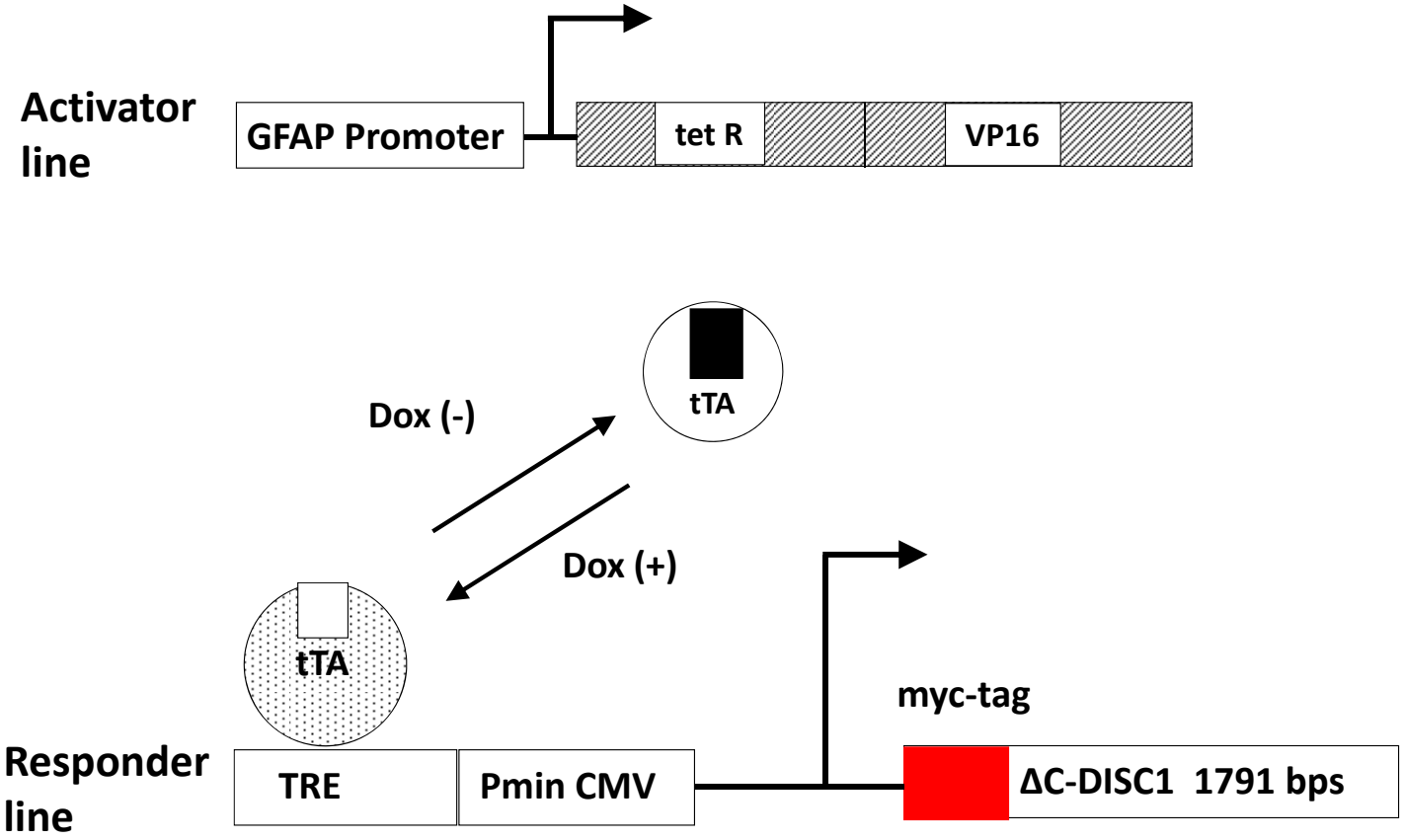
Supplementary Figure 1



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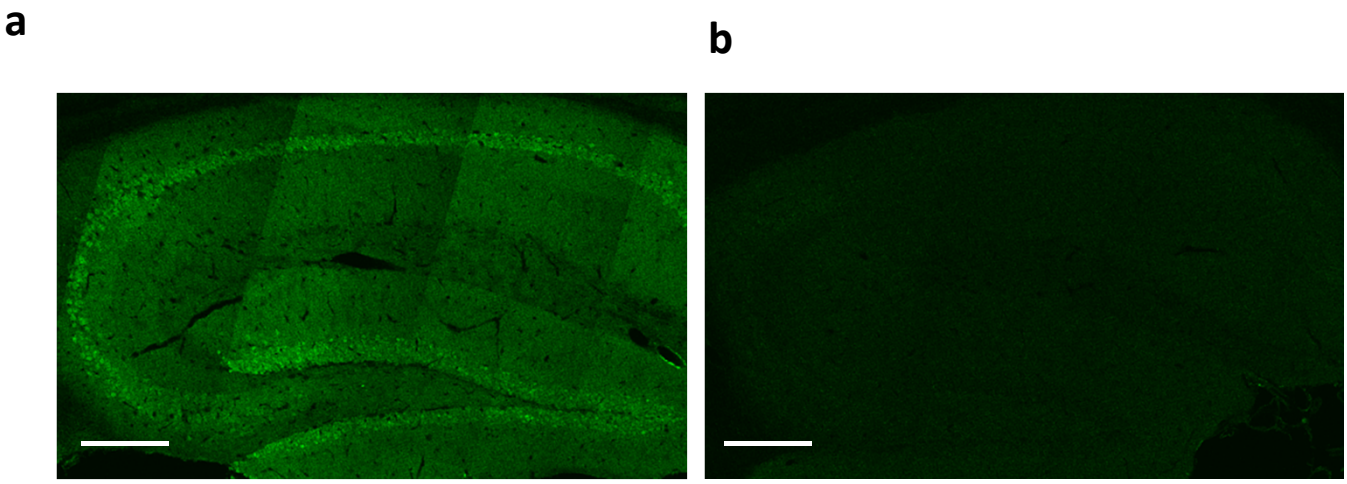

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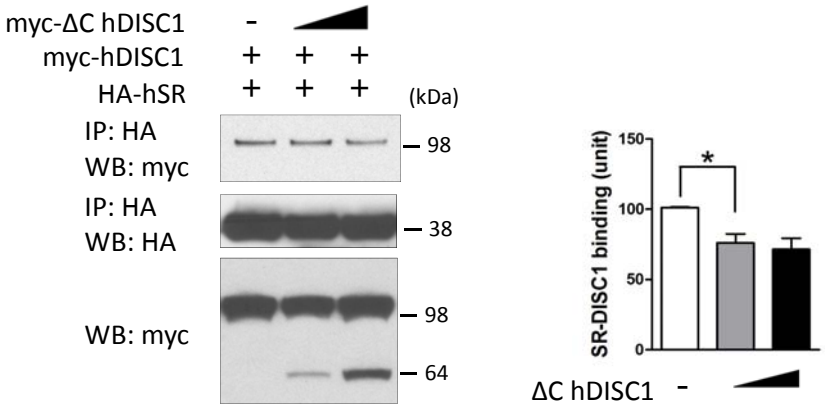

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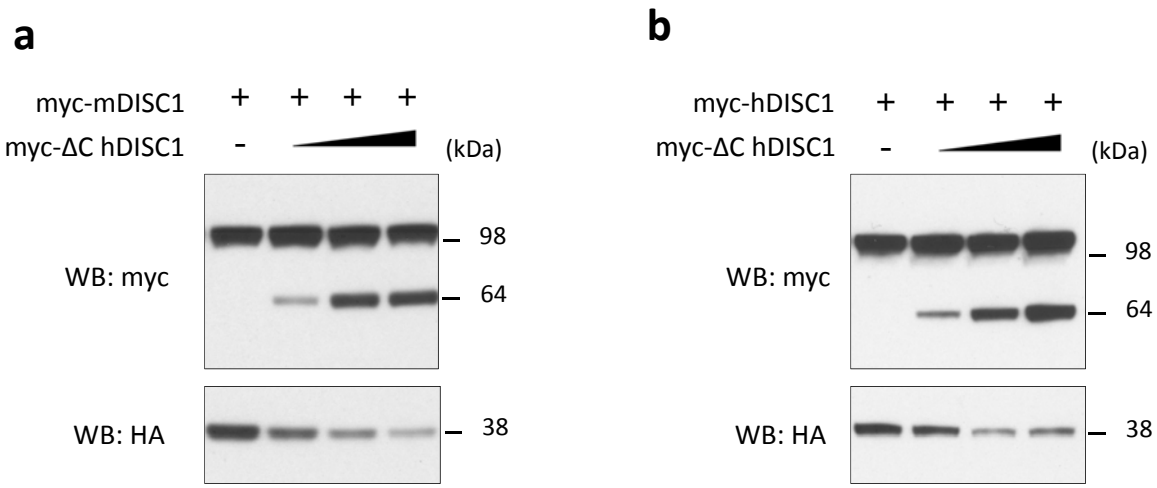

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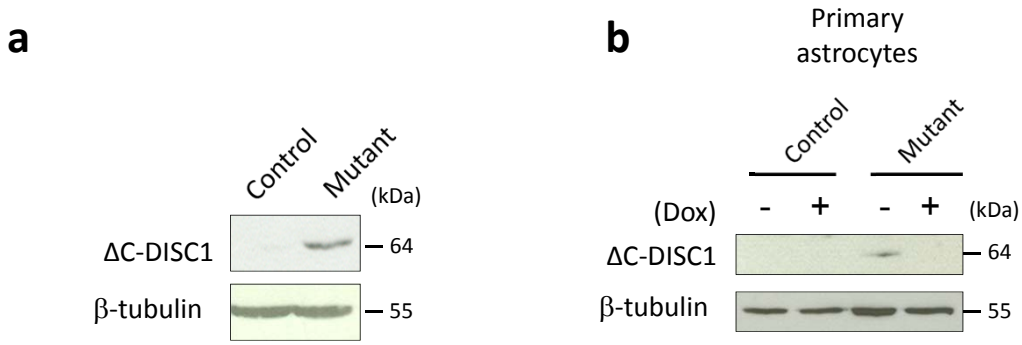
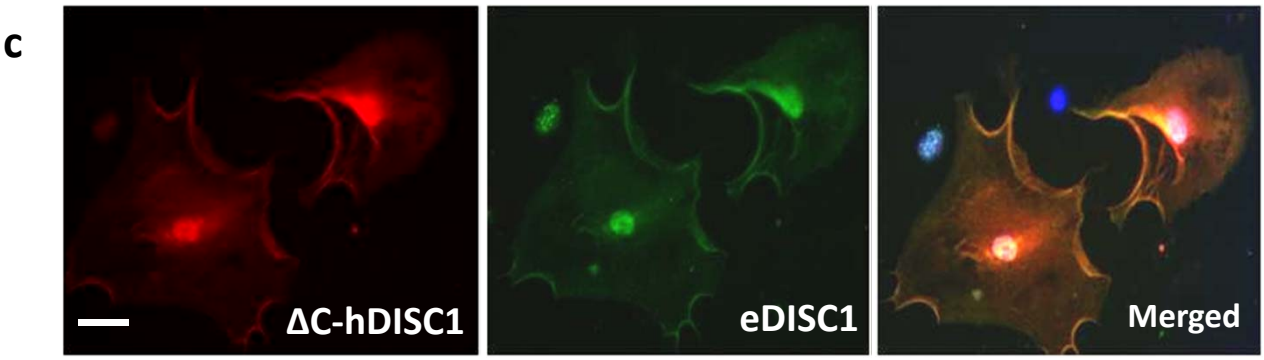
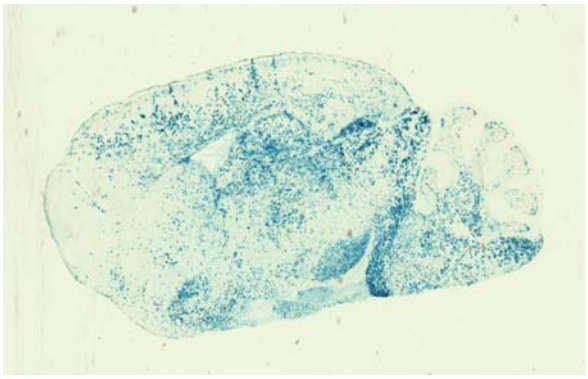
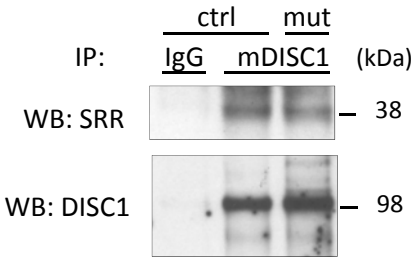


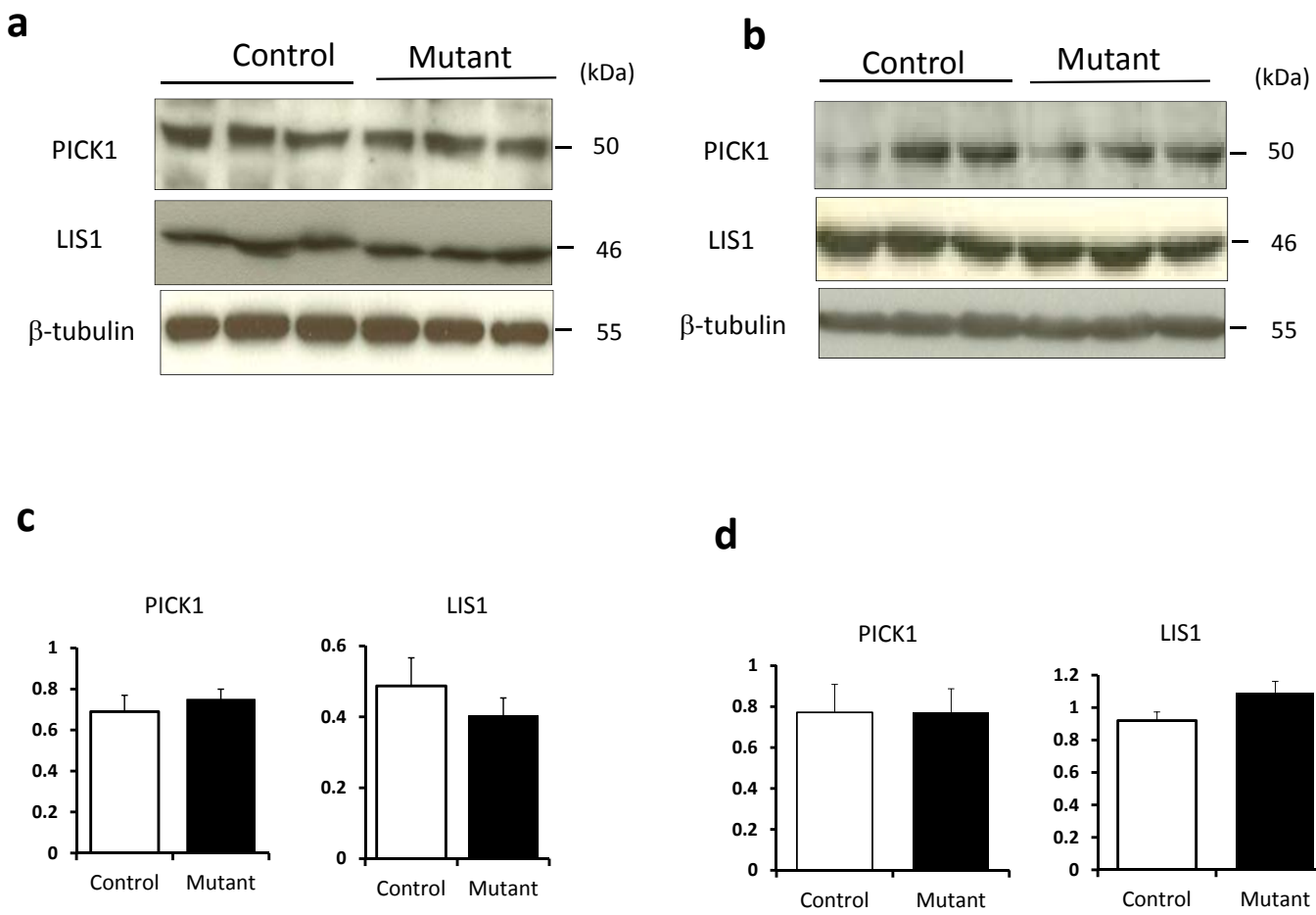




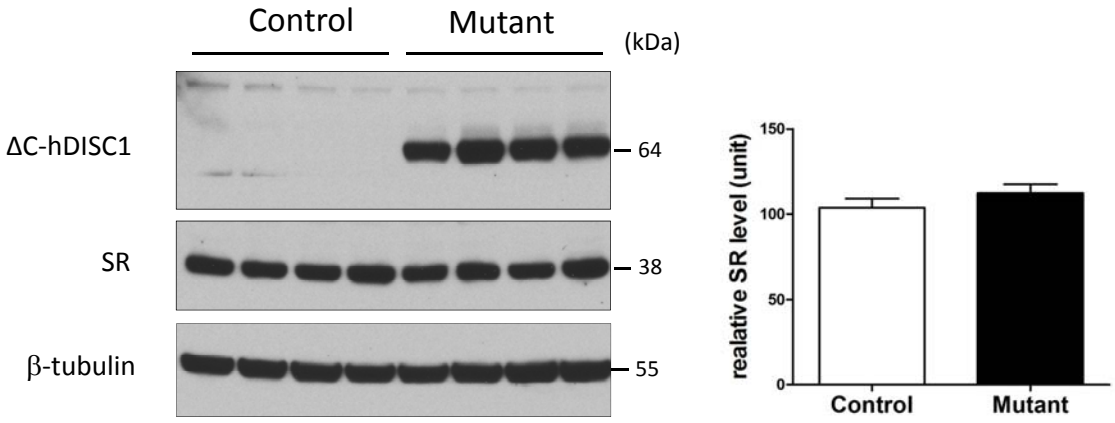
Supplementary Figure 6



Supplementary Figure 7

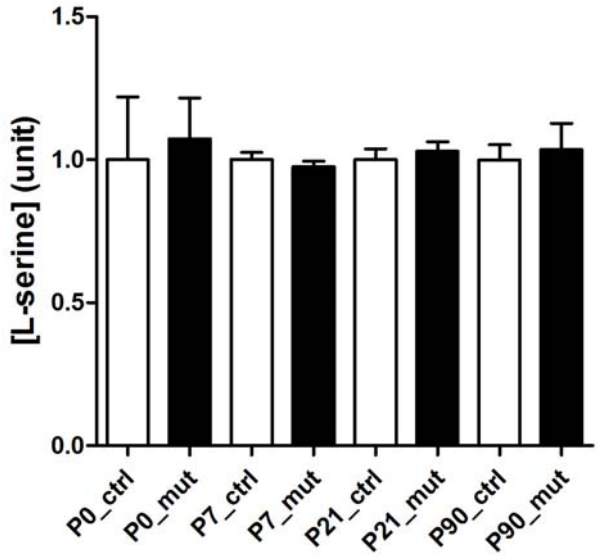


Supplementary Figure 8



Supplementary Figure 9

a



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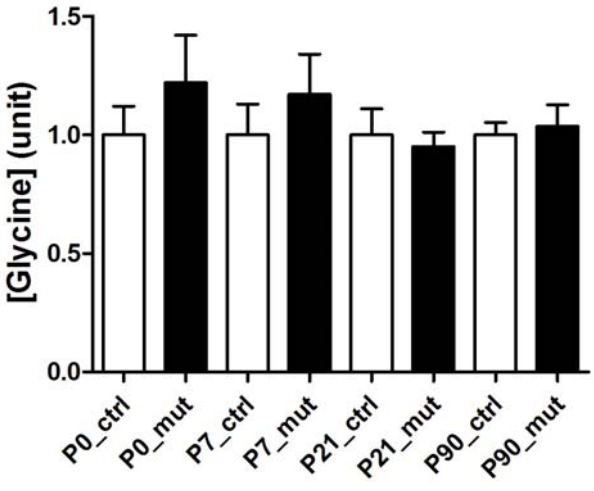
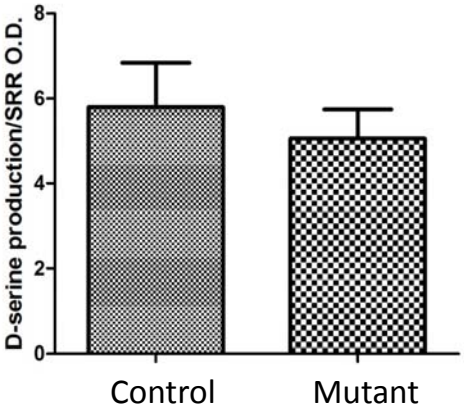
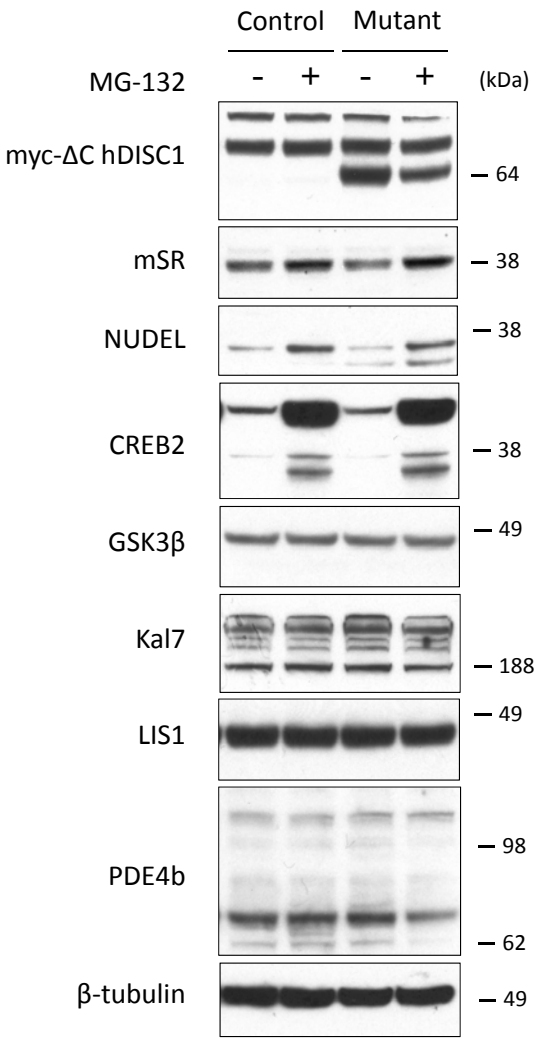


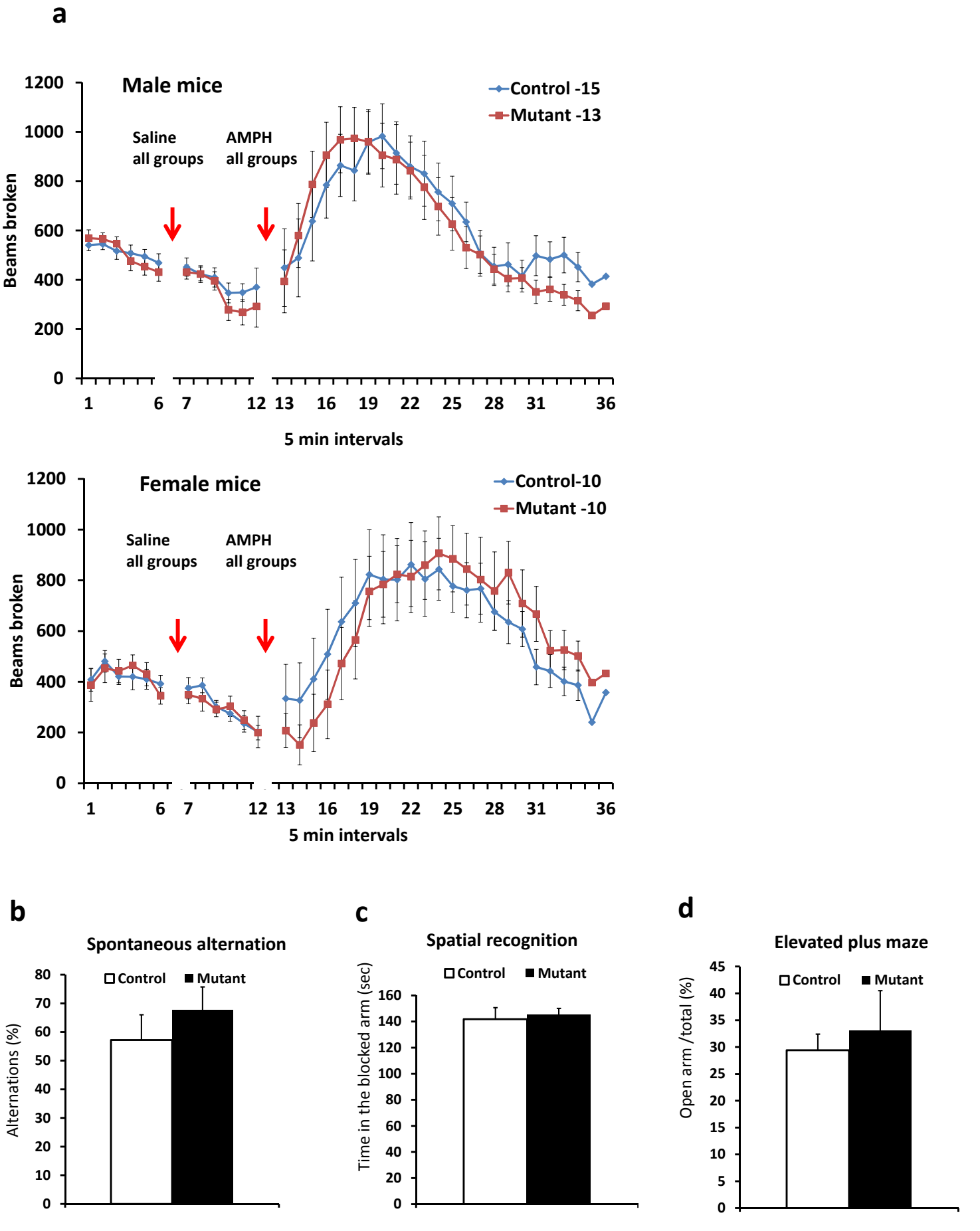
Supplementary Figure 10



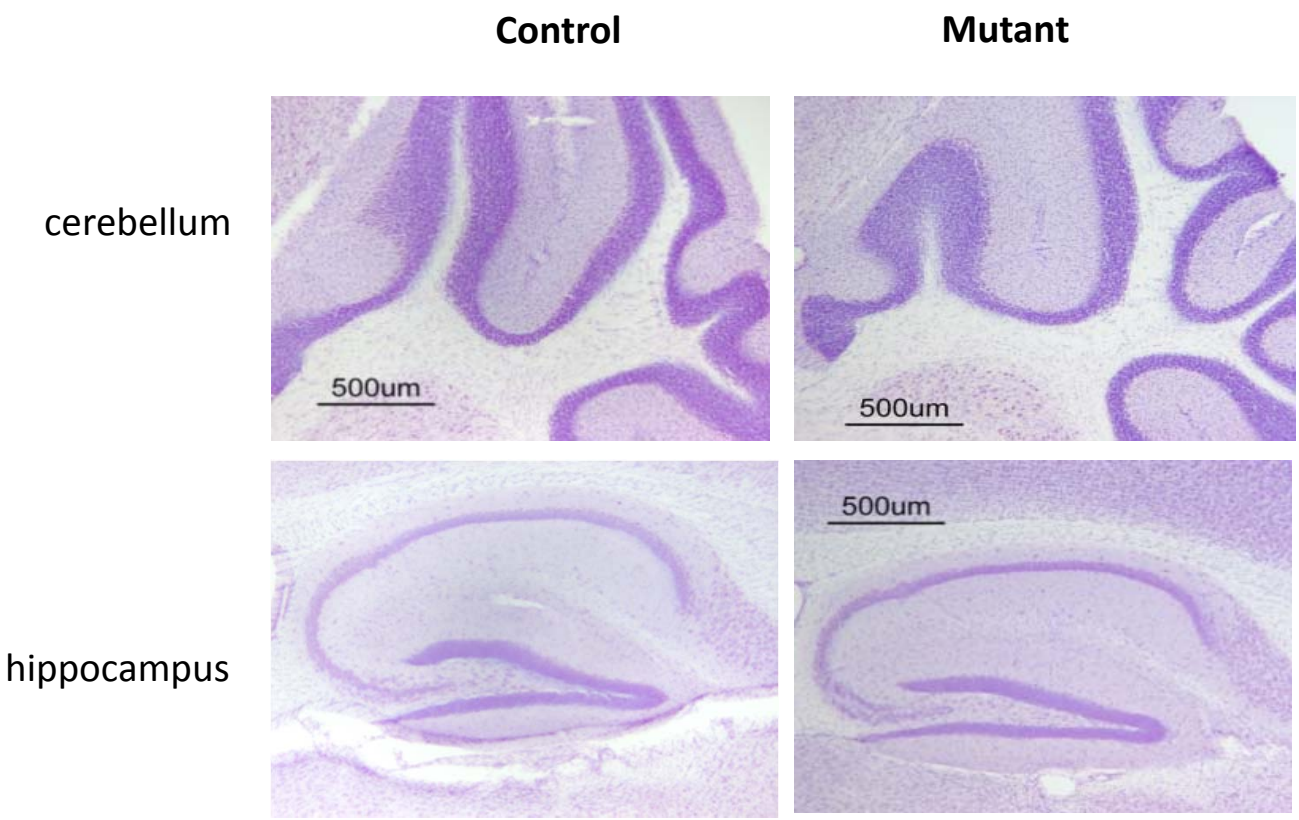
Supplementary Figure 11



Supplementary Figure 12



Supplementary Figure 13



Supplementary Figure legends

Supplementary Figure 1 Scheme of the tet-off system

The tet-off system was used to generate transgenic mice with inducible expression of mutant DISC1 in astrocytes. Two mouse lines, an activator line (single transgenic tTA mice, B6.Cg-Tg(GFAP-tTA)110Pop/J) and a responder line (single transgenic mutant human DISC1 mice, lines 1302B or 70) were mated to generate mice with expression of mutant DISC1 in astrocytes (mutant mice). Single transgenic mutant DISC1 mice carrying the mutant DISC1 transgene but not expressing mutant protein were used as controls.

Supplementary Figure 2 Specificity of SR antibody

Six-week-old WT **[a]** or SR knockout mouse **[b]** brains were sectioned into 30-µm slices on a freezing microtome and immunofluorescence staining was carried out using the SR antibody (BD Biosciences, 1:1000) as described in the Materials and Methods section. The entire hippocampal region is shown. Note that the lack of fluorescence from the SR knockout mouse **[b].** Scale bar - 200µm.

Supplementary Figure 3 Mutant DISC1 disrupts binding of full-length DISC1 to SR

Mutant DISC1 disrupts binding of full-length DISC1 and SR in HEK-293 cells, which is quantified on the right. Data is representative of 3 independent experiments, * $p<0.05$.

Supplementary Figure 4 Mutant DISC1 co-expressed with full-length DISC1 depletes SR in a dose-dependent manner

Mutant DISC1 was co-expressed with full-length mouse DISC1 **[a]** or human DISC1 **[b]** in HEK-293 cells and their effects on the level of mouse and human SR (HA-tagged) were respectively monitored. Note that in both cases, SR level decreases with expression of the mutant DISC1 in a dose-dependent manner.

Supplementary Figure 5 Inducible expression of ΔC-hDISC1 in astrocytes

[a] Expression of ΔC-hDISC1 in the brain of mutant and control mouse; expression of ΔC-hDISC1 was detected with anti-myc antibody (1:1000) as a 64-kDa band. Anti- β-tubulin antibody (1:10000) was used as a loading control;

[b] Regulation of expression with doxycycline (Dox); adding Dox to primary astrocytes medium shut down expression of ΔC-hDISC1;

[c] Co-expression of ΔC-hDISC1 (red) and endogenous mouse DISC1 (eDISC1, green) in primary cortical astrocytes derived from mutant mice. Nuclei are stained with DAPI. Scale bar - 5μm;

[d] Regional activity of the GFAP promoter in the brain. A single transgenic GFAP-tTA mouse was mated with a reporter single transgenic mouse carrying a β-galactosidase (*lacZ*) reporter gene under the control of a tetracycline-responsive promoter element. X-Gal staining was performed on the brain sections to evaluate β-galactosidase expression.

Supplementary Figure 6 Endogenous SR binds to DISC1 in primary astrocytes

Note that in the primary astrocytes derived from mutant mouse, the binding is weaker compared to that of control mice.

Supplementary Figure 7 Expression of endogenous PICK1 and LIS1 is not changed

Representative blots for PICK1 and LIS1 in the samples from primary astrocytes **[a]** or the forebrain of newborn mice **[b]**; no significant changes in expression of PICK1 **[c]** or LIS1 **[d]** were detected, n=4-5 samples per group.

Supplementary Figure 8 Unaltered SR level in neurons that express ΔC-hDISC1

There are no significant alterations in SR level in the primary neurons derived from transgenic mice with expression of mutant DISC1 in neurons under the CamKII promoter compared to the controls[44]; control, n=10; mutant, n=11.

Supplementary Figure 9 Unaltered L-serine and glycine levels in the brain

No significant change in the L-serine [a] and glycine [b] level in the mutant mouse brain was detected by HPLC. The levels in the control and mutant samples are presented as the relative units normalized to the averaged value of the corresponding control group n=5 in each group for L-serine measurements; n=3 in each group for glycine measurements.

Supplementary Figure 10 Unaltered activity of SR in primary astrocytes expressing ΔC-hDISC1

In vitro SR activity was measured by incubating control and mutant primary astrocytes lysates with L-serine. SR activity is expressed as D-serine produced from one unit of SR protein, n=3 in each group.

Supplemental Figure 11 Analysis of ubiquitination/ proteasomal degredation of DISC1 interacting partners

Primary astrocytes derived from control or mutant mice were treated with 30 μM proteasome inhibitor MG-for 10h. Several validated DISC1-interacting partners, including NUDEL, CREB2, GSK3, Kal7, LIS1 and PDE were assayed by western blotting.

Supplementary Figure 12 Neurobehavioral effects of astrocytic mutant DISC1 in mice

[a] No significant effect of mutant DISC1 was observed on responses to amphetamine (AMPH, 2.5 mg/kg, i.p. numbers of mice are indicated on the graphs).

No significant effect of mutant DISC1 was observed on spontaneous alternation **[b]**, spatial recognition **[c]** or anxiety in elevated plus maze **[d]**. n=7 per group.

Supplementary Figure 13 Brain cyto-architectonics of the WT and ΔC-hDISC1 mutant mice

No gross effects on the brain cyto-architectonics or layering of the cerebellum (upper panels) or hippocampus (bottom panels), scale bar - 500 μm.