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The *DISC1* R264Q variant increases affinity for the dopamine D2 receptor and increases GSK3 activity

Ping Su¹, Hailong Zhang¹, Albert H. C. Wong^{1,2,3} and Fang Liu^{1,2,3,4*} 

Abstract

The *Disrupted in schizophrenia 1 (DISC1)* gene encodes a scaffolding protein that is involved in many neural functions such as neurogenesis, neural differentiation, embryonic neuron migration and neurotransmitter signalling. *DISC1* was originally implicated in schizophrenia in a single family with a drastic mutation, a chromosomal translocation severing the mid-point of the gene (aa 598). Some common *DISC1* variants have also been associated with schizophrenia in the general population, but those located far from the chromosomal translocation breakpoint likely have a different functional impact. We previously reported that *DISC1* forms a protein complex with dopamine D2 receptor (D2R), the main target for antipsychotic medications. The D2R-*DISC1* complex is elevated in brain tissue from schizophrenia patients and facilitates glycogen synthase kinase (GSK)-3 signaling. The *DISC1* R264Q variant is located within the region that binds the D2R, and we found that this polymorphism increases the affinity of *DISC1* for the D2R and promotes GSK3 activity. Our results suggest a possible mechanism by which this common polymorphism could affect aspects of brain function that are relevant to psychosis and schizophrenia. This provides additional insight into molecular mechanisms underlying schizophrenia that could be exploited in the development of novel pharmacological treatments.

Keywords: Dopamine D2 receptor (D2R), Disrupted in schizophrenia 1 (*DISC1*), Glycogen synthase kinase (GSK) -3, Schizophrenia

Introduction

Disrupted in schizophrenia 1 (DISC1) is an important susceptibility gene for many psychiatric disorders because it codes for a powerful regulatory protein with a large interacting network that regulates fundamental brain functions [1]. The *DISC1* gene was originally discovered in a single large family carrying a chromosomal translocation that severs *DISC1* roughly in half [2, 3]. Although common *DISC1* variants are not the strongest associations with schizophrenia in genome-wide

association study (GWAS), the drastic phenotype in the *DISC1* translocation family and in *Disc1* mutant animal models provides a useful entry point to understand the pathobiology of psychiatric symptoms and potential disease mechanisms [4, 5].

Our group previously discovered that the *DISC1* protein forms a protein-protein complex with the dopamine D2 receptor (D2R), the main target of all existing antipsychotic medications [6]. We found that the *DISC1*-D2R complex is elevated in post-mortem brain samples from patients with schizophrenia, and in *Disc1*-L100P mutant mice, an animal model for schizophrenia. The complex facilitates glycogen synthase kinase (GSK)-3 signaling and inhibits agonist-induced D2R internalization. Disrupting the

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complex with an interfering peptide can reverse abnormal behaviours relevant to schizophrenia in *Disc1*-L100P mice. Thus, we hypothesized that the common *DISC1* gene variant R264Q *DISC1*, located within the binding region with the D2R could alter the strength of the *DISC1*-D2R interaction and have functional consequences related to the pathophysiology of schizophrenia. The *DISC1* R264Q variant has previously been associated with schizophrenia [7], and has been reported to impair GSK-3 signaling and neurodevelopment [8].

The D2 receptor is one of five dopamine receptors that are all G-protein coupled transmembrane monomeric receptors, each encoded by a single discrete gene [9]. The D2, D3 and D4 receptors couple to Gi/o and thereby inhibit adenylyl cyclase, while the D1 and D5 receptors have the opposite functional effect by coupling with Gs to activate adenylyl cyclase [10]. All established antipsychotic medications target the dopamine D2 receptor and thus it is one of the most robust modulators of psychotic symptoms [11]. GSK3 is a hub protein on which numerous signal paths converge, including Wnt [12], insulin [13], Trk [14], and several subtypes of dopamine and serotonin receptors [15]. Many antipsychotics inhibit GSK3 through increased serine phosphorylation [16, 17], and so does lithium [17–19], which is the oldest and still most effective prophylactic medication for bipolar disorder [20, 21]. Thus, we sought to discover additional mechanistic links between *DISC1* and these other known regulators of psychosis by investigating the functional impact of a schizophrenia-associated *DISC1* variant located within the region that binds the D2 receptor.

Materials and methods

Drugs

Quinpirole was purchased from Sigma-Aldrich, and was freshly prepared every time before treatment by dissolving into distilled water with a concentration of 10 mM.

GST fusion protein constructs and DNA subcloning

GST-fusion proteins encoding N-terminus of *DISC1* were amplified by PCR from full-length human or mouse cDNA clones. All constructs were sequenced to confirm the absence of spurious PCR-generated nucleotide errors. GST-fusion proteins were prepared from bacterial lysates with Glutathione Sepharose 4B beads as instructed by the manufacturer (Amersham) as previously described. To construct GST-fusion proteins encoding *DISC1*_{NT}, cDNA fragments were amplified by PCR with specific primers, and subcloned into pGEX-4 T-3 vector. All constructs were re-sequenced to confirm

appropriate splice fusion and the absence of spurious PCR generated nucleotide errors.

Plasmid mutation

Mutants of GST-*DISC1*_{NT} and Flag-*DISC1* were created with the QuickChange site-directed mutagenesis kit (Stratagene). All mutants were confirmed by DNA sequencing.

Cell culture and DNA transfection

HEK293T cells were maintained at 37 °C in Dulbecco's Modified Eagle Medium (DMEM) (Gibco) supplemented with 10% fetal bovine serum (Gibco). Cells were grown to 90% confluency before being transiently transfected with DNA constructs using Xtreme gene 9 transfection reagent (Roche), following the manufacturer's instruction. Cells were used for various experiments after 48 h of transfection.

Co-immunoprecipitation, protein affinity purification and western blot

Co-immunoprecipitation and western blot assays were conducted as previously described [6, 22, 23]. For co-immunoprecipitation experiments, 500–700 µg solubilized protein extracted from HEK293T cells (ATCC) was incubated in the presence of primary anti-HA antibody (Roche) or IgG (negative control) (1–2 µg) together with protein A/G plus agarose (Santa Cruz Biotechnology) at 4 °C for 12 h. Pellets were washed, boiled for 5 min in SDS sample buffer (Bio-Rad) and subjected to SDS-PAGE. 50–100 µg of protein extracted from HEK293T cells was used as a control in each experiment. For affinity purification experiments, 500 µg of protein extracted from mouse striatum was incubated with glutathione-sepharose beads (Amersham) bound to the indicated GST-fusion proteins (50–150 µg) at 4 °C for 12 h. Beads were washed, boiled for 5 min in SDS sample buffer and subjected to SDS-PAGE. After transfer of proteins onto nitrocellulose, membranes were western blotted with the primary antibodies: anti-HA (1:1000, rat, Roche), anti-Flag (1:2000, mouse, Sigma-Aldrich), anti-D2R (1:200, mouse, Santa Cruz Biotechnology). The intensity of protein level was quantified by densitometry (software: ImageLab, Bio-Rad). For detection of phosphorylation of GSK3, the antibodies used include: anti-pGSK-3α/β (S21/S9) (Cell Signaling Technology, rabbit), anti-GSK-3α (Cell Signaling Technology, rabbit), anti-GSK-3β (Cell Signaling Technology, rabbit).

Surface Plasmon resonance (SPR) spectroscopy

All SPR experiments were performed on a SR7500DC (Reichert, USA) at 25 °C in the running buffer TBS-

T, which contains 150 mM NaCl, 1 mM CaCl₂, 1 mM MgCl₂, 10 mM Tris, pH 7.4, and 0.005% Surfactant P-20. TAT-D2pep peptide (10 μM) were covalently coupled via amine groups onto the carboxymethylated dextran surface sensor chips (Reichert, USA) using 26 EDC/Sulfo-NHS crosslinking strategy. During coupling, TAT-D2pep peptide was injected in 10 mM sodium formate (pH 5.0) to reach 600 Response Units (RU). A flow rate 50 μl/min was set to perform the binding and kinetic analysis in case of the effect of mass transportation limitation. Binding affinity was measured using a range of concentrations from 0 μM to 4.0 μM for GST-DISC1_{NT}, respectively. For mouse GST-*Disc1*-L100P_{NT} and GST-DISC1_{NT}, binding affinity was measured using a range of concentrations from 25 nM to 400 nM for GST-*Disc1*-L100P_{NT}, 100 nM to 1.6 μM for GST-DISC1_{NT}, respectively. The duration of the association and dissociation phases was set to 180 s, 300 s, respectively. Regeneration of the sensor chip was achieved by adding 10 mM NaOH, 1 M NaCl. Flow rate was set to 50 μl/min to reduce the effect of mass transport limitations. GST alone was injected as a negative control in the same condition. Data were assembled and analyzed using Scrubber and Clamp XP software packages (University of Utah). All SPR were tested for mass transfer to make sure that curves observed were not limited by mass transfer (data not shown). Equilibrium analysis was conducted for GST-DISC1_{NT} based on the binding affinity of the interactions.

Statistical analysis

Depending on the experiment, data were analyzed by t-test, one-way analysis of variance (ANOVA) followed by Tukey's post hoc test or two-way ANOVA followed by Bonferroni's post hoc test (Prism 6, GraphPad Software). All data were expressed as mean ± standard error of mean (SEM). The highest significance level of $p < 0.05$ was used for all analyses.

Results

DISC1 variant facilitates DISC1-D2R complex formation

Because some common *DISC1* variants have been associated with schizophrenia [24], we investigated possible functional effects on DISC1-D2R complex formation and GSK3 α/β Ser21/9 phosphorylation. We focused on the R264Q *DISC1* variant because the mutation is within the DISC1 region that interacts with D2R [6]. As shown in Fig. 1a, we found that the human R264Q *DISC1* variant, but not the control A83V variant located outside the binding domain, is associated with significantly lower DISC1 protein levels compared to wildtype (WT) DISC1, when

transfected into HEK-293 T cells. However, DISC1-D2R complex levels are significantly increased in DISC1_{R264Q} (Fig. 1a-c), but not DISC1_{A83V} (Fig. 1d-f), cells as shown by co-immunoprecipitation, despite the decreased expression of DISC1_{R264Q} protein. The levels of directly-immunoprecipitated D2R were not significantly different between the two DISC1 variants.

DISC1 variant has a higher affinity for D2R

To investigate whether the R264Q mutation can alter the binding affinity between DISC1 and D2R, we measured the affinity between D2pep[K₂₁₁-T₂₂₅] and GST-DISC1-NT_{R264Q} or GST-DISC1-NT using surface plasmon resonance (SPR). D2 [K₂₁₁-T₂₂₅] is the region interacting with DISC1 as previously reported. Our data show that GST-DISC1-NT has a K_D value of 653 ± 6 nM (Fig. 2a), while GST-DISC1_{R264Q} has a much higher affinity with a K_D value of 243 ± 3 nM (Fig. 2b). Thus, the R264Q *DISC1* variant has a higher binding affinity for D2R, which could account for the greater DISC1-D2R complex levels.

The DISC1_{R264Q} variant decreases GSK3 α/β Ser-21/9 phosphorylation

We found that the basal level of GSK3 α/β Ser21/9 phosphorylation in R264Q *DISC1* cells is significantly lower than that in cells expressing WT DISC1. Although quinpirole stimulation still reduces GSK3 α/β Ser21/9 phosphorylation in R264Q *DISC1* cells, the percent reduction is smaller than that in wild-type DISC1 expressing cells (Fig. 3a-c). Thus, either activation of D2R or the R264Q *DISC1* mutation can both enhance DISC1-D2R complex formation and decreases GSK3 α/β Ser21/9 phosphorylation.

The mouse *DISC1*-L100P mutation facilitates DISC1-D2R complex formation

Many different mutant *Disc1* mouse models have shown the important role of this gene in neurodevelopment, neurotransmitter signaling and behaviours relevant to neuropsychiatric disease [25–28]. One of the earliest such models was generated through ENU mutagenesis, and was a point mutation resulting in a single amino-acid substitution, L100P [26]. This mouse line displayed a variety of schizophrenia-related abnormalities including hyperlocomotion, impaired pre-pulse inhibition/latent inhibition, deficient neurogenesis/neuron migration, enhanced dopamine function and dendritic spine deficits rescued by genetic inactivation of GSK3α [26, 29, 30]. Furthermore, in our previous study, we have found that the level of D2R-DISC1 complex is elevated and the

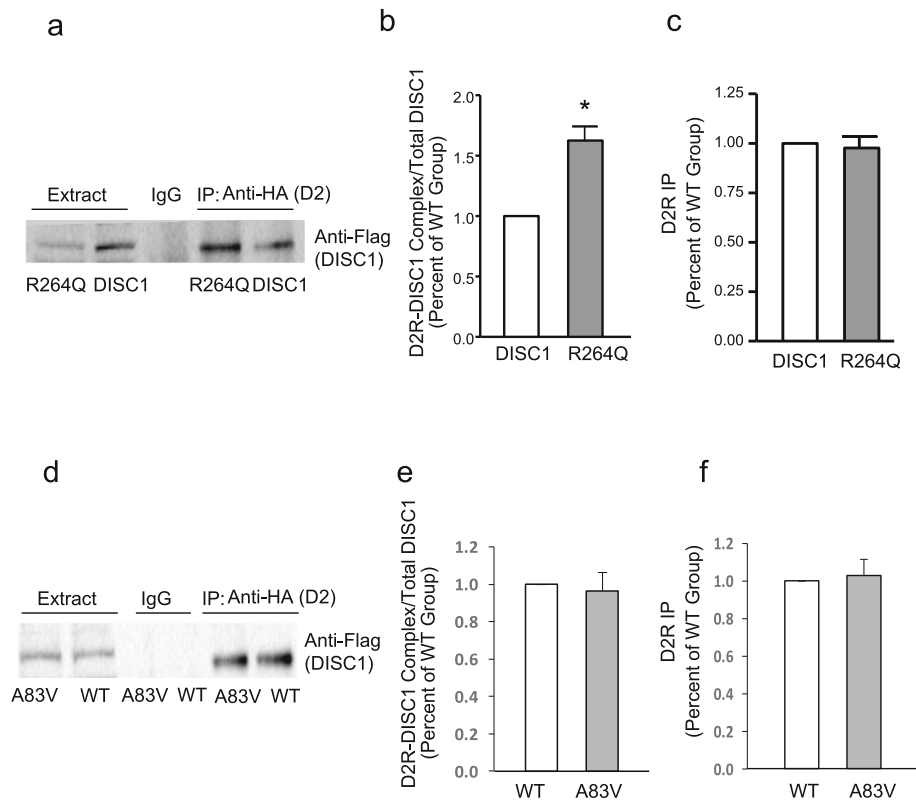


Fig. 1 The R264Q *DISC1* variant facilitates the *DISC1*-D2R complex formation. **a**. *DISC1*-D2R complex formation is significantly increased in HEK-293 T cells expressing HA-D2R/Flag-*DISC1*_{R264Q} (R264Q) compared to HEK-293 T cells expressing HA-D2R/Flag-*DISC1* (*DISC1*). Cell lysate was subjected to immunoprecipitation with anti-HA or IgG and immunoblotted with anti-Flag or anti-HA antibodies. **b-c**. Densitometric analysis of precipitated *DISC1* or D2R. The intensity of *DISC1* or D2R was quantified by densitometry (software: ImageLab, Bio-Rad). * $p < 0.05$. **d**. *DISC1*-D2R complex formation does not change in HEK-293 T cells expressing HA-D2R/Flag-*DISC1*_{A83V} (A83V) compared to HEK-293 T cells expressing HA-D2R/Flag-*DISC1* (WT). Cell lysate was subjected to immunoprecipitation with anti-HA or IgG and immunoblotted with anti-Flag or anti-HA antibodies. **e-f**. Densitometric analysis of precipitated *DISC1* or D2R. The intensity of *DISC1* or D2R was quantified by densitometry (software: ImageLab, Bio-Rad). Data was shown as mean \pm SEM, and was analyzed by t-test. $n = 3$

GSK3 α/β Ser21/9 phosphorylation is decreased in the *DISC1*-L100P mice [6].

The *Disc1*-L100P mutation is located within the *Disc1* interacting site with the D2R, we further tested the *Disc1*-L100P mutation could affect the binding affinity between the two proteins. We confirmed this hypothesis with two different methods: affinity pull-down assay and surface plasmon resonance (SPR). We found that GST-*Disc1*-L100P_{NT} is able to “pull down” much higher amounts of D2R compared to GST-*DISC1*_{NT} (Fig. 4a-b). SPR analysis of affinity between TAT-D2pep[K₂₁₁-T₂₂₅] peptides and GST-*Disc1*-L100P_{NT} or GST-*DISC1*_{NT} allowed estimation of association and dissociation rates corresponding to a K_D value of 760 ± 20 nM for GST-*DISC1*_{NT}, while GST-*Disc1*-L100P_{NT} had a 7.6-fold higher affinity with a K_D value of 100 ± 2 nM (Fig. 4c-d). Thus, similar to the R264Q *DISC1* variant, the *Disc1*-L100P mutation has a higher binding affinity for D2R, which

could account for the greater *DISC1*-D2R complex levels observed in our previous study.

Discussion

In summary, we found that the *DISC1* R264Q variant has higher binding affinity for the dopamine D2 receptor, and results in higher levels of the *DISC1*-D2R protein complex in conjunction with decreased GSK3 α/β Ser21/9 phosphorylation. These results suggest possible molecular mechanisms contributing to schizophrenia because the *DISC1*-D2R complex is higher in patients with schizophrenia [6] and the *DISC1* R264Q variant has been associated with schizophrenia [7]. Similar results were seen with the *Disc1*-L100P mutation in the mouse, which has a similar effect to the *DISC1* R264Q variant. These data converge with the accumulating evidence for the important role of *DISC1* in the pathophysiology of schizophrenia and other major psychiatric disorders.

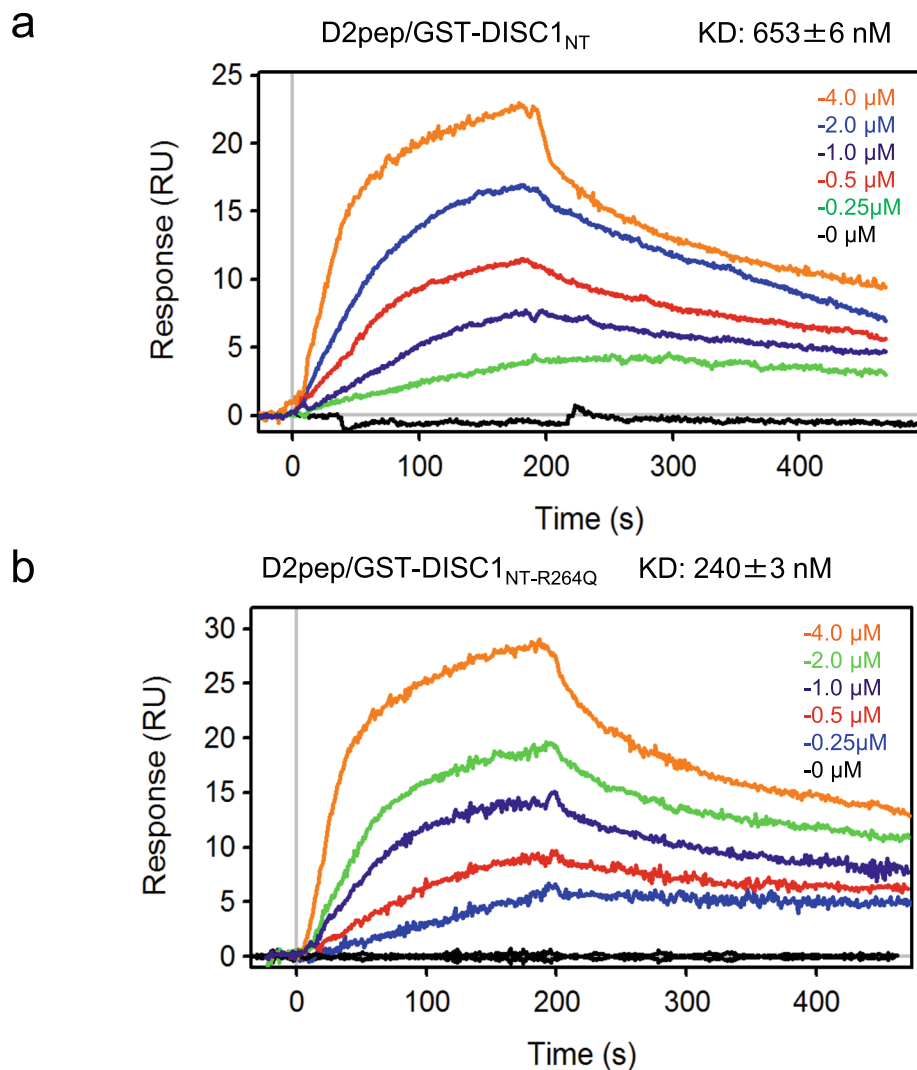


Fig. 2 The R264Q *DISC1* variant enhances the binding affinity between *DISC1* and D2R. Surface Plasmon Resonance (SPR) analysis of the concentration-dependent binding of GST-DISC1_{NT} (a) or GST-DISC1_{NT-R264Q} (b) with immobilized TAT-D2pep[K₂₁₁-T₂₂₅] peptide. Binding affinity was measured using a range of concentrations from 0 nM to 4000 nM. The duration of the association and dissociation phases was set to 180 s, 300 s, respectively. Flow rate was set to 50 μ L/min to reduce the effect of mass transport limitations. Regeneration of the sensor chip was achieved by adding 10 mM NaOH, 1 M NaCl. Equilibrium analysis was conducted for GST-DISC1_{NT} based on the binding affinity of the interactions

The *DISC1* R264Q variant has previously been shown to disrupt Wnt/GSK3 β signaling and brain development [8], through decreased *DISC1* R264Q binding to GSK3 β . That group also found that *DISC1* R264Q increases GSK3 β Y216 phosphorylation, leading to higher GSK3 β activation and reducing Wnt signaling, all in human-derived lymphoblast cell lines. They did not observe changes in GSK3 β Serine 9 phosphorylation. In contrast, our experiments used transfected HEK293T cells and we found phosphorylation of Serine 21 and 9 to be reduced in cells transfected with *DISC1* R264Q compared with wild type *DISC1*. An important difference between our

experimental designs was our use of the dopamine agonist quinpirole to activate the D2 receptor. However, there were still differences in our data at baseline, without agonist stimulation, that could be due to differences in the cell model system used.

Another possible factor that could cause these divergent results is that Singh et al. studied lymphoblasts from patients homozygous for one of the two *DISC1* R264Q alleles [8]. These cell lines were obtained from a NIMH sample of bipolar disorder and had been transformed using Epstein-Barr virus. Thus, there are numerous possible biological differences between our transfected HEK293T cells and the

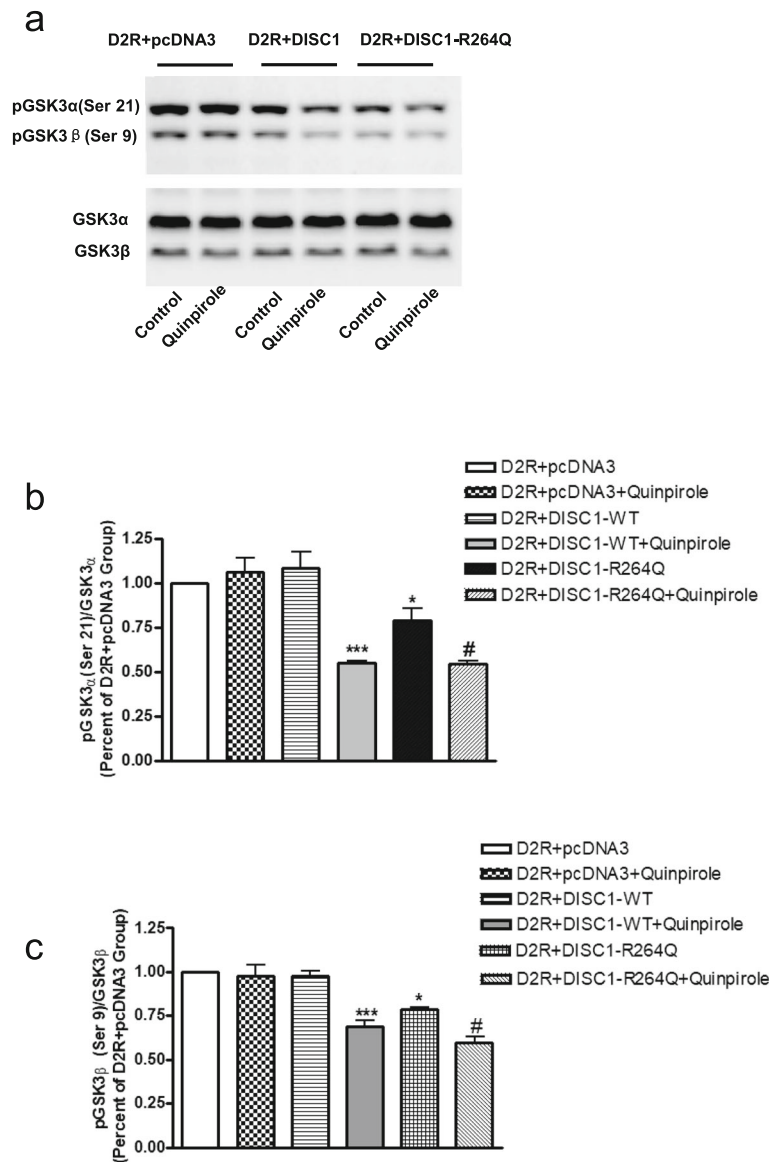


Fig. 3 The DISC1_{R264Q} variant decreases GSK3 α/β Ser21/9 phosphorylation. **a.** Activation of D2R reduces GSK-3α/β (Ser21/9) phosphorylation in HEK-293 T cells expressing D2R and DISC1, D2R and DISC1-R264Q, but not in HEK-293 cells expressing D2R with pcDNA3, the mammalian expression vector in which DISC1 is sub-cloned. Western blot analysis of phosphorylated GSK-3α/β levels in extract prepared from HEK 293 T cells transfected with D2R with pcDNA3 or D2R with DISC1 or D2R and DISC1-R264Q in the presence or absence of quinpirole (10 μM, 30 min). GSK-3α/β was used as a loading control. **b-c.** Densitometric analysis of phosphorylated GSK-3α/β (Ser21/9). The intensity of phospho-GSK-3α/β (Ser21/9) was quantified by densitometry (software: ImageLab, Bio-Rad). Data were analyzed by one-way ANOVA followed by Tukey's post hoc test. (**p* < 0.05, ****p* < 0.001, compared to D2R + DISC1-WT group, #*p* < 0.05 as compared to D2R + DISC1-R264Q, *n* = 6). Data was shown as mean ± SEM

transformed human lymphoblastoid cell lines that could lead to differences in the observed baseline GSK3β Serine 9 phosphorylation. Finally, we used an antibody against phosphorylated GSK-3α/β Ser21/9 (Cell Signaling Technology, rabbit), while Singh et al. did not specify the antibody used to detect GSK3β Serine 9 phosphorylation. It is possible that there are significant differences only in GSK3α Serine 21 that

account for the apparent discrepancy between our two observations.

The significance our findings is to link human genetic associations between a common DISC1 gene variant and functional molecular biological changes that could contribute to the pathophysiology of schizophrenia. Research on DISC1 and psychiatric disorders has generated many new insights into the

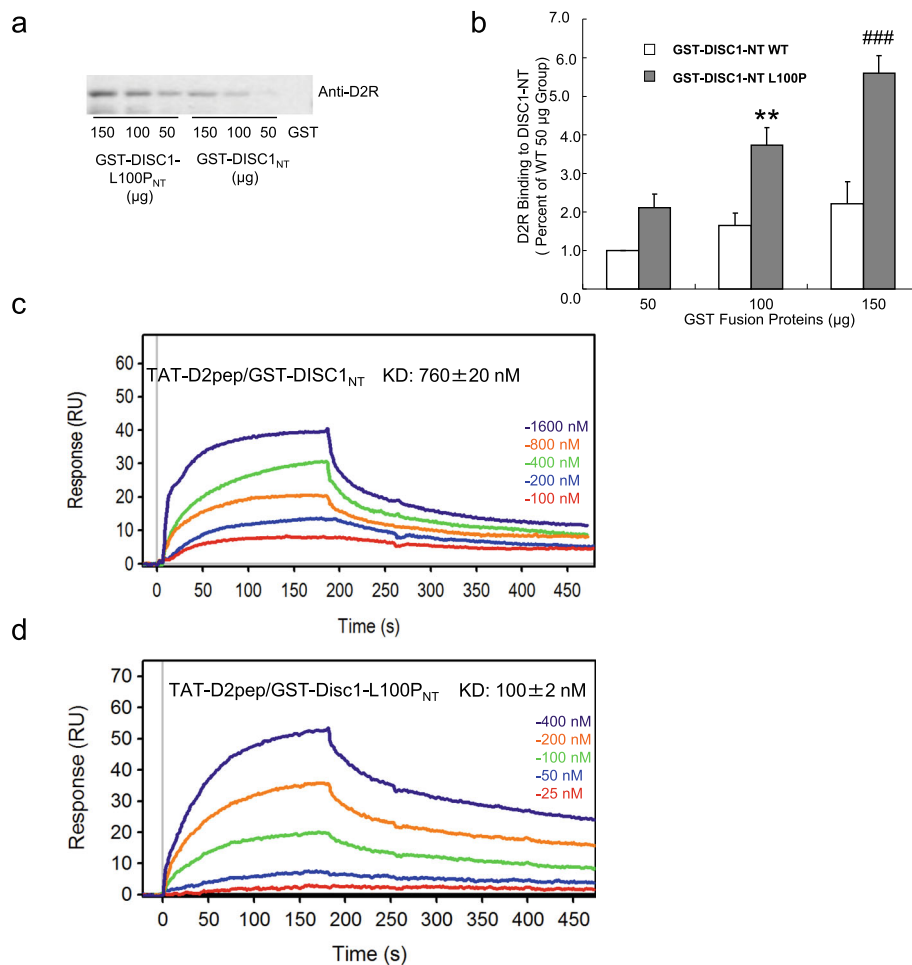


Fig. 4 The mouse *Disc1*-L100P mutation increases the binding affinity between DISC1 and D2R. **a.** GST-DISC1_{NT} and GST-*Disc1*-L100P_{NT} affinity “pull-down” of D2R from mouse striatal tissue. Various concentrations (50, 100, 150 µg) of GST-DISC1_{NT} or GST-*Disc1*-L100P_{NT} were incubated with mouse striatal extract and the precipitated proteins were immunoblotted with anti-D2R. **b.** Densitometric analysis of precipitated D2R. The intensity of D2R was quantified by densitometry (software: ImageLab, Bio-Rad). GST-DISC1_{NT} compared with GST-*Disc1*-L100P_{NT} by two-way ANOVA followed by Bonferroni post hoc test (***p* < 0.01 as compared to that of 100 µg GST-DISC1_{NT}, ###*p* < 0.001 as compared to that of 150 µg GST-DISC1_{NT}, *n* = 3). Data was shown as mean ± SEM. **c-d.** Surface Plasmon Resonance (SPR) analysis of the concentration-dependent binding of GST-DISC1_{NT} (**c**) or GST-*Disc1*-L100P_{NT} (**d**) with immobilized TAT-D2pep[K211-T225] peptide. Binding affinity was measured using a range of concentrations from 25 nM to 400 nM for GST-*Disc1*-L100P_{NT}, and 100 nM to 1.6 µM for GST-DISC1_{NT}, respectively. The duration of the association and dissociation phases was set to 180 s, 300 s, respectively. Flow rate was set to 50 µL/min to reduce the effect of mass transport limitations. Regeneration of the sensor chip was achieved by adding 10 mM NaOH, 1 M NaCl

origins of schizophrenia, especially the role of DISC1 in cortical neurogenesis, neuroblast migration and early development [8, 31, 32]. The DISC1-D2R protein complex and enhancement by the R264Q variant provides additional insights into schizophrenia biology because we found previously that schizophrenia patients in general have higher DISC1-D2R complex levels. The increased DISC1-D2R complex levels with DISC1 R264Q provides further evidence for the mechanism by which schizophrenia-associated DISC1 variants can increase disease susceptibility. We also proposed that disrupting the DISC1-D2R complex with a therapeutic peptide or small molecule

drugs could be a novel treatment strategy for schizophrenia. Identifying genetic markers for patients with increased DISC1-D2R complex levels could allow treatments to be personalized and focused on patients most likely to benefit.

Abbreviations

D2R: Dopamine D2 receptor; DISC1: Disrupted in schizophrenia 1; GSK-3: Glycogen synthase kinase - 3; SPR: Surface plasmon resonance; GST: Glutathione S-transferase; TAT: Trans-activator of transcription; GWAS: Genome-wide association study

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Authors' contributions

F.L. designed and supervised the project, and write the paper with help from A.H.C.W. P.S. planned and conducted co-immunoprecipitation (co-ip), western blot analysis and cloned the *DISC1* mutant plasmids. H. Z. conducted the Surface Plasmon Resonance (SPR) analysis. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

All animal experimental procedures were conducted in accordance with the protocols approved by the Animal Care Committee of Centre for Addiction and Mental Health (no. 824).

Consent for publication

Not applicable.

Competing interests

All authors claim that there are no conflicts of interest.

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References

- Soares DC, Carlyle BC, Bradshaw NJ, Porteous DJ. *DISC1*: structure, function, and therapeutic potential for major mental illness. *ACS Chem Neurosci*. 2011;2(11):609–32.
- St Clair D, Blackwood D, Muir W, Carothers A, Walker M, Spowart G, et al. Association within a family of a balanced autosomal translocation with major mental illness. *Lancet*. 1990;336(8706):13–6.
- Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CA, et al. Disruption of two novel genes by a translocation co-segregating with schizophrenia. *Hum Mol Genet*. 2000;9(9):1415–23.
- Brandon NJ, Sawa A. Linking neurodevelopmental and synaptic theories of mental illness through *DISC1*. *Nat Rev Neurosci*. 2011;12(12):707–22.
- Porteous DJ, Millar JK, Brandon NJ, Sawa A. *DISC1* at 10: connecting psychiatric genetics and neuroscience. *Trends Mol Med*. 2011;17(12):699–706.
- Su P, Li S, Chen S, Lipina TV, Wang M, Lai TK, et al. A dopamine D2 receptor-*DISC1* protein complex may contribute to antipsychotic-like effects. *Neuron*. 2014;84(6):1302–16.
- Song W, Li W, Feng J, Heston LL, Scaringe WA, Sommer SS. Identification of high risk *DISC1* structural variants with a 2% attributable risk for schizophrenia. *Biochem Biophys Res Commun*. 2008;367(3):700–6.
- Singh KK, De Rienzo G, Drane L, Mao Y, Flood Z, Madison J, et al. Common *DISC1* polymorphisms disrupt Wnt/GSK3beta signaling and brain development. *Neuron*. 2011;72(4):545–58.
- Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. Dopamine receptors: from structure to function. *Physiol Rev*. 1998;78(1):189–225.
- Neve KA, Seamans JK, Trantham-Davidson H. Dopamine receptor signaling. *J Recept Signal Transduct Res*. 2004;24(3):165–205.
- Seeman P, Lee T, Chau-Wong M, Wong K. Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature*. 1976;261(5562):717–9.
- Patel P, Woodgett JR. Glycogen synthase kinase 3: a kinase for all pathways? *Curr Top Dev Biol*. 2017;123:277–302.
- McCubrey JA, Steelman LS, Bertrand FE, Davis NM, Sokolosky M, Abrams SL, et al. GSK-3 as potential target for therapeutic intervention in cancer. *Oncotarget*. 2014;5(10):2881–911.
- Koros E, Dorner-Ciossek C. The role of glycogen synthase kinase-3beta in schizophrenia. *Drug News Perspect*. 2007;20(7):437–45.
- Beaulieu JM. A role for Akt and glycogen synthase kinase-3 as integrators of dopamine and serotonin neurotransmission in mental health. *J Psychiatry Neurosci*. 2012;37(1):7–16.
- Beaulieu JM. Not only lithium: regulation of glycogen synthase kinase-3 by antipsychotics and serotonergic drugs. *Int J Neuropsychopharmacol*. 2007;10(1):3–6.
- Beaulieu JM, Gainetdinov RR, Caron MG. Akt/GSK3 signaling in the action of psychotropic drugs. *Annu Rev Pharmacol Toxicol*. 2009;49:327–47.
- Beaulieu JM, Sotnikova TD, Yao WD, Kockeritz L, Woodgett JR, Gainetdinov RR, et al. Lithium antagonizes dopamine-dependent behaviors mediated by an AKT/glycogen synthase kinase 3 signaling cascade. *Proc Natl Acad Sci U S A*. 2004;101(14):5099–104.
- Frelaud L, Beaulieu JM. Inhibition of GSK3 by lithium, from single molecules to signaling networks. *Front Mol Neurosci*. 2012;5:14.
- Dandekar MP, Valvassori SS, Dal-Pont GC, Quevedo J. Glycogen synthase kinase-3beta as a putative therapeutic target for bipolar disorder. *Curr Drug Metab*. 2018;19(8):663–73.
- Tondo L, Baldessarini RJ. Long-term lithium treatment in the prevention of suicidal behavior in bipolar disorder patients. *Epidemiol Psychiatr Soc*. 2009;18(3):179–83.
- Li H, Su P, Lai TK, Jiang A, Liu J, Zhai D, et al. The glucocorticoid receptor-FKBP51 complex contributes to fear conditioning and posttraumatic stress disorder. *J Clin Invest*. 2020;130(2):877–89.
- Pei L, Li S, Wang M, Diwan M, Anisman H, Fletcher PJ, et al. Uncoupling the dopamine D1-D2 receptor complex exerts antidepressant-like effects. *Nat Med*. 2010;16(12):1393–5.
- Thomson PA, Parla JS, McRae AF, Kramer M, Ramakrishnan K, Yao J, et al. 708 common and 2010 rare *DISC1* locus variants identified in 1542 subjects: analysis for association with psychiatric disorder and cognitive traits. *Mol Psychiatry*. 2014;19(6):668–75.
- Koike H, Arguello PA, Kvajo M, Karayiorgou M, Gogos JA. *Disc1* is mutated in the 129S6/SvEv strain and modulates working memory in mice. *Proc Natl Acad Sci U S A*. 2006;103(10):3693–7.
- Clapcote SJ, Lipina TV, Millar JK, Mackie S, Christie S, Ogawa F, et al. Behavioral phenotypes of *Disc1* missense mutations in mice. *Neuron*. 2007;54(3):387–402.
- Dahoun T, Trossbach SV, Brandon NJ, Korth C, Howes OD. The impact of disrupted-in-schizophrenia 1 (*DISC1*) on the dopaminergic system: a systematic review. *Transl Psychiatry*. 2017;7(1):e1015.
- Lipina TV, Roder JC. Disrupted-in-Schizophrenia-1 (*DISC1*) interactome and mental disorders: impact of mouse models. *Neurosci Biobehav Rev*. 2014;45:271–94.
- Lipina TV, Wang M, Liu F, Roder JC. Synergistic interactions between PDE4B and GSK-3: *DISC1* mutant mice. *Neuropharmacology*. 2012;62(3):1252–62.
- Lee FH, Kaidanovich-Belil O, Roder JC, Woodgett JR, Wong AH. Genetic inactivation of GSK3alpha rescues spine deficits in *Disc1*-L100P mutant mice. *Schizophr Res*. 2011;129(1):74–9.
- Lee FH, Fadel MP, Preston-Maher K, Cordes SP, Clapcote SJ, Price DJ, et al. *Disc1* point mutations in mice affect development of the cerebral cortex. *J Neurosci*. 2011;31(9):3197–206.
- Lee FH, Zai CC, Cordes SP, Roder JC, Wong AH. Abnormal interneuron development in disrupted-in-schizophrenia-1 L100P mutant mice. *Mol Brain*. 2013;6:20.

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