**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)).