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Review

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Decoding causal m^{6}A: a bioinformatics roadmap for psychiatric disorders

Shuhe Liu[1,2,3], Xichen Zhao[1,3], Zhen Wei[1,2,4,*], Daniel F Carr[3,5], John Moraros[1,2,6,*]

[1]Department of Biosciences and Bioinformatics, School of Science, Xi'an Jiaotong-Liverpool University, 111 Ren'ai Road, Suzhou Industrial Park, Suzhou, Jiangsu 215123, China
[2]Suzhou Municipal Key Laboratory of AI4Health, 111 Ren'ai Road, Suzhou Industrial Park, Suzhou, Jiangsu 215123, China
[3]Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Crown Street, L69 7BE Liverpool, United Kingdom
[4]Institute of Life Course and Medical Sciences, University of Liverpool, 6 West Derby Street, L7 8TX Liverpool, United Kingdom
[5]Department of Pharmacology and Therapeutics, University of Liverpool, Crown Street, L69 7BE Liverpool, United Kingdom
[6]Institute of Population Health, University of Liverpool, Brownlow Street, L69 3GF Liverpool, United Kingdom

*Corresponding authors. Zhen Wei, Department of Biosciences and Bioinformatics, School of Science, Xi'an Jiaotong-Liverpool University, Suzhou, Jiangsu 215123, China. E-mail: Zhen.Wei01@xjtlu.edu.cn; John Moraros, Department of Biosciences and Bioinformatics, School of Science, Xi'an Jiaotong-Liverpool University, Suzhou, Jiangsu 215123, China. E-mail: John.Moraros@xjtlu.edu.cn.

Abstract

***N*^{6}-methyladenosine (m^{6}A), the most prevalent internal RNA modification, is an emerging key regulator of gene expression in the central nervous system, and its dysregulation is connected to psychiatric disorders. However, disentangling the causal links between specific m^{6}A sites and diseases phenotypes remain challenging. This review presents a comprehensive survey of practical bioinformatics strategies to address it. Our review outlines four analytical themes: (i) the reliable calibration of false-positive signals, (ii) causal inference via statistical genetics, (iii) the acquisition of cell-type-specific functional insights, and (iv) the application of machine learning to predict clinical biomarkers. We validate these analytical strategies through a case study in major depressive disorder, specifically by intersecting m^{6}A effects with psychiatric genetic risk. By streamlining these workflows, we provide a roadmap for formulating testable hypotheses regarding epitranscriptome-targeted therapeutic interventions in psychiatric disorders.**

Keywords **m^{6}A epitranscriptomics, psychiatric disorders, m^{6}A-QTL, causal inference, mendelian randomization, multi-omics integration**

Introduction

Gene expression in the central nervous system (CNS) depends on factors beyond the static DNA sequence and chromatin-based epigenetic regulation [1]. RNA molecules themselves carry dynamic chemical marks, collectively known as the epitranscriptome, that fine-tune post-transcriptional gene control [2]. Among more than 170 identified RNA modifications, *N*^{6}-methyladenosine (m^{6}A) has emerged as one of the most extensively studied and functionally significant [3]. As the most abundant internal mark on messenger RNA (mRNA), m^{6}A modulates multiple stages of the mRNA life cycle, including stability, export, splicing, and translation [3]. Neuronal tissues display particularly enriched m^{6}A modification, playing critical roles in neurodevelopment and synaptic plasticity [4]. Recent findings suggest that these patterns may be neuron-type specific; motivating the development of single cell m^{6}A profiling experiments in brain [5–8].

Given its important regulatory role in neuronal gene expression, altered m^{6}A signaling has been reported in several studies of psychiatric disorders including Major Depressive Disorder (MDD) and Schizophrenia (SCZ) [9]. These observations suggest that m^{6}A may act as a link between environmental factors and gene expression. However, defining the functional contributions of individual m^{6}A sites to the genetic risk architecture of psychiatric disorders remains a significant challenge [10]. Addressing this gap necessitates a shift from simple association or overlap analyses toward rigorous statistical genetic frameworks for causal inference [11, 12].

However, revealing this landscape remains methodologically challenging. The primary hurdle lies in the measurement accuracy of omics data, where technical artifacts, batch effects, and model mis-specification often obscure the molecular drivers of psychiatric vulnerability [13]. This challenge is compounded by the brain-specific nature of psychiatric pathology, as the blood-brain barrier frequently decouples peripheral m^{6}A signatures from CNS processes [14].

Despite the wealth of data from consortia like PsychENCODE, which link epigenetics to psychiatric risk, there is no equivalent, tailored paradigm for epitranscriptomics [15, 16]. Bridging this gap requires

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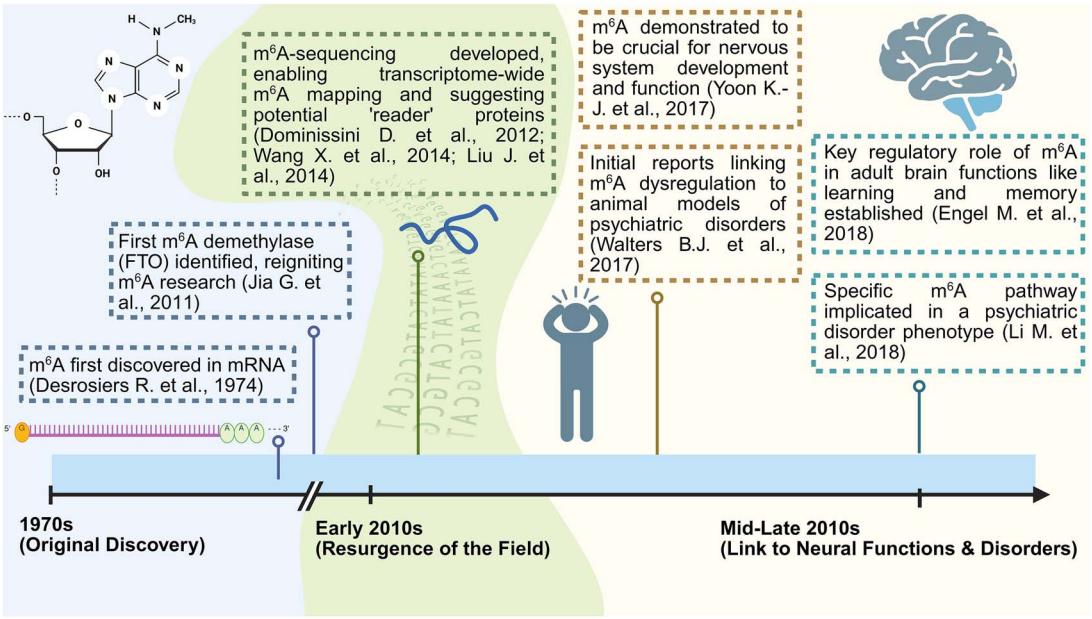

Figure 1 Major advances in m^{6}A research and their relevance to molecular psychiatry. This timeline summarizes landmark discoveries in m^{6}A biology: from its initial identification and the characterization of its regulatory machinery to recent studies revealing its emerging associations with neural processes and psychiatric conditions.

a dedicated computational strategy capable of handling the unique challenges of RNA modification data [17]. This review outlines a bioinformatics pipeline for decoding the epitranscriptomic architecture of psychiatric disorders. The proposed modules facilitate robust m^{6}A quantitative trait loci (m^{6}A-QTL) analysis and genetic causal inference, while incorporating advanced predictive models for marker discovery and large languamodels (LLMs) for large-scale knowledge integration.

Furthermore, we validate our proposed roadmap through a case study in MDD. By applying causal inference and cell-type-specific functional insights, we demonstrate how specific m^{6}A sites can be mapped to depressive phenotypes with summary-data-based mendelian randomization (SMR). Through integrating conceptual strategies with practical validation, we demonstrate how to prioritize causal mediators from diverse omics data. Consequently, this work establishes a scalable pipeline for psychiatric epitranscriptomics, informing both basic and translational research. Ultimately, we conclude by outlining a methodological vision, emphasizing that the future progress of the field depends on prioritizing data quality, leveraging orthogonal validation, and enhancing biological resolution.

The co-evolution of *N*^{6}-methyladenosine biology and its data challenge

After its discovery in 1974, m^{6}A research progressed slowly for several decades, with only sporadic biochemical investigations into its presence and enzymatic formation [18]. A renewed wave of interest emerged in the early 2010s, driven by two parallel advances (Fig. 1) [19, 20]. Biologically, the discovery of the fat mass and obesity-associated protein (FTO) demethylase demonstrated that the m^{6}A mark is dynamic and reversible, establishing m^{6}A as part of a regulated RNA modification system [19, 21]. Technologically, the independent development of transcriptome-wide m^{6}A sequencing (MeRIP-Seq) by two groups in 2012 provided the first global map of the epitranscriptome at regional resolution [22–24].

The emergence of transcriptome-wide m^{6}A sequencing has generated large-scale datasets that pose new challenges: specifically, the need to distinguish genuine methylation sites from background noise [12, 25]. Early bioinformatics tools, many adapted from epigenomic analyses, began addressing this by mapping putative m^{6}A sites across the transcriptome. Yet, a central difficulty persisted: separating true m^{6}A signals from false positives arising from non-specific antibody binding [26]. An influential experimental advance was the use of *in vitro* transcribed (IVT) RNA, which lacks m^{6}A, as a negative control to identify antibody-related artifacts [27, 28]. Building on this experimental system, bioinformatics tools such as m6ACali employed machine-learning models trained on IVT-controlled data to characterize systematic biases and calibrate new datasets without requiring an IVT control for each sample [26]. These methodological advances substantially improved data reliability enabling more confident investigations of m^{6}A's role in neural function and other biological contexts [3, 12, 29–33].

As the field expanded from basic molecular topological studies to disease contexts, more complex analytical challenges appeared. The focus shifted from simply mapping m^{6}A sites to integrating these profiles with genomic, transcriptomic, and clinical data to identify potential molecular mechanisms underlying pathology [34]. This progression also highlighted the growing need to characterize the specific functions of m^{6}A "writer," "reader," and "eraser" proteins, which constitute the molecular machinery mediating interactions between genetic variation, epitranscriptomic regulation, and disease phenotypes [35–38].

The protein machinery governing *N*^{6}-methyladenosine installation and consequences

The m^{6}A modification is regulated by a coordinated set of enzymes that install, remove, and interpret this mark. "Writer" proteins, such

as the METTL3–METTL14 complex together with cofactors like WTAP, catalyze methylation at specific sites, while "erasers," including FTO and ALKBH5, can demethylate m^{6}A-modified RNA [39].

The functional consequences of m^{6}A modification are largely mediated by "reader" proteins that recognize and bind to this mark [40]. Depending on the cellular context, these interactions can yield opposing effects: YTH-family readers (YTHDF1-3) often promote mRNA decay, whereas IGF2BP-family readers tend to enhance transcript stability [37]. Coordinated activity among writers, erasers, and readers is critical for fine-tuning gene expression, particularly in the brain. Disruption of these regulatory components has been associated with altered neural function and may contribute to the molecular basis of psychiatric disorders [38].

N^6-methyladenosine dysregulation in psychiatric disorders

Dysregulation of the m^{6}A machinery is a common finding in psychiatric illnesses [12, 33, 41–43]. For instance, in addition to MDD and SCZ, aberrant m^{6}A pathways and regulators have been documented in Autism Spectrum Disorder, Bipolar Disorder (BD), and stress-related anxiety disorders [12, 33, 41–43]. Evidence suggests a transdiagnostic pattern, in which altered m^{6}A pathways disrupt core processes such as synaptic plasticity and cognitive function across multiple disorders [12].

MDD provides an illustrative case. Several studies have reported associations between variants in the *FTO* gene and MDD risk [9, 44], though these links may partly reflect shared metabolic mechanisms rather than a direct causal effect [45]. Post-mortem brain analyses and animal models have revealed region-specific alterations in m^{6}A levels and dysregulation of related enzymes [46–49]. MDD therefore highlights a key analytical challenge: connecting genetic susceptibility, such as variants near *FTO*, to downstream epitranscriptomic and molecular changes that may contribute to disease pathology [9]. Similar observations have been reported in SCZ, where several risk loci include genes encoding m^{6}A regulatory proteins [41].

m^{6}A regulation also responds to environmental and experiential factors beyond inherited genetic variation. In Alcohol Use Disorder (AUD) [50], chronic alcohol exposure has been associated with altered expression of m^{6}A-related enzymes, whereas in Post-traumatic Stress Disorder (PTSD) [51], changes in m^{6}A-related transcripts have been observed in relation to stress adaptation and treatment outcomes. Together, these findings point to recurring patterns of m^{6}A dysregulation across disorders that affect cognition and synaptic function. This cross-diagnostic perspective resonates with the NIMH Research Domain Criteria framework, which emphasizes biological dimensions that cut across conventional diagnostic categories [52].

A bioinformatics roadmap: from data to mechanism

To deepen and validate current molecular insights into m^{6}A-related mechanisms in psychopathology, researchers need to integrate multi-omics datasets and computational approaches that enhance the detection of key regulatory genes and pathways. We summarize these strategies as a conceptual "bioinformatics roadmap" (Fig. 2).

While ENCODE and PsychENCODE provide essential genomic catalogs, they lack the specialized architecture needed to resolve the epitranscriptomic nuances of mental illness [15, 53, 54]. We bridge this gap by developing a targeted causal-inference roadmap for RNA modification. As detailed in Table 1, our framework ensures rigorous de-confounding during initial data processing via m6ACali-based calibration, while strengthening causal evidence through the integration of SMR and colocalization analyses [26, 55, 56].

Rather than simply listing techniques, this section discusses how each method is applied, the rationale for its use, and its methodological limitations. Each analytical step aims to generate interpretable biological insights and strengthen the evidence linking genetic risk to m^{6}A-associated disease mechanisms.

(1) **Phase 1: high-fidelity m^{6}A profiling.** This foundational stage focuses on the reliable generation and processing of high-throughput m^{6}A sequencing data, as the technical artifacts are the key confounding factor of the downstream causality analysis [57]. A critical step involves false-positive calibration, using experimental controls such as IVT RNA or computational correction methods such as to filter genomic features induced antibody biases [26, 58].

(2) **Phase 2: MR and colocalization analysis.** To establish the link between m^{6}A modification and psychiatric risk, Summary-data-based Mendelian Randomization (SMR) should be applied [55, 56]. This approach utilizes genetic variants as instrumental variables (IVs) to estimate the causal effect of m^{6}A (**X**) on the phenotype (**Y**) via the Wald ratio:

$$\beta_{\mathrm{SMR}} = \frac{\beta_{\mathrm{Y}}}{\beta_{\mathrm{X}}} \tag{1}$$

where β_{Y} and β_{X} represent the effect sizes from GWAS and m^{6}A-QTL studies, respectively [55]. To distinguish true mediation from potential linkage disequilibrium (LD) or horizontal pleiotropy, colocalization analysis can be used to ensure the observed association is driven by the same genetic variant [59].

(3) **Phase 3: Cell-type-specific annotation.** The integration of m^{6}A profiles with high-resolution technologies, including sc/snRNA-seq and spatial transcriptomics (ST), overcomes the inherent resolution limits of bulk analysis [60]. This multimodal approach enables the identification of epitranscriptomic modifications that are uniquely confined to distinct cellular populations or anatomical niches in the brain.

(4) **Phase 4: Psychiatric translation & predictive modeling.** This stage employs machine-learning approaches for biomarker discovery and clinical stratification. Feature selection is optimized via Least Absolute Shrinkage and Selection Operator (LASSO) regression or Random Forests (RF), while Deep Learning (DL) architectures are applied for patient stratification based on high-dimensional inputs [61, 62].

A survey of *N*^{6}-methyladenosine resources useful for causality inference

The successful implementation of our proposed roadmap relies heavily on access to robust public datasets and computational pipelines. Over the past decade, the rapid accumulation of epitranscriptomic data has led to the development of numerous specialized databases and open-source software tools. To facilitate the practical application of our framework, we systematically summarize the key m^{6}A-related resources, including comprehensive databases for m^{6}A-QTLs,

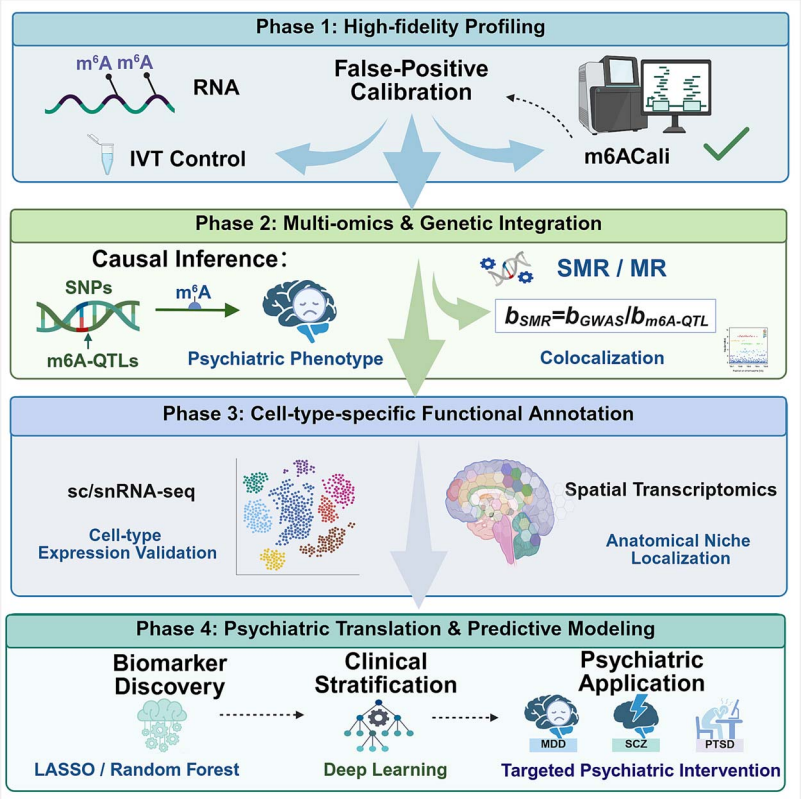

Figure 2 A multilayer bioinformatics roadmap for deciphering the roles of m^{6}A in mental disorders. The framework outlines four major methodological domains, from sequencing calibration to causal inference and predictive modeling, highlighting how integrated analyses can bridge m^{6}A methylation dynamics with genetic architecture and disease phenotypes in neuropsychiatric disorders.

Table 1 Conceptual comparison between existing multi-omics consortia and the proposed psychiatric m^{6}A roadmap.

Analytical feature	ENCODE/roadmap epigenomics [15, 53, 54]	Data types used	Our proposed roadmap (psychiatric m^{6}A)
Primary objective	General functional cataloging	Brain-specific regulatory networks	Causal psychiatric etiology
Analytical paradigm	Descriptive / Associative	Multivariate eQTL / Associative	Targeted Causal Inference (e.g., SMR) [55, 56]
Resolution focus	Bulk tissues / Cell lines	Bulk brain & emerging Single-cell	snRNA-seq validated Cell-type specificity
Data calibration	Standard peak calling	Standard RNA-seq QC	Rigorous false-positive filtering (IVT/m6ACali) [26]
Clinical translation	Broad biological function	Brain evolution and disorders	Machine/Deep Learning for patient stratification

This table highlights the critical methodological toolbox required for causal inference in epitranscriptomic research, and emphasizing the necessity of false-positive calibration and neuron-type specific insights [15, 26, 53–56].

functional annotations, and essential algorithmic pipelines for peak calibration and calling [26, 63–68]. Table 2 provides a comprehensive overview of these resources, complete with descriptions, access links, and source code repositories, serving as a practical toolkit for researchers investigating psychiatric epitranscriptomics from the perspectives of statistical genetics and causality inference.

Accurate quantification: the foundation of analysis

The first step of the roadmap focuses on ensuring the accuracy of the quantification of m^{6}A from sequencing data. MeRIP-seq, the classical method for transcriptome-wide detection of m^{6}A, remains central to most studies but has notable technical limitations [69]. Because MeRIP-Seq is derived from NGS, a platform sensitive to PCR amplification bias as observed peak signals are confounded by the fragment level GC content, while the bias is correlated with experimental batches, contributing in part to batch effects [70]. To mitigate this issue, bioinformatics frameworks such as exomePeak2 incorporate GC content biases and IP efficiency variation correction directly into its statistical model, thereby improving the precision of peak calling and differential methylation analysis [71].

A persistent challenge lies in distinguishing genuine m^{6}A signals from artifacts introduced by non-specific antibody binding [72]. Because the antibody exhibits off-targets binding, IP read density partially reflects transcript abundance. Highly expressed genes may appear enriched even when methylation levels are unchanged,

Table 2 Systematic overview of key m6A-related databases and computational resources [26, 63–70].

Resource name	Category	Description	Access link/GitHub
m6AConquer [63]	Database	A unified, IVT-calibrated framework providing re-quantified m^{6}A-QTLs and paired multi-omics data.	https://m6aconquer.com
m^{6}A-Atlas 2.0 [64, 69]	Database	A comprehensive knowledgebase unraveling the m^{6}A epitranscriptome across multiple species with high-confidence sites.	http://www.xjtlu.edu.cn/biologicalsciences/atlas
RMVar 2.0 [65, 70]	Database	A database of functional variants associated with RNA modification, highly relevant for bridging GWAS and m^{6}A.	http://rmvar.renlab.cn
m6A2Target 2.0 [66]	Database	A comprehensive database for target genes of m^{6}A writers, erasers, and readers.	http://m6a2target.canceromics.org
m6ACali [26]	Software	A machine-learning based calibration tool trained on IVT-RNA to eliminate false-positive m^{6}A signals.	https://github.com/RNAModLab/m6ACali
exomePeak2 [67]	Software	A peak-calling pipeline that robustly models and corrects GC-content and IP-efficiency biases in MeRIP-seq.	https://bioconductor.org/packages/exomePeak2
FastQTL [68]	Software	Highly efficient software for mapping quantitative trait loci (eQTLs / m^{6}A-QTLs) with covariate adjustments.	https://github.com/francois-a/fastqtl

producing expression-related confounding [73]. To mitigate this bias, data calibration procedures are typically applied. One effective strategy uses IVT RNA, lacking m^{6}A, as a negative control to approximate and correct background enrichment [73]. Building on this concept, machine-learning frameworks such as m6ACali are trained on IVT-controlled datasets to recognize systematic patterns of false-positive signals, enabling computational calibration of new data without requiring additional IVT experiments [26]. Performing these quantification and calibration steps substantially improves the reliability of downstream differential methylation and m^{6}A-QTL analyses.

m^{6}A quantitative trait loci: linking *N*^{6}-methyladenosine quantitative profiling to disease genetics regulations

Following accurate quantification, the focus shifts to understanding the genetic basis of m^{6}A variation and its disease relevance using m^{6}A quantitative trait loci (m^{6}A-QTLs) [10]. m^{6}A-QTL analysis is typically performed on MeRIP-Seq data using a procedure similar to that of eQTL analysis. The association between genotypes and m^{6}A methylation levels is tested using linear regression models implemented in FastQTL [68]. To control for latent batch effects, the model is often adjusted with covariates derived from PEER factors or PCA [10, 34]. Since m^{6}A quantification from MeRIP-Seq data is sensitive to GC content bias and variations in IP efficiency, these technical issues are corrected, usually through regression methods, before conducting QTL analysis [10].

Interpretation of m^{6}A-QTLs under molecular biology context often involves examining genomic annotations, which can suggest upstream or functional consequences of the genetic regulated m^{6}A locus [10]. Important annotation for interpreting m^{6}A is domain knowledge-informed genomic features, such as using the transcript regions (e.g. exon, transcript, 5'UTR, CDS, 3'UTR), their properties (e.g. length, evolutionary conservation), and the relative positions of m^{6}A on the transcript. The associations are either presented visually (e.g. pie charts of transcript regions or meta-gene plot), or statistically (e.g. association with sites using Fisher's test). Other important region-based annotations include histone modifications (e.g. H3K36me3 and H3K36me2) and RBP binding sites (e.g. m^{6}A writers, erasers, readers) [10].

The m^{6}A-QTLs datasets also serve as crucial resources for interpreting GWAS findings under psychiatric context, particularly the numerous non-coding risk variants. An m^{6}A-QTL overlapping a GWAS locus suggests a candidate molecular cause: genetic risk might be mediated through altered epitranscriptomic regulation [74]. However, a major complexity arises from the frequent overlap between m^{6}A-QTLs and mQTLs or splicing QTLs (sQTLs). This potential confounding effect creates the "Causality Gap" [75–77]—it becomes difficult to determine if the genetic effect on disease is primarily driven by changes in m^{6}A, transcription, splicing, or a combination [78].

While m^{6}A-QTLs provide a valuable molecular link between genotype and epitranscriptome, their interpretation is often complicated by potential confounding factors and artifacts in current datasets [78]. There are several key challenges that include, but may not be limited to (i) low statistical power due to smaller cohort sizes compared to eQTL studies, (ii) the persistent confounding by mQTLs and sQTLs, (iii) technical limitations such as antibody off-target binding in MeRIP-Seq, and (iv) the high tissue- and cell-type specificity of m^{6}A regulation [79]. Therefore, while m^{6}A-QTL analysis generates important hypotheses for prioritizing m^{6}A linked variants, rigorous IVT calibration and normalization, along with careful downstream causal inference analysis, are essential for establishing causality between m^{6}A and diseases. The causal inference requires the use of statistical genetics frameworks, which are discussed in the following section.

Interacting with psychiatric genetic risk architectures

Crucially, understanding psychiatric etiology requires moving beyond generic spatial overlaps with GWAS loci to decipher how m^{6}A effects interact with broader genetic risk architectures. Recent landmark genetic analyses have demonstrated that m^{6}A-QTLs are largely different from standard expression QTLs (eQTLs) and sQTLs [10, 34]. This divergence suggests that psychiatric genetic risk variants often mediate disease not by altering overall transcript abundance, but by fine-tuning RNA metabolism (such as translation efficiency or RNA-protein interactions) via locus-specific m^{6}A deposition [80]. Furthermore, recent multi-omics integrations [e.g. combining SMR with transcriptome-wide association studies (TWAS)] [41] and epigenome-epitranscriptome crosstalk analyses [81] highlight a complicated risk architecture. Genetic variants may initially perturb local chromatin

states (e.g. H3K27ac), which subsequently dictate m^{6}A writer recruitment [38]. Hence, our roadmap intends to capture these dynamics, thereby establishing a directional causal chain from genetic variants to epigenomic modifications, epitranscriptomic regulation, and ultimately, psychiatric phenotypes.

Establishing causality: from genetic risk to molecular function

While functional interpretation identifies what is altered, the central aim of psychiatric genetics is to trace a causal chain linking genetic risk variants to molecular and cellular consequences [82]. Achieving this requires moving beyond correlation-based analyses and applying statistical genetics frameworks designed for causal mediation and integrative modeling.

The pipeline begins with m^{6}A-QTL analysis, which measures whether genetic variants are associated with inter-sample variation in m^{6}A levels [78]. It is common to use GWAS data to annotate m^{6}A-QTLs in order to link the m^{6}A changing genetic variants to potential diseases. However, implying causality from such associations is often problematic due to the "causality gap" [76]. For instance, a substantial proportion of m^{6}A-QTLs are also found to be eQTLs of different genes harboring the m^{6}A site. This makes it difficult to disentangle whether a disease-associated m^{6}A-QTL exerts its effect by directly altering m^{6}A modification, by changing gene expression (not mediated by m^{6}A), or through a combination of both pathways [10]. To rigorously dissect these possibilities, existing literatures applied a hierarchy of methods, each designed to reveal a distinct type of causal structure involving m^{6}A.

(1) **Two-sample MR**: As a widely used causal inference framework in statistical genomics. Two-sample MR leverages genetic variants as IVs to infer the causal effect of an exposure (e.g. m^{6}A level) on an outcome (e.g. disease risk) [83]. This approach uses summary statistics (coefficient estimates with standard error) from GWAS and QTL analyses conducted in independent cohorts. For a SNP to serve as a valid IV, it must satisfy three core assumptions [84]: (i) the variant is strongly associated with the exposure; (ii) the variant is not associated with any confounders affecting both exposure and outcome; and (iii) the variant influences the outcome only through its effect on the exposure [85]. The first assumption is often ensured through the selection of genetic variants with strong significance and the prevention of the so called "weak IV bias" [86]. A range of sensitivity analyses, such as MR-Egger regression, weighted median approach, and HEIDI test, have been developed to detect the violations of the third assumption [84, 87]. Regarding the second assumption, although its violation is difficult to test, it is generally assumed that two-sample MR is less likely to yield false-positive results due to confounding [88].

As mentioned, most sensitivity analyses in two-sample MR focus on evaluating violations of the third assumption (horizontal pleiotropy) [89]. Consider a simple causal chain where one tests whether genetic variants influence disease risk through m^{6}A modification (SNP $\rightarrow$ m^{6}A $\rightarrow$ disease). In reality, an SNP may also affect disease risk through alternative routes, such as other epigenetic mechanisms or direct effects on gene expression, independent of m^{6}A [34]. Approaches like MR-Egger regression or Steiger filtering can detect and adjust for horizontal pleiotropy, though they often suffer from low statistical power and sensitive to weak instruments bias [90]. Another major limitation is that these sensitivity and correction methods require at least three independent SNPs per m^{6}A site, which remain scarce in current m^{6}A-QTL datasets due to limited sample sizes [91]. Consequently, traditional two-sample MR, commonly implemented with R package *TwoSampleMR*, are usually not implementable for most m^{6}A sites, or should be interpreted cautiously as the sensitivity analyses are not powerful [92]. A superior alternative for single-instrument MR in m^{6}A setting is SMR, which employs the HEIDI test as a sensitivity analysis to detect heterogeneity in effect sizes within the local LD region [55, 93].

(2) **Colocalization**: Another key statistical test often performed in parallel with MR is colocalization [94]. It is a Bayesian statistical framework that tests whether two genetic association signals, such as those between a GWAS disease locus and an m^{6}A-QTL site [59], originate from a shared causal variant or are the result of LD contamination. Using R package like coloc, this test provides posterior probabilities of genuine overlap between variants and the alternative possibilities of spurious associations due to LD [95]. The framework has been adopted to link m^{6}A sites to disease, one large-scale study reported that approximately 184 GWAS loci significantly linked with m^{6}A-QTLs after the colocalization filter, suggesting that genetic risk variants for depression and SCZ can really change methylation levels on specific m^{6}A sites [10]. However, the fidelity of colocalization outcomes still depend on the quality of GWAS and QTL summary statistics. Furthermore, the model often assumes that a single source variant per trait exist within each locus, which is difficult to define in regions with allelic heterogeneity.

(3) **TWAS**: Once MR and colocalization established causal connections between m^{6}A-QTL and a disease risk locus, the TWAS strategy can be used to further test whether the genetically predicted m^{6}A level on specific m^{6}A sites is associated with the disease label across multiple NGS samples [96]. Frameworks such as FUSION build predictive models trained on reference m^{6}A-QTL datasets to infer m^{6}A levels from sample-wised genotype data [96]. These models can then be applied to large GWAS cohorts to assess whether the predicted m^{6}A levels on each site are significantly associated with disease traits across samples. TWAS is particularly valuable when it is possible to reliably predict m^{6}A changes from genetic mutations. However, the reliability of *in silico* models in predicting the effects of variants on m^{6}A changes remains questionable. As difficulties still arise from data quality reasons such as systematic biases in m^{6}A quantification data and the LD contamination in m^{6}A-QTL [97].

Current limitations in genetics based causal inference

Although the summarized methods offer a coherent strategy for linking genetic variation to m^{6}A regulation, its practical implementation remains constrained by several interrelated limitations that warrant a cautious interpretation of results.

Technical reliability of m^{6}A sequencing techniques remains the most immediate obstacle. Antibody-based profiling methods such as MeRIP-Seq still contain a high proportion of off-target binding sites,

which exhibit substantial inter-sample variation and thereby obscure QTL detection and confound causal inference. Machine learning (ML)-based calibration such as m6ACali [26] will become essential in the preprocessing of futural m^6A-QTL calling pipeline. As the m^6AQTL data [63] are calibrated with m6ACali and restricted to orthogonally validated (OV) sites, they represent the first dataset suitable for MR analyses with reduced antibody and batch biases. Eventually, emerging high-performance methods such as GLORI and eTAM-Seq may fundamentally alleviate these constraints, but current m^6A-QTL datasets remain coarse-grained and require substantial computational effort for normalization.

A second challenge arises from the entanglement between transcriptional and epitranscriptomic regulation. Because m^6A deposition frequently occurs co-transcriptionally, genetic effects on transcription can be statistically confounded with those on DNA 5mC methylation [98]. Although colocalization and HEIDI tests can help mitigate this problem, they cannot fully exclude confounding in complex loci where transcriptional and post-transcriptional mechanisms overlap [99].

Additional sources of uncertainty stem from heterogeneity across datasets. m^6A-QTL studies differ in experimental batches, antibody efficiency, and computational pipelines, while GWAS and expression datasets often vary in ethnicity composition [34].

Ancestry mismatch between QTL and GWAS data—such as European-derived m^6A-QTLs analyzed alongside trans-ethnic GWAS results—can further reduce power and introduce bias, even though some causal variants appear to be shared across populations [10, 100].

A third limitation involves the biological relevance of proxy tissues, particularly given the isolation provided by the blood-brain barrier [101]. m^6A-QTLs identified in the periphery may not capture the unique epitranscriptomic regulatory patterns of the brain [79, 102]. Signals detected in non-neural tissues often reflect systemic responses to illness rather than etiological drivers [10, 103]. Therefore, robust causal inference requires the use of brain-derived m^6A-QTLs [41]. Alternatively, one can ensure that the identified genes having suspected causal m^6A are biologically active within the relevant neural circuits (such as enriched with cell types in brain) [7].

Finally, data quantity and statistical power are important barriers to overcome. Current m^6A-QTL cohorts are far smaller than eQTL or GWAS datasets; for instance, a key study mapping m^6A-QTLs used only 60 Yoruba (YRI) cell lines [34], with most cohorts numbering only a few hundred samples [78]. Such limited power means that only variants with relatively strong effects on m^6A levels are detectable, leaving most true associations undetected. Moreover, the small number of independent SNPs per locus makes it difficult to apply multi-instrument sensitivity analyses such as MR-Egger, which require at least three valid instruments to test for pleiotropy [91].

Taken together, the outlined strategies, from m^6A-QTL mapping to MR, offer an causal inference framework for linking genetic variation to molecular mechanisms [104]. As illustrated by several recent studies (Table 3), such integrative analyses can effectively prioritize candidate loci and mechanistic hypotheses. Nonetheless, IV analysis by itself cannot confirm causality. Establishing a reliable causal relationship between m^6A and psychiatric disorders will ultimately rely on cross-validation with orthogonal computational and experimental results, such as CRISPR-based perturbation assays, which test how specific genetic variants influence m^6A deposition and downstream disease-related phenotypes [105].

Overcoming current limitations and future directions in causal inference

In an effort to mitigate the aforementioned limitations of m^6A-QTLs and causal inference, future research must prioritize stringent quality control and calibration of raw data to isolate confounding artifacts that induce spurious non-biological linkages [63]. Although cell-type specificity is paramount, the inherent noise across various m^6A detection platforms often masks genuine cell-type-specific signals [106]. Consequently, characterizing these specificities requires a cautious approach, ideally using sensitive, orthogonally-validated computational frameworks to resolve m^6A profiles across multiple cell types and tissues [63]. Alternatively, a pragmatic approach for gaining tissue-specific insights involves mapping identified IVs and genetic drivers onto brain-specific scRNA-Seq and ST datasets [107]. This approach, facilitated by frameworks such as TWAS-Hub or FOCUS (Fine-mapping Of CaUsal gene Sets), allows researchers to verify whether a given locus is functionally active within relevant neural circuits [108, 109].

Machine learning for prediction and discovery

The final stage of the bioinformatics roadmap applies ML for two main objectives: (i) constructing predictive models for potential clinical diagnosis and (ii) biomarker discovery (e.g. m^6A sites or genes related to disease) using omics features as input [110]. This approach is particularly relevant in psychiatric research, where datasets are typically high-dimensional, with the number of genomic features (p) greatly exceeding the number of patient samples (n). Such imbalance creates substantial statistical challenges that ML methods can help address [111].

Feature selection strategies and challenges

The primary challenge in predicting psychiatric outcomes from m^6A data is the curse of dimensionality. Raw epitranscriptomic profiles often contain tens of thousands of methylation peaks, harboring significant multicollinearity and noise [112]. Directly feeding such high-dimensional data into predictive classifiers invariably leads to severe overfitting [113]. Therefore, robust feature selection strategies are imperative to isolate a parsimonious, informative subset of biomarkers.

Regularization techniques, particularly LASSO regression, are widely employed to overcome this challenge [114]. LASSO introduces an L1 penalty that forces the coefficients of less informative features to exactly zero, performing feature selection and model fitting simultaneously [115]. As examples, Wang *et al.* applied LASSO to identify key m^6A regulators in their depression prediction model [116], while Li *et al.* reduced 42 candidate genes to 19 features associated with Alzheimer's disease (AD) [117].

Representative algorithms: from tree-based models to deep learning

Once informative features are selected, representative ML algorithms are deployed based on the analytical objective. Tree-based models, such as RF and Gradient Boosting, are highly effective for discovery tasks [118]. They naturally handle non-linear interactions between multiple m^6A sites without requiring extensive data scaling, and they provide interpretable "feature importance" scores [119]. For instance, RF can be utilized to rank the top m^6A targets driving stress-induced

Table 3 Applications of causal inference methods in m^{6}A neuropsychiatric research [10, 34, 41, 76, 81].

Study/title	Causal inference methods	Data types used	Causal pathway tested (DAG model)	Identified causal mediators/genes	Potential drug targets
Integration of multi-omics summary data reveals the role of *N*^{6}-methyladenosine in neuropsychiatric disorders [41]	TWAS (FUSION), SMR, Colocalization	GWAS, m^{6}A-QTL, eQTL, pQTL	Primary: SNP → m^{6}A Level → Gene Expression → Disease Risk Secondary: SNP → Gene Expression → m^{6}A Level → Disease Risk	SCZ: SPATA2L, MAPK3, INO80EBP: PLEC, GRINA (Identified 58 risk genes in total)	MAPK3 (for SCZ)
Crosstalk between epitranscriptomic and epigenomic modifications and its implication in human diseases [76]	MR, Colocalization, SMR/HEIDI	m^{6}A-QTLs, mQTLs, haQTLs, GWAS	SNP → m^{6}A Level ↔ Epigenomic Mark (DNAme/H3K27ac) → Disease Risk	Bipolar Disorder: LINGO1Neuroticism/ Depression: SGIP1(Interpreted 20 GWAS loci for brain traits)	N/A (focus on mechanism interpretation)
Genetic drivers of m^{6}A methylation in human brain, lung, heart and muscle [10]	m^{6}A-QTL mapping, Colocalization, S-LDSC	meRIP-seq, Genotype data, GWAS	SNP → m^{6}A Level → Disease Trait/Risk	Depression: GRM5 Schizophrenia: LINC00634 Neuroticism: KCNJ3 Anxiety: ANKS1B	N/A (focus on mechanism interpretation)
Multi-omics integration reveals the role of *N*^{6}-methyladenosine in epilepsy, ischemic stroke, and vascular dementia [81]	TWAS (FUSION), MR	GWAS (VaD), m^{6}A-QTL, eQTL	SNP → Gene Expression → Disease Risk	Vascular Dementia: SERINC2Epilepsy: NBL1, PARP1Ischemic Stroke: TPGS2	PARP1 (for Epilepsy)
Genetic analyses support the contribution of mRNA *N*^{6}-methyladenosine (m^{6}A) modification to human disease heritability [34]	m^{6}A-QTL mapping, TWAS, S-LDSC, Colocalization	m^{6}A-seq & Genotype data (LCLs), GWAS	(SNP →) Genetically Predicted m^{6}A Level → Disease Trait/Risk	Bipolar Disorder & Schizophrenia: Heritability contribution confirmed. Example Risk Gene (for blood traits): DDX55	N/A (focus on heritability contribution)

anhedonia, revealing biological priorities that linear models might miss [120].

For complex prediction tasks, such as diagnosis classification or patient stratification, DL methods are increasingly applied [121]. DL architectures, particularly Transformer, is strong at modeling unstructured and complex biological data [122]. While traditional models like RF and SVMs have shown promising accuracy in tabular data and proof-of-concept settings (e.g. Yang *et al.* classified AD samples using *METTL3* and *NDUFA10* expression [123]). Graph Neural Network based approach advances this front by modeling multi-layered and complex regulatory networks [124]. In addition, unsupervised deep clustering such as Variational Auto-Encoder, can move beyond simple case-control contrasts to reveal biologically distinct patient subgroups, addressing the clinical heterogeneity inherent in psychiatric disorders [117].

Model interpretation for mechanistic insight

Predictive ML models are often criticized for their limited interpretability [125]. In this context, the objective extends beyond achieving high predictive accuracy to improving understanding of the prediction mechanism. Interpretation techniques such as SHAP (SHapley Additive exPlanations) and feature importance analysis are increasingly used to identify omics features that contribute most strongly to a model's predictions [126, 127]. By linking statistical importance to biological meaning, these approaches allow predictive models to serve as useful sources of new hypotheses. For example, Li *et al.* and Yang *et al.* found that the expression levels of m^{6}A regulator genes *NOTCH2*, *NME1*, and *NDUFA10* were among the top-ranked predictive features predicting in AD pathogenesis [117, 123]. However, it is important to note that the feature importance and SHAP values from predictive models only suggest correlational significance, rather than causal or scientific significance.

Critical challenges and future directions

Although ML frameworks have gained traction across molecular biology, their use in epitranscriptomics (particularly for m^{6}A) remains constrained not by algorithmic sophistication but by the epistemic limits of available data. As summarized in Table 4, most published analyses still depend on small, heterogeneous public datasets with narrow technique and platform diversity, resulting in unstable feature selection and limited generalizability across populations [117, 129]. Attempts to expand coverage by pooling studies or sequencing platforms often amplify rather than resolve heterogeneity. Differences in ancestry, library chemistry, and normalization pipelines generate systematic shifts that obscure genuine methylation patterns [130].

Table 4 Examples of the application of ML methods in m^{6}A psychiatric research [110, 111, 116, 117, 123, 128].

Study/title	Method/model	Data type	Application objective (output targets)	Input features	Identified biomarkers or potential drug targets
Integrating genome-wide association study and methylation functional [128]	Prediction Model: Random Forest (within m^{6}AVar tool)	GWAS, DNA methylation, m^{6}A modification data	Identify candidate genes & pathways related to SCZ	Whole-genome meQTL, SNP loci, m^{6}A annotation data	Identified 25 candidate m^{6}A-annotated genes (e.g., ZSCAN12, HLA-DQA1), 17 of which were verified in SCZ patients.
Influence of *N*^{6}-methyladenosine (m^{6}A) modification on cell phenotype in Alzheimer's disease [116]	Drug Repositioning: CMAP (Connectivity Map)	Gene expression data	Drug repositioning using hub genes identified from m^{6}A-related DEGs	Upregulated & downregulated m^{6}A-related hub genes (e.g., YAP1, MSX1)	Identified 10 potential therapeutic compounds, including LDN-193189 (ALK inhibitor) and sarmentogenin (ATPase inhibitor).
Downregulation of FTO in the hippocampus is associated with mental disorders induced by fear stress during pregnancy [117]	Prediction Model: m^{6}Am-seq, m^{6}Am-Exo-seq	RNA sequence data	Predict potential m^{6}Am modification sites	41-base sequence from 5′ end of target gene (Fgf10)	Predicted a potential m^{6}Am site in the 5′ UTR of Fgf10.
m^{6}A Regulator-Mediated RNA Methylation Modification Patterns are Involved in the Pathogenesis and Immune Microenvironment of Depression [123]	Feature Selection: LASSO Regression- Prediction Model: Back-Propagation Neural Network	Gene expression data	Classify depressive subtypes based on m^{6}A regulator expression profiles	Expression levels of m^{6}A regulatory factors	Constructed a depressive subtype classification model and identified 7 key m^{6}A regulatory genes (FTO, RBM15B, METTL3, etc.).
Novel Roles of RNA m^{6}A Methylation Regulators in the Occurrence of Alzheimer's Disease and the Subtype Classification [110]	Feature Selection: LASSO Regression- Clustering: WGCNA	Gene expression data	Study m^{6}A-related gene regulation in AD, identify critical genes	Expression levels of m^{6}Am^{6}A regulatory factors	Identified 19 key AD-associated genes, highlighting NOTCH2 and NME1 as potential m^{6}A-regulated targets.
An Exploration of the Coherent Effects between METTL3 and NDUFA10 on Alzheimer's Disease [111]	Prediction Model: Support Vector Machine (SVM)	Gene expression data	Build a diagnostic model for AD based on the expression of an m^{6}A writer and a target gene.	Expression levels of METTL3 and NDUFA10	Built a diagnostic model for AD using SVM; identified a potential drug target pathway involving METTL3/NDUFA10 and mitochondrial function.

To fully realize the potential of ML and DL, the field should consider transitioning toward consistent quantification frameworks with IVT calibration (e.g. m6AConquer) [63]. Also, training datasets should be built with OV data by integrating multiple platforms. Furthermore, future advances may harness the power of LLMs and knowledge graph (KG) generation to quickly represent the discoveries and strategies used by different studies and platforms [131]. Such AI-driven knowledge representation will be useful in automating omic data discoveries and facilitating the translation to precision medicine [132].

AI-driven knowledge synthesis for hypothesis generation

Beyond analyzing new data, a complete bioinformatics work flow must also effectively synthesize established knowledge. The biomedical literature is a vast, largely unstructured repository of mechanistic information. Traditional natural language processing tools often struggle to capture the complex, directional, and hierarchical causalities inherent in neurobiology [133]. However, the advent of LLMs and AI-driven KGs has mitigated this limitation [134]. Recent advancements demonstrate the potential of LLMs in cognitive neuroscience [133, 135]. For instance, frameworks like ExKG-LLM utilize LLMs to automate the expansion of cognitive neuroscience KGs by accurately parsing complex hierarchical relationships from scientific literature [136]. Advanced prompting strategies, such as analogical reasoning (e.g. MetaphorPrompt), have further enhanced the ability of LLMs to extract nuanced causal links from unstructured biological text [137]. Moreover, hybrid architectures like PKG-LLM have successfully integrated KGs with LLMs to predict specific psychiatric outcomes, such as Generalized Anxiety Disorder and MDD [138, 139]. By leveraging these models, systems can read and interpret thousands of scientific papers, transforming unstructured text into a structured network of genes, proteins, and their interactions [140].

This section provides a demonstration of how these knowledge synthesis pipelines can be used to construct a comprehensive mechanistic map of m^{6}A's role in psychiatric disease. From a curated set of 43 research articles (listed in Supplementary Table S1 available online at http://bib.oxfordjournals.org/; a summary is provided in Supplementary Table S2 available online at http://bib.oxfordjournals.org/ and complete lists are in Supplementary Tables S3–S13 available online at http://bib.oxfordjournals.org/), we applied ReguloGPT, an LLM-based KG generator to construct a molecular network for

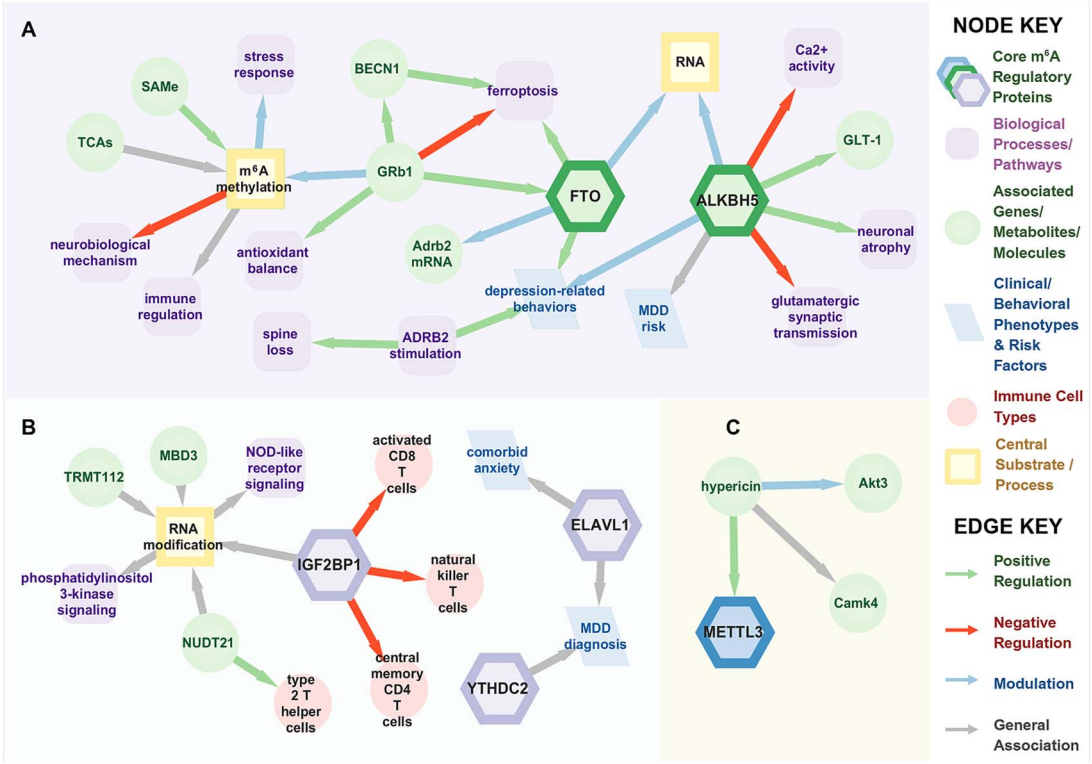

Figure 3 KG of m^{6}A regulatory mechanisms in MDD.

m^{6}A mediated biological mechanism. The tool first extracts biological entities (e.g. genes, proteins, pathways, and disorders) and their directional relationships (e.g. "activates," "inhibits," "is associated with") in the abstract section of the manuscripts. Then, the resulting network is synthesized to display the regulatory relationship between molecular elements. Furthermore, we then verify each extracted fact against its source publication to reduce the model-generated "hallucinations" and ensure scientific accuracy [141].

The resulting KG (Fig. 3) moves beyond simple association to map multi-step mechanistic pathways. For instance, it contextualizes the link between the *FTO* gene and MDD, showing its risk is likely mediated through its influence on glutamatergic transmission and neuronal atrophy [142]. Similarly, the graph connects the m^{6}A reader protein IGF2BP1 to neuroinflammation by highlighting its role in modulating T-cell populations—a potential link between the epitranscriptome and the immune system in depression [143].

The graph centers on core m^{6}A regulatory proteins (hexagons), such as the demethylases FTO and ALKBH5 and the reader protein IGF2BP1. Edges represent regulatory relationships: green for positive, red for negative, blue for modulation, and gray for association. The graph links these proteins to downstream biological processes (rounded rectangles), cellular phenotypes (pink circles), and behavioral outcomes (parallelograms). For example, FTO is shown to influence depression-related behaviors, while ALKBH5 is associated with MDD risk and glutamatergic synaptic transmission.

KGs for other psychiatric disorders AUD, SCZ, and PTSD reveal their own distinct mechanistic landscapes (Fig. 4). They can also trace pathways from different triggers, whether environmental, genetic, or therapeutic. In AUD, for instance, the graph displays a pathway where chronic alcohol consumption alters the epitranscriptome, with ALKBH5 and the m^{6}A-modified lncRNA GAS5 being key players in the resulting behavioral neuroadaptation [144]. For SCZ, it connects genetic risk factors to neurodevelopment and synaptic plasticity [145]. And in PTSD, it delineates a potential therapeutic mechanism, suggesting the N-acetylcysteine (NAC)'s therapeutic effects are mediated through global m^{6}A levels via the ATF4 signaling pathway [146].

These graphs illustrate the central role of m^{6}A-related mechanisms in each disorder. (i) In AUD, ALKBH5 and the overall epitranscriptome are linked to chronic alcohol consumption and behavioral neuroadaptation. (ii) In SCZ, m^{6}A-SNPs, circRNAs, and risk genes converge on neurodevelopment and synaptic plasticity. (iii) In PTSD, NAC is shown to modulate m^{6}A levels and affect cognition and ATF4 expression.

The ultimate value of this AI-driven synthesis extends beyond data visualization; it serves as a useful tool for literature summarization and hypothesis generation. By structuring the vast landscape of published research, LLM-powered KGs allow algorithms to perform "link prediction"—identifying "cold spots" or latent relationships between m^{6}A regulators and psychiatric phenotypes that have not yet been explicitly studied but are logically probable based on network topology. These identified gaps become the foundation for novel, testable hypotheses. More importantly, when integrated with the SMR causal inference pipelines discussed in Phase 2 of our roadmap, these AI-generated hypotheses can be immediately cross-validated against empirical genetic data. This closed-loop integration systematically guides future research and accelerates the entire discovery cycle. While this review focuses on psychiatric conditions, corresponding KGs for AD, Intellectual Disability (ID), Down Syndrome (DS), Huntington's Disease (HD), Fragile X Syndrome (FXS), and Traumatic Brain Injury are provided in Supplementary Figs S1–S3 available online at http://bib.oxfordjournals.org/.

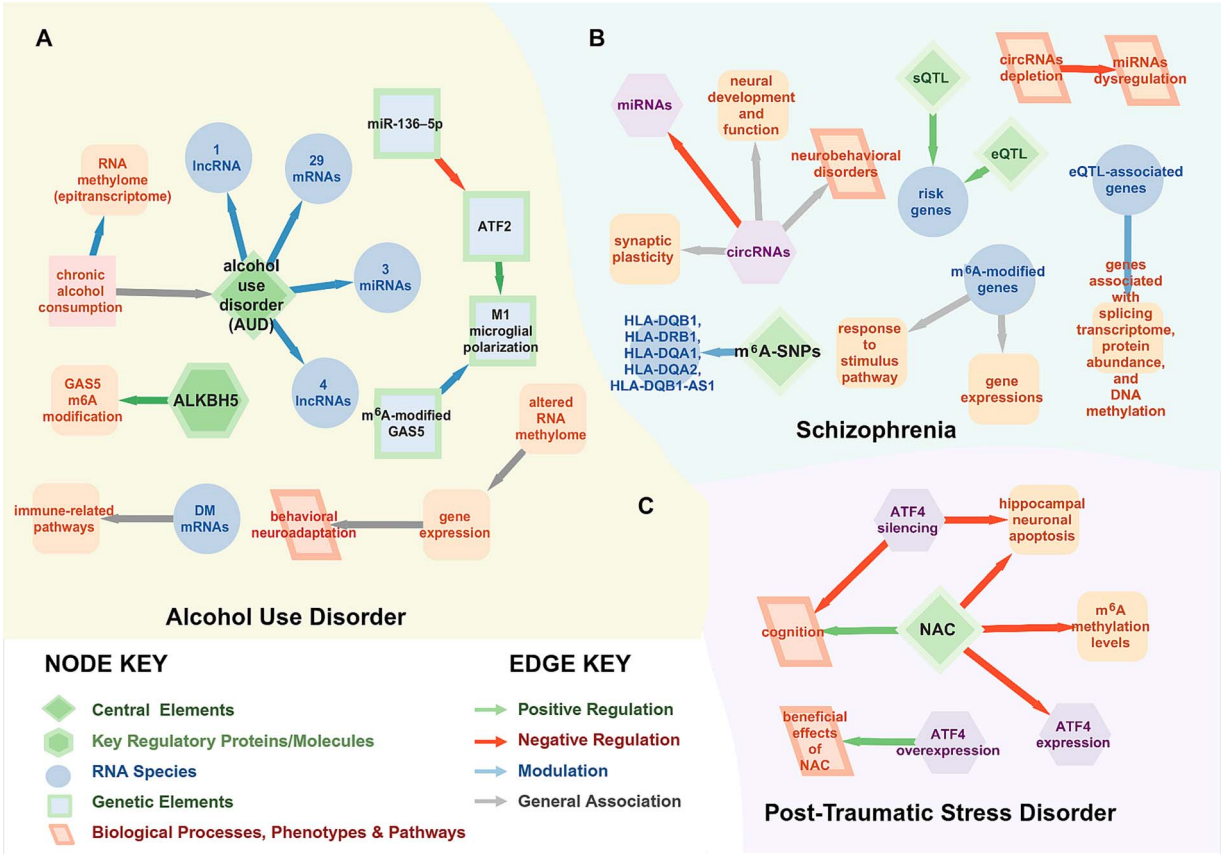

Figure 4 KGs of m^{6}A-related mechanisms in (A) AUD, (B) SCZ, and (C) PTSD.

Case study: identifying causal *N*^{6}-methyladenosine mediators in depression through an integrated end-to-end pipeline

To demonstrate the practical utility of our proposed bioinformatics roadmap, we conducted a case study on linking m^{6}A with depression (MDD). Individual omics studies are often constrained by small sample sizes and descriptive methodologies, which complicate the replication of findings and fail to establish causality. To address this, we transitioned from a conventional cross-study descriptive comparison to a genetics based causal-inference framework, directly applying Phase 2 and Phase 3 of our roadmap.

Establishing functional context via cross-study convergence

We first applied an exploratory re-analysis pipeline (Phase 1) to five publicly available MeRIP-seq datasets on depression, ensuring a spread across human and mouse models (Table 5) [43, 147, 148, 151, 152]. To explicitly trace our data sources, these datasets are denoted as Study 1 (Human; GEO: GSE144136/microarray meta), Study 2 (Mouse; GSA: CRA005192), Study 3 (Mouse; GSA: CRA012006 & GEO: GSE102556), Study 4 (Human; GEO: GSE275676), and Study 5 (Mouse; GEO: GSE113801).

To ensure a standardized comparison across these heterogeneous sources, we implemented a rigorous screening process. First, differentially methylated peaks (DMPs) were extracted using a uniform significance threshold ($P < .05$). These peaks were then annotated to their host genes, taking into account potential technical confounders such as peak GC content bias, which can skew peak distributions and density across different sequencing batches. Subsequently, Gene Ontology (GO) functional enrichment—calculated based on gene overlap analysis (using R packages such as clusterProfiler)—was performed independently for the three mouse studies (Studies 2, 3, and 5) to establish a within-species baseline.

As shown in Fig. 5B, the number and nature of enriched GO terms varied considerably, with a particularly substantial difference between Study 2 and Study 5. To understand this divergence, we examined the non-overlapping terms (Supplementary Table S14 available online at http://bib.oxfordjournals.org/). For instance, Study 2 was uniquely enriched in distinct metabolic processes (e.g. branched-chain amino acid catabolism and coenzyme A metabolic process). In contrast, Study 3 highlighted structural and synaptic dynamics (e.g. protein localization to synapse and organelle transport along microtubule), while Study 5 captured a much broader systemic stress response. This discrepancy is likely driven by variations in experimental designs (e.g. distinct acute vs. chronic stress paradigms), varying sequencing depths, and tissue-specific sensitivities, leading Study 5 to capture a much broader systemic stress response compared to Study 2. Despite this baseline heterogeneity, when intersecting the enriched term lists, "cognition" (GO:0050890) emerged as the universally shared category across all three mouse datasets (Fig. 5C). Building on this functional convergence, we sought to identify the core gene-level drivers. Rather than relying on simple overall significance, candidate genes were screened requiring two strict conditions: (i) harboring significantly differential m^{6}A peaks ($P < .05$) in multiple independent mouse studies, and (ii) being explicitly annotated under the shared

Table 5 Experimental design summary of five selected omics studies investigating m^{6}A methylation in depression [43, 147–150].

PMID/DOI	Research topic	Species	Brain region/tissue	Peak calling & differential analysis method/tool	Main conclusion
10.1016/j.psycom.2022.100089 [147]	The m^{6}A-methylome in major depression: A bioinformatic analysis of publicly available datasets	Human	DLPFC / vmPFC	exomepeak2	Altered m^{6}A profiles in depression, with sex-specific changes impacting neuronal function and immune response.
34836959 [148]	Fat mass and obesity-associated protein regulates RNA methylation associated with depression-like behavior in mice	Mouse	Cortex, Hippocampus, mPFC, AMY	MetPeak; DiffBind/DESeq2	FTO is crucial for m^{6}A methylation in the brain, influencing depression-like behaviors by regulating neuronal function.
38773146 [43]	Astrocytic ALKBH5 in stress response contributes to depressive-like behaviors	Mouse	mPFC	MACS2; Homer & MetDiff	Astrocytic ALKBH5 plays a significant role in stress response and the development of depressive-like behaviors by regulating m^{6}A RNA demethylation.
39650737 [149]	Altered m^{6}A RNA methylation profiles in depression implicate the dysregulation of discrete cellular functions in males and females	Human	vmPFC	TRESS	Depression involves altered m^{6}A methylation profiles, with distinct changes in males and females affecting cellular functions.
30048615 [150]	The Role of m^{6}A/m-RNA Methylation in Stress Response Regulation	Mouse	Cortex, BLCLs	exomePeak; DiffBind/DESeq2	Stress exposure significantly alters m^{6}A/m-RNA methylation, impacting gene expression and contributing to stress-related disorders.

"cognition" (GO:0050890) pathway. This precise functional filtering yielded an intersection of exactly seven candidate genes: *Cacna1e, Map1a, Gnas, Arc, Cacna1c, Mfsd2a, and Rcan2* (Fig. 5D and E, detailed IGV plots for each gene are provided in Supplementary Figs S4–S10). While this cross-study descriptive analysis highlights reproducible molecular patterns, descriptive overlap does not equate to causality. To bridge this gap, we advanced to statistical genetic integration.

Prioritizing causal *N*^{6}-methyladenosine targets via summary-data-based Mendelian randomization integration

To explicitly address the "causality gap" highlighted in our framework, we advanced beyond the descriptive MeRIP-seq datasets used above. We applied SMR to integrate large-scale MDD GWAS summary statistics (sourced from the Psychiatric Genomics Consortium (PGC) with human brain-specific m^{6}A-QTL datasets (sourced from the m6AConquer database) (Phase 2). Unlike basic expression correlation, SMR utilizes genetic variants as IVs to test whether the effect of an SNP on MDD risk is functionally mediated through alterations in specific m^{6}A methylation sites.

Our SMR analysis prioritized a robust set of causal m^{6}A targets in MDD (Supplementary Table S15 available online at http://bib.oxfordjournals.org/, containing full SMR calculations). Specifically, *ADARB1* and *ZBTB37* were identified among the top-ranked mediators, with *ADARB1* emerging as the primary causal mediator (Fig. 5F). The SMR locus plot illustrates the co-localization of GWAS risk signals with the m^{6}A-QTL architecture at the *ADARB1* locus, indicating that the genetic risk for MDD is potentially mediated by local epitranscriptomic dysregulation rather than merely generic transcriptional changes.

Resolving cell-type specificity via single-nucleus RNA-seq annotation

A critical limitation of bulk sample based SMR analysis is the obscuring of cell-type-specific patterns. To demonstrate Phase 3 of our roadmap and adhere to a cell-type specific annotation strategy, we validated our top causal target, *ADARB1*, using single-nucleus RNA-seq (snRNA-seq) data from the Human Protein Atlas (HPA) (database access links are provided in Supplementary Methods). As illustrated in Fig. 5G, the expression profile of *ADARB1* is not uniformly distributed across the brain parenchyma; rather, it exhibits profound enrichment specifically within excitatory and inhibitory neurons, with minimal to no expression in glial populations (e.g. astrocytes and microglia).

This cell-type-specific annotation provides a potential biological explanation for our MR analysis. It suggests that the m^{6}A-mediated genetic risk prioritized by SMR may operates within the neuronal circuits governing cognition and mood, rather than representing a peripheral or glia-driven stress response. Together, this case study present a complete workflow demonstrating targeted SMR and single-cell annotation pipeline can synthesize actionable, causal hypotheses for psychiatric etiology.

Resolving cellular heterogeneity in psychiatric risk

Since the m^{6}A-QTL is derived from general tissue or cell type data, it could omit cell-type unique m^{6}A patterns and lead to potentially reduced power and false negatives in MR results [78]. Recent work

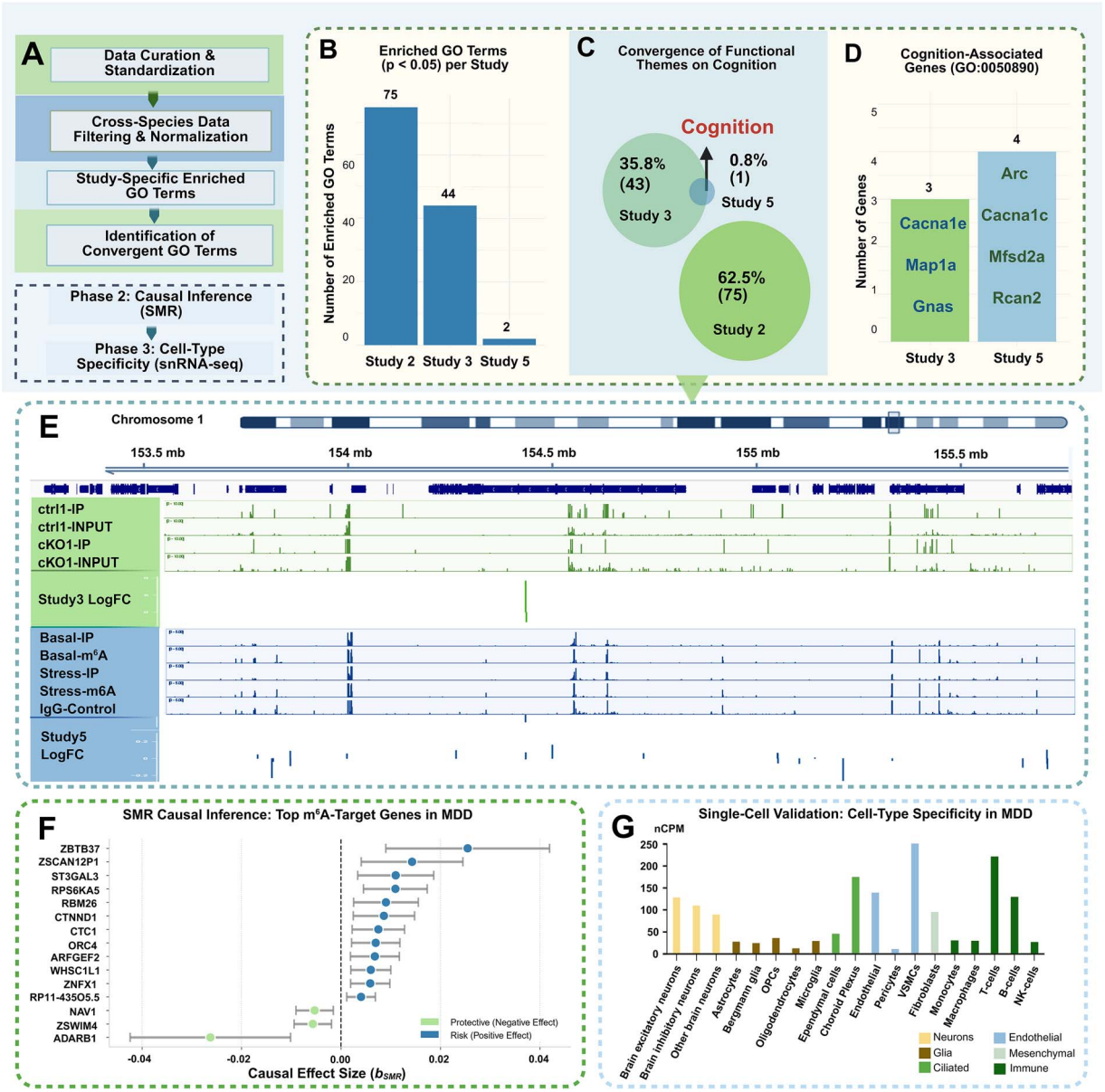

Figure 5 An end-to-end bioinformatics pipeline identifying causal m^{6}A targets in depression. (A) The integrated workflow illustrating two distinct analytical phases: transitioning from descriptive functional convergence (using MeRIP-seq datasets: Study 2, 3, and 5) to causal SMR inference (using MDD GWAS summary statistics from the PGC and brain m^{6}A-QTL datasets). (B) Number of enriched GO terms in the mouse studies. (C) Venn diagram showing the convergence of functional themes on "cognition". (D) The seven specifically screened cognition-associated genes with differential m^{6}A peaks. (E) Example IGV plot for the *Cacna1e* gene (see Supplementary Figs S4–S10 for the full set of identified genes), showing differential m^{6}A peaks from two of the analyzed studies. Where the regions with visible logFC value corresponds to the significantly DMPs. The log2 fold-change (logFC) values represent the ratio of m^{6}A enrichment levels between depression models and their corresponding controls. (F) SMR locus plot, illustrating the causal mediation of MDD genetic risk through brain-specific m^{6}A-QTLs at the *ADARB1* locus. (G) snRNA-seq validation from the HPA, demonstrating that the prioritized causal target (*ADARB1*) is highly specific to excitatory and inhibitory neuronal lineages, supporting a "Brain-First" functional etiology.

in single-cell m^{6}A profiling have suggested epitranscriptomic heterogeneity within the mammalian brain plasticity [7]. Consequently, our workflow introduced the integration of sc/sn or spatial transcriptomic data (Phase 3). Projecting bulk-derived causal m^{6}A targets onto single-cell atlases, as demonstrated by our neuronal-specific *ADARB1* validation in the case study is useful to resolve whether a genetic risk variant linked to m^{6}A act through the mediation of specific neural biology pathways. However, one must account for the fact that genetic variants associated with psychiatric diseases are naturally enriched in brain tissues [149]. Consequently, sc/snRNA-Seq or spatial transcriptome annotation should be conducted within a statistical framework that accounts for the high baseline brain association inherent in GWAS data.

Conclusion and future directions

The bioinformatics roadmap outlined in this review offers a structured framework for integrating high-dimensional omics data

in psychiatric research. It describes a sequential analytical process that begins with reliable quantitative assessment of m^6A, proceeds through functional and integrative interpretation, and extends to causal modeling and predictive analyses using statistical and machine-learning approaches. By combining these complementary strategies, researchers can move beyond correlational findings toward causal inferences that link m^6A regulation to psychiatric mechanisms, providing a conceptual guideline for future translational studies.

Despite substantial progress, several persistent, field-wide challenges continue to constrain m^6A research in psychiatry. The most pressing is the issue of reproducibility and data quality [151]. As our own cross-study analysis illustrates, individual investigations often comprise small sample sizes and distinct experimental designs, resulting in low reproducibility for differential methylation at both the gene and peak level [150]. Our focus on convergence at the level of functional categories (e.g. cognition-related processes) provides an alternative approach for identifying reproducible functional themes. However, the methodology requires further refinement, for instance through the computation of a permutation-based *P*-value to mitigate spurious term overlap, given that highly expressed genes in the brain are often linked to cognitive processes [153].

Future perspectives: prioritizing quality and standardization

Looking forward, and to move beyond current limitations, we propose that the next stage of m^6A research must prioritize three crucial pillars to ensure clinical translation.

First, the field must place greater emphasis on data quality and standardization. This entails a shift from relative to absolute quantification (e.g. eTAM-Seq and GLORI), or the use of lower-resolution techniques that are carefully calibrated and cross-validated. Reliable m^6A-QTL inference likewise depends on calibrating sequencing technologies using IVT controls or machine-learning-based correction methods such as m6ACali [26]. Achieving the goals of this roadmap will also require community-agreed standards for data generation, processing, and integration, similar to those established by ENCODE [153]. Our recently established m6AConquer project, which aims for consistent quantification and orthogonal validation across 10 high-quality m^6A profiling techniques, represents a positive step in this direction [63].

Second, realizing the clinical relevance of epitranscriptomic findings will require integrative efforts across orthogonal lines of evidence. A key direction lies in developing statistical synthesis frameworks that combine signals from independent analytical streams, including different m^6A profiling technologies, causal inference pipelines, ML models, and KG representations. Each of singular techniques is susceptible to distinct biases and artifacts. However, when their signals demonstrate quantitative concordance under consistent criteria, such as reproducibility metrics or cross-method overlap, the resulting conclusions gain both statistical and biological credibility.

Third, progress will depend on enhancing biological resolution and cohort scale, addressing the current limitations of bulk tissue analysis. Most available datasets, including those in our case study, are derived from bulk brain tissue, which averages molecular signals across multiple cell types (neurons, astrocytes, microglia, and others). Each of these cell types may exhibit distinct epitranscriptomic profiles and contribute differently to disease mechanisms [154]. Future progress will depend on the application of single-cell technologies capable of quantitative or absolute m^6A mapping (e.g. sc-GLORI or sc-eTAM-Seq), which may help clarify how cell-type-specific m^6A dysregulation contributes to psychiatric disease pathophysiology [155].

While promising, AI-assisted KGs should be applied judiciously and interpreted with caution. Our analysis illustrates their capacity to integrate large volumes of literature and to suggest hypotheses that might otherwise be difficult to formulate manually. However, the core issue is that these KGs only collect information about what is claimed to have been discovered in the literature, rather than assessing the quality of the experimental systems that produced those claims. Furthermore, underlying LLMs can produce "hallucinations", creating plausible yet factually incorrect relationships [156]. Accordingly, such KGs should not be regarded as repositories of verified truth but as an efficient tool for literature review and hypothesis generation. Future work on AI-assisted KG tools should focus not only on extracting the ontology of molecular networks, but also on representing the structure of the experimental systems.

Furthermore, our bioinformatics roadmap focused on m^6A is also transferable for other RNA covalent modifications (e.g. m^5C, PSI, m^7G, m^1A) [157]. As technologies for profiling of other RNA modifications are validated, the same frameworks can help identify which of the more than 170 potential RNA markers may play roles in psychiatric disorders [158]. In the long term, linking computational insights with mechanistic validation of m^6A pathways may open new directions for understanding, and ultimately treating, the molecular complexity of psychiatric disease.

Key Points

- N^6-methyladenosine (m^6A) dysregulation is strongly implicated in psychiatric disorders, but deciphering causal mechanisms from complex multi-omics data remains a significant methodological challenge.
- We propose a comprehensive bioinformatics roadmap targeting robust causal inference to derive psychiatric clinical insights. The roadmap leverages calibrated m^6A-QTL data, SMR, and cell-type-specific annotation to link m^6A dysregulation to disease phenotypes.
- Interpretable ML approaches and LLM-driven Knowledge Graphs facilitate refined patient stratification and hypothesis generation.
- Future clinical translation in psychiatric epitranscriptomics will critically depend on the availability of large-scale, absolutely quantified m^6A datasets and the development of computational frameworks capable of integrating orthogonal lines of evidence.

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Author contributions

Shuhe Liu (Conceptualization, Methodology, Formal analysis, Investigation, Data Curation, Visualization, Writing—original draft), Xichen Zhao (Methodology, Resources), Daniel F Carr (Writing—review & editing), Zhen Wei and John Moraros (Conceptualization, Supervision, Project administration, Funding acquisition, Writing—review & editing). All authors read and approved the final manuscript.

Supplementary material

Supplementary material is available at *Briefings in Bioinformatics* online.

Conflicts of interest

The authors declare no conflict of interest.

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Data availability

The data underlying this article are available in the article and in its online supplementary materials.

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