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RESEARCH PAPER

INVESTIGATING THE PLEIOTROPIC ROLE OF KIF21B IN SCHIZOPHRENIA AND MULTIPLE SCLEROSIS: A BIOINFORMATICS ANALYSIS

Ela Doruk Korkmaz, Elif Everest

Abstract

Objective: Genome-wide association studies have identified shared genetic risk loci between schizophrenia (SCZ) and multiple sclerosis (MS), suggesting overlapping biological mechanisms despite distinct clinical presentations. Here, we aimed to characterize the biological plausibility of *KIF21B* as a shared genetic risk gene for SCZ and MS, two disorders with overlapping genetic risk loci despite distinct clinical presentations.

Method: We performed bioinformatics analyses of *KIF21B* using publicly available data from GTEx, STRING, and the GWAS Catalog, including tissue-specific expression profiling, protein interaction network analysis, transcriptome-wide co-expression analysis, and phenome-wide association analysis.

Results: *KIF21B* expression was significantly enriched in both brain and immune tissues compared to other tissue types. Protein interaction network analysis demonstrated that *KIF21B* functions within microtubule-based transport machinery essential for axonal function. Co-expression analysis identified significant correlation with immune-related genes, including the established MS susceptibility gene *ANKRD55*, with pathway enrichment for T cell activation and lymphocyte differentiation. Phenome-wide association analysis confirmed *KIF21B* pleiotropy across multiple autoimmune and psychiatric conditions.

Conclusions: These findings support *KIF21B* as a biologically plausible shared risk gene whose dual neural and immune functions may contribute to susceptibility for both neuropsychiatric and autoimmune diseases of the central nervous system.

Key words: schizophrenia, multiple sclerosis, pleiotropy

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Introduction

Genome-wide association studies have revealed extensive genetic pleiotropy across complex human disorders, with many risk variants influencing multiple distinct phenotypes. Ahangari et al. (2022) demonstrated shared genetic architecture between schizophrenia (SCZ) and multiple sclerosis (MS), identifying 36 genomic loci jointly associated with both disorders. Although the overall genetic correlation was negligible, indicating that global genetic architectures of SCZ and MS remain largely distinct, the observed focal polygenic overlap suggests that common biological pathways or shared molecules may contribute to both neuropsychiatric and autoimmune disease susceptibility. Earlier analyses of SCZ-MS pleiotropy found that much of the shared signal was driven by the MHC region, where HLA risk alleles showed opposite directions of effect between the two disorders (Andreassen et al., 2015). Among the non-MHC shared loci identified by Ahangari et al. (2022), the *KIF21B* gene (rs12126806) showed robust association with both SCZ ($p = 2.89\times10^{-8}$) and MS ($p = 2.68\times10^{-10}$) with concordant direction of effects, making it a particularly compelling candidate for investigating shared biological mechanisms outside the MHC. *KIF21B* encodes a member of the kinesin superfamily, a plus-end directed motor protein that regulates microtubule dynamics and is essential for neuronal morphology and synaptic function (Marszalek et al., 1999; Muhia et al., 2016). While kinesins are best known for their roles in neuronal function, including axonal transport, they also participate in immune cell trafficking and activation (Hooikaas et al., 2020; Kurowska et al., 2012). This dual biological context makes *KIF21B* a good candidate for investigating how a single gene might contribute to risk for both a neuropsychiatric disorder and an autoimmune disease of the central nervous system.

In this study, we performed bioinformatics analyses of *KIF21B* using publicly available genomic and transcriptomic data. We examined tissue expression patterns, protein interaction networks, transcriptome-wide co-expression, and phenome-wide association to

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characterize the functional context of this pleiotropic risk gene and evaluate its relevance to both SCZ and MS pathophysiology.

Methods

Gene selection and data sources

KIF21B was selected for follow-up analysis based on findings from Ahangari et al. (2022), which identified 36 genomic loci jointly associated with SCZ and MS using Gaussian causal mixture modeling and conditional/conjunctional false discovery rate frameworks. The *KIF21B* locus (rs12126806) demonstrated significant association with both disorders (SCZ $p = 2.89\times10^{-8}$; MS $p = 2.68\times10^{-10}$) with concordant direction of effects. To characterize the functional context of this pleiotropic risk gene, we analyzed publicly available data from three primary resources: the Genotype-Tissue Expression (GTEx) version 10 for tissue expression and expression quantitative trait locus (eQTL) data (Aguet et al., 2020), the STRING database version 12 for protein-protein interactions (Szklarczyk et al., 2023), and the NHGRI-EBI GWAS Catalog for phenome-wide associations (Cerezo et al., 2025).

Expression and co-expression analyses

Median transcripts per million (TPM) values across 68 human tissues were extracted for *KIF21B* (ENSG00000116852) from GTEx v10. Tissues were categorized into three functional groups: brain (n = 13 tissues), immune (n = 4 tissues), and other (n = 51 tissues). Statistical comparisons between tissue categories were performed using the Kruskal-Wallis H-test for overall differences and pairwise Mann-Whitney U tests with Bonferroni correction ($\alpha = 0.017$), with effect sizes calculated using Cohen's d. To identify genes with correlated expression patterns, we calculated Pearson correlations between *KIF21B* and all other genes across the 68 tissues, applying Bonferroni correction for multiple testing. To assess whether the GWAS lead variant rs12126806 influences *KIF21B* expression, we queried the GTEx single-tissue cis-eQTL dataset for significant variant-gene pairs (q-value ≤ 0.05) across all 49 tissues with available data.

Functional annotation

Protein-protein interactions for KIF21B were retrieved from the STRING database using a minimum interaction score of 0.4 (medium confidence), and the top 20 interaction partners were visualized as a network using the NetworkX Python library. Gene Ontology (GO) Biological Process enrichment analysis was performed on both the protein interaction network and the co-expression module using the STRING API, with terms ranked by false discovery rate (FDR < 0.05). To assess phenotypic pleiotropy, we queried the GWAS Catalog for all variants mapped to *KIF21B* and retained the most significant p-value for each unique trait. Traits were categorized as psychiatric, autoimmune/inflammatory, neurological, or other, with statistical significance assessed relative to the genome-wide threshold ($p < 5\times10^{-8}$). All analyses were performed using Python 3.11 with pandas, matplotlib, scipy, and seaborn libraries.

Results

KIF21B expression is enriched in brain and immune tissues

Analysis of GTEx expression data revealed that *KIF21B* is preferentially expressed in tissues relevant to both SCZ and MS pathophysiology (**figure 1A**). Among 68 tissues examined, the highest expression levels were observed in small intestine terminal ileum (36.8 TPM), whole blood (28.6 TPM), testis (26.6 TPM), brain cortex (25.1 TPM), and spleen (23.7 TPM).

When tissues were grouped by functional category, immune-related tissues showed the highest mean expression (mean = 19.83 TPM, median = 20.95 TPM, n = 4), followed by brain tissues (mean = 12.66 TPM, median = 12.87 TPM, n = 13), while other tissues showed substantially lower expression (mean = 3.34 TPM, median = 1.60 TPM, n = 51) (**figure 1B**). The difference in *KIF21B* expression across tissue categories was statistically significant (Kruskal-Wallis $H = 28.43$, $p = 6.70\times10^{-7}$). Pairwise comparisons confirmed that both brain tissues (Mann-Whitney $U = 614$, $p = 1.26\times10^{-6}$, Cohen's $d = 1.42$) and immune tissues ($U = 194$, $p = 2.76\times10^{-4}$, $d = 2.51$) showed significantly higher *KIF21B* expression compared to other tissue types. The difference between immune and brain tissues did not reach statistical significance ($p = 0.10$, $d = 0.97$), indicating that *KIF21B* is comparably enriched in both compartments. This dual enrichment in both neural and immune compartments is consistent with *KIF21B* contributing to disease risk in both SCZ and MS.

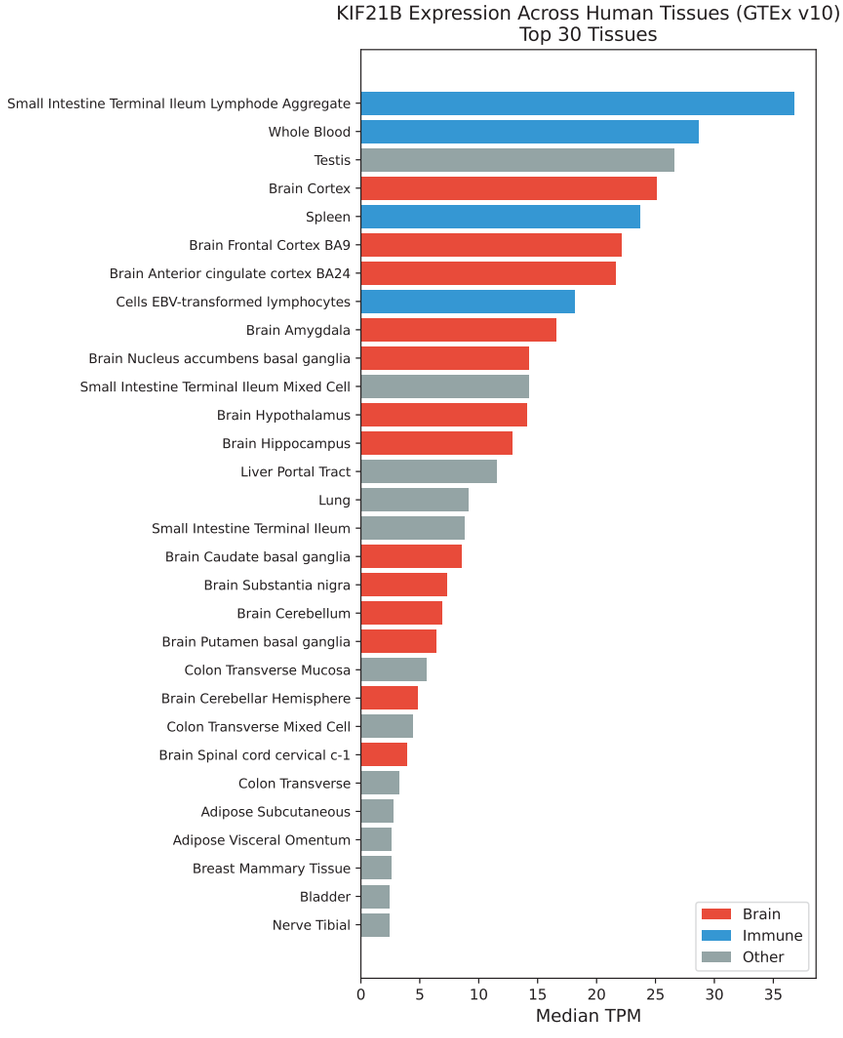
Examination of GTEx eQTL data revealed that while *KIF21B* has significant eQTLs in multiple tissues (including 13 eQTLs in brain cortex, 51 in brain frontal cortex, and 12 in whole blood), the GWAS lead variant rs12126806 was not among the significant cis-eQTLs in any of the 49 tissues tested. This suggests that rs12126806 is likely tagging a nearby causal variant in linkage disequilibrium rather than being directly functional.

KIF21B interacts with microtubule transport machinery

To understand the functional context of KIF21B protein, we queried the STRING database for protein-protein interactions (**figure 2A**). KIF21B interacts predominantly with other members of the kinesin superfamily, including KIF5A, KIF5B, KIF5C, KIF1A, KIF1B, KIF2A, and KIF21A (interaction scores 0.63–0.70). The strongest interaction was observed with TRIM3 (score = 0.77), an E3 ubiquitin ligase involved in neuronal function (Schreiber et al., 2015; Dong et al., 2020). Additional interactors included SMO (score = 0.69), a key component of the Hedgehog signaling pathway important for neurodevelopment (Twigg et al., 2016), and STK36 (score = 0.69), a serine/threonine kinase also involved in Hedgehog signaling (Murone et al., 2000).

Gene Ontology enrichment analysis of the KIF21B interaction network revealed highly significant enrichment for microtubule-based cellular processes (**figure 2B**). The most significantly enriched term was "microtubule-based movement" (FDR = 1.64×10^{-26}), followed by "microtubule-based transport" (FDR = 1.37×10^{-7}) and "anterograde axonal transport" (FDR = 3.43×10^{-6}). These findings indicate that KIF21B

Figure 1. *KIF21B tissue expression profile. (A) KIF21B expression across human tissues. Horizontal bar plot displaying median KIF21B transcript levels (TPM, transcripts per million) in the 30 highest-expressing tissues from the GTEx v10 dataset. Bars are colored by tissue category: brain regions (red), immune-related tissues (blue), and other tissues (gray). KIF21B shows notably high expression in both immune tissues and multiple brain regions, consistent with a role in both neurological and immune function. (B) KIF21B expression is enriched in brain and immune tissues compared to other tissue types. Boxplots showing distribution of median KIF21B expression (TPM) across tissues grouped by functional category: brain (n = 13 tissues), immune (n = 4 tissues), and other (n = 51 tissues). Individual tissues are shown as overlaid points. Immune tissues showed the highest mean expression (19.83 TPM), followed by brain tissues (12.66 TPM), while other tissues showed substantially lower expression (3.34 TPM)*



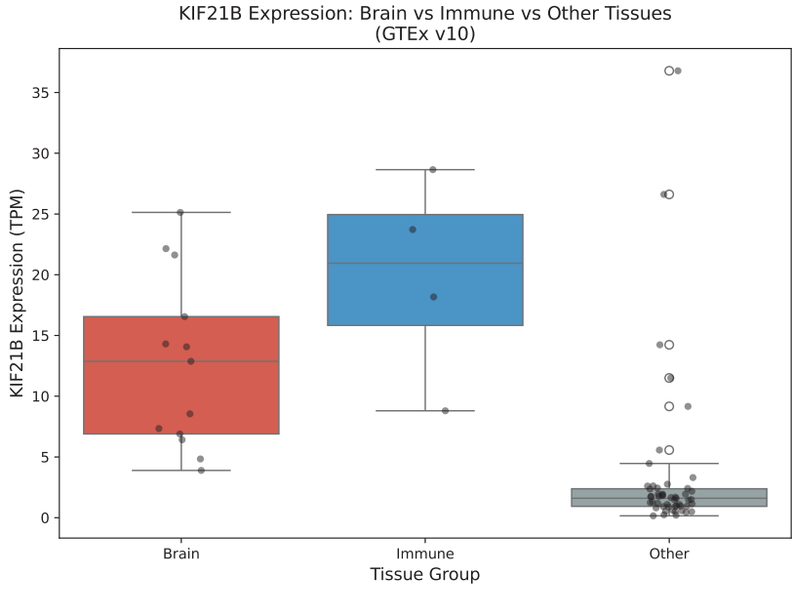
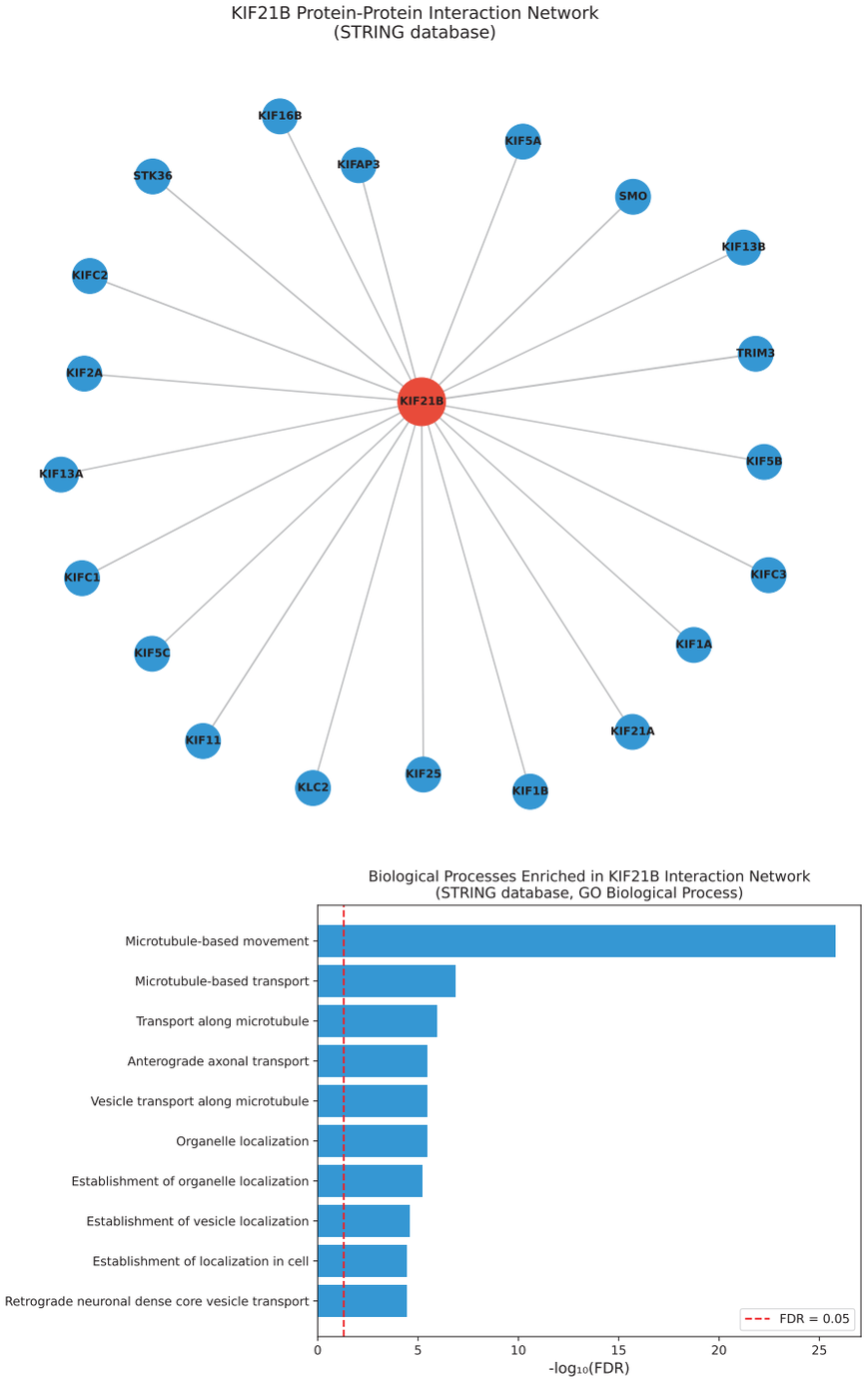


Figure 2. *KIF21B protein interaction network and functional enrichment. (A) Protein-protein interaction network for KIF21B derived from the STRING database. KIF21B (red) is shown as the central node, with its top 20 interaction partners (blue) arranged radially. (B) Gene Ontology Biological Process enrichment analysis of the KIF21B interaction network. Bar plot shows the top 10 enriched terms ranked by significance (-log₁₀ FDR). Red dashed line indicates FDR = 0.05 threshold*

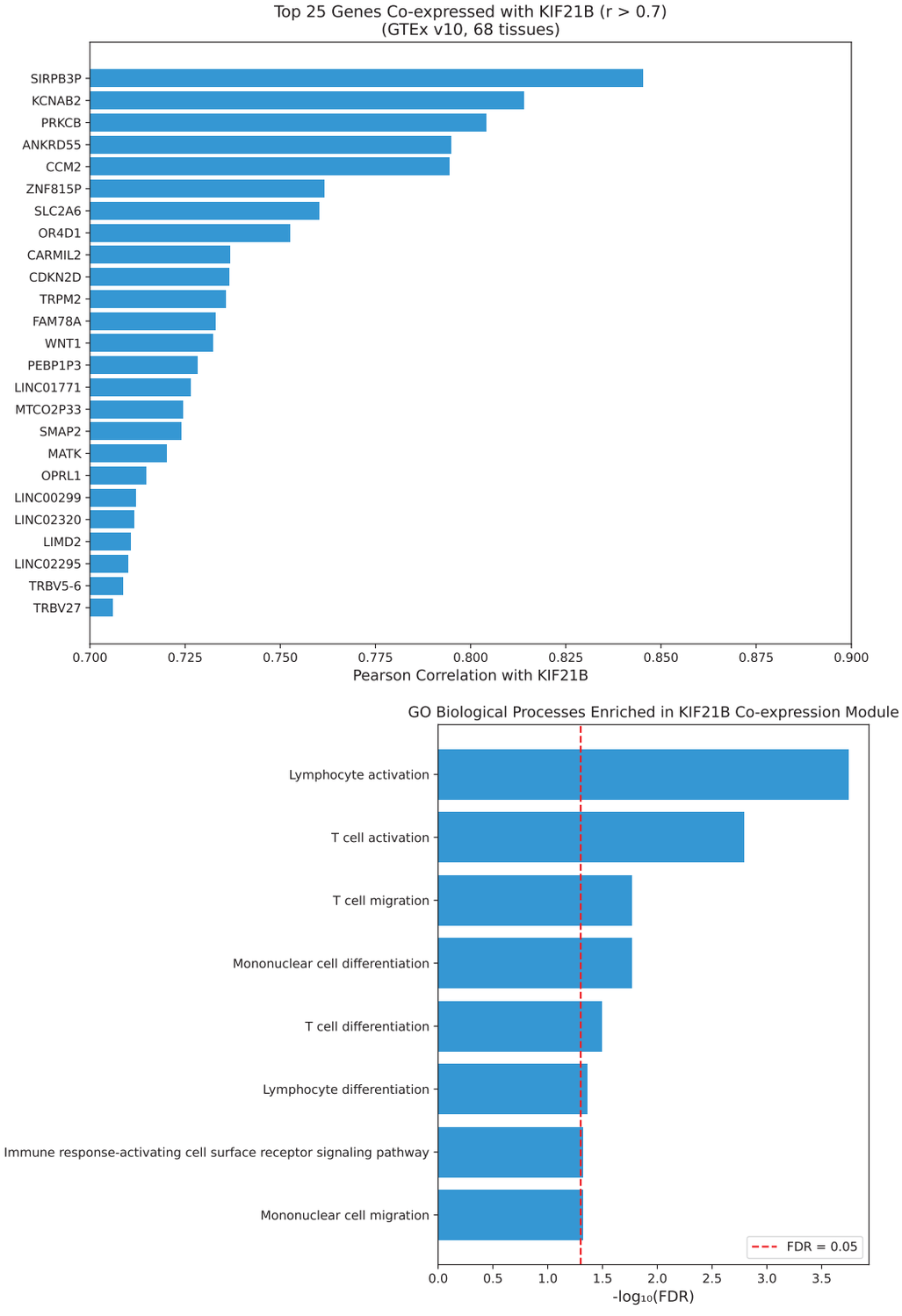


functions within a network of motor proteins responsible for transporting cellular cargo along microtubules, a process essential for neuronal function and particularly critical for axonal transport over long distances (Hirokawa et al., 2009).

KIF21B co-expression analysis reveals immune pathway involvement

To identify genes functionally related to *KIF21B*, we performed transcriptome-wide co-expression analysis across 68 GTEx tissues. We identified 50 genes significantly co-expressed with *KIF21B* ($r > 0.7$, adjusted $p < 0.05$). The most strongly correlated genes included *SIRPB3P* (r = 0.85), *KCNAB2* (r = 0.81), *PRKCB* (r = 0.80), *ANKRD55* (r = 0.79), and *CCM2* (r = 0.79) (**figure 3A**). Notably, *ANKRD55* is an established MS susceptibility gene identified in genome-wide association studies (Patsopoulos et al., 2019), and its strong co-expression with *KIF21B* provides independent support for shared biological

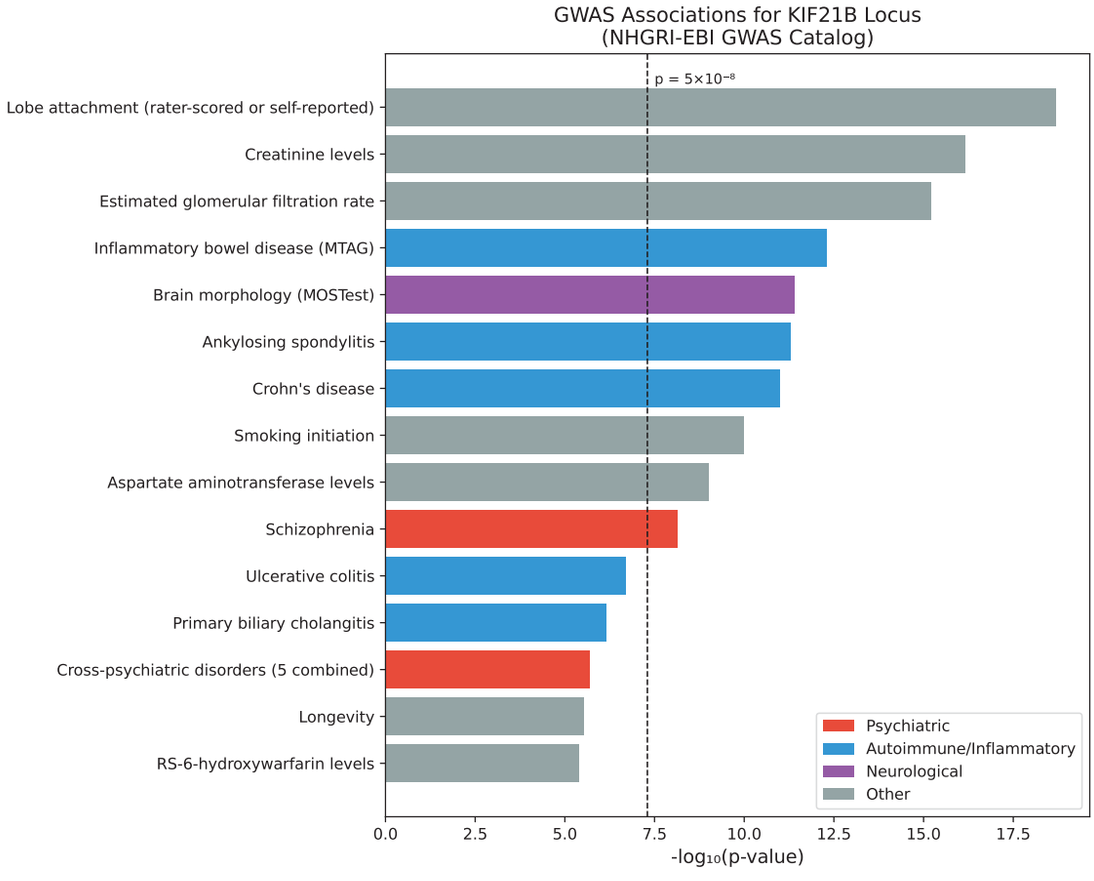
Figure 3. *Co-expression analysis reveals KIF21B association with immune gene networks. (A) Top 25 genes co-expressed with KIF21B across 68 human tissues (GTEx). Genes were ranked by Pearson correlation coefficient (r > 0.7, Bonferroni-adjusted p < 0.05). (B) Gene Ontology Biological Process enrichment analysis of the KIF21B co-expression module (72 protein-coding genes with r > 0.65). The module is significantly enriched for T cell and lymphocyte activation and differentiation processes. Red dashed line indicates FDR = 0.05 significance threshold*



pathways between these risk loci.

GO enrichment analysis of genes co-expressed with *KIF21B* (r > 0.65, n = 72 protein-coding genes) revealed significant enrichment for immune-related biological processes (**figure 3B**). The most significantly enriched terms were "lymphocyte activation" (FDR = 0.0016) and "T cell activation" (FDR = 0.0055). Additional enriched processes included T cell migration (FDR = 0.017), mononuclear cell differentiation (FDR = 0.017), T cell differentiation (FDR = 0.032), and lymphocyte

Figure 4. *KIF21B is associated with multiple disease phenotypes. Bar plot showing all traits associated with the KIF21B locus in the NHGRI-EBI GWAS Catalog. The x-axis displays -log₁₀(p-value) for the most significant association per trait. Bars are colored by trait category: psychiatric (red), autoimmune/inflammatory (blue), neurological (purple), and other (gray). The dashed vertical line indicates genome-wide significance threshold ($p = 5\times10^{-8}$). The locus shows significant associations with both psychiatric disorders and autoimmune conditions*



differentiation (FDR = 0.044). These findings indicate that *KIF21B* is embedded within a transcriptional program associated with adaptive immune function, particularly T cell biology, which is directly relevant to the immunopathogenesis of MS.

KIF21B shows pleiotropy across autoimmune and psychiatric traits

To contextualize *KIF21B* beyond MS and SCZ, we examined all phenotypic associations reported in the GWAS Catalog. The KIF21B locus showed genome-wide significant associations ($p < 5\times10^{-8}$) with 10 distinct traits spanning multiple categories (**figure 4**). These included psychiatric disorders (schizophrenia, $p = 7\times10^{-9}$; cross-psychiatric disorders, $p = 2\times10^{-6}$), autoimmune and inflammatory conditions (inflammatory bowel disease, $p = 5\times10^{-13}$; Crohn's disease, $p = 1\times10^{-11}$; ankylosing spondylitis, $p = 5\times10^{-12}$; ulcerative colitis, $p = 2\times10^{-7}$; primary biliary cholangitis, $p = 7\times10^{-7}$), and brain morphology ($p = 4\times10^{-12}$). The convergence of psychiatric and autoimmune associations at this locus supports *KIF21B* as a pleiotropic gene influencing both neurological and immune system function.

Discussion

This study provides an in silico functional characterization of *KIF21B*, a pleiotropic risk gene jointly associated with SCZ and MS (Ahangari et al., 2022). Our analyses reveal that *KIF21B* is preferentially expressed in both brain and immune tissues, interacts with a network of motor proteins involved in microtubule-based transport, and is co-expressed with genes enriched for T cell and lymphocyte functions. These findings support the biological plausibility of *KIF21B* as a shared risk gene influencing both neurological and immunological processes.

The observation that *KIF21B* shows elevated expression in both brain regions and immune tissues is notable given the distinct pathophysiology of SCZ and MS. In the central nervous system, kinesin motor proteins are essential for axonal transport, delivering organelles, proteins, and mRNA from the cell body to synaptic terminals over distances that can span a meter in motor neurons (Hirokawa et al., 2009). Disruption of this transport has been implicated in multiple neurological conditions (Millecamps & Julien, 2013). In the immune system, kinesins participate in

T cell polarization, immune synapse formation, and intracellular trafficking during activation (Hooikaas et al., 2020; Lamason et al., 2010). The expression pattern of *KIF21B* thus positions it at the intersection of neuronal function and adaptive immunity, providing a mechanistic basis for its genetic association with both diseases.

Our eQTL analysis revealed that while *KIF21B* has significant cis-eQTLs in multiple brain and immune tissues, the GWAS lead variant rs12126806 is not among them. Given that *KIF21B* does have significant eQTLs in disease-relevant tissues, the most parsimonious explanation is that rs12126806 is not itself the causal variant but rather tags a nearby functional variant through linkage disequilibrium. The variant lies in an intronic region with a relatively low CADD score (0.457), consistent with this interpretation. Fine-mapping studies will be required to identify the risk variant(s) at this locus and clarify the mechanism by which genetic variation at *KIF21B* might influence disease risk. Moreover, whether altered *KIF21B* expression or function is a driver of disease susceptibility or a consequence of disease-related processes remains an open question. Mendelian randomization and longitudinal functional studies are needed to clarify the directionality of this relationship.

Several mechanisms may underlie KIF21B's contribution to both disorders. In neurons, KIF21B's interaction with TRIM3, an E3 ubiquitin ligase involved in GABA receptor regulation, suggests a potential link to inhibitory neurotransmission and the synaptic dysfunction hypothesized to underlie SCZ (Cheung et al., 2010). Independently, rare de novo mutations in *KIF21B* have been shown to cause neurodevelopmental disorders characterized by brain malformations including microcephaly and corpus callosum agenesis (Asselin et al., 2020), providing convergent evidence that KIF21B is critical for brain development. While these rare, highly penetrant mutations produce distinct clinical phenotypes from the common variant associations examined here, they reinforce the neurobiological importance of this gene. In immune cells, the co-expression of *KIF21B* with *ANKRD55*, a known MS susceptibility gene, along with the enrichment for lymphocyte activation pathways, supports a role in adaptive immunity (Patsopoulos et al., 2019). Autoreactive T cells are central to MS pathogenesis, and genetic variants affecting T cell function could plausibly influence disease susceptibility. These functions need not be mutually exclusive: given that MS involves both autoimmune attack and subsequent neurodegeneration, a gene expressed in both neural and immune compartments could influence multiple stages of disease pathophysiology. Our GWAS catalog analysis confirmed that *KIF21B* is associated with a broad range of phenotypes beyond SCZ and MS, including inflammatory bowel disease, Crohn's disease, ankylosing spondylitis, and primary biliary cholangitis. Such extensive pleiotropy is increasingly recognized in complex disease genetics and underscores the limitations of disease-centric approaches to understanding gene function (Solovieff et al., 2013; Watanabe et al., 2019).

This study has limitations. First, our analyses relied on bulk tissue expression data from GTEx, which represent averages across heterogeneous cell populations; single-cell RNA sequencing would enable more refined cell-type-specific characterization. Second, co-expression analysis identifies genes with correlated expression patterns but does not establish causal relationships. Third, this study is purely computational; experimental validation in neuronal and immune cell models will be necessary to confirm the proposed biological roles. Fourth, the datasets used in this study are predominantly derived from individuals of European ancestry. Genetic architecture, linkage disequilibrium patterns, and gene expression profiles may differ across populations, and the generalizability of these findings to non-European ancestries remains to be established. It is also important to note that while our findings support locus-specific pleiotropy at *KIF21B*, the negligible genome-wide genetic correlation between SCZ and MS (r_G = 0.057; Ahangari et al., 2022) indicates that such shared loci do not reflect global genetic overlap, and the pleiotropic role of *KIF21B* should be interpreted within this context.

Conclusions

This bioinformatics analysis of *KIF21B*, a gene jointly associated with SCZ and MS, reveals expression enrichment in both brain and immune tissues, a protein interaction network centered on microtubule-based transport, and co-expression with genes involved in T cell activation including the established MS risk gene *ANKRD55*. These findings support *KIF21B* as a biologically plausible shared risk gene whose dual neural and immune functions may contribute to its pleiotropic disease associations. Future functional studies are warranted to elucidate the specific mechanisms by which genetic variation at this locus influences susceptibility to neuropsychiatric and autoimmune disease.

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