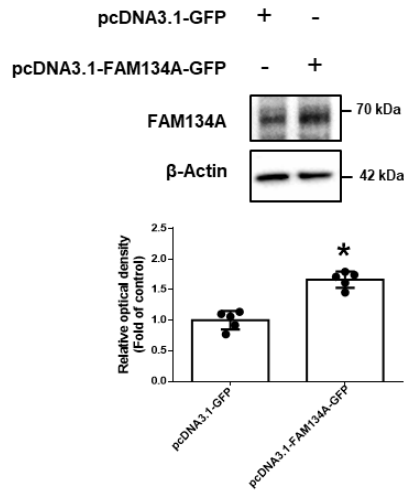
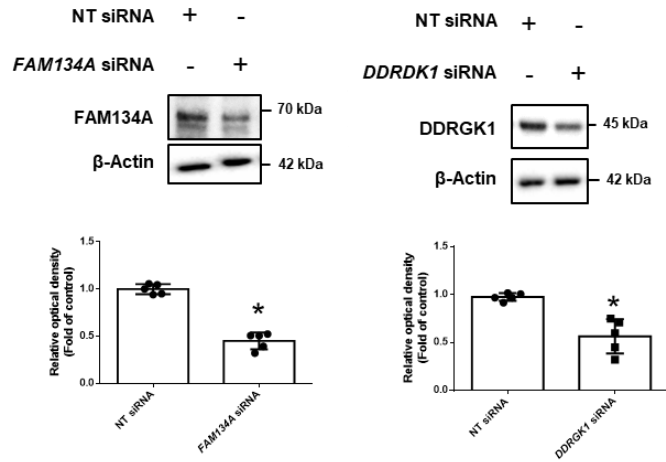
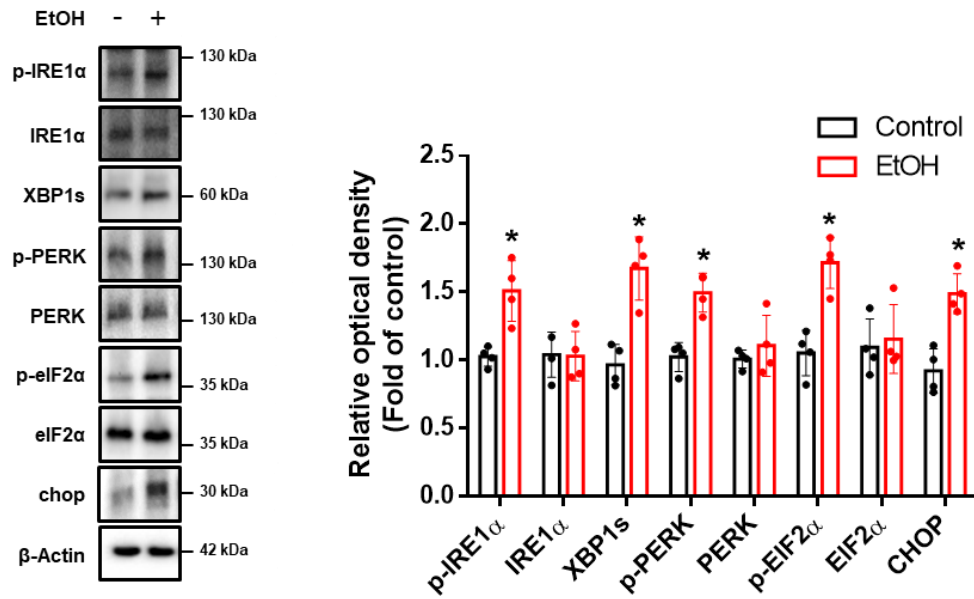


**A****B**

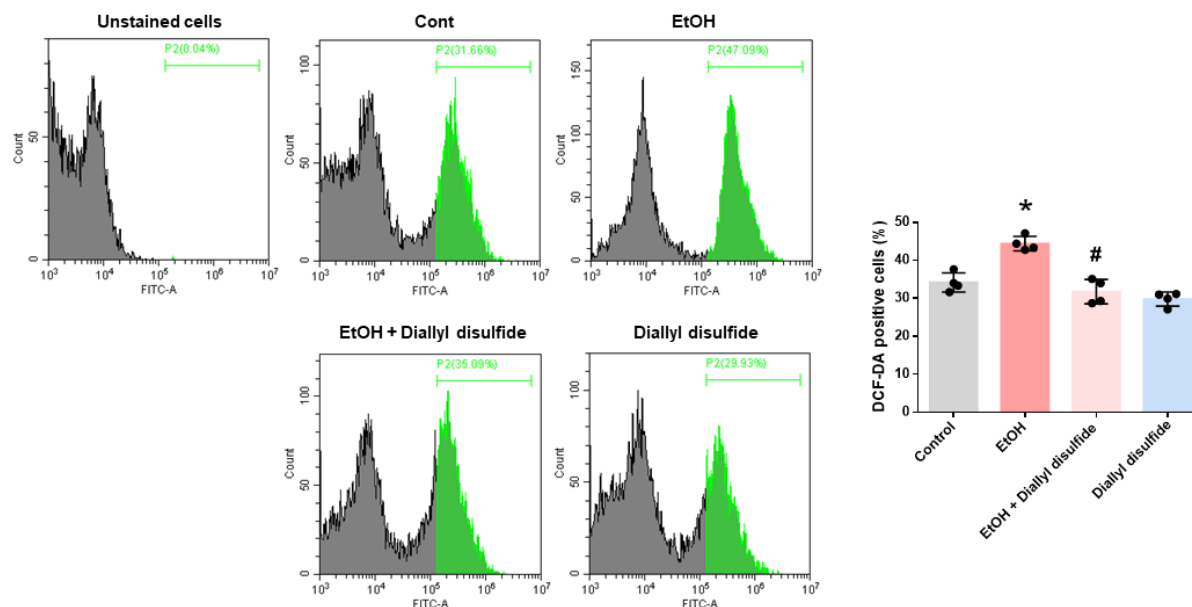
### Supplementary Fig 1. Confirmation of the efficiency of siRNA and plasmid DNA.

(A) SH-SY5Y cells were transfected with pcDNA3.1-FAM134A-GFP for 24 h,  $n = 5$ . (B) Cells were transfected with either FAM134A siRNA or DDRGK1 siRNA for 24 h, respectively.  $n = 5$ . All blot images are representative. Quantitative data are presented as a mean  $\pm$  SD. \* indicates  $p < 0.05$  versus control.



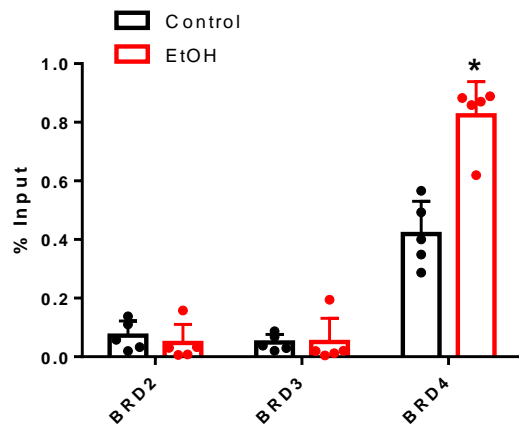
**Supplementary Fig 2. Effect of ethanol on ER stress.**

EtOH was treated to SH-SY5Y cells for 24 h. The levels of ER stress marker proteins were measured by western blotting.  $n = 4$ . All blots are representative. Quantitative data are presented as a mean  $\pm$  SD. \* indicates  $p < 0.05$  versus control.



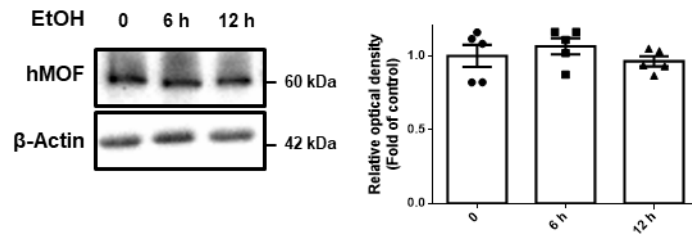
**Supplementary Fig 3. Effect of ethanol metabolism on ethanol-induced ROS production.**

Diallyl disulfide (10  $\mu$ M) was applied for 30 min prior to the treatment of EtOH for 24 h in SH-SY5Y cells. H<sub>2</sub>DCF-DA staining was performed to detect ROS and it was analyzed with flow cytometer.  $n = 4$ . Flow cytometer images are representative. Quantitative data are presented as a mean  $\pm$  SD. \* indicates  $p < 0.05$  versus control, # indicates  $p < 0.05$  versus EtOH.



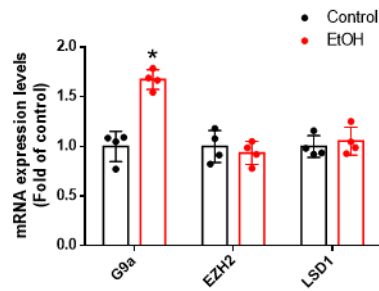
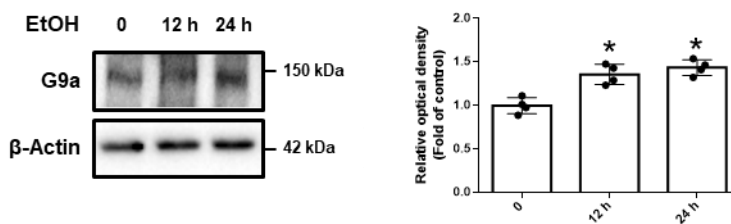
**Supplementary Fig 4. Effect of ethanol on BRD proteins binding to the FAM134A promoter.**

iPSC-neurons were exposed to EtOH for 12 h. DNA was immunoprecipitated with antibodies against BRD2, BRD3, and BRD4, respectively. The immunoprecipitation samples were amplified with primer of *FAM134A* gene. Data were obtained using qPCR.  $n = 5$ . Quantitative data are presented as a mean  $\pm$  SD. \* indicates  $p < 0.05$  versus control.



**Supplementary Fig 5. Effect of ethanol on hMOF expression.**

EtOH was treated for 0, 6, and 12 h to iPSC-neurons. Western blotting was conducted to determine the levels of hMOF.  $n = 5$ . Blot images are representative. Quantitative data are presented as a mean  $\pm$  SD.

**A****B**

**Supplementary Fig 6. Effect of ethanol on the expression of histone-modifying enzymes.**

(A) EtOH was treated to iPSC-neurons for 12 h. The mRNA expression levels of G9a, *EZH2*, and *LSD1* were analyzed by real-time PCR.  $n = 4$ . (B) iPSC-neurons were treated with EtOH for 0, 12, and 24 h. Protein expression level of G9a was analyzed by western blotting.  $n = 4$ . Blot images are representative. Quantitative data are presented as a mean  $\pm$  SD. \* indicates  $p < 0.05$  versus control.

**A**

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**B**

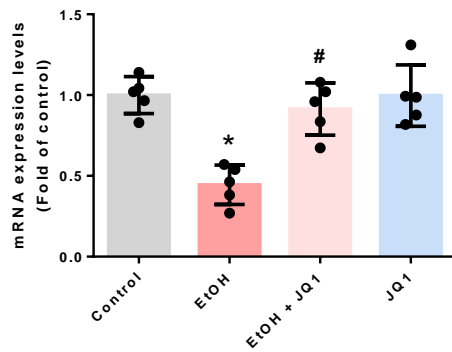
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# Supplementary Fig 7. Binding sequences of ATF4 and ATF6 in FAM134A promoter regions.

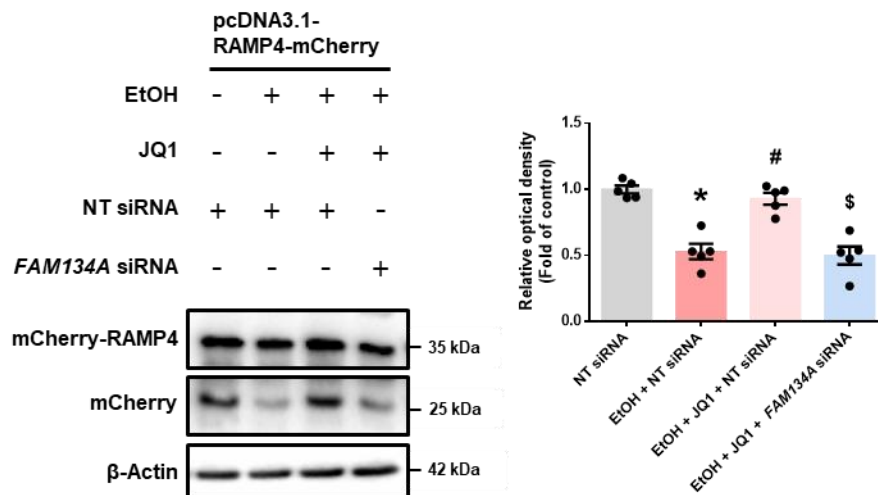
(A-B) The thousand base pair upstream of the first codon of FAM134A was described and the putative ATF4 and ATF6 binding sequences were emphasized with yellow labeling, respectively.



**Supplementary Fig 8. Effect of JQ1 on ethanol-inhibited FAM134A mRNA expression.**

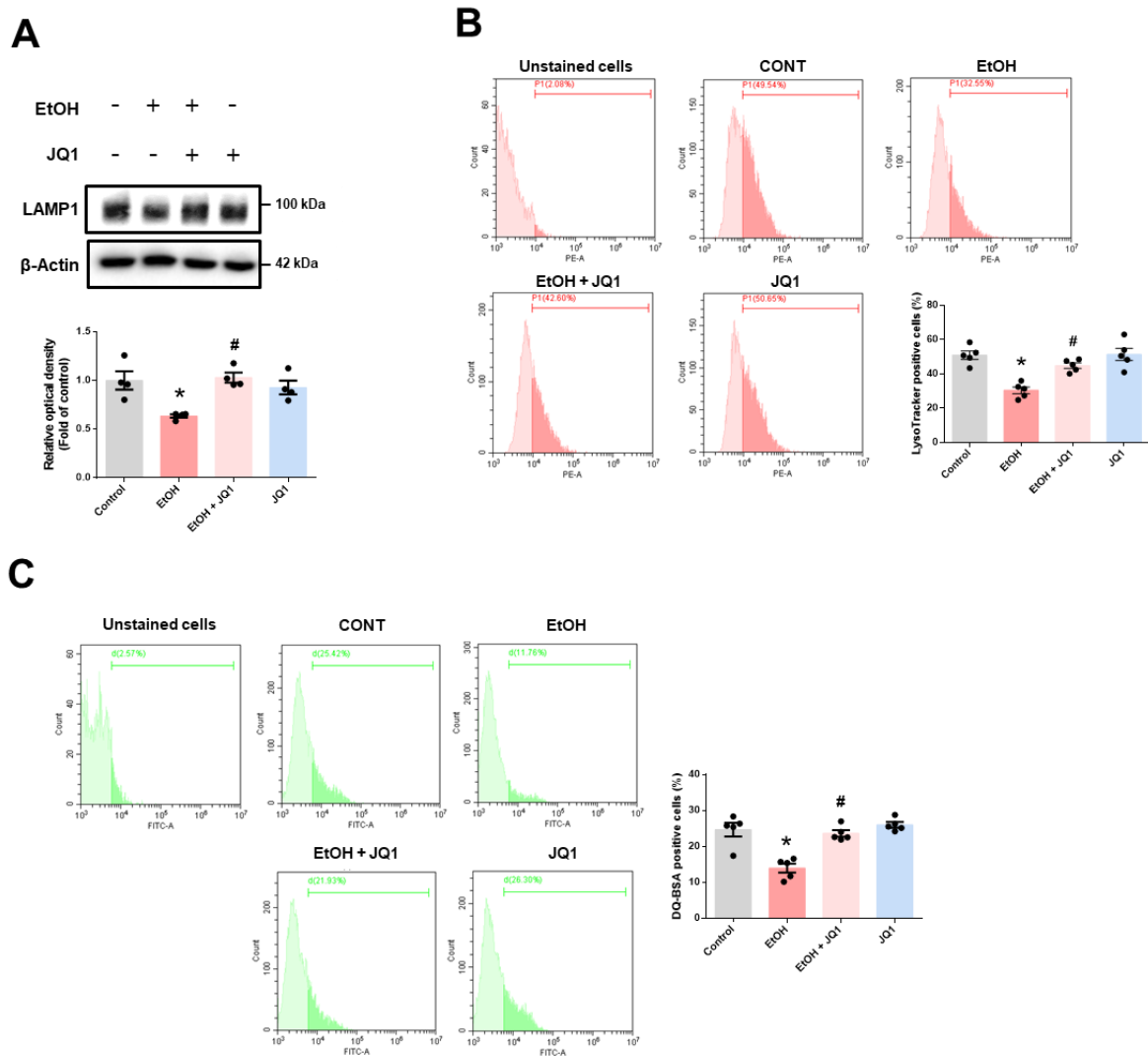
JQ1 (25 nM) was applied for 30 min prior to the treatment of EtOH for 12 h in iPSC-neurons. The mRNA expression levels of *FAM134A* were analyzed by real-time PCR,  $n = 5$ . Quantitative data are presented as a mean  $\pm$  SD. \* indicates  $p < 0.05$  versus control, # indicates  $p < 0.05$  versus EtOH.





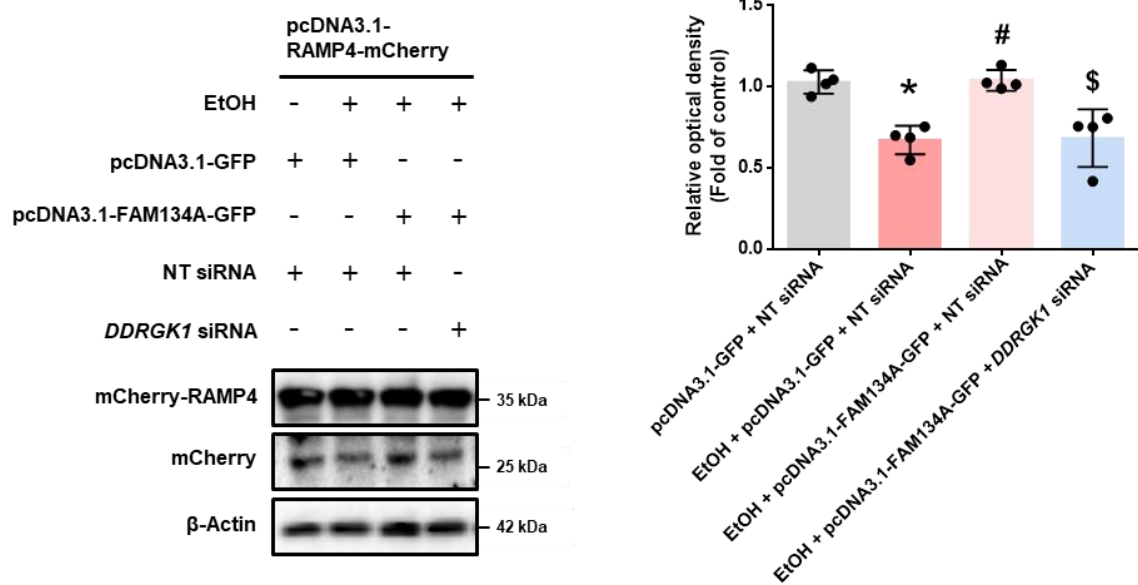
**Supplementary Fig 9. Role of FAM134A in restoring ER-phagy through BRD4 inhibition.**

Cells were transfected with pcDNA3.1-RAMP4-mCherry and either NT siRNA or FAM134A siRNA, then pretreated with JQ1 (25 nM) for 30 min prior to treatment with EtOH for 24 h. The protein expression of mCherry-RAMP4 and mCherry were detected by western blotting.  $n = 5$ . Blot images are representative. Quantitative data are presented as a mean  $\pm$  SD. \* indicates  $p < 0.05$  versus NT siRNA, # indicates  $p < 0.05$  versus EtOH + NT siRNA, \$ indicates  $p < 0.05$  versus EtOH + JQ1 + NT siRNA.



**Supplementary Fig 10. Effect of JQ1 on ethanol-inhibited lysosome biogenesis.**

(A-C) JQ1 (25 nM) was applied for 30 min prior to the treatment of EtOH for 24 h in iPSC-neurons. (A) LAMP1 was detected by western blotting.  $n = 4$ . (B-C) LysoTracker- and DQ-BSA-positive cells were analyzed with flow cytometer.  $n = 5$ . All data are representative. Quantitative data are presented as a mean  $\pm$  SD. \* indicates  $p < 0.05$  versus control, # indicates  $p < 0.05$  versus EtOH.



**Supplementary Fig 11. DDRGK1-mediated UFMylation regulates FAM134A-mediated ER-phagy in neuronal cells exposed to ethanol.**

After CCER system construction, cells were transfected with pcDNA3.1-GFP or pcDNA3.1-FAM134A-GFP and NT siRNA or DDRGK1 siRNA. Cells were incubated with EtOH for 24 h. mCherry-RAMP4 and mCherry protein expressions were detected by western blotting.  $n = 4$ . Blot images are representative. Quantitative data are presented as a mean  $\pm$  SD. \* indicates  $p < 0.05$  versus pcDNA3.1-GFP + NT siRNA, # indicates  $p < 0.05$  versus EtOH + pcDNA3.1-GFP + NT siRNA, \$ indicates  $p < 0.05$  versus EtOH + pcDNA3.1-FAM134A-GFP + NT siRNA.