**Name of Journal:** *World Journal of Stem Cells*

**Manuscript NO:** 66559

**Manuscript Type:** REVIEW

**Adult neural stem cells and schizophrenia**

Hu L *et al*. Adult neural stem cells and schizophrenia

Ling Hu, Lei Zhang

**Ling Hu,** Department of Laboratory Animal Science andInstitutes of Brain Science, Fudan University, Shanghai 200032, China

**Lei Zhang,** Shanghai Yangzhi Rehabilitation Hospital (Shanghai Sunshine Rehabilitation Center) and Department of Anatomy and Neurobiology, Tongji University School of Medicine, Shanghai 200092, China

**Author contributions:** Hu L and Zhang L wrote the manuscript and prepared the table.

**Supported by** Shanghai Pujiang Program, No. 20PJ1413300.

**Corresponding author: Lei Zhang, PhD, Associate Professor,** Shanghai Yangzhi Rehabilitation Hospital (Shanghai Sunshine Rehabilitation Center) and Department of Anatomy and Neurobiology, Tongji University School of Medicine, No. 1239 Siping Road, Shanghai 200092, China. leizhang1120@outlook.com

**Received:** April 6, 2021

**Revised:** June 18, 2021

**Accepted: March 7, 2022**

**Published online:**

**Abstract**

Schizophrenia (SCZ) is a devastating and complicated mental disorder accompanied by variable positive and negative symptoms and cognitive deficits. Although many genetic risk factors have been identified, SCZ is also considered as a neurodevelopmental disorder. Elucidation of the pathogenesis and the development of treatment is challenging because complex interactions occur between these genetic risk factors and environment in essential neurodevelopmental processes. Adult neural stem cells share a lot of similarities with embryonic neural stem cells and provide a promising model for studying neuronal development in adulthood. These adult neural stem cells also play an important role in cognitive functions including temporal and spatial memory encoding and context discrimination, which have been shown to be closely linked with many psychiatric disorders, such as SCZ. Here in this review, we focus on the SCZ risk genes and the key components in related signaling pathways in adult hippocampal neural stem cells and summarize their roles in adult neurogenesis and animal behaviors. We hope that this would be helpful for the understanding of the contribution of dysregulated adult neural stem cells in the pathogenesis of SCZ and for the identification of potential therapeutic targets, which could facilitate the development of novel medication and treatment.

**Key Words:** Neural stem cells; Adult hippocampal neurogenesis; Schizophrenia; Risk genes; Signaling pathways; Behavior

Hu L, Zhang L. Adult neural stem cells and schizophrenia. *World J Stem Cells* 2022; In press

**Core Tip:** This review focuses on the role of schizophrenia risk genes and related signaling pathways in adult hippocampal neurogenesis, which has been shown to play an essential role in many psychiatric disorders. We summarize the outcome of adult neural stem cells and animal behavior when these risk genes or the key components in related signaling pathways are dysregulated. We hope this will shed light on the elusive pathogenesis of schizophrenia.

**INTRODUCTION**

Schizophrenia (SCZ) is a devastating brain disorder with a prevalence of 1% worldwide. Patients typically show a subset of positive symptoms including delusions, auditory and visual hallucinations, disorganized speech and thought disorder, negative symptoms including a lack of motivation, interest and emotional blunting, lack of thought and content of speech, and/or cognitive deficits[1-3]. Although SCZ has been extensively investigated in the past few decades, the underlying cellular defects and molecular mechanism of SCZ have not been clearly established. Considerable evidence supports the notion that SCZ is the behavioral outcome of neurodevelopmental disturbance long before the onset of clinical symptoms[4]. However, it is known that neurodevelopment is not confined to the embryonic stages, and is a prolonged process continuing in adults. On the basis that the first psychotic symptoms in most patients occur in late adolescence[3], abnormal adult hippocampal neurogenesis might facilitate the emergence of hippocampal-dependent cognitive and affective deviation.

Adult neurogenesis is a complex and complicated process, which occurs in the subgranular zone (SGZ) of the dentate gyrus (DG) in mammalian brain[5]. Quiescent neural stem cells in the SGZ become activated, proliferate, differentiate, mature into glutamatergic neurons and receive innervations from the entorhinal cortex while projecting axons to the cornu ammonis 3 (CA3) region[6]. The direct evidence that defective adult neurogenesis might be involved in the etiology of SCZ originates from studies on post-mortem samples, in which the number of cells expressing Ki67, the cell proliferation marker, was reduced by 50%-60% in the SGZ[7]. In addition, patients diagnosed with SCZ present with an immature DG with impaired maturation of adult-born neurons[8].

Recently, several risk genes associated with SCZ have been identified through genome-wide association studies (GWAS), some of which are components of important signaling pathways. Given the evidence that numerous genes are implicated in the etiology of SCZ, the disease is currently accepted as a polygenic disorder caused by the complex interplay between genetic and environmental factors[9-11]. In this review, we mainly focus on the roles of some risk genes and key signaling pathways implicated in SCZ, during the process of adult neurogenesis.

**SCZ RISK GENES**

***Disrupted in SCZ 1***

Disrupted in SCZ 1(DISC1), one of the widely-studied risk genes for SCZ, was originally identified in a large Scottish family. A balanced chromosomal translocation t(1;11)(q42.1;q14.3) leads to disruption of the C-terminal region in *DISC1* gene, which is co-segregated with mental disorders such as SCZ and depression[12-15]. Suppression of *Disc1* expression perturbs neural progenitor proliferation during adult neurogenesis through the glycogen synthase kinase 3β (Gsk-3β)/β-catenin pathway. Furthermore, Gsk-3 inhibitors attenuate progenitor proliferation and behavioral defects caused by *Disc1* suppression[16]. Various studies have shown that alteration of *Disc1* expression impedes the maturation of new-born neurons including aberrant morphological development, mis-positioning of new DG granule cells, enhanced dendritic outgrowth and defects in axonal targeting[17-20]. In addition, Disc1 works as a scaffold protein and interacts with many signaling effectors to regulate adult neurogenesis. For example, Disc1 directly interacts with Girdin, which regulates the differentiation, maturation, migration, and cytoskeleton organization of adult neural progenitors and inhibits Akt activity[21,22]. Interestingly, the cellular defects and hippocampal-dependent behavioral deficits caused by *Disc1* deficiency can be largely rescued by the administration of rapamycin, an inhibitor of mammalian target of rapamycin (mTOR), which is the Akt downstream effector[23]. In addition, an interplay between intrinsic Disc1 and extrinsic γ-amino butyric acid (GABA) signaling also contributes to dendritic growth and synapse formation in immature neurons *via* the Akt-mTOR pathway[24-26]. Collectively, *DISC1* regulates multiple steps of adult neurogenesis through interaction with key effectors of various signaling pathways directly and indirectly.

***Neuregulin-1***

Neuregulin-1 (NRG1) was identified as a risk factor for SCZ more than a decade ago through a genome-wide scan of SCZ families in Iceland, which was later supported by many associated studies[27-29]. NRG1 binds to ErbB2-4, a family of epidermal growth factor-like tyrosine kinases, and defective NRG1/ErbB4 signaling is found in the prefrontal cortex and hippocampus of SCZ patients[30-32]. Moreover, multiple studies have proven that NRG1 is associated with affective behavior and the pathology of SCZ[33-36]. It has been reported that the administration of Nrg1 displays robust antidepressant-like behaviors accompanied by increased ventral DG cell proliferation and neurogenesis in the caudal DG without alteration of neuronal fate[37]. The finding that it interacts with molecules in the glutamatergic synapse implies a role of Nrg1 in adult plasticity[38,39]. These observations suggest that NRG1/ErbB4 signaling might participate in the process of adult neurogenesis.

***Synaptosomal-associated protein, 25 kDa***

Synaptosomal-associated protein, 25 kDa (SNAP-25) is a soluble N-ethylmaleimide-sensitive factor attachment protein receptor protein, which plays a crucial role in modulating synaptic exocytosis[40-42]. Genetic studies and genome-wide meta-analyses have revealed its close association with multiple mental diseases including SCZ[43-46]. *Snap-25* mutant mice display histologically and electrophysiologically immature DG neurons, leading to a severe working memory deficit[47]. Interestingly, selective inactivation of *Snap-25* in adult neural stem cells results in enhancement in proximal dendritic branching of new-born neurons in the DG and robust efferent mossy fiber output to the CA3 region[48]. So far, the immature DG phenotype and similar schizophrenic-like behaviors have been found in *Schnurri-2* knockout[49], *Snap-25* mutant[47], and calmodulin-dependent protein kinase II (CaMKII) knockout mice[49]. Importantly, this immature DG phenomenon has also been observed in the post-mortem brains from schizophrenic patients[8,50], suggesting a close link between disrupted maturation of adult-born cells and schizophrenic-like behaviors.

***Calcium voltage-gated channel subunit alpha1 C***

Calcium voltage-gated channel subunit alpha1 C (CACNA1C) encodes the Cav1.2 subunit of voltage-gated calcium channels, whose genetic variations have been reported to increase the risk of psychiatric disorders including SCZ[51,52]. GWAS have identified several single-nucleotide polymorphisms (SNPs) of the *CACNA1C* gene, which show a close link with SCZ[53-55]. Furthermore, large exome sequencing studies have defined disruptive mutations within calcium ion channels in schizophrenic patients[56]. With regard to the functions of *CACNA1C*, it has received a lot of attention and been studied extensively in animal models. The results obtained from mice have shown that reduced gene dosage of *Cacna1c* leads to behavioral impairments includingreduced locomotion and fear learning as well as impaired spatial memory[57-59]. Cacna1c has also been found to mediate brain-derived neurotrophic factor production and thus might also play a role in regulating adult neurogenesis. Indeed, studies on mice with ablation of *Cacna1c* showed that adult neurogenesis was impaired as revealed by decreased proliferation of progenitors and survival of new-born neurons, which coincides with its cognitive deficits[60,61].

***Reelin***

Reelin, an extracellular matrix glycoprotein which is mainly synthesized by Cajal-Retzius cells in the cortical marginal zone of the telencephalon at embryonic stages and in a subpopulation of GABAergic interneurons in adulthood, has been shown to play an essential role in embryonic and adult brains[62-66]. Reelin exerts its biological functions by binding to integrin receptors and then triggers phosphorylation of disabled-1 (Dab1). Phosphorylated Dab1 then recruits downstream molecules such as Crk/CrkL, phosphatidylinositol 3-kinase and Nckβ to their functional compartment[67,68]. It has been reported that *Reelin* mRNA and protein levels are reduced by almost 50% in cortical and hippocampal regions in post-mortem brains and serum of schizophrenic patients[69-71]. In the adult brain, Reelin is synthesized and secreted by GABAergic interneurons, and the reduction of glutamic acid decarboxylase 67 (Gad67), an enzyme which catalyzes the transition of glutamate to GABA, has also been observed in the same brains[72]. Thus, the authors postulate that decreases in neuropil and dendritic spines observed in the prefrontal cortex of post-mortem brains may be an outcome of disturbed GABAergic function and an associated decrease in Reelin secretion[73]. In addition, Li *et al* identified six SNPs located in Intron 29 of the *REELIN* gene, which have a significant association with the risk of SCZ in the Chinese population[74]. Similarly, other groups have reported a gender-specific (women) association between SNPs in *REELIN* and SCZ[75-77]. Studies on animal models have also found that heterozygous Reeler mice (*Reelin* mutant) display many neuroanatomic and neurochemical changes similar to those described in patients with SCZ. These changes include altered synaptic plasticity, decreased dendritic spine density, reduced *Gad67* mRNA and protein levels in the frontal cortex and behavioral disturbances in associative memory and prepulse inhibition, whereas supplementation with REELIN can partially restore these abnormalities[78-83]. Inactivation of Reelin signaling also leads to impaired adult neurogenesis as shown by decreased proliferation, aberrant migration and dendritic development of new-born neurons[84-86]. Taken together, these findings suggest that reduced *REELIN* expression in SCZ might have an impact on adult neurogenesis.

***Other molecules***

Apart from the susceptibility genes mentioned above, other molecules are also implicated in adult neurogenesis and SCZ, such as miR-19. A recent study revealed that miR-19 is enriched in adult hippocampal neural progenitor cells and regulates the migration of newborn neurons, highlighting its critical role in adult hippocampal neurogenesis[87]. Furthermore, miR-19 is found to be abnormally expressed in neural progenitor cells derived from induced pluripotent stem cells of schizophrenic patients[87], who show aberrant cell migration in brain. Thus, these data suggest that miR-19 may be a molecule associated with adult hippocampal neurogenesis and SCZ.

**SCZ AND RELATED SIGNALING PATHWAYS CONTROLLING ADULT NEUROGENESIS**

***Wnt signaling***

Wnt signaling, one of the most conserved molecular pathways, plays a vital role in the neurodevelopmental process and regulates the function and structure of the adult nervous system[88-90]. Wnts comprise a large cohort of secreted glycoproteins which interact with extracellular receptors, Frizzled or Low-density lipoprotein receptors 5/6[91]. Consequently, the activation of scaffold protein Dishevelled (Dvl) leads to inactivation of the serine/threonine kinase, Gsk-3β. Normally, Gsk-3β promotes the degradation of β-catenin viaphosphorylation. The inactivation of *Gsk-3β* finally causes the accumulation and translocation of β-catenin to the nucleus where it binds to the transcription factor Tcf/Lef family and activates target genes.

Wnt signaling is involved in brain development during the embryonic stages including cortical patterning, cell adhesion, migration, cell fate determination and proliferation[38,92,93]. In the adult brain, growing evidence indicates that components of Wnt signaling regulate multiple stages of adult neurogenesis including proliferation, fate commitment and synaptic plasticity[90,94,95]. For example, loss of *Wnt7a* expression dramatically reduced the neural stem cell population, increased the rate of cell cycle exit in neural progenitors and dramatically impaired dendritic development in the hippocampal DG of adult mice by modulating the β-catenin-cyclin D1 and β-catenin-neurogenin 2 pathway, respectively[96]. Knockdown of *Wnt5a* impaired neuronal differentiation and dendritic development of adult-born neurons by activating Wnt/c-Jun N-terminal kinase (JNK) and Wnt/CaMKII signaling[97].

Disturbances in components of the Wnt signaling pathway have been reported in post-mortem brains of patients diagnosed with SCZ. These abnormalities include: (1) Reduced GSK-3β levels in the prefrontal cortex, hippocampus and cerebrospinal fluid of patients[98-100]. It is noteworthy that medications which may treat symptoms of SCZ in clinical use, also modulate the levels and activity of AKT, GSK-3 and WNT-related intracellular signaling[101,102]; (2) A reduction in Dickkopf WNT signaling pathway inhibitor 3 (DKK3) mRNA, a suppressive factor of WNT signaling, in the cerebral cortex and an increase in the Adenomatous polyposis coli (APC) expression, acting as an antagonist of the WNT signaling pathway, is found in schizophrenic brain[103]; and (3) The expression of WNT-related genes in canonical WNT signaling was attenuated in whole blood in a sample of SCZ patients using an enzyme immunoassay. Furthermore, plasma levels of soluble DKK1 and SCLEROSTIN were downregulated in patients[104]. Wnt signaling in SCZ was further confirmed in animal studies. One of the first animal models included *Dvl* knockout mice, which exhibited reduced social interaction and deficits in prepulse inhibition of acoustic and tactile startle[105]. In addition, Disc1 exerts its function through Wnt signaling directly or indirectly[17]. Subsequent studies have shown that *Apc* and *β-catenin* knockout mice also display behavioral deviations related to SCZ[106,107]. In addition, the component of Wnt signaling, T-cell factor 4 (Tcf4), has received increased attention as the SNPs in its non-coding regions are associated with an increased risk of SCZ in GWAS[108-111]. *Tcf4* also plays an important role in adult neurogenesis. *Tcf4* heterozygous mice showed a decreased hippocampal neural stem cell pool, and impaired maturation and survival of adult-born neurons[112]. Thus, it is likely that dysregulation of the WNT signaling pathway contributes to adult neurogenesis deficits observed in SCZ patients.

***Notch signaling***

The Notch signaling pathway plays a crucial role in a wide array of neurodevelopmental processes and adult neurogenesis. Notch receptors are single-pass transmembrane heterodimers and four isoforms (Notch1-4) have been identified. In mammals, there are several types of Notch ligands including three Delta/Delta-like molecules (Dll/Dlk-1, -3, and -4) and two Serrate/Jagged molecules (Jag-1 and Jag-2). The heterodimeric Notch receptor undergoes proteolytic cleavage after binding to one of its ligands. This process liberates the Notch intracellular domain (NICD) which later translocates to the nucleus and interacts with the DNA-binding protein RBPj. The NICD-RBPj conjugation in turn works as a transcriptional activator and stimulates the expression of basic helix-loop-helix transcription factors, such as the Hairy-Enhancer of Split[113-115]. A number of *NOTCH4* variants and haplotypes have been found to be associated with SCZ[116,117]. This finding was subsequently confirmed by large GWAS[118]. Recent studies showed that the plasma levels of secreted NOTCH ligands (DLL1 and DLK-1) were elevated, whereas the levels of PRESENILIN-1, CREB-binding protein and RBPj were decreased in microarray analyses of whole blood from a large sample of SCZ patients[119]. In the study by Xue *et al*[120], Risperidone, one of medications used to treat SCZ, ameliorated cognitive deficits and cell proliferation by modulating the activity of Notch signaling in a murine model of SCZ. Mice deficient in Notch signaling have been shown to display spatial learning and memory impairment[121,122].

Notch signaling has long been identified as a factor which plays a primary role in adult neurogenesis. Notch receptors are expressed in neural stem cells and progenitors in the SGZ (Type-1 cells)[123,124]. In neural stem cells, the components of Notch signaling mainly work together to maintain an undifferentiated, proliferative state and therefore preserve the neural stem cell pool[125-127]. Indeed, inactivation of *Notch1* leads to reduced mitotic progenitors and neurogenesis[128], whereas activation of Notch1 signaling increases neural stem cells and results in the generation of glial cells at the expense of neurons[124]. Adult deletion of *RBPj* results in depletion and exhaustion of neural stem cells[129]. Therefore, NOTCH signaling might be involved in the etiology of SCZ and especially cognitive deficits.

**CONCLUSION**

Accumulating evidence shows that impaired adult neurogenesis in the hippocampus is implicated in the pathogenesis of SCZ (Table 1). Decreased proliferation of adult neural stem cells in the DG and reduced hippocampal volume often coincide with impaired cognitive and affective functions, which are commonly identified in animal models and schizophrenic patients. The question of how dysregulation of neurogenesis in the adult brain participates in the progression of SCZ arouses more and more interests. As SCZ is a neurodevelopmental disorder, many risk genes have an impact on both early brain development and adult neurogenesis. Thus, adult neurogenesis provides an attractive model to study the neurodevelopmental process, as it generalizes each step of neuronal development, including proliferation, specification, migration, dendritic branching and synapse formation. Although numerous susceptibility genes/molecules have been uncovered by genetic analysis and high-throughput sequencing, their functions still remain elusive. The studies on the roles of these susceptibility genes/signaling pathways in adult neurogenesis might shed some light on the understanding the etiology of SCZ and identifying potential therapeutic targets, which could facilitate the development of novel medication and treatment.

**REFERENCES**

1 **Andreasen NC**. Symptoms, signs, and diagnosis of schizophrenia. *Lancet* 1995; **346**: 477-481 [PMID: 7637483 DOI: 10.1016/s0140-6736(95)91325-4]

2 **Jones CA**, Watson DJ, Fone KC. Animal models of schizophrenia. *Br J Pharmacol* 2011; **164**: 1162-1194 [PMID: 21449915 DOI: 10.1111/j.1476-5381.2011.01386.x]

3 **Marder SR**, Cannon TD. Schizophrenia. *N Engl J Med* 2019; **381**: 1753-1761 [PMID: 31665579 DOI: 10.1056/NEJMra1808803]

4 **Birnbaum R**, Weinberger DR. Genetic insights into the neurodevelopmental origins of schizophrenia. *Nat Rev Neurosci* 2017; **18**: 727-740 [PMID: 29070826 DOI: 10.1038/nrn.2017.125]

5 **Gage FH**, Temple S. Neural stem cells: generating and regenerating the brain. *Neuron* 2013; **80**: 588-601 [PMID: 24183012 DOI: 10.1016/j.neuron.2013.10.037]

6 **Toda T**, Parylak SL, Linker SB, Gage FH. The role of adult hippocampal neurogenesis in brain health and disease. *Mol Psychiatry* 2019; **24**: 67-87 [PMID: 29679070 DOI: 10.1038/s41380-018-0036-2]

7 **Reif A**, Fritzen S, Finger M, Strobel A, Lauer M, Schmitt A, Lesch KP. Neural stem cell proliferation is decreased in schizophrenia, but not in depression. *Mol Psychiatry* 2006; **11**: 514-522 [PMID: 16415915 DOI: 10.1038/sj.mp.4001791]

8 **Walton NM**, Zhou Y, Kogan JH, Shin R, Webster M, Gross AK, Heusner CL, Chen Q, Miyake S, Tajinda K, Tamura K, Miyakawa T, Matsumoto M. Detection of an immature dentate gyrus feature in human schizophrenia/bipolar patients. *Transl Psychiatry* 2012; **2**: e135 [PMID: 22781168 DOI: 10.1038/tp.2012.56]

9 **International Schizophrenia Consortium.**, Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, Sullivan PF, Sklar P. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 2009; **460**: 748-752 [PMID: 19571811 DOI: 10.1038/nature08185]

10 **Lewis DA**, Lieberman JA. Catching up on schizophrenia: natural history and neurobiology. *Neuron* 2000; **28**: 325-334 [PMID: 11144342 DOI: 10.1016/s0896-6273(00)00111-2]

11 **Owen MJ**, Sawa A, Mortensen PB. Schizophrenia. *Lancet* 2016; **388**: 86-97 [PMID: 26777917 DOI: 10.1016/S0140-6736(15)01121-6]

12 **Blackwood DH**, Fordyce A, Walker MT, St Clair DM, Porteous DJ, Muir WJ. Schizophrenia and affective disorders--cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and P300 findings in a family. *Am J Hum Genet* 2001; **69**: 428-433 [PMID: 11443544 DOI: 10.1086/321969]

13 **Taylor MS**, Devon RS, Millar JK, Porteous DJ. Evolutionary constraints on the Disrupted in Schizophrenia locus. *Genomics* 2003; **81**: 67-77 [PMID: 12573262 DOI: 10.1016/s0888-7543(02)00026-5]

14 **St Clair D**, Blackwood D, Muir W, Carothers A, Walker M, Spowart G, Gosden C, Evans HJ. Association within a family of a balanced autosomal translocation with major mental illness. *Lancet* 1990; **336**: 13-16 [PMID: 1973210 DOI: 10.1016/0140-6736(90)91520-k]

15 **Kuroda K**, Yamada S, Tanaka M, Iizuka M, Yano H, Mori D, Tsuboi D, Nishioka T, Namba T, Iizuka Y, Kubota S, Nagai T, Ibi D, Wang R, Enomoto A, Isotani-Sakakibara M, Asai N, Kimura K, Kiyonari H, Abe T, Mizoguchi A, Sokabe M, Takahashi M, Yamada K, Kaibuchi K. Behavioral alterations associated with targeted disruption of exons 2 and 3 of the Disc1 gene in the mouse. *Hum Mol Genet* 2011; **20**: 4666-4683 [PMID: 21903668 DOI: 10.1093/hmg/ddr400]

16 **Mao Y**, Ge X, Frank CL, Madison JM, Koehler AN, Doud MK, Tassa C, Berry EM, Soda T, Singh KK, Biechele T, Petryshen TL, Moon RT, Haggarty SJ, Tsai LH. Disrupted in schizophrenia 1 regulates neuronal progenitor proliferation *via* modulation of GSK3beta/beta-catenin signaling. *Cell* 2009; **136**: 1017-1031 [PMID: 19303846 DOI: 10.1016/j.cell.2008.12.044]

17 **Wu Q**, Li Y, Xiao B. DISC1-related signaling pathways in adult neurogenesis of the hippocampus. *Gene* 2013; **518**: 223-230 [PMID: 23353011 DOI: 10.1016/j.gene.2013.01.015]

18 **Duan X**, Chang JH, Ge S, Faulkner RL, Kim JY, Kitabatake Y, Liu XB, Yang CH, Jordan JD, Ma DK, Liu CY, Ganesan S, Cheng HJ, Ming GL, Lu B, Song H. Disrupted-In-Schizophrenia 1 regulates integration of newly generated neurons in the adult brain. *Cell* 2007; **130**: 1146-1158 [PMID: 17825401 DOI: 10.1016/j.cell.2007.07.010]

19 **Kang E**, Burdick KE, Kim JY, Duan X, Guo JU, Sailor KA, Jung DE, Ganesan S, Choi S, Pradhan D, Lu B, Avramopoulos D, Christian K, Malhotra AK, Song H, Ming GL. Interaction between FEZ1 and DISC1 in regulation of neuronal development and risk for schizophrenia. *Neuron* 2011; **72**: 559-571 [PMID: 22099459 DOI: 10.1016/j.neuron.2011.09.032]

20 **Faulkner RL**, Jang MH, Liu XB, Duan X, Sailor KA, Kim JY, Ge S, Jones EG, Ming GL, Song H, Cheng HJ. Development of hippocampal mossy fiber synaptic outputs by new neurons in the adult brain. *Proc Natl Acad Sci U S A* 2008; **105**: 14157-14162 [PMID: 18780780 DOI: 10.1073/pnas.0806658105]

21 **Kim JY**, Duan X, Liu CY, Jang MH, Guo JU, Pow-anpongkul N, Kang E, Song H, Ming GL. DISC1 regulates new neuron development in the adult brain *via* modulation of AKT-mTOR signaling through KIAA1212. *Neuron* 2009; **63**: 761-773 [PMID: 19778506 DOI: 10.1016/j.neuron.2009.08.008]

22 **Enomoto A**, Murakami H, Asai N, Morone N, Watanabe T, Kawai K, Murakumo Y, Usukura J, Kaibuchi K, Takahashi M. Akt/PKB regulates actin organization and cell motility *via* Girdin/APE. *Dev Cell* 2005; **9**: 389-402 [PMID: 16139227 DOI: 10.1016/j.devcel.2005.08.001]

23 **Zhou M**, Li W, Huang S, Song J, Kim JY, Tian X, Kang E, Sano Y, Liu C, Balaji J, Wu S, Zhou Y, Zhou Y, Parivash SN, Ehninger D, He L, Song H, Ming GL, Silva AJ. mTOR Inhibition ameliorates cognitive and affective deficits caused by Disc1 knockdown in adult-born dentate granule neurons. *Neuron* 2013; **77**: 647-654 [PMID: 23439118 DOI: 10.1016/j.neuron.2012.12.033]

24 **Platel JC**, Stamboulian S, Nguyen I, Bordey A. Neurotransmitter signaling in postnatal neurogenesis: The first leg. *Brain Res Rev* 2010; **63**: 60-71 [PMID: 20188124 DOI: 10.1016/j.brainresrev.2010.02.004]

25 **Kim JY**, Liu CY, Zhang F, Duan X, Wen Z, Song J, Feighery E, Lu B, Rujescu D, St Clair D, Christian K, Callicott JH, Weinberger DR, Song H, Ming GL. Interplay between DISC1 and GABA signaling regulates neurogenesis in mice and risk for schizophrenia. *Cell* 2012; **148**: 1051-1064 [PMID: 22385968 DOI: 10.1016/j.cell.2011.12.037]

26 **Wei J**, Graziane NM, Gu Z, Yan Z. DISC1 Protein Regulates γ-Aminobutyric Acid, Type A (GABAA) Receptor Trafficking and Inhibitory Synaptic Transmission in Cortical Neurons. *J Biol Chem* 2015; **290**: 27680-27687 [PMID: 26424793 DOI: 10.1074/jbc.M115.656173]

27 **Stefansson H**, Sigurdsson E, Steinthorsdottir V, Bjornsdottir S, Sigmundsson T, Ghosh S, Brynjolfsson J, Gunnarsdottir S, Ivarsson O, Chou TT, Hjaltason O, Birgisdottir B, Jonsson H, Gudnadottir VG, Gudmundsdottir E, Bjornsson A, Ingvarsson B, Ingason A, Sigfusson S, Hardardottir H, Harvey RP, Lai D, Zhou M, Brunner D, Mutel V, Gonzalo A, Lemke G, Sainz J, Johannesson G, Andresson T, Gudbjartsson D, Manolescu A, Frigge ML, Gurney ME, Kong A, Gulcher JR, Petursson H, Stefansson K. Neuregulin 1 and susceptibility to schizophrenia. *Am J Hum Genet* 2002; **71**: 877-892 [PMID: 12145742 DOI: 10.1086/342734]

28 **Li D**, Collier DA, He L. Meta-analysis shows strong positive association of the neuregulin 1 (NRG1) gene with schizophrenia. *Hum Mol Genet* 2006; **15**: 1995-2002 [PMID: 16687441 DOI: 10.1093/hmg/ddl122]

29 **Agim ZS**, Esendal M, Briollais L, Uyan O, Meschian M, Martinez LA, Ding Y, Basak AN, Ozcelik H. Discovery, validation and characterization of Erbb4 and Nrg1 haplotypes using data from three genome-wide association studies of schizophrenia. *PLoS One* 2013; **8**: e53042 [PMID: 23301017 DOI: 10.1371/journal.pone.0053042]

30 **Mei L**, Nave KA. Neuregulin-ERBB signaling in the nervous system and neuropsychiatric diseases. *Neuron* 2014; **83**: 27-49 [PMID: 24991953 DOI: 10.1016/j.neuron.2014.06.007]

31 **Barakat A**, Dean B, Scarr E, Evin G. Decreased Neuregulin 1 C-terminal fragment in Brodmann's area 6 of patients with schizophrenia. *Schizophr Res* 2010; **124**: 200-207 [PMID: 20926259 DOI: 10.1016/j.schres.2010.09.001]

32 **Chong VZ**, Thompson M, Beltaifa S, Webster MJ, Law AJ, Weickert CS. Elevated neuregulin-1 and ErbB4 protein in the prefrontal cortex of schizophrenic patients. *Schizophr Res* 2008; **100**: 270-280 [PMID: 18243664 DOI: 10.1016/j.schres.2007.12.474]

33 **Bertram I**, Bernstein HG, Lendeckel U, Bukowska A, Dobrowolny H, Keilhoff G, Kanakis D, Mawrin C, Bielau H, Falkai P, Bogerts B. Immunohistochemical evidence for impaired neuregulin-1 signaling in the prefrontal cortex in schizophrenia and in unipolar depression. *Ann N Y Acad Sci* 2007; **1096**: 147-156 [PMID: 17405926 DOI: 10.1196/annals.1397.080]

34 **Georgieva L**, Dimitrova A, Ivanov D, Nikolov I, Williams NM, Grozeva D, Zaharieva I, Toncheva D, Owen MJ, Kirov G, O'Donovan MC. Support for neuregulin 1 as a susceptibility gene for bipolar disorder and schizophrenia. *Biol Psychiatry* 2008; **64**: 419-427 [PMID: 18466881 DOI: 10.1016/j.biopsych.2008.03.025]

35 **Réthelyi JM**, Bakker SC, Polgár P, Czobor P, Strengman E, Pásztor PI, Kahn RS, Bitter I. Association study of NRG1, DTNBP1, RGS4, G72/G30, and PIP5K2A with schizophrenia and symptom severity in a Hungarian sample. *Am J Med Genet B Neuropsychiatr Genet* 2010; **153B**: 792-801 [PMID: 19937977 DOI: 10.1002/ajmg.b.31049]

36 **Mei L**, Xiong WC. Neuregulin 1 in neural development, synaptic plasticity and schizophrenia. *Nat Rev Neurosci* 2008; **9**: 437-452 [PMID: 18478032 DOI: 10.1038/nrn2392]

37 **Mahar I**, MacIsaac A, Kim JJ, Qiang C, Davoli MA, Turecki G, Mechawar N. Effects of neuregulin-1 administration on neurogenesis in the adult mouse hippocampus, and characterization of immature neurons along the septotemporal axis. *Sci Rep* 2016; **6**: 30467 [PMID: 27469430 DOI: 10.1038/srep30467]

38 **Toro CT**, Deakin JF. Adult neurogenesis and schizophrenia: a window on abnormal early brain development? *Schizophr Res* 2007; **90**: 1-14 [PMID: 17123784 DOI: 10.1016/j.schres.2006.09.030]

39 **Seshadri S**, Faust T, Ishizuka K, Delevich K, Chung Y, Kim SH, Cowles M, Niwa M, Jaaro-Peled H, Tomoda T, Lai C, Anton ES, Li B, Sawa A. Interneuronal DISC1 regulates NRG1-ErbB4 signalling and excitatory-inhibitory synapse formation in the mature cortex. *Nat Commun* 2015; **6**: 10118 [PMID: 26656849 DOI: 10.1038/ncomms10118]

40 **Jahn R**, Lang T, Südhof TC. Membrane fusion. *Cell* 2003; **112**: 519-533 [PMID: 12600315 DOI: 10.1016/s0092-8674(03)00112-0]

41 **Sudhof TC**. The synaptic vesicle cycle. *Annu Rev Neurosci* 2004; **27**: 509-547 [PMID: 15217342 DOI: 10.1146/annurev.neuro.26.041002.131412]

42 **Karmakar S**, Sharma LG, Roy A, Patel A, Pandey LM. Neuronal SNARE complex: A protein folding system with intricate protein-protein interactions, and its common neuropathological hallmark, SNAP25. *Neurochem Int* 2019; **122**: 196-207 [PMID: 30517887 DOI: 10.1016/j.neuint.2018.12.001]

43 **Lewis CM**, Levinson DF, Wise LH, DeLisi LE, Straub RE, Hovatta I, Williams NM, Schwab SG, Pulver AE, Faraone SV, Brzustowicz LM, Kaufmann CA, Garver DL, Gurling HM, Lindholm E, Coon H, Moises HW, Byerley W, Shaw SH, Mesen A, Sherrington R, O'Neill FA, Walsh D, Kendler KS, Ekelund J, Paunio T, Lönnqvist J, Peltonen L, O'Donovan MC, Owen MJ, Wildenauer DB, Maier W, Nestadt G, Blouin JL, Antonarakis SE, Mowry BJ, Silverman JM, Crowe RR, Cloninger CR, Tsuang MT, Malaspina D, Harkavy-Friedman JM, Svrakic DM, Bassett AS, Holcomb J, Kalsi G, McQuillin A, Brynjolfson J, Sigmundsson T, Petursson H, Jazin E, Zoëga T, Helgason T. Genome scan meta-analysis of schizophrenia and bipolar disorder, part II: Schizophrenia. *Am J Hum Genet* 2003; **73**: 34-48 [PMID: 12802786 DOI: 10.1086/376549]

44 **Ramos-Miguel A**, Barakauskas V, Alamri J, Miyauchi M, Barr AM, Beasley CL, Rosoklija G, Mann JJ, Dwork AJ, Moradian A, Morin GB, Honer WG. The SNAP25 Interactome in Ventromedial Caudate in Schizophrenia Includes the Mitochondrial Protein ARF1. *Neuroscience* 2019; **420**: 97-111 [PMID: 30610939 DOI: 10.1016/j.neuroscience.2018.12.045]

45 **Thompson PM**, Sower AC, Perrone-Bizzozero NI. Altered levels of the synaptosomal associated protein SNAP-25 in schizophrenia. *Biol Psychiatry* 1998; **43**: 239-243 [PMID: 9513732 DOI: 10.1016/S0006-3223(97)00204-7]

46 **Thompson PM**, Egbufoama S, Vawter MP. SNAP-25 reduction in the hippocampus of patients with schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* 2003; **27**: 411-417 [PMID: 12691775 DOI: 10.1016/S0278-5846(03)00027-7]

47 **Ohira K**, Kobayashi K, Toyama K, Nakamura HK, Shoji H, Takao K, Takeuchi R, Yamaguchi S, Kataoka M, Otsuka S, Takahashi M, Miyakawa T. Synaptosomal-associated protein 25 mutation induces immaturity of the dentate granule cells of adult mice. *Mol Brain* 2013; **6**: 12 [PMID: 23497716 DOI: 10.1186/1756-6606-6-12]

48 **Gustus KC**, Li L, Chander P, Weick JP, Wilson MC, Cunningham LA. Genetic inactivation of synaptosomal-associated protein 25 (SNAP-25) in adult hippocampal neural progenitors impairs pattern discrimination learning but not survival or structural maturation of newborn dentate granule cells. *Hippocampus* 2018; **28**: 735-744 [PMID: 29995325 DOI: 10.1002/hipo.23008]

49 **Yamasaki N**, Maekawa M, Kobayashi K, Kajii Y, Maeda J, Soma M, Takao K, Tanda K, Ohira K, Toyama K, Kanzaki K, Fukunaga K, Sudo Y, Ichinose H, Ikeda M, Iwata N, Ozaki N, Suzuki H, Higuchi M, Suhara T, Yuasa S, Miyakawa T. Alpha-CaMKII deficiency causes immature dentate gyrus, a novel candidate endophenotype of psychiatric disorders. *Mol Brain* 2008; **1**: 6 [PMID: 18803808 DOI: 10.1186/1756-6606-1-6]

50 **Shin R**, Kobayashi K, Hagihara H, Kogan JH, Miyake S, Tajinda K, Walton NM, Gross AK, Heusner CL, Chen Q, Tamura K, Miyakawa T, Matsumoto M. The immature dentate gyrus represents a shared phenotype of mouse models of epilepsy and psychiatric disease. *Bipolar Disord* 2013; **15**: 405-421 [PMID: 23560889 DOI: 10.1111/bdi.12064]

51 **Takahashi S**, Glatt SJ, Uchiyama M, Faraone SV, Tsuang MT. Meta-analysis of data from the Psychiatric Genomics Consortium and additional samples supports association of CACNA1C with risk for schizophrenia. *Schizophr Res* 2015; **168**: 429-433 [PMID: 26276307 DOI: 10.1016/j.schres.2015.07.033]

52 **Hamshere ML**, Walters JT, Smith R, Richards AL, Green E, Grozeva D, Jones I, Forty L, Jones L, Gordon-Smith K, Riley B, O'Neill FA, Kendler KS, Sklar P, Purcell S, Kranz J; Schizophrenia Psychiatric Genome-wide Association Study Consortium; Wellcome Trust Case Control Consortium+; Wellcome Trust Case Control Consortium 2, Morris D, Gill M, Holmans P, Craddock N, Corvin A, Owen MJ, O'Donovan MC. Genome-wide significant associations in schizophrenia to ITIH3/4, CACNA1C and SDCCAG8, and extensive replication of associations reported by the Schizophrenia PGC. *Mol Psychiatry* 2013; **18**: 708-712 [PMID: 22614287 DOI: 10.1038/mp.2012.67]

53 **Zheng F**, Zhang Y, Xie W, Li W, Jin C, Mi W, Wang F, Ma W, Ma C, Yang Y, Du B, Li K, Liu C, Wang L, Lu T, Zhang H, Wang Y, Lu L, Lv L, Zhang D, Yue W. Further evidence for genetic association of CACNA1C and schizophrenia: new risk loci in a Han Chinese population and a meta-analysis. *Schizophr Res* 2014; **152**: 105-110 [PMID: 24355530 DOI: 10.1016/j.schres.2013.12.003]

54 **He K**, An Z, Wang Q, Li T, Li Z, Chen J, Li W, Wang T, Ji J, Feng G, Lin H, Yi Q, Shi Y. CACNA1C, schizophrenia and major depressive disorder in the Han Chinese population. *Br J Psychiatry* 2014; **204**: 36-39 [PMID: 24262814 DOI: 10.1192/bjp.bp.113.126979]

55 **Green EK**, Grozeva D, Jones I, Jones L, Kirov G, Caesar S, Gordon-Smith K, Fraser C, Forty L, Russell E, Hamshere ML, Moskvina V, Nikolov I, Farmer A, McGuffin P; Wellcome Trust Case Control Consortium, Holmans PA, Owen MJ, O'Donovan MC, Craddock N. The bipolar disorder risk allele at CACNA1C also confers risk of recurrent major depression and of schizophrenia. *Mol Psychiatry* 2010; **15**: 1016-1022 [PMID: 19621016 DOI: 10.1038/mp.2009.49]

56 **Purcell SM**, Moran JL, Fromer M, Ruderfer D, Solovieff N, Roussos P, O'Dushlaine C, Chambert K, Bergen SE, Kähler A, Duncan L, Stahl E, Genovese G, Fernández E, Collins MO, Komiyama NH, Choudhary JS, Magnusson PK, Banks E, Shakir K, Garimella K, Fennell T, DePristo M, Grant SG, Haggarty SJ, Gabriel S, Scolnick EM, Lander ES, Hultman CM, Sullivan PF, McCarroll SA, Sklar P. A polygenic burden of rare disruptive mutations in schizophrenia. *Nature* 2014; **506**: 185-190 [PMID: 24463508 DOI: 10.1038/nature12975]

57 **Kabitzke PA**, Brunner D, He D, Fazio PA, Cox K, Sutphen J, Thiede L, Sabath E, Hanania T, Alexandrov V, Rasmusson R, Spooren W, Ghosh A, Feliciano P, Biemans B, Benedetti M, Clayton AL. Comprehensive analysis of two Shank3 and the Cacna1c mouse models of autism spectrum disorder. *Genes Brain Behav* 2018; **17**: 4-22 [PMID: 28753255 DOI: 10.1111/gbb.12405]

58 **Bader PL**, Faizi M, Kim LH, Owen SF, Tadross MR, Alfa RW, Bett GC, Tsien RW, Rasmusson RL, Shamloo M. Mouse model of Timothy syndrome recapitulates triad of autistic traits. *Proc Natl Acad Sci U S A* 2011; **108**: 15432-15437 [PMID: 21878566 DOI: 10.1073/pnas.1112667108]

59 **White JA**, McKinney BC, John MC, Powers PA, Kamp TJ, Murphy GG. Conditional forebrain deletion of the L-type calcium channel Ca V 1.2 disrupts remote spatial memories in mice. *Learn Mem* 2008; **15**: 1-5 [PMID: 18174367 DOI: 10.1101/lm.773208]

60 **Völkening B**, Schönig K, Kronenberg G, Bartsch D, Weber T. Deletion of psychiatric risk gene Cacna1c impairs hippocampal neurogenesis in cell-autonomous fashion. *Glia* 2017; **65**: 817-827 [PMID: 28230278 DOI: 10.1002/glia.23128]

61 **Temme SJ**, Bell RZ, Fisher GL, Murphy GG. Deletion of the Mouse Homolog of *CACNA1C* Disrupts Discrete Forms of Hippocampal-Dependent Memory and Neurogenesis within the Dentate Gyrus. *eNeuro* 2016; **3** [PMID: 27957527 DOI: 10.1523/ENEURO.0118-16.2016]

62 **D'Arcangelo G**, Miao GG, Chen SC, Soares HD, Morgan JI, Curran T. A protein related to extracellular matrix proteins deleted in the mouse mutant reeler. *Nature* 1995; **374**: 719-723 [PMID: 7715726 DOI: 10.1038/374719a0]

63 **Sekine K**, Kubo K, Nakajima K. How does Reelin control neuronal migration and layer formation in the developing mammalian neocortex? *Neurosci Res* 2014; **86**: 50-58 [PMID: 24969097 DOI: 10.1016/j.neures.2014.06.004]

64 **Kubo K**, Honda T, Tomita K, Sekine K, Ishii K, Uto A, Kobayashi K, Tabata H, Nakajima K. Ectopic Reelin induces neuronal aggregation with a normal birthdate-dependent "inside-out" alignment in the developing neocortex. *J Neurosci* 2010; **30**: 10953-10966 [PMID: 20720102 DOI: 10.1523/JNEUROSCI.0486-10.2010]

65 **Hirotsune S**, Takahara T, Sasaki N, Hirose K, Yoshiki A, Ohashi T, Kusakabe M, Murakami Y, Muramatsu M, Watanabe S. The reeler gene encodes a protein with an EGF-like motif expressed by pioneer neurons. *Nat Genet* 1995; **10**: 77-83 [PMID: 7647795 DOI: 10.1038/ng0595-77]

66 **Jossin Y**, Cooper JA. Reelin, Rap1 and N-cadherin orient the migration of multipolar neurons in the developing neocortex. *Nat Neurosci* 2011; **14**: 697-703 [PMID: 21516100 DOI: 10.1038/nn.2816]

67 **Howell BW**, Gertler FB, Cooper JA. Mouse disabled (mDab1): a Src binding protein implicated in neuronal development. *EMBO J* 1997; **16**: 121-132 [PMID: 9009273 DOI: 10.1093/emboj/16.1.121]

68 **Simó S**, Pujadas L, Segura MF, La Torre A, Del Río JA, Ureña JM, Comella JX, Soriano E. Reelin induces the detachment of postnatal subventricular zone cells and the expression of the Egr-1 through Erk1/2 activation. *Cereb Cortex* 2007; **17**: 294-303 [PMID: 16514107 DOI: 10.1093/cercor/bhj147]

69 **Impagnatiello F**, Guidotti AR, Pesold C, Dwivedi Y, Caruncho H, Pisu MG, Uzunov DP, Smalheiser NR, Davis JM, Pandey GN, Pappas GD, Tueting P, Sharma RP, Costa E. A decrease of reelin expression as a putative vulnerability factor in schizophrenia. *Proc Natl Acad Sci U S A* 1998; **95**: 15718-15723 [PMID: 9861036 DOI: 10.1073/pnas.95.26.15718]

70 **Fatemi SH**, Earle JA, McMenomy T. Reduction in Reelin immunoreactivity in hippocampus of subjects with schizophrenia, bipolar disorder and major depression. *Mol Psychiatry* 2000; **5**: 654-663, 571 [PMID: 11126396 DOI: 10.1038/sj.mp.4000783]

71 **Bai W**, Niu Y, Yu X, Yi J, Zhen Q, Kou C. Decreased serum levels of reelin in patients with schizophrenia. *Asian J Psychiatr* 2020; **49**: 101995 [PMID: 32143141 DOI: 10.1016/j.ajp.2020.101995]

72 **Guidotti A**, Auta J, Davis JM, Di-Giorgi-Gerevini V, Dwivedi Y, Grayson DR, Impagnatiello F, Pandey G, Pesold C, Sharma R, Uzunov D, Costa E. Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. *Arch Gen Psychiatry* 2000; **57**: 1061-1069 [PMID: 11074872 DOI: 10.1001/archpsyc.57.11.1061]

73 **Costa E**, Davis J, Grayson DR, Guidotti A, Pappas GD, Pesold C. Dendritic spine hypoplasticity and downregulation of reelin and GABAergic tone in schizophrenia vulnerability. *Neurobiol Dis* 2001; **8**: 723-742 [PMID: 11592844 DOI: 10.1006/nbdi.2001.0436]

74 **Li M**, Luo XJ, Xiao X, Shi L, Liu XY, Yin LD, Ma XY, Yang SY, Pu XF, Yu J, Diao HB, Shi H, Su B. Analysis of common genetic variants identifies RELN as a risk gene for schizophrenia in Chinese population. *World J Biol Psychiatry* 2013; **14**: 91-99 [PMID: 21745129 DOI: 10.3109/15622975.2011.587891]

75 **Kuang WJ**, Sun RF, Zhu YS, Li SB. A new single-nucleotide mutation (rs362719) of the reelin (RELN) gene associated with schizophrenia in female Chinese Han. *Genet Mol Res* 2011; **10**: 1650-1658 [PMID: 21863557 DOI: 10.4238/vol10-3gmr1343]

76 **Li W**, Song X, Zhang H, Yang Y, Jiang C, Xiao B, Li W, Yang G, Zhao J, Guo W, Lv L. Association study of RELN polymorphisms with schizophrenia in Han Chinese population. *Prog Neuropsychopharmacol Biol Psychiatry* 2011; **35**: 1505-1511 [PMID: 21549172 DOI: 10.1016/j.pnpbp.2011.04.007]

77 **Marzan S**, Aziz MA, Islam MS. Association Between REELIN Gene Polymorphisms (rs7341475 and rs262355) and Risk of Schizophrenia: an Updated Meta-analysis. *J Mol Neurosci* 2021; **71**: 675-690 [PMID: 32889693 DOI: 10.1007/s12031-020-01696-4]

78 **Costa E**, Davis J, Pesold C, Tueting P, Guidotti A. The heterozygote reeler mouse as a model for the development of a new generation of antipsychotics. *Curr Opin Pharmacol* 2002; **2**: 56-62 [PMID: 11786309 DOI: 10.1016/s1471-4892(01)00121-7]

79 **Rogers JT**, Rusiana I, Trotter J, Zhao L, Donaldson E, Pak DT, Babus LW, Peters M, Banko JL, Chavis P, Rebeck GW, Hoe HS, Weeber EJ. Reelin supplementation enhances cognitive ability, synaptic plasticity, and dendritic spine density. *Learn Mem* 2011; **18**: 558-564 [PMID: 21852430 DOI: 10.1101/lm.2153511]

80 **Glantz LA**, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. *Arch Gen Psychiatry* 2000; **57**: 65-73 [PMID: 10632234 DOI: 10.1001/archpsyc.57.1.65]

81 **Katsuyama Y**, Terashima T. Developmental anatomy of reeler mutant mouse. *Dev Growth Differ* 2009; **51**: 271-286 [PMID: 19379278 DOI: 10.1111/j.1440-169X.2009.01102.x]

82 **Tueting P**, Costa E, Dwivedi Y, Guidotti A, Impagnatiello F, Manev R, Pesold C. The phenotypic characteristics of heterozygous reeler mouse. *Neuroreport* 1999; **10**: 1329-1334 [PMID: 10363948 DOI: 10.1097/00001756-199904260-00032]

83 **Qiu S**, Korwek KM, Pratt-Davis AR, Peters M, Bergman MY, Weeber EJ. Cognitive disruption and altered hippocampus synaptic function in Reelin haploinsufficient mice. *Neurobiol Learn Mem* 2006; **85**: 228-242 [PMID: 16376115 DOI: 10.1016/j.nlm.2005.11.001]

84 **Teixeira CM**, Kron MM, Masachs N, Zhang H, Lagace DC, Martinez A, Reillo I, Duan X, Bosch C, Pujadas L, Brunso L, Song H, Eisch AJ, Borrell V, Howell BW, Parent JM, Soriano E. Cell-autonomous inactivation of the reelin pathway impairs adult neurogenesis in the hippocampus. *J Neurosci* 2012; **32**: 12051-12065 [PMID: 22933789 DOI: 10.1523/JNEUROSCI.1857-12.2012]

85 **Kim HM**, Qu T, Kriho V, Lacor P, Smalheiser N, Pappas GD, Guidotti A, Costa E, Sugaya K. Reelin function in neural stem cell biology. *Proc Natl Acad Sci U S A* 2002; **99**: 4020-4025 [PMID: 11891343 DOI: 10.1073/pnas.062698299]

86 **Zhao S**, Chai X, Frotscher M. Balance between neurogenesis and gliogenesis in the adult hippocampus: role for reelin. *Dev Neurosci* 2007; **29**: 84-90 [PMID: 17148951 DOI: 10.1159/000096213]

87 **Han J**, Kim HJ, Schafer ST, Paquola A, Clemenson GD, Toda T, Oh J, Pankonin AR, Lee BS, Johnston ST, Sarkar A, Denli AM, Gage FH. Functional Implications of miR-19 in the Migration of Newborn Neurons in the Adult Brain. *Neuron* 2016; **91**: 79-89 [PMID: 27387650 DOI: 10.1016/j.neuron.2016.05.034]

88 **MacDonald BT**, Tamai K, He X. Wnt/beta-catenin signaling: components, mechanisms, and diseases. *Dev Cell* 2009; **17**: 9-26 [PMID: 19619488 DOI: 10.1016/j.devcel.2009.06.016]

89 **Steinhart Z**, Angers S. Wnt signaling in development and tissue homeostasis. *Development* 2018; **145** [PMID: 29884654 DOI: 10.1242/dev.146589]

90 **Arredondo SB**, Valenzuela-Bezanilla D, Mardones MD, Varela-Nallar L. Role of Wnt Signaling in Adult Hippocampal Neurogenesis in Health and Disease. *Front Cell Dev Biol* 2020; **8**: 860 [PMID: 33042988 DOI: 10.3389/fcell.2020.00860]

91 **Niehrs C**. The complex world of WNT receptor signalling. *Nat Rev Mol Cell Biol* 2012; **13**: 767-779 [PMID: 23151663 DOI: 10.1038/nrm3470]

92 **Clevers H**, Nusse R. Wnt/β-catenin signaling and disease. *Cell* 2012; **149**: 1192-1205 [PMID: 22682243 DOI: 10.1016/j.cell.2012.05.012]

93 **Nusse R**, Clevers H. Wnt/β-Catenin Signaling, Disease, and Emerging Therapeutic Modalities. *Cell* 2017; **169**: 985-999 [PMID: 28575679 DOI: 10.1016/j.cell.2017.05.016]

94 **Zhang L**, Yang X, Yang S, Zhang J. The Wnt /β-catenin signaling pathway in the adult neurogenesis. *Eur J Neurosci* 2011; **33**: 1-8 [PMID: 21073552 DOI: 10.1111/j.1460-9568.2010.7483.x]

95 **Zylka MJ**, Rice FL, Anderson DJ. Topographically distinct epidermal nociceptive circuits revealed by axonal tracers targeted to Mrgprd. *Neuron* 2005; **45**: 17-25 [PMID: 15629699 DOI: 10.1016/j.neuron.2004.12.015]

96 **Qu Q**, Sun G, Murai K, Ye P, Li W, Asuelime G, Cheung YT, Shi Y. Wnt7a regulates multiple steps of neurogenesis. *Mol Cell Biol* 2013; **33**: 2551-2559 [PMID: 23629626 DOI: 10.1128/MCB.00325-13]

97 **Arredondo SB**, Guerrero FG, Herrera-Soto A, Jensen-Flores J, Bustamante DB, Oñate-Ponce A, Henny P, Varas-Godoy M, Inestrosa NC, Varela-Nallar L. Wnt5a promotes differentiation and development of adult-born neurons in the hippocampus by noncanonical Wnt signaling. *Stem Cells* 2020; **38**: 422-436 [PMID: 31721364 DOI: 10.1002/stem.3121]

98 **Nadri C**, Dean B, Scarr E, Agam G. GSK-3 parameters in postmortem frontal cortex and hippocampus of schizophrenic patients. *Schizophr Res* 2004; **71**: 377-382 [PMID: 15474909 DOI: 10.1016/j.schres.2004.02.020]

99 **Kozlovsky N**, Regenold WT, Levine J, Rapoport A, Belmaker RH, Agam G. GSK-3beta in cerebrospinal fluid of schizophrenia patients. *J Neural Transm (Vienna)* 2004; **111**: 1093-1098 [PMID: 15254796 DOI: 10.1007/s00702-003-0127-0]

100 **Lovestone S**, Killick R, Di Forti M, Murray R. Schizophrenia as a GSK-3 dysregulation disorder. *Trends Neurosci* 2007; **30**: 142-149 [PMID: 17324475 DOI: 10.1016/j.tins.2007.02.002]

101 **Freyberg Z**, Ferrando SJ, Javitch JA. Roles of the Akt/GSK-3 and Wnt signaling pathways in schizophrenia and antipsychotic drug action. *Am J Psychiatry* 2010; **167**: 388-396 [PMID: 19917593 DOI: 10.1176/appi.ajp.2009.08121873]

102 **Alimohamad H**, Rajakumar N, Seah YH, Rushlow W. Antipsychotics alter the protein expression levels of beta-catenin and GSK-3 in the rat medial prefrontal cortex and striatum. *Biol Psychiatry* 2005; **57**: 533-542 [PMID: 15737669 DOI: 10.1016/j.biopsych.2004.11.036]

103 **Ftouh S**, Akbar MT, Hirsch SR, de Belleroche JS. Down-regulation of Dickkopf 3, a regulator of the Wnt signalling pathway, in elderly schizophrenic subjects. *J Neurochem* 2005; **94**: 520-530 [PMID: 15998302 DOI: 10.1111/j.1471-4159.2005.03239.x]

104 **Hoseth EZ**, Krull F, Dieset I, Mørch RH, Hope S, Gardsjord ES, Steen NE, Melle I, Brattbakk HR, Steen VM, Aukrust P, Djurovic S, Andreassen OA, Ueland T. Exploring the Wnt signaling pathway in schizophrenia and bipolar disorder. *Transl Psychiatry* 2018; **8**: 55 [PMID: 29507296 DOI: 10.1038/s41398-018-0102-1]

105 **Lijam N**, Paylor R, McDonald MP, Crawley JN, Deng CX, Herrup K, Stevens KE, Maccaferri G, McBain CJ, Sussman DJ, Wynshaw-Boris A. Social interaction and sensorimotor gating abnormalities in mice lacking Dvl1. *Cell* 1997; **90**: 895-905 [PMID: 9298901 DOI: 10.1016/s0092-8674(00)80354-2]

106 **Gould TD**, O'Donnell KC, Picchini AM, Dow ER, Chen G, Manji HK. Generation and behavioral characterization of beta-catenin forebrain-specific conditional knock-out mice. *Behav Brain Res* 2008; **189**: 117-125 [PMID: 18299155 DOI: 10.1016/j.bbr.2007.12.028]

107 **Koshimizu H**, Fukui Y, Takao K, Ohira K, Tanda K, Nakanishi K, Toyama K, Oshima M, Taketo MM, Miyakawa T. Adenomatous polyposis coli heterozygous knockout mice display hypoactivity and age-dependent working memory deficits. *Front Behav Neurosci* 2011; **5**: 85 [PMID: 22347851 DOI: 10.3389/fnbeh.2011.00085]

108 **Stefansson H**, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, Werge T, Pietiläinen OP, Mors O, Mortensen PB, Sigurdsson E, Gustafsson O, Nyegaard M, Tuulio-Henriksson A, Ingason A, Hansen T, Suvisaari J, Lonnqvist J, Paunio T, Børglum AD, Hartmann A, Fink-Jensen A, Nordentoft M, Hougaard D, Norgaard-Pedersen B, Böttcher Y, Olesen J, Breuer R, Möller HJ, Giegling I, Rasmussen HB, Timm S, Mattheisen M, Bitter I, Réthelyi JM, Magnusdottir BB, Sigmundsson T, Olason P, Masson G, Gulcher JR, Haraldsson M, Fossdal R, Thorgeirsson TE, Thorsteinsdottir U, Ruggeri M, Tosato S, Franke B, Strengman E, Kiemeney LA; Genetic Risk and Outcome in Psychosis (GROUP), Melle I, Djurovic S, Abramova L, Kaleda V, Sanjuan J, de Frutos R, Bramon E, Vassos E, Fraser G, Ettinger U, Picchioni M, Walker N, Toulopoulou T, Need AC, Ge D, Yoon JL, Shianna KV, Freimer NB, Cantor RM, Murray R, Kong A, Golimbet V, Carracedo A, Arango C, Costas J, Jönsson EG, Terenius L, Agartz I, Petursson H, Nöthen MM, Rietschel M, Matthews PM, Muglia P, Peltonen L, St Clair D, Goldstein DB, Stefansson K, Collier DA. Common variants conferring risk of schizophrenia. *Nature* 2009; **460**: 744-747 [PMID: 19571808 DOI: 10.1038/nature08186]

109 **Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium.**. Genome-wide association study identifies five new schizophrenia loci. *Nat Genet* 2011; **43**: 969-976 [PMID: 21926974 DOI: 10.1038/ng.940]

110 **De Rubeis S**, He X, Goldberg AP, Poultney CS, Samocha K, Cicek AE, Kou Y, Liu L, Fromer M, Walker S, Singh T, Klei L, Kosmicki J, Shih-Chen F, Aleksic B, Biscaldi M, Bolton PF, Brownfeld JM, Cai J, Campbell NG, Carracedo A, Chahrour MH, Chiocchetti AG, Coon H, Crawford EL, Curran SR, Dawson G, Duketis E, Fernandez BA, Gallagher L, Geller E, Guter SJ, Hill RS, Ionita-Laza J, Jimenz Gonzalez P, Kilpinen H, Klauck SM, Kolevzon A, Lee I, Lei I, Lei J, Lehtimäki T, Lin CF, Ma'ayan A, Marshall CR, McInnes AL, Neale B, Owen MJ, Ozaki N, Parellada M, Parr JR, Purcell S, Puura K, Rajagopalan D, Rehnström K, Reichenberg A, Sabo A, Sachse M, Sanders SJ, Schafer C, Schulte-Rüther M, Skuse D, Stevens C, Szatmari P, Tammimies K, Valladares O, Voran A, Li-San W, Weiss LA, Willsey AJ, Yu TW, Yuen RK; DDD Study; Homozygosity Mapping Collaborative for Autism; UK10K Consortium, Cook EH, Freitag CM, Gill M, Hultman CM, Lehner T, Palotie A, Schellenberg GD, Sklar P, State MW, Sutcliffe JS, Walsh CA, Scherer SW, Zwick ME, Barett JC, Cutler DJ, Roeder K, Devlin B, Daly MJ, Buxbaum JD. Synaptic, transcriptional and chromatin genes disrupted in autism. *Nature* 2014; **515**: 209-215 [PMID: 25363760 DOI: 10.1038/nature13772]

111 **Schizophrenia Working Group of the Psychiatric Genomics Consortium.**. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014; **511**: 421-427 [PMID: 25056061 DOI: 10.1038/nature13595]

112 **Braun K**, Häberle BM, Wittmann MT, Lie DC. Enriched environment ameliorates adult hippocampal neurogenesis deficits in Tcf4 haploinsufficient mice. *BMC Neurosci* 2020; **21**: 50 [PMID: 33228529 DOI: 10.1186/s12868-020-00602-3]

113 **Kopan R**, Ilagan MX. The canonical Notch signaling pathway: unfolding the activation mechanism. *Cell* 2009; **137**: 216-233 [PMID: 19379690 DOI: 10.1016/j.cell.2009.03.045]

114 **Hatakeyama J**, Bessho Y, Katoh K, Ookawara S, Fujioka M, Guillemot F, Kageyama R. Hes genes regulate size, shape and histogenesis of the nervous system by control of the timing of neural stem cell differentiation. *Development* 2004; **131**: 5539-5550 [PMID: 15496443 DOI: 10.1242/dev.01436]

115 **Matsuno K**. Notch signaling. *Dev Growth Differ* 2020; **62**: 3 [PMID: 31995851 DOI: 10.1111/dgd.12642]

116 **Wei J**, Hemmings GP. The NOTCH4 Locus is associated with susceptibility to schizophrenia. *Nat Genet* 2000; **25**: 376-377 [PMID: 10932176 DOI: 10.1038/78044]

117 **Allen NC**, Bagade S, McQueen MB, Ioannidis JP, Kavvoura FK, Khoury MJ, Tanzi RE, Bertram L. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. *Nat Genet* 2008; **40**: 827-834 [PMID: 18583979 DOI: 10.1038/ng.171]

118 **Shayevitz C**, Cohen OS, Faraone SV, Glatt SJ. A re-review of the association between the NOTCH4 Locus and schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 2012; **159B**: 477-483 [PMID: 22488909 DOI: 10.1002/ajmg.b.32050]

119 **Hoseth EZ**, Krull F, Dieset I, Mørch RH, Hope S, Gardsjord ES, Steen NE, Melle I, Brattbakk HR, Steen VM, Aukrust P, Djurovic S, Andreassen OA, Ueland T. Attenuated Notch signaling in schizophrenia and bipolar disorder. *Sci Rep* 2018; **8**: 5349 [PMID: 29593239 DOI: 10.1038/s41598-018-23703-w]

120 **Xue F**, Chen YC, Zhou CH, Wang Y, Cai M, Yan WJ, Wu R, Wang HN, Peng ZW. Risperidone ameliorates cognitive deficits, promotes hippocampal proliferation, and enhances Notch signaling in a murine model of schizophrenia. *Pharmacol Biochem Behav* 2017; **163**: 101-109 [PMID: 29037878 DOI: 10.1016/j.pbb.2017.09.010]

121 **Marathe S**, Alberi L. Notch in memories: Points to remember. *Hippocampus* 2015; **25**: 1481-1488 [PMID: 25656274 DOI: 10.1002/hipo.22426]

122 **Costa RM**, Honjo T, Silva AJ. Learning and memory deficits in Notch mutant mice. *Curr Biol* 2003; **13**: 1348-1354 [PMID: 12906797 DOI: 10.1016/s0960-9822(03)00492-5]

123 **Lugert S**, Vogt M, Tchorz JS, Müller M, Giachino C, Taylor V. Homeostatic neurogenesis in the adult hippocampus does not involve amplification of Ascl1(high) intermediate progenitors. *Nat Commun* 2012; **3**: 670 [PMID: 22334073 DOI: 10.1038/ncomms1670]

124 **Breunig JJ**, Silbereis J, Vaccarino FM, Sestan N, Rakic P. Notch regulates cell fate and dendrite morphology of newborn neurons in the postnatal dentate gyrus. *Proc Natl Acad Sci U S A* 2007; **104**: 20558-20563 [PMID: 18077357 DOI: 10.1073/pnas.0710156104]

125 **Engler A**, Zhang R, Taylor V. Notch and Neurogenesis. *Adv Exp Med Biol* 2018; **1066**: 223-234 [PMID: 30030829 DOI: 10.1007/978-3-319-89512-3\_11]

126 **Mason HA**, Rakowiecki SM, Gridley T, Fishell G. Loss of notch activity in the developing central nervous system leads to increased cell death. *Dev Neurosci* 2006; **28**: 49-57 [PMID: 16508303 DOI: 10.1159/000090752]

127 **Artavanis-Tsakonas S**, Rand MD, Lake RJ. Notch signaling: cell fate control and signal integration in development. *Science* 1999; **284**: 770-776 [PMID: 10221902 DOI: 10.1126/science.284.5415.770]

128 **Ables JL**, Decarolis NA, Johnson MA, Rivera PD, Gao Z, Cooper DC, Radtke F, Hsieh J, Eisch AJ. Notch1 is required for maintenance of the reservoir of adult hippocampal stem cells. *J Neurosci* 2010; **30**: 10484-10492 [PMID: 20685991 DOI: 10.1523/JNEUROSCI.4721-09.2010]

129 **Imayoshi I**, Sakamoto M, Yamaguchi M, Mori K, Kageyama R. Essential roles of Notch signaling in maintenance of neural stem cells in developing and adult brains. *J Neurosci* 2010; **30**: 3489-3498 [PMID: 20203209 DOI: 10.1523/JNEUROSCI.4987-09.2010]

130 **Chubb JE**, Bradshaw NJ, Soares DC, Porteous DJ, Millar JK. The DISC locus in psychiatric illness. *Mol Psychiatry* 2008; **13**: 36-64 [PMID: 17912248 DOI: 10.1038/sj.mp.4002106]

131 **Facal F**, Costas J. Evidence of association of the DISC1 interactome gene set with schizophrenia from GWAS. *Prog Neuropsychopharmacol Biol Psychiatry* 2019; **95**: 109729 [PMID: 31398428 DOI: 10.1016/j.pnpbp.2019.109729]

132 **Wang HY**, Liu Y, Yan JW, Hu XL, Zhu DM, Xu XT, Li XS. Gene polymorphisms of DISC1 is associated with schizophrenia: Evidence from a meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; **81**: 64-73 [PMID: 29031911 DOI: 10.1016/j.pnpbp.2017.10.008]

133 **Mahar I**, Tan S, Davoli MA, Dominguez-Lopez S, Qiang C, Rachalski A, Turecki G, Mechawar N. Subchronic peripheral neuregulin-1 increases ventral hippocampal neurogenesis and induces antidepressant-like effects. *PLoS One* 2011; **6**: e26610 [PMID: 22028923 DOI: 10.1371/journal.pone.0026610]

134 **Chenn A**, Walsh CA. Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. *Science* 2002; **297**: 365-369 [PMID: 12130776 DOI: 10.1126/science.1074192]

135 **Qu Q**, Sun G, Li W, Yang S, Ye P, Zhao C, Yu RT, Gage FH, Evans RM, Shi Y. Orphan nuclear receptor TLX activates Wnt/beta-catenin signalling to stimulate neural stem cell proliferation and self-renewal. *Nat Cell Biol* 2010; **12**: 31-40; sup pp 1-9 [PMID: 20010817 DOI: 10.1038/ncb2001]

**Footnotes**

**Conflict-of-interest statement:** Authors declare no conflict of interests for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** April 6, 2021

**First decision:** June 5, 2021

**Article in press:**

**Specialty type:** Neurosciences

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C, C

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Durán Alonso MB, Spain; Gaitanou M, Greece; Khan MM, India; Tanabe S, Japan **S-Editor:** Chang KL **L-Editor:** A **P-Editor:**

**Table 1 Studies of schizophrenia risk genes and related signaling pathways in adult neurogenesis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Genes or signaling pathways** | **Effects on adult neurogenesis** | **Behavior deviations** | **Ref.** | **Post-mortem or genetic studies** |
| *DISC1* | Suppression of *Disc1* expression results in accelerated neuronal integration, mispositioning of new DG granule cells, accelerated dendritic development, premature cell cycle exit and differentiation | Hyper-locomotion, depressive-like behavior, cognitive deficits (object place recognition test, Morris water maze test) | [16,18,20,23] | [130-132] |
| *NRG1* | NRG1 treatment induces increased ventral DG cell proliferation and neurogenesis.  NRG1 regulates both excitatory and inhibitory synaptic transmission in the adult brain and abnormal neurotransmission and/or synaptic plasticity have been observed in the schizophrenic brain | *Nrg1* hypomorphs showed hyperactivity in a number of tests, including the novel open-field test and the alternating-Y maze, impaired social behavior and increased aggression | [36,37,133] | [30-32] |
| *SNAP-25* | *Snap-25* mutant mice display histologically and electrophysiologically immature DG neurons. Inactivation of *Snap-25* in adult neural stem cells results in enhancement of proximal dendritic branching of new-born neurons in the DG and robust efferent mossy fiber output to the CA3 region | Working memory deficits, impaired contextual fear-discrimination learning | [47,48] | [43,44] |
| *CACNA1C* | *Cacna1c* deletion results in decreased progenitor proliferation and reduced survival of new-born neurons | *Cacna1c* heterozygous mice display reduced locomotion, fear learning, and impaired spatial memory | [57-61] | [53-56] |
| *Reelin* | Adult Reeler mutants show decreased proliferation, aberrant migration and dendritic development of new-born neurons | Heterozygous Reeler mice show a significant reduction in contextual fear conditioned learning and an age-dependent decrease in prepulse inhibition of startle | [82-84,86] | [69-71,74-77] |
| *Wnt signaling* | Overexpression of stabilized β-catenin leads to enlarged brain and expanded neural precursor population. *Wnt7a* knockout mice show fewer neural stem cells. *Wnt5a* knockdown decreases the number of immature neurons. *Tcf4* heterozygotes show reduced size of neural stem cell pool and impaired maturation and survival of adult-born neurons | *Dvl* knockout mice display reduced social interaction and deficits in prepulse inhibition of acoustic and tactile startle. Forebrain-specific *β-catenin* knockout mice show a depression-like phenotype. *Apc* heterozygote shows hypoactivity and a severe performance deficit in working memory | [90,96,106,107,134,135] | [98-100,112] |
| *Notch signaling* | Inactivation of *Notch1* blocks self-renewal of neural stem cells, reduces mitotic progenitors and neurogenesis. Adult deletion of *RBPj* leads to depletion and exhaustion of neural stem cells | *Notch1* heterozygote displays deficits in spatial learning and memory | [100,121,122,128,129] | [116-118] |

APC: Adenomatous polyposis coli; CA3: Cornu ammonis 3; CACNA1C: Calcium voltage-gated channel subunit alpha1 c; DG: Dentate gyrus; DISC1: Disrupted in schizophrenia 1; Dvl: Dishevelled; NRG1: Neuregulin-1; SNAP-25: Synaptosomal-associated protein, 25kDa; Tcf4: T-cell factor 4.