Supplementary figure 1. X-Chromosome inactivation study in III-2 patient (P75 family). Analyzes of genomic DNA (gDNA) from fibroblast by PCR and Sanger sequencing shows that female III-2 patient is heterozygous (C/T alleles) for the SNP (rs8680) in the 3'UTR of APOO gene. Amplification and sequencing of the APOO transcript using cDNAs from III-2 patient's fibroblasts reveals that both alleles

are expressed at similar levels suggesting the absence of X-inactivation bias in patient's fibroblasts. The exon 8/intron 8 and exon8/exon9 boundaries of APOO gene and transcript respectively are indicated by grey dash lines with arrow.

Supplementary figure 2. Protein expression of IL1RAPL1 mutants in HEK293 cells. Protein detection by immunoblot on lysates from HEK293 cells co-transfected with different HA-IL1RAPL1 constructs and GFP. IL1RAPL1 proteins were revealed by an anti-HA tag antibody, and signal was normalized to GAPDH expression. GFP is used as a control of transfection efficiency. Bar graphs show the mean + SEM of IL1RAPL1 protein expression normalized to the WT - transfected cells (6 independent experiments, $*p < 0.01$ *** $p < 0.001$).

Supplementary figure 3. Consequences of IL1RAPL1 mutations on pre-synaptic formation. Mouse hippocampal neurons were co-transfected with GFP and the different IL1RAPL1 constructs, and were stained at DIV18 with synaptophysin antibody to label excitatory post-synapses. Each column of images shows double-labeling for GFP (top panel) and synaptophysin (middle panel); the merged images are shown in the bottom panel (scale bar 10 μm). Bar graphs show the mean + SEM of the synaptophysin clusters per micron in at least 50 neurons for each condition from 3 independent experiments (*** $p < 0.001$, compared to control neurons).

Supplementary figure 4. Consequences of IL1RAPL1 mutations on inhibitory synapse formation. (A) Mouse hippocampal neurons co-transfected with GFP and different HA-IL1RAPL1 constructs were stained with anti-VGAT antibody to label inhibitory pre-synapses. Each

column of images shows double- labeling for GFP (top panel) and VGAT (middle panel); the merged images are shown in the bottom panel (scale bar 20 μm). Bar graphs show the mean + SEM of VGAT intensity (15 neurons from 3 independent experiments for each condition). (B) Typical recording of sIPSC from mouse hippocampal neurons at 18- 21 DIV transfected with different IL1RAPL1 constructs. Bars represent the average frequency and amplitude of these events (14 to 21 transfected neurons per condition and 61 non transfected neurons (nt)).

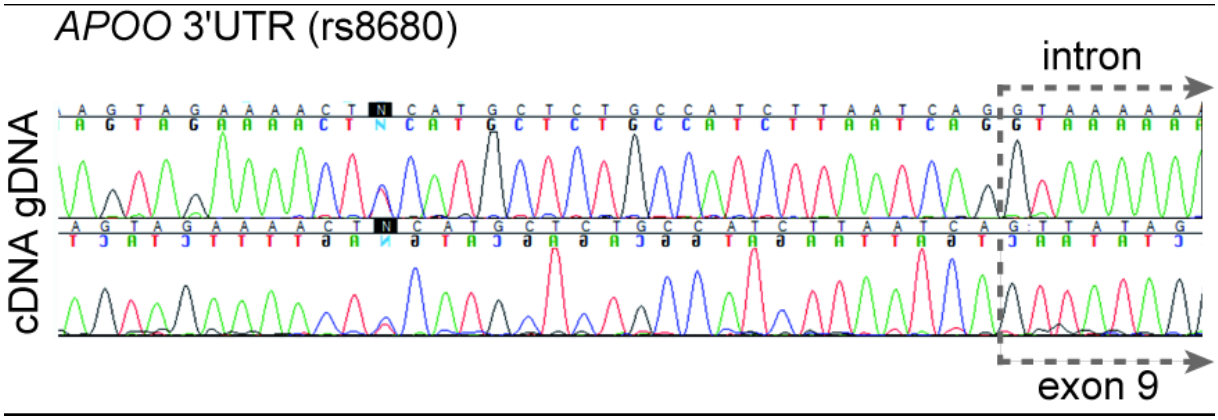
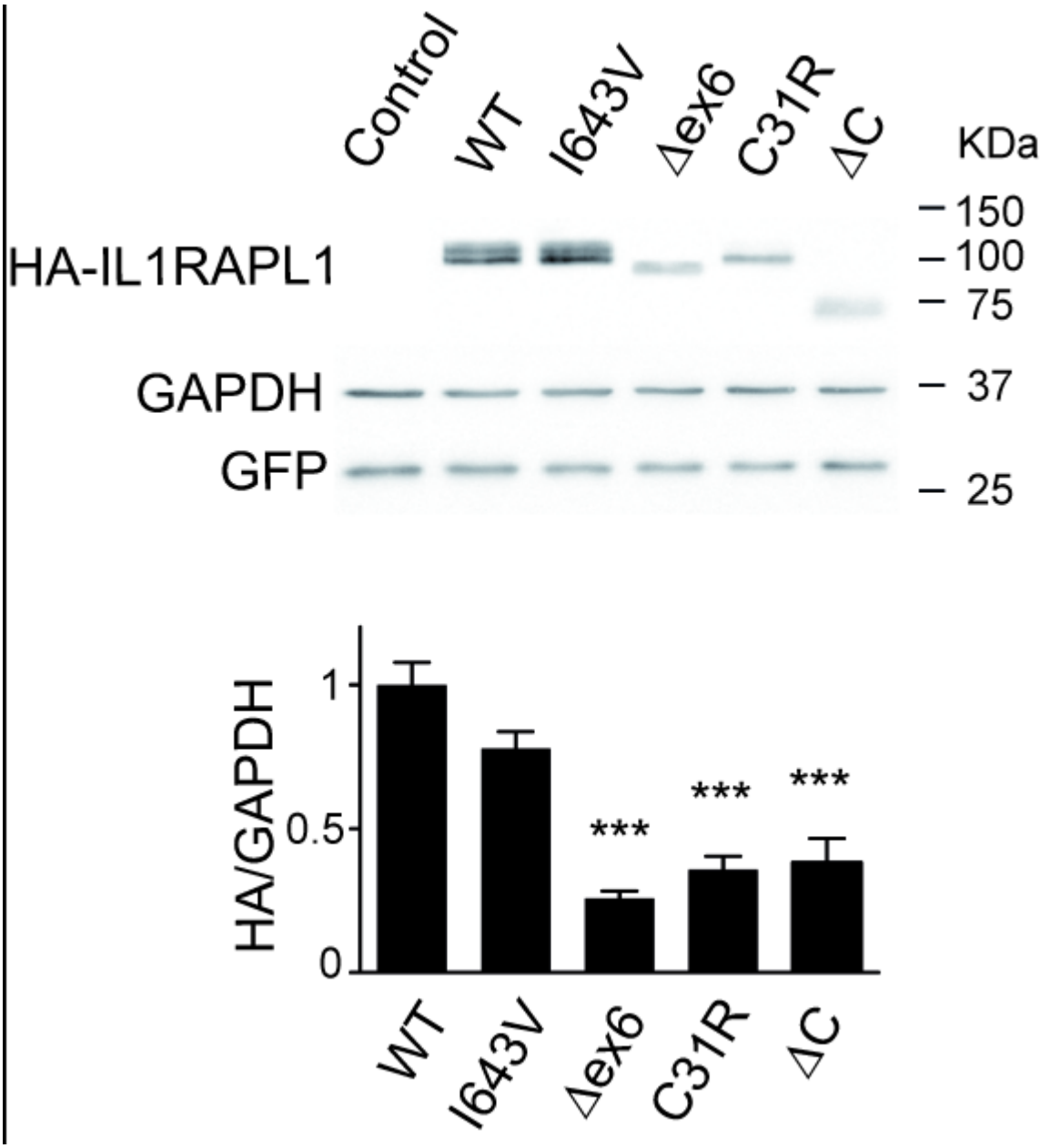


Figure S1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C31R
ΔC
KDa
150
100
75
37
25
HA-IL1RAPL1
GAPDH
GFP
HA/GAPDH
1
0.5
0
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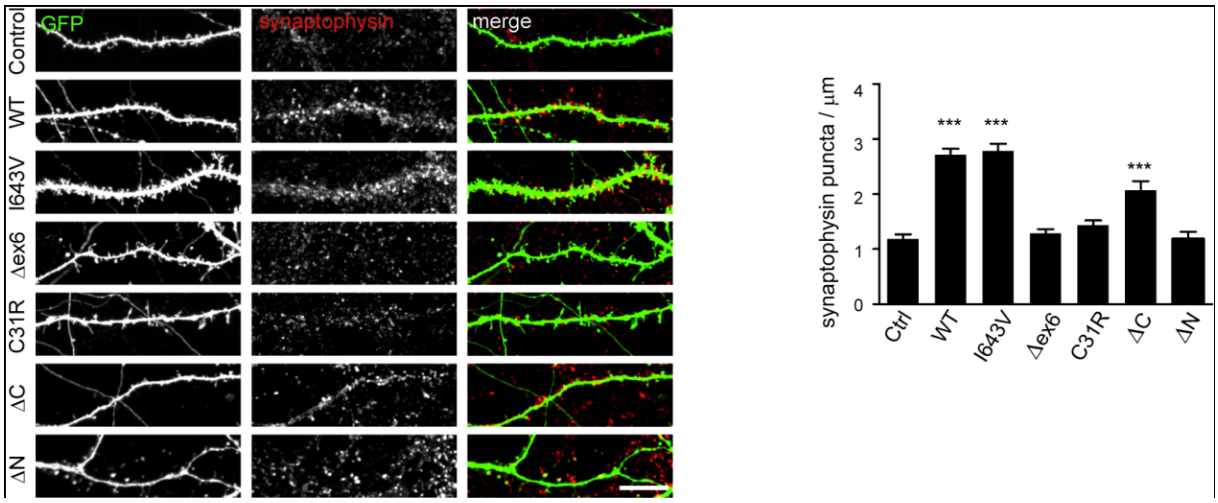
***
WT
I643V
Δex6
C31R
ΔC

Figure S2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Control
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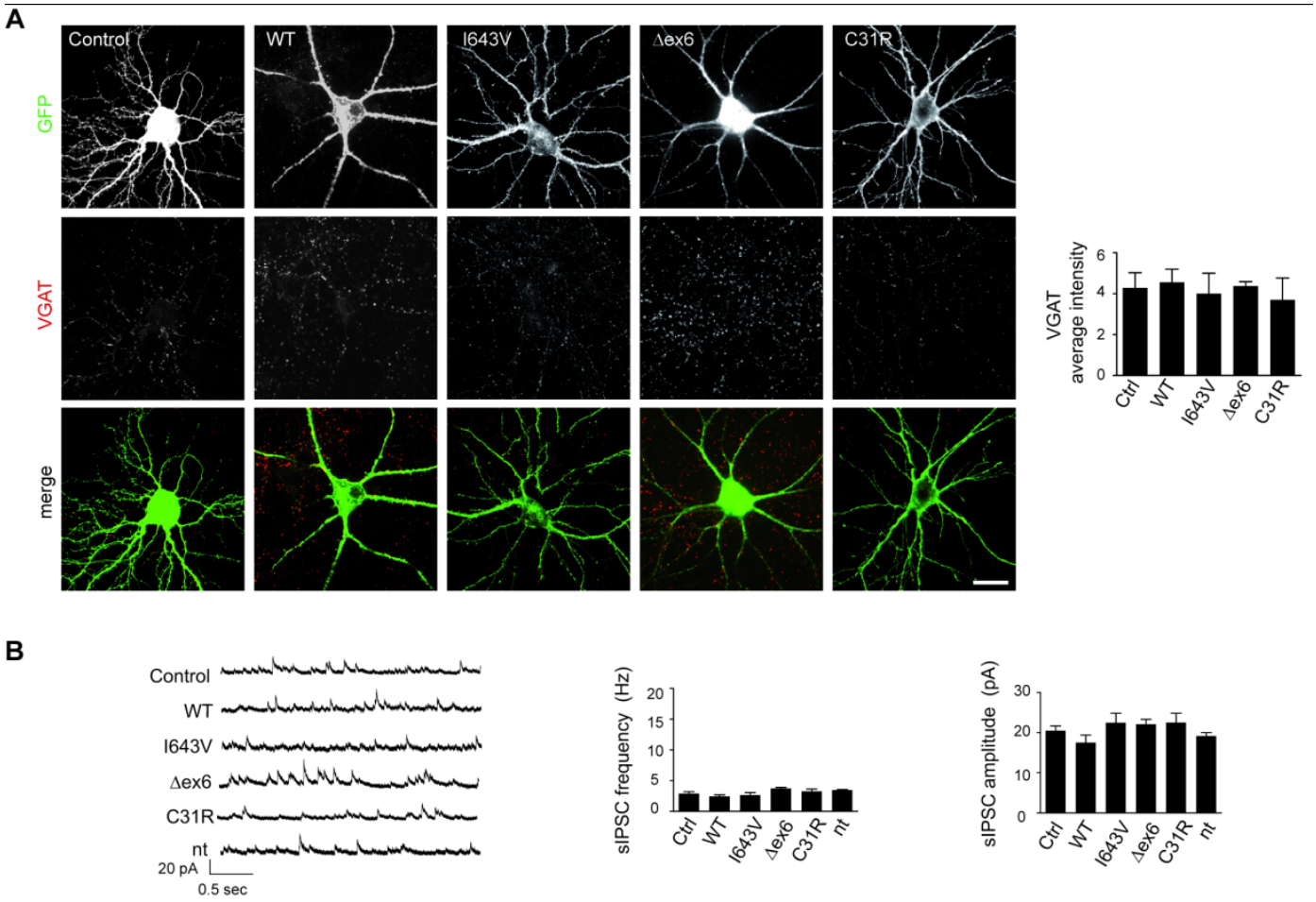
C31R
ΔC
ΔN

Figure S3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B
Control
WT
I643V
Δex6
C31R
nt
20 pA
0.5 sec
sIPSC frequency (Hz)
sIPSC amplitude (pA)
Ctrl
WT
I643V
Δex6
C31R
nt

Figure S4