ULK4 in Neurodevelopmental and Neuropsychiatric Disorders

Shilin Luo1,2, Nanxi Zheng3* and Bing Lang3*

1Department of Pharmacy, The Second Xiangya Hospital, Central South University, Changsha, China, 2Hunan Provincial Engineering Research Center of Translational Medicine and Innovative Drug, Changsha, China, 3Department of Psychiatry, National Clinical Research Center for Mental Disorders, The Second Xiangya Hospital of Central South University, Changsha, China

The gene Unc51-like kinase 4 (ULK4) belongs to the Unc-51-like serine/threonine kinase family and is assumed to encode a pseudokinase with unclear function. Recently, emerging evidence has suggested that ULK4 may be etiologically involved in a spectrum of neuropsychiatric disorders including schizophrenia, but the underlying mechanism remains unaddressed. Here, we summarize the key findings of the structure and function of the ULK4 protein to provide comprehensive insights to better understand ULK4-related neurodevelopmental and neuropsychiatric disorders and to aid in the development of a ULK4-based therapeutic strategy.

Keywords: ULK4, neurodevelopmental disorder, neuropsychiatric disorder, pseudokinase, schizophrenia

INTRODUCTION

Neuropsychiatric disorders are a wealth of debilitating brain diseases with overlapping etiologies, including genetic variants and environmental stress. The concordance rate is high and the heritability is substantial, although the influence of de novo mutations cannot be ignored especially in autism spectrum disorders (ASDs) (Alonso-Gonzalez et al., 2018). During the past decades, genome-wide association studies (GWASs) have reported numerous genetic alleles with single nucleotide polymorphisms (SNPs) (Uffelmann et al., 2021). In addition, recent progress in whole genome interrogation has also demonstrated massive genetic variants that are not covered by GWAS (Rao et al., 2021). The advances in research methodologies have expanded our understanding of the genetic architecture of psychiatric patients but also revealed further complexity. Hence, it is compelling to identify the predisposing risk alleles and to fully elucidate the associated mechanisms underpinning neuropsychiatric disorders. Unfortunately, thus far, only limited success has been achieved. Intriguingly, recent studies have revealed overwhelming evidence in neurodevelopmental elements in neuropsychiatric disorders (Cristino et al., 2014; Cardoso et al., 2019; Al-Naama et al., 2020). Various genetic alterations that occur during the embryonic stages can lead to pathological brain development and may precipitate the onset of psychosis in adolescence. These developmental insults are believed to disturb the neuronal connectivity and cellular architecture within the brain. The most common neurodevelopmental and neuropsychiatric disorders include depression, schizophrenia, autism spectrum disorders (ASD), bipolar disorder, attention deficit hyperactivity disorder, and X-linked intellectual disability, among others. The prevalence of these disorders is growing rapidly, which has caused a tremendous socioeconomic burden, primarily due to their high incidence in children and adolescents (Androutsos, 2012; Robertson et al., 2015; Hansen et al., 2018; Ghandour et al., 2019; Post and Grunze, 2021). During the past several decades, strenuous research has been performed in these fields. Unfortunately, the etiology and underlying mechanisms remain poorly understood.
In 2014, we first reported that Unc-51-like kinase 4 (ULK4) is crucial for neuritogenesis and neuronal motility and, when defective, may predispose people to neuropsychiatric disorders including schizophrenia (Lang et al., 2014). Since then, accumulating evidence has strongly suggested that ULK4 participates in corticogenesis, cilia maintenance, myelination, and white matter integrity, although the precise downstream signaling pathways and interacting substrates remain elusive. Recently, we have provided evidence that ULK4 deletion can cause decreased intermediate neural progenitors and increased apoptosis, which strongly disrupt normal cortical development (Hu et al., 2021). In addition, ULK4 can form an interactome by physically binding with PP2A and PP1α, the two most abundant phosphatases, and is responsible for over 90% of total Ser/Thr dephosphorylation in eukaryotes. This interactome closely regulates the expression of p-Akt and p-GSK-3α/β, and mice with ULK4-targeted deletion in the excitatory neurons of the forebrain present a spectrum of core features of schizophrenia. These data collectively suggest that ULK4 is a rare susceptibility gene for psychiatric disorders, especially schizophrenia. In this review, we will summarize the current knowledge of the roles of ULK4 in neurodevelopmental and neuropsychiatric disorders.

**MAIN TEXT**

**Unc-51-like Serine/Threonine Kinase (ULK) Family**

In 1998, a novel mouse ortholog of the *Caenorhabditis elegans* serine/threonine kinase uncoordinated-51 (UNC-51) was first cloned (Yan et al., 1998), and thereafter, five related genes in total were found and grouped into the UNC-51-like serine/threonine kinase (ULK) family: ULK1, ULK2, ULK3, ULK4, and serine/threonine kinase 36 (STK36). The kinase domains of ULKs are conserved and located at the N-terminus, and the C-terminal region contains protein interaction motifs important for substrate recruitment (Figure 1). In mammals, ULK1 and ULK2 are evolutionarily conserved serine/threonine kinase orthologs of the yeast autophagy-related (ATG) family member ATG1, and play a necessary but somewhat redundant function in proper autophagy initiation (Wang et al., 2018). The high-resolution structure analysis shows that ULK1 and ULK2 share a high degree of conservative domain architecture, including an N-terminal catalytic kinase, extensive middle linker, and C-terminal domain essential for interaction with their binding partners (Lazarus et al., 2015; Chaikuad et al., 2019). During autophagy, the canonical early regulatory complex consists of ULK1/ULK2, ATG13, RB1-inducible coiled-coil protein 1 (RB1CC1, also known as FIP200), and ATG101, which translate upstream nutrient and energy signals (e.g., mTOR and AMPK) into the downstream autophagy pathway (Ganley et al., 2009; Jung et al., 2009; Wong et al., 2013; Lin and Hurley, 2016). Disrupting ULK1 expression in mice leads to defective autophagy-mediated clearance of mitochondria, and mice lacking both ULK1 and ULK2 die shortly after birth due to a defect in glycolgen metabolism, which is similar to what occurs with other autophagy-defective mice (Kundu et al., 2008; Cheong et al., 2014). Apart from these processes, ULK1/ULK2 also regulates TrkA receptor trafficking and signaling, which instructs filopodia extension and neurite branching during sensory axon outgrowth (Zhou et al., 2007). Knockdown of ULK2 reduced asymmetric neuropil elaboration and affected habenular development in the brain (Taylor et al., 2011). Recently, Kang et al. revealed an association between ULK2 polymorphisms and schizophrenia in the Korean population (Kang et al., 2022).

The other three homologs, ULK3, ULK4, and STK36, contain kinase domains homologous to ULK1/2 but do not have a conserved C-terminal sequence, and they participate in many physiological processes to maintain tissue homeostasis. ULK3 has been reported to be involved in the autophagy induction during senescence (Young et al., 2009). It also has a dual function in the Sonic hedgehog signal transduction pathway, which controls a variety of developmental processes and is implicated in tissue homeostasis and neurogenesis in adults (Fuccillo et al., 2006;
ULK4 Protein Structure

ULK4 is a large protein (142 kDa) encoded by the gene Unc51-Like Kinase 4, which is located on human chromosome 3p22.1 (Went et al., 2019). Unlike the homolog family member ULK1-3, the ULK4 protein contains a pseudokinase domain at the N-terminus and is thus predicted to be catalytically inactive. There are five HEAT repeats at the C-terminal of STK36. This strongly indicates that ULK4 can regulate active kinases and phosphatases, which require further functional validation (Preuss et al., 2020).

ULK4 and Unc-51

The unc-51 gene was initially described in the nematode C. elegans by Brenner in 1974 and showed extensive expression during embryonic brain development when neurons were actively extending their axons, particularly in the head region of late embryos (Brenner, 1974). Surprisingly, worms with the unc-51 mutation were mostly paralyzed, egg-laying defective, and dumpy (McIntire et al., 1992; Ogura et al., 1994). These data strongly suggested that the unc-51 protein is essential for axon maintenance and elongation. In the brains of Drosophila individuals, unc-51-mediated membrane vesicle transport is pivotal in the targeted localization of guidance molecules and organelles that regulate the elongation and compartmentalization of developing neurons as well as motor-cargo assembly (Mochizuki et al., 2011). Similarly, the unc-51 protein was reported to localize in the vesicular structures of growth cones of cerebellar granule cells and spinal sensory neurons in mice, which controls axon formation in granule cells through the endocytic membrane trafficking pathway (Tomoda et al., 1999; Tomoda et al., 2004). As a homologous serine/threonine kinase of unc-51 in humans, ULK4 was initially reported to be associated with blood pressure and hypertension (Levy et al., 2009; Ehret and Caulfield, 2013; Konigorski et al., 2014). Meanwhile, it may be involved in cell cycle control, as its polymorphisms (rs1052501 and rs2272007) were associated with multiple myelomas (Broderick et al., 2011; Greenberg et al., 2013). Inspired by the physiological functions of unc-51, we reanalyzed the common and rare variants of ULK4 in the databases of the International Schizophrenia Consortium (ISC) and among the bipolar Icelandic cases genotyped by deCODE Genetics, and we discovered that it may serve as a rare susceptibility gene for human mental disorders, especially schizophrenia (Lang et al., 2014). Our subsequent functional study further revealed that ULK4 is involved in the remodeling of cytoskeletal components, such as acetylation of α-tubulin, and in this way regulates neurite branching and elongation as well as cell motility.

ULK4 and Neurogenesis

Both in vivo and in vitro studies have suggested that ULK4 may play a key role in neurogenesis and corticogenesis during developmental stages. In Xenopus embryos, ULK4 mRNA is mostly expressed in the ventricular (VZ) and subventricular zones (SVZ) zones and distributed throughout the brain after the closure of the neural tube. Constant expression of ULK4 has also been found in neural stem cells in adult Xenopus (Dominguez et al., 2015). Similarly, ULK4 transcripts are widely found in the VZ, SVZ, and cortical plate in the E15.5 cortex in mice, and ULK4 protein is widely expressed in all cortical layers after postnatal Day 7. Knockdown of ULK4 at E15.5 significantly inhibited cell proliferation and corticogenesis in mice (Lang et al., 2016). Meanwhile, the size of the neural stem cell pool in the forebrain that is important for adult neurogenesis was remarkably reduced in ULK4 null knockout mice at birth (Liu et al., 2016a). Although normal cortical lamination was preserved, the knockout mice showed a thinner cortex due to defective cell proliferation. As abnormal neurogenesis is often associated with neurodevelopmental or neuropsychiatric diseases (Kang et al.,
2016; Guarnieri et al., 2018), it is therefore believed that ULK4 may contribute to the development of these diseases. Liu et al. further identified that ULK4 expression was dependent on the cell cycle, with a peak expression in the G2/M phases, and it decreased during both embryonic and adult neurogenesis in ULK4 mutant mice, probably because of a dysregulated Wnt signaling pathway (Liu et al., 2017).

**ULK4 and Neurite Arborization**

It has been well documented that Unc-51 regulates the dendritic development in the brains of individuals of the genus Drosophila through kinesin-mediated membrane transport (Mochizuki et al., 2011). In C. elegans, Unc-51 mutation often leads to abnormal axonal elongation and structures (Ogura et al., 1994). Consistently, appropriate neurite arborization is important in establishing synaptic connectivity and neuronal plasticity, which is critical for preventing the onset of schizophrenia (Mochizuki et al., 2011; Mizutani et al., 2019). Therefore, it is assumed that the ULK family plays an important role in the establishment of the appropriate neural network and, when defective, may promote the development of neurological diseases. In line with this hypothesis, our data suggest that the proper expression of ULK4 is critical for neurite branching and brain development. Knockdown of ULK4 in SH-SY5Y cells led to less expression of acetylated α-tubulin, which may underlie the reduced dendrite length and/or branching and compromised neuronal migration (Lang et al., 2014). Defective neuritogenesis may involve multiple signaling pathways including protein kinase C (PKC), mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinases (JNK) (Lang et al., 2014). Similarily, our in utero electroporation study in utero also demonstrated that knockdown of ULK4 caused perturbed neurite arborization in the pyramidal neurons of the cortex (Lang et al., 2016).

**ULK4 and the Integrity of White Matter**

Children’s performance in cognition, intelligence, processing speed, and problem solving is closely associated with the thickness of the white matter, such as the corpus callosum and defective myelination is a hallmark related to neurodevelopmental and neuropsychiatric disorders (Liu et al., 2018b). We previously showed that ULK4 null knockout mice displayed impaired genesis of the corpus callosum (Lang et al., 2014). Liu et al. further reported a 50% decrease in myelination in ULK4−/− mice together with a general reduction in myelin components (Liu et al., 2018b). Myelin is produced by oligodendrocytes and controls impulse conduction speed along the axon, which is important to cognitive performance. Children with a less myelinated white matter in their brains often display developmental delay problems. Meanwhile, ULK4 mutant mice also present thin axons and extensive neuroinflammation, which also promote the occurrence of hypomyelination. In addition, ULK4 deficiency significantly attenuated the enrichment of oligodendrocyte transcription factors, the newly formed oligodendrocytes, and myelinating oligodendrocytes (Liu et al., 2018b). These data collectively indicate that ULK4 may be a crucial factor for the integrity of white matter and myelin.

**ULK4 and Ciliopathy**

The cilium is an antenna-like structure that protrudes from the surface of almost all mammalian cells. It participates in multiple signaling transduction pathways and when defective, can result in a series of inherited disorders called “ciliopathies”. The most common features of ciliopathy include cystic liver and/or kidney, blindness, neural tube defects, brain anomalies, mental disability, skeletal abnormalities, obesity, and infertility, among others (Oud et al., 2017). Genomic and bioinformatics research has revealed that some primary cilia genes are linked to psychiatric disorders, such as the genes CC2D2A and Disc1, which are involved in ciliogenesis (Shen et al., 2008; Marley and von Zastrow, 2010; Veleri et al., 2014), and their defects can lead to psychiatric disorders, including Joubert syndrome (Bachmann-Gagescu et al., 2012), mental retardation (Noor et al., 2008; Shi et al., 2012), Meckel syndrome (Tallila et al., 2008), and Bardet Biedl syndrome (BBS) (Haq et al., 2019). In addition, several signaling pathways and crucial factors highly associated with schizophrenia, such as Wnt signaling, the fibroblast growth factor signaling system, neuronal migration, and the dopamine hypothesis, are dependent on the complete functionality of the cilium, although the specific mechanism is not yet well understood (Marley and von Zastrow, 2010; Muraki and Tanigaki, 2015; Narla et al., 2017; Hoseth et al., 2018). In the mouse brain, ULK4 is strongly expressed in the choroid plexus and ependymal cells lining the ventricles (Lang et al., 2014). Both ULK4 null knockout and hypomorphic mice present disturbed motile cilia development and disorganized ciliary beating which impair CSF flow and eventually lead to congenital hydrocephalus (Vogel et al., 2012; Liu et al., 2016b). These data strongly indicate the potential connection between ULK4 haploinsufficiency and ciliopathy. Acetylated α-tubulin is an important cytoskeletal component of cilia that is instrumental for cilium assembly. Our study, however, revealed that knockdown of ULK4 in human neuroblastoma cells (SH-SY5Y) and the mouse brain led to reduced expression of acetylated α-tubulin (Lang et al., 2014; Lang et al., 2016). In addition, whole-genome RNA sequencing also revealed massive disruption of genes closely related to ciliogenesis including Foxl1, Pcm1, Tubb4a, Dnah9, Rsp4a, Gsn, Kif5a, Lgals3, Lgals3bp, and Dnal1 in ULK4 mice carrying hypomorphic alleles. Interestingly, it has been reported that Foxj1 may target downstream substrates including Spag6, Rsp9, Rsp9a, Dnah9, Dnal1, Tll1, Tekt2 which consequently impairs ciliary development and results in hydrocephalus (Liu et al., 2016b). A recent study also reported that patients with a microdeletion of the ULK4 gene and a microduplication of the BRWD3 gene manifested core features of ciliopathy such as psychomotor delay, epilepsy, autistic features, hearing loss, obesity, minor facial dysmorphisms, peculiar ear malformations, and skeletal abnormalities (such as dorsal kyphosis and/or valgus knees and flat feet) (Tassano et al., 2018). Thus, it is highly likely that ULK4 contributes to ciliopathies. The results demonstrate that ULK4 is crucial for ciliogenesis and ciliopathies.
The Progress of Current Research on ULK4 in Mental Disorders

Although previous GWAS studies have suggested that ULK4 is a risk locus for multiple myeloma and interindividual diastolic blood pressure variation, emerging evidence also supports the idea that ULK4 genetic variants may cosegregate with multiple neuropsychiatric disorders (Levy et al., 2009; Broderick et al., 2011). In our previous research using the cohort data from the International Schizophrenia Consortium, we identified four schizophrenia patients with ULK4 intragenic fragment deletions spanning from exon 21 to exon 34 among 3,391 schizophrenia patients (Lang et al., 2014). Another study implicated that SNPs rs7651623 and rs2030431 of ULK4 are associated with the risk of discontinuing the use of antipsychotics in patients with schizophrenia (Ou et al., 2019). In the Decode database, ULK4 deletion was also enriched in patients with schizophrenia (2/708), bipolar disorder (2/1,136), and autism (1/507) (Lang et al., 2014). In addition, association signals were observed at SNPs rs1052501, rs1716975, and rs2272007, which are located in exons 2, 7, and 17 of ULK4, respectively, for allelic transmission disequilibrium from parents to their children with ASD (Ou et al., 2019). Similarly, SNP rs17210774 of ULK4 is significantly associated with bipolar disorder (Ou et al., 2019). Consistently, in the follow-up functional analysis, we have revealed that knockdown of ULK4 altered the activity of Wnt, PKC, MAPK, ERK1/2, and JNK signaling pathways commonly found in human mental disorders, especially schizophrenia (Figure 2). In addition, both ULK4 knockout and hypomorphic mice presented congenital hydrocephalus featuring dilated ventricles and CSF accumulation. Interestingly, a proportion of schizophrenia patients also display increased global or regional CSF (Vogel et al., 2012; Lang et al., 2014). Moreover, Liu et al. revealed that ULK4 heterozygous mice displayed anxiety-like behavior with reduced GABAergic neurons in the basolateral amygdala and hippocampus (Liu et al., 2018a), and ULK4−/− mice showed a significant hypomyelination phenotype (Liu et al., 2018b). All these studies strongly suggest that ULK4 may be a rare risk factor for neuropsychiatric disorders including schizophrenia but more evidence is warranted in the future.

### TABLE 1 | Summary of ULK4 variants and relevant manifestation in human patients.

| SO Term | Ref Allele | Alt Allele | SNP Number | Related Disease | Ref |
|---------|------------|------------|------------|----------------|-----|
| intron  | C          | T          | rs17210774 | bipolar disorder| Lang et al. (2014) |
| intron  | T          | C          | rs1722850  | depressive disorder| Lang et al. (2014) |
| 5 UTR   | A          | G          | rs7651623  | risk of discontinuing use of antipsychotic medications in the patients with schizophrenia| Ou et al. (2019) |
| intron  | C          | T          | rs2030431  | risk of discontinuing use of antipsychotic medications in the patients with schizophrenia| Ou et al. (2019) |
| missense (A542P/A542T) | C          | G/T        | rs1052501  | ASD/multiple myeloma| (Broderick et al., 2011; Greenberg et al., 2013) |
| missense (K39R/K39T) | T          | G/C        | rs2272007  | ASD/multiple myeloma| Ou et al. (2019) |
| intron  | T          | A/C        | rs1717027  | diastolic blood pressure| Franceschini et al. (2013) |
| missense (I224F/I224Y) | T          | A/C        | rs1716975  | ASD| Ou et al. (2019) |
| intron  | T          | G          | rs4973978  | ASD| |
| intron  | T          | C          | rs9824775  | ASD| |
| intron  | T          | C          | rs6599175  | ASD| |
| intron  | G          | A          | rs6783612  | ASD| |
| intron  | C          | T          | rs9852303  | ASD| |
| intron  | A          | G          | rs4973893  | ASD| |
| intron  | T          | C          | rs1716670  | ASD| |

**FIGURE 2** | A schematic representation of altered activities of multiple signaling pathways including p38 MAPK, JNK, ERK1/2, PKC, and Wnt signaling pathways by ULK4. These alterations contribute to deficient neuritogenesis, a common feature frequently represented by human mental disorders.
CONCLUSION AND PERSPECTIVES

Although ULK4 is a member of the Unc-51-like kinase family, unlike its ortholog members ULK1-3 and STK36, it is predicted to be catalytically inactive and to function as a pseudokinase. Initially, ULK4 was found to be associated with blood pressure and hypertension but further research has indicated its important functions during neurodevelopment. Knockdown of ULK4 in vitro also altered the activities of multiple signaling pathways, including Wnt, PKC, p38 MAPK, ERK1/2, and JNK, and mice with ULK4 deletion showed anxiety-like behaviors, perturbed neurogenesis, and decreased myelination. As mentioned above, ULK4 may be a rare risk factor for a range of psychiatric disorders, including schizophrenia, ASD, bipolar disorder, and depression, whose genetic variants were found in relevant patients and are crucial for ciliogenesis and ciliopathies. Further studies are warranted to fully understand the important function of ULK4, especially in neurodevelopment, and the specific underlying mechanisms for psychiatric disorders. With the successful resolution of the protein structure of ULK4 and further elucidation of its function, a series of small molecules targeting ULK4 may be developed to alleviate relevant neurodevelopmental and neuropsychiatric disorders in the future.

AUTHOR CONTRIBUTIONS

This work was primarily written by SL, NZ, and BL. Figure was produced by SL. All authors read and approved the final manuscript.

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REFERENCES

Al-Naama, N., Mackeh, R., and Kino, T. (2020). C2H2-Type Zinc Finger Proteins in Brain Development, Neurodevelopmental, and Other Neuropsychiatric Disorders: Systematic Literature-Based Analysis. Front. Neurol. 11. doi:10.3389/fneur.2020.00332

Alonso-Gonzalez, A., Rodriguez-Fontenla, C., and Carracedo, A. (2018). De Novo Mutations (DNMs) in Autism Spectrum Disorder (ASD): Pathway and Network Analysis. Front. Genet. 9. 406. doi:10.3389/fgene.2018.00406

Andrade, M. A., Petosa, C., and Costin, A. S., Williams, S. M., Hawi, Z., An, J.-Y., Bellgrove, M. A., Schwartz, C. E., and Broderick, P., Chubb, D., Johnson, D. C., Weinhold, N., Försti, A., Lloyd, A., et al. (2014). Neurodevelopmental and Neuropsychiatric Disorders Represent Aberrations in Principal Neurons. Transl Psychiatry 4 (1), 304. doi:10.1038/tp.2014.16

Androutsos, Ch. (2012). Schizophrenia in Children and Adolescents: Relevance and Differentiation from Adult Schizophrenia. Psychiatriki 23 (Suppl. 1), 82–93.

Bachmann-Gagescu, R., Ishak, G. E., Dempsey, J. C., Adkins, J., O’Day, D., Phelps, I. G., et al. (2012). Genotype-phenotype Correlation inCC2D2A-Related Joubert Syndrome Reveals an Association with Ventriculomegaly and Seizures. J. Med. Genet. 49 (2), 126–137. doi:10.1136/jmedgenet-2011-100552

Brenner, S. (1974). The Genetics of Caenorhabditis elegans. Genetics 77 (1), 71–94. doi:10.1093/genetics/77.1.71

Broderick, P., Chubb, D., Johnson, D. C., Weinhold, N., Försti, A., Lloyd, A., et al. (2011). Common Variation at 3p22.1 and 7p15.3 Influences Multiple Myeloma Risk. Nat. Genet. 44 (1), 58–61. doi:10.1038/ng.993

Cardoso, A. B., Lopes-Marques, M., Silva, R. M., Serrano, C., Amorim, A., Prata, M. J., et al. (2019). Essential Genetic Findings in Neurodevelopmental Disorders. Hum. Genomics 13 (1), 31. doi:10.1186/s40246-019-0126-4

Chaikud, A., Koschade, S. E., Stolz, A., Zivkovic, K., Pohl, C., Shaid, S., et al. (2019). Conservation of Structure, Function and Inhibitor Binding in UNC-51-like Kinase 1 and 2 (ULK1/2). Biochem. J. 476 (5), 875–887. doi:10.1042/ bjci20190038

Cheong, H., Wu, J., Gonzales, L. K., Guttenag, S. H., Thompson, C. B., and Lindsten, T. (2014). Analysis of a Lung Defect in Autophagy-Deficient Mouse Strains. Autophagy 10 (1), 45–56. doi:10.4161/auto.26505

Cristino, A. S., Williams, S. M., Hawi, Z., An, J.-Y., Bellgrove, M. A., Schwartz, C. E., et al. (2014). Neurodevelopmental and Neuropsychiatric Disorders Represent an Interconnected Molecular System. Mol. Psychiatry 19 (3), 294–301. doi:10.1038/mp.2013.16

Domínguez, L. Schlosser, G., and Shen, S. (2015). Expression of a Novel Serine/threonine Kinase Gene, ULk4, in Neural Progenitors during Xenopus laevis Forebrain Development. Neuroscience 290, 61–79. doi:10.1016/j.neuroscience.2014.12.060

Ehret, G. R., and Caulfield, M. J. (2013). Genes for Blood Pressure: an Opportunity to Understand Hypertension. Eur. Heart J. 34 (13), 951–961. doi:10.1093/eurheartj/ehs455

Franceschini, N., Fox, E., Zhang, Z., Edwards, T. L., Nalls, M. A., Sung, Y. J., et al. (2013). Genome-wide Association Analysis of Blood-Pressure Traits in African-Ancestry Individuals Reveals Common Associated Genes in African and Non-African Populations. Am. J. Hum. Genet. 93 (3), 545–554. doi:10.1016/j.ajhg.2013.07.010

Fuccillo, M., Joiner, A. L., and Fishell, G. (2006). Morphogen to Mitogen: the Multiple Roles of Hedgehog Signalling in Vertebrate Neural Development. Nat. Rev. Neurosci. 7 (10), 772–783. doi:10.1038/nrn1990

Ganley, I. G., Lam, D. H., Wang, J., Ding, X., Chen, S., and Jiang, X. (2009). ULK1-ATG13-FIP200 Complex Mediates mTOR Signaling and Is Essential for Autophagy. J. Biol. Chem. 284 (18), 12297–12305. doi:10.1074/jbc.M900573200

Ghandour, R. M., Sherman, L. J., Vladutiu, C. J., Ali, M. M., Lynch, S. E., Bitsko, R. H., et al. (2019). Prevalence and Treatment of Depression, Anxiety, and Conduct Problems in US Children. J. Pediatr. 206, 256–257. e2525. doi:10.1016/j.jpeds.2018.09.021

Greenberg, A. J., Lee, A. M., Serie, D. J., McDonnell, S. K., Cerhan, J. R., Liebow, M., et al. (2013). Single-nucleotide Polymorphism Rs1052501 Associated with Monoclonal Gammopathy of Undetermined Significance and Multiple Myeloma. Leukemia 27 (2), 515–516. doi:10.1038/leu.2012.232

Guarnieri, F., c. de Chevigny, A., c. de Chevigny, A., Falace, A., and Cardoso, C. (2018). Disorders of Neurogenesis and Cortical Development. Dialogues Clin. Neurosci. 20 (4), 255–266. doi:10.31877/DCNS.2018.20.4/ccardoso

Hansen, B. H., Oerbeck, B., Skirbekk, B., Petrovski, B. E., and Kristensen, H. (2018). Neurodevelopmental Disorders: Prevalence and Comorbidity in Children Referred to Mental Health Services. Nordic J. Psychiatry. Psychiatry 72 (4), 285–291. doi:10.1080/00390440.2018.1444087

Haq, N., Schmidt-Hieber, C., Szlaf, J. F., Cani, L., Heller, J. P., Stewart, M., et al. (2019). Correction: Loss of Bardet-Biedl Syndrome Proteins Causes Synaptic Aberrations in Principal Neurons. PloS Biol. 17 (10), e3000520. doi:10.1371/journal.pbio.3000520

Hoseth, E. Z., Krull, F., Dietz, I., March, R. H., Hope, S., Gardsjord, E. S., et al. (2018). Exploring the Wnt Signaling Pathway in Schizophrenia and Bipolar Disorder. Transl Psychiatry 8 (1), 55. doi:10.1038/s41398-018-0102-1

Hu, L., Chen, Y., Yang, C.-P., Huang, Y., Song, N.-N., Chen, J.-Y., et al. (2021). ULK4, a Newly Discovered Susceptibility Gene for Schizophrenia, Regulates Corticogenesis in Mice. Front. Cell Dev. Biological. 9. doi:10.3389/fcell.2021.645368

Jung, C. H., Jun, C. B., Ro, S.-H., Kim, Y.-M., Otto, N. N., Cao, J., et al. (2009). ULK-Atg13-FIP200 Complexes Mediate mTOR Signaling to the Autophagy Machinery. MBoC 20 (7), 1992–2003. doi:10.1091/molc.e08-12-1249
Kundu, M., Lindsten, T., Yang, C.-Y., Wu, J., Zhao, F., Zhang, J., et al. (2008). Ulk1
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Luo et al. ULK4 and Neuropsychiatric Disorders
Konigorski, S., Yilmaz, Y. E., and Bull, S. B. (2014). Bivariate Genetic Association
Kang, W. S., Lee, S. M., Hwang, D., Park, H. J., and Kim, J. W. (2022). Association
Lazarus, M. B., Novotny, C. J., and Shokat, K. M. (2015). Structure of the Human
Lang, B., Zhang, L., Jiang, G., Hu, L., Lan, W., Zhao, L., et al. (2016). Control of
Lang, B., Pu, J., Hunter, I., Liu, M., Martin-Granados, C., Reilly, T. J., et al. (2014).
Liu, M., Fitzgibbon, M., Wang, Y., Reilly, J., Qian, X., O
Liu, M., Xu, P., Guan, Z., Qian, X., Dockery, P., Fitzgerald, U., et al. (2018b).
Liu, M., Guan, Z., Shen, Q., Lalor, P., Fitzgerald, U., et al. (2018b). Ulk4 Regulates Neural Stem Cell Pool.
Mizutani, R., Saiga, R., Takeuchi, A., Uesugi, K., Terada, Y., Suzuki, Y., et al. (2019).
Mochizuki, H., Toda, H., Ando, M., Kurusu, M., Tomoda, T., and Furukubo-
Mochizuki, H., Toda, H., Ando, M., Kurusu, M., Tomoda, T., and Furukubo-
Mochizuki, H., Toda, H., Ando, M., Kurusu, M., Tomoda, T., and Furukubo-
Lang, B., Zhang, L., Jiang, G., Hu, L., Lan, W., Zhao, L., et al. (2016). Control of
Cerebellar Granule Neurons.
Lang, B., Pu, J., Hunter, I., Liu, M., Martin-Granados, C., Reilly, T. J., et al. (2014). Genetic Variants Have Pleiotropic Effect on Risk of Autism, Associated with Brain mRNA Expression and Antipsychotic Treatment Response. J. Psychiatry Brain Sci. 19, 00101.0:
Ou, J.-J., Li, K.-K., Guo, H., Xia, K., Hu, Z. M., Zhao, J. P., et al. (2019). ULK4 Is Essential for Directed Axonal Elongation or Fasciculation in C. elegans. Cell 175 (1), 1–16.
Preuss, F., Chatterjee, D., Mathe, S., Shresha, S., St- Germain, J., Saha, M., et al. (2020). Nucleotide Binding, Evolutionary Insights, and Interaction Partners of the Pseudokinase ULK1 in C. elegans 4 Kinase Structure 21 (11), 1184–1196. e1186. doi:10.1016/j.str.2020.07.016
Rao, S., Yao, Y., and Bauer, D. E. (2011). Editing GWA: Experimental Approaches to Dissect and Exploit Disease-Associated Genetic Variation. Genome Med. 13 (41), 1. doi:10.1186/1130-0188-4-38
Robertson, J., Hatton, C., Emerson, E., and Baines, S. (2015). Prevalence of Epilepsy Among People with Intellectual Disabilities: A Systematic Review. Seizure 29, 46–62. doi:10.1016/j.seizure.2013.05.016
Shen, S., Lang, B., Nakamoto, C., Zhang, F. P., Ju, K., Kuan, S.-L., et al. (2008). Schizophrenia-related Neural and Behavioral Phenotypes in Transgenic Mice Expressing Truncated Disc1. J. Neurosci. 28 (43), 10983–10994. doi:10.1523/jneurosci.3299-08.2008
Shi, Z.-Y., Li, Y.-J., Zhang, K.-J., Gao, X.-C., Zheng, Z.-J., Han, N., et al. (2012). Positive Association of CC2D1A and CC2D2A Gene Haplotypes with Mental Retardation in a Han Chinese Population. DNA Cell Biol. 31 (1), 80–87. doi:10.1089/dna.2011.1253
Tallila, J., Jakkula, E., Peltonen, L., Salonen, R., and Kestilä, M. (2008). Identification of CC2D2A as a Meckel Syndrome Gene Adds an Important Piece to the Ciliopathy Puzzle. Am. J. Hum. Genet. 82 (6), 1361–1367. doi:10.1016/j.ajhg.2008.03.004
Tassano, E., Uccella, S., Giaconini, T., Satriano, P., Severino, M., Porta, S., et al. (2018). Intragenic Microdeletion of ULK4 and Partial Microduplication of BRWD3 in Siblings with Neuropsychiatric Features and Obesity. Cytogetgen. Genome Res. 156, 14–21. doi:10.1159/000491871
Taylor, R. W., Qi, J. Y., Talaga, A. K., Ma, T. P., Pan, L., Bartholomew, C. R., et al. (2011). Asymmetric Inhibition of ULK2 Causes Left-Right Differences in Habenular Neuronal Formation. J. Neurosci. 31 (27), 9869–9878. doi:10.1523/jneurosci.0435-11.2011
Tomoda, T., Bhatt, R. S., Kuroyanagi, H., Shirasawa, T., and Hatten, M. E. (1999). A Mouse Serine/threonine Kinase Homologous to C. elegans UNC51 Functions in Parallel Fiber Formation of Cerebellar Granule Neurons. Neuron 24 (4), 833–846. doi:10.1016/S0896-6273(00)81031-4
Tomoda, T., Kim, J. H., Zhan, C., and Hatten, M. E. (2004). Role of Ulk1 and its Binding Partners in CNS Axon Outgrowth. Genes Dev. 18 (5), 541–558. doi:10.1101/gad.115204
Uffelmann, E., Huang, Q. Q., Munung, N. S., de Vries, J., Okada, Y., Martin, A. R., et al. (2021). Genome-wide Association Studies. Nat. Rev. Methods Primers 1 (1), 59. doi:10.1038/s43586-021-00056-9

Veleri, S., Manjunath, S. H., Fariss, R. N., May-Simera, H., Brooks, M., Foskett, T. A., et al. (2014). Ciliopathy-associated Gene Cc2d2a Promotes Assembly of Subdistal Appendages on the Mother Centriole during Cilia Biogenesis. Nat. Commun. 5, 4207. doi:10.1038/ncomms5207

Vogel, P., Read, R. W., Hansen, G. M., Payne, B. J., Small, D., Sands, A. T., et al. (2012). Congenital Hydrocephalus in Genetically Engineered Mice. Vet. Pathol. 49 (1), 166–181. doi:10.1177/0300985811415708

Wang, B., Iyengar, R., Li-Harms, X., Joo, J. H., Wright, C., Lavado, A., et al. (2018). The Autophagy-Inducing Kinases, ULK1 and ULK2, Regulate Axon Guidance in the Developing Mouse Forebrain via a Noncanonical Pathway. Autophagy 14 (5), 796–811. doi:10.1080/15548627.2017.1386820

Went, M., Kinnersley, B., Sud, A., Johnson, D. C., Weinhold, N., Forsti, A., et al. (2019). Transcriptome-wide Association Study of Multiple Myeloma Identifies Candidate Susceptibility Genes. Hum. Genomics 13 (1), 37. doi:10.1186/s40246-019-0231-5

Wong, P.-M., Puente, C., Ganley, I. G., and Jiang, X. (2013). The ULK1 Complex. Autophagy 9 (2), 124–137. doi:10.4161/auto.25323

Yan, J., Kuroyanagi, H., Kuroiwa, A., Matsuda, Y.-i., Tomod, T., et al. (1998). Identification of Mouse ULK1, a Novel Protein Kinase Structurally Related to C. elegansUNC-51. Biochem. Biophysical Res. Commun. 246 (1), 222–227. doi:10.1006/bbrc.1998.8546

Young, A. R. J., Narita, M., Ferreira, M., Kirschner, K., Sadaie, M., Darot, J. F. J., et al. (2009). Autophagy Mediates the Mitotic Senescence Transition. Genes Dev. 23 (7), 798–803. doi:10.1101/gad.519709

Zeqiraj, E., Filippi, B. M., Deak, M., Alessi, D. R., and van Aalten, D. M. F. (2009). Structure of the LKB1-STRAD-MO25 Complex Reveals an Allosteric Mechanism of Kinase Activation. Science 326 (5960), 1707–1711. doi:10.1126/science.1178377

Zeqiraj, E., and van Aalten, D. M. (2010). Pseudokinases-remnants of Evolution or Key Allosteric Regulators? Curr. Opin. Struct. Biol. 20 (6), 772–781. doi:10.1016/j.sbi.2010.10.001

Zhou, X., Babu, J. R., da Silva, S., Shu, Q., Graef, I. A., Oliver, T., et al. (2007). Unc-51-like Kinase 1/2-mediated Endocytic Processes Regulate Filopodia Extension and Branching of Sensory Axons. Proc. Natl. Acad. Sci. U.S.A. 104 (14), 5842–5847. doi:10.1073/pnas.0701402104

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