Supplementary Figure 1. Characterization of patient and control iPSCs. (A) RT-PCR for *SCN1A* using RNA from iPSCs, induced neurons and fetal brain shows that the DS patient iPSCs and induced neurons continue to show the exon-14-skipped allele (arrows) that is absent from control (Con) iPSCs or induced neurons, or from fetal brain. (B) H&E-stained section from a teratoma that formed after injection of iPSCs (from patient DS2) in a NOD scid gamma mouse. Pigmented neural epithelium (ectoderm), cartilage (mesoderm) and glandular tissue (endoderm) are evident. (C) RT-PCR of DS1 or control (Con) iPSCs or fibroblasts (Fb), or of H7 hESCs, shows expression of pluripotency markers in iPSCs and H7, but not in Fb. (D) Scatter plots of microarray data comparing global gene expression patterns of human iPSCs vs. human fibroblasts from the patient DS1 (top), and human iPSCs vs. hESCs (bottom). The position of individual pluripotency genes labeled in the panels is indicated with arrows pointing to red dots. (E) Quantitative RT-PCR analysis of retroviral transgene (Tg) expression in human fibroblasts five days after infection with the four factors Oct3/4, Sox2, cMyc, and Klf4 (Fb4f/5d), uninfected human fibroblasts (Fb), 2

patient (DS1 and DS2) and 2 control (C1 and C2) iPSCs, and their NPC derivatives. Data are representative of three independent experiments (mean ± s.d.). Transgene expression in Fb 4f/5d was set to 1. Scale bar in B, 100 μm.

Supplementary Figure 2. iPSC-derived NPCs show a forebrain regionalization. (A) RT-PCR using DS or control (Con) iPSCs show expression of many forebrain-specific genes but not those specific for hindbrain/spinal cord or related to pluripotency. (B-D) Immunolabeling of iPSC-derived NPCs shows expression of NPC markers Pax6 and Sox3 (B), forebrain markers Forse1 (C), Otx2 (D) and Tbr1 (E), but not Engrailed 1 (En1, D). Scale bar, 50 μm.

Supplementary Figure 3. Expression of voltage-gated sodium channel α subunits and interneuron markers in induced neurons. (A) RT-PCR for selected sodium channel alpha subunits from control iPSCs before or after neuronal differentiation. *ATP7A* is an internal control, and RT is replaced by water in the control lane on the right. (B-D) iPSC-derived neurons express various interneuron markers including calretinin (red in B), calbindin (red in C), parvalbumin (green in D) and somatostatin (not shown). Cells are co-labeled with neuron-specific β-tubulin (TuJ1 antibody, green in B, C) or MAP2 (red in D) and bisbenzimide (BB) nuclear stain (blue in B-D). Scale bar, 75 μm.

Supplementary Figure 4. Sodium current densities in 5-7-day differentiated induced neurons, and sodium current voltage-dependence properties in 3-5-week differentiated induced neurons. (A, B) Mean sodium current densities in 5-7-day differentiated bipolar-

shaped (A) and pyramidal-shaped (B) induced neurons from controls (Ctrl; black bars, n=10 bipolar and n=9 pyramidal) and patient DS1 (gray bars; n=16 bipolar, p=0.473 vs. control and n=9 pyramidal, p=0.693 vs. control) are not significantly different, and no differences were seen between bipolar and pyramidal neurons within groups (p=0.85 and 0.47 for control and DS1, respectively). (C) Representative I_{Na} from a 4-week differentiated DS1 induced neuron. Current is blocked with the addition of 300 nM TTX. (D, E) Activation and inactivation curves for pyramidal (D, n=9 control; n=9 DS1) and bipolar (E, n=10 control; n=15 DS1) induced neurons after 3-5-week differentiation. (i) Mean parameters from the inactivation curves; control in black and DS1 in gray. (ii) Mean data (symbols; triangles for pyramidal neurons and circles for bipolar neurons) and average curves from fit (lines). (iii) Mean parameters from the activation curves. Error bars indicate means ± s.e.m.

Supplementary Figure 5. DS1 or DS2 induced neurons show spontaneous firing and bursting behavior. (A) A representative recording of spontaneous action potential (AP) firing with bursting activity from a DS1 pyramidal cell-like neuron. (B) Part of the trace in (A) indicated by the asterisk (*) is shown on an expanded time scale. The arrows indicate some sub-threshold spontaneous depolarizations that failed to generate APs. (C) A representative recording of spontaneous AP firing with bursting activity from a DS2 bipolar-shaped neuron. Each trace is a representative example of 16-20 individual cells.

Supplementary Figure 6. Sodium current (I_{Na}) density is increased in pyramidal and bipolar induced neurons with the *SCN1A* mutation after 5-7 weeks of differentiation. (A, B)

Bipolar-shaped (A) and pyramidal-shaped (B) induced neurons from controls (Con; black bars, n=15 bipolar and n=17 pyramidal) and patient DS1 (gray bars, n=5 bipolar; **p = 0.001 vs. control and n=5 pyramidal; *p = 0.029 vs. control. Sodium current densities between bipolar and pyramidal neurons within groups were not significantly different (p=0.105 and 0.106 for control and DS1, respectively). Error bars indicate means ± s.e.m.