SYSTEMATIC REVIEW

Single Nucleotide Polymorphisms in *ANK3* and Psychiatric Risk: A Meta-Analysis, Systematic Review, and Quantitative Trait Locus Insights

[version 1; peer review: awaiting peer review]

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Abstract

Background

Ankyrin 3 (Ankyrin G), encoded by the *ANK3* gene, is a membrane-associated scaffold protein critical for neuronal signaling and highly enriched in axonal initial segments and nodes of Ranvier. *ANK3* variants have been implicated in several neuropsychiatric disorders.

Objectives

To identify single nucleotide polymorphisms (SNPs) in *ANK3* associated with psychiatric disorders, assess population-specific significance, determine variant locations, and explore regulatory effects through quantitative trait locus (QTL) analysis.

Methods

A meta-analysis and systematic literature review were conducted to identify disease-associated SNPs in *ANK3.* QTL analyses were performed using datasets from the eQTL Catalogue and GTEx v10 to evaluate regulatory effects in brain tissues.

Results

Meta-analysis identified significant associations between *ANK3* SNPs and psychiatric disorders. In bipolar disorder, rs10994336 (OR = 1.28,

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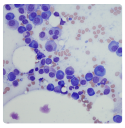
P = 1.04×10^{-4}) was significant in European+North American populations; rs9804190 was protective in Europeans (OR = 0.88, P = 0.020); and rs1938526 was significant in both European+North American (OR = 1.32, P = 7.26×10^{-12}) and Asian populations (OR = 1.08, P = 4.68×10^{-12}), with an overall effect (OR = 1.17, P = 0.003). In schizophrenia, rs10761482 showed opposite effects: protective in Chinese (OR = 0.74, P = 0.002) and risk-associated in Iranian cohorts (OR = 1.57, P = 0.025). rs10994359 was protective in major depressive disorder in Asians (OR = 0.69, P = 0.016), and three SNPs reduced PTSD risk (OR = 0.48, P = 0.045). All significant variants were intronic. QTL analyses showed rs10761482 increased *ANK3* expression in neocortex (P = 0.001) and neurons (P = 0.038); three PTSD SNPs showed robust cerebellar splicing effects (FDR = 0.010); and apaQTLs indicated modest 3′-UTR effects in putamen.

Conclusion

Multiple intronic *ANK3* SNPs are significantly associated with psychiatric disorders and display tissue-specific regulatory effects. Integrating QTL data provides insights into their potential functional roles in neuropsychiatric pathogenesis.

Keywords
ANK3, psychiatric disorders, bipolar disorder, schizophrenia, major depression, post-traumatic stress disorder, single nucleotide polymorphism, QTL analysis



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Introduction

ANK3 (Ankyrin-G) is a membrane-associated scaffold protein encoded by the *ANK3* gene on chromosome 10q21.2. It plays a fundamental role in organizing the axon initial segment (AIS) by anchoring voltage-gated sodium channels and adhesion molecules to the cytoskeleton, thereby ensuring proper neuronal polarity and efficient action potential initiation. Disruption of ANK3 function compromises AIS integrity and has been implicated in neuropsychiatric disorders such as bipolar disorder and schizophrenia, highlighting its importance in maintaining neuronal excitability and circuit stability.[1] In the central nervous system, *ANK3* is abundantly expressed in the neocortex and hippocampus—key regions involved in cognitive processing, emotional regulation, and behavioral control. Owing to its essential role in neuronal development, membrane organization, and signal transduction, ANK3 expressed as multiple isoforms arising from alternative splicing, which differ in both molecular weight and subcellular localization. The high-molecular-weight isoforms (~270–480 kDa) are predominantly enriched at the axon initial segment (AIS), where they interact with voltage-gated sodium channels and cytoskeletal components to maintain neuronal polarity and excitability.[2] In contrast, shorter isoforms are typically localized at postsynaptic densities and are thought to contribute to dendritic spine formation and synaptic plasticity.[3] *ANK3* has been repeatedly identified as a candidate gene in genetic and functional studies of neuropsychiatric disorders.[4]

Over the past decade, genome-wide association studies have identified significant associations between *ANK3* single nucleotide polymorphisms (SNPs) and a range of psychiatric disorders, including bipolar disorder (BD), schizophrenia (SZ), major depressive disorder (MD), and post-traumatic stress disorder (PTSD). These findings suggest that genetic variation within the *ANK3* locus may contribute to shared pathophysiological mechanisms underlying multiple neuropsychiatric phenotypes.[5,6] However, despite accumulating evidence, considerable inconsistencies remain regarding which *ANK3* SNPs are most robustly associated with psychiatric disorders and whether these associations are consistent across diverse populations. Such uncertainties highlight the need for systematic synthesis of existing findings and comprehensive functional characterization of disease-associated variants.

To address this gap, the present study integrates meta-analysis with QTL-based transcriptomic analysis to comprehensively evaluate the role of *ANK3* genetic variants in psychiatric disorders. We first conducted a meta-analysis of published association studies to identify statistically significant *ANK3* SNPs across bipolar disorder (BD), schizophrenia (SZ), major depressive disorder (MD), and post-traumatic stress disorder (PTSD), incorporating population stratification to examine potential ethnic differences. Candidate SNPs identified through this approach were subsequently subjected to functional investigation using large-scale transcriptomic and QTL datasets to elucidate their molecular regulatory effects.

Specifically, we performed expression quantitative trait locus (eQTL) analysis using the eQTL Catalogue to determine whether disease-associated *ANK3* SNPs modulate gene expression levels in brain tissues. In parallel, alternative polyadenylation QTL (apaQTL) data from GTEx v10 were utilized to investigate the impact of these variants on *ANK3* 3′-end processing, which may influence transcript isoform usage, mRNA stability, and translational efficiency. To further assess regulatory effects on transcript structure, splice QTL (sQTL) data from GTEx v10 were analyzed to examine whether the identified SNPs affect alternative exon inclusion or splice junction usage within *ANK3*.[7]

By integrating statistical associations with multilayered transcriptomic evidence—including gene expression, alternative polyadenylation, and splicing—this study seeks to elucidate the functional relevance of *ANK3* genetic variants in the pathogenesis of psychiatric disorders. Our findings reconcile prior inconsistencies in GWAS through meta-analysis and uncover potential mechanisms by which noncoding intronic SNPs contribute to disease via modulation of *ANK3* expression and post-transcriptional regulation in a tissue-specific context. This comprehensive framework underscores the value of combining genetic epidemiology with functional genomics to advance our understanding of psychiatric disease biology and to inform the development of targeted therapeutic strategies.

Method

Criteria for inclusion

In this analysis, we included both randomized controlled trials (RCTs) and observational studies involving individuals diagnosed with neurological or psychiatric disorders across diverse geographic regions. For each patient cohort, a matched control group comprising healthy individuals from the same population and study was selected. Eligible studies were published in English between January 1, 2000, and recent years, and were required to report associations between *ANK3* SNPs and disease risk. Risk estimates were extracted in the form of odds ratios (OR), while SNP relationships were assessed using either minor allele frequency (MAF) or specific genotype distributions. For cohorts stratified by region, meta-analysis was performed only when a consistent direction of effect was observed across all subgroups. SNPs reported in two or more independent studies were included in the quantitative meta-analysis, whereas those reported in a single study were synthesized narratively.

Criteria for exclusion

Studies employing hazard ratios (HR) for SNP risk estimation were excluded. We also omitted investigations not focused on neurological or psychiatric disorders, as well as those lacking clear information regarding the geographic or national origin of participants outside Europe, America, or Asia. Articles that did not specifically address risk associations with *ANK3* SNPs were disregarded. In addition, animal studies, medical records, case reports, expert commentaries, and review articles were excluded. Only peer-reviewed articles published in English were included in the final dataset.

Literature retrieval and selection

In accordance with the predefined inclusion criteria, two independent researchers (TG and YW) systematically searched PubMed, Web of Science, and MEDLINE using combinations of the terms "genome-wide association study" with "*ANK3*", as well as "nucleotide polymorphisms" with "ankyrin 3" or "Ankyrin-G". Relevant studies were screened, and data were extracted independently by both reviewers using a standardized data extraction form. Any discrepancies were resolved through discussion with a third researcher until consensus was achieved. All analyses were subsequently conducted by two researchers. This multi-reviewer approach was implemented to minimize subjective bias and enhance the reproducibility of the findings.

Quality assessment of included studies

The studies with controlled trials were evaluated by the Newcastle-Ottawa Scale (NOS)[8,9] by two different researchers independently. NOS include 1. Selection: 1) Is the case definition adequate? 2) Representativeness of the cases. 3) Selection of controls. 4) Definition of Controls. 2. Comparability. 1) Comparability of cases and controls based on the design or analysis. 3. Exposure. 1) Ascertainment of exposure. 2) Same method of ascertainment for cases and controls. 3) Non-Response rate. The total score is 9, and if a study can get over 5, it can be assessed as good quality. Those articles which did not meet the quality requirement were excluded.

Extraction of data

In accordance with our eligibility criteria, studies were evaluated based on study design, characteristics of patient and control cohorts, and clearly defined outcome measures. From each eligible study, we extracted key variables including lead author, year of publication, number of cases, participant nationality, age distribution, gender ratio, smoking status, reported odds ratio (OR), corresponding 95% confidence interval (CI), and associated p-value. The complete extracted dataset used for conducting the meta-analysis, including all OR and confidence intervals for each *ANK3* SNP across psychiatric disorders, is available as Extended dataset 1 (Figshare, https://doi.org/10.6084/m9.figshare.29886620).[10]

Synthesis and analysis of data and assessment of publication bias

Utilizing the "meta (version 4.18-0)" package within R 4.0.1 and RStudio, we conducted a meta-analysis on the specified SNPs. Odds ratios (OR) and 95% confidence intervals (95%CI) were input to yield synthesized outcomes. For studies presenting results as MAF with case numbers for both patient and control groups, preliminary calculations for OR and 95%CI were necessary. We combined the funnel plot and the Egger test[11] to assess the publication bias of the meta-analysis. As none of the meta-analyses included 10 or more studies, publication bias was not assessed, in accordance with Cochrane guidance.[12]

Plotting the SNPs in *ANK3* gene sequence

SNPs discerned from the meta-analysis and synthetic review were mapped onto the human *ANK3* gene. Intron and exon details for human *ANK3* were sourced from the Ensembl protein database (https://www.ensembl.org/Homo_sapiens/Transcript/Exons?db=core;g=ENSG00000151150;r=10:60012155-60747633;t=ENST00000280772).[13] Subsequent visualization was crafted using PowerPoint'.

QTL analysis

Following the meta-analysis of psychiatric trait SNPs, we conducted an integrative QTL examination to determine how the ten *identified ANK3*-associated variants influence transcript regulation in brain tissue. eQTL slopes and p values were retrieved from the eQTL Catalogue (https://www.ebi.ac.uk/eqtl/)[14]; when the same SNP–tissue pair appeared in more than one study, a fixed-effect inverse variance model was used to obtain a single β estimate. apaQTL (alternative polyadenylation) and sQTL (splicing) summary statistics were retrieved from the GTEx v10 resource (https://gtexportal.org/home/datasets)[15] and filtered to chromosome 10 entries mapping to *ANK3.* For every brain tissue, we extracted the slope (β), its standard error, and the nominal p value.

To correct for multiple testing across tissues and regulatory layers, we applied Benjamini–Hochberg false discovery rate (FDR)[16] correction to the nominal p-values within each QTL modality (eQTL, apaQTL, and sQTL). Associations with FDR < 0.05 were considered statistically significant. In cases where nominal significance ($p < 0.05$) was observed but

FDR correction yielded non-significant results, the findings were interpreted as suggestive and reported with appropriate caution. All datasets were parsed and harmonised by rsID using custom Python 3.11 and Bash scripts. Data were visualised using GraphPad Prism 9 and matplotlib in Python. Throughout all analyses, β values are reported to indicate the direction and magnitude of allele effects on gene expression (eQTL), 3′-end/poly(A) site usage (apaQTL), or splice junction usage (sQTL).

Results

Literature extraction and quality assessment

Using the predefined search strategy, a total of 1,140 articles were retrieved from the selected databases. Following title and abstract screening, duplicate entries were removed. Full-text review resulted in the exclusion of 214 studies, primarily due to methodological insufficiencies or unclear study protocols. Ultimately, 27 English-language studies met the inclusion criteria and were retained for analysis. All included studies satisfied the quality standards as assessed by the Newcastle–Ottawa Scale. The key characteristics of the selected studies are summarized in Extended dataset 2 (https://doi.org/10.6084/m9.figshare.30090913),[17] and the literature selection process is outlined in Figure 1.

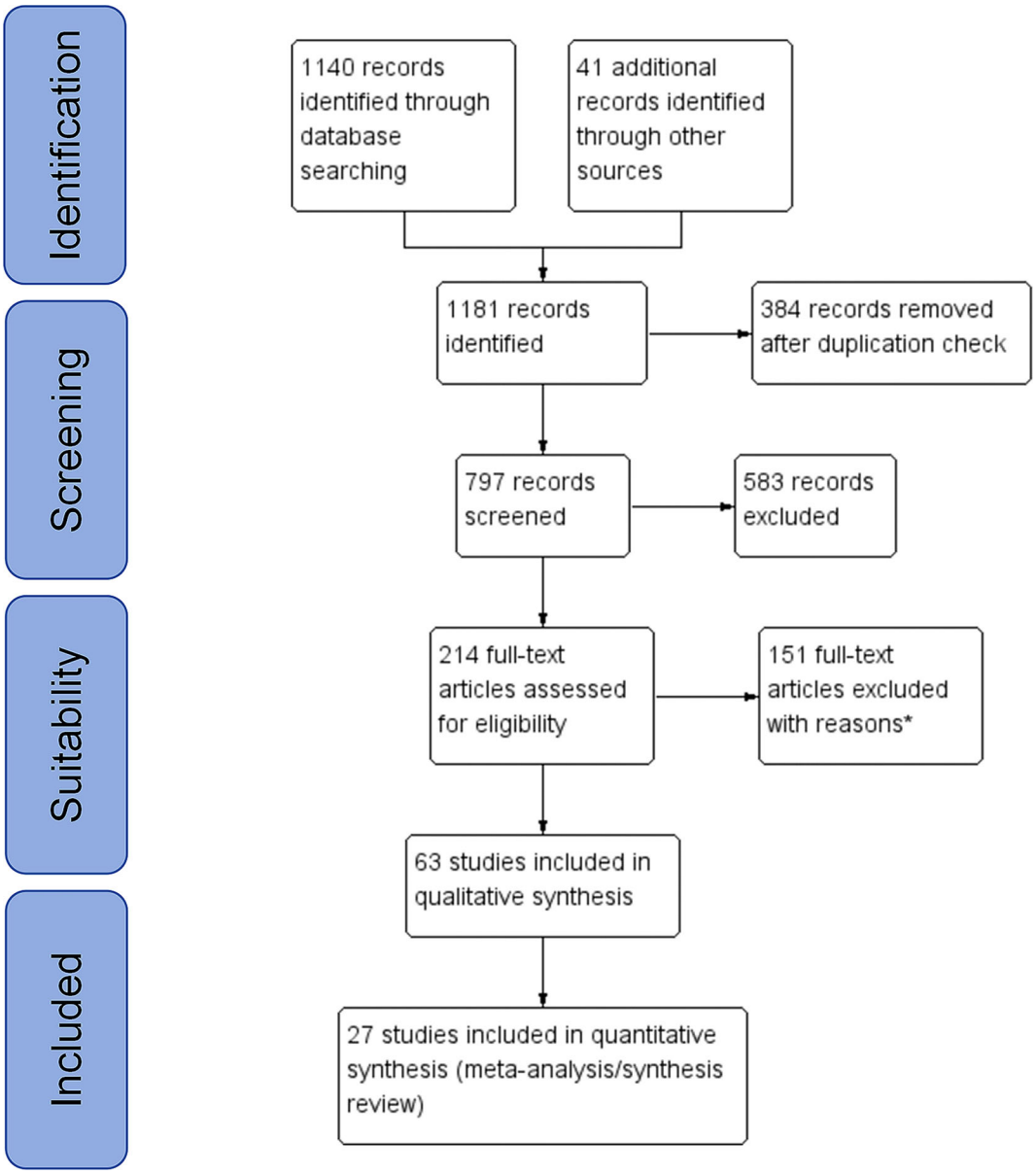

Figure 1. The process of literature screening. *For exclusion, please refer to section *Criteria for Exclusion.*

Meta-analysis and synthetic review of the risk of ANK3 SNPs with bipolar disorder

The meta-analysis identified five *ANK3* SNPs—rs10994336, rs9804190, rs10994397, rs1938526, and rs139972937—as loci of interest across psychiatric disorders. Rs10994336, included in nine studies from European and North American populations, emerged as a significant risk locus (OR = 1.28, 95% CI: 1.13–1.45, $P = 1.04 \times 10^{-4}$), but did not show significance in Asian populations (P = 0.600). Rs9804190 was reported in three European studies, where it showed a significant protective effect (OR = 0.88, 95% CI: 0.79–0.98, $P = 0.020$), though this association was not observed when extended to the combined European and North American cohort ($P = 0.173$). Rs10994397 was identified as a significant risk variant in two European studies (OR = 1.35, 95% CI: 1.24–1.47, $P = 4.71 \times 10^{-12}$), but this effect was not replicated in the broader dataset ($P = 0.254$). In contrast, rs1938526 demonstrated consistent risk associations across both European + North American (five studies; OR = 1.32, 95% CI: 1.22–1.43, $P = 7.26 \times 10^{-12}$) and Asian populations (three studies; OR = 1.08, 95% CI: 1.04–1.12, $P = 4.68 \times 10^{-12}$), with pooled analysis confirming its significance (OR = 1.17, 95% CI: 1.05–1.29, $P = 0.003$). Additionally, rs139972937, although reported in a single European study, was significantly associated with bipolar disorder ($P = 0.040$) and was thus retained for synthetic review (Figure 2 and Extended dataset 3 (https://doi.org/10.6084/m9.figshare.30090964)[18]).

Meta-analysis and synthetic review of the risk of ANK3 SNPs with schizophrenia

This segment of the meta-analysis focused on four *ANK3* SNPs previously implicated in schizophrenia—rs1938526, rs10761482, rs10994336, and rs9804190. Across all included studies, none of these variants demonstrated a statistically significant association with schizophrenia in their respective populations ($P > 0.05$). To further explore potential population-specific effects, subgroup analysis was conducted for rs10761482 within the Asian population, which was stratified into three subgroups based on Hardy–Weinberg equilibrium (HWE) status and ethnicity. The first subgroup comprised Chinese cohorts not in HWE (details regarding HWE evaluation are presented in the Discussion), the second subgroup included Iranian participants, and the third subgroup consisted of Chinese cohorts with significant HWE conformity. Notably, in the Chinese subgroup conforming to HWE, rs10761482 exhibited a significant protective association (OR = 0.74, 95% CI: 0.61–0.90, $P = 0.002$), while in the Iranian subgroup, it was identified as a potential risk

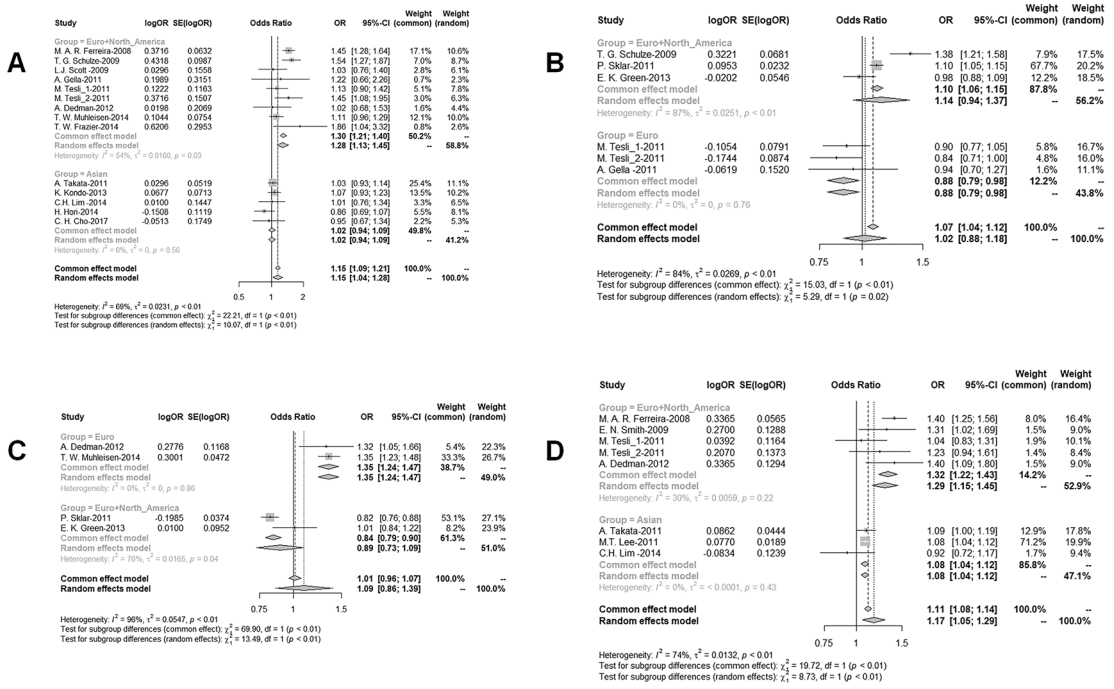

Figure 2. Forrest plots of the risk of *ANK3* SNPs in patients with bipolar disorder. (A) Comparison of *ANK3* (rs10994336) MAF risks in BP patients and healthy control. Forest plot showing meta-analysis of *ANK3* (rs10994336) MAF risks. (B) Comparison of *ANK3* (rs9804190) MAF risks in BP patients and healthy control. Forest plot showing meta-analysis of *ANK3* (rs9804190) MAF risks. (C) Comparison of *ANK3* (rs10994397) MAF risks in BP patients and healthy control. Forest plot showing meta-analysis of *ANK3* (rs10994397) MAF risks. (D) Comparison of *ANK3* (rs1938526) MAF risks in BP patients and healthy control. Forest plot showing meta-analysis of *ANK3* (rs1938526) MAF risks.

locus (OR = 1.57, 95% CI: 1.06–2.33, *P* = 0.025), suggesting possible ethnic or population-specific heterogeneity in the genetic architecture of schizophrenia (Figures 3 & 4; Extended dataset 3 (https://doi.org/10.6084/m9.figshare.30090964)[18]).

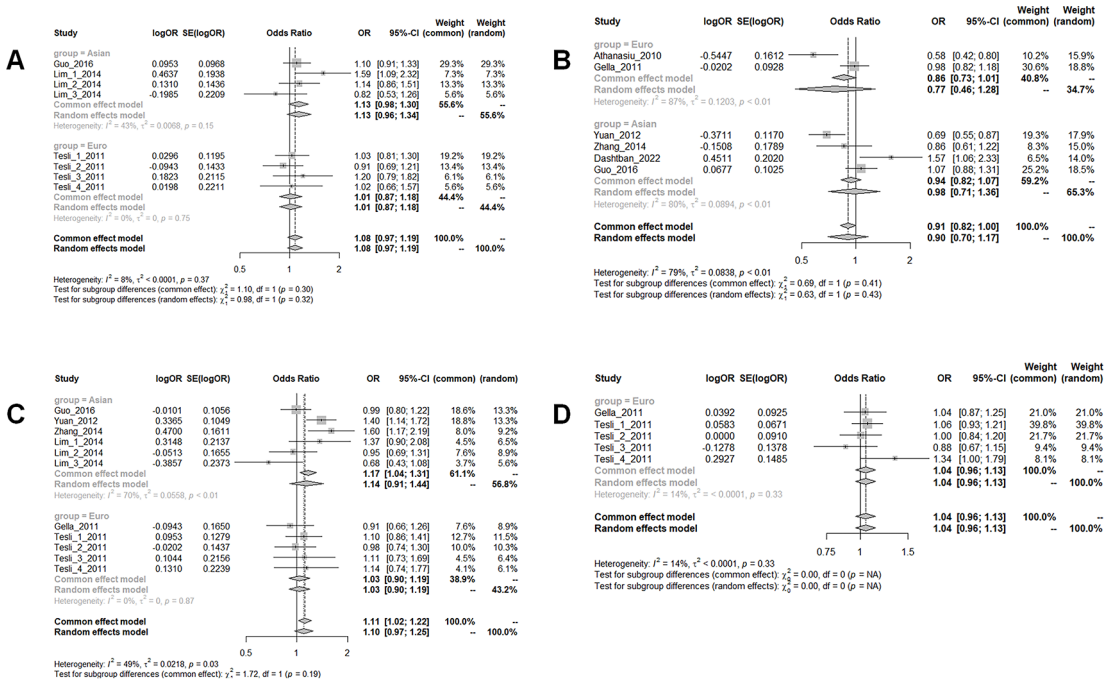

Figure 3. Forrest plots of meta-analysis of the risk of *ANK3* SNPs in patients with Schizophrenia. (A) Comparison of *ANK3* (rs1938526) MAF risks in SZ patients and healthy control. Forest plot showing meta-analysis of *ANK3* (rs1938526) MAF risks. (B) Comparison of *ANK3* (rs10761482) MAF risks in SZ patients and healthy control. Forest plot showing meta-analysis of *ANK3* (rs10761482) MAF risks. (C) Comparison of *ANK3* (rs10994336) MAF risks in SZ patients and healthy control. Forest plot showing meta-analysis of *ANK3* (rs10994336) MAF risks. (D) Comparison of *ANK3* (rs9804190) MAF risks in SZ patients and healthy control. Forest plot showing meta-analysis of *ANK3* (rs9804190) MAF risks.

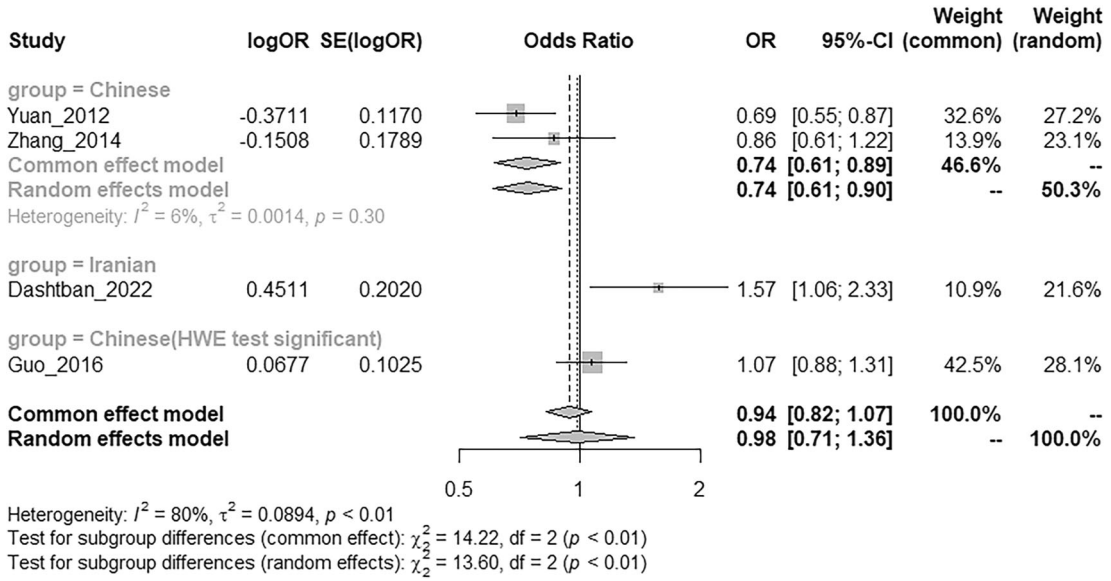

Figure 4. Forrest plots of subgroup meta-analysis of the risk of *ANK3* rs10761482 in Asian patients with Schizophrenia. Comparison of *ANK3* (rs10761482) MAF risks in SZ patients and healthy control of Asian population. Forest plot showing meta-analysis of *ANK3* (rs10761482) MAF risks.

Meta-analysis and synthetic review of the risk of ANK3 SNPs with major depression and posttraumatic stress disorder

This portion of the meta-analysis examined the association between *ANK3* variants and two psychiatric conditions: major depressive disorder (MD) and post-traumatic stress disorder (PTSD). Specifically, the analysis focused on rs10994336 and rs10994359 in relation to MD, and on rs28932171, rs11599164, and rs17208576 in relation to PTSD. Rs10994336 did not demonstrate a significant association with MD in either North American or Asian populations ($P > 0.05$). In contrast, rs10994359 was identified as a significant protective variant in Asian populations (OR = 0.69, 95% CI: 0.51–0.93, $P = 0.016$), suggesting potential ethnic-specific effects. For PTSD, all three investigated variants—rs28932171, rs11599164, and rs17208576—were found to be significantly associated with reduced risk, each exhibiting the same odds ratio (OR = 0.48) and a nominally significant P-value ($P = 0.045$), indicating their potential role as protective loci (Figure 5; Extended dataset 3 (https://doi.org/10.6084/m9.figshare.30090964)).[18]

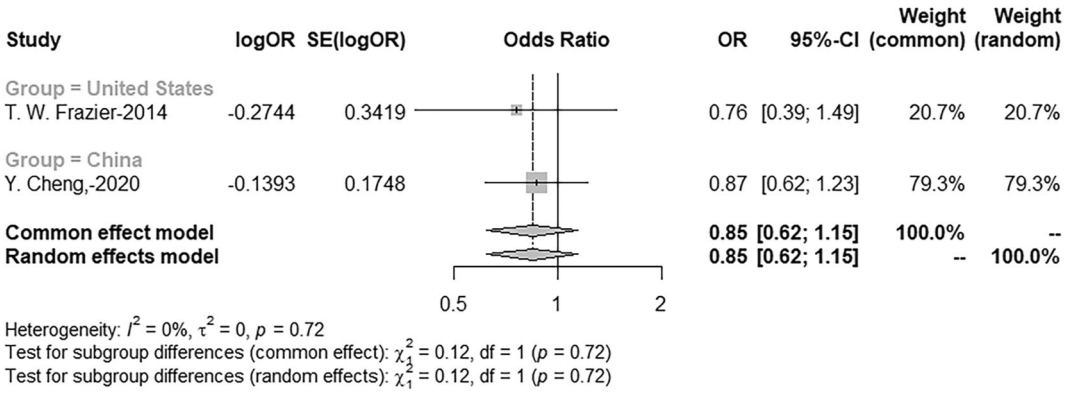

Figure 5. Forrest plot of meta-analysis of the risk of *ANK3* SNPs in patients with major depression. Comparison of *ANK3* (rs10994336) MAF risks in MD patients and healthy control. Forest plot showing meta-analysis of *ANK3* (rs10994336) MAF risks.

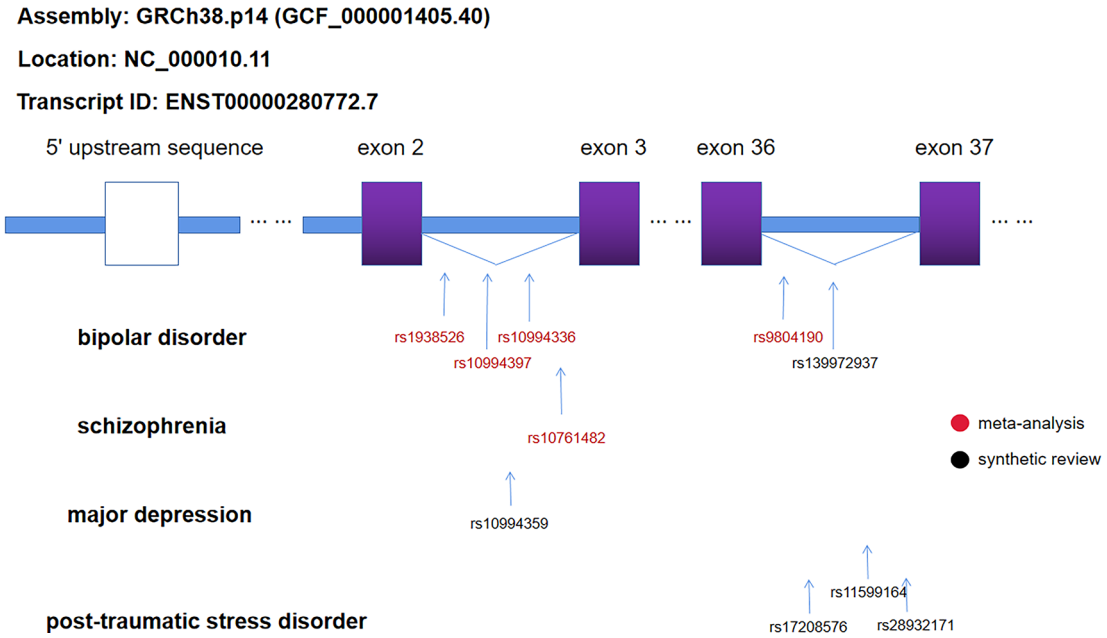

Figure 6. Location of SNPs in the *ANK3* gene significantly associated with psychiatric disorders. The gene map was derived from the human genome reference sequence Assembly: GRCh38.p14 (GCF_000001405.40) with locus: NC_000010.11. The transcript ID referenced for intron and exon information is ENST00000280772.7. SNPs obtained from meta-analysis are labelled in red, whereas SNPs obtained by synthetic review are labelled in black at the corresponding positions.

Table 1. Summary of results of Localisation of SNPs in the *ANK3* gene significantly associated with psychiatric disorders.

Exon No.	Exon/Intron	Start	End	Bipolar disorder	Schizophrenia	Major depression	Posttraumatic stress disorder
	5' upstream sequence						
//							
2	ENSE00003669229	60,615,224	60,615,186				
	Intron 2-3	60,615,185	60,279,640	rs10994336,rs10994397, rs1938526	rs10761482	rs10994359	
3	ENSE00002439064	60,279,639	60,279,538				
//							
36	ENSE00001736354	60,080,618	60,080,537				
	Intron 36-37	60,080,536	60,068,010	rs9804190,rs139972937			rs28932171,rs11599164,rs17208576
37	ENSE00001671026	60,068,009	60,067,935				
//							

(The gene information was derived from the human genome reference sequence Assembly: GRCh38.p14 (GCF_000001405.40) with locus: NC_000010.11. The transcript ID referenced for intron and exon information is ENST00000280772.7.; Numbers starting with the prefix ENSE refer to specific exon data in the Ensembl database.)

Plotting of ANK3 significant SNPs

To further elucidate the potential functional relevance of *ANK3* risk variants, we mapped the SNPs identified as significantly associated with bipolar disorder (BD), schizophrenia (SZ), major depressive disorder (MD), and post-traumatic stress disorder (PTSD) onto the *ANK3* gene structure. Genomic localization was determined using the GRCh38.p14 assembly (GCF_000001405.40), with chromosomal coordinates corresponding to NC_000010.11 and transcript ENST00000280772.7. Structural annotation revealed that rs9804190 and rs139972937 (associated with BD), as well as rs28932171, rs11599164, and rs17208576 (associated with PTSD), are all located within the same intronic region between exon 36 (ENSE00001736354) and exon 37 (ENSE00001671026). Notably, all SNPs showing significant associations across the four psychiatric disorders investigated reside within intronic regions of *ANK3*, suggesting that noncoding regulatory elements within introns may contribute to disease susceptibility through transcriptional or post-transcriptional mechanisms (Figure 6; Table 1).

QTL analysis of psychiatric risk SNPs at the ANK3 locus

Among the ten SNPs associated with psychiatric disorders within the *ANK3* locus, we identified significant regulatory effects on gene expression, alternative polyadenylation (APA), and splicing in human brain tissues. In the expression quantitative trait locus (eQTL) analysis using the eQTL Catalogue, rs10761482 demonstrated a notable association with *ANK3* expression in both neuron-enriched and neocortical cell populations. In neurons, the variant was associated with increased expression ($\beta = 0.12$, SE = 0.06, $P = 0.038$), although the signal did not remain significant following false discovery rate (FDR) correction (FDR = 0.999). In contrast, a stronger effect was observed in the neocortex ($\beta = 0.14$, SE = 0.04, $P = 0.001$), with marginal significance after multiple testing adjustment (FDR = 0.162). These findings suggest that rs10761482 may exert cell-type-specific regulatory effects on *ANK3* expression, particularly within neuronal populations. (Figure 7A, B; Table 2).

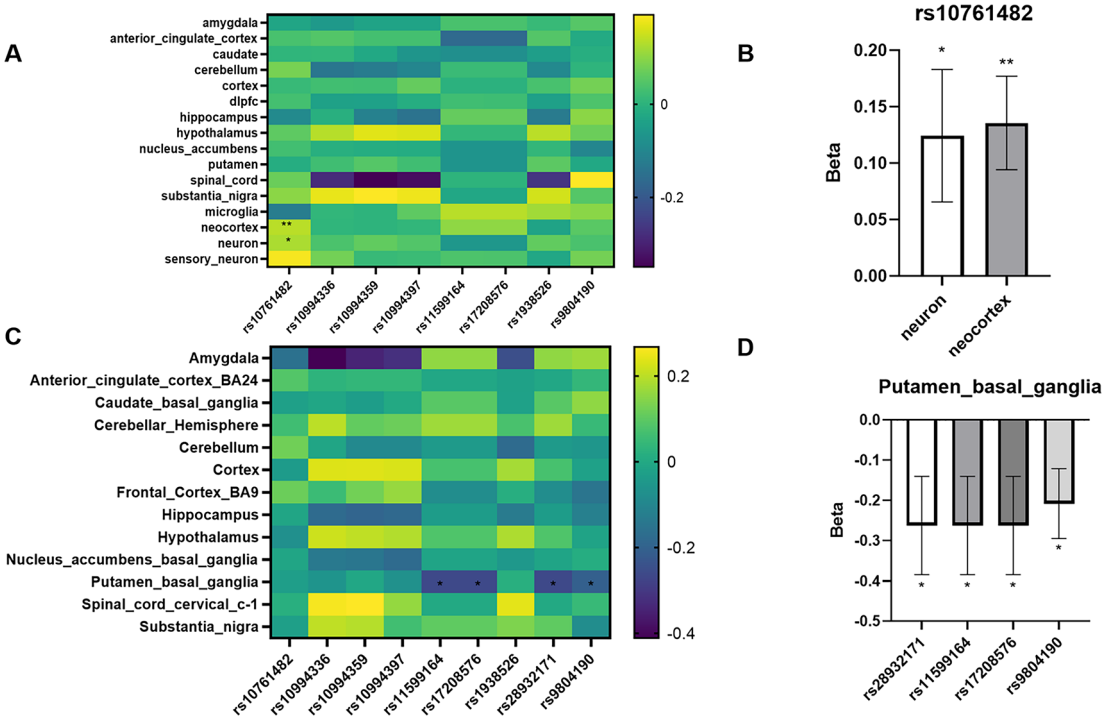

Figure 7. Comparative analysis of eQTL and apaQTL effects of *ANK3*-associated SNPs across brain tissues and cell types. (A) Heatmap displaying β values (slope estimates) of expression quantitative trait loci (eQTLs) for ten *ANK3*-associated SNPs across various brain regions and cell types. The eQTL data were obtained from the eQTL Catalogue, and included both bulk tissues and fine-grained cellular populations (e.g., neuron, neocortex, microglia). (B) Bar plot showing the β value ± standard error (SE) of rs10761482 in neuron and neocortex cell types, indicating differential eQTL effects across these populations. (C) Heatmap showing β values of alternative polyadenylation QTLs (apaQTLs) for the same SNP set across multiple bulk brain tissues. The apaQTL data were derived from GTEx v10 apaQTLs database. (D) Bar plot of β ± SE for four SNPs with significant apaQTL associations ($p < 0.05$) in the Putamen basal ganglia, illustrating their negative effect on *ANK3* 3' end usage. All SNPs were selected based on their reported association with psychiatric disorders and genomic proximity to *ANK3* in meta-analyses. β values represent slope estimates from linear regression models. Significance was determined by nominal p-value < 0.05.

Table 2. Summary of *ANK3* SNPs associated expression QTL (eQTL) effects on *ANK3* in brain-related tissues.

Tissue_label	Rsid	Beta	SE	*P*-val_nominal	*P*-value_FDR
Neocortex	rs10761482	0.14	0.04	**0.001**	0.162
Neuron	rs10761482	0.12	0.06	**0.038**	0.999

(Rsid: Reference SNP ID number from dbSNP; Beta: Effect size estimate of the SNP on gene expression (regression slope); SE: Standard error of the Beta estimate; *P*-val_nominal: Nominal p-value from eQTL association test (unadjusted for multiple comparisons); *P*-value_FDR: False discovery rate (FDR)-adjusted *P*-value accounting for multiple testing).

Table 3. Summary of *ANK3* SNPs associated alternative polyadenylation (APA) QTL of *ANK3* in brain-related tissues.

Tissue_label	Rsid	Beta	SE	*P*-val_nominal	*P*-value_FDR
Putamen_basal_ganglia	rs28932171	-0.26	0.12	**0.033**	0.965
Putamen_basal_ganglia	rs11599164	-0.26	0.12	**0.033**	0.965
Putamen_basal_ganglia	rs17208576	-0.26	0.12	**0.033**	0.965
Putamen_basal_ganglia	rs9804190	-0.21	0.09	**0.018**	0.965

(See *Table 2* for abbreviation definitions).

In the alternative polyadenylation QTL (apaQTL) analysis using GTEx v10 data, four SNPs—rs28932171, rs11599164, rs17208576, and rs9804190—were found to significantly influence the 3′-end processing of *ANK3* transcripts in the putamen, a region of the basal ganglia. All four variants exhibited negative slope values, indicating that the presence of risk alleles was associated with decreased usage of distal polyadenylation sites. Rs28932171, rs11599164, and rs17208576 showed identical effect sizes ($\beta = -0.26$, SE = 0.12, $P = 0.033$), while rs9804190 displayed a slightly weaker but still nominally significant association ($\beta = -0.21$, SE = 0.09, $P = 0.018$). However, none of these associations remained significant following false discovery rate (FDR) correction (FDR = 0.965), suggesting that the observed APA effects are modest and require further validation in independent datasets (Figure 7C, D; Table 3).

In contrast to the more modest effects observed in eQTL and APAQTL analyses, the splice QTL (sQTL) analysis revealed robust associations between the same three SNPs—rs28932171, rs11599164, and rs17208576—and a specific splicing

Table 4. Significant *ANK3* SNPs associated Splicing QTL (sQTL) of *ANK3* in brain-related tissues.

Tissues	Phenotype_id	Rsid	Beta	Se	*P*-val_nominal	*P*-val_FDR
Cerebellum	chr10:60029826:60042667:clu_6403_-:ENSG00000151150.22	rs28932171	0.67	0.15	**1.64e-05**	**0.010**
Cerebellum	chr10:60029826:60042667:clu_6403_-:ENSG00000151150.22	rs11599164	0.67	0.15	**1.64e-05**	**0.010**
Cerebellum	chr10:60029826:60042667:clu_6403_-:ENSG00000151150.22	rs17208576	0.67	0.15	**1.64e-05**	**0.010**
Cerebellum	chr10:60029826:60042672:clu_6403_-:ENSG00000151150.22	rs28932171	-0.70	0.15	**1.06e-05**	**0.010**
Cerebellum	chr10:60029826:60042672:clu_6403_-:ENSG00000151150.22	rs11599164	-0.70	0.15	**1.06e-05**	**0.010**
Cerebellum	chr10:60029826:60042672:clu_6403_-:ENSG00000151150.22	rs17208576	-0.70	0.15	**1.06e-05**	**0.010**

(Phenotype_id: Identifier of the splicing event (includes genomic coordinates, splicing cluster ID, and Ensembl gene ID); others see Table 2 for abbreviation definitions).

event within *ANK3* in the cerebellum. These variants exhibited strong and consistent effect sizes (β = 0.67–0.70, SE = 0.15), accompanied by highly significant nominal P-values ($P = 1.06 \times 10^{-5}$ to 1.64×10^{-5}) and false discovery rate (FDR) values of 0.010. These findings provide compelling evidence for the role of these SNPs in modulating alternative splicing of *ANK3* in brain tissue (Table 4). Collectively, the integration of eQTL, APAQTL, and sQTL analyses demonstrates that psychiatric disorder-associated *ANK3* variants may exert regulatory effects through multiple layers of RNA regulation. Among these, splicing alterations in the cerebellum show the most statistically robust signal, whereas expression and polyadenylation effects appear more modest and context dependent. Full results for each QTL analysis are provided in the extended data: eQTL (Extended dataset 4, https://doi.org/10.6084/m9.figshare.29901494),[19] APAQTL (Extended dataset 5, https://doi.org/10.6084/m9.figshare.29901641),[20] and sQTL (Extended dataset 6, https://doi.org/10.6084/m9.figshare.29901662).[21]

Discussion

Previous studies have demonstrated that *ANK3* single nucleotide polymorphisms (SNPs) contribute to the genetic risk of various psychiatric disorders. However, a comprehensive meta-analysis integrating cross-disorder associations and functional mapping has been lacking. In this study, we systematically analyzed the relationship between *ANK3* SNPs and four major psychiatric conditions—bipolar disorder (BD), schizophrenia (SZ), major depressive disorder (MD), and post-traumatic stress disorder (PTSD)—using both meta-analysis and systematic review approaches. Several SNPs showed significant associations with disease risk, with notable differences in effect size and direction across populations. When mapped onto the *ANK3* gene structure, all significantly associated variants were found within intronic regions. This intronic clustering suggests that noncoding regulatory mechanisms, rather than direct coding sequence alterations, may underlie the pathogenic effects of these variants—potentially through modulation of splicing, transcriptional regulation, or alternative polyadenylation.

The meta-analysis revealed that all the SNPs related to psychiatric disorders are concentrated in two introns. In particular, five SNPs related to BD and PTSD are found within the intron preceding the brain-specific exon 37. This exon 37 (ENSE00001671026) of *ANK3* encodes a key element of the AIS targeting motif, influencing the subcellular localization of Ankyrin-G in neurons. Transcript structure analysis revealed that it is retained in longer isoforms such as ENST00000280772.7 (*ANK3*-201), but absent in several shorter splice variants, including ENST00000616444.4 (*ANK3*-228).[13] It is partially or fully included in the transcripts giving rise to the AIS-localised protein isoforms of 270 kDa and 480 kDa, respectively, but excluded from the postsynaptic 190 kDa isoform of AnkyrinG. Loss of exon 37 affects action potential generation and neuronal signal integration.[22] Interestingly, three of the SNPs significantly associated with psychiatric disorders—rs28932171, rs11599164, and rs17208576— that are located in the intronic region between exon 36 (ENSE00001736354) and exon 37 exhibit strong splicing QTL (sQTL) signals specifically in cerebellum tissue (Table 4). These findings suggest that the risk variants may influence alternative splicing decisions that determine exon 37 inclusion. Such splice isoform shifts could lead to changes in the intracellular distribution of Ankyrin-G, potentially altering its ability to cluster ion channels at the AIS and thereby affecting neuronal polarity, excitability, or signaling, leading to cellular and circuit-level changes in neuronal signalling, and to disease in the long term.

Additionally, SNPs in the intron of *ANK3* may also affect binding of miRNAs (microRNAs) or disrupt enhancer or suppressor elements that regulate gene expression.[23,24] For example, it has been shown that a SNP in miR-137 is associated with an increased risk of schizophrenia. SNPs may alter the binding pattern of miRNAs, leading to overexpression or repression of key genes. The same may be true for *ANK3*. The concentration of SNPs in both introns could mean that these regions are evolutionarily conserved and therefore may have some functionality.[25] So in summary, although the specific functions of these two regions are currently unknown, it would be interesting to explore the specific biological functions of these two introns in further studies.

In our meta-analysis, we found that the significance of associations between some SNPs in *ANK3* and disease varied considerably in different populations. For example, some single nucleotide polymorphisms are significant in some populations in Europe but not in the study of both European and North American populations; or significant in European and American populations but not in Asian populations; or even the same SNPs show opposite trends or significance in different populations. This has a significant relationship with their different populations and genetic backgrounds. For example, Asian populations are very diverse and contain East Asians Central Asians and others. In our meta-analysis of schizophrenia, we found that the significance of rs10761482 in Chinese and Iranian populations showed completely opposite characteristics, one being a risk locus and the other a protective locus. There are some differences between the Chinese and Iranian populations, as most of the Chinese population belongs to East Asian ethnicity, while the Iranians belong to West Asian or Middle Eastern ethnicity. Our meta-analyses revealed greater heterogeneity within some subgroups, which may be related to the fact that there are still differences in the populations included in the same population subgroup. And as we mentioned in the research methodology, we can only further meta-analyse these subgroups if the different population subgroups show the same significance and are all significant. Otherwise, if one

population shows significance and the other does not, then even if they show significance as a whole, it is meaningless and is a false positive.[26–28]

In our meta-analysis of rs10761482 for schizophrenia, we conducted further subgroup analyses of Asian populations into Chinese and Iranian, and one study of Chinese was separated into a separate group because it was significant for the HWE test. The HWE (Hardy-Weinberg Equilibrium) test is a statistical test based on the Hardy-Weinberg equilibrium law. The Hardy-Weinberg law of equilibrium describes how the gene and genotype frequencies of a population remain constant under certain conditions. Significant deviation from Hardy–Weinberg equilibrium (HWE) may indicate non-random mating, population stratification, genotyping error, selection pressure, or recent mutation or migration events that alter genotype frequencies. To minimize potential confounding from such factors, studies with significant HWE deviation were analyzed as a separate subgroup.[29]

We also conducted a targeted QTL analysis of ten pre-selected *ANK3* SNPs previously associated with psychiatric disorders through meta-analysis. Although the scope of variant testing was limited, we applied false discovery rate (FDR) correction to account for multiple comparisons across tissues and regulatory modalities. Unlike genome-wide QTL studies, which necessitate stringent correction due to the extensive number of hypotheses tested, our focused design involved a comparatively small set of SNP–phenotype pairs. Nonetheless, implementing FDR correction in this context strengthens the statistical rigor of our analysis and increases confidence in the robustness and reproducibility of the identified associations.

The application of FDR correction enabled us to differentiate nominal associations from those with stronger statistical support after accounting for multiple testing. In the eQTL analysis, rs10761482 demonstrated nominal significance in both neurons and neocortex, with only the neocortex association approaching FDR significance (FDR = 0.162), suggesting moderate evidence for a cell type–specific regulatory effect. In contrast, apaQTL signals for rs28932171, rs11599164, rs17208576, and rs9804190 in the putamen were all nominally significant ($P < 0.05$), yet none withstood FDR correction (FDR = 0.965), indicating that these intronic variants may influence 3′-end transcript processing, but further validation is required. Most notably, sQTL analysis revealed strong and FDR-significant associations (FDR = 0.010) between rs28932171, rs11599164, and rs17208576 and a specific *ANK3* splicing event in the cerebellum, providing robust evidence that these SNPs exert a functional impact on transcript structure in a brain region–specific manner.

It is important to recognize that nominally significant but FDR-nonsignificant results may still carry biological relevance, particularly within hypothesis-driven, low-dimensional analyses. While FDR correction is essential for controlling the expected proportion of false discoveries across multiple comparisons, its statistical stringency can obscure true signals—especially when effect sizes are moderate or sample sizes are limited. In our study, the consistency of effect direction across tissues and regulatory modalities—for instance, the increased *ANK3* expression associated with rs10761482 in both neurons and neocortex, and the concordant negative APA effects of four SNPs in the putamen—supports the plausibility of underlying regulatory activity. These findings, although not FDR-significant, may reflect genuine biological effects and warrant further validation through functional assays or replication in independent cohorts.

Moreover, the brain regions exhibiting the strongest regulatory signals in our QTL analysis—namely, the neocortex and cerebellum—are well-established contributors to the pathophysiology of psychiatric disorders. The neocortex plays a central role in higher-order cognitive functions, emotional regulation, and sensory integration, and structural and functional abnormalities in this region have been consistently reported in schizophrenia, bipolar disorder, and major depressive disorder. The observed association between rs10761482 and *ANK3* expression in neocortical cells thus offers a plausible molecular link between genetic risk and cortical dysfunction. Similarly, although historically considered a motor coordination center, the cerebellum is increasingly recognized for its involvement in mood regulation, cognitive processing, and social behavior. The robust sQTL effects observed in the cerebellum suggest that *ANK3* splicing regulation in this region may contribute to psychiatric vulnerability, aligning with growing evidence implicating cerebellar dysfunction in conditions such as schizophrenia and autism spectrum disorder.

Together with our findings, a previous methylation QTL (meQTL) study,[30] which reported that rs10994336 was significantly associated with *ANK3* methylation levels in the prefrontal cortex, further reinforcing the regulatory relevance of disease-associated *ANK3* variants. Together, these results suggest that intronic *ANK3* SNPs may modulate disease risk not only through genetic association but also via transcriptional and post-transcriptional regulatory mechanisms.

Although there is no previous comprehensive meta-analysis and systematic review specifically addressing the relationship between *ANK3* variants and multiple psychiatric disorders, prior studies have performed meta-analyses focused on

individual SNPs—such as rs10994336 in bipolar disorder.[31] Compared to these, our study incorporates a broader scope of psychiatric phenotypes, includes a wider range of population data, and adopts stricter criteria for population-level meta-analysis. Specifically, we argue that meta-analysis across populations should only be conducted when consistent significance is observed in each population, as combining heterogeneous signals risks generating false positives.

A key strength of this study lies in the integration of multi-layered QTL analyses to functionally annotate SNPs identified through meta-analysis. By leveraging publicly available datasets from the eQTL Catalogue and GTEx v10, we systematically assessed the impact of disease-associated *ANK3* variants on gene expression (eQTL), transcript splicing (sQTL), and 3′UTR processing (apaQTL) in brain tissues and neuron-enriched cell types. This functional annotation framework, which has been largely absent in prior *ANK3*-focused genetic studies, enabled the identification of regulatory effects for several intronic SNPs. Nonetheless, our study has limitations. We did not perform genotype-stratified analyses, which could refine population-specific effects, nor did we incorporate epigenetic QTLs—such as methylation QTLs—that may modulate *ANK3* expression. For instance, rs10994336 has been previously linked to *ANK3* methylation in brain tissue. Future studies integrating epigenetic data and expanding functional validation may offer a more comprehensive understanding of the regulatory networks through which *ANK3* contributes to psychiatric disease risk.

Ethical considerations

This study was based entirely on publicly available summary-level genomic data (*e.g.*, GWAS, QTL datasets), and does not involve any human participants, animal experiments, or the use of identifiable personal information. Therefore, no ethical approval or informed consent was required. All data used comply with relevant institutional and national guidelines for research integrity and data usage.

Data availability

The data used in this meta-analysis[32–58] and QTLs analysis, including the eQTL Catalogue (https://www.ebi.ac.uk/eqtl/)[14] and GTEx v10 (https://gtexportal.org/home/datasets),[15] were obtained from published articles and public databases, as listed in the Methods and References sections. No new data were generated in this study. Extended data supporting this study, including the extracted datasets used for the meta-analysis (Extended dataset 1), are openly available in Figshare: https://doi.org/10.6084/m9.figshare.29886620.[10] Additional extended data comprise the characteristics of the included studies (Extended dataset 2; https://doi.org/10.6084/m9.figshare.30090913[17]), the summary of meta-analysis results and synthetic review of the risk of ANK3 SNPs with psychiatric disorders (Extended dataset 3; https://doi.org/10.6084/m9.figshare.30090964[18]), and the complete QTL analyses for ANK3 SNPs in human brain tissues, including: Extended dataset 4 – eQTL results (https://doi.org/10.6084/m9.figshare.29901494),[19] Extended dataset 5 – apaQTL results (https://doi.org/10.6084/m9.figshare.29901641),[20] and Extended dataset 6 – sQTL results (https://doi.org/10.6084/m9.figshare.29901662).[21]

Extended datasets

Extended dataset 1: Extracted dataset for the meta-analysis of psychiatric disorder-associated *ANK3* SNPs.

https://doi.org/10.6084/m9.figshare.29886620.[10]

Extended dataset 2: Characteristics of the studies included.

https://doi.org/10.6084/m9.figshare.30090913.[17]

Extended dataset 3: Summary of results of meta-analysis and synthetic review of the risk of ANK3 SNPs with psychiatric disorders.

https://doi.org/10.6084/m9.figshare.30090964.[18]

Extended dataset 4: Complete eQTL analysis results for *ANK3* SNPs in human brain tissues.

https://doi.org/10.6084/m9.figshare.29901494.[19]

Extended dataset 5: Complete apaQTL analysis results for *ANK3* SNPs in human brain tissues.

https://doi.org/10.6084/m9.figshare.29901641.[20]

Extended dataset 6: Complete sQTL analysis results for *ANK3* SNPs in human brain tissues.

https://doi.org/10.6084/m9.figshare.29901662.[21]

Reporting guidelines

The PRISMA 2020 checklist used to guide the reporting of this systematic review and meta-analysis has been deposited in Figshare: https://doi.org/10.6084/m9.figshare.29849501.

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