VRK2, a Candidate Gene for Psychiatric and Neurological Disorders

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Keywords

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Abstract

Recent large-scale genetic approaches, such as genome-wide association studies, have identified multiple genetic variations that contribute to the risk of mental illnesses, among which single nucleotide polymorphisms (SNPs) within or near the vaccinia related kinase 2 (VRK2) gene have gained consistent support for their correlations with multiple psychiatric and neurological disorders including schizophrenia (SCZ), major depressive disorder (MDD), and genetic generalized epilepsy. For instance, the genetic variant rs1518395 in VRK2 showed genome-wide significant associations with SCZ (35,476 cases and 46,839 controls, $p = 3.43 \times 10^{-8}$) and MDD (130,620 cases and 347,620 controls, $p = 4.32 \times 10^{-12}$) in European populations. This SNP was also genome-wide significantly associated with SCZ in Han Chinese population (12,083 cases and 24,097 controls, $p = 3.78 \times 10^{-13}$), and all associations were in the same direction of allelic effects. These studies highlight the potential roles of VRK2 in the central nervous system, and this gene therefore

might be a good candidate to investigate the shared genetic and molecular basis between SCZ and MDD, as it is one of the few genes known to show genome-wide significant associations with both illnesses. Furthermore, the VRK2 gene was found to be involved in multiple other congenital deficits related to the malfunction of neurodevelopment, adding further support for the involvement of this gene in the pathogenesis of these neurological and psychiatric illnesses. While the precise function of VRK2 in these conditions remains unclear, preliminary evidence suggests that it may affect neuronal proliferation and migration via interacting with multiple essential signaling pathways involving other susceptibility genes/proteins for psychiatric disorders. Here, we have reviewed the recent progress of genetic and molecular studies of VRK2, with an emphasis on its role in psychiatric illnesses and neurological functions. We believe that attention to this important gene is necessary, and further investigations of VRK2 may provide hints into the underlying mechanisms of SCZ and MDD.

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Introduction

Schizophrenia (SCZ) and major depressive disorder (MDD) are seriously disabling public health problems. The worldwide lifetime prevalence and incidence of SCZ are 0.30–0.66% and 10.2–22.0 per 100,000 person-years, respectively, if its diagnostic category is considered in isolation [1–3], and this illness shows strong heritability (around 0.80) based on previous twin and family studies [1, 4–6]. A previous review reported that MDD has a 12-month prevalence of 6.6% and a lifetime prevalence of 16.2% [7, 8]. Meanwhile, the lifetime incidence of MDD (broad definition) in the United States is more than 12% in men and 20% in women [8, 9]. MDD also shows substantial heritability (approx. 0.37) [9, 10] and polygenic inheritance [11, 12]. However, promising genetic risk candidates for SCZ and MDD had not been well implicated until the emergence of recent large-scale genome-wide association studies (GWAS) [13–21]. GWAS is believed to be an ideal approach for studying common genetic variations across the genome, given its key feature that no a priori hypotheses are established [22]. Indeed, GWAS of psychiatric disorders have led to the identification of multiple novel risk variants with known or unknown function relevant to the biology of illnesses [23–25], and substantial progress has been obtained toward understanding the genetic architecture and molecular pathogenesis (e.g., dendritic spine pathology) of these psychiatric disorders [26, 27]. Among the risk candidates discovered through SCZ and MDD GWAS studies [13–20], *VRK2* (vaccinia-related kinase 2) is one of the few genes showing consistent genome-wide significant associations with both disorders. In addition, this gene has been implicated in a variety of neurological disorders, further supporting its potential roles in the central nervous system. However, despite strong genetic evidence and a relatively rudimentary understanding of the biological mechanisms of *VRK2* in SCZ and MDD susceptibility, a systematic overview of existing evidence to depict the potential involvement and relevant biological mechanisms of this gene in these illnesses is lacking. Thus, we examined recent discoveries regarding the role of *VRK2* in psychiatric and neurological disorders, including genetics, molecular biology, and neurophysiology to propose recommendations for future research.

Identification of *VRK2* Variants in Psychiatric Disorders among World Populations

VRK2 was first implicated in psychiatric disorders by Stefansson et al. [28]. By conducting a GWAS study, the authors reported several risk polymorphisms conferring risk of SCZ in 47,536 European subjects [28]. The single nucleotide polymorphism (SNP) rs2312147, which is located in the intron 1 of *VRK2* (Fig. 1a), was identified as a potential SCZ risk SNP ($p = 3.00 \times 10^{-7}$), although it did not achieve conventional genome-wide significance (which is $p = 5.00 \times 10^{-8}$). Later, Steinberg et al. [29] confirmed the association between rs2312147 and SCZ in larger European samples ($n = 60,742$, $p = 1.9 \times 10^{-9}$). Following these, the Irish Schizophrenia Genomics Consortium and the Wellcome Trust Case Control Consortium 2 further replicated this significant association of rs2312147 and SCZ in a European GWAS [30]. These series of studies motivated researchers worldwide to pay attention to the genetic risk for SCZ conferred by *VRK2* polymorphisms, and replication studies in populations other than Europeans were also conducted [31–33]. For example, Li et al. [34] replicated the association between rs2312147 and SCZ in independent Asian samples ($n = 6,565$, $p = 4.24 \times 10^{-4}$). More recently, several meta-analytic studies have further confirmed the role of this SNP in the risk of SCZ in both East Asians and Europeans [35, 36]. In addition, in the recent PGC2 SCZ GWAS, rs2312147 again displayed genome-wide significance (35,476 cases and 46,839 controls, $p = 2.02 \times 10^{-8}$, Fig. 2) [13]. These results are particularly intriguing as the effect sizes of rs2312147 for SCZ are similar between European and Asian populations, suggesting that it is likely an authentic risk variant for SCZ in general populations.

In addition to rs2312147, other SNPs in the *VRK2* gene have also been found to be associated with SCZ in both East Asian and European populations. For example, in a recent SCZ GWAS in Han Chinese population, a genetic variant (rs1518395) in the intron 1 of *VRK2* showed a genome-wide significant association in a total of 12,083

Fig. 1. a Schematic of mRNA structure of *VRK2* isoforms and locations of representative SNPs. **b** mRNA expression of *VRK2* isoforms in diverse human tissues and cells from GTEx dataset [44]. **c** mRNA expression of *VRK2* gene in brain single-cell RNA-seq dataset (GSE67835) [84]. **d** Schematic of domain structure of predicted Vrk2 protein. The source of this figure was previous literature [104, 175]. SCZ, schizophrenia; MDD, major depressive disorder; GGE, genetic generalized epilepsy; OPC, oligodendrocyte progenitor cell.

(For figure see next page.)

Fig. 2. Associations of *VRK2* common variants with schizophrenia in PGC2 genome-wide association studies of European ancestry [13]. This figure was made using LocusZoom [176].

cases and 24,097 controls ($p = 3.78 \times 10^{-13}$, OR = 1.160 for G allele) [15]. This is one of the most significant SNPs for SCZ in Chinese, and this SNP was also genome-wide significantly associated with SCZ in European populations (35,476 cases and 46,839 controls, $p = 3.43 \times 10^{-8}$, OR = 1.061 for G allele, Fig. 2) [13]. More interestingly, in a recent GWAS of MDD in European populations (130,620 cases and 347,620 controls), rs1518395 again showed genome-wide significant associations with MDD ($p = 4.32 \times 10^{-12}$, OR = 1.034 for G allele) [14], and the same allele of rs1518395 increased the risk of both SCZ and MDD, suggesting the involvement of the variant(s) in *VRK2* in a broad spectrum of mood-psychosis conditions, at least in the European populations. More importantly, rs1518395 is also one of the few SNPs showing genome-wide significant associations with SCZ in both European and Chinese populations; such observations greatly enhance our understanding of the shared genetic basis of SCZ between populations. We retrieved the distributions of rs1518395 in 53 populations worldwide using the HGDP Selection Browser (<http://hgdp.uchicago.edu/>) [37–39], and its allelic frequencies between East Asians and Europeans were similar (Fig. 3). We then examined the linkage disequilibrium (LD) between rs1518395 and nearby SNPs in East Asian and European populations using the SNAP website ([http://archive.](http://archive.broadinstitute.org/mpg/snap/ldplot.php)

[broadinstitute.org/mpg/snap/ldplot.php](http://archive.broadinstitute.org/mpg/snap/ldplot.php)) and identified sharp differences in the LD pattern of this genomic region between the two populations (Fig. 4). Briefly, there were more SNPs in high LD ($r^2 > 0.8$) with rs1518395 in Europeans, and the linked SNPs spanned a wide region, while in East Asians, there were fewer SNPs in strong LD with rs1518395 covering a smaller genomic region (Fig. 4). Nevertheless, this trans-ethnic analysis added further evidence for the involvement of rs1518395 (or its LD SNPs) in the risk of psychiatric disorders.

Notably, rs1518395 and rs2312147 are in high LD ($r^2 = 1.000$ in Europeans and $r^2 = 0.876$ in East Asians), and both SNPs are located in the noncoding region (Fig. 1a). Prior evidence has suggested that noncoding SNPs might exert their function by affecting gene expression levels [40–43], and we thus examined the associations of rs2312147 and rs1518395 with nearby gene expression using the existing expression quantitative trait loci (eQTL) datasets, such as GTEx [44], Braineac [45], and BrainCloud [46]. However, no significant associations were observed, and the potential impact of those risk SNPs is still unclear.

In addition to rs1518395 and rs2312147, several other SNPs in low to moderate LD in the *VRK2* gene are also associated with SCZ. For instance, in the PGC2 GWAS of SCZ using samples mainly from European populations

Fig. 3. Global distributions of rs1518395 in 53 world populations from HGP dataset [37–39].

[13], multiple genomic variants in low to high LD with rs1518395 showed genome-wide significant associations. Rs7596038, a SNP located 175 kb from rs1518395 and in moderate LD ($r^2 = 0.500$ in Europeans, and $r^2 = 0.288$ in East Asians) showed the strongest association with SCZ among *VRK2* regions ($p = 1.15 \times 10^{-10}$, Fig. 2); rs7596038 is located in the intron region of *VRK2* and is predicted to be nonfunctional through the epigenomic analyses using ENCODE data [47], but further studies are necessary to examine its functional impact. Furthermore, in a recent GWAS of SCZ in Han Chinese populations, Yu et al. [48] reported that rs1051061 ($r^2 = 0.224$ with rs1518395 in Europeans, $r^2 = 0.178$ with rs1518395 in East Asians) in an exon of *VRK2* was genome-wide significantly associated with SCZ in a total of 8,723 cases and 12,813 controls ($p = 1.14 \times 10^{-12}$, see Fig. 1a). Although this SNP did not achieve genome-wide significance in European populations (35,476 cases and 46,839 controls, $p = 1.26 \times 10^{-6}$) [13], the same direction of allelic effects was observed in both Europeans and Chinese, further strengthening the link between *VRK2* and SCZ. Overall, these data suggest that there are (at least partially) independent association signals for SCZ within *VRK2* in global populations.

Additionally, the association between *VRK2* and bipolar disorder (BPD) has also been implicated in a recent BPD GWAS conducted in European populations [49]. Briefly, an intergenic variant rs57681866 near *VRK2*,

rather than the earlier reported SCZ-associated SNP rs1518395 (these two SNPs are 232.3 kb away from each other, and in low LD in Europeans [$r^2 = 0.001$]), showed genome-wide significant association ($p = 5.00 \times 10^{-8}$) with the illness in the discovery stage of this study (20,352 cases and 31,358 controls). However, the association between rs57681866 and BPD was not observed in the replication stage of this GWAS (9,412 cases and 137,760 controls) [49]. This leaves questions to be further investigated: Is *VRK2* truly associated with BPD? Is the nonsignificant result during replication stage attributed to the limited sample size of BPD patients? Expanded analyses including more subjects might provide clues.

While the association of *VRK2* with psychiatric disorders is supported by convincing evidence, the precise impacts of the risk SNPs on neuronal function and brain development remain unclear. Recent studies suggest that changes in regional brain structures and functions are core features of SCZ [50–54] and MDD [55–59], and neuroimaging approaches may provide clues into the underlying pathophysiology of these illnesses. In fact, it is proposed that there are intermediate phenotypes reflecting alterations in brain structure and function in psychiatric patients and their unaffected relatives compared to unrelated healthy individuals [60]. These intermediate phenotypes are assumed to involve the same biological pathways as the illness but to relate more closely

Fig. 4. Comparisons of rs1518395 LD SNPs between European and East Asian populations. This figure was obtained from the SNAP website.

to the effects of relevant genes [61–65]. Recent studies of several psychiatric candidate genes including *ZNF804A* [66–68] and *CACNA1C* [69–72] have already demonstrated the validity and reliability of this approach. We previously also analyzed the association between *VRK2* SNPs and brain phenotypes related to psychiatric disorders [34] and found that the psychiatric risk allele [C] in rs2312147 was associated with reduced total brain volume and white matter volume in healthy individuals, which was in line with clinical characteristics in the brains of psychiatric patients compared with healthy controls [73]. This finding was further supported by Sohn et al. [74], as they reported significant differences in the white matter connectivity between rs2312147 CC and CT/TT genotype groups of SCZ patients for many

brain regions. These data provided initial evidence for the effects of *VRK2* on white matter development, and investigations dissecting the underlying biological mechanisms and etiological relevance in psychosis and mood disorders are necessary.

***VRK2* and Genetic Generalized Epilepsies**

In addition to SCZ and MDD, variants in *VRK2* have been implicated in genetic generalized epilepsies (GGEs). GGEs have a lifetime prevalence of 0.3% [75] and account for 20–30% of all epilepsies [76]. In 2012, the EPICURE Consortium conducted a two-stage GWAS of 3,020 patients with GGEs and 3,954 controls of European ancestry

Fig. 5. A hypothesized molecular mechanism for *VRK2* in the pathogenesis of psychiatric disorders. This figure was made according to previous published studies regarding the function of *Vrk2* and its interactions with other molecules, such as *Erk* [104, 105, 141, 142].

and revealed genome-wide significant association signals for GGEs at 2p16.1 (rs13026414, $p = 2.5 \times 10^{-9}$, see Fig. 1a) [75]. The associated chromosomal segment consists of ~900 kb encompassing *VRK2* and the gene encoding the Fanconi-anemia-complementation L polypeptide (*FANCL*). Notably, in an independent GWAS sample set, rs13026414 was found to be nominally significantly associated with GGEs at $p = 7.0 \times 10^{-3}$ [77]. In this later GWAS, a meta-analysis of 2,606 cases and 18,990 controls revealed that a variant rs2947349 in close proximity to the transcription start site of the long *VRK2* isoform was the most significant SNP for GGEs ($p = 9.99 \times 10^{-9}$, see Fig. 1a) [77]. Both studies suggested that *VRK2* was likely a risk factor for GGEs. Interestingly, the psychiatric risk SNP rs2312147 was found to show modest to strong LD (r^2 : 0.25–0.87) with the susceptibility variants of GGEs at 2p16.1 and showed a strong signal with GGEs (rs2312147, $p = 2.3 \times 10^{-6}$) [77]. Collectively, these overlapping association signals indicate that *VRK2* may be involved in the shared etiological and genetic basis of psychiatric disorders and GGEs. However, the directions of the allelic effects were inconsistent, as the risk allele at rs2312147 of psychiatric disorders actually conferred protective effects against GGEs [77]. This result was in contrast with epidemiologic evidence of the prevalent comorbidities of psychiatric disorders (such as mood, anxiety, and psychotic

disorders) and epilepsy [78], and there may be an unidentified complex mechanism underlying this inconsistency that should be elucidated.

***VRK2* Expression in Psychiatric Disorders and Epilepsies**

The involvement of the *VRK2* gene in the genetic risk and heritability of psychiatric and neurological disorders calls for further characterization of its role in these illnesses. It is suggested that most genetic risk variants contribute to diseases via modulating mRNA expression of susceptible genes [40, 43, 79], and earlier studies have examined the mRNA expression of *VRK2* in patients with psychiatric disorders. For instance, Tesli et al. [80] have measured *VRK2* mRNA level in the whole blood of 652 European individuals (SCZ, $n = 201$; BPD, $n = 167$; psychosis not otherwise specified [PNOS], $n = 61$; healthy controls, $n = 223$) and analyzed the difference in expression levels (as stated in their study, “the probe used for measuring *VRK2* expression was chosen so as to produce an aggregate measure of expression over all RefSeq transcripts”) across diagnostic categories and subcategories. They found that *VRK2* mRNA levels differed significantly between the SCZ, BPD, PNOS, and control groups, and pairwise comparisons revealed significantly lower *VRK2* mRNA levels in the SCZ group than in healthy controls [80]. Interestingly, they did not observe significant alteration of *VRK2* mRNA levels in patients treated with antipsychotics, anticonvulsants, lithium, hypnotics, or psychostimulants [80]. In another study, the authors also compared the peripheral blood *VRK2* gene expression (measuring the aggregate expression of all isoforms) in SCZ or epilepsy patients to that of normal subjects; the authors found significant downregulation of *VRK2* mRNA levels in SCZ ($p < 0.0001$) and epilepsy ($p = 0.008$) compared with healthy individuals [81]. Collectively, these data suggest that lower *VRK2* mRNA in the blood is likely an indicator (or a risk factor) of SCZ and epilepsy, presenting a potential opportunity for the future development of new biomarkers.

As shown in the Ensembl, *VRK2* has two primary mRNA transcripts, a longer transcript (ENST00000435505) with generally lower expression levels that is enriched in the brain, and a shorter transcript (ENST00000340157) that is widely expressed in nonbrain tissues at higher levels (these data have been retrieved from the GTEx dataset, Fig. 1b). Nevertheless, both isoforms encode the same protein. The hypothesis that SCZ and MDD are mental

illnesses mostly originated from brain dysfunctions, and thus, it is of great interest to clarify whether mRNA levels of *VRK2* in the brain tissues from psychiatric individuals exhibit alterations compared with healthy subjects. For this purpose, we performed analyses using data from the Stanley Medical Research Institute (SMRI) dataset (<http://sncid.stanleyresearch.org/>) [82]. Compared with healthy controls, *VRK2* (aggregate expression of all isoforms) was not significantly altered in the dorsolateral prefrontal cortex region from the brains of patients with SCZ or MDD in this analysis. However, this result does not deny the putative involvement of *VRK2* in these illnesses, as the gene may exert its effects in other brain regions such as the hippocampus and amygdala and might also undergo post-transcriptional modulations and thereby contribute to the pathogenesis of the illnesses. To this end, we examined the brain cell types in which the *VRK2* was dominantly expressed using scRNASeqDB (<https://bioinfo.uth.edu/scrnaseqdb/index.php>), an online single-cell RNA-seq dataset [83]. In this dataset, we utilized the data from GSE67835 [84], which used single-cell RNA-seq on hundreds of cells to capture the cellular complexity at the whole-brain transcriptome level during different developmental stages. Intriguingly, *VRK2* is abundantly expressed in the hippocampus oligodendrocyte progenitor cell (OPC), followed by cortex fetal-replicating, cortex oligodendrocytes, hippocampus microglia, and other cells, while this gene is weakly expressed in the cortex OPC and cortex microglia (Fig. 1c) [84]. These data suggest that the *VRK2* may exert variable functions in different brain cell types.

***VRK2* and Other Congenital Abnormalities**

There has been a consensus that individuals with congenital developmental abnormalities are prone to develop psychiatric disorders later in life [85, 86], and the prevalence of major psychiatric illnesses in children with mental retardation is significantly higher than that in general populations [87–89]. Indeed, the etiological contribution of developmental deficits to psychiatric and neurological disorders including SCZ [50, 90], autism [91, 92], MDD [93, 94], and potentially BPD [95] have been recognized. A core mechanism underlying this neurodevelopmental hypothesis for psychiatric disorders is impaired brain development, which might also be manifested as a series of congenital abnormalities, such as microcephaly [96, 97] and intellectual disability [98]. In fact, several studies have examined the correlation between genetic variants

affecting *VRK2* and major developmental abnormalities and have revealed a potentially pivotal role for this gene in neurodevelopment.

Chandler et al. [99] reported a novel neurodevelopmental disorder characterized by “congenital microcephaly with severe failure of postnatal brain growth, neonatal onset of intractable seizures associated with lack of developmental progression and death within the first 3 years of life.” In a few cases, a homozygous deletion within the 2p16 region, which harbors the gene *VRK2*, was found to be associated with these phenotypes. Intriguingly, this region was later highlighted, respectively, in studies of idiopathic intellectual disability and other related developmental disorders by Rajcan-Separovic et al. [100] and de Leeuw et al. [101]. In their studies, deletions encompassing *VRK2* within this genomic region were consistently identified in intellectually disabled individuals, suggesting a potential contribution by *VRK2* to these phenotypes. However, whether *VRK2* actually accounts for these developmental deficits remains to be clarified.

In addition to the aforementioned developmental problems, longitudinal studies have revealed a significant correlation between sleeping problems and behavioral and emotional abnormalities (including depression and anxiety) that develop later in life [102]. Interestingly, Jones et al. [103] found that two conditionally independent SNPs near the *VRK2* gene, rs1380703 ($p = 7.6 \times 10^{-9}$, see Fig. 1a) and rs17190618 ($p = 1.2 \times 10^{-9}$), exhibited genome-wide significant associations with sleep duration using the self-reported chronotype data from 89,283 individuals of European ancestry, which were replicated in another 128,266 British individuals. These data have provided preliminary but enlightening evidence for the involvement of *VRK2* in neurological activities and likely for brain function.

Functions of *VRK2* in the Neurological System

While the genetic associations between variants in *VRK2* and a variety of psychiatric and neurological conditions have been reported, the potential roles of *VRK2* and its protein product, the vaccine-related serine/threonine kinase 2 (Vrk2), are largely unknown. However, studies analyzing their structure and function have been continuously progressing [104, 105] and have provided valuable implications for future investigations.

The *VRK2* gene is located on human chromosome 2p16.1 and codes for a serine/threonine kinase of the ca-

sein kinase I group (Fig. 1d) [106]. Vrk2 has two protein isoforms: Vrk2A with a transmembrane domain that is mainly anchored in the endoplasmic reticulum and the mitochondria, and Vrk2B, which lacks the transmembrane domain and is present in both the cytosol and nucleus [107]. A detailed comparison of these two isoforms is beyond the scope of the current review. Since a majority of functional studies on Vrk2 in the psychiatric field either do not differ between these two isoforms or report an important function of Vrk2A, this review will focus on the function of Vrk2A (referred as Vrk2 in the following discussion). Earlier studies on the function of Vrk2 were primarily based on the nature of this protein as a kinase and were largely conducted through comparative analyses of its structurally similar protein, Vrk1 [106]. For example, a recent study showed that Vrk2 is a transmembrane kinase in the nuclear envelope (NE) and phosphorylates a highly dynamic chromatin-binding protein BAF (barrier to autointegration factor), which will likely affect NE reassembly and chromatin changes during cell cycle [108]. Also, Vrk2 was initially proposed to play potential roles in cell proliferation and survival [106]. The enriched expression of this protein in organs containing highly proliferative cells (e.g., fetal liver, skeletal muscles, pancreas, heart, peripheral blood leukocytes, and the testis) further supported this hypothesis [106, 109]. Indeed, researchers have found that the expression levels of Vrk2 predict tumor growth and prognostic responses in patients with astrocytoma [110] and rectal cancer [111]. In addition, there is evidence that higher Vrk2 levels confer protection against apoptosis and promote cell survival [112], while overexpression of Vrk2 in human neuroblastoma (SH-SY5Y) cells also reduced neurite outgrowth induced by retinoic acid [113]. These functions of Vrk2 have been linked to SCZ and MDD, given the neurodevelopmental hypothesis for their pathogenesis. For example, it is speculated that reduced Vrk2 levels might induce apoptosis [112, 114], thereby affecting normal neurodevelopment during the early stages of life. In fact, Yu et al. [48] recently explored the potential functions of Vrk2 in developing mouse brains. They reported that Vrk2 was expressed in the developing cerebral cortex, and the silencing of Vrk2 resulted in the impairment of multipolar–bipolar neuron transition and neural progenitor proliferation [48]. Therefore, Vrk2 likely plays regulatory roles in cytoskeleton remodeling and progenitor cell recycling/differentiation [48].

While the exact mechanisms underlying the functions of Vrk2 in cell proliferation and survival are not fully understood, it is suggested that Vrk2 likely involves

JIP1 (Fig. 5), a crucial mediator of neurite initiation and axon outgrowth in neuronal cells [115, 116]. Moreover, a previous study found that in the intracellular signaling pathways Vrk2 is also an upstream modulator of Erk1/MAPK and CREB transcription factor [117], and activation of Vrk2 will affect MEK-induced gene transcription through reducing phosphorylation of key proteins in the relevant pathways (Fig. 5) [115, 118]. Notably, both *MAPK3* (encodes Erk1) [13, 119, 120] and *CREB1* [121, 122] are potentially involved in genetic susceptibility to SCZ, and *CREB1* has also repeatedly been implicated in the genetic and molecular risk of BPD and MDD [123–126]. In a recent study, Jeong et al. showed that Vrk2 directly interacts with dysbindin [113], a protein encoded by the important SCZ susceptibility gene *DTNBP1* [127–130]. Vrk2 could phosphorylate dysbindin, which will consequently enhance its ubiquitination and decrease protein stability [113]. Moreover, Hirata et al. [131] found that Vrk2 interacts with Akt in the lysosomes, and the lysosomal Vrk2-Akt complex controls cellular proliferation and mitochondrial outer-membrane stabilization in the process of autophagy. Intriguingly, *AKT1* is also one of the best candidate genes for SCZ [132–137]. Since the susceptibility genes/proteins of psychiatric disorders usually form a highly interconnected protein-protein interaction network and are enriched in specific pathways involved in brain function and neurodevelopment [138–140], these data collectively provide essential hints for the biological mechanisms underlying the genetic susceptibility to psychiatric disorders conferred by *VRK2*.

In addition to its pivotal roles in cell proliferation and neurodevelopment, *VRK2* has been shown to participate in major posttranslational processes such as protein ubiquitination that could affect neurodegenerative disorders. For instance, Kim et al. [141] revealed that Vrk2 controlled the stability of the eukaryotic chaperonin TRiC (TCP-1 Ring Complex – also known as CCT, for chaperonin containing TCP-1) by inhibiting the deubiquitinating enzyme USP25, and Vrk2 could mediate accumulation of polyglutamine aggregates via negative regulation of TRiC [142]. Recently, Lee et al. [143] further showed that GSK3 β directly bound to Vrk2, resulting in inhibition of Vrk2 catalytic activity, reduction of ubiquitination-proteosomal degradation of TRiC, and suppression of polyglutamine protein aggregation (Fig. 5). While these data suggest a potential involvement of Vrk2 in the development of neurodegenerative disorders, it remains an interesting topic for future investigations whether these pathways contribute to the

pathogenesis of major psychiatric disorders (e.g., SCZ), given that GSK3 β is likely a psychiatric susceptibility gene [144–156].

Another intriguing finding regarding Vrk2 function is the discovery of its role in inflammatory responses. In fact, this protein has been recognized for its involvement in the viral infection processes [157, 158]. It has long been hypothesized that brain inflammation contributes to pathological alterations in SCZ, and a recent study indicates that Vrk2 can reduce the transcriptional response to interleukin-1b (IL-1b, encoded by *IL-1B*) [115], a cytokine involved in inflammatory activity and psychiatric disorders [159–161]. Therefore, it also remains to be elucidated whether Vrk2 affects the major psychiatric disorders via IL-1b-related pathways. Additionally, in line with the inflammatory hypothesis for psychiatric disorders, researchers have studied proteins encoded by genes highlighted in previous GWAS studies to determine whether they could elicit autoantibody production, and thus be involved in inflammatory processes in the brain [162]. They found that Vrk2 was expressed by both neurons and B lymphocytes, and the serum levels of autoantibody against Vrk2 were significantly lower in SCZ patients compared with healthy subjects, suggesting a protective effect of the IgG against Vrk2 [162]. However, the exact mechanisms explaining this observation remain unclear. More interestingly, the administration of antipsychotic risperidone, whose anti-inflammatory effects have been previously described, could increase the level of IgG against Vrk2 [162]. While these findings need further replication, they strongly suggest the correlation between Vrk2 and brain inflammation in SCZ.

Implications for Overlapped Genetic and Biological Basis of SCZ and MDD

The discovery of *VRK2* in genetic studies of SCZ and MDD adds convincing support for the shared genetic susceptibility factors between these two psychiatric disorders [11, 163–166]. Although this hypothesis has long been raised based on the discoveries of susceptibility loci for both SCZ and major mood disorders [164, 167–169], the number of risk genes known to transcend the diagnostic categories remains limited. It is therefore intriguing to see that the same allele in *VRK2* showed genome-wide significant associations with both SCZ and MDD. These results not only indicate that *VRK2* is a common risk gene in psychiatric disorders but also suggest that *VRK2* may be involved in the shared biological pathways

or intermediate phenotypes underlying both illnesses. It should also be noted that debates remain over the boundaries between the clinical symptoms and the degree to which they delineate distinct diagnostic categories of psychiatric disorders [4, 164, 170–173]. Systematic variations introduced by different researchers in sample recruitment during GWAS analyses or other genetic studies are therefore inevitable. This phenomenon, on the other hand, highlights the importance of further elucidation of the genetic and biological basis underlying the shared susceptibility components between psychiatric disorders, and future studies identifying the loci conferring risk of more specific symptoms may provide valuable insights for refining classifications of psychiatric conditions.

Future Perspectives

It is clear that *VRK2* is of considerable interest, given its function in physiological processes as well as its association with major psychiatric and neurological diseases. While current knowledge of this gene and its protein product is relatively rudimentary, there are many unexplored questions that arise from these exciting findings. First, the effects of variants in *VRK2* on the genetic risk of psychiatric disorders are considered to be only modest (odds ratio ~ 1.10) [13–15, 29], and the functions of the risk variants are still unclear. It is therefore under debate whether *VRK2* could be directly used as a possible target in the future clinical management of these disorders. The detailed genetic mechanisms for its role in such disorders will provide essential information. In addition, studies describing the effects of *VRK2* on neurodevelopment and brain function are still lacking. Although there is preliminary evidence that this gene may affect neuronal migration [48] and inflammation [115, 159, 160], whether it could affect other aspects of neuronal function, e.g. synaptic development and transmission, is still unclear. Furthermore, several studies have reported that proteins interact with Vrk2 or regulate its function [143, 174]. Whether these mechanisms facilitate the pathogenesis of certain psychiatric and neurological disorders should be examined to reveal potential therapeutic opportunities.

In summary, in the present review, we have outlined the compelling evidence suggesting that *VRK2* is a significant factor in the onset or/and development of SCZ and MDD. To the best of our knowledge, *VRK2* is also one of the few genes showing genome-wide significant

associations with both SCZ and MDD, making it an important subject for studies in the field of psychiatric genetics. Moreover, we have discussed the urgent need for further exploration of its role in the genetic architecture of psychiatric disorders (especially SCZ and MDD), the biological impact on neurodevelopment and brain function, and the roles of associated molecules in diseases. As the majority of studies on *VRK2* were conducted in vitro, future utilization of animal- and/or human-derived tissues may provide valuable insights and information.

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Disclosure Statement

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