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THOUGHT LEADERS INVITED REVIEW

Roles of alternative polyadenylation in psychiatric disorder risk

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Alternative polyadenylation (APA) is a pervasive regulatory mechanism in the human brain that controls the stability and cellular localization of mRNA transcripts. Single-nucleotide polymorphisms associated with psychiatric disorders may exert their deleterious effects by altering 3′ untranslated site usage, which may change the stability and processing of mRNA transcripts. The authors previously performed a 3′APA transcriptomic-wide association study using the DePars2 framework and the GTEx v8, PsychENCODE, and ROS/MAP datasets to identify APA-linked genes associated with eleven brain disorders. Here we focus on 3′APA-linked genes associated with the major psychiatric conditions: schizophrenia, bipolar disorder, and depression. There are 286 APA-linked genes associated with these psychiatric disorders, and 60%–65% of these genes have not been associated with the major psychiatric disorders through their expression and/or splicing. Protein–protein interaction networks indicate that APA-linked genes associated with schizophrenia are involved in intracellular transport and cellular localization pathways. Future research is needed to elucidate the role of alternative 3′ untranslated region usage of APA-linked genes on neuronal function and phenotypic expression in psychiatric disorders.

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Introduction

Over the past 15 years, genome-wide association studies (GWAS) have uncovered hundreds of single-nucleotide polymorphisms (SNPs) associated with the major psychiatric disorders. However, translating these genetic associations to biologically relevant mechanisms remains a major challenge. The majority of GWAS-significant SNPs localize to non-coding regions of the genome and often reside within loci demonstrating a high degree of linkage disequilibrium. Thus, identifying causal genes responsible for the phenotypic expression of psychiatric conditions can be an arduous process. Transcriptome-wide association studies (TWAS) serve as one method of nominating putative causal genes by integrating population-level transcriptomic datasets and GWAS summary statistics (1–4). Leveraging population-level datasets with both genotype and gene expression information, TWAS impute the *cis*-component of gene expression of common variants to prioritize genes at trait-associated loci, referred to as quantitative trait loci (QTL).

While the majority of TWAS have focused on total gene expression, it has become increasingly realized that disease-relevant SNPs may have regulatory effects that alter transcript splicing, epigenetic regulation, and protein expression, among many other potential mechanisms (5, 6). Recently, alternative 3′ untranslated polyadenylation site usage has been recognized as a mechanism by which GWAS significant SNPs may affect the abundance of transcript isoforms (7, 8). Alternative polyadenylation (APA) is a pervasive regulatory mechanism of mRNA trafficking and translation that is particularly critical in the central nervous system (CNS). Aberrant APA plays a role in multiple neurological disorders, including Parkinson's disease (PD) (9), Huntington's disease (10), and certain forms of intellectual disability (11). Unlike total expression levels or alternatively spliced mRNA isoforms, the impact of APA on disease-related gene expression has not been accounted for in the majority of TWAS analyses.

Polyadenylation is an important step in the production of mature mRNA species. Following transcription, the 3′ end of a mRNA is cleaved at either a proximal or distal 3′ APA site, and a poly(A) tail is synthesized at the 3′ terminus. APA sites are located within the 3′ untranslated regions (3′UTRs) of genes. Approximately 70% of human genes include multiple APA sites that produce 3′UTRs of different lengths (12). Use of a proximal APA site produces a shorter mRNA with a short 3′UTR, while use of a distal APA site produces a longer mRNA with a long 3′UTR (Figure 1A). 3′UTRs contribute to posttranscriptional regulation of gene expression in multiple ways. Regulatory elements residing within 3′UTRs affect mRNA stability, translation efficiency, and cellular localization (13). 3′UTRs produced by distal APA sites tend to contain more target sequences for RNA-binding proteins and microRNAs (miRNA), which can destabilize mRNAs and promote degradation (Figure 1B) (14, 15). As longer 3′UTRs tend to contain a greater number of regulatory elements, genetic mutations that lead to a change in APA site usage can alter mRNA stability.

APA may serve as a regulatory mechanism with important developmental implications. As cells and tissues evolve from primitive to fully differentiated forms, the APA of their expressed transcripts often changes. Transcriptomic studies of embryonic mouse tissue have shown that mouse genes tend to express transcripts with longer 3′UTRs as embryonic development progresses (16). Additionally, 3′UTR length varies according to cell type. Amongst the major cell types, stromal cells and neuronal cell types express transcripts with the longest 3′UTRs, while blood cells, hepatocytes, chondrocytes, and osteoblasts express transcripts with the shortest 3′UTRs (17). Furthermore, among cells of a given lineage, use of long 3′UTRs tends to increase as primitive cells differentiate to mature cell

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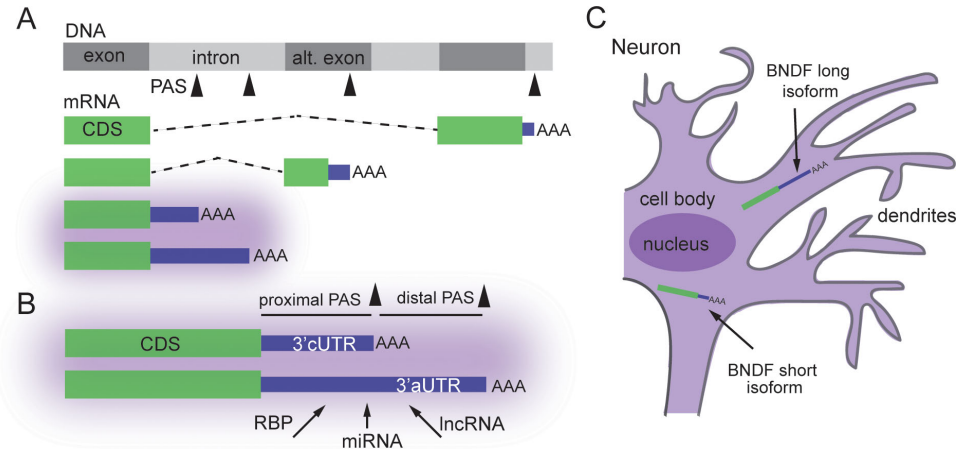

Figure 1. Alternative polyadenylation (APA). (**A**) Splicing can lead to mRNA isoforms with different 3′ UTRs and/or APA based on is polyadenylation site (PAS) usage in various combinations. (**B**) Two mRNA isoforms with different 3′ UTRs due to APA. Only the constitutive UTR (cUTR) is present in the short isoform, whereas the the alternative UTR (aUTR) is also present in the long isoform. Interactions between the UTRs and RNA-binding proteins (RBPs), miRNAs and long non-coding RNAs (lncRNAs) can have functional consequences. (**C**) BDNF 3′ UTR-APA isoform localization in neurons supports dendritic protein synthesis—the long isoform localizes to dendrites more than the short isoform (adapted from Tian and Manley, 2017, Nat. Rev. Mol. Cell Biol).

types. For example, in the hematopoietic lineage, the switch from short to long 3′UTRs is explained by the evolution from primitive to definitive erythropoiesis (17). Thus, APA is a dynamic process that is particularly critical during prenatal development.

Changes in APA site usage may alter the distribution and localization of translated proteins. For example, the short isoform of brain-derived neurotropic factor (BDNF) is restricted to the neural cell body while the long isoform localizes to dendrites (Figure 1C) (18). The role of 3′UTRs in influencing the cellular localization of mRNA is particularly consequential for neurons since dendrites, axon terminals and cell bodies have distinct roles in health and disease. APA of the alpha synuclein (aSyn) transcript was implicated in a familial form of PD (9). For example, SNPs associated with a familial form of PD were found to increase the abundance of the long 3′UTR isoform of alpha synuclein relative to the short 3′UTR isoform. Overproduction of the long 3′UTR isoform was found to lead to the accumulation of alpha synuclein protein with the mitochondria of neurons, leading to neuronal dysfunction. Thus, genetic variants that alter APA site usage may have a significant impact on cellular homeostasis, particularly in the brain where the majority of transcripts are regulated by APA.

APA in Psychiatric Conditions

The CNS harbors the longest 3′UTRs of any tissue, suggesting that regulatory elements within 3′UTRs play an important role in protein expression throughout the brain. While traditional TWAS methods have identified mRNA expression levels and isoform level changes due to alternative splicing, they have not investigated APA. To address this gap, Cui *et al.* (8) performed a 3′UTR TWAS to identify local genetic effects associated with variation of 3′UTR usage among the GTEx v8 (19), ROS/MAP (20), and psychENCODE (21) datasets. The authors implemented the DaPars2 framework (22) to calculate the percentage of distal poly(A) site usage and to identify 3′UTR lengthening and shortening events. The DePars2 framework calculates a 3′UTR usage value for each transcript across samples. A linear regression framework is then applied to test the association between normalized values of 3′UTR usage and SNPs within an interval of 1Mbp of the 3′UTR region, adjusting for covariates. They identified *cis*-SNPs associated with 3′UTR usage and examined the association between GWAS summary statistics and 3′UTR usage. Transcriptome and individual-matched genotype data from the ROS/MAP, PsychENCODE, and GTEx Consortia was then implemented to establish 3′aTWAS single-tissue prediction models for 3′UTR usage using FUSION (2). They discovered 354 APA-linked disease susceptibility genes identified among 11 brain disorders, including the major psychiatric disorders, schizophrenia (SCZ), bipolar disorder (BD), and depression (DEP) (Figure 2A–C). The largest number of 3′aTWAS-signficant genes was found for SCZ, with 281 non-HLA APA-linked genes associated with the disorder among the three datasets. A comprehensive list of APA-linked genes for SCZ, BD, and DEP from Cui et al. can be found in Supplementary Table S1.

Some of the genetic risk loci associated with APA (3′aQTLs) were also implicated in expression and splicing TWAS. Many 3′aTWAS genes had a more significant 3′aQTL signal than eQTL or sQTL signals, indicating that their GWAS signal is better explained by their effect on APA. One validated example of this is the detection of a known APA-susceptibility gene, SNCA (encoding aSyn) associated with PD. SNCA was the most significant gene identified in all three reference panels, and longer 3′UTR usage was associated with increased PD risk, consistent with prior evidence (9). The leading PD GWAS SNP near *SNCA* is less strongly associated with differential expression and splicing, supporting that 3′UTR usage is primarily responsible for PD risk. Among the major psychiatric disorders, 49 of 151 (32%) non-HLA, APA-linked genes associated with SCZ were also implicated in expression TWAS, splicing TWAS, or both. Eighty-seven genes, including *ZFN592*, *PBX2* and *RBX1*, were associated with SCZ only through APA and not previously implicated in other TWAS (Figure 3A). Seventeen of 71 (24%) APA-linked genes associated with BD were also implicated in expression and splicing TWAS (Figure 3B), and 24 of 64 (37.5%) APA-linked genes associated with DEP were also implicated through expression and/or splicing (Figure 3C).

In the following paragraphs, we will discuss the implications of some APA-linked genes, identified in Cui *et al.* associated with the major psychiatric conditions, SCZ, BD, and DEP.

DDHD2 (DDHD-Domain-Containing 2)

The *DDHD2* gene on chromosome 8p encodes a triacylglyceride hydrolase that is involved in membrane trafficking between the endoplasmic reticulum and Golgi body. *DDHD2* is ubiquitously expressed in the brain, and multiple transcript variants result from alternative splicing. Missense mutations in *DDHD2* cause an autosomal recessive form of hereditary spastic paraplegia, which includes intellectual disability among its clinical features (23). Furthermore, *DDHD2* knockout mice demonstrate motor and cognitive deficits as well as lipid accumulation within neurons (24). Although the role of *DDHD2* in cognitive function has not been fully elucidated, *DDHD2* has been linked to caudate, putamen, and pallidum volume and is downregulated in the dorsolateral prefrontal cortex (DLPFC) of patients with SCZ (25). The 8p12 genomic region, near the *DDHD2* gene, has been identified as a significant risk locus for SCZ among Han Chinese and European populations (26, 27) as well as for autism spectrum disorder (28) and BD (6, 29). Decreased expression of *DDHD2* has been associated with SCZ in multiple TWAS (6, 30), including eQTLs derived from prenatal brain and dopaminergic neurons (6, 8, 29, 31).

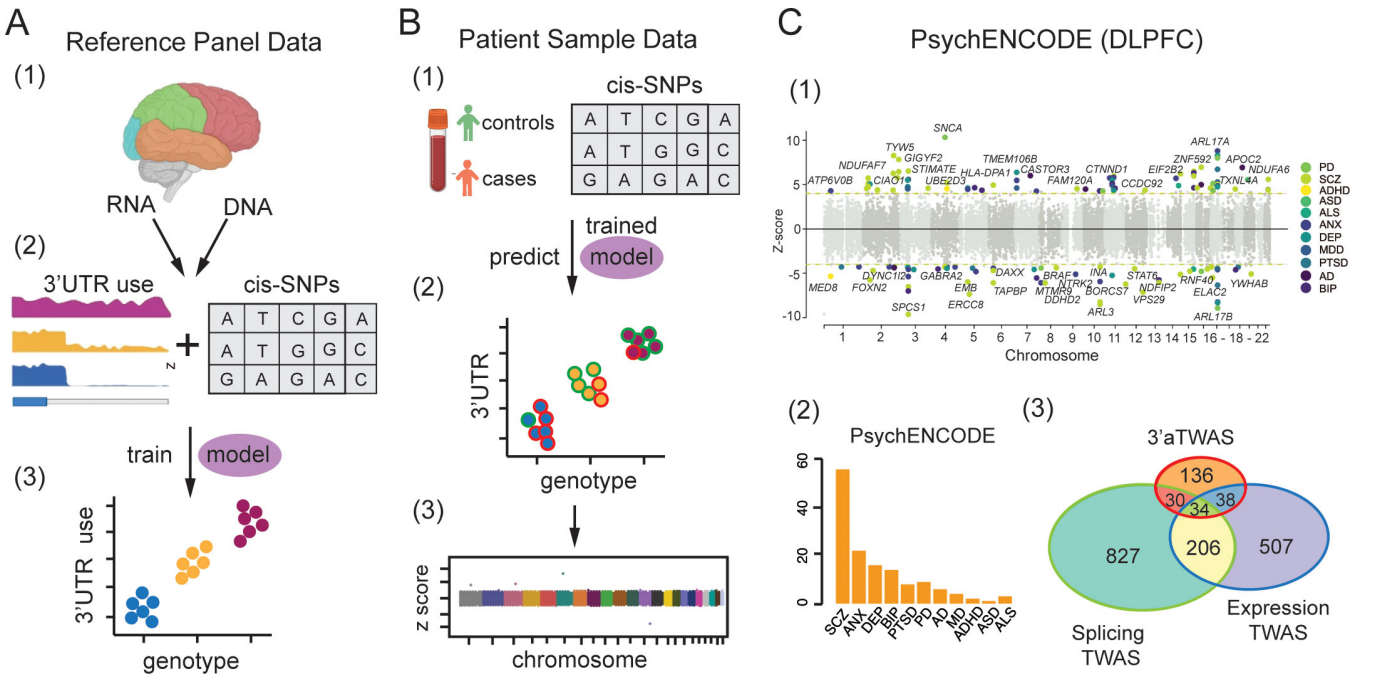

Figure 2. Psychiatric 3′aTWAS. (**A1**) RNA sequencing and matched genotype data were collected from the GTEx, ROS/MAP, and PsychENCODE cohorts as reference panels. (**A2**) 3′aQTL analysis was performed, and then a 3′aTWAS model (**A3**) was built to predict the APA usage of target genes with cis-SNPs in the reference panels. (**B1**) We used GWAS summary statistics and the (**B2**) 3′aTWAS models for each reference panel to (**B3**) perform 3′aTWAS analysis to nominate susceptibility genes in brain disorders. (**C1**) APA-linked susceptibility genes in brain disorders identified by 3′aTWAS (only PsychENOCDE data shown). (**C2**) Bar plot shows the number of 3′aTWAS significant genes for 11 brain disorders in PsychENCODE DLPFC. (**C3**) Venn diagram shows the overlap of 3′aTWAS significant genes for 11 brain disorders with expression and splicing TWAS (includes the GTEx, ROS/MAP, and PsychENCODE cohorts) (adapted from Cui *et al*., 2023, Nat Commun).

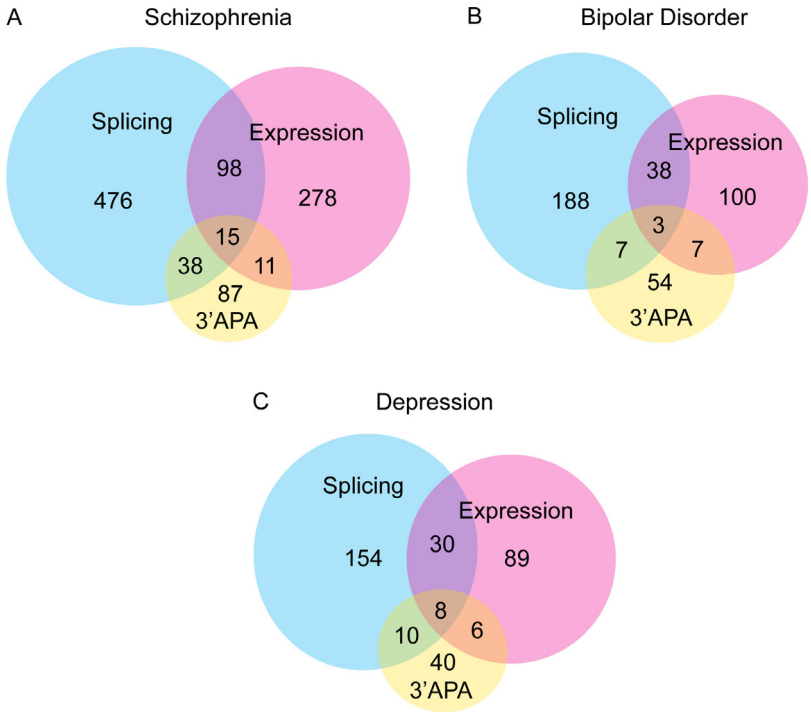

Figure 3. Venn diagrams demonstrating the overlap between significant genes implicated in the expression, splicing and 3′aTWAS in Cui *et al*. (2023) for SCZ (**A**), BD (**B**), and DEP (**C**).

In the 3′aTWAS analysis, the short 3′UTR isoform of *DDHD2* was significantly associated with SCZ in the GTEx v8, ROS/MAP, and psychENCODE datasets. This is consistent with previous analyses which identified a GWAS-significant SNP within the 3′UTR of the *DDHD2* mRNA transcript that disrupts binding of the quaking RNA-binding protein (32). Interestingly, downregulation of the quaking RNA-binding protein was associated with risk of SCZ in a large Swedish pedigree, indicating that the RNA-binding protein target sequence within the 3′UTR of *DDHD2* plays a role in risk of SCZ (33). Elimination of target sequences for RNA-binding proteins, such as that for the quaking RNA-binding protein, may occur with use of proximal 3′UTR sites that omit portions of the extended 3′UTR, yielding a similar result.

ARL3 (ADP Ribosylation Factor-Like GPTase 3)

The product of the *ARL3* gene on chromosome 10q is a GTP-binding protein that localizes to cilia and microtubules and plays a role in the formation of axons and cilia. Mutations in *ARL3* can result in ciliopathies, including neurodevelopmental disorders such as Joubert syndrome, characterized by hypoplasia of the cerebellar vermis, brainstem abnormalities, psychomotor delay, hypotonia, and retinal abnormalities (34). A SNP located within an intron of *ARL3* was significantly associated with SCZ in a Han Chinese population (35), and decreased expression of *ALR3* has been associated with SCZ in TWAS (6, 31) and in a proteome-wide association study (36). The short 3′UTR isoform was associated with SCZ in all three datasets examined in Cui *et al*., however, the biological significance of increased short 3′UTR usage by the *ARL3* gene in regards to either ciliary function or neuronal development has yet to be explored.

SNX19 (Sorting Nexin 19)

SNX19 on chromosome 11q encodes a protein that belongs to a family of sorting nexins that function in endosomal trafficking regulation and sorting. Expression and alternative splicing of *SNX19* has been associated with SCZ in multiple TWAS (6, 37–39), while short 3′UTR usage of *SNX19* was associated with SCZ in transcriptomic data from multiple brain regions of the GTEx v8 dataset. Greater expression of an isoform with skipping of exon 9 was associated with a downstream SCZ risk locus, with most unaffected individuals expressing very low levels of this transcript isoform. Skipping of exon 9 produces a frameshift that is predicted to result in the absence of the sorting C-terminal domain (38). In situ hybridization studies support that *SNX19* is localized to glutamatergic neurons in the DLPFC (40). *SNX19* may be associated with the sodium-coupled neutral amino acid transporter 1 (SLC38A1), which supplies neurons with glutamine for synthesis of neurotransmitters (40). The impact of short 3′UTR usage of *SNX19* on neuronal function has yet to be investigated.

ZNF592 (Zinc Finger RNA-binding Protein 2)

The *ZNF592* gene encodes a 1,267 amino acid zinc finger protein that is expressed in the CNS (41). Zinc finger proteins function as transcriptional regulators, mediating interactions between DNA and proteins. Missense mutations in *ZNF592* cause cerebellar ataxia with mental retardation, optic atrophy, and skin abnormalities (41). In the 3′aTWAS, short 3′UTR usage of *ZNF592* was associated with both SCZ and BD in the ROS/MAP and psychENCODE datasets. Importantly, *ZNF592* has not been previously identified in expression or splicing TWAS, indicating that the GWAS signal at this locus is almost entirely explained by alternative polyadenylation.

FADS1 (Fatty Acid Desaturase 1)

FADS1 encodes a fatty acid desaturase, which is a rate limiting enzyme in desaturation of long-chain polyunsaturated fatty acids. The *FADS1* and *FADS2* genes in 11q12.2 locus are in tight LD, and this locus has been associated with BD in multiple populations. A GWAS significant SNP at the 11q12.2 locus, containing the *FADS1/2* gene, was associated with BP in Asian populations (42, 43) and then replicated in GWAS of European populations.(44, 45) In Cui *et al*., expression, alternative splicing, and short 3′UTR usage of *FADS1* was associated with BP in the ROS/MAP dataset. Multiple mRNA isoforms of *FADS1* are generated by alternative transcript initiation, alternative polyadenylation site usage, and internal exon deletions (46). There are seven possible isoforms of *FADS1* that differ only in the length of their poly(A) tail due to use of alternative poly(A) sites.

Since the commencement of crop agriculture leading to increased intake of grain oils, there has been an increase in the proportion of individuals carrying a haplotype associated with greater *FADS1/2* activity that has a protective effect against BD (47). Transgenic mice with decreased *FADS1/2* activity demonstrate behavioral changes including bouts of hyperactivity interspersed with periods of depressive-like hypoactivity as well as abnormal circadian rhythms, suggesting that reduced FADS1/2 activity produces a robust animal model of BD (48). Furthermore, these behavioral deficits were rescued with dietary supplementation of polyunsaturated fatty acids (48). However, dietary supplementation with omega-3 fatty acids to treat mood fluctuations in BD have demonstrated mixed results (49, 50).

GABRA2 (Gamma-Aminobutyric Acid Type A Receptor Alpha 2)

GABRA2 encodes the alpha subunit of the GABAA receptor, which mediates anxiolytic-like, reward-enhancing, and anti-hyperalgesic actions of benzodiazepines (51). *GABRA2* has been implicated in alcoholism and substance abuse disorders (52, 53), and SNPs residing within GABAA receptor subunit genes have been associated with risk of BD (54–56). GABA receptor mRNAs display long 3′UTRs, and increased 3′UTR length is linked to reduced translation (57, 58). In our 3′aTWAS, short 3′UTR usage was associated with BD in the GTEx v8, ROS/MAP, and psychENCODE datasets. Strong 3′aQTLs but weak eQTLs were found for *GABRA2* in 3′aTWAS, indicating that the 3′aQTL association with *GABRA2* almost entirely explains the BD GWAS signal at this locus.

CACAN1B (Calcium Voltage-gated Channel Subunit Alpha 1B)

Genes encoding subunits of calcium channels have been repeatedly implicated in BD GWAS (44, 59, 60). *CACNA1B* encodes the alpha-1B subunit; the pore-forming subunit, of the presynaptic N-type voltage-dependent calcium channel ($Ca_V2.2$). Two mRNA isoforms of *CACNA1B* are produced by alternative splicing based on the inclusion of one of two mutually exclusive exons, e37a and e37b, which encode sequences of the C-terminus (61). Compared to channels containing e37b, channels containing e37a are trafficked more efficiently to the cell membrane and are inhibited more strongly by G-protein–coupled receptors (62, 63). E37a-rich channels are abundant in calcium/calmodulin-dependent excitatory projection neurons, including those comprising excitatory cortico-hippocampal synapses (64). Mice expressing only the e37b isoform display decreased novelty-induced anxiety, suggesting that alternative splicing of *CACN1B* influences withdrawal and anxiety-related behaviors.

It has been demonstrated in sympathetic neurons that the half-life of the alpha-1B subunit mRNA is regulated by its 3′UTR and modulated by voltage-dependent calcium entry (65). In the analysis by Cui *et al*., short 3′UTR usage, expression, and splicing of *CACNA1B* were all associated with BD in the GTEx v8 and ROS/MAP cohorts.

The replicated association of multiple calcium channel subunit genes with BD has prompted the investigation of calcium channel blockers as adjunctive therapy in the treatment of BD, however, with about half of patients demonstrating a clinical benefit (66). In a small cohort of 38 patients with BD, two SNPs in the *CACNA1B* locus were associated with treatment response to calcium channel blockers. However, no significant difference in the predicted expression of *CACNA1B* was found between responders and non-responders (67).

ARL17A (ADP Ribosylation Factor Like GTPase 17A)

ARL17A encodes a GTP-binding protein which is a member of the ADP-ribosylation factor family. ADP ribosylation factor like GTPase 17A plays a role in vesicle-mediated intracellular protein transport between the endoplasmic reticulum and the Golgi apparatus and is important for neuronal development. Long 3′UTR usage of ARL17A was significantly associated with both SCZ and DEP among the GTEx v8, ROS/MAP, and psychENCODE datasets. Although the contribution of *ARL17A* to psychiatric conditions has yet to be fully elucidated, expression of *ARL17A* in the DLPFC, putamen, and cerebellum has been implicated in SCZ (68). *ARL17A* expression has additionally been associated with intracranial brain volume (69), thalamic volume in childhood (68), and reaction time and cognitive function (69).

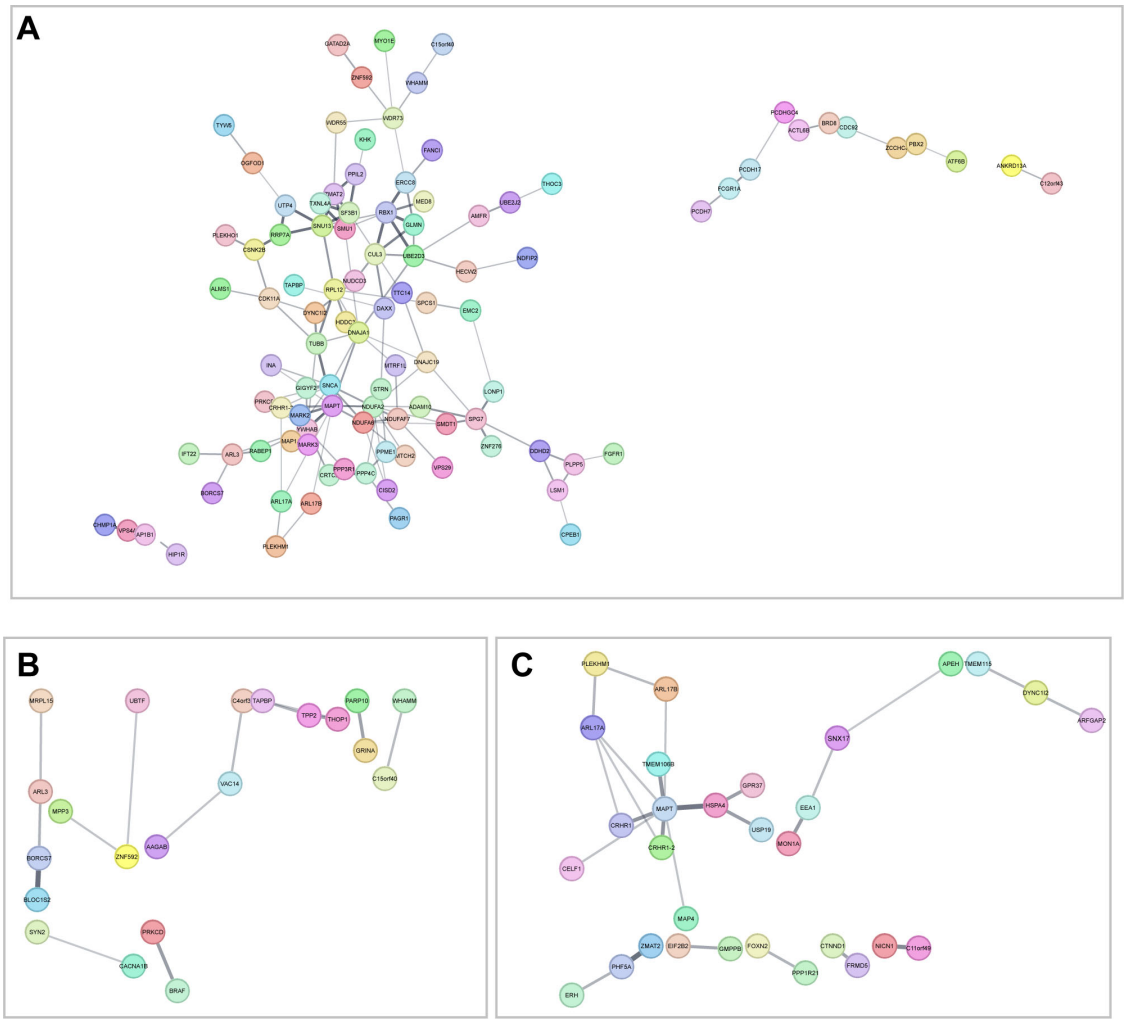

Figure 4. Protein–protein interaction networks for 3′aTWAS significant genes for SCZ (**A**), BD (**B**), and DEP (**C**). Pathway analysis demonstrates that 3′aTWAS significant genes associated with SCZ are enriched in intracellular transport and cellular localization pathways.

MTCH2 (Mitochondrial Carrier Homolog 2)

MTCH2 encodes a member of the SLC25 family of nuclear-encoded transporters, which is localized to the outer mitochondrial membrane and plays an important role in oxidative phosphorylation (70). *MTCH2* has been associated with body-mass index in multiple obesity GWAS (71, 72) as well as with neuroticism (73) and susceptibility to loneliness (74). The SNP implicated in neuroticism was found to regulate *MTCH2* in the cerebellum (73). Long 3′UTR usage by *MTCH2* was significantly associated with DEP in all three reference panels. Manjunath and colleagues (75) demonstrated that transcription of *MTCH2* is subject to stop codon readthrough in which three different transcript isoforms may be produced depending on which stop codon is used. The long isoform localizes to the cytoplasm where it is rapidly degraded, and this leads to reduced mitochondrial membrane potential and decreased production of reactive oxygen species (75). While APA of the *MTCH2* has not been studied, APA may similarly regulate the cellular localization of the *MTCH2* transcript and consequently alter mitochondrial function in neurons.

Protein Interaction Networks

We used STRING (76) to evaluate the interconnectivity of non-HLA 3′aTWAS genes by physical protein–protein interactions (PPIs) and Cytoscape (v3.3.0) (77) to visualize the PPI networks for APA-linked genes associated with SCZ, BD, and DEP (Figure 4). APA-linked genes associated with the major psychiatric conditions are enriched in biological pathways, including intracellular transport ($p = 0.0152$) and establishment of localization in a cell ($p = 0.0152$). Nodes in the SCZ PPI network, the largest network, include genes involved in pre-mRNA splicing, such as *SNU1*, *SMU1*, *TXNL4A*, and *ZMAT2*. Another prominent node is centered on *RBX1*, an E3 ubiquitin protein ligase, which interacts with *GLMN*, an ubiquitin ligase inhibitor, and *CUL3*, a component of ubiquitin protein ligase complexes. For the DEP PPI network, the most prominent node is centered on *MAPT*, microtubule-associated tau protein, which functions in promoting microtubule assembly and stability. While 3′aTWAS significant genes represent a small portion of SCZ QTLs, pathways are notably distinct from those that have been associated with differentially expressed and spliced genes, such as metabolic pathways, synaptic plasticity, excitatory synapses, and immune-related pathways (5, 78). A summary of the prominent protein–protein interaction networks identified in this analysis is provided in Supplementary Table S2.

Conclusions and Future Directions

In the post-GWAS era, the field of psychiatric genomics is challenged with interpreting the biological significance of hundreds of risk loci. TWAS has become a widely implemented method of nominating putative causal genes by leveraging relatively small transcriptomic datasets. However, there are multiple mechanisms by which SNPs may contribute to a biological phenotype, which are not all considered in most TWAS analyses. The discovery of 3′aQTLs helps explain some GWAS-significant SNPs that are not associated with differential expression or splicing in traditional TWAS analyses. While a percentage of APA-linked genes are also implicated in expression and splicing TWAS analyses, approximately 60%–75% of APA-linked genes for SCZ, BD, DEP have not been associated with total gene

expression or isoform expression in the largest TWAS. For example, GWAS-significant SNPs, rs2024566 and rs5751204, on chromosome 22 near the *SNU13* gene did not reach significance in a large isoform-level TWAS (6); however, alternative 3′UTR usage of this gene was associated with SCZ in the analysis of Cui *et al*., which utilized the same transcriptomic datasets. The association of genes with differential 3′UTR usage in 3′aTWAS suggests that aberrancies in mRNA translocation or degradation may play a role in disease risk. However, further confirmatory studies are needed to determine the impact of differential 3′UTR usage of 3′aTWAS significant genes on neuronal function and homeostasis. As transcriptomic reference sets continue to grow, it may eventually become possible to directly measure differential expression, splicing, 3′UTR usage between cases and controls. This will be critical for validating the findings of TWAS and guiding focused efforts to decipher downstream mechanisms.

In addition to APA of SNCA in PD, there several well-studied examples of APA alterations having significant neurological consequences that help explain phenotypic traits. A relatively well-characterized example is the MECP2 gene, which encodes methyl-CpG binding protein 2 (MeCP2), involved in the regulation of transcription of many different genes. Loss-of-function mutations of MECP2 result in Rett syndrome, which is characterized by developmental regression and intellectual disability beginning at around 18 months of age (79). The MECP2 transcript exists in two isoforms with either a long 3′UTR or short 3′UTR (80). The proximal APA site of the gene, which produces the short isoform, is increasingly used throughout postnatal development and is associated with increased protein abundance (81). The long MECP2 isoform, on the other hand, is translated less efficiently compared to the short isoform and leads to decreased protein abundance. Mutations in gene products that regulate APA of MECP2 can also cause forms intellectual disability and autism spectrum disorders. An example of this is copy number variants (CNV) duplications of NUDT21 (11). The protein product of NUDT21, a component of mammalian cleavage factor 1 complex (CFIm25), binds to the distal APA sites of genes, including MECP2, and facilitates production of transcripts with long 3′UTRs (82). Lymphoblastoid cell lines derived from patients with NUDT21 duplications have ∼50% less MeCP2 protein and increased abundance of the long MECP2 transcript (82). In this scenario, the reduction in MeCP2 protein is not quite as severe as in Rett syndrome, yet it is sufficient to produce intellectual disability (11).

More detailed investigations as described above are needed to examine the impact of APA of genes associated with psychiatric disorders. As we learn more about how APA alterations affect the brain, we will better define the molecular and biological underpinnings of neuropsychiatric disorders, which will guide the development of treatment strategies. Efforts to determine the critical stages of development during which APA alterations contribute to phenotypic expression will also be informative for identifying opportunities for therapeutic intervention.

Author Contributions

M.P. performed the literature review and wrote the manuscript. S.G. conceptualized the review, edited the manuscript and produced the figures for the manuscript. Y.C. contributed content for the review and edited the manuscript. O.A.A. reviewed and edited the manuscript. A.L.S. supervised preparation and edited the manuscript. W.L. conceptualized and edited the manuscript. X.X. supervised and edited the manuscript.

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