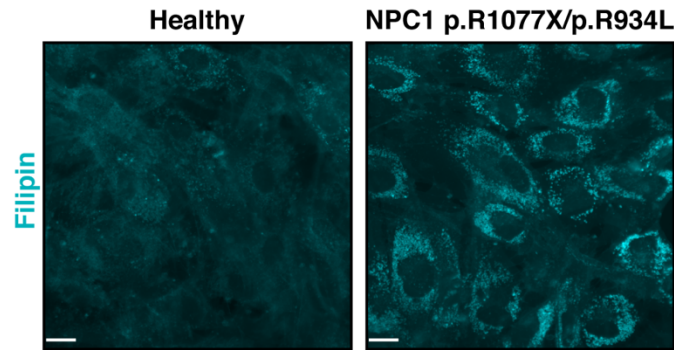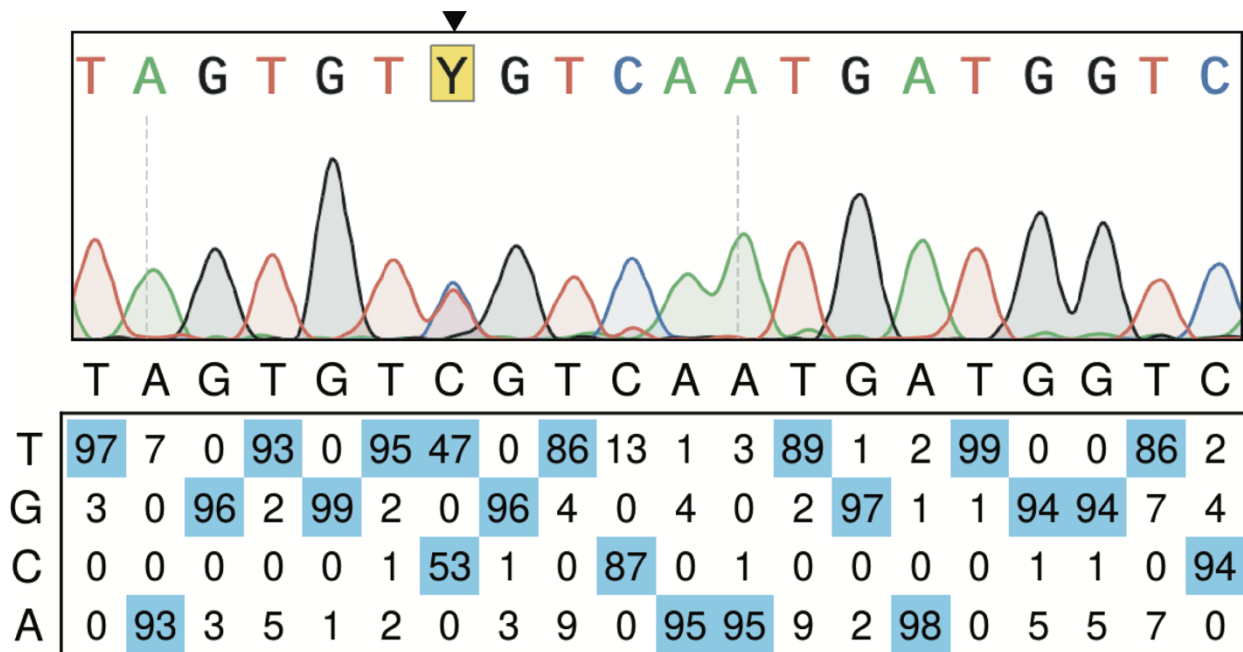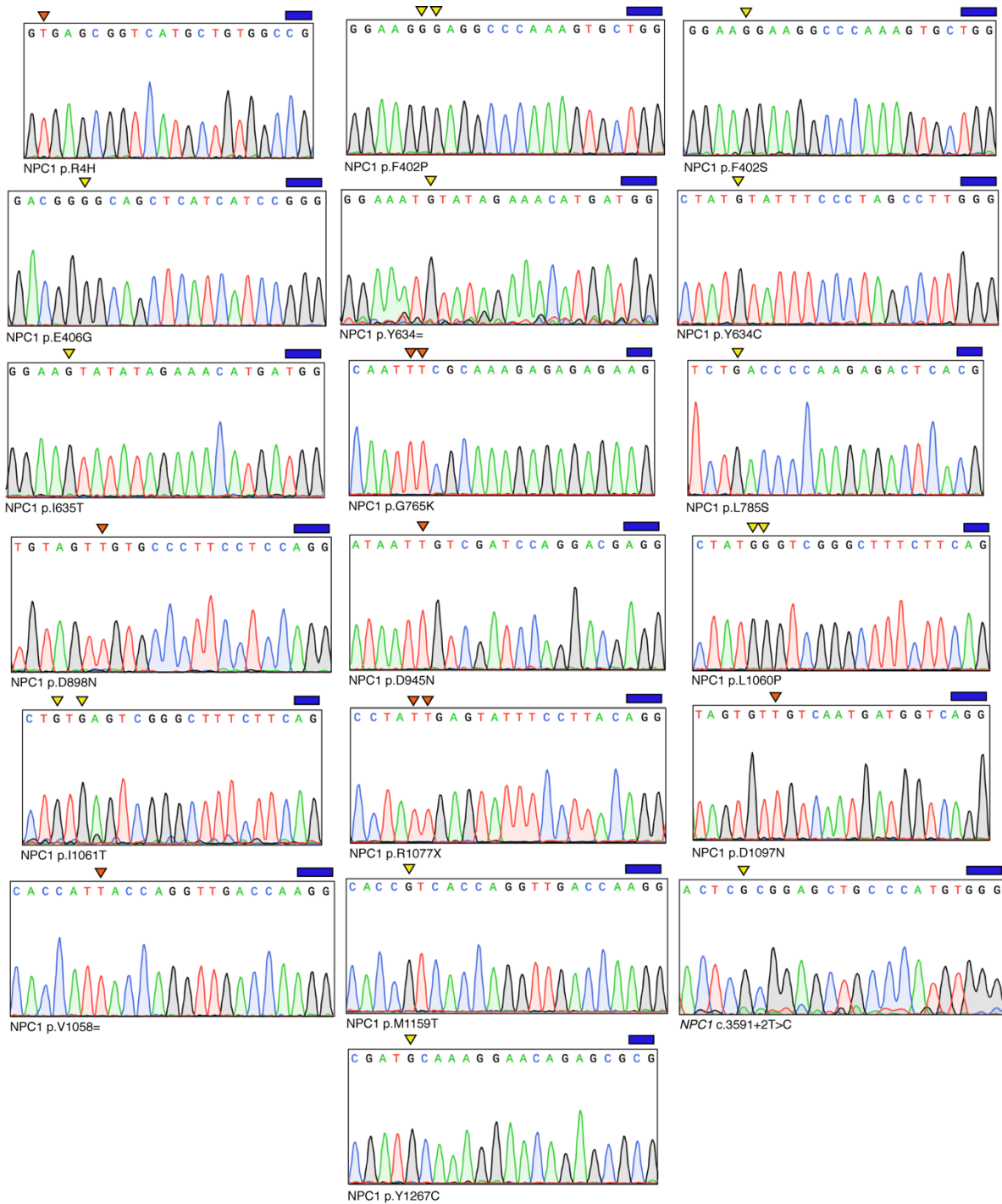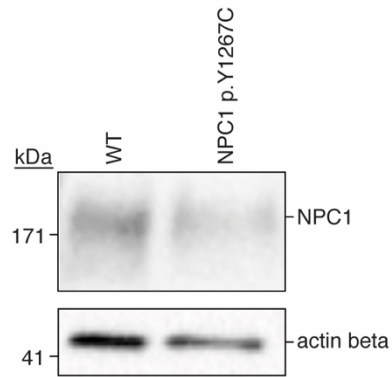# Supplemental Figures

Supplemental Figure S1. NPC patient-derived fibroblasts exhibit distinct foci of filipin staining. Healthy donor (left) and patient-derived fibroblasts (right) display differential staining with filipin. Scale bars: 20μm.


Supplemental Figure S2. Base editing is detectable in a bulk population. Top, a sequencing chromatograph from a bulk population of edited HAP1 cells targeting the NPC1 c.3289G>A locus (NPC1 p.D1097N). Arrowhead indicates the targeted base; Y annotation indicates a pyrimidine. Bottom, editing plot estimating the percent contribution of each nucleotide to each Sanger sequencing base call, demonstrating an editing rate of 47%.

Supplemental Figure S3. Variant generation was confirmed via Sanger sequencing. Sequencing reads from each variant modelled, showing the sgRNA binding site and associated PAM sequence. Mutated nucleotides are marked with a colured arrowhead. Yellow arrowheads indicate a change made via adenine base editing, while orange arrowheads indicate a change made via cytosine base editing. The blue bar indicates the PAM sequence of the targeted region.

Supplemental Figure S4. Expression of NPC1 protein expression in NPC1 p.Y1267C. Expression of NPC1 protein was assayed using an N-terminal antibody. Actin beta was used as a loading control.
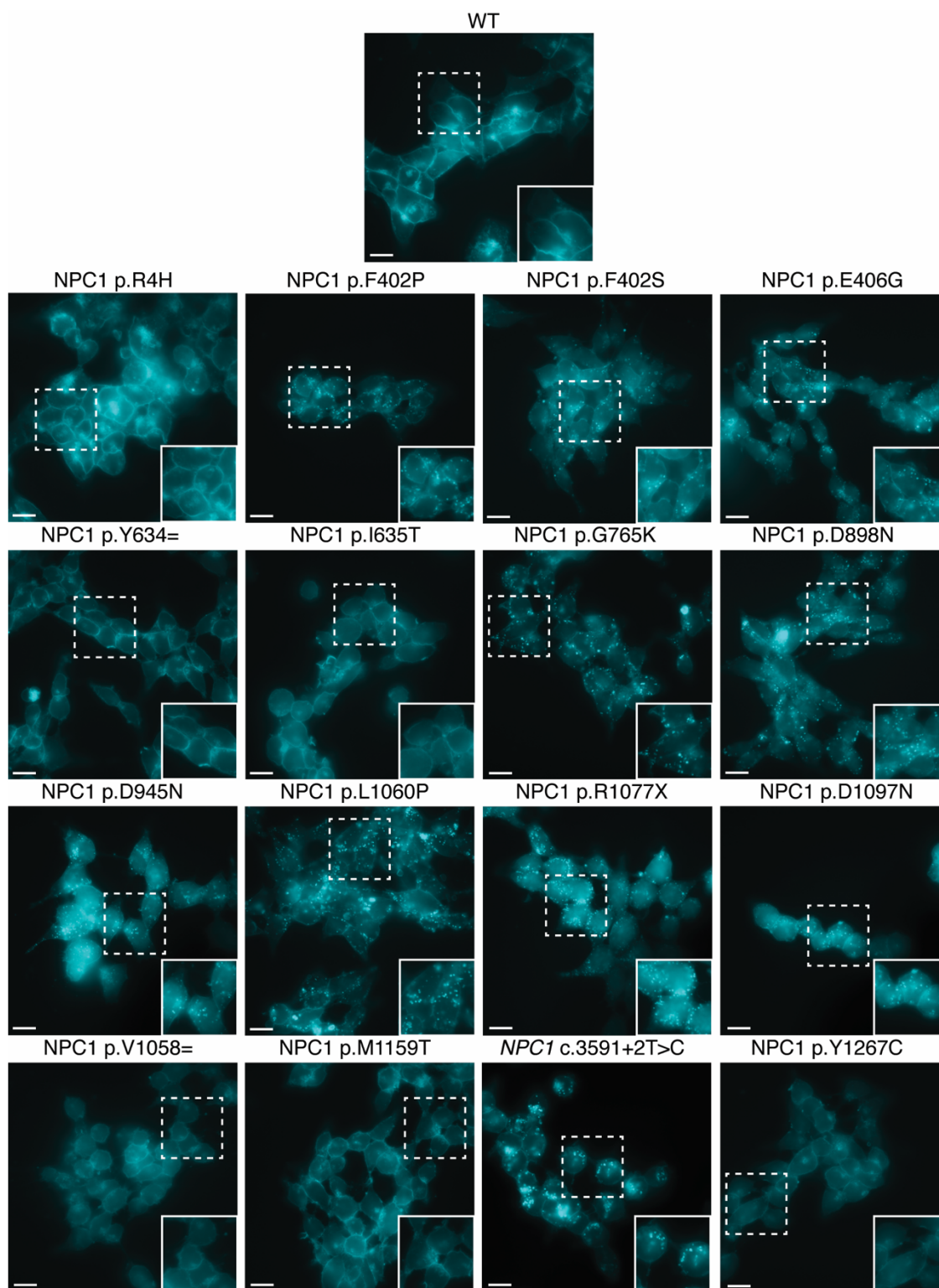
Supplemental Figure S5. Functional characterization of NPC1 variants by filipin staining. White dashed-bordered box has been enlarged twofold and inset at bottom right. Scale bars: 13µm.
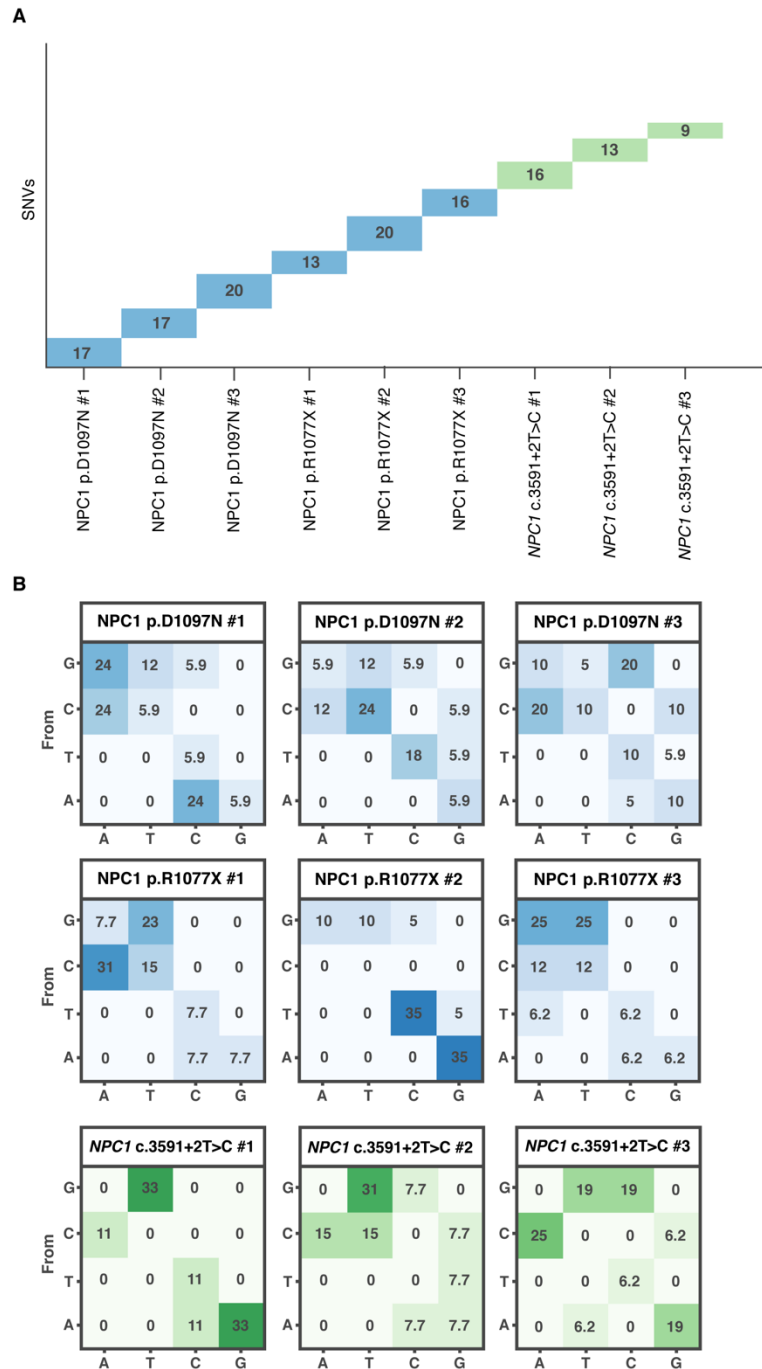
Supplemental Figure S6. Evaluation of off-target editing by CRISPR-Cas9-mediated base editing. RNA-sequencing was performed to evaluate off-targeting editing in the transcriptome of a subset of the NPC models generated. (A) Mutations found in the transcriptome of each cell model ranged in number from 9 to 20 mutations and all were non-overlapping. (B) Heatmaps indicating the specific base changes found in variant calling of RNA-sequencing. Specific nucleotide substitution frequencies appear random. (A, B) Blue colours indicate models where cytosine base editors were used and green colours indicate models where adenine base editors were used.