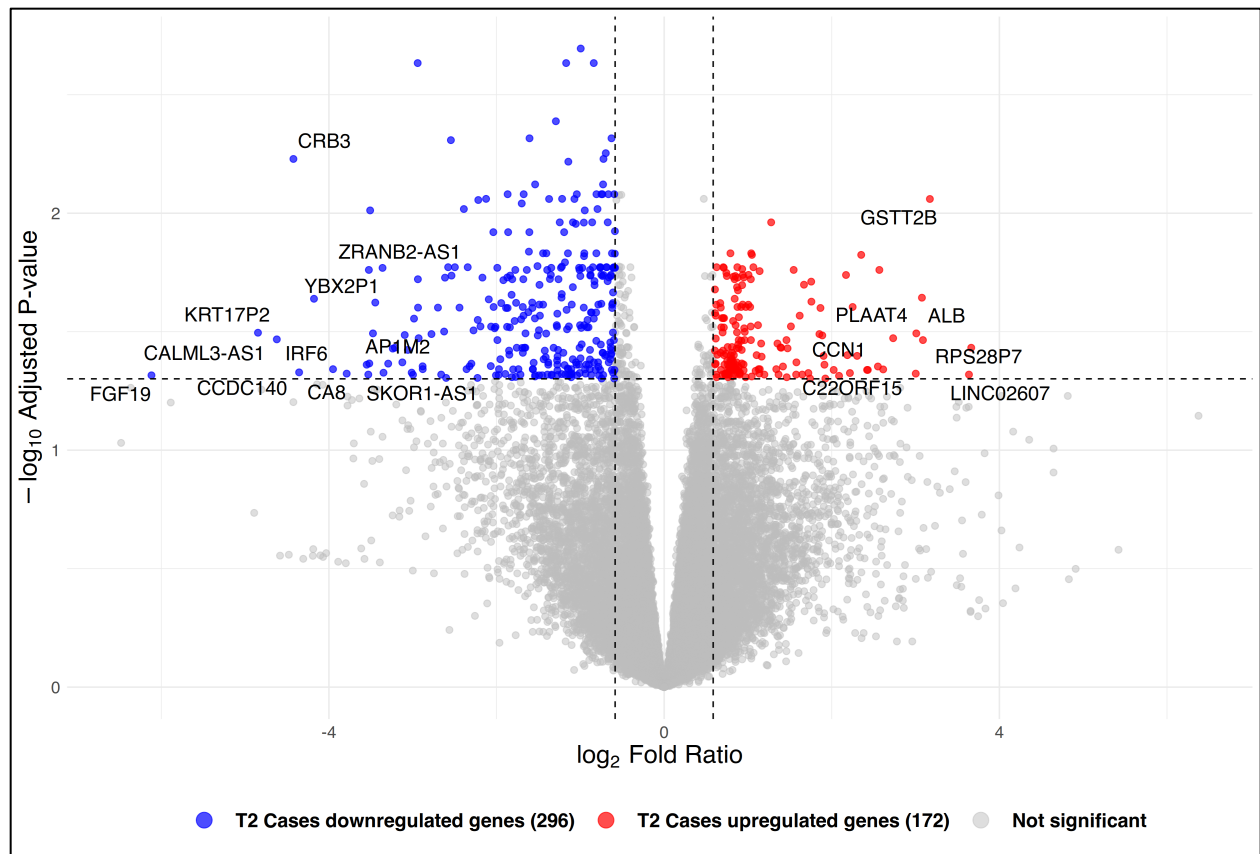


Figure S4. Transcriptomic alterations in T2 fetal brains associated with prenatal cannabis exposure (males and females). Transcriptomic comparison of T2 Cases vs. Controls showing genes associated with prenatal cannabis exposure. Volcano plot showing quantified genes plotted by $\log_2$ fold ratio and Benjamini-Hochberg adjusted P value. Dashed vertical lines indicate the fold-ratio threshold ($|\log_2 \text{FR}| \geq 0.58$), and the horizontal dashed line indicates the adjusted P-value cutoff ($\text{adjusted } P \leq 0.05$). A total of 468 DEGs were identified. Significantly downregulated (blue) and upregulated (red) genes are highlighted, with selected genes labeled.

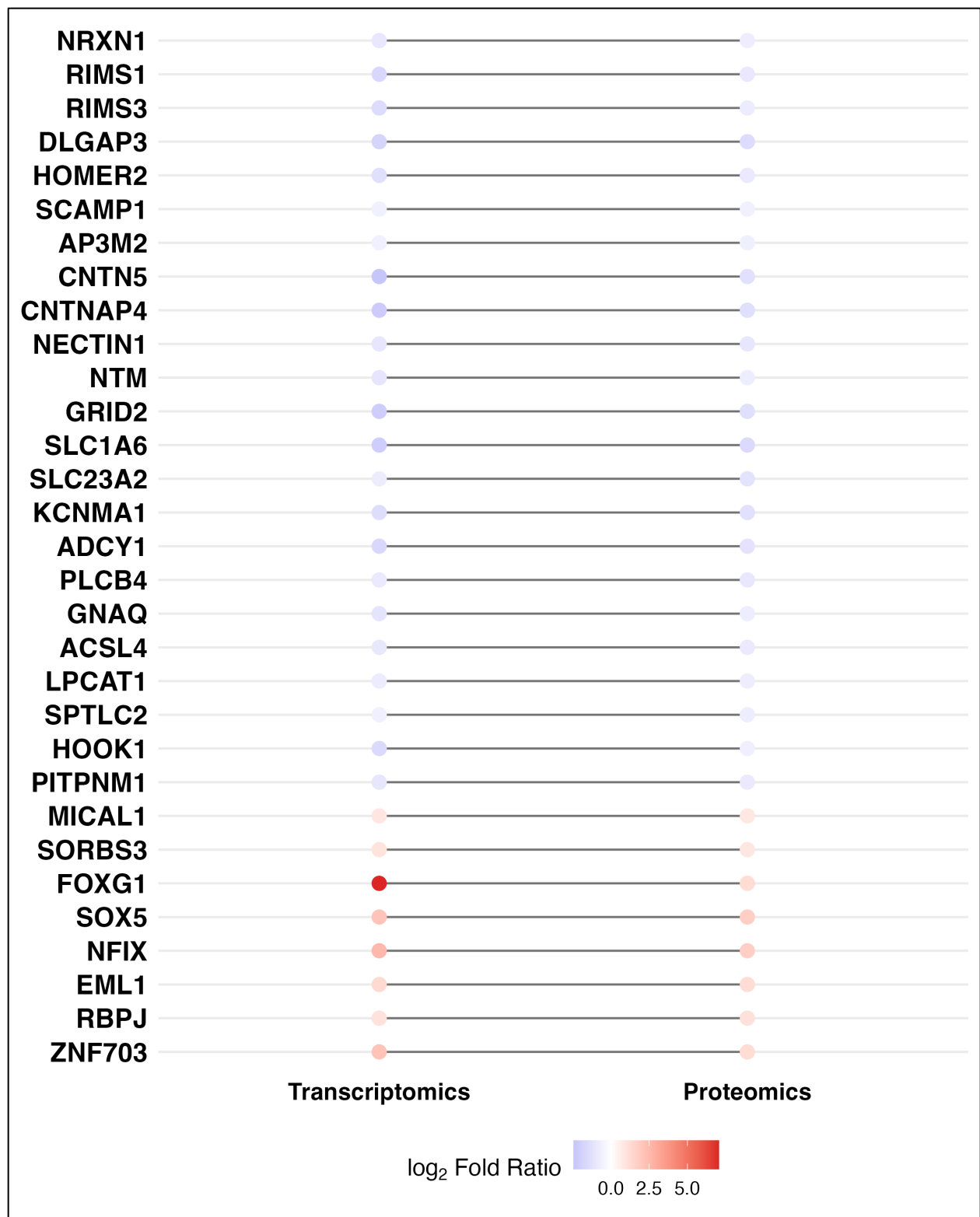


Figure S5. Selected concordant transcriptomic and proteomic alterations in male T2 Cases vs. Controls. Transcriptomic and proteomic expression changes for selected concordantly regulated genes and proteins that met our differential expression criteria (adjusted $P \leq 0.05$ and

$|\log_2FR| \geq 0.58$) in both datasets. Blue indicates downregulation in T2 Cases, whereas red indicates upregulation in T2 Cases. Concordant reductions in T2 Cases were observed for synaptic scaffold and vesicle-associated components (NRXN1, RIMS1, RIMS3, DLGAP3, HOMER2, SCAMP1, AP3M2), neuronal adhesion systems (CNTN5, CNTNAP4, NECTIN1, NTM), excitatory signaling, glutamate/ascorbate transport, and membrane excitability regulators (GRID2, SLC1A6, SLC23A2, KCNMA1, ADCY1, PLCB4, GNAQ), lipid metabolism regulators (ACSL4, LPCAT1, SPTLC2), and intracellular trafficking proteins (HOOK1, PITPNM1). Concordant increases in T2 Cases were observed for cytoskeletal remodeling proteins (MICAL1, SORBS3) and developmental regulators (FOXG1, SOX5, NFIX, EML1, RBPJ, ZNF703). Lines connect the transcriptomics and proteomics data.

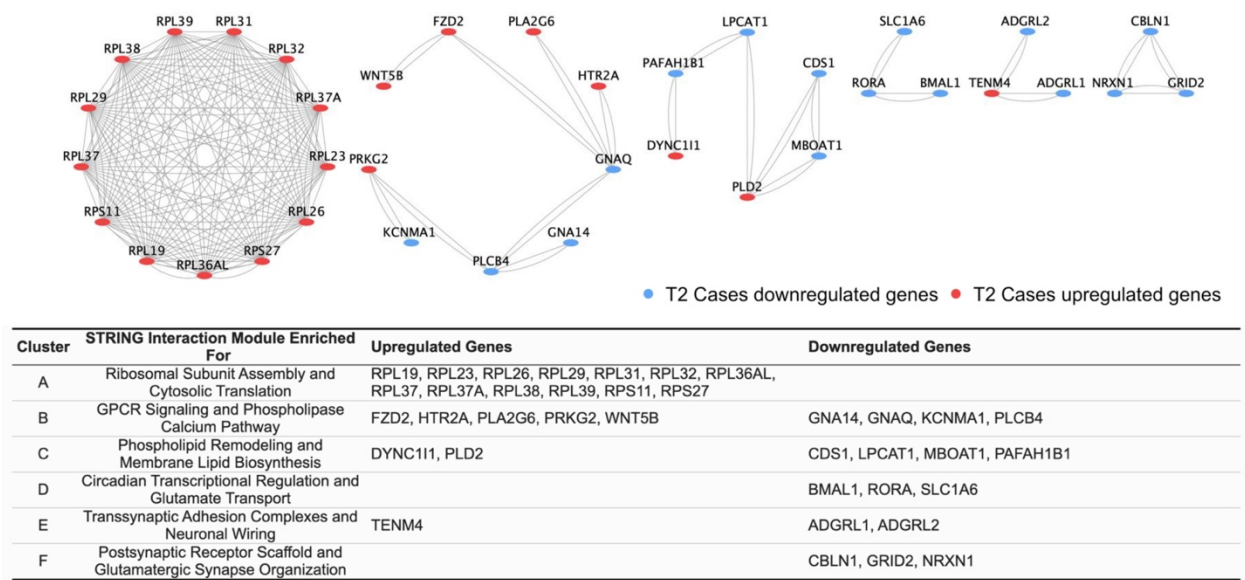
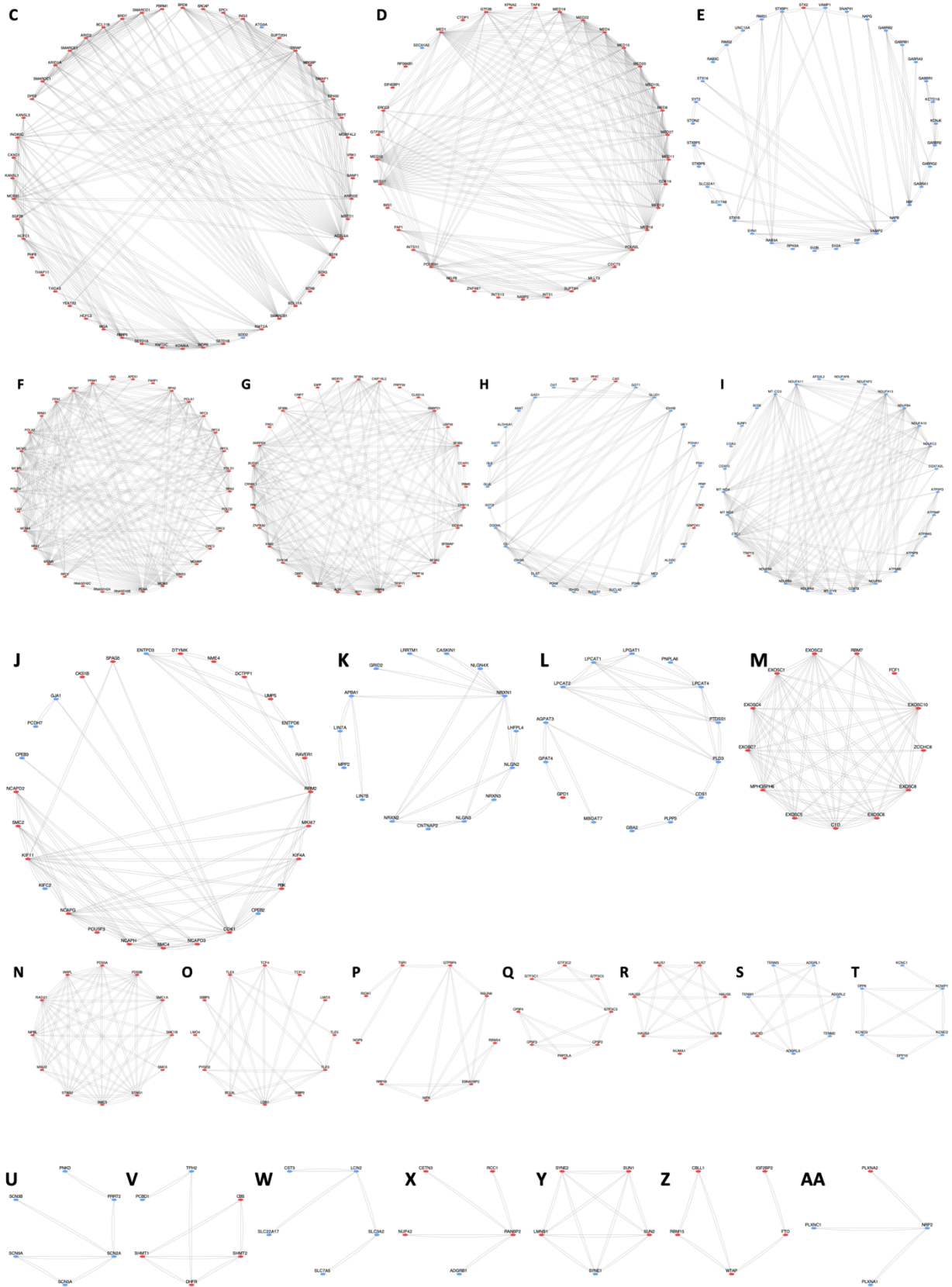
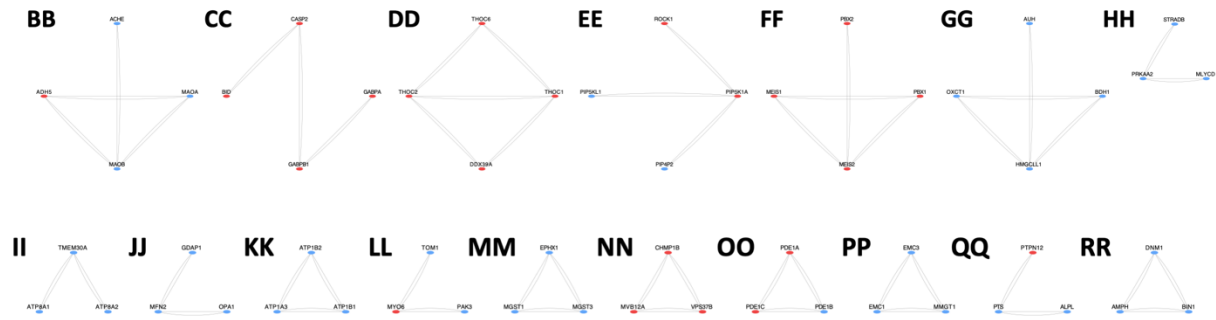


Figure S6. STRING-based transcriptomic interaction networks in male T2 Cases vs. Controls. (A–F) STRING-derived transcriptomic interaction subnetworks constructed from significantly altered genes in male T2 Cases vs. Controls. Blue nodes indicate genes downregulated in T2 Cases, whereas red nodes indicate genes upregulated in T2 Cases. The table summarizes the major functional modules represented in each interaction cluster.





● T2 Cases downregulated proteins ● T2 Cases upregulated proteins

Cluster	STRING Interaction Module Enriched For	Upregulated Proteins	Downregulated Proteins
A	Calcium-Dependent Signaling and Synaptic Plasticity Pathways	ARHGEF1, ARRB2, BRAP, CHUK, DACT1, DVL2, EFN1, EFN2, EZR, FKBP5, FLNA, FLNB, FZD2, GPC4, IQGAP1, IQGAP2, ITGA2, ITGB1, LGALS3, MSN, MYD88, PLA2G6, PRKD2, SDCBP, SFRP1, TGFB1, TRAF6, WNT7A	ACVR2A, ADAM22, ADAM23, ADCY1, ADCY2, ADCY7, ADCY9, ADD3, AGAP2, ALCAM, ANK1, ATP2B4, ATP6A1, ATP6AP2, ATP6V0A1, ATP6V0D1, ATP6V0D2, CACNA1A, CACNA2D1, CACNA2D2, CACNA2D3, CACNG2, CACNG4, CAMK2A, CAMK2B, CAMK2D, CAMK2G, CD81, CD82, CHRM3, CNTN1, CNTNAP1, DLGAP3, EPB41L1, EPHA4, EPHB2, EPHB3, ERBB4, FUND1, GNAQ, GRIA1, GRIA2, GRIA4, GRIN1, GRM1, GRM4, GRM5, GUCY1A1, GUCY1A2, GUCY1B1, HOMER2, HRAS, IL1RAP, INPP5A, ISG15, ITGA3, ITPR2, KIT, L1CAM, LGI1, MAP1A, NCAM2, NHERF2, NOS1, PLCB4, PLCD3, PRKCA, PRKCB, PRKCD, PRNP, RAPGEF4, RASGRP2, RGS3, RYR2, SDC2, SHANK1, SHC2, SPTB, TNC, USP33, VCAM1, VMA21
AA	Plexin-Semaphorin Signaling and Axon Guidance	PLXNA2	NRP2, PLXNA1, PLXNC1
B	Chromatin Remodeling and Histone Deacetylation	AGO1, AGO3, ARID4B, ASF1A, CBX2, CDK2AP1, CDK4, CDK6, CHD3, CREBBP, CTBP2, EHMT1, EHMT2, EMSY, EP300, GATAD2B, GPS2, GSE1, HAT1, HDAC1, HDAC2, HDAC3, ING1, KDM1A, KDM2B, LIN54, MBD3, MIER1, MORC3, MRE11, MSH2, MSH6, MTA2, NASP, NBN, NCOA1, NCOR1, NFYB, NFYC, NOTCH1, PAXX, PHC2, PHF12, PHF21A, PML, RAD50, RB1, RBBP4, RBBP7, RBL2, RBPJ, RCOR1, RCOR2, REPIN1, RERE, RFX1, RING1, SAE1, SAP130, SAP30, SAP30L, SIN3A, SIRT1, SMAD4, SMARCA1, TBL1XR1, TERF2, TLK2, TRIM24, TRIM28, TRIM33, UBE21, UBE2S, VIM, WIZ, XPO5, XRCC5, XRCC6, ZBTB33, ZEB1, ZEB2, ZMYM2, ZNF451	CHD5, EPCAM, NNMT
BB	Monoamine Oxidation and Neurotransmitter Catabolism	ADH5	ACHE, MAOA, MAOB
C	SWI/SNF Chromatin Remodeling and Transcriptional Regulation	ACTL6A, ANP32E, ARID1A, ARID2, BANF1, BCL11A, BCL11B, BRD7, BRD8, CXXC1, DMAP1, DPF2, EP400, EPC1, HCFC1, HCFC2, ING3, INO80C, KANSL1, KANSL3, KDM6A, KMT2A, KMT2C, MBDT1, MCRS1, MGA, MORF4L2, MRGBP, PBRM1, PHF8, RBBP5, SETD1A, SETD1B, SGF29, SMARCB1, SMARCC1, SMARCD1, SMARCE1, SOX5, SOX6, SRCAP, SS18, SUPT20H, TADA3, TFPT, THAP11, TRRAP, VRK1, WDR5, YEATS2	ATG9A, SOD2
CC	Apoptotic Signaling and GABP Transcriptional Regulation	BID, CASP2, GABPA, GABPB1	
D	Mediator Complex and RNA Polymerase II Transcription	CDC73, CDK19, CTD1P1, EIF4EBP1, ERCC3, GTF2B, GTF2H1, INTS1, INTS11, INTS13, IWS1, KPNA2, MED1, MED10, MED11, MED12, MED13L, MED15, MED17, MED18, MED19, MED20, MED22, MED27, MED4, MED8, MLLT3, NABP2, NELFB, PAF1, POLR2H, POLR2L, RPS6KB1, SUPT5H, TAF8, ZNF687	SEC61A2
DD	mRNA Nuclear Export and TREX Complex Function	DDX39A, THOC1, THOC2, THOC6	
E	Synaptic Vesicle Fusion and Presynaptic Exocytosis	STX2	GABBR1, GABBR2, GABRA1, GABRA3, GABRB1, GABRB2, GABRG2, KCNJ6, KCTD16, NABP, NAPG, NSF, RAB3A, RAB3C, RIMS1, RIMS2, RPH3A, SLC17A6, SLC32A1, SNAP91, STON2, STX16, STX1B, STXBP1, STXBP5, STXBP6, SV2A, SV2B, SYN1, SYP, SYT2, UNC13A, VAMP1, VAMP2
EE	Phosphoinositide Signaling and PI(4,5)P ₂ Metabolism	PIP5K1A, ROCK1	PIP4P2, PIP5K1
F	DNA Replication Licensing and Replication Fork Progression	APEX1, FEN1, GINS3, LIG1, MCM2, MCM3, MCM4, MCM5, MCM6, MCM7, MCMBP, ORC2, ORC3, PARP1, PCNA, POLA1, POLA2, POLD1, POLD2, POLD3, PRIM1, RFC2, RFC3, RFC4, RFC5, RNASEH2A, RNASEH2B, RNASEH2C, RPA1, RPA2, RPA3, RRM1, UNG	
FF	MEIS Homeobox Transcription Factors and Developmental Patterning	MEIS1, MEIS2, PBX1, PBX2	
G	Pre-mRNA Splicing and Spliceosome Assembly	AQR, BUD31, CCAR1, CLNS1A, CRIPT, CRNKL1, CWF19L2, DBR1, DDX46, DHX15, DHX38, EAPP, FRG1, ISY1, PPIE, PRPF18, PRPF39, PRPF8, RBM22, RBM5, SF3A3, SF3B2, SF3B4, SF3B6, SFSWAP, SNRPD1, SNRPD3, TFIP11, USP39, WDR70, XAB2, ZNF830	
GG	Ketone Body Metabolism and Mitochondrial Energy Utilization		AUH, BDH1, HMGCLL1, OXCT1

H	Central Carbon Metabolism and Amino Acid Biosynthesis	CAD, GNPDA1, PAICS, PPAT, SORD	ABAT, ALDH5A1, ALDOC, CS, DLAT, GAD1, GGT7, GLS, GLUD1, GLUL, GOT1, GOT2, HK1, IDH3A, IDH3B, IDH3G, ME1, ME3, OAT, OGDHL, PDHA1, PDHB, PDHX, PDK1, PFKP, SUCLA2, SUCLG1
HH	AMPK Energy Sensing and Metabolic Stress Signaling		MLYCD, PRKAA2, STRADB
I	Mitochondrial Respiratory Chain and Oxidative Phosphorylation	TRIP13	AFG3L2, ATP5ME, ATP5MF, ATP5MG, ATP5PB, ATP5PO, COA3, COX15, COX7A2L, COX7B, CYC1, MT-CO3, MT-CYB, MT-ND4, MT-ND5, NDUFA10, NDUFA11, NDUFA13, NDUFA9, NDUFAF3, NDUFAF6, NDUFB3, NDUFB4, NDUFB9, NDUFC2, NDUFS8, SCO2, SURF1
II	Phospholipid Flippase Activity and Membrane Asymmetry		ATP8A1, ATP8A2, TMEM30A
J	Cell Cycle Progression and Mitotic Chromosome Segregation	CDK1, CKS1B, DCTPP1, DTYMK, KIF11, KIF4A, MKI67, NCAPD2, NCAPD3, NCAPG, NCAPH, NME4, PBK, POU3F3, RAVER1, RRM2, SMC2, SMC4, SPAG5, UMP5	CPEB2, CPEB3, ENTPD3, ENTPD6, GJA1, KIFC2, PCDH7
JJ	Mitochondrial Dynamics and Outer Membrane Remodeling		GDAP1, MFN2, OPA1
K	Neurexin Adhesion Complex and Synaptic Organization		APBA1, CASKIN1, CNTNAP2, GRID2, LHFPL4, LIN7A, LIN7B, LRRTM1, MPP2, NLGN2, NLGN3, NLGN4X, NRXN1, NRXN2, NRXN3
KK	Na ⁺ /K ⁺ -ATPase Ion Transport and Neuronal Membrane Potential		ATP1A3, ATP1B1, ATP1B2
L	Phospholipid Remodeling and Membrane Lipid Metabolism	GPD1	AGPAT3, CDS1, GBA2, GPAT4, LPCAT1, LPCAT2, LPCAT4, LPGAT1, MBOAT7, PLD3, PLPP3, PNPLA6, PTSSS1
LL	Actin-Based Vesicle Transport and Synaptic Trafficking	MYO6	PAK3, TOM1
M	RNA Exosome and Nuclear RNA Surveillance	C1D, EXOSC1, EXOSC10, EXOSC2, EXOSC4, EXOSC5, EXOSC6, EXOSC7, EXOSC8, FCF1, MPHOSPH6, RBM7, ZCCHC8	
MM	Glutathione Conjugation and Xenobiotic Detoxification		EPHX1, MGST1, MGST3
N	Cohesin Complex and Sister Chromatid Cohesion	MAU2, NIPBL, PDS5A, PDS5B, RAD21, SMC1A, SMC1B, SMC3, SMC5, STAG1, STAG2, WAPL	
NN	ESCRT-III Complex and Endosomal Cargo Sorting	CHMP1B, MVB12A, VPS37B	
O	LDB1 Transcriptional Complex and Developmental Gene Regulation	BCL9L, LDB1, LMO3, LMO4, PYGO2, SSBP2, SSBP3, TCF12, TCF4, TLE3, TLE4, TLE5	
OO	Calcium-Dependent Phosphodiesterases and cAMP/cGMP Signaling	PDE1A, PDE1C	PDE1B
P	Ribosome Biogenesis and Nucleolar rRNA Processing	EBNA1BP2, GTPBP4, NIFK, NOP9, NSUN6, RBM34, RIOK1, RRP1B, TSR1	
PP	Endoplasmic Reticulum Membrane Complex and Protein Insertion		EMC1, EMC3, MGMT1
Q	RNA Polymerase III Transcription and mRNA 3' End Processing	CPSF2, CPSF3, CPSF4, GTF3C1, GTF3C2, GTF3C3, GTF3C5, PAPOLA	
QQ	Pterin Metabolism and Tyrosine Hydroxylase Cofactor Pathways	PTPN12	ALPL, PTS
R	Mitotic Spindle Assembly and Microtubule Organization	HAUS1, HAUS3, HAUS4, HAUS5, HAUS6, HAUS7, NUMA1	
RR	Synaptic Endocytosis and Membrane Curvature Machinery		AMPH, BIN1, DNM1
S	Latrophilin Adhesion Receptors and Synapse Formation	UNC5D	ADGRL1, ADGRL2, ADGRL3, TENM1, TENM2, TENM3
T	Voltage-Gated Potassium Channels and Neuronal Excitability		DPP10, DPP6, KCNC1, KCND2, KCND3, KCNIP1
U	Voltage-Gated Sodium Channels and Neuronal Action Potentials		PNKD, PRRT2, SCN2A, SCN3A, SCN3B, SCN9A
V	One-Carbon Metabolism and Folate Cycle Enzymes	CBS, DHFR, SHMT1, SHMT2	PCBD1, TPH2
W	Iron Transport and Lipocalin-Associated Immune Response		CST3, LCN2, SLC22A17, SLC3A2, SLC7A5
X	Nuclear Pore Transport and Ran-Dependent Nuclear Trafficking	CETN3, NUP42, RANBP2, RCC1	ADGRB1
Y	Nuclear Lamina Structure and Nucleocytoplasmic Coupling	LMNB1, SUN1, SUN2, SYNE2	SYNE1
Z	m6A RNA Methylation and Post-Transcriptional Regulation	CBLL1, FTO, IGF2BP2, RBM15, WTAP	

Figure S7. STRING-based proteomics interaction networks in male T2 Cases vs. Controls. (A–RR) STRING-derived proteomic interaction subnetworks constructed from significantly altered proteins in male T2 Cases vs. Controls. Blue nodes indicate proteins downregulated in T2 Cases, whereas red nodes indicate proteins upregulated in T2 Cases. The table summarizes the major functional modules represented in each interaction cluster.

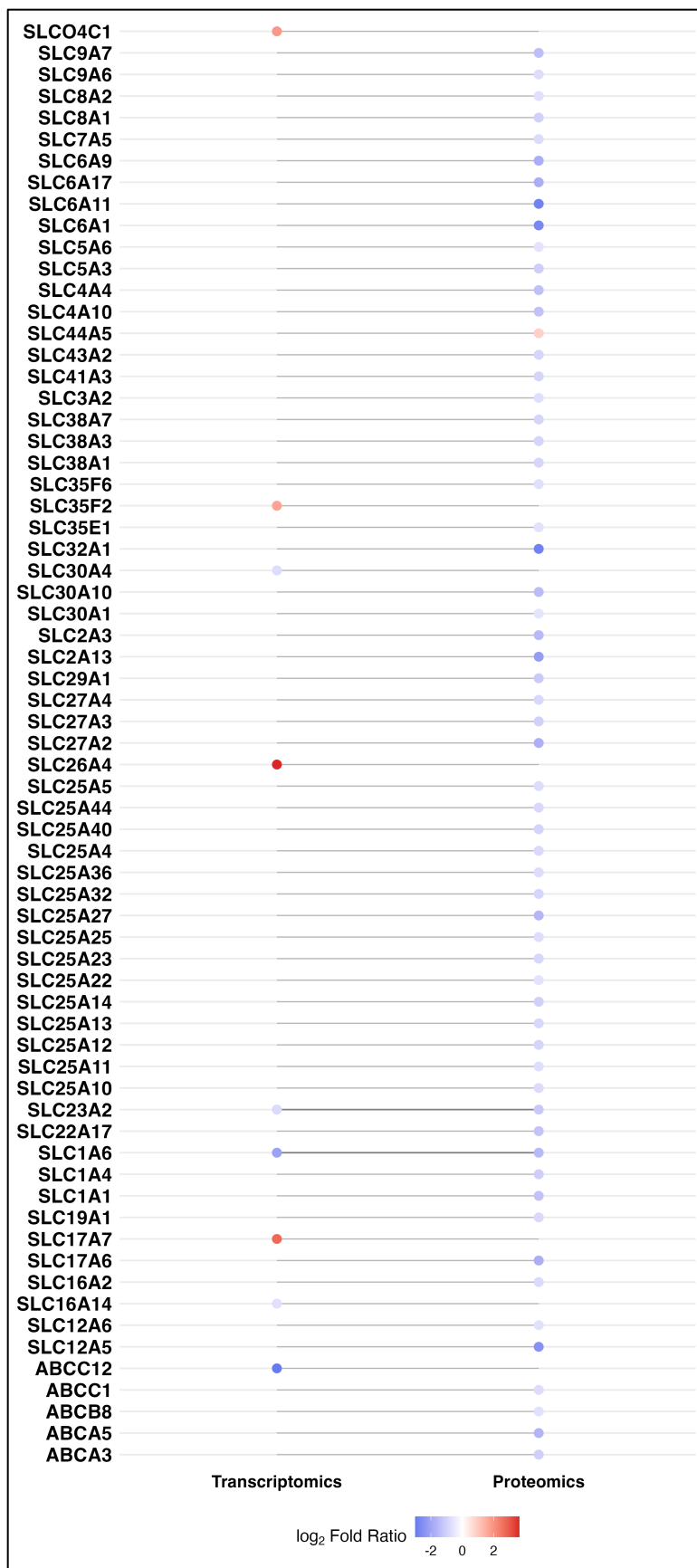


Figure S8. Coordinated transporter dysregulation in T2 cannabis-exposed male fetal brains. Transcriptomic and proteomic log₂ fold ratios (T2 Cases vs. Controls) are shown for all significantly altered solute carrier (SLC) and ATP-binding cassette (ABC) transporters identified (adjusted $P \leq 0.05$, $|\log_2 FR| \geq 0.58$). Each gene is displayed across molecular layers when detected, with lines connecting transcriptomic and proteomic measurements where both were observed. Proteomic data reveal a broad and consistent reduction in transporter abundance, whereas transcriptomic changes were fewer and more heterogeneous. Together, these data indicate a global decrease in membrane transport capacity at the protein level in T2 cannabis-exposed male fetal brains.

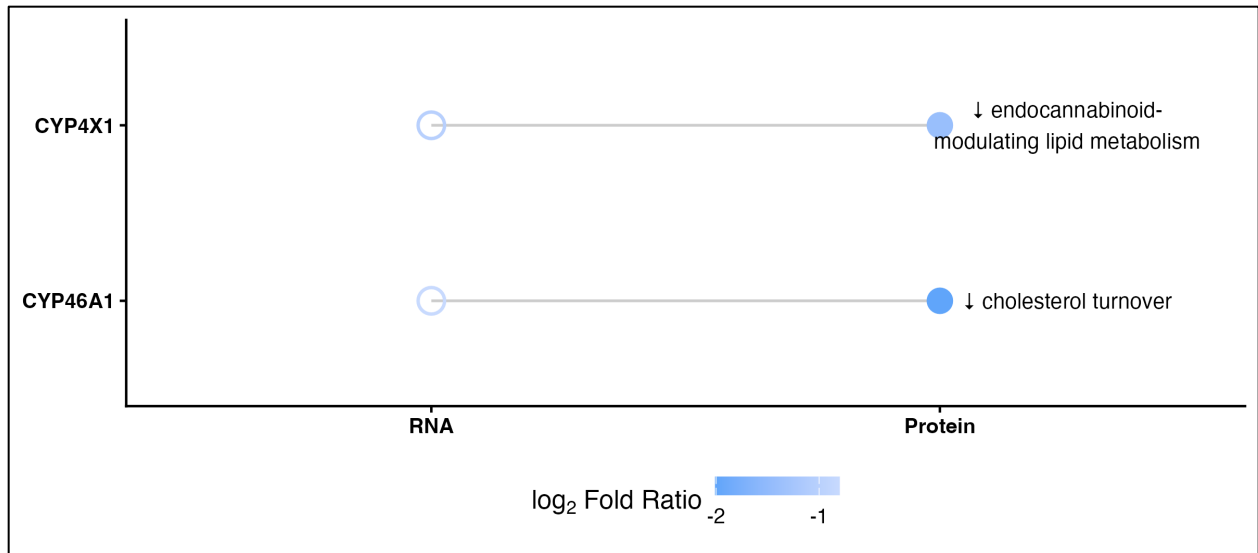


Figure S9. Disruption of cholesterol turnover and endocannabinoid-related lipid metabolism in second-trimester male fetal brains. Transcriptomic and proteomic log₂ fold ratios (T2 Cases vs. Controls) are shown for CYP46A1 and CYP4X1 in male samples. Points represent log₂ fold ratios, with color indicating the magnitude of the ratio. Opaque points denote statistically significant ratios (adjusted $P \leq 0.05$), whereas semi-transparent points indicate non-significant ratios.

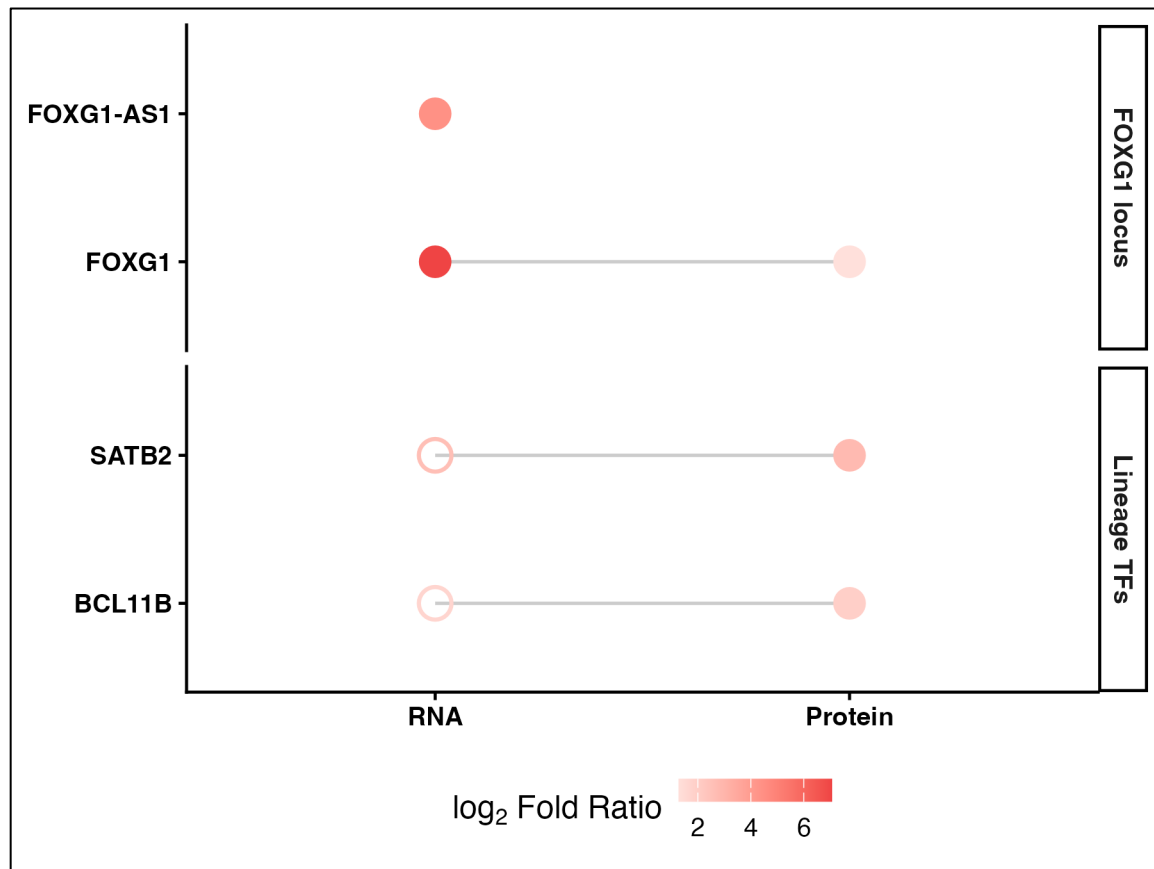
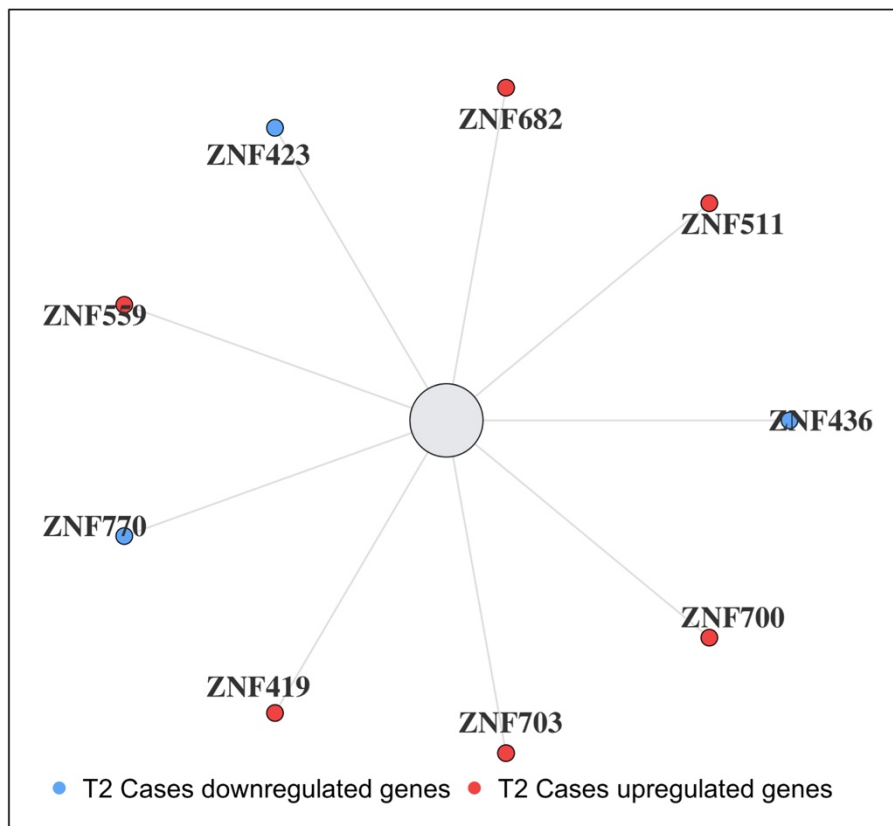


Figure S10. Activation of developmental transcriptional programs in T2 male fetal brains, T2 Cases vs. Controls. RNA and protein abundance changes for FOXG1, FOXG1-AS1, BCL11B, and SATB2 in T2 Cases vs. Controls. Points represent log₂ fold ratio, with color indicating magnitude of the ratio. Opaque points denote statistically significant ratios (adjusted $P \leq 0.05$), whereas semi-transparent points indicate non-significant ratios. FOXG1-AS1 is represented at the RNA level only. Genes are grouped by functional category (FOXG1 locus and lineage transcription factors, TFs).

A



B

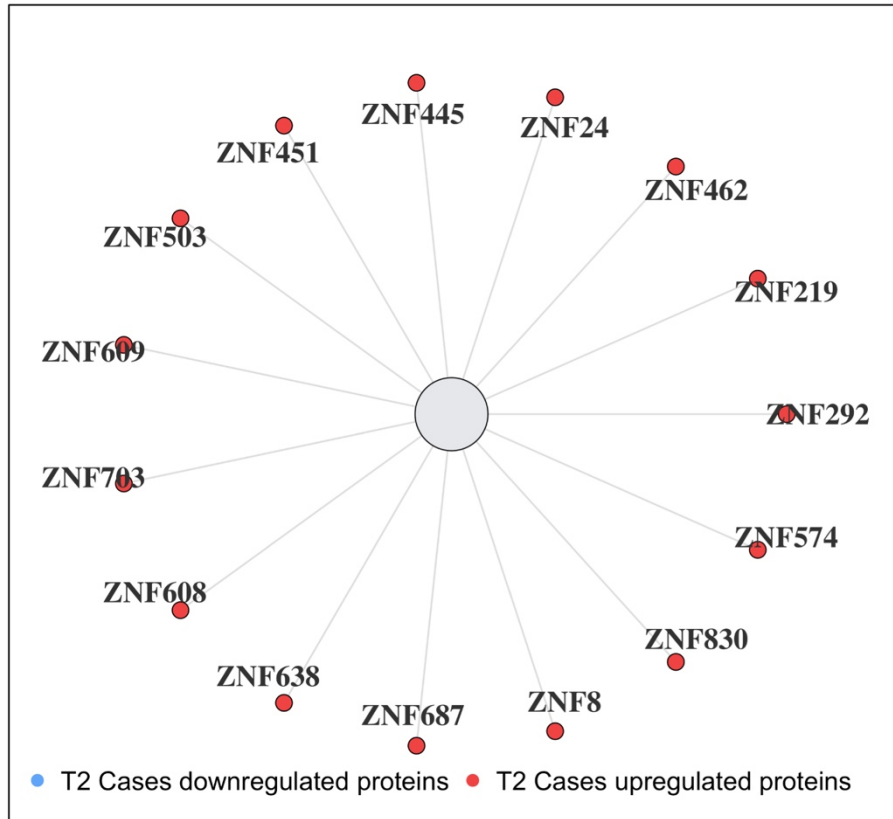


Figure S11. Zinc finger transcription factor expression in male fetal brains, T2 Cases vs. Controls. (A) Transcriptomic and (B) proteomic changes in zinc finger transcription factors in T2 Cases versus Controls. Nodes represent individual genes or proteins, colored by direction of ratio (red, upregulated; blue, downregulated) based on $\log_2$ fold ratio. Only statistically significant features (adjusted $P \leq 0.05$) are shown.

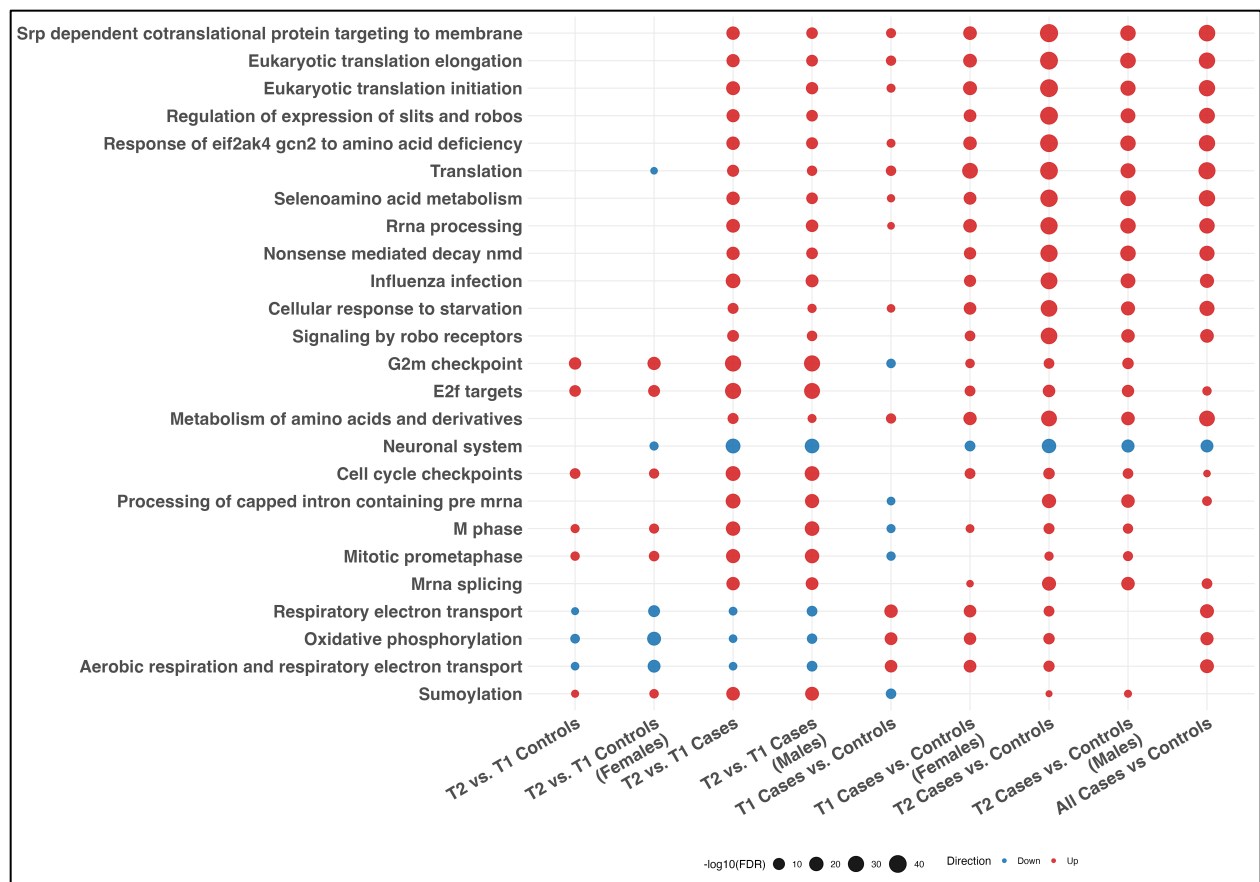


Figure S12. Gene set enrichment analysis (GSEA) of transcriptomic changes in fetal brains across multiple comparisons. Dot plot showing enriched pathways across multiple transcriptomic contrasts, with pathways ranked on the y-axis and comparisons on the x-axis. Point size reflects enrichment significance ($-\log_{10} \text{FDR}$), and color indicates direction of enrichment (red, upregulated; blue, downregulated). Neuronal signaling pathways are consistently downregulated in cannabis exposure comparisons, whereas ribosomal, translational, and SRP-dependent targeting pathways, along with amino acid stress response programs, are enriched, indicating global reweighting of the transcriptome.

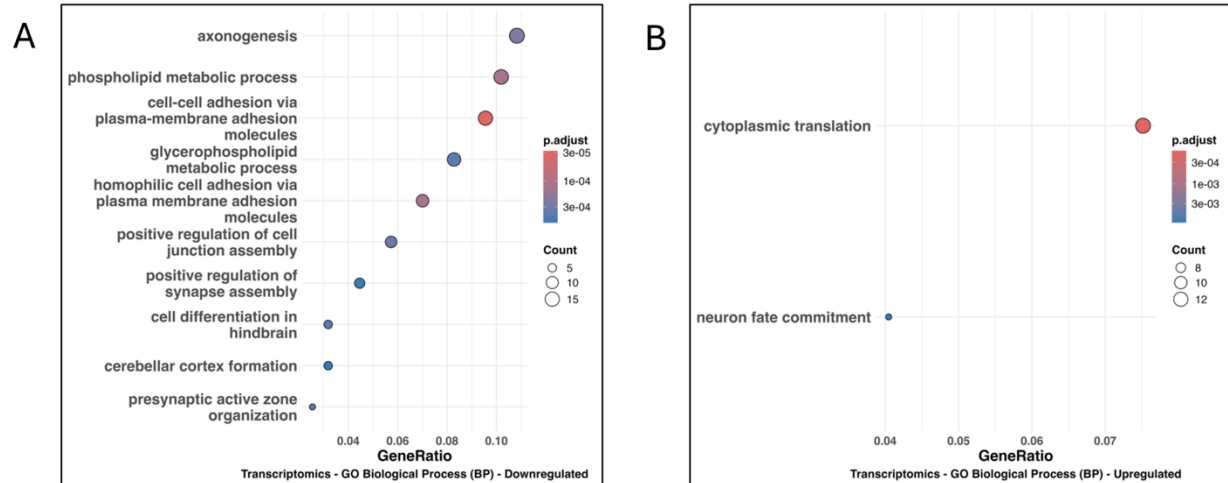


Figure S13. GO Biological Process enrichment analysis of transcriptomic changes in male T2 Cases vs. Controls. Gene Ontology (Biological Process) enrichment analysis of downregulated (**A**) and upregulated (**B**) genes. Dot plots show enriched terms ranked by gene ratio, with point size indicating gene count and color representing adjusted P value. Downregulated genes were enriched for axonogenesis, cell-cell adhesion, and phospholipid metabolic processes, whereas upregulated genes were enriched for cytoplasmic translation.

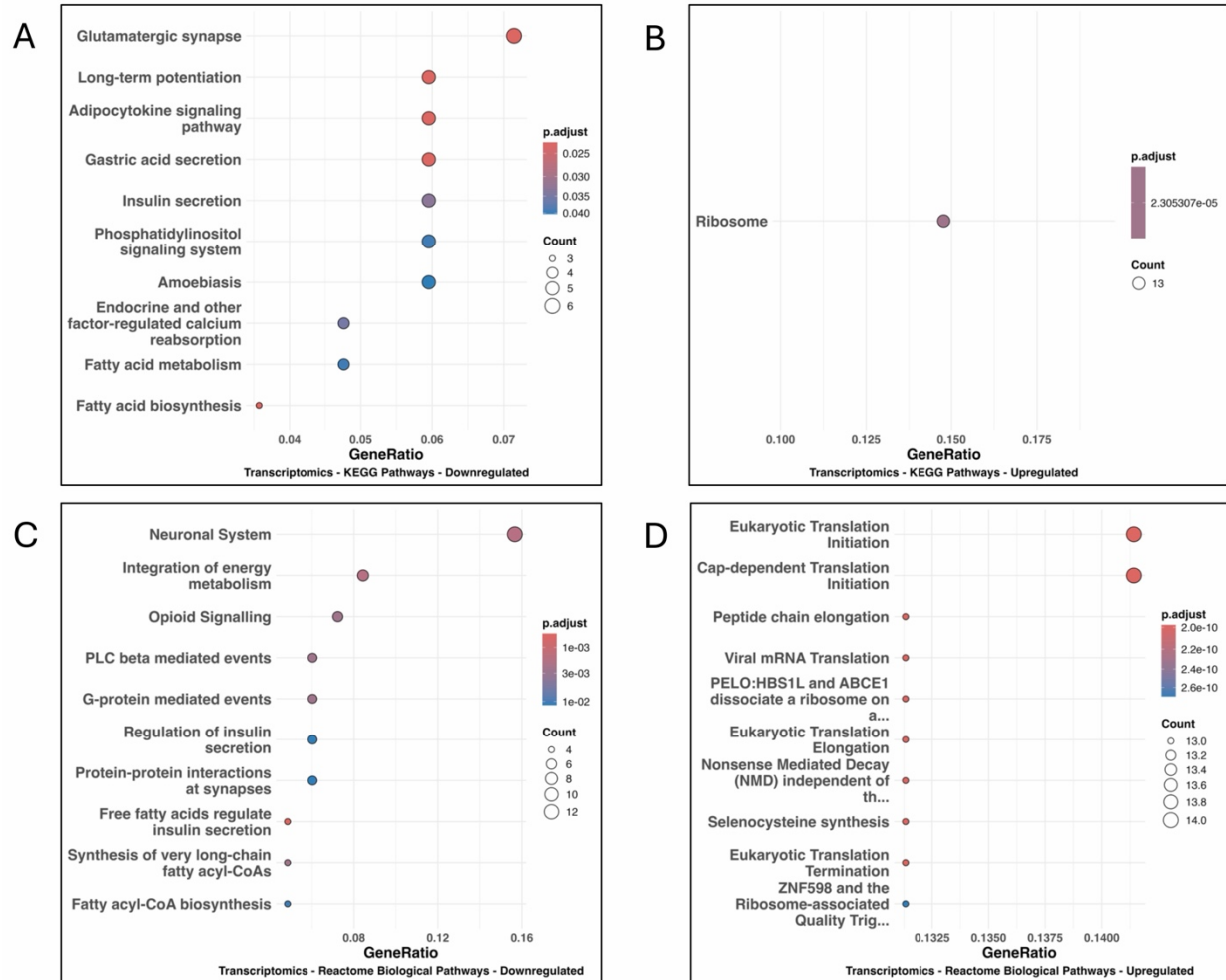


Figure S14. KEGG and Reactome pathway enrichment analysis of transcriptomic changes in male T2 Cases vs. Controls. KEGG pathway enrichment of downregulated (A) and upregulated (B) genes. Downregulated genes were enriched for neuronal and membrane-associated pathways, including glutamatergic synapse, long-term potentiation, phosphatidylinositol signaling, and lipid metabolism. In contrast, upregulated genes showed enrichment primarily for the ribosome pathway. Reactome pathway enrichment of downregulated (C) and upregulated (D) genes. Downregulated genes were enriched for neuronal system and G protein-mediated signaling pathways, whereas upregulated genes were enriched for eukaryotic translation, including initiation and elongation processes. Dot plots show enriched terms ranked by gene ratio, with point size indicating gene count and color representing adjusted P value.

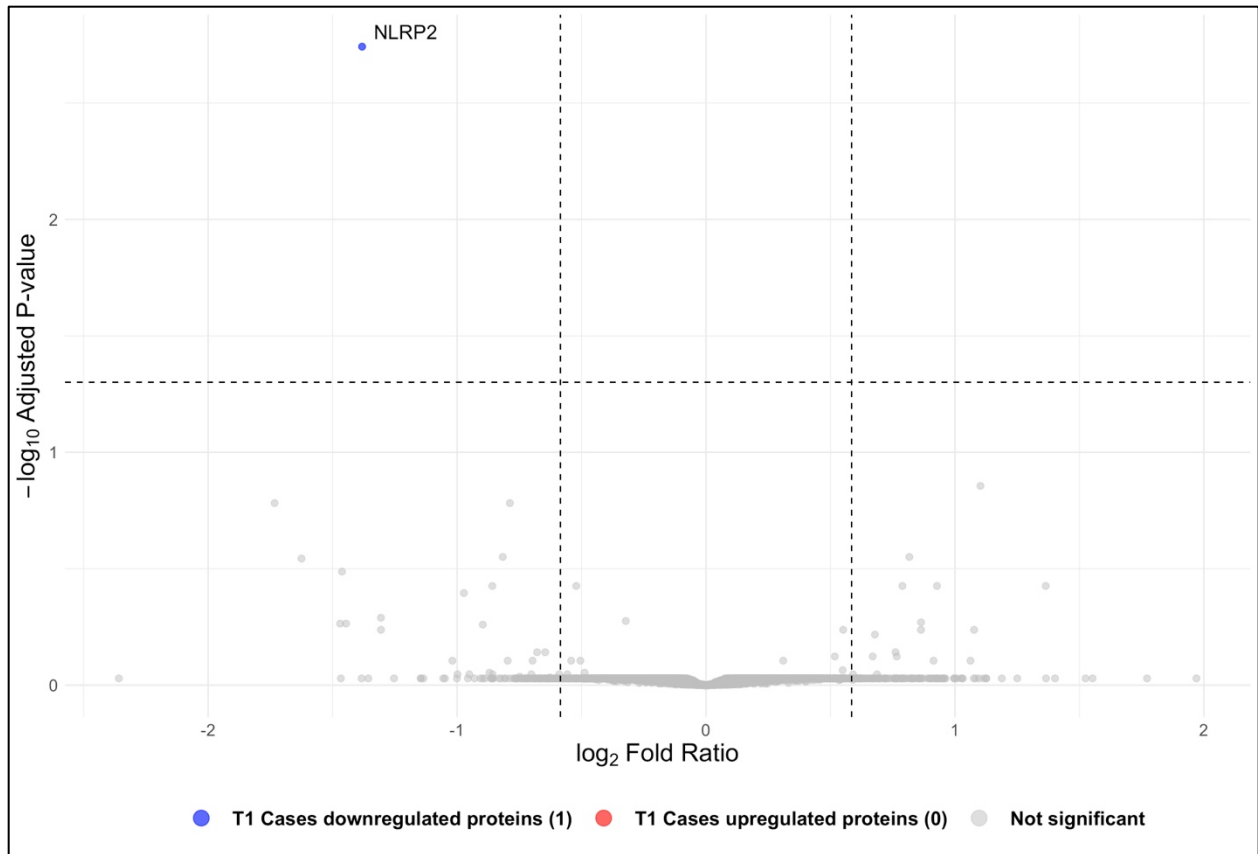


Figure S15. Proteomic comparison of prenatal cannabis exposure of female T1 Cases vs. Controls. Proteomic comparison of T1 Cases vs. Controls showing proteins associated with prenatal cannabis exposure. Volcano plot showing quantified proteins plotted by log₂ fold ratio and Benjamini-Hochberg adjusted P value. Dashed vertical lines indicate the fold-ratio threshold ($|\log_2\text{FR}| \geq 0.58$), and the horizontal dashed line indicates the adjusted P-value cutoff (adjusted P ≤ 0.05). A single DEP, NLRP2, met the predefined significance criteria and was downregulated in T1 Cases relative to T1 Controls.

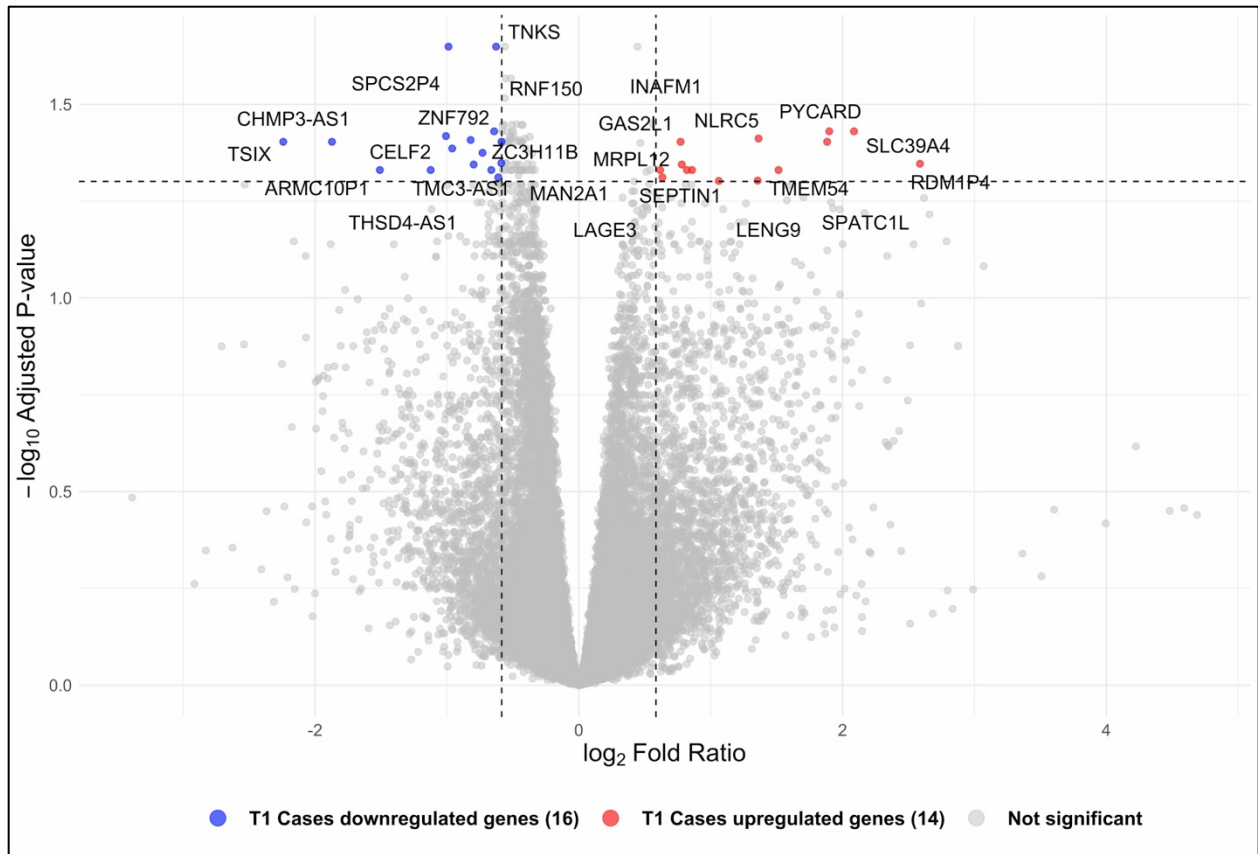


Figure S16. Transcriptomic comparison of prenatal cannabis exposure in T1 fetal brains Cases vs. Controls (males and females). Transcriptomic comparison of T1 Cases vs. Controls showing genes associated with prenatal cannabis exposure. Volcano plot showing quantified genes plotted by $\log_2$ fold ratio and Benjamini-Hochberg adjusted P value. Dashed vertical lines indicate the fold-ratio threshold ($|\log_2 \text{FR}| \geq 0.58$), and the horizontal dashed line indicates the adjusted P-value cutoff ($\text{adjusted } P \leq 0.05$). A total of 30 DEGs met the predefined significance criteria, with both upregulated and downregulated genes observed in T1 Cases relative to T1 Controls.

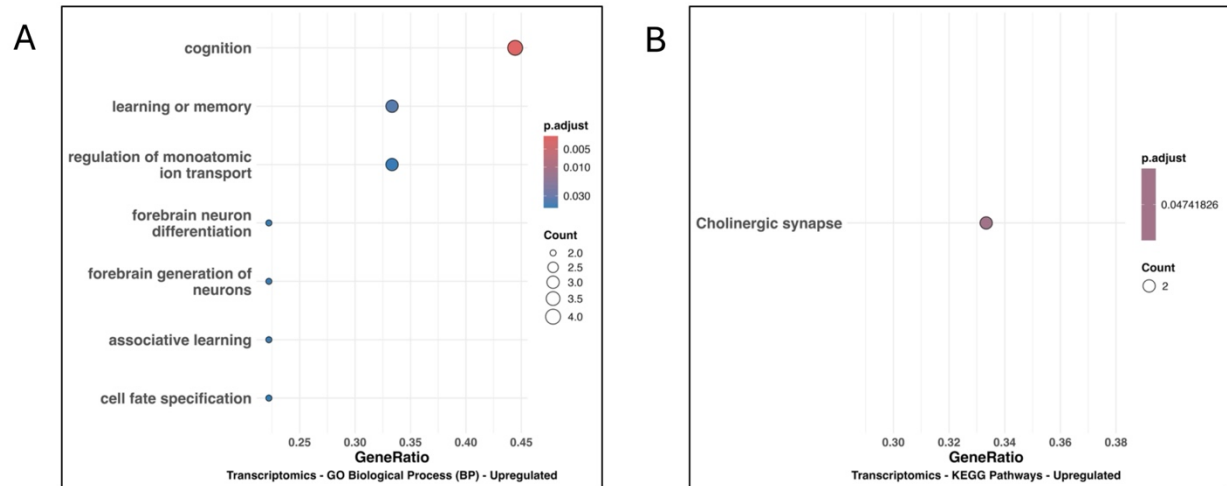


Figure S17. Transcriptomic enrichment associated with development of control female fetal brains (T2 vs. T1 Controls). (A) Gene Ontology (Biological Process) enrichment analysis of upregulated genes. Dot plot shows enriched terms ranked by gene ratio, with point size indicating gene count and color representing adjusted P value. Upregulated genes were enriched for processes related to cognition, learning and memory, ion transport regulation, and neuronal differentiation. (B) KEGG pathway enrichment analysis of upregulated genes. The cholinergic synapse pathway was enriched, indicating increased neurotransmission-related signaling during development. Dot plots show enriched terms ranked by gene ratio, with point size indicating gene count and color representing adjusted P value.

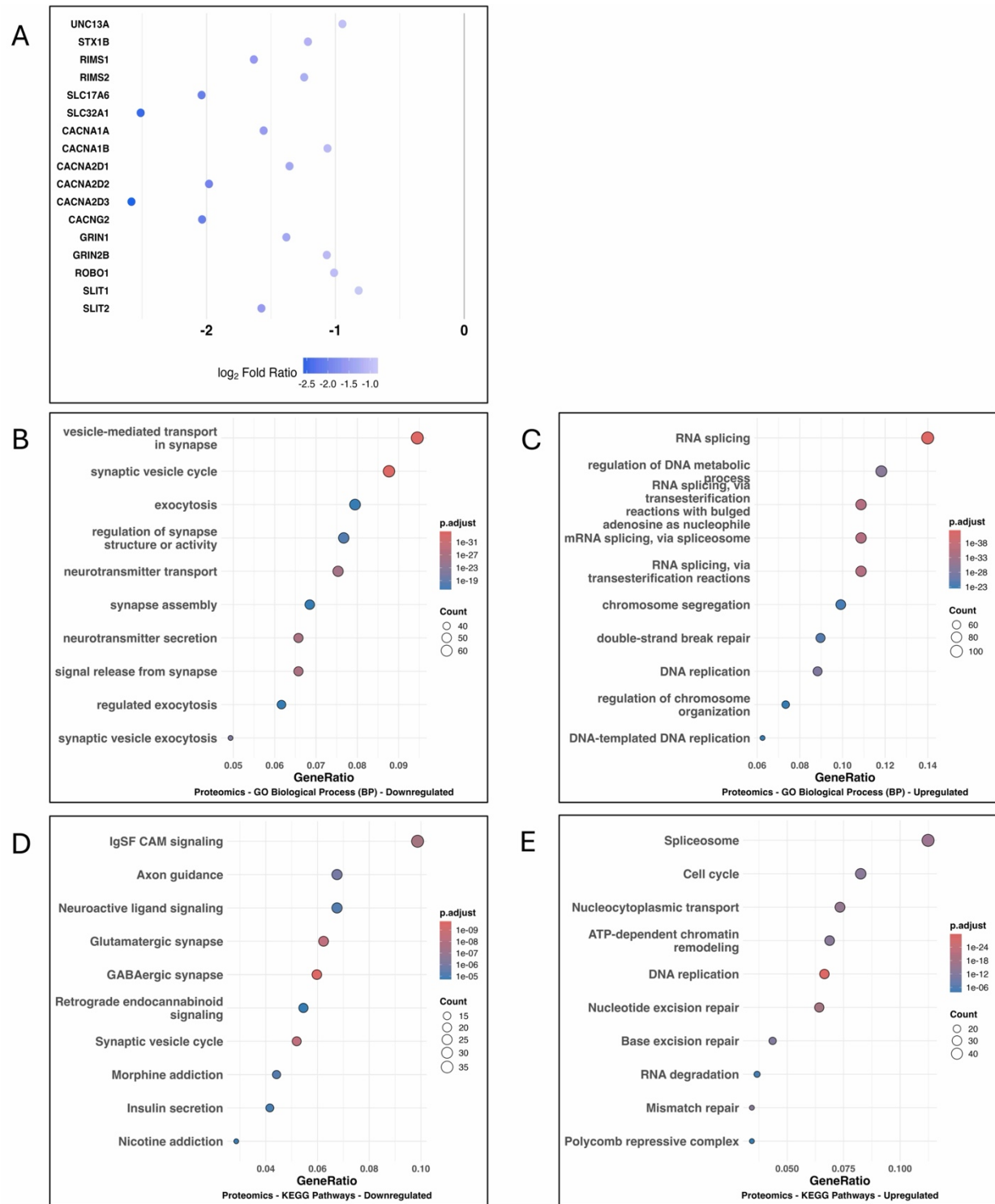
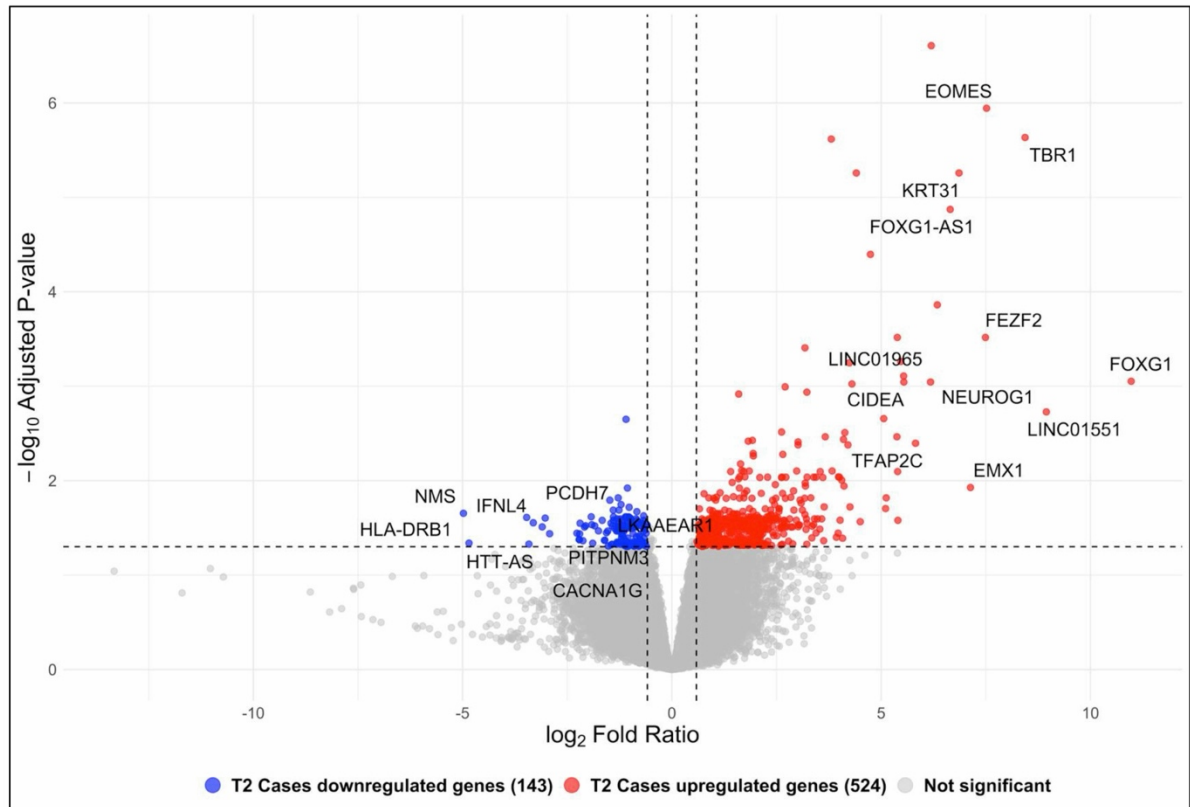


Figure S18. Proteomic remodeling associated with control female fetal brain development (T2 vs. T1 Controls). (A) Selected synaptic and excitability-related proteins showing reduced abundance in T2 relative to T1. Points represent $\log_2$ fold ratio for individual proteins. Gene Ontology (Biological Process) enrichment analysis of downregulated (B) and upregulated (C)

proteins. Dot plots show enriched terms ranked by gene ratio, with point size indicating protein count and color representing adjusted P value. Downregulated proteins were enriched for synapse-related processes, whereas upregulated proteins were enriched for RNA processing, transcriptional regulation, and cell cycle activity. KEGG pathway enrichment analysis of downregulated (**D**) and upregulated (**E**) proteins. Downregulated pathways include neuronal signaling and synaptic transmission, whereas upregulated pathways were enriched for spliceosome, chromatin remodeling, and cell cycle-associated programs.

A



B

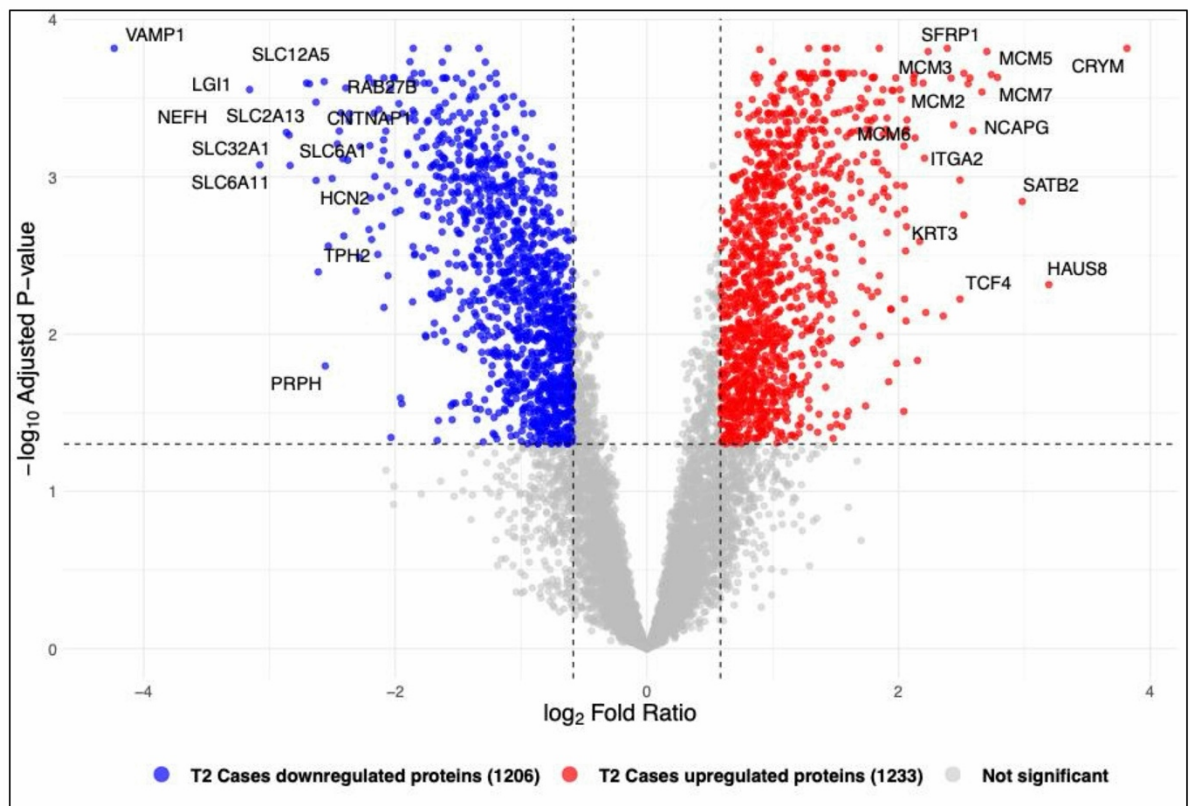


Figure S19. Transcriptomic and proteomic association with brain development in male fetuses (T2 vs. T1 Cases). Transcriptomic (**A**) and proteomic (**B**) comparisons of T2 versus T1 case fetal brains showing gene products associated with development. Volcano plots showing quantified genes or proteins plotted by $\log_2$ fold ratio and Benjamini-Hochberg adjusted P value. Dashed vertical lines indicate the fold-ratio threshold ($|\log_2\text{FR}| \geq 0.58$), and the horizontal dashed line indicates the adjusted P-value cutoff (adjusted $P \leq 0.05$). In **A**, 667 DEGs were identified, with prominent upregulation of neurodevelopmental regulators including TBR1, EOMES, and FOXP1 in T2 relative to T1. In **B**, 2,439 DEPs were identified, indicating extensive proteomic remodeling during development in Cases.

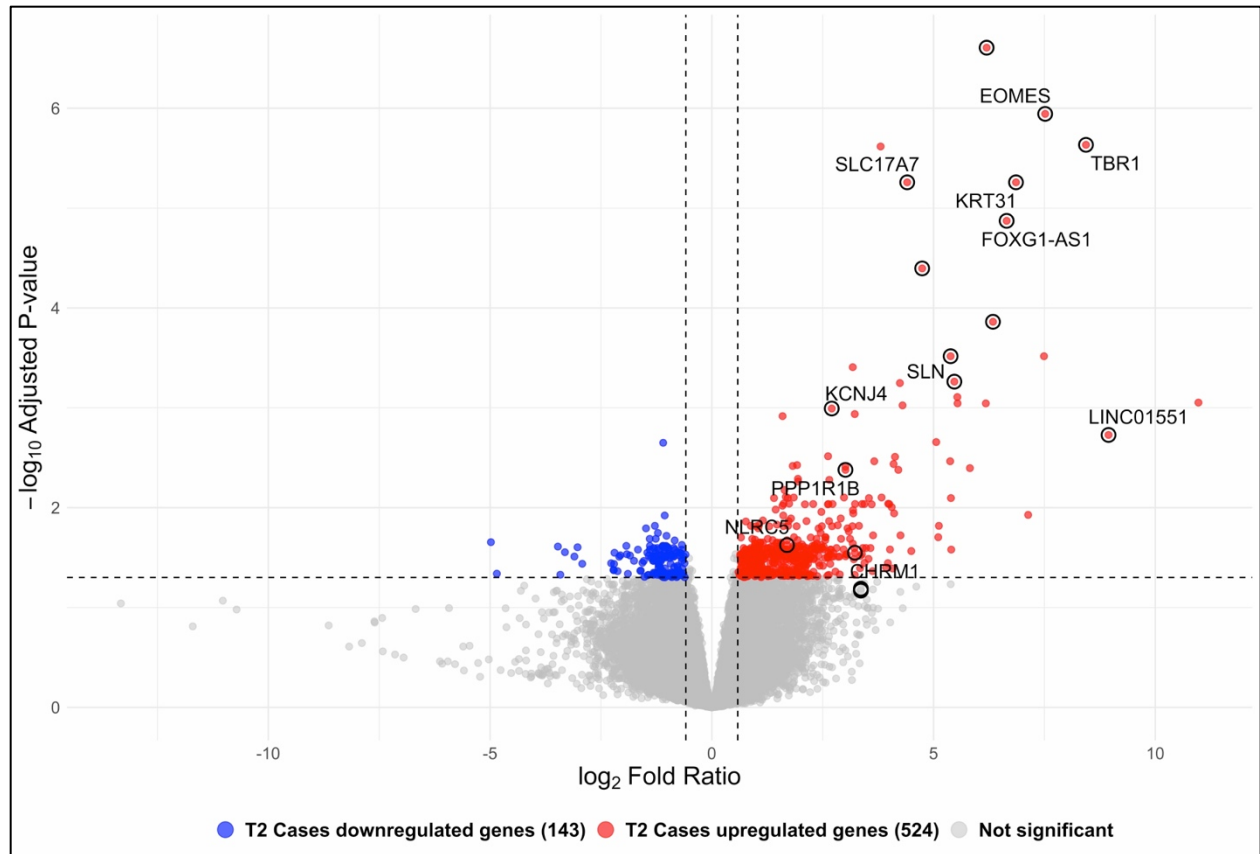


Figure S20. Transcriptomic association with brain development in male fetuses (T2 vs. T1 Cases) with female control development overlaid. Transcriptomic comparison of T2 versus T1 case brains showing genes associated with developmental progression. Volcano plot showing quantified genes plotted by $\log_2$ fold ratio and Benjamini-Hochberg adjusted P value. Dashed vertical lines indicate the fold-ratio threshold ($|\log_2 \text{FR}| \geq 0.58$), and the horizontal dashed line indicates the adjusted P-value cutoff (adjusted $P \leq 0.05$). Genes defining female control development (T2 Controls versus T1 Controls) are overlaid and highlighted by black circles. Red and blue points indicate genes significantly upregulated in T2 and T1 case samples, respectively.

Figure S21. Cross-development concordance of transcriptomic and proteomic data between control females and case males. (A) Transcriptomic concordance plot comparing log₂ fold ratio between control female development (T2 versus T1) and case male development (T2 versus T1). Each point represents a gene quantified in both datasets and is classified as significant in both conditions, control-only, case-only, or non-significant. A positive correlation (Pearson $r = 0.69$) indicates shared directionality of transcriptional changes across conditions. (B) Proteomic concordance plot comparing log₂ fold ratios between control female development (T2 versus T1) and case male development (T2 versus T1). Each point represents a protein quantified in both datasets and is classified as above. A stronger positive correlation (Pearson $r = 0.90$) indicated highly consistent directional change at the proteome level.

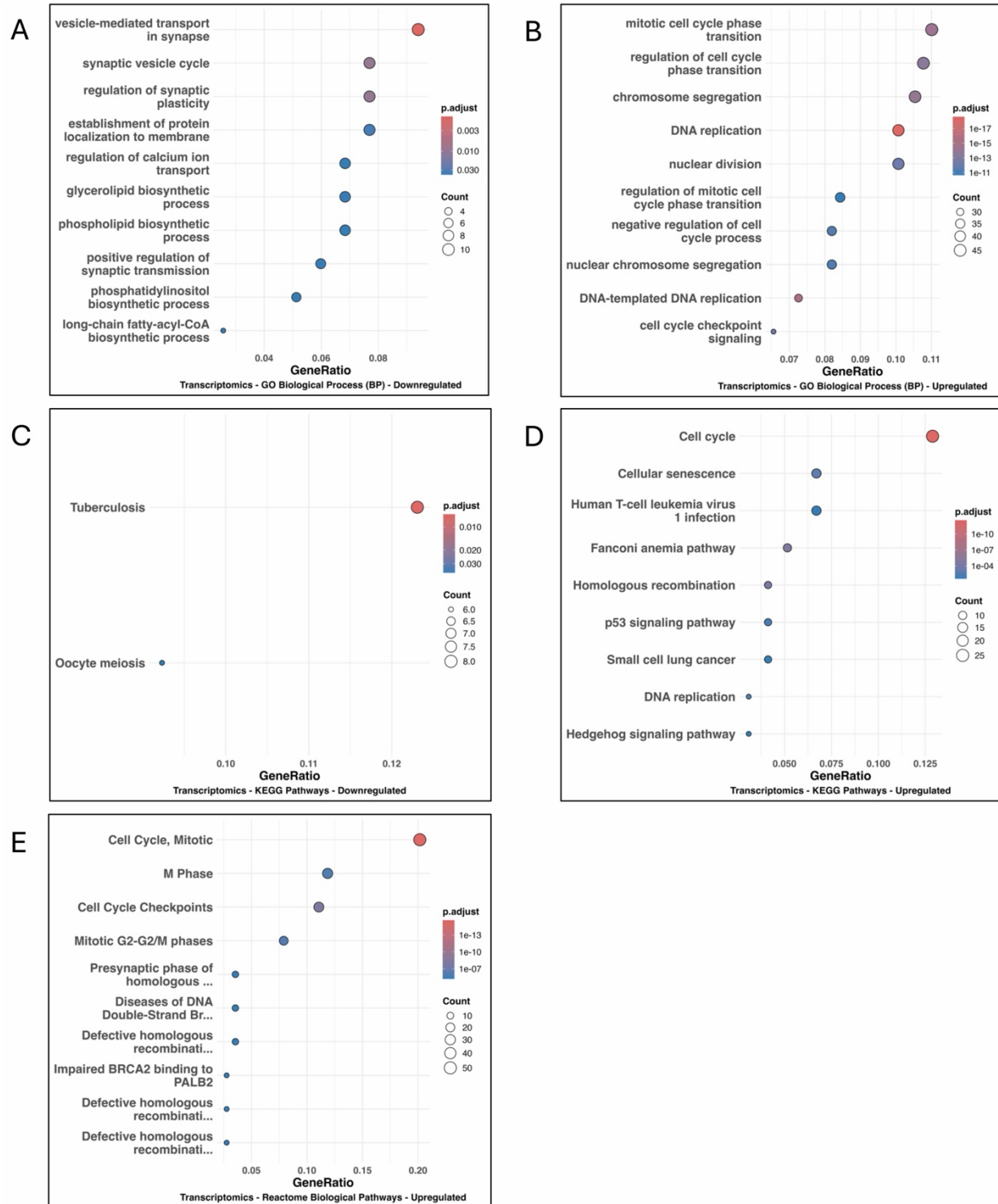
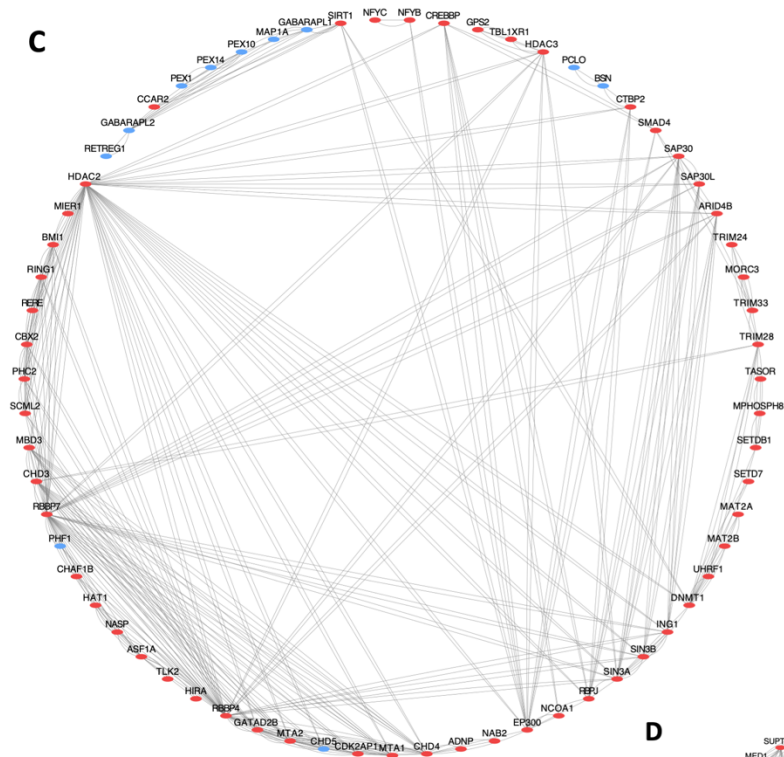


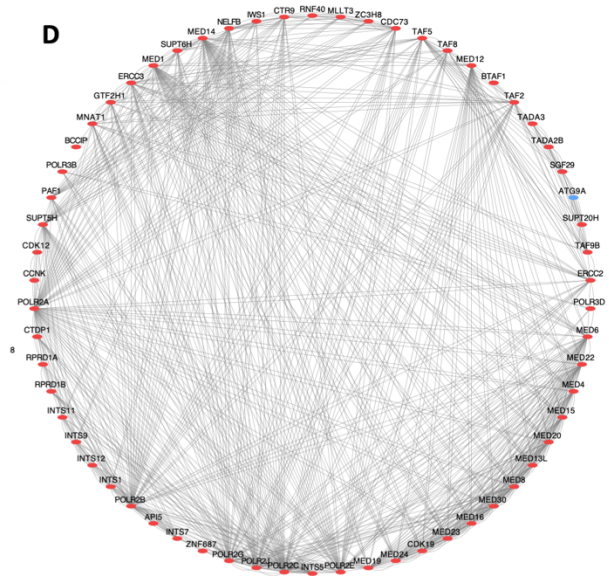
Figure S22. Transcriptomic enrichment associated with development in male T2 Cases vs. T1 Cases. Gene Ontology (Biological Process) enrichment analysis of downregulated (A) and upregulated (B) genes. Dot plots show enriched terms ranked by gene ratio, with point size indicating gene count and color representing adjusted P value. Downregulated genes were enriched for synaptic vesicle cycling, synaptic transmission, and lipid metabolic processes,

whereas upregulated genes were enriched for cell cycle progression, DNA replication, and nuclear division. KEGG pathway enrichment analysis of downregulated (**C**) and upregulated (**D**) genes. Downregulated pathways were limited and do not form a coherent program, whereas upregulated pathways were dominated by cell cycle and DNA replication processes. Reactome pathway enrichment analysis of upregulated (**E**) genes. Upregulated pathways were enriched for mitotic cell cycle, DNA repair, and homologous recombination processes.

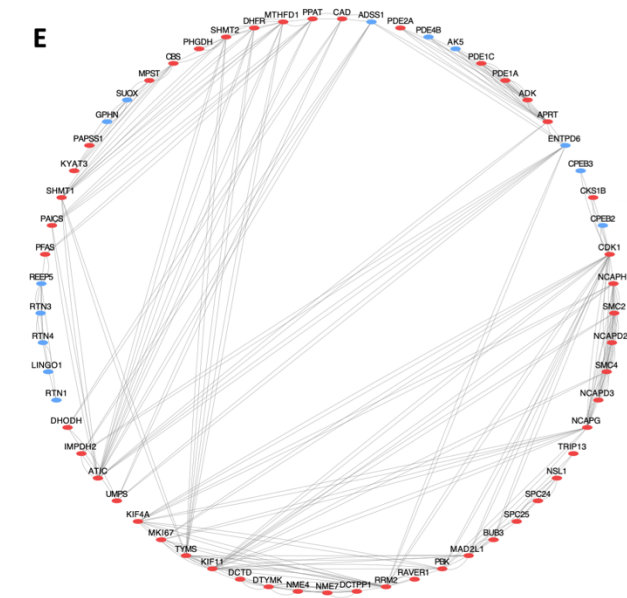
C

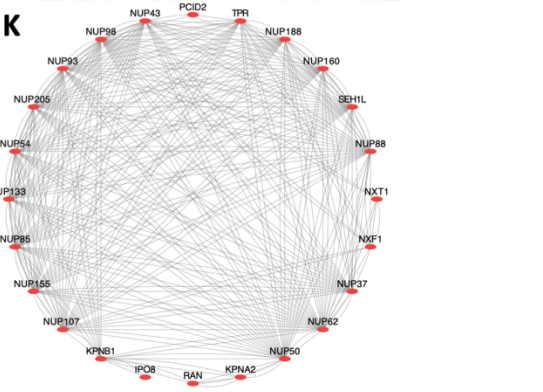
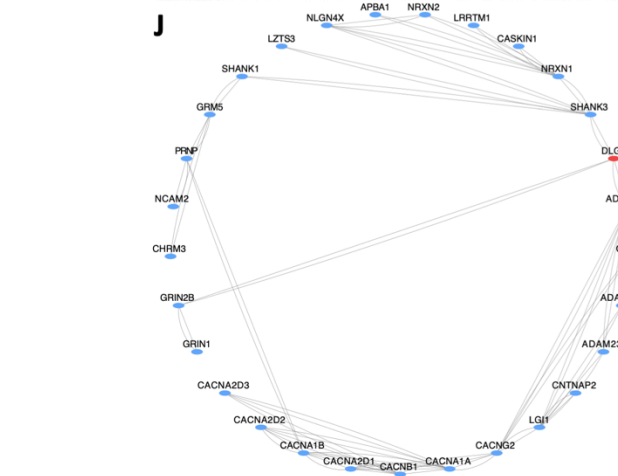
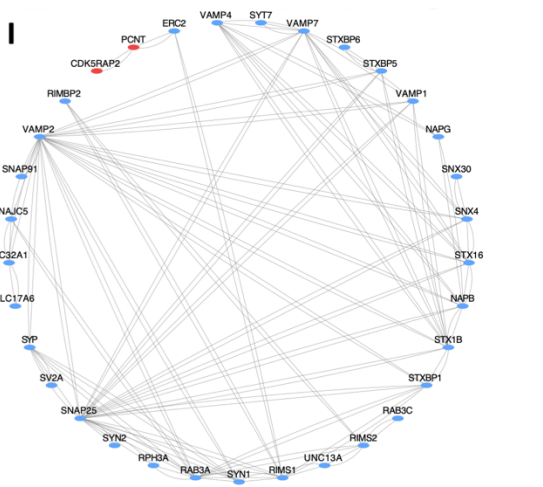
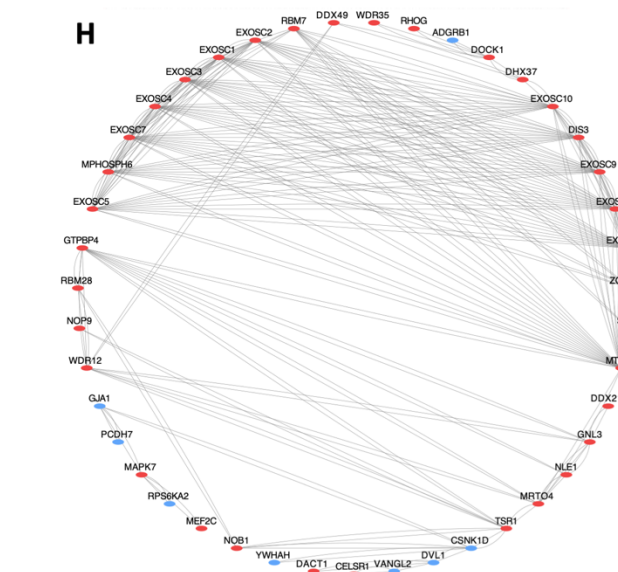
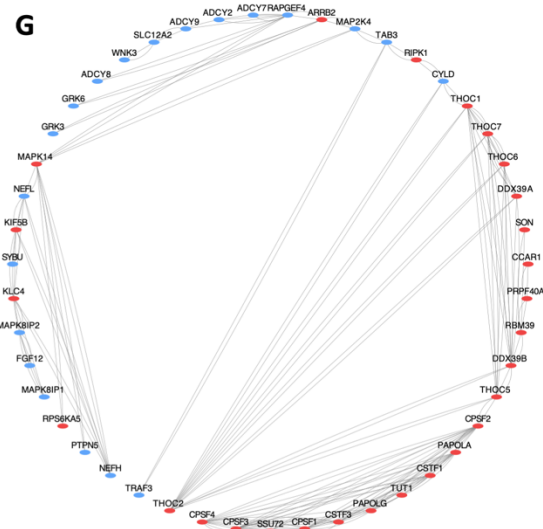
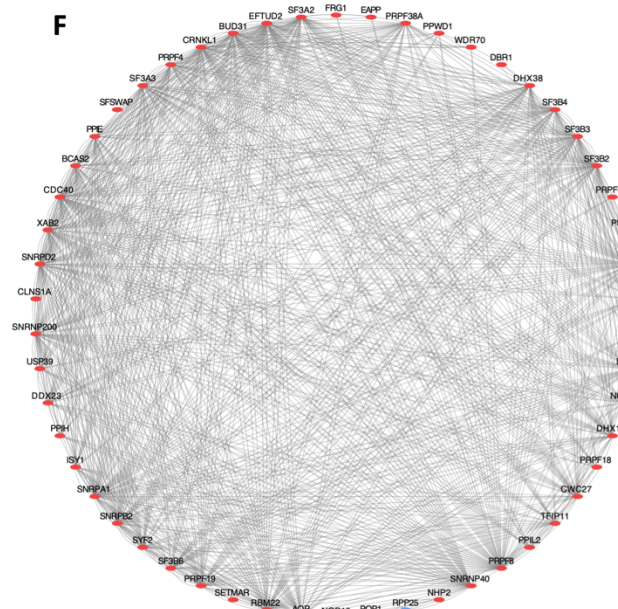


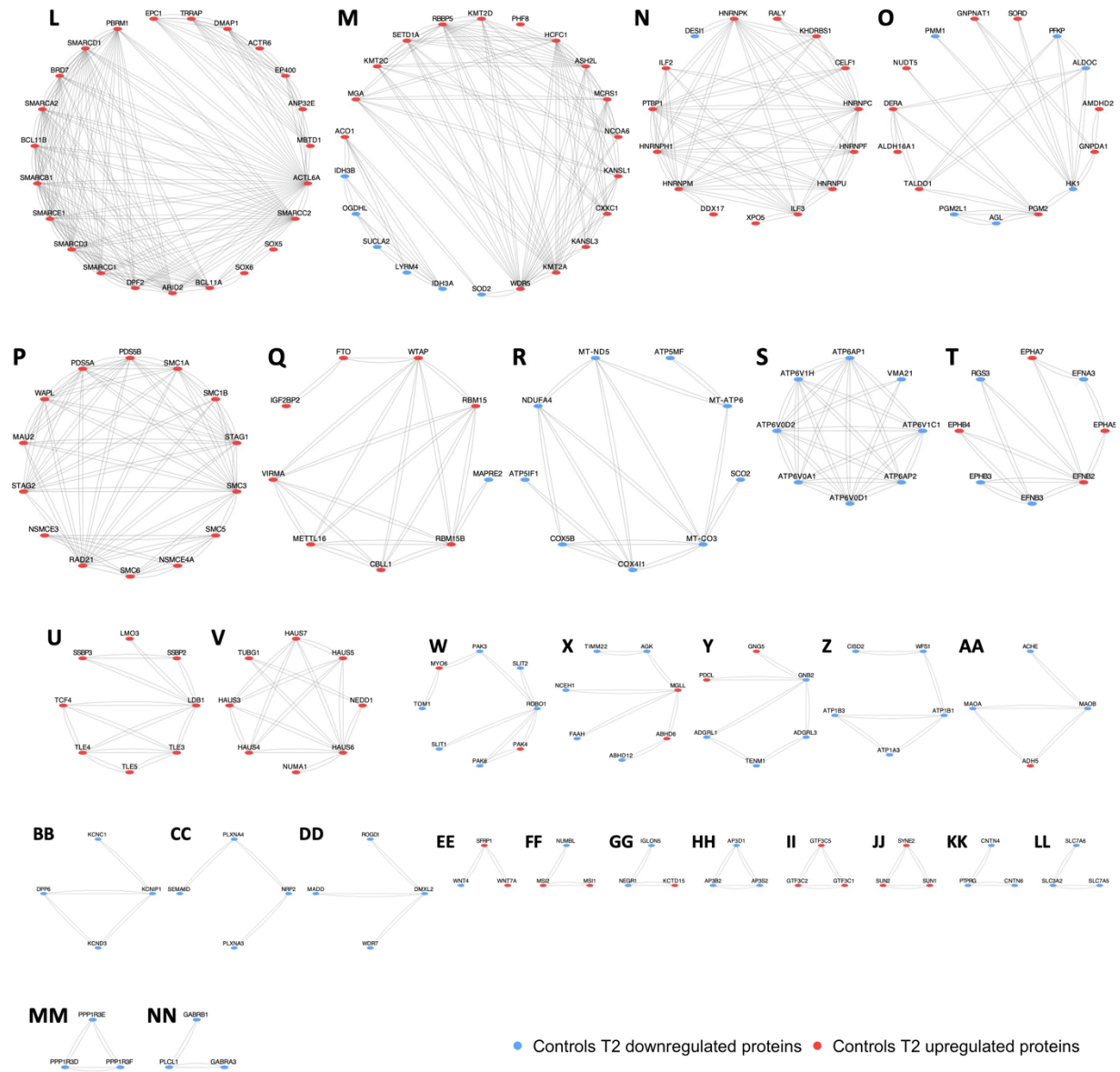
D



E







Cluster	STRING Interaction Module Enriched For	Upregulated Proteins	Downregulated Proteins
A	DNA Replication Machinery and Genome Maintenance	APEX1, APTX, ATM, CDK2, CDK4, CDK6, DCAF1, DCAF10, DCAF7, ERCC1, ERCC4, ERCC8, FANCI, FEN1, GINS1, GINS3, GINS4, GSE1, HUS1, KDM1A, KDM5A, LIG1, LRWD1, MAD2L2, MCM2, MCM3, MCM4, MCM5, MCM6, MCM7, MCM8, MRE11, MSH2, MSH6, ORC2, ORC3, ORC5, PARP1, PAXX, PCNA, PIAS3, PIAS4, POLA1, POLA2, POLB, POLD1, POLD2, POLD3, POLE3, POLE4, PRIM1, PRIM2, PRKDC, RAD50, RB1, RBL2, RCOR1, RCOR2, RCOR3, RFC1, RFC2, RFC3, RFC4, RFC5, RNASEH2A, RNASEH2B, RNASEH2C, RPA1, RPA2, RPA3, RRM1, SAE1, TDG, UBA2, UBE2I, UNG, XRCC5, XRCC6, ZMYM2, ZNF451	
AA	Monoamine Oxidation and Neurotransmitter Catabolism	ADH5	ACHE, MAOA, MAOB
B	PI3K Signaling and Neuronal Ion Channel Regulation	ARHGEF1, CIAO2A, CIAO2B, DAB1, EZR, FARP2, GSN, IGF1R, IQGAP1, ITGA2, LGALS3, MSN, PIK3R2, PLCB3, PRKD2, ROCK1, RPS6KB1, SDCBP	ADD3, ALCAM, AMPH, ANK2, ANK3, BIN1, CD44, CHRNA4, DEPTOR, DNAJC6, DNM1, ERBB4, HCN2, HCN3, HCN4, IL1RAP, INPP1, INPP4B, INPP5A, INPP5F, IRS1, ITGA3, ITPR2, JAK2, KCNQ2, KIT, L1CAM, NHERF2, OCRL, PHETA1, PIK3R1, PIP5K1C, PLCB4, PNKD, PRKCB, PRKCE, PRR5, PRRT2, SCN2A, SCN3A, SCN3B, SCN9A, SDC2, SH3GL3, SHC2, SHROOM2, SLC25A6, SPTAN1, SPTBN1, SYNJ1, TRIM16, VAV3
BB	Kv4 Potassium Channel Complex and Neuronal Excitability		DPP6, KCNC1, KCND3, KCNIP1

C	Chromatin Remodeling Complexes and Histone Deacetylation	ADNP, ARID4B, ASF1A, BMI1, CBX2, CCAR2, CDK2AP1, CHAF1B, CHD3, CHD4, CREBBP, CTBP2, DNMT1, EP300, GATAD2B, GPS2, HAT1, HDAC2, HDAC3, HIRA, ING1, MAT2A, MAT2B, MBD3, MIER1, MORC3, MPHOSPH8, MTA1, MTA2, NAB2, NASP, NCOA1, NFYB, NFYC, PHC2, RBBP4, RBBP7, RBPJ, RERE, RING1, SAP30, SAP30L, SCML2, SETD7, SETDB1, SIN3A, SIN3B, SIRT1, SMAD4, TASOR, TBL1XR1, TLK2, TRIM24, TRIM28, TRIM33, UHRF1	BSN, CHD5, GABARAPL1, GABARAPL2, MAP1A, PCLO, PEX1, PEX10, PEX14, PHF1, RETREG1
CC	Semaphorin–Plexin Signaling and Axon Guidance		NRP2, PLXNA3, PLXNA4, SEMA6D
D	RNA Polymerase II Transcription Machinery and Mediator Regulation	API5, BCCIP, BTAF1, CCNK, CDC73, CDK12, CDK19, CTDP1, CTR9, ERCC2, ERCC3, GTF2H1, INTS1, INTS11, INTS12, INTS5, INTS7, INTS9, IWS1, MED1, MED12, MED13L, MED14, MED15, MED16, MED19, MED20, MED22, MED23, MED24, MED30, MED4, MED6, MED8, MLLT3, MNAT1, NELFB, PAF1, POLR2A, POLR2B, POLR2C, POLR2E, POLR2G, POLR2J, POLR3B, POLR3D, RNF40, RPRD1A, RPRD1B, SGF29, SUPT20H, SUPT5H, SUPT6H, TADA2B, TADA3, TAF2, TAF5, TAF8, TAF9B, ZC3H8, ZNF687	ATG9A
DD	Rab3/Rabconnectin Vesicle Trafficking and Synaptic Regulation		DMXL2, MADD, ROGDI, WDR7
E	Cell Cycle Progression and Nucleotide Biosynthesis	ADK, APRT, ATIC, BUB3, CAD, CBS, CDK1, CKS1B, DCTD, DCTPP1, DHFR, DHODH, DTYMK, IMPDH2, KIF11, KIF4A, KYAT3, MAD2L1, MKI67, MPST, MTHFD1, NCAPD2, NCAPD3, NCAPG, NCAPH, NME4, NME7, NSL1, PAICS, PAPSS1, PBK, PDE1A, PDE1C, PDE2A, PFAS, PHGDH, PPAT, RAVR1, RRM2, SHMT1, SHMT2, SMC2, SMC4, SPC24, SPC25, TRIP13, TYMS, UMP5	ADSS1, AK5, CPEB2, CPEB3, ENTPD6, GPHN, LINGO1, PDE4B, REEP5, RTN1, RTN3, RTN4, SUOX
EE	WNT Ligand Signaling and Developmental Patterning	SFRP1, WNT7A	WNT4
F	Spliceosomal snRNP Assembly and Pre-mRNA Splicing	AQR, BCAS2, BUD31, CDC40, CLNS1A, CRNKL1, CWC27, DBR1, DDX23, DDX42, DDX46, DHX15, DHX16, DHX38, EAPP, EFTUD2, FRG1, ISY1, NCBP1, NHP2, NOP10, POP1, PPIE, PPIH, PPI2, PPWD1, PRPF18, PRPF19, PRPF38A, PRPF39, PRPF4, PRPF8, PUF60, RBM22, SETMAR, SF3A2, SF3A3, SF3B1, SF3B2, SF3B3, SF3B4, SF3B6, SFSWAP, SNRNP200, SNRNP40, SNRPA1, SNRPB2, SNRPD2, SYF2, TFIP11, USP39, WDR70, XAB2	RPP25
FF	Neural Stem Cell RNA Binding and Notch Fate Regulation	MSI1, MSI2	NUMBL
G	mRNA Cleavage and Polyadenylation with MAPK Signaling	ARRB2, CCAR1, CPSF1, CPSF2, CPSF3, CPSF4, CSTF1, CSTF3, DDX39A, DDX39B, KIF5B, KLC4, MAPK14, PAPOLA, PAPOLG, PRPF40A, RBM39, RIPK1, RPS6KA5, SON, SSU72, THOC1, THOC2, THOC5, THOC6, THOC7, TUT1	ADCY2, ADCY7, ADCY8, ADCY9, CYLD, FGF12, GRK3, GRK6, MAP2K4, MAPK8IP1, MAPK8IP2, NEFH, NEFL, PTPN5, RAPGEF4, SLC12A2, SYBU, TAB3, TRAF3, WNK3
GG	IgLON Adhesion Molecules and Neuronal Connectivity	KCTD15	IGLON5, NEGR1
H	RNA Exosome Surveillance and Ribosomal Biogenesis	CELSR1, DACT1, DDX21, DDX49, DHX37, DIS3, DOCK1, EXOSC1, EXOSC10, EXOSC2, EXOSC3, EXOSC4, EXOSC5, EXOSC6, EXOSC7, EXOSC8, EXOSC9, GNL3, GTPBP4, MAPK7, MEF2C, MPHOSPH6, MRT04, MTREX, NLE1, NOB1, NOP9, RBM28, RBM7, RHOG, SRRT, TSR1, WDR12, WDR35, ZCCHC8	ADGRB1, CSNK1D, DVL1, GJA1, PCDH7, RPS6KA2, VANGL2, YWHAH
HH	AP-3 Vesicle Trafficking Complex and Synaptic Transport		AP3B2, AP3D1, AP3S2
I	Synaptic Vesicle Docking and Neurotransmitter Release	CDK5RAP2, PCNT	DNAJC5, ERC2, NAPB, NAPG, RAB3A, RAB3C, RIMBP2, RIMS1, RIMS2, RPH3A, SLC17A6, SLC32A1, SNAP25, SNAP91, SNX30, SNX4, STX16, STX1B, STXBP1, STXBP5, STXBP6, SV2A, SYN1, SYN2, SYP, SYT7, UNC13A, VAMP1, VAMP2, VAMP4, VAMP7
II	RNA Polymerase III Transcription Complex Assembly	GTF3C1, GTF3C2, GTF3C5	
J	Postsynaptic Receptor Scaffold and Glutamatergic Signaling	DLG2	ADAM11, ADAM22, ADAM23, APBA1, CACNA1A, CACNA1B, CACNA2D1, CACNA2D2, CACNA2D3, CACNB1, CACNG2, CASKIN1, CHRM3, CNTNAP2, GRIA4, GRIN1, GRIN2B, GRM5, LGI1, LRRTM1, LZTS3, NCAM2, NLGN4X, NRXN1, NRXN2, PRNP, SHANK1, SHANK3
JJ	LINC Nuclear Envelope Complex and Nuclear Positioning	SUN1, SUN2, SYNE2	
K	Nuclear Pore Complex Assembly and Nucleocytoplasmic Transport	IPO8, KPN2A, KPNB1, NUP107, NUP133, NUP155, NUP160, NUP188, NUP205, NUP37, NUP43, NUP50, NUP54, NUP62, NUP85, NUP88, NUP93, NUP98, NXF1, NXT1, PCID2, RAN, SEH1L, TPR	
KK	Contactin Adhesion Complexes and Axon Guidance		CNTN4, CNTN6, PTPRG
L	SWI/SNF Chromatin Remodeling and Transcriptional Regulation	ACTL6A, ACTR6, ANP32E, ARID2, BCL11A, BCL11B, BRD7, DMAP1, DPF2, EP400, EPC1, MBTD1, PBRM1, SMARCA2, SMARCB1, SMARCC1, SMARCC2, SMARCD1, SMARCD3, SMARCE1, SOX5, SOX6, TRRAP	
LL	Large Neutral Amino Acid Transport and mTOR Nutrient Signaling		SLC3A2, SLC7A5, SLC7A6
M	SET1/MLL Histone Methyltransferase Complex and Chromatin Activation	ACO1, ASH2L, CXXC1, HCF1, KANSL1, KANSL3, KMT2A, KMT2C, KMT2D, MCRS1, MGA, NCOA6, PHF8, RBBP5, SETD1A, WDR5	IDH3A, IDH3B, LYRM4, OGDHL, SOD2, SUCLA2
MM	Protein Phosphatase-1 Glycogen Regulation and Metabolic Control		PPP1R3D, PPP1R3E, PPP1R3F
N	Heterogeneous Nuclear RNP Complexes and RNA Processing	CELF1, DDX17, HNRNPC, HNRNPF, HNRNPH1, HNRNPK, HNRNPM, HNRNPU, ILF2, ILF3, KHDRBS1, PTBP1, RALY, XPO5	DESI1
NN	GABA Receptor Signaling and Inhibitory Synaptic Regulation		GABRA3, GABRB1, PLCL1
O	Glycolysis and Hexose Phosphate Metabolism	ALDH16A1, AMDHD2, DERA, GNPDA1, GNPAT1, NUDT5, PGM2, SORD, TALDO1	AGL, ALDOC, HK1, PFKF, PGM2L1, PMM1
P	Cohesin Complex Assembly and Chromosome Segregation	MAU2, NSMCE3, NSMCE4A, PDS5A, PDS5B, RAD21, SMC1A, SMC1B, SMC3, SMC5, SMC6, STAG1, STAG2, WAPL	
Q	m6A RNA Methylation Machinery and Post-transcriptional Regulation	CBLL1, FTO, IGF2BP2, METTL16, RBM15, RBM15B, VIRMA, WTAP	MAPRE2
R	Mitochondrial Electron Transport and Oxidative Phosphorylation		ATP5IF1, ATP5MF, COX4I1, COX5B, MT-ATP6, MT-CO3, MT-ND5, NDUFA4, SCO2

S	V-ATPase Proton Pump Assembly and Vesicular Acidification		ATP6AP1, ATP6AP2, ATP6V0A1, ATP6V0D1, ATP6V0D2, ATP6V1C1, ATP6V1H, VMA21
T	Ephrin-EPH Receptor Signaling and Axon Guidance	EFNB2, EPHA5, EPHA7, EPHB4	EFNA3, EFNB3, EPHB3, RGS3
U	TCF4 Transcriptional Regulation and Neuronal Differentiation	LDB1, LMO3, SSBP2, SSBP3, TCF4, TLE3, TLE4, TLE5	
V	Augmin Microtubule Nucleation and Mitotic Spindle Assembly	HAUS3, HAUS4, HAUS5, HAUS6, HAUS7, NEDD1, NUMA1, TUBG1	
W	SLIT-ROBO Signaling and Axon Guidance	MYO6, PAK4	PAK3, PAK6, ROBO1, SLIT1, SLIT2, TOM1
X	Endocannabinoid Hydrolysis and Lipid Metabolism	ABHD6, MGLL	ABHD12, AGK, FAAH, NCEH1, TIMM22
Y	Latrophilin Adhesion Receptors and Transsynaptic Signaling	GNG5, PDCL	ADGRL1, ADGRL3, GNB2, TENM1
Z	Na ⁺ /K ⁺ ATPase Ion Transport and ER Stress Regulation		ATP1A3, ATP1B1, ATP1B3, CISD2, WFS1

Figure S23. STRING interaction network modules identified from proteomic analysis of female fetal brain development in the absence of prenatal cannabis exposure (Controls T2 vs. T1). (A–NN) STRING-derived proteomic interaction subnetworks constructed from significantly altered proteins identified in female Controls T2 vs. T1. Blue nodes indicate proteins downregulated in T2 Controls, whereas red nodes indicate proteins upregulated in T2 Controls. The table summarizes the major functional modules represented within each interaction cluster.

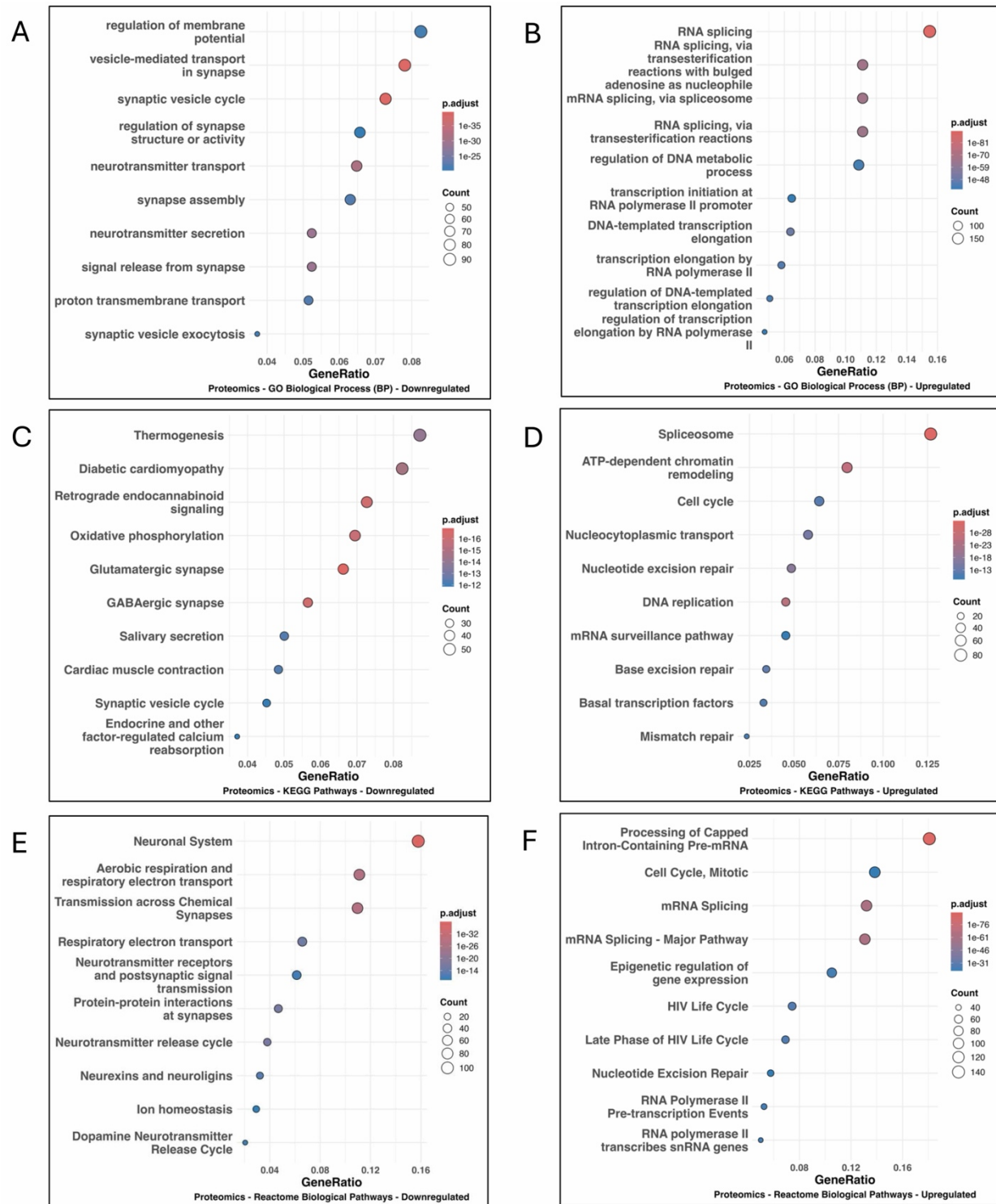


Figure S24. Proteomic enrichment associated with development in male T2 Cases vs. T1 Cases. Gene Ontology (Biological Process) enrichment analysis of downregulated (A) and upregulated (B) proteins. Dot plots show enriched terms ranked by gene ratio, with point size indicating protein count and color representing adjusted P value. Downregulated proteins were

enriched for synaptic vesicle cycling, neurotransmitter transport, and synapse organization, whereas upregulated proteins were enriched for RNA splicing, transcriptional regulation, and DNA metabolic processes. KEGG pathway enrichment analysis of downregulated (**C**) and upregulated (**D**) proteins. Downregulated pathways include oxidative phosphorylation, retrograde endocannabinoid signaling, and synaptic transmission pathways, whereas upregulated pathways were enriched for spliceosome, chromatin remodeling, and cell cycle processes. Reactome pathway enrichment analysis of downregulated (**E**) and upregulated (**F**) proteins. Downregulated pathways were enriched for neuronal system, synaptic transmission, and respiratory electron transport, whereas upregulated pathways were enriched for cell cycle progression, RNA processing, and DNA repair pathways. Dot plots show enriched terms ranked by gene ratio, with point size indicating gene count and color representing adjusted P value.