HHS Public Access

Author manuscript

Brain Behav Immun. Author manuscript; available in PMC 2023 September 27.

Published in final edited form as:

Brain Behav Immun. 2023 August ; 112: 175–187. doi:10.1016/j.bbi.2023.06.009.

The human lncRNA *GOMAFU* suppresses neuronal interferon response pathways affected in neuropsychiatric diseases

Peng Teng[a,1], **Yangping Li**[b,1], **Li Ku**[a], **Feng Wang**[b], **David R. Goldsmith**[c], **Zhexing Wen**[c,d,e], **Bing Yao**[b,*], **Yue Feng**[a,*]

[a]Department of Pharmacology and Chemical Biology, Emory University School of Medicine, 1510 Clifton Road, Atlanta, GA 30322, United States

[b]Department of Human Genetics, Emory University School of Medicine, 615 Michael Street, Atlanta, GA 30322, United States

[c]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, United States

[d]Department of Cell Biology, Emory University School of Medicine, Atlanta, GA, United States

[e]Department of Neurology, Emory University School of Medicine, Atlanta, GA, United States

Abstract

Long noncoding RNAs (lncRNAs) play multifaceted roles in regulating brain gene networks. LncRNA abnormalities are thought to underlie the complex etiology of numerous neuropsychiatric disorders. One example is the human lncRNA gene *GOMAFU*, which is found dysregulated in schizophrenia (SCZ) postmortem brains and harbors genetic variants that contribute to the risk of SCZ. However, transcriptome-wide biological pathways regulated by *GOMAFU* have not been determined. How *GOMAFU* dysregulation contributes to SCZ pathogenesis remains elusive. Here we report that *GOMAFU* is a novel suppressor of human neuronal interferon (IFN) response pathways that are hyperactive in the postmortem SCZ brains. We analyzed recently released transcriptomic profiling datasets in clinically relevant brain areas derived from multiple SCZ cohorts and found brain region-specific dysregulation of *GOMAFU*. Using CRISPR-Cas9 to delete the *GOMAFU* promoter in a human neural progenitor cell model, we identified transcriptomic alterations caused by *GOMAFU* deficiency in pathways commonly affected in postmortem brains of SCZ and autism spectrum disorder (ASD), with the most striking effects on upregulation of numerous genes underlying IFN signaling. In addition, expression levels of *GOMAFU* target genes in the IFN pathway are differentially affected in SCZ brain regions and negatively associated with *GOMAFU* alterations. Furthermore, acute exposure to IFN-γ causes a rapid decline of *GOMAFU* and activation of a subclass of *GOMAFU* targets in stress and

*Corresponding authors. bing.yao@emory.edu (B. Yao), yfeng@emory.edu (Y. Feng).

[1]These authors made equal contributions in this study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2023.06.009.

immune response pathways that are affected in SCZ brains, which form a highly interactive molecular network. Together, our studies unveiled the first evidence of lncRNA-governed neuronal response pathways to IFN challenge and suggest that *GOMAFU* dysregulation may mediate environmental risks and contribute to etiological neuroinflammatory responses by brain neurons of neuropsychiatric diseases.

Keywords

Neuroinflammation; long non-coding RNA (lncRNA); *GOMAFU*; Schizophrenia; Interferon signaling pathway

1. Introduction

Long non-coding RNAs (lncRNAs), which carry>200 nucleotides without appreciable protein coding capacity, play critical roles in governing normal cell development and function through sophisticated regulation of broad downstream pathways by transcriptional and post-transcriptional mechanisms (Derrien et al., 2012; Yao et al., 2019). LncRNA expression often displays a cell type-specific manner, with nearly half of known lncRNAs preferentially enriched or uniquely expressed in the human brain (Derrien et al., 2012; Zimmer-Bensch, 2019). The functional importance of lncRNAs in the human brain is evidenced by accumulating evidence that demonstrates lncRNA abnormalities in various neurodevelopmental and neurodegenerative disorders (Aliperti et al., 2021; Srinivas et al., 2023). In contrast to the highly conserved microRNAs, lncRNAs are often poorly conserved. Thus, it is postulated that brain lncRNAs may underlie the evolution of cognitive sophistication of humans, but also increase the fragility and vulnerability for neuropsychiatric diseases (Rusconi et al., 2020; Walker and Goldsmith, 2022). Indeed, many genetic variants associated with schizophrenia (SCZ) and/or Autism Spectrum Disorders (ASD) have been identified in lncRNA gene loci (Parikshak et al., 2016; Trubetskoy et al., 2022). In addition, a fast growing list of lncRNAs are found dysregulated in neuropsychiatric disorders, represented by SCZ and ASD (Ni et al., 2021; Wang et al., 2015; Yang et al., 2021). Noticeably, besides commonly dysregulated lncRNAs, SCZ and ASD postmortem brains also display overlapping transcriptomic alterations (Ardesch et al., 2023; Gandal et al., 2018). This leads to an intriguing hypothesis that disruption of lncRNA-regulated gene networks may underlie shared clinical manifestations and pathological mechanisms in multiple psychiatric diseases. Moreover, emerging evidence suggests that dysregulated lncRNAs may serve as biomarkers for the diagnosis and treatment for neuropsychiatric diseases (Cui et al., 2016; Jia et al., 2021).

Aberrant neurodevelopment in-utero is thought to contribute to the etiology of various psychiatric diseases long before the onset of clinical phenotypes. In particular, stress and immune/inflammatory insults, especially maternal immune activation (MIA), are well-documented environmental risk factors (Knuesel et al., 2014). MIA, often due to microbial infection, is associated with increased occurrence of SCZ and ASD in the offspring (Estes and McAllister, 2016; Prata et al., 2017). In fact, inflammatory and innate immune genes are enriched in SCZ and ASD affected pathways (Hughes et al., 2023; Khandaker et al.,

2015; Voineagu et al., 2011). Interestingly, emerging evidence indicates the involvement of lncRNAs in innate immune responses upon virus infection (Hadjicharalambous and Lindsay, 2019). The multifaceted functions of lncRNAs in regulating wide molecular pathways (Marchese et al., 2017; Statello et al., 2021) raise a question whether genetic and environmental risk factors converge their etiologic influences on dysregulation of brain lncRNAs, which in turn results in broad transcriptomic alterations and formation of pathological molecular networks that underlie the complexity of pathogenesis in neuropsychiatric diseases. Nonetheless, whether and how dysfunction of neuronal lncRNAs affects neuro-immune responses in neuropsychiatric diseases remain unknown.

Multiple lines of evidence suggest the involvement of the human lncRNA *GOMAFU* in SCZ (Barry et al., 2014; Chung et al., 2016; Rao et al., 2015; Zakutansky and Feng, 2022). *GOMAFU* is produced from the lncRNA gene originally named *MIAT* (Myocardial Infarction Associated Transcript), due to genetic variants in this gene associated with the susceptibility of myocardial infarction (Ishii et al., 2006). However, in recent years, growing discoveries indicated enriched expression of *GOMAFU* in brain neurons and its potential roles in SCZ (Barry et al., 2014; Chung et al., 2016). Reduced *GOMAFU* expression was first found in SCZ postmortem superior temporal gyrus (Barry et al., 2014). In addition, *Gomafu* KO mice was found to exhibit hyperactivity with enhanced responsiveness to the psychostimulant methamphetamine (Ip et al., 2016). Later on, aberrantly increased *GOMAFU* expression was detected in parvalbumin interneurons of the SCZ dorsolateral prefrontal cortex (DLPFC), which was correlated with dysregulated ERBB4 splice variant mRNAs associated with SCZ (Chung et al., 2016). Consistent with the idea that *GOMAFU* regulates RNA splicing, *GOMAFU* displays restricted localization within nuclear bodies of undefined composition and function (Sone et al., 2007) and regulates several selected splice variant mRNAs known to be affected in SCZ (Barry et al., 2014). Moreover, recent linkage analysis identified *GOMAFU* as a susceptibility gene for SCZ (Rao et al., 2015). However, transcriptome-wide gene networks under control of *GOMAFU* in human neurons have not been identified. Whether and how *GOMAFU* is dysregulated in clinically relevant brain regions in SCZ patients thus affects SCZ pathological pathways remains elusive. Furthermore, whether and how environmental risk factors of neuropsychiatric disorders may affect *GOMAFU* and its downstream molecular targets stay unexplored.

We report here that silencing *GOMAFU* in a model of human neural progenitor cell (NPC) results in broad transcriptomic dysregulation, with the most striking effects on up-regulation of genes in the interferon (IFN) signaling pathways. Moreover, we find differential dysregulation of *GOMAFU* that is negatively associated with its targets in IFN- γ pathways in clinically relevant regions of SCZ brains. Finally, we show that acute IFN- γ treatment of human NPC models in culture induces a rapid decline of *GOMAFU*, which mediates selective upregulation of stress and immune response genes known to be dysregulated in SCZ brains, forming a highly interactive pathological network. These findings uncover novel roles of the lncRNA *GOMAFU* in suppressing genes that underlie neuronal responses to extracellular IFN- γ, a well-recognized environmental risk factor for neuropsychiatric disorders due to maternal and/or postnatal viral infection.

2. Methods

2.1. Cell culture and treatment

For deletion of the *GOMAFU* promoter (*ΔGOMAFU*), BE(2)-M17 cells that harbor Cas9 expression were transfected with two pairs of gRNAs separately with comparable cleavage efficiency (gRNA pair #1: 5′-AUAUGUCGUGAGCCCUUACU-3′; 5′-AUUAGGCUGUUCCCCGUUAG-3′; gRNA pair #2: 5′-AUAUGUCGUGAGCCCUUACU-3′; 5′-CCGCCUGAAGUGUCCCGCAU-3′). Cells were harvested 48 h after transfection for molecular analysis. For IFN-γ treatment, BE(2)-M17 cells were treated with IFN-γ (NOVUS biologicals, 285-IF-100) at the concentration of 10 ng/ml for 24 h before harvest for RNA extraction.

2.2. Identification of the neuronal transcription start site and the promoter of the human GOMAFU gene

Transcription start site of *GOMAFU* was identified based on phase1 and phase2 datasets of the 5th edition of the RIKEN FANTOM project (FANTOM5) for functional annotation of the mammalian genome (https://fantom.gsc.riken.jp/5/) (Lizio et al., 2015). All the Cap analysis gene expression (CAGE) sequencing reads were normalized by relative log expression (RLE). Chromatin accessibility at the promoter of *GOMAFU* in posterior cingulate cortex of a 20-year-old adult (ENCFF752ZXK) was obtained by analyzing ATAC-seq in the Encyclopedia of DNA Elements (ENCODE) project (https://www.encodeproject.org/).

2.3. RNA isolation, RNA-seq library preparation and high-throughput sequencing

Cultured cells were harvested for RNA isolation by TRIzol following manufacturer's instructions (Invitrogen). RNA was dissolved in RNase-free water, quantified by NanoDrop, and the quality was confirmed by Bioanalyzer. For the IFN-γ treated cells, rRNA depleted RNA-seq libraries were generated using KAPA HyperPrep with RiboErase. For cells harboring *ΔGOMAFU*, poly-A-enriched RNA-seq libraries were generated using TruSeq mRNA Stranded. RNA-seq libraries were subjected to paired-end sequencing (150 bp), targeting 80 M total reads per sample (40 M in each direction), on an Illumina HiSeq platform (Admera Health, LLC, South Plainfield, NJ, USA).

2.4. RNA-seq analysis

Paired-end RNA-seq reads were aligned to human genome assembly version (GRCh38/hg38) using TopHat2 version 2.1.0 (Kim et al., 2013) with default parameter. Differential expression gene analysis was conducted by Cuffdiff, with all samples normalized to their own library size by Cuffdiff. Genes with FDR < 0.05 were considered as differentially expressed genes (DEGs) (Trapnell et al., 2013). DEGs were subject to Gene Ontology (GO) analysis using DAVID (Sherman et al., 2022) and PANTHER (Thomas et al., 2022). GOChord plot displayed connection of genes and GO terms were generated by R package GOplot (Walter et al., 2015). Gene interaction analysis was performed by STRING 11.5 (Szklarczyk et al., 2019). For alternative splicing analysis, RNA-seq reads from three biological replicates were pooled for detection of alternative splicing events using

SpliceTrap with default parameter (Wu et al., 2011). Alternative slicing events with FDR < 0.05 and splice changes>0.15 were used for downstream analysis. Splice changes were calculated by SpliceTrap using the following formula:

$$Splice\ Change = \frac{Inclusion\ Level\ in\ \Delta\ GOMAFU - Inclusion\ Level\ in\ Control}{Inclusion\ Level\ in\ \Delta\ GOMAFU + Inclusion\ Level\ in\ Control}$$

Transcriptomic profile of differentiation of BE (2)-M17 cells and human iPSC derived neurons were compared using GSE181636 and GSE106589. The FPKM matrix of all gene expression for each sample was used for Pearson correlation pairwise in R by function "cor". The Pearson correlation coefficient was then subject for heatmap in R by function "pheatmap".

2.5. Analysis of transcriptomic datasets derived from psychiatric disease cohorts in comparison with controls

Four published transcriptomic datasets, including RNA-seq data (GSE80655, PRJNA379666) and Gene expression microarray data (GSE53987, GSE93987) derived from control and psychiatric disease cohorts, were used to assess expression of *GOMAFU* and its targets in psychiatric diseases. Detailed information of each dataset is shown in (Table 1). RNA-seq datasets were analyzed by TopHat2 and Cuffdiff as described for RNA-seq data derived from BE (2)-M17 cells. For microarray datasets, the expression level of each gene was calculated by the average level of all specific probes used for that gene. Potential impact of covariates in each dataset are described in the corresponding studies cited in Table 1.

2.6. Quantitative RT-PCR

For quantification of mRNAs and lncRNAs, TRIzol–isolated total RNA was reverse-transcribed using random primers (Promega) and SSII reverse transcriptase (Thermo Fisher Scientific, Waltham, MA, USA) following manufacturer's instructions. Quantitative PCR (qPCR) was performed using SYBR Green Fast Mix on a CFX96 Real Time PCR System (Bio Rad, Hercules, CA, USA). The RNA expression levels were normalized to that of *ACTIN* mRNA calculated by $2^{-\Delta CT}$. The primers for RT-qPCR of mRNAs and lncRNAs are summarized in (Table S1).

2.7. Statistical analysis

Statistical analysis was performed as described in the corresponding figure legend. Two tailed Student's *t*-test was applied for two-group comparison using Prism8.0 (GraphPad Software). For multiple-group comparison, one-way ANOVA was carried out followed by Tukey's post hoc test. Pearson's chi-squared test was performed in R software (https://www.r-project.org/). All results were presented as mean ± SEM. *denotes $p < 0.05$, **denotes $p < 0.01$, ***denotes $p < 0.001$, ****denotes $p < 0.0001$, and ns denotes no significant difference.

3. Results

3.1. Brain region-specific dysregulation of GOMAFU in cohorts of psychiatric diseases

To explore whether and how *GOMAFU* dysregulation may contribute to pathogenesis of psychiatric disorders, we analyzed several transcriptomic profiling datasets derived from various postmortem brain regions with pathological and clinical relevance to SCZ that are recently made available online (Arion et al., 2015; Chang et al., 2017; Gandal et al., 2018; Lanz et al., 2019; Ramaker et al., 2017). Despite different methods used for RNA detection and data processing from distinct brain regions in multiple independent cohorts, significant dysregulation of *GOMAFU* was found in each SCZ cohort relative to healthy controls (Table 1). In the PsychENCODE cross-disorder transcriptomic consortium study (Gandal et al., 2018) that includes large numbers of subjects of SCZ (n = 559), ASD (n = 51), and bipolar disorder (BD, n = 222), *GOMAFU* was significantly reduced in the frontal and temporal cortex regions derived from SCZ and ASD subjects, but not in BD subjects, compared to healthy controls (n = 936). In contrast, in several independent studies from three additional distinct cohorts, *GOMAFU* was significantly increased in the dorsolateral prefrontal cortex (DLPFC), nucleus accumbens (NAcc), hippocampus, striatum, and amygdala of SCZ subjects relative to healthy controls (Chang et al., 2017; Lanz et al., 2019; Ramaker et al., 2017). Moreover, in DLPFC pyramidal cells, which play important roles in sustained firing that underlies working memory and display abnormalities in SCZ (Garey et al., 1998; Glantz and Lewis, 2000; Goldman-Rakic, 1995), *GOMAFU* was selectively increased in laser-dissected layer 5, but not layer 3, pyramidal cells from the BA9 region of DLPFC of SCZ and schizoaffective disorder subjects (Arion et al., 2015). Collectively, the differential dysregulation of *GOMAFU* that stands out from transcriptomic profiling studies of various postmortem brain regions from multiple SCZ cohorts strongly suggests the functional involvement of this lncRNA in SCZ pathogenesis, likely in a brain region-specific manner.

3.2. Silencing GOMAFU expression in a human neuronal progenitor cell model by CRISPR/Cas9-mediated deletion of the GOMAFU promoter

Psychiatric disorders, represented by SCZ and ASD, can affect neuronal development as early as formation of NPCs in the embryonic brain (Bhat et al., 2022; Boksa, 2010; Brennand et al., 2012; Jenkins, 2013; Kaushik and Zarbalis, 2016). From the recently published transcriptomic datasets that examined various germinal zones when NPCs migrate and differentiate during human fetal neocortex formation (Fietz et al., 2012), we found low levels of *GOMAFU* in the ventricular zone (VZ) enriched of proliferating apical progenitors (APs) (Fig.S1A and B). Progressive upregulation of *GOMAFU*, which peaked at the 14th gestational week, was detectable in the inner- and outer- subventricular zone (ISVZ and OSVZ) enriched of migrating basal progenitors (BPs) and in cortical plate (CP) enriched of terminally differentiated neurons (Fig. S1B). Increased expression of *GOMAFU* in neurons than NPCs in the human embryonic brains was also evidenced in single cell RNA-seq datasets (Zhong et al., 2018) with higher *GOMAFU* abundance in interneurons than excitatory neurons (Fig.S1C). These data suggest increased functional requirements of *GOMAFU* during progenitor cell migration and differentiation, hence the importance for studying the function of *GOMAFU* in NPCs.

We chose to identify transcriptome-wide functional targets of *GOMAFU* in a human NPC model by silencing *GOMAFU* expression. Although human induced pluripotent stem cells (hiPSCs) have been used as a model to produce NPCs and differentiating neurons (Wen et al., 2014), altered *GOMAFU* expression was reported to affect neuron-glia fate specification and differentiation (Aprea et al., 2013; Rapicavoli et al., 2010). Thus, we chose to silence *GOMAFU* in the immortalized human neuroblastoma cell line BE(2)-M17, which is not pluripotent but can be induced to differentiate (Li et al., 2022)(GSE181729) and display significantly overlapping transcriptomic profile alterations recapitulating those when hiPSC-derived NPCs differentiate into neurons (Fig. S2) (Hoffman et al., 2017). It is important to point out that the commonly used strategy for silencing protein expression by deleting a coding intragenic fragment does not guarantee complete ablation of the expression and function of lncRNA genes. The *GOMAFU/MIAT* gene occupies ~ 19 kb on Chromosome 22q12.1. We thus decided to delete the *GOMAFU/MIAT* promoter based on CRISPR-Cas9 mediated genome editing, which avoids the difficulty in maintaining high concentrations of anti-lncRNA GapmeRs to achieve sustained *GOMAFU* KD and minimizes potential off-target effects.

To identify the *GOMAFU/MIAT* promoter, we first searched for the transcription start site (TSS) based on the 5th edition of the RIKEN FANTOM project (FANTOM5) datasets for cap analysis of gene expression (CAGE) sequencing (Lizio et al., 2015). A major TSS peak is found at the 5′end of exon 1, which is flanked by canonical promoter elements in a human genomic DNA fragment, which is highly conserved between human and primates but less conserved between human and mouse (Fig. S3A). Luciferase reporter assay demonstrated promoter activity of this genomic fragment (Fig.S3B). Moreover, Assay for Transposase-Accessible Chromatin with high-throughput sequencing (ATAC-Seq) in ENCODE identified a peak surrounding the *GOMAFU/MIAT* TSS and the core promoter region in the human posterior cingulate cortex (Fig. 1A), further supporting the role of this genomic region in transcription of *GOMAFU/MIAT* in human neurons.

We used undifferentiated BE(2)-M17 cells as a model of human NPC and transiently transfected a pair of synthetic gRNAs in cells harboring Cas-9 expression to delete the ATAC-Seq peak region that contains the *GOMAFU* promoter (Fig. 1B). Transfected pools of cells were harvested forty-eight hours later for RNA isolation to achieve immediate CRISPR-Cas9 editing within a short window, aiming to minimize off-target effects and avoid indirect adaptive influence on the transcriptome. Deletion of the *GOMAFU* promoter region can be achieved using two distinct pairs of synthetic gRNAs, each evidenced by PCR of genomic DNA (*ΔGOMAFU*, Fig. 1C). The precise cleavage was verified by sequencing of the PCR product (Fig. S4A). RT-qPCR detected significantly decreased *GOMAFU* expression using primers specific for the 5′ and 3′ exons of *GOMAFU* in separate reactions (Fig. 1D, E), indicating successful reduction of the entire lncRNA. Consistent cleavage efficiency of the *GOMAFU* promoter and reduction of the *GOMAFU* lncRNA were achieved in independently transfected cultures (Fig. S4B and C).

3.3. GOMAFU deficiency leads to aberrant up-regulation of genes in broad molecular pathways affected in SCZ and ASD, with a striking enrichment of IFN response genes

We next performed RNA-seq and genome-wide transcriptomic analysis in *ΔGOMAFU* and the parent BE(2)-M17 cells. Considering the previously reported roles of *GOMAFU* in regulating alternative splicing (AS) of specific transcripts (Barry et al., 2014), we first examined transcriptomic alterations of AS variants caused by *ΔGOMAFU*. Significant alterations in Percent Spliced In (PSI) (FDR < 0.05, PSI change > 0.15) of hundreds of exons were detected (Fig. 2A and Table S2), represented by the reduced inclusion of Exon 20 of the calcium/calmodulin dependent protein kinase II delta (*CAMK2D*) validated by RT-qPCR (Fig. 2B). Gene Ontology (GO) analyses revealed pathways enriched of genes subjected to *ΔGOMAFU*-regulated AS, including neuron axon guidance, microtubule-based process, dendritic morphogenesis, and several intracellular signaling pathways (Fig. 2C and Table S3). Further analysis showed that alternative cassette exons (CA) were the major type of AS events affected by *ΔGOMAFU*, whereas alternative usage of 3′ and 5′ splice sites (A3SS and A5SS) were less affected (Fig. 2D). Among these AS events, *GOMAFU* deficiency appeared to affect exon inclusion and exclusion equally. Several previously reported *GOMAFU* AS targets were undetectable in either hiPSC-derived NPCs or BE(2)-M17 cells, represented by the previously reported *ERBB4* splice isoforms, suggesting *GOMAFU*'s influence on its AS targets may be developmental stage-specific.

Unexpectedly, *ΔGOMAFU* resulted in much more robust fold changes of Differentially Expressed Genes (DEGs, FDR < 0.05, Table S4) as compared to fold changes of AS. Interestingly, all significant DEGs due to *ΔGOMAFU* were upregulated (Fig. 3A and Table S4), suggesting that the primary biological function of *GOMAFU* is to suppress gene expression in human NPCs. Interestingly, the majority of *GOMAFU* regulated DEGs are either up- or down-regulated during differentiation of human iPSC-derived NPCs and BE(2)-M17 cells (Fig. S5). To elucidate molecular pathways affected by *GOMAFU* deficiency, GO analysis was carried out on *GOMAFU* regulated DEGs. Strikingly, multiple top GO terms affected by *ΔGOMAFU* were enriched of DEGs that underlie IFN signaling and immune responses (Fig. 3B and Table S5), suggesting a major role of *GOMAFU* in controlling expression of genes that underlie neuronal responses to extracellular inflammatory cytokines. RT-qPCR validated the elevated expression of mRNAs that encode IFN Induced Transmembrane Protein 1 (*IFITM1*) and *IFITM3* by *ΔGOMAFU* (Fig. 3C), both are previously reported to display aberrant increase in SCZ prefrontal cortex from two independent cohorts (Arion et al., 2007; Gandal et al., 2018).

We next questioned whether and how *ΔGOMAFU* downstream molecular pathways are affected in SCZ postmortem brains. We identified GO terms commonly affected in the frontal and temporal cortex of SCZ and ASD that both harbor significant reduction of *GOMAFU* (Gandal et al., 2018) and cross compared with GO terms affected in BE(2)-M17 cells that harbor *ΔGOMAFU*. As shown in Fig. 3D, multiple overlapping GO terms are found, which may represent *GOMAFU* deficiency affected pathways in neurons shared in the SCZ and ASD frontal and temporal cortical regions. Interestingly, the top hits include pathways of IFN-γ mediated signaling, defense response to virus, response to cytokine, and inflammatory response. In contrast, no GO terms enriched of *ΔGOMAFU* AS targets were

found to overlap with GO terms affected in the SCZ frontal and temporal cortex (Gandal et al., 2018).

Furthermore, *ΔGOMAFU* enhanced DEGs significantly overlap with upregulated DEGs in the postmortem frontal and temporal cortex of SCZ and ASD subjects (Fig. 3E, F, and Table S6) but not DEGs found in BD subjects (Fig. 3G), suggesting disease-specific dysfunction of *GOMAFU* coupled with its targets. Interestingly, a significant subgroup of *ΔGOMAFU* DEGs in the IFN-related pathways were commonly affected in SCZ and ASD subjects (Fig. 3H). Further analysis revealed that many *ΔGOMAFU* DEG targets were enriched in multiple GO terms related to IFN signaling and inflammatory responses as shown in the GOChord plot (Fig. 3I), suggesting cross-talk and integrated function of these *GOMAFU* targets. RT-qPCR validated the aberrant increase of several *GOMAFU* DEG targets involved in multiple signaling pathways, including *IRF1*, *IRF9*, *IFIT1, OAS1*, *OAS3* and *CCL2* (Fig. 3J). These results suggest that a major function of *GOMAFU* is to suppress expression of neuronal IFN response genes, leading to an intriguing possibility that *GOMAFU* deficiency in neurons may contribute to dysregulation of neuroinflammatory response pathways in the brains of SCZ and ASD.

3.4. Elevated GOMAFU expression is associated with suppression of a subset of interferon pathway genes in postmortem brain regions of schizophrenia subjects

We next questioned whether elevated *GOMAFU* expression in SCZ brain regions may lead to reduced expression of its targets. In contrast to the large numbers of *ΔGOMAFU* regulated DEGs found in SCZ frontal and temporal cortex that harbor *GOMAFU* deficiency (Fig. 3E and Table S6), a small subset of *ΔGOMAFU* regulated DEGs were downregulated in the SCZ hippocampus, NAcc, and striatum (Fig. S6), each displays significantly increased *GOMAFU* expression (Table 1). Most *ΔGOMAFU* targets in IFN signaling and immune response pathways are not suppressed by increased *GOMAFU* expression. Thus, increase of *GOMAFU* may only partly compromise the aberrant upregulation of inflammatory response genes in specific SCZ brain regions. Nonetheless, stringent multiple testing corrections revealed significant downregulation of several *GOMAFU* target DEGs shared in the SCZ hippocampus and NAcc (FDR < 0.05, Fig. 4A and B). These include the IFN Induced Protein with Tetratricopeptide Repeats 1 (*IFIT1*) and *STAT1*, both are core components of IFN signaling (Diamond, 2014; Ramana et al., 2001), and the Ring Finger Protein 19B (*RNF19B)* involved in innate immune system activity (Lawrence et al., 2020). Of note, although *GOMAFU* is significantly increased in the SCZ striatum, the reduction of *IFIT1*, *STAT1*, and *RNF19B* did not reach FDR < 0.05 by multiple testing corrections (Fig. 4C). Thus, the effects of elevated *GOMAFU* expression on its targets also display a brain region-specific manner in SCZ patients. In the hippocampus, significant negative correlations were observed between the abundance of *GOMAFU* and the aforementioned *GOMAFU* targets that showed FDR < 0.05 (Fig. 4D), supporting the idea that *GOMAFU* acts to suppress these IFN pathway genes. SCZ and Control subjects showed very similar trends of negative correlation between *GOMAFU* and its targets, but not all reached statistical significance due to small sample sizes (Fig. S7).

3.5. Acute IFN-γ exposure downregulates GOMAFU and enhances expression of a SCZ-affected network composed of GOMAFU targets in stress and immune response pathways

Given the association of increased IFN-γ with the risk of SCZ and ASD (Chen et al., 2021; Heuer et al., 2019), we next explored whether and how IFN-γ may influence the expression of *GOMAFU* and its downstream pathways. Acute IFN-γ treatment of BE(2)-M17 cells caused broad transcriptomic alterations (Fig. 5A and Table S7), much beyond immune and inflammatory pathways (Table S8). Substantial overlaps in IFN-γ -regulated GO terms were found in BE(2)-M17 cells and hiPSC-derived NPCs (Warre-Cornish et al., 2020) undergone acute treatment by a single dose of IFN-γ (Fig. S8A). Importantly, a significant downregulation of *GOMAFU* was observed in both BE(2)-M17 cells (Fig. 5B,C) and hiPSC-derived NPCs (Fig. S8B). Conversely, *GOMAFU* suppressed DEGs in the IFN-γ signaling pathway, represented by *IRF1* and *IFIT1*, were markedly increased by IFN-γ (Fig. 5D and Fig. S8B). Approximately 80% (142/177) and 65% (114/177) of *GOMAFU* suppressed DEGs were induced by an acute IFN-γ treatment in BE(2)-M17 cells and hiPSC-derived NPCs, respectively (Fig. S8C, and Table S9). Moreover, acute IFN-γ exposure induced $\log_2$ fold changes of *GOMAFU* targets in BE(2)-M17 cells and hiPSC-derived NPCs display significant correlation ($p < 0.0001$, Fig. S8D).

Of note, GO terms affected by *ΔGOMAFU* only overlap with a subclass of IFN-γ regulated GO terms, which are highly enriched of genes known to underlie immune response and responses to stress and cytokines (Fig. 5E, Table S8). *GOMAFU* targets that are regulated by IFN-γ were rarely found in GO terms related to nervous system development, metabolic process, transport, and localization (Table S8). In addition, among the 142 common DEGs induced by *ΔGOMAFU* and IFN-γ, a significant correlation of $\log_2$ fold change ($p < 0.0001$) was detected (Fig. 5F and Table S9), supporting the conclusion that downregulation of *GOMAFU* contributes to IFN-γ induced expression of these genes.

Interestingly, acute IFN-γ treatment of hiPSC-derived NPCs (Warre-Cornish et al., 2020) caused a much broader spectrum of DEGs than that in hiPSC-derived neurons (Fig. S9A) whereas repeated IFN-γ treatments of neurons induced additional DEGs (Fig. S9B). The majority of IFN-γ induced *GOMAFU targets in* BE(2)-M17 cells are up-regulated in hiPSC-derived neurons by either acute or repeated IFN-γ treatments (Fig. S9C). However, unlike NPCs and BE(2)-M17 cells in which *GOMAFU* was rapidly downregulated upon a single acute IFN-γ treatment (Fig. 5B, C and Fig.S8B), only repeated IFN-γ treatments reduced *GOMAFU* in neurons (Fig. S9D), indicating that *GOMAFU* expression in NPCs is more sensitive to IFN-γ regulation than in neurons. Along with the significant reduction of *GOMAFU*, eight *GOMAFU* target genes were specifically induced in neurons exposed to repeated, but NOT an acute, IFN-γ treatments (Fig. S9 C and D). These include the *N-Myc* and *STAT* Interactor (*NMI*) and the Myeloid Differentiation Primary Response Protein 88 (*MYD88*), both are indicated in innate immune responses (Deguine and Barton, 2014; Ouyang et al., 2021). Moreover, despite the overlapping spectrum of *GOMAFU* targets induced by acute and repeated IFN-γ treatments (Fig. S9C), ~81% of *GOMAFU* targets displayed significantly increased fold induction in neurons exposed to repeated IFN-γ treatments (Fig. S9E and F). These include *MT2A* and *TRIM5*, which are significantly increased in frontal cortex of SCZ along with reduced *GOMAFU* (Gandal et al., 2018)

and *HLA-B/C* known to be induced by IFN-γ in NPC and neurons derived from different paradigms (Pavlinek et al., 2022; Warre-Cornish et al., 2020). These data are consistent with the hypothesis that *GOMAFU* downregulation may contribute to enhanced IFN-γ responses.

Importantly, 65 DEGs commonly induced by *ΔGOMAFU* and IFN-γ are affected in SCZ cohorts analyzed in Table 1 (red dots in Fig. 5F). Furthermore, STRING analysis (https://string-db.org) revealed a highly interactive network formed by these genes commonly affected by *ΔGOMAFU*, IFN-γ and SCZ, which are predicted to underlie stress and immune responses (Fig. 5G). Together, these data suggest that *GOMAFU* selectively mediates IFN-γ stimulated stress and immune responses in human neurons, supporting the hypothesis that lncRNAs can serve as molecular hubs for environmental risk factors to affect etiological molecular networks that underlie the vulnerability and/or pathogenesis of SCZ.

4. Discussion

Our studies provided the first evidence for lncRNA-dependent regulation of human neuronal inflammatory response pathways and demonstrated that the lncRNA *GOMAFU* suppresses a novel gene network affected in SCZ brains involved in IFN-γ induced neuronal responses. A comprehensive working model is provided in Fig. 6, in which *GOMAFU* acts as a brake to suppress IFN-γ signaling pathway genes in human neural progenitor cells and neurons in the brain. In addition, the rapid decline of *GOMAFU* upon exposure to increased extracellular IFN-γ, as a result of maternal or postnatal virus infection and/or stress insults, contributes to the marked surge of IFN signaling pathway known to potentiate innate cellular antiviral signaling and pro-inflammatory cytokine responses. Furthermore, dysregulation of *GOMAFU* in NPCs and/or neurons affects a stress and inflammatory gene network in the brain, which is predicted to alter neuronal responses to inflammatory cytokine insults thus contributes to the vulnerability and pathogenesis of psychiatric disorders represented by SCZ.

SCZ and ASD share overlapping clinical manifestations and molecular pathways (Ardesch et al., 2023; Hommer and Swedo, 2015), including dysregulated lncRNAs (Gandal et al., 2018). The lncRNA *GOMAFU* has attracted substantial attention due to the reported genetic variants associated with SCZ risk (Rao et al., 2015), altered expression in SCZ postmortem brains (Barry et al., 2014), and potential as a biomarker for SZ diagnosis and/or treatment (Jia et al., 2021; Rao et al., 2015). Our findings of *GOMAFU* dysregulation in clinically relevant brain regions of multiple SCZ cohorts that stood out from newly released transcriptomic profiling datasets (Table 1) greatly expanded the previously reported candidate gene-based detection of *GOMAFU* dysregulation (Barry et al., 2014) and strongly supported the involvement of this lncRNA in SCZ pathogenesis. Moreover, we found *GOMAFU* deficiency in the frontal and temporal cortex of SCZ and ASD cohorts from the PsychENCODE datasets (Table 1), which is accompanied by aberrant upregulation of *GOMAFU* targets commonly found in SCZ and ASD subjects (Fig. 3). These discoveries suggest that *GOMAFU* deficiency in the brain may underlie common etiological molecular mechanisms for the pathogenesis of SCZ and ASD.

Even with limited SCZ subjects analyzed, we found that dysregulation of *GOMAFU* is brain region-specific. At this point, molecular mechanisms that lead to such phenomenon still remain elusive. The difference of *GOMAFU* abundance in various geminal zones and neuronal subtypes (Fig. S1) suggests that differential regulation of *GOMAFU* in distinct neuronal subpopulations begins early in normal embryonic brain development. Besides intrinsic developmental regulation, maternal immune activation (MIA) causes brain region-specific changes of cytokines in the offspring, including IFN-γ, IL-6, IL-1β (Garay et al., 2013), which may contribute to the brain region-specific dysregulation of *GOMAFU* (Table 1) and its targets in SCZ patients (Figs. 3 and 4 and Fig. S6). Furthermore, *GOMAFU* expression also rapidly declines upon KCL-triggered global activation of cortical neurons (Barry et al., 2014). Thus, differential dysregulation of *GOMAFU* in various brain regions of SCZ subjects may also reflect neuronal subtypes in response to malfunction of distinct neurotransmitter circuits.

The most striking function of *GOMAFU* discovered in our study is the suppression of pathways that underlie neuronal responses to IFN signaling and cytokine stimuli (Fig. 3). Although ectopic microglia activation and increased secretion of inflammatory cytokines in SCZ and ASD are well-documented (Gober et al., 2022; Na et al., 2014; Rodriguez and Kern, 2011), whether and how intrinsic neuronal properties that govern responses to the inflammatory environment are altered in psychiatric subjects is a challenging and unsolved problem. Considering the well-documented risk of neuropsychiatric disorders due to MIA, understanding the responses of NPCs and developing neurons to extracellular inflammatory insults is of particular importance. The BE(2)-M17 human neuroblastoma cells are not pluripotent NPCs. However, differentiation induced transcriptomic changes in BE(2)-M17 cells that recapitulate hiPSC-derived NPCs (Fig. S2) argues for the usefulness of these cells as a model of human NPCs, with an advantage of efficient transfection and acute silencing of *GOMAFU* by CRISPR-cas9. However, such an approach could not distinguish homozygous or heterozygous deletion of *GOMAFU*. Nonetheless, the acute silencing of *GOMAFU* is sufficient to cause elevated expression of a substantial spectrum of stress and immune response genes (Fig. 3). In this regard, alterations of intrinsic neuronal immune response pathways in SCZ neurons due to *GOMAFU* deficiency uncovered a new risk component of neuropsychiatric diseases in addition to the well-documented environmental risks that lead to increased extracellular inflammatory cytokines upon viral infection and chronic stress (Califano et al., 2018).

Aberrant increases of a large number of *GOMAFU* targets in IFN-signaling pathways are shared in BE(2)-M17 cells harboring *ΔGOMAFU* and the postmortem frontal and temporal cortex of SCZ and ASD subjects that harbor *GOMAFU* deficiency (Fig. 3). Thus, *GOMAFU* deficiency could enhance basal inflammatory responses in neural progenitor cells as well as in mature neurons in the adult brains. Given the vigorous up-regulation of *GOMAFU* during NPC migration and differentiation in the embryonic brain (Fig. S1), *GOMAFU* deficiency in early neuronal development may contribute to SCZ vulnerability whereas dysregulation of the *GOMAFU* pathway in neurons of the adult brain may facilitate the progression of SCZ pathogenesis. Reciprocally, increased *GOMAFU* expression is accompanied by reduction of a selected small group of IFN signaling targets affected in specific SCZ brain regions (Fig. 4). This result on the one hand supports the function of

GOMAFU as a suppressor, but on the other hand suggests that upregulation of *GOMAFU* is unlikely sufficient for complete correction of the exacerbated neuronal response to inflammatory cytokines in SCZ brains.

Besides governing the basal level expression of IFN response pathways, the rapid decline of *GOMAFU* upon acute exposure to IFN-γ selectively de-represses IFN signaling genes in stress and immune response pathways (Fig. 5E) but not other IFN-γ regulated pathways related to neuronal differentiation and metabolic process (Table S8). The IFN-γ induced DEGs that are suppressed by *GOMAFU* in neuroinflammatory pathways in BE(2)-M17 cells largely recapitulate those found in hiPSC-derived NPCs (Warre-Cornish et al., 2020) (Fig. S8), including many *GOMAFU* DEG targets affected in SCZ brains (Fig. 5F). These data support the roles of *GOMAFU* in mediating immediate inflammatory responses to extracellular IFN-γ insults, such as upon viral infection.

Severe infections and autoimmune disorders are well-recognized risk factors of neuropsychiatric disorders with a developmental origin (Eaton et al., 2006; Enstrom et al., 2009). In particular, elevated cytokines levels in MIA, often due to viral infections during early pregnancy, were reported to associate with significantly increase vulnerability of the offspring to SCZ and ASD (Estes and McAllister, 2016; Lombardo et al., 2018; Racicot and Mor, 2017). Specifically, IFN-γ is increased in the mid-pregnancy maternal serum and circulatory IFN-γ levels are elevated in neonates subsequently diagnosed with ASD (Chen et al., 2021; Goines et al., 2011; Heuer et al., 2019). Moreover, IFN-γ was found increased in the fetal brain within hours of MIA in a mouse model and persisted in specific brain regions in the offspring that display schizophrenia-related dysfunctions (Garay et al., 2013). Interestingly, NPCs display broader responses to acute IFN-γ exposure than neurons (Fig. S9A), including downregulation of *GOMAFU* and elevated expression of its targets (Fig S8 and S9)(Warre-Cornish et al., 2020). These results suggest that NPCs may be more prone to the insult of maternal infection/immune activation, and *GOMAFU* dysregulation, as early as in NPCs, may contribute to the prenatal risk of neuropsychiatric diseases. Unfortunately, no cell models are currently available that carry SCZ-associated genetic alterations of *GOMAFU*, limiting our ability to address the genetic risk of *GOMAFU*-regulated IFN-γ pathway for SCZ. In addition, *GOMAFU* is not dysregulated in all SCZ or ASD cohorts, which may contribute to the complex and diverse responses to cytokine insults in various disease cohorts and experimental paradigms (Bhat et al., 2022; Garay et al., 2013).

In postnatal brains, IFN-γ is also implicated in the risk of progression of psychiatric diseases. IFN-γ serum levels were associated with the severity of symptoms in SCZ (Kovacs et al., 2019). Moreover, elevated plasma IFN-γ was found in first-episode (Lesh et al., 2018; Miller et al., 2011), drug-free SCZ subjects as well as acute relapse SCZ subjects (Miller et al., 2011) whereas antipsychotics treatments significantly lowered IFN-γ (Miller et al., 2011). Noticeably, antipsychotics also increased plasma *GOMAFU* in SCZ subjects (Liu et al., 2018), suggesting that the IFN-γ-*GOMAFU* pathway may be a potential biomarker for SCZ treatment. Besides infection, sustained stress can also lead to chronic increase of pro-inflammatory cytokines, including IFN-γ, in SCZ (Dhabhar et al., 2000; Muller et al., 2015). How *GOMAFU* and its downstream targets are affected by stress-induced pro-inflammatory responses is an interesting question to be addressed by future studies.

5. Conclutions and perspectives

Taken together, our findings suggest that *GOMAFU* is a critical link that connects neuronal inflammatory responses with environmental risks of SCZ. This is the first example how lncRNA abnormalities affect neuronal gene networks that are indicated in responses to insults by extracellular inflammatory cytokines. Given the fact that immune disturbance during early life could trigger lifelong increase in immune reactivity and alter neural circuitry development (Bilbo and Schwarz, 2009, 2012; Brenhouse et al., 2019; Danese and Lewis, 2017), the function of *GOMAFU* in suppressing immune response pathways in NPCs is particularly important for the vulnerability of many neurodevelopmental disorders that involve elevated inflammatory cytokines. At this point, the functional importance of *GOMAFU* in neuronal development, through regulating alternative splicing and developmentally programmed DEG expression, in addition to immune and neuroinflammatory responses, still remains elusive. How to integrate the functional impacts of *GOMAFU* on abnormalities of neuronal development, neurotransmitter-dependent plasticity, and inflammatory responses in diseased brains is a challenging task for future studies, which may uncover additional pathological mechanisms that underlie neuropsychiatric diseases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by NIH grants R01NS110110, R01NS118819, and R01NS093016 to YF; R01AG062577, R01MH117122, and R01AG064786 to B.Y.; R01AG065611 and R21MH12711 to W.Z.

Data availability

Data availability: All genome-wide sequencing datasets have been deposited to Gene Expression Omnibus (GEO) repository with the accession ID GSE182370 and GSE206720.

References

Aliperti V, Skonieczna J, Cerase A, 2021. Long non-coding RNA (lncRNA) roles in cell biology, neurodevelopment and neurological disorders. Noncoding RNA 7, 36. [PubMed: 34204536]

Aprea J, Prenninger S, Dori M, Ghosh T, Monasor LS, Wessendorf E, et al. , 2013. Transcriptome sequencing during mouse brain development identifies long non-coding RNAs functionally involved in neurogenic commitment. EMBO J. 32, 3145–3160. [PubMed: 24240175]

Ardesch DJ, Libedinsky I, Scholtens LH, Wei Y, van den Heuvel MP, 2023. Convergence of Brain Transcriptomic and Neuroimaging Patterns in Schizophrenia, Bipolar Disorder, Autism Spectrum Disorder, and Major Depressive Disorder. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 10.1016/j.bpsc.2022.12.013.

Arion D, Unger T, Lewis DA, Levitt P, Mirnics K, 2007. Molecular evidence for increased expression of genes related to immune and chaperone function in the prefrontal cortex in schizophrenia. Biol. Psychiatry 62, 711–721. [PubMed: 17568569]

Arion D, Corradi JP, Tang S, Datta D, Boothe F, He A, et al. , 2015. Distinctive transcriptome alterations of prefrontal pyramidal neurons in schizophrenia and schizoaffective disorder. Mol. Psychiatry 20, 1397–1405. [PubMed: 25560755]

Barry G, Briggs JA, Vanichkina DP, Poth EM, Beveridge NJ, Ratnu VS, et al. , 2014. The long non-coding RNA Gomafu is acutely regulated in response to neuronal activation and involved in schizophrenia-associated alternative splicing. Mol. Psychiatry 19, 486–494. [PubMed: 23628989]

Bhat A, Irizar H, Couch ACM, Raval P, Duarte RRR, Dutan Polit L, et al. , 2022. Attenuated transcriptional response to pro-inflammatory cytokines in schizophrenia hiPSC-derived neural progenitor cells. Brain Behav. Immun. 105, 82–97. [PubMed: 35716830]

Bilbo SD, Schwarz JM, 2009. Early-life programming of later-life brain and behavior: a critical role for the immune system. Front. Behav. Neurosci. 3, 14. [PubMed: 19738918]

Bilbo SD, Schwarz JM, 2012. The immune system and developmental programming of brain and behavior. Front. Neuroendocrinol. 33, 267–286. [PubMed: 22982535]

Boksa P, 2010. Effects of prenatal infection on brain development and behavior: a review of findings from animal models. Brain Behav. Immun. 24, 881–897. [PubMed: 20230889]

Brenhouse HC, Danese A, Grassi-Oliveira R, 2019. Neuroimmune impacts of early-life stress on development and psychopathology. Curr. Top. Behav. Neurosci. 43, 423–447. [PubMed: 30003509]

Brennand KJ, Simone A, Tran N, Gage FH, 2012. Modeling psychiatric disorders at the cellular and network levels. Mol Psychiatr. 17, 1239–1253.

Califano D, Furuya Y, Roberts S, Avram D, McKenzie ANJ, Metzger DW, 2018. IFN-γ increases susceptibility to influenza A infection through suppression of group II innate lymphoid cells. Mucosal Immunol. 11, 209–219. [PubMed: 28513592]

Chang X, Liu Y, Hahn CG, Gur RE, Sleiman PMA, Hakonarson H, 2017. RNA-seq analysis of amygdala tissue reveals characteristic expression profiles in schizophrenia. Transl. Psychiatry 7, e1203. [PubMed: 28809853]

Chen L, Zheng WH, Du Y, Li XS, Yu Y, Wang H, et al. , 2021. Altered peripheral immune profiles in first-episode, drug-free patients with schizophrenia: response to antipsychotic medications. Front Med (Lausanne). 8, 757655. [PubMed: 34901070]

Chung DW, Volk DW, Arion D, Zhang Y, Sampson AR, Lewis DA, 2016. Dysregulated ErbB4 splicing in schizophrenia: selective effects on parvalbumin expression. Am. J. Psychiatry 173, 60–68. [PubMed: 26337038]

Cui X, Sun X, Niu W, Kong L, He M, Zhong A, et al. , 2016. Long non-coding RNA: potential diagnostic and therapeutic biomarker for major depressive disorder. Med. Sci. Monit. 22, 5240–5248. [PubMed: 28039689]

Danese A, Lewis SJ, 2017. Psychoneuroimmunology of Early-Life Stress: The Hidden Wounds of Childhood Trauma? Neuropsychopharmacology 42, 99–114. [PubMed: 27629365]

Deguine J, Barton GM, 2014. MyD88: a central player in innate immune signaling. F1000Prime Rep. 6, 97. [PubMed: 25580251]

Derrien T, Johnson R, Bussotti G, Tanzer A, Djebali S, Tilgner H, et al. , 2012. The GENCODE v7 catalog of human long noncoding RNAs: analysis of their gene structure, evolution, and expression. Genome Res. 22, 1775–1789. [PubMed: 22955988]

Dhabhar FS, Satoskar AR, Bluethmann H, David JR, McEwen BS, 2000. Stress-induced enhancement of skin immune function: a role for gamma interferon. PNAS 97, 2846–2851. [PubMed: 10706626]

Diamond MS, 2014. IFIT1: A dual sensor and effector molecule that detects non-2'-O methylated viral RNA and inhibits its translation. Cytokine Growth Factor Rev. 25, 543–550. [PubMed: 24909568]

Eaton WW, Byrne M, Ewald H, Mors O, Chen CY, Agerbo E, et al. , 2006. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. Am. J. Psychiatry 163, 521–528. [PubMed: 16513876]

Enstrom AM, Van de Water JA, Ashwood P, 2009. Autoimmunity in autism. Curr. Opin. Invest. Drugs 10, 463–473.

Estes ML, McAllister AK, 2016. Maternal immune activation: implications for neuropsychiatric disorders. Science 353, 772–777. [PubMed: 27540164]

Fietz SA, Lachmann R, Brandl H, Kircher M, Samusik N, Schroder R, et al. , 2012. Transcriptomes of germinal zones of human and mouse fetal neocortex suggest a role of extracellular matrix in progenitor self-renewal. PNAS 109, 11836–11841. [PubMed: 22753484]

Gandal MJ, Zhang P, Hadjimichael E, Walker RL, Chen C, Liu S, et al. , 2018. Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. Science 362.

Garay PA, Hsiao EY, Patterson PH, McAllister AK, 2013. Maternal immune activation causes age- and region-specific changes in brain cytokines in offspring throughout development. Brain Behav. Immun. 31, 54–68. [PubMed: 22841693]

Garey LJ, Ong WY, Patel TS, Kanani M, Davis A, Mortimer AM, et al. , 1998. Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. J. Neurol. Neurosurg. Psychiatry 65, 446–453. [PubMed: 9771764]

Glantz LA, Lewis DA, 2000. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Arch. Gen. Psychiatry 57, 65–73. [PubMed: 10632234]

Gober R, Ardalan M, Shiadeh SMJ, Duque L, Garamszegi SP, Ascona M, et al. , 2022. Microglia activation in postmortem brains with schizophrenia demonstrates distinct morphological changes between brain regions. Brain Pathol. 32, e13003. [PubMed: 34297453]

Goines PE, Croen LA, Braunschweig D, Yoshida CK, Grether J, Hansen R, et al. , 2011. Increased midgestational IFN-gamma, IL-4 and IL-5 in women bearing a child with autism: a case-control study. Mol Autism. 2, 13. [PubMed: 21810230]

Goldman-Rakic PS, 1995. Cellular basis of working memory. Neuron 14, 477–485. [PubMed: 7695894]

Hadjicharalambous MR, Lindsay MA, 2019. Long non-coding RNAs and the innate immune response. Noncoding RNA. 5, 34. [PubMed: 31010202]

Heuer LS, Croen LA, Jones KL, Yoshida CK, Hansen RL, Yolken R, et al. , 2019. An exploratory examination of neonatal cytokines and chemokines as predictors of autism risk: the early markers for autism study. Biol. Psychiatry 86, 255–264. [PubMed: 31279535]

Hoffman GE, Hartley BJ, Flaherty E, Ladran I, Gochman P, Ruderfer DM, et al. , 2017. Transcriptional signatures of schizophrenia in hiPSC-derived NPCs and neurons are concordant with post-mortem adult brains. Nat. Commun. 8, 2225. [PubMed: 29263384]

Hommer RE, Swedo SE, 2015. Schizophrenia and Autism—Related Disorders. Schizophr. Bull. 41, 313–314.

Hughes HK, Moreno RJ, Ashwood P, 2023. Innate immune dysfunction and neuroinflammation in autism spectrum disorder (ASD). Brain Behav. Immun. 108, 245–254. [PubMed: 36494048]

Ip JY, Sone M, Nashiki C, Pan Q, Kitaichi K, Yanaka K, et al. , 2016. Gomafu lncRNA knockout mice exhibit mild hyperactivity with enhanced responsiveness to the psychostimulant methamphetamine. Sci. Rep. 6, 27204. [PubMed: 27251103]

Ishii N, Ozaki K, Sato H, Mizuno H, Susumu S, Takahashi A, et al. , 2006. Identification of a novel non-coding RNA, MIAT, that confers risk of myocardial infarction. J. Hum. Genet. 51, 1087–1099. [PubMed: 17066261]

Jenkins TA, 2013. Perinatal complications and schizophrenia: involvement of the immune system. Front. Neurosci. 7, 110. [PubMed: 23805069]

Jia J, Liu X, Ma L, Xu Y, Ren Y, 2021. A preliminary analysis of LncRNA biomarkers for schizophrenia. Epigenomics 13, 1443–1458. [PubMed: 34528440]

Kaushik G, Zarbalis KS, 2016. Prenatal neurogenesis in autism spectrum disorders. Front. Chem. 4, 12. [PubMed: 27014681]

Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB, 2015. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. Lancet Psychiatry 2, 258–270. [PubMed: 26359903]

Kim D, Pertea G, Trapnell C, Pimentel H, Kelley R, Salzberg SL, 2013. TopHat2: accurate alignment of transcriptomes in the presence of insertions, deletions and gene fusions. Genome Biol. 14, R36. [PubMed: 23618408]

Knuesel I, Chicha L, Britschgi M, Schobel SA, Bodmer M, Hellings JA, et al. , 2014. Maternal immune activation and abnormal brain development across CNS disorders. Nat. Rev. Neurol. 10, 643–660. [PubMed: 25311587]

Kovacs MA, Tenyi T, Kugyelka R, Prenek L, Hau L, Magyar EE, et al. , 2019. Elevated osteopontin and interferon gamma serum levels and increased neutrophil-to-lymphocyte ratio are associated with the severity of symptoms in schizophrenia. Front. Psych. 10, 996.

Lanz TA, Reinhart V, Sheehan MJ, Rizzo SJS, Bove SE, James LC, et al. , 2019. Postmortem transcriptional profiling reveals widespread increase in inflammation in schizophrenia: a comparison of prefrontal cortex, striatum, and hippocampus among matched tetrads of controls with subjects diagnosed with schizophrenia, bipolar or major depressive disorder. Transl. Psychiatry 9, 151. [PubMed: 31123247]

Lawrence DW, Willard PA, Cochran AM, Matchett EC, Kornbluth J, 2020. Natural killer lytic-associated molecule (NKLAM): an E3 ubiquitin ligase with an integral role in innate immunity. Front. Physiol. 11, 573372. [PubMed: 33192571]

Lesh TA, Careaga M, Rose DR, McAllister AK, Van de Water J, Carter CS, et al. , 2018. Cytokine alterations in first-episode schizophrenia and bipolar disorder: relationships to brain structure and symptoms. J. Neuroinflammation 15, 165. [PubMed: 29803226]

Li Y, Wang F, Teng P, Ku L, Chen L, Feng Y, et al. , 2022. Accurate identification of circRNA landscape and complexity reveals their pivotal roles in human oligodendroglia differentiation. Genome Biol. 23, 48. [PubMed: 35130952]

Liu YS, Rao SQ, Xu Y, Zhang FQ, Wang ZQ, Zhao XD, 2018. Changes in the level of Long Non-Coding RNA Gomafu gene expression in schizophrenia patients before and after antipsychotic medication. Schizophr. Res. 195, 318–319. [PubMed: 28911914]

Lizio M, Harshbarger J, Shimoji H, Severin J, Kasukawa T, Sahin S, et al. , 2015. Gateways to the FANTOM5 promoter level mammalian expression atlas. Genome Biol. 16, 22. [PubMed: 25723102]

Lombardo MV, Moon HM, Su J, Palmer TD, Courchesne E, Pramparo T, 2018. Maternal immune activation dysregulation of the fetal brain transcriptome and relevance to the pathophysiology of autism spectrum disorder. Mol. Psychiatry 23, 1001–1013. [PubMed: 28322282]

Marchese FP, Raimondi I, Huarte M, 2017. The multidimensional mechanisms of long noncoding RNA function. Genome Biol. 18, 206. [PubMed: 29084573]

Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B, 2011. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol. Psychiatry 70, 663–671. [PubMed: 21641581]

Muller N, Weidinger E, Leitner B, Schwarz MJ, 2015. The role of inflammation in schizophrenia. Front Neurosci-Switz. 9.

Na KS, Jung HY, Kim YK, 2014. The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 48, 277–286. [PubMed: 23123365]

Ni C, Jiang W, Wang Z, Wang Z, Zhang J, Zheng X, et al. , 2021. LncRNA-AC006129.1 reactivates a SOCS3-mediated anti-inflammatory response through DNA methylation-mediated CIC downregulation in schizophrenia. Mol. Psychiatry 26, 4511–4528. [PubMed: 32015466]

Ouyang W, Cen M, Yang L, Zhang W, Xia J, Xu F, 2021. NMI Facilitates Influenza A Virus Infection by Promoting Degradation of IRF7 through TRIM21. Am. J. Respir. Cell Mol. Biol. 65, 30–40. [PubMed: 33761305]

Parikshak NN, Swarup V, Belgard TG, Irimia M, Ramaswami G, Gandal MJ, et al. , 2016. Genome-wide changes in lncRNA, splicing, and regional gene expression patterns in autism. Nature 540, 423–427. [PubMed: 27919067]

Pavlinek A, Matuleviciute R, Sichlinger L, Dutan Polit L, Armeniakos N, Vernon AC, et al. , 2022. Interferon-gamma exposure of human iPSC-derived neurons alters major histocompatibility complex I and synapsin protein expression. Front. Psych. 13, 836217.

Prata J, Santos SG, Almeida MI, Coelho R, Barbosa MA, 2017. Bridging Autism Spectrum Disorders and Schizophrenia through inflammation and biomarkers - pre-clinical and clinical investigations. J Neuroinflamm. 14, 179.

Racicot K, Mor G, 2017. Risks associated with viral infections during pregnancy. J. Clin. Invest. 127, 1591–1599. [PubMed: 28459427]

Ramaker RC, Bowling KM, Lasseigne BN, Hagenauer MH, Hardigan AA, Davis NS, et al. , 2017. Post-mortem molecular profiling of three psychiatric disorders. Genome Med. 9, 72. [PubMed: 28754123]

Ramana CV, Gil MP, Han Y, Ransohoff RM, Schreiber RD, Stark GR, 2001. Stat1-independent regulation of gene expression in response to IFN-gamma. Proc. Natl. Acad. Sci. U.S.A. 98, 6674–6679. [PubMed: 11390994]

Rao SQ, Hu HL, Ye N, Shen Y, Xu Q, 2015. Genetic variants in long non-coding RNA MIAT contribute to risk of paranoid schizophrenia in a Chinese Han population. Schizophr. Res. 166, 125–130. [PubMed: 26004688]

Rapicavoli NA, Poth EM, Blackshaw S, 2010. The long noncoding RNA RNCR2 directs mouse retinal cell specification. BMC Dev. Biol 10, 49. [PubMed: 20459797]

Rodriguez JI, Kern JK, 2011. Evidence of microglial activation in autism and its possible role in brain underconnectivity. Neuron Glia Biol. 7, 205–213. [PubMed: 22874006]

Rusconi F, Battaglioli E, Venturin M, 2020. Psychiatric Disorders and lncRNAs: A Synaptic Match. Int. J. Mol. Sci. 21.

Sherman BT, Hao M, Qiu J, Jiao X, Baseler MW, Lane HC, Imamichi T, Chang W, 2022. DAVID: a web server for functional enrichment analysis and functional annotation of gene lists (2021 update). Nucleic Acids Res. 50, W216–W221. [PubMed: 35325185]

Sloan CA, Chan ET, Davidson JM, Malladi VS, Strattan JS, Hitz BC, et al. , 2016. ENCODE data at the ENCODE portal. Nucleic Acids Res. 44, D726–D732. [PubMed: 26527727]

Sone M, Hayashi T, Tarui H, Agata K, Takeichi M, Nakagawa S, 2007. The mRNA-like noncoding RNA Gomafu constitutes a novel nuclear domain in a subset of neurons. J. Cell Sci. 120, 2498–2506. [PubMed: 17623775]

Srinivas T, Mathias C, Oliveira-Mateos C, Guil S, 2023. Roles of lncRNAs in brain development and pathogenesis: Emerging therapeutic opportunities. Mol. Ther. 10.1016/j.ymthe.2023.02.008.

Statello L, Guo CJ, Chen LL, Huarte M, 2021. Gene regulation by long non-coding RNAs and its biological functions. Nat. Rev. Mol. Cell Biol. 22, 96–118. [PubMed: 33353982]

Szklarczyk D, Gable AL, Lyon D, Junge A, Wyder S, Huerta-Cepas J, et al. , 2019. STRING v11: protein-protein association networks with increased coverage, supporting functional discovery in genome-wide experimental datasets. Nucleic Acids Res. 47, D607–D613. [PubMed: 30476243]

Trapnell C, Hendrickson DG, Sauvageau M, Goff L, Rinn JL, Pachter L, 2013. Differential analysis of gene regulation at transcript resolution with RNA-seq. Nat. Biotechnol. 31, 46–53. [PubMed: 23222703]

Thomas PD, Ebert D, Muruganujan A, Mushayahama T, Albou LP, Mi H, 2022. PANTHER: Making genome-scale phylogenetics accessible to all. Protein Sci. 31, 8–22. [PubMed: 34717010]

Trubetskoy V, Pardinas AF, Qi T, Panagiotaropoulou G, Awasthi S, Bigdeli TB, et al. , 2022. Mapping genomic loci implicates genes and synaptic biology in schizophrenia. Nature 604, 502–508. [PubMed: 35396580]

Voineagu I, Wang X, Johnston P, Lowe JK, Tian Y, Horvath S, et al. , 2011. Transcriptomic analysis of autistic brain reveals convergent molecular pathology. Nature 474, 380–384. [PubMed: 21614001]

Walker EF, Goldsmith DR, 2022. Schizophrenia: A scientific graveyard or a pragmatically useful diagnostic construct? Schizophr. Res. 242, 141–143. [PubMed: 35090774]

Walter W, Sanchez-Cabo F, Ricote M, 2015. GOplot: an R package for visually combining expression data with functional analysis. Bioinformatics 31, 2912–2914. [PubMed: 25964631]

Wang Y, Zhao X, Ju W, Flory M, Zhong J, Jiang S, et al. , 2015. Genome-wide differential expression of synaptic long noncoding RNAs in autism spectrum disorder. Transl. Psychiatry 5, e660. [PubMed: 26485544]

Warre-Cornish K, Perfect L, Nagy R, Duarte RRR, Reid MJ, Raval P, et al. , 2020. Interferon-gamma signaling in human iPSC-derived neurons recapitulates neurodevelopmental disorder phenotypes. Sci. Adv. 6, eaay9506. [PubMed: 32875100]

Wen Z, Nguyen HN, Guo Z, Lalli MA, Wang X, Su Y, et al. , 2014. Synaptic dysregulation in a human iPS cell model of mental disorders. Nature 515, 414–418. [PubMed: 25132547]

Wu J, Akerman M, Sun SY, McCombie WR, Krainer AR, Zhang MQ, 2011. SpliceTrap: a method to quantify alternative splicing under single cellular conditions. Bioinformatics 27, 3010–3016. [PubMed: 21896509]

Yang S, Lim KH, Kim SH, Joo JY, 2021. Molecular landscape of long noncoding RNAs in brain disorders. Mol. Psychiatry 26, 1060–1074. [PubMed: 33173194]

Yao RW, Wang Y, Chen LL, 2019. Cellular functions of long noncoding RNAs. Nat. Cell Biol. 21, 542–551. [PubMed: 31048766]

Zakutansky PM, Feng Y, 2022. The Long Non-Coding RNA GOMAFU in Schizophrenia: Function, Disease Risk, and Beyond. Cells. 11, 1949. [PubMed: 35741078]

Zhong S, Zhang S, Fan X, Wu Q, Yan L, Dong J, et al. , 2018. A single-cell RNA-seq survey of the developmental landscape of the human prefrontal cortex. Nature 555, 524–528. [PubMed: 29539641]

Zimmer-Bensch G, 2019. Emerging Roles of Long Non-Coding RNAs as Drivers of Brain Evolution. Cells. 8.

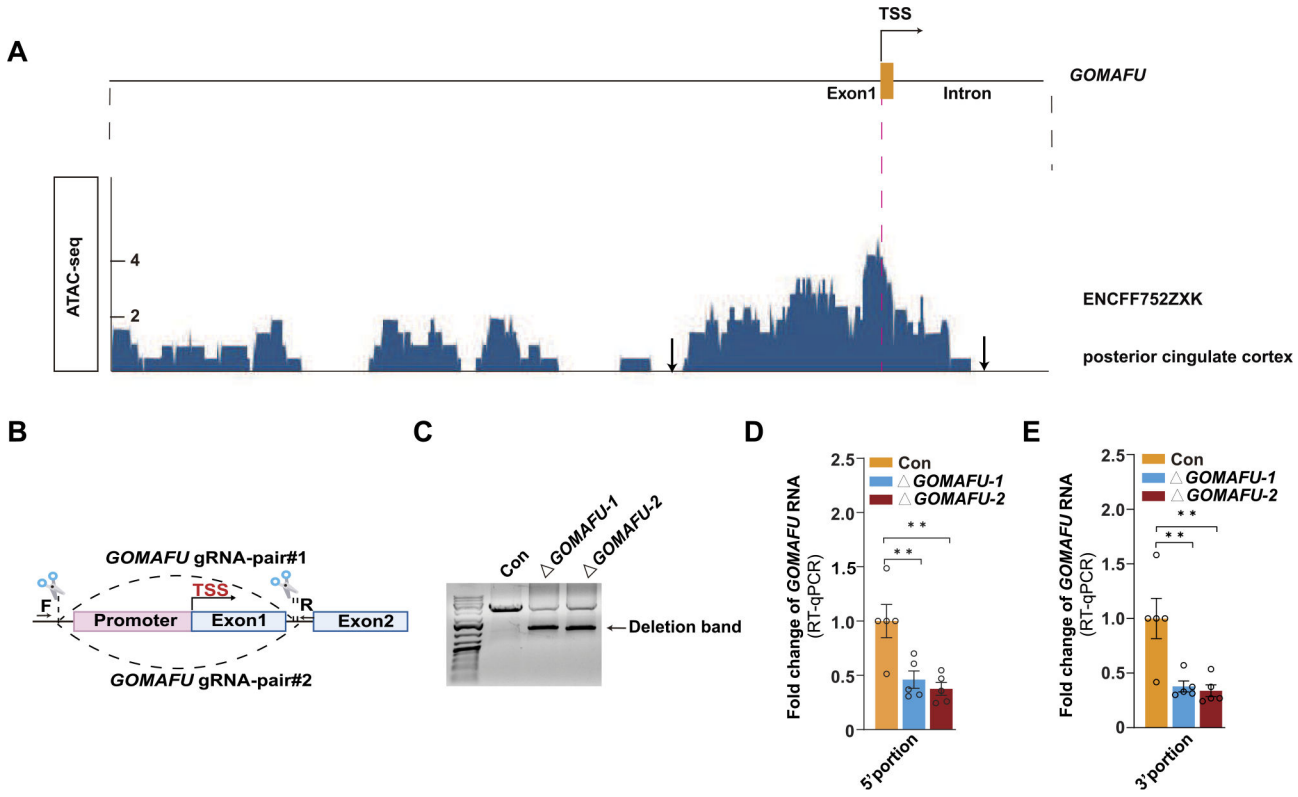

Fig. 1. Identification and deletion of the *GOMAFU* promoter by CRISPR/Cas9 in a human NPC model.

(**A**) ATAC-seq reads at the *GOMAFU* gene 5′ end derived from posterior cingulate cortex (ENCODE) (Sloan et al., 2016). Arrows indicate a peak flanking the *GOMAFU* transcription start site (TSS) and the core promoter. (**B**) Schematic illustration of the target sites by two gRNA pairs for deletion of the *GOMAFU* promoter region indicated by scissors at the dashed lines. Arrows marked by F and R indicate PCR primers for genotyping. (**C**) PCR of genomic DNA from the parental BE(2)-M17 cells and cells subjected to acute deletion of the *GOMAFU* promoter region by CRISPR-Cas9 using two different gRNA pairs (*ΔGOMAFU*-1 and *ΔGOMAFU*-2) in separate transfections, respectively. The arrow indicates the PCR products that contain the expected deletions. (**D-E**) RT-qPCR analysis of the 5′ and 3′ regions of the *GOMAFU* lncRNA (one-way ANOVA followed by Tukey's multiple comparison, n = 5; **denotes $p < 0.01$).

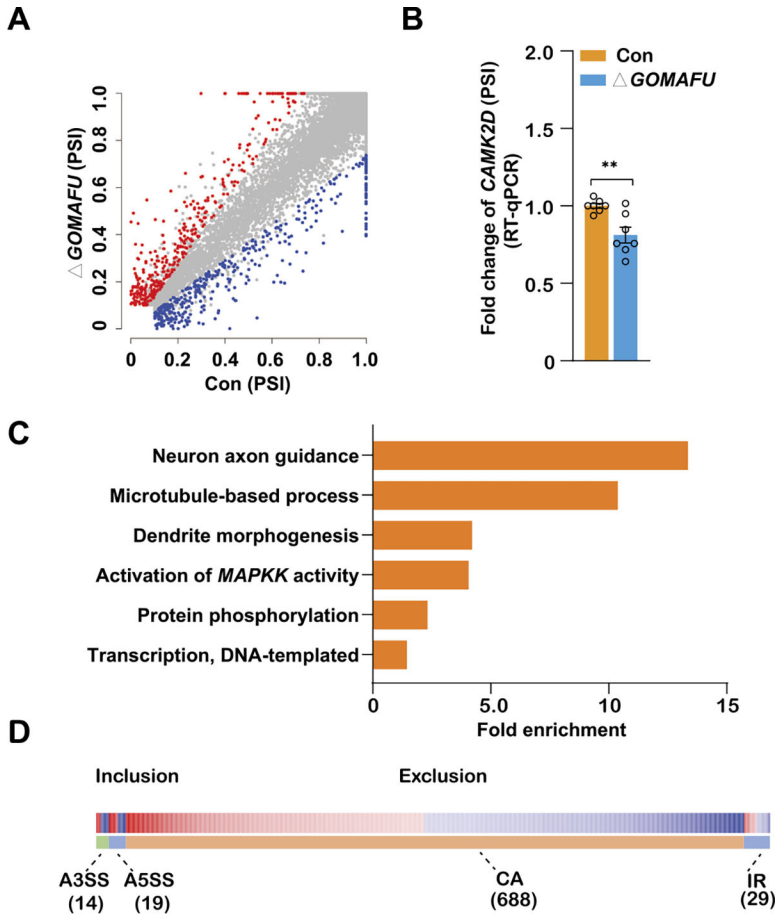

Fig. 2. Transcriptome-wide alterations of alternative splicing caused by CRISPR-Cas9 mediated acute deletion of *GOMAFU*.

(**A**) Scatter plot illustrates alterations of alternative splicing events (FDR < 0.05, splice change > 15%), indicated by Percent Spliced In (PSI), upon acute deletion of the *GOMAFU* promoter (*ΔGOMAFU*) in BE(2)-M17 cells. Red and blue dots represent increased and reduced PSI events due to *ΔGOMAFU* whereas grey dots represent no significant changes. (**B**) RT-qPCR validation of altered inclusion of *CAMK2D* exon20 caused by *ΔGOMAFU* in BE(2)-M17 cells (*denotes $p < 0.05$, student *t*-test, n = 7). (**C**) Gene Ontology (GO) analysis of alternative splicing events regulated by *GOMAFU* (FDR < 0.05, Fold enrichment > 1.3). (**D**) Heatmap indicates changes in different types of alternative splicing events caused by *ΔGOMAFU* (FDR < 0.05, splice change > 15%). A3SS represents alternative 3′ splicing site. A5SS represents alternative 5′ splicing site. CA represents cassette exon. IR represents intron retention. The number of altered splicing events for each type of alternative splicing is provided.

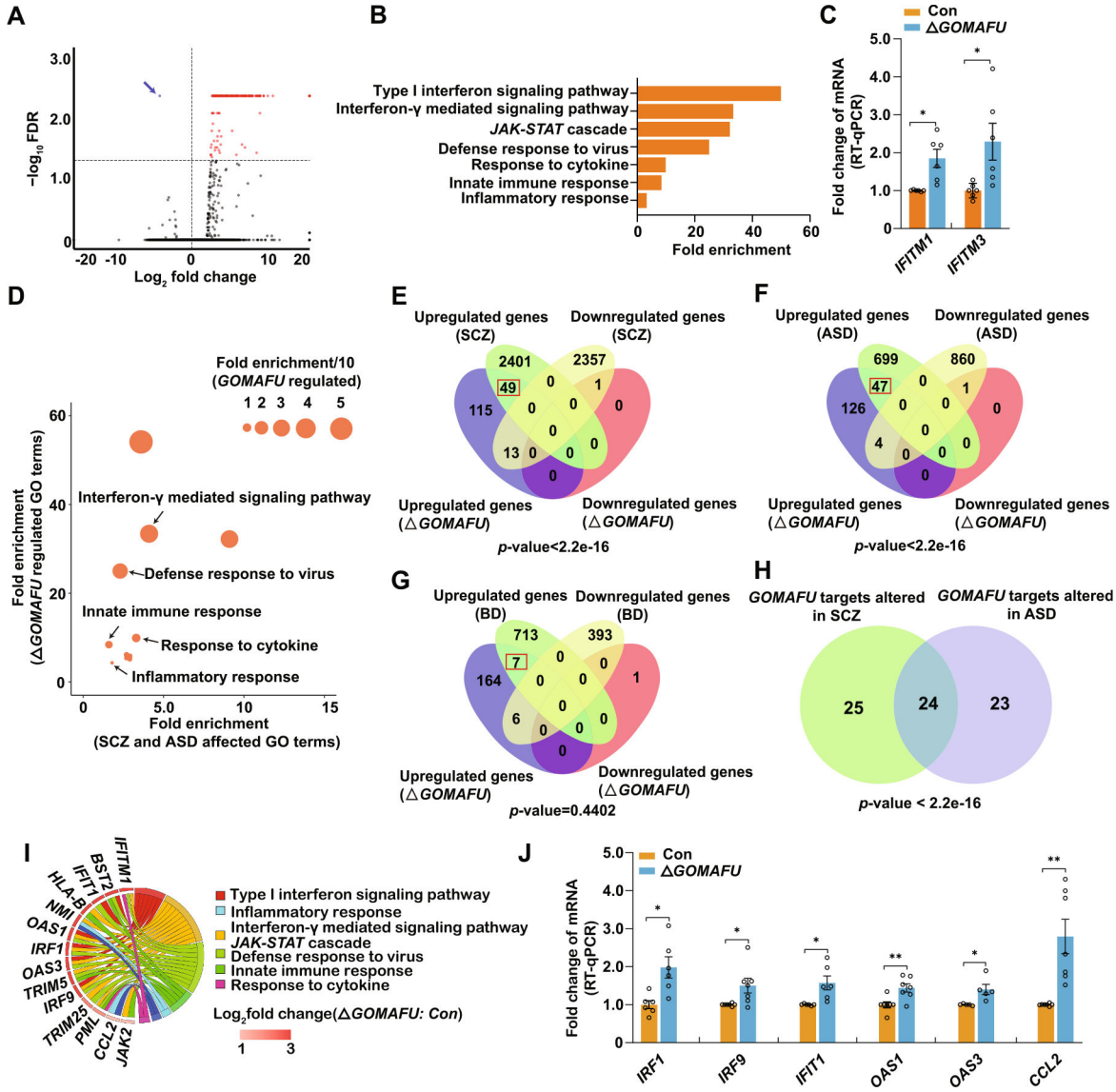

Fig. 3. *GOMAFU* deficiency affects wide molecular networks implicated in neuropsychiatric diseases.

(**A**) Volcano plot indicates differentially expressed genes (DEGs) in BE(2)-M17 cells caused by *ΔGOMAFU*. Red dots represent DEGs with significantly increased expression. The single blue dot marked by a blue arrow represents reduced *GOMAFU* expression. Grey dots represent genes that do not show significant changes in expression. Significant changes were defined by FDR < 0.05. (**B**) Gene Ontology (GO) analysis of *ΔGOMAFU* regulated DEGs in (**A**) (FDR < 0.05). (**C**) RT-qPCR of *IFITM1* and *IFITM3* mRNAs in parental BE(2)-M17 cells and *ΔGOMAFU* cells (*denotes $p < 0.05$, student *t*-test, n = 6). (**D**) Scatter plot illustrates GO terms (FDR < 0.05) commonly affected in SCZ and ASD postmodern brains (x-axis) and by *ΔGOMAFU* in BE(2)-M17 cells (y-axis). The size of each dot represents numbers of *ΔGOMAFU* regulated DEGs in the corresponding GO term. (**E-G**) Venn diagrams show significant overlaps (red squares) between genes upregulated by *ΔGOMAFU* in BE(2)-M17 cells and in the postmortem frontal and temporal cortex of

SCZ (**E**) and ASD (**F**) that harbor reduced *GOMAFU* expression ($p < 2.2e-16$, Chi-Squared test). No significant overlaps with DEGs affected in BD was detected ($p = 0.4402$. Chi-Squared test) (**G**). (**H**) Venn diagrams show SCZ and ASD display significant overlaps of *GOMAFU* upregulated targets ($p < 2.2e-16$, Chi-Squared test). (**I**) GOChord plot illustrates representative *ΔGOMAFU* regulated DEGs enriched in multiple GO terms (color-coded). Log_2 fold changes of gene expression are indicated by the intensity of colored rectangles. (**J**) RT-qPCR validation of representative *ΔGOMAFU* regulated DEGs enriched in multiple GO terms (*denotes $p < 0.05$, **denotes $p < 0.01$, student *t*-test, n = 5).

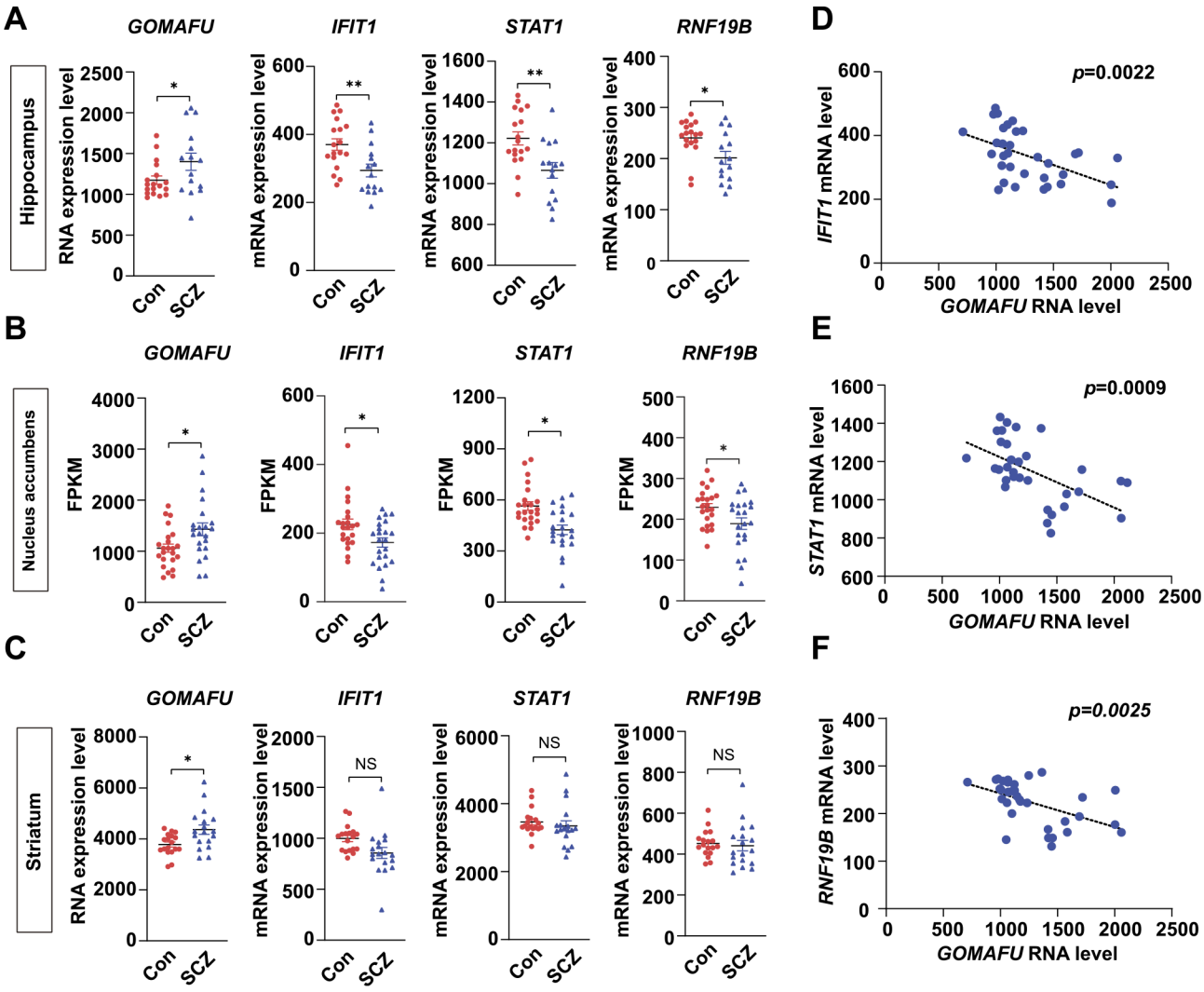

Fig. 4. Elevated *GOMAFU* expression suppresses a subset of IFN pathway genes in specific postmortem brain regions of SCZ subjects.

(**A-C**) Reduction of selective Interferon Stimulated Genes (ISGs) identified as DEGs of Δ*GOMAFU* in brain regions derived from SCZ subjects (GSE53987, GSE80655) that harbor increased *GOMAFU* expression. Hippocampus (n = 15), Nucleus accumbens (n = 22), Striatum (n = 18). Multiple test corrections were conducted, with *denotes false discovery rate (FDR) < 0.05, **denotes FDR < 0.01. (**D-F**) Linear regression analysis shows significant negative correlation between expression levels of *GOMAFU* and ISG mRNAs in postmortem hippocampus (GSE53987). (*GOMAFU* and *IFIT1*, $p = 0.0022$, $R^2 = 0.2641$; *GOMAFU* and *STAT1*, $p = 0.0009$, $R^{2=}0.3013$; *GOMAFU* and *RNF19B*, $p = 0.0025$, $R^2 = 0.2584$). The SCZ and CON subjects showed similar trends of negative correlation between *GOMAFU* and its targets, but not all reached statistical significance due to small sample sizes (Fig. S7), hence data are combined for the above plots.

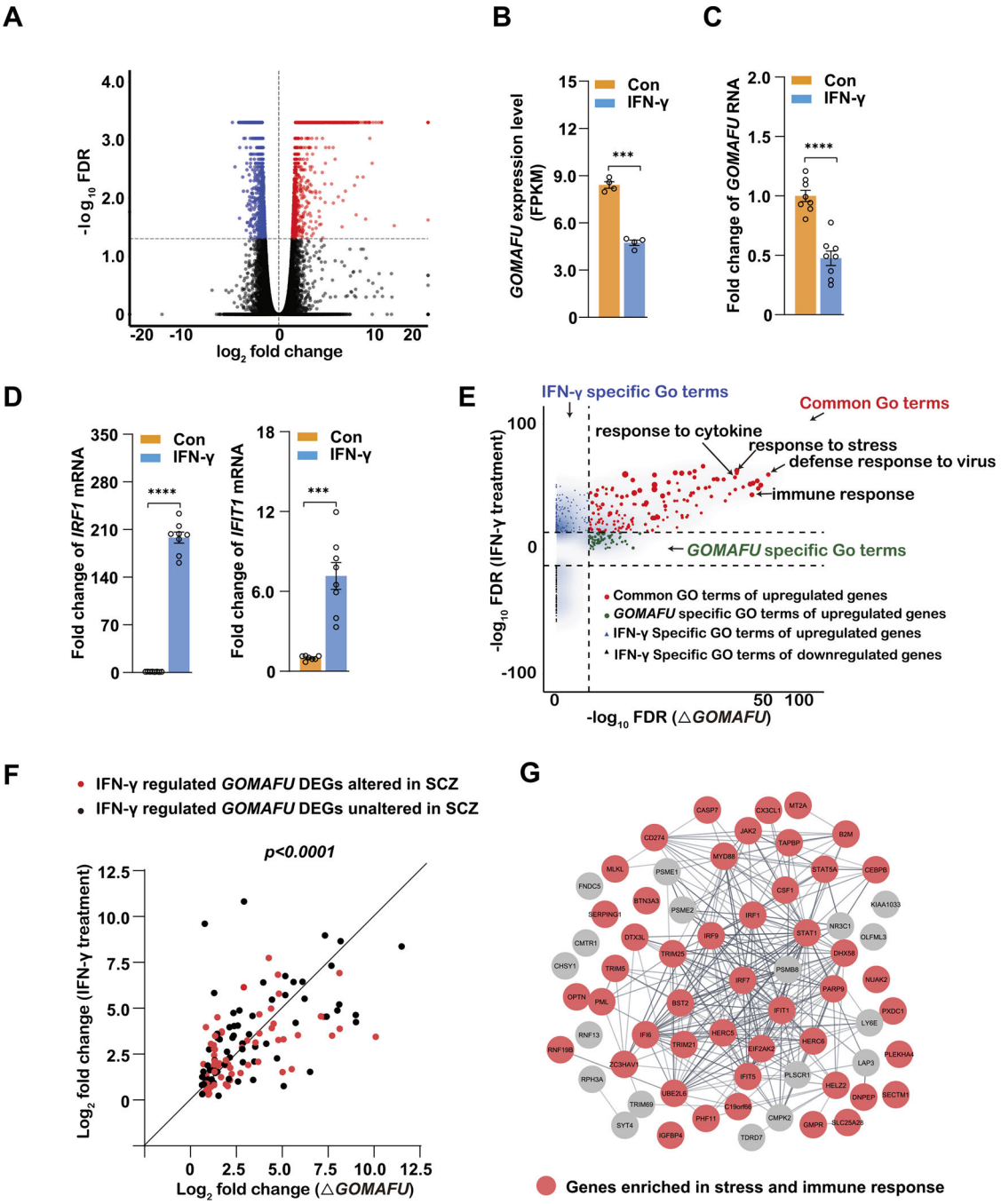

Fig. 5. Acute exposure to IFN-γ reduced *GOMAFU* expression, which mediates de-repression of a subclass of ISGs enriched in stress and immune response pathways affected in SCZ brains.

(**A**) Volcano plot indicates IFN-γ regulated DEGs in BE(2)-M17 cells. Blue and red dots represent DEGs with significantly decreased or increased expression (FDR < 0.05), respectively. (**B** and **C**) RNA-seq analysis (**B**, n = 4) and RT-qPCR validation (**C**, n = 8) indicate significant reduction of *GOMAFU* in BE(2)-M17 cells treated with IFN-γ for 24 h (***denotes < 0.001; ****denotes $p < 0.0001$, student *t*-test). (**D**) RT-qPCR validation of changes of *IRF1* and *IFIT1* mRNAs in BE(2)-M17 cells treated with IFN-γ (***denotes

< 0.001, ****denotes $p < 0.0001$, student *t*-test, n = 8). (**E**) Gene Ontology (GO) analysis shows that *GOMAFU* selectively regulates a subgroup of IFN-regulated pathways. The top hits include immune response, response to cytokine, defense response to virus, and response to stress. Red dots represent common GO terms regulated by *ΔGOMAFU* and IFN- γ. Green dots represent GO terms specifically regulated by *ΔGOMAFU* but not affected by acute IFN-γ treatment. The size of each red and green dot represents the number of *GOMAFU* regulated DEGs in the corresponding GO term. Blue and black triangles represent specific GO terms enriched of IFN-γ upregulated and downregulated genes, respectively. (**F**) Scatter plot shows correlation between $\log_2$ fold changes of genes commonly regulated by IFN-γ and *ΔGOMAFU* ($p < 0.0001$, $R^2 = 0.36$). Red dots indicate genes affected in SCZ brains. (**G**) String analysis of IFN-γ regulated *ΔGOMAFU* DEGs that are also affected in SCZ brains (red dots in **F**) suggests the formation of a highly interactive molecular network. Red circles represent genes enriched in stress and immune response pathways.

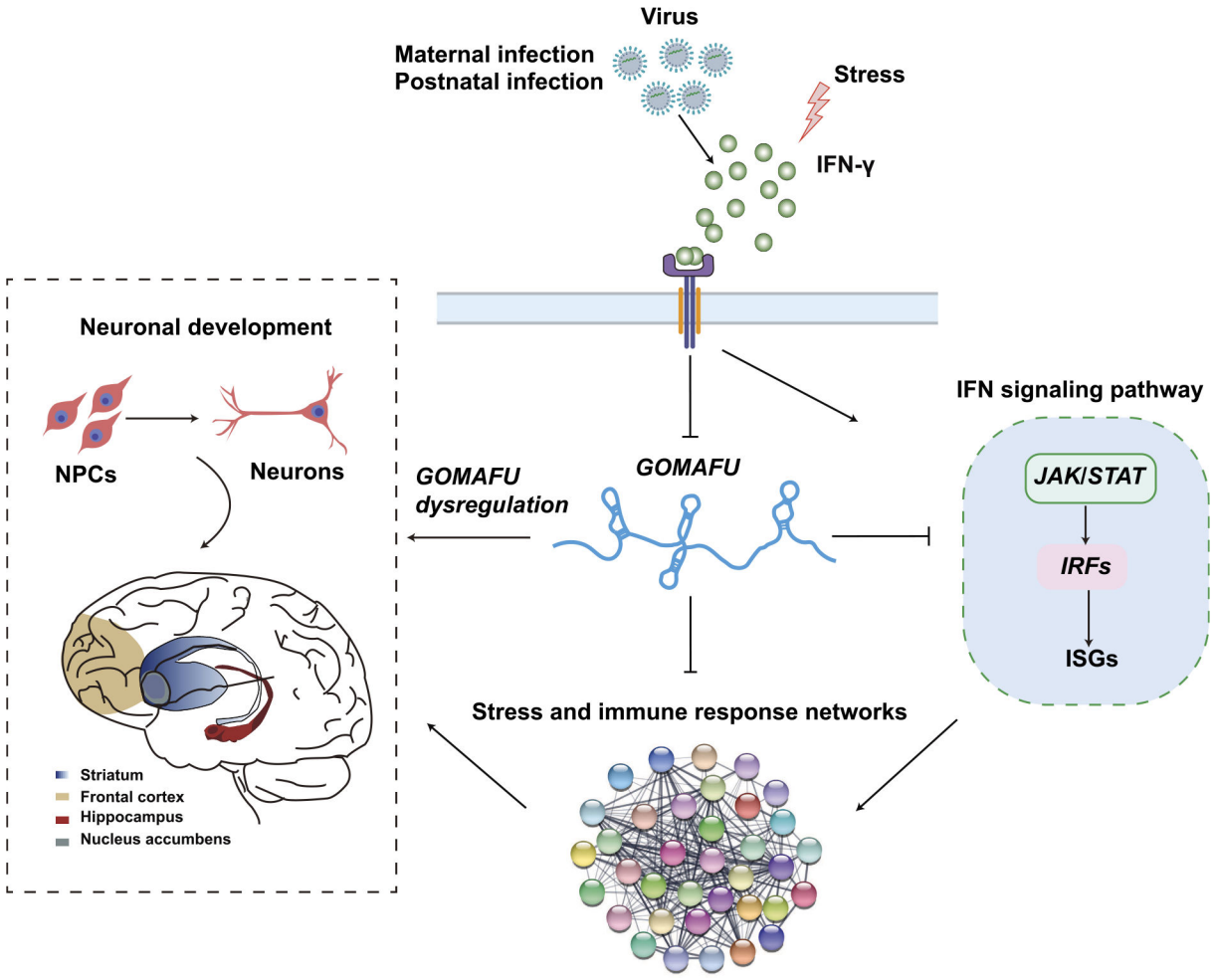

Fig. 6. A model for the roles of *GOMAFU* in suppressing neuronal IFN responses and dysregulation of the *GOMAFU* pathway in SCZ pathogenesis.

GOMAFU is an intrinsic suppressor of IFN signaling pathways in human neural progenitor cells (NPCs) and neurons of the brain, which governs basal level expression of IFN response genes. Diverse dysregulation of *GOMAFU* and its targets in SCZ brain regions may alter neuronal responses to environmental risk factors that trigger neuroinflammation, which increases SCZ vulnerability. Exposure to pathological increase of IFN-γ, such as maternal and/or postnatal virus infection and stress, induces decline of *GOMAFU* in neuronal cells, which de-represses genes selectively enriched in the stress and immune response pathways. These genes form a molecular network affected in the SCZ brain, which contributes to SCZ pathogenesis.

Table 1

Brain region-specific dysregulation of *GOMAFU* in multiple schizophrenia cohorts. Altered *GOMAFU* expression levels (Log2 fold Change) in brain regions of SCZ cohorts and subjects of other neuropsychiatric diseases (Patients) relative to controls (Con) are derived from analyzing transcriptomic profiling datasets by RNAseq or microarray in the cited publications described in the Methods. Brain regions showing significant changes of *GOMAFU* in patients ($p < 0.05$) are bolded. Abbreviations of brain regions are indicated.

Accession number	Brain region	Data type	Disease	Con (n)	Patients (n)	Log2 fold change	*p* value	Reference
	Frontal and temporal cortex	RNAseq	Schizophrenia	936	559	**−0.046**	* **0.04**	Gandal et al., 2018
			Autism spectrum disorder	936	51	**−0.13**	* **0.049**	
			Bipolar disorder	936	222	0.03	0.3	
GSE80655	Dorsolateral (DLPFC)	RNAseq	Schizophrenia	24	24	**0.25**	* **0.044**	Ramaker et al., 2017
	Nucleus accumbens (NAcc)	RNAseq	Schizophrenia	23	22	**0.41**	* **0.02**	
	Anterior Cingulate Cortex (AnCg)	RNAseq	Schizophrenia	24	24	0.23	0.1	
PRJNA379666	Amygdala	RNAseq	Schizophrenia	24	22	**0.45**	* **0.03**	Chang et al., 2017
GSE53987	Hippocampus	Array	Schizophrenia	18	15	**0.25**	* **0.049**	Lanz et al., 2019
	Striatum	Array	Schizophrenia	18	18	**0.20**	** **0.009**	
GSE93987	Pyramidal cells (layer3 of DLPFC)	Array	Schizophrenia	53	52	0.06	0.247	Arion et al., 2015
	Pyramidal cells (layer5 of DLPFC)	Array	Schizophrenia	53	50	**0.144**	** **0.008**	

*denotes $p < 0.05$

**denotes $p < 0.01$. The potential impacts of covariates are described in original studies cited.