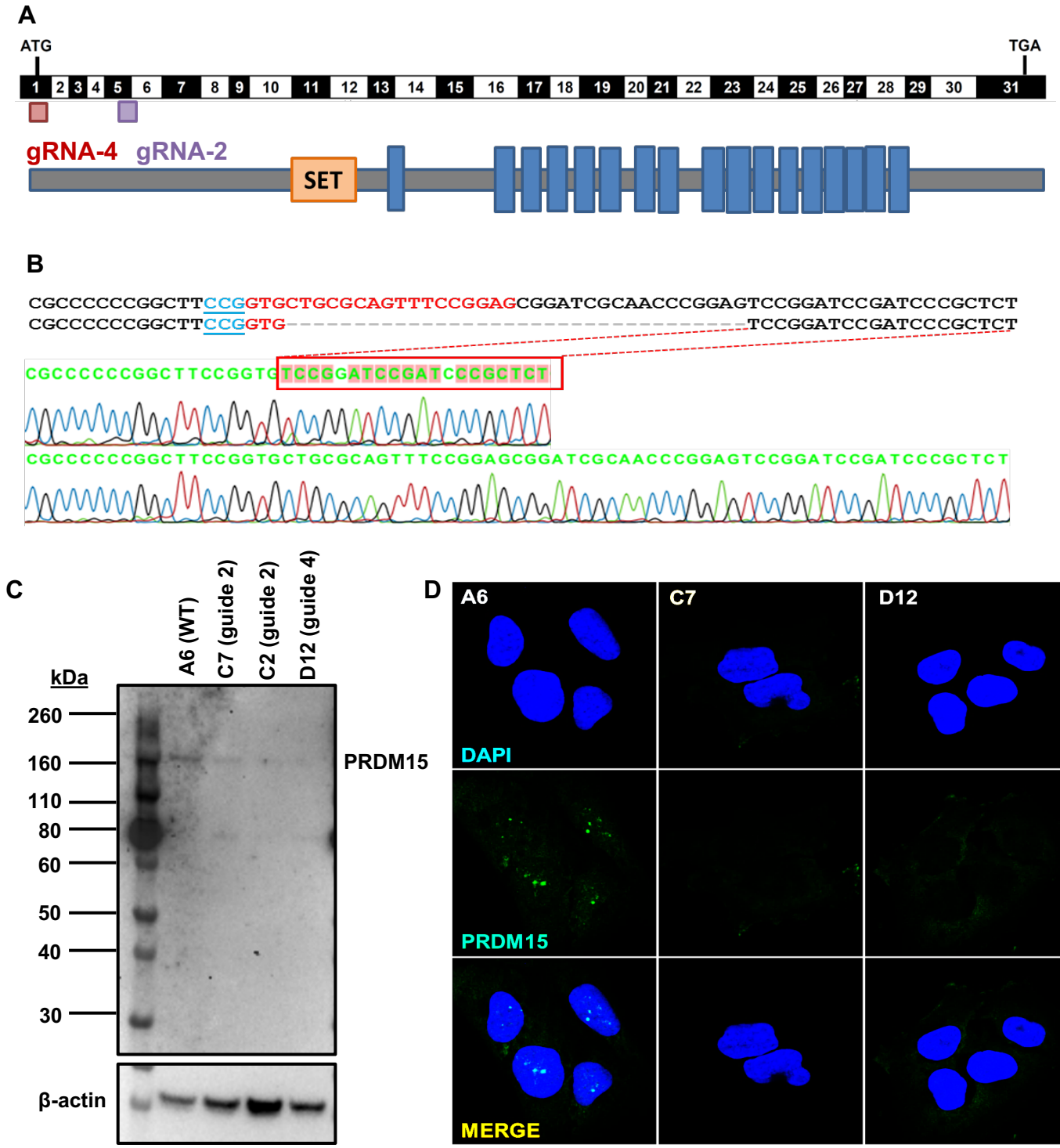


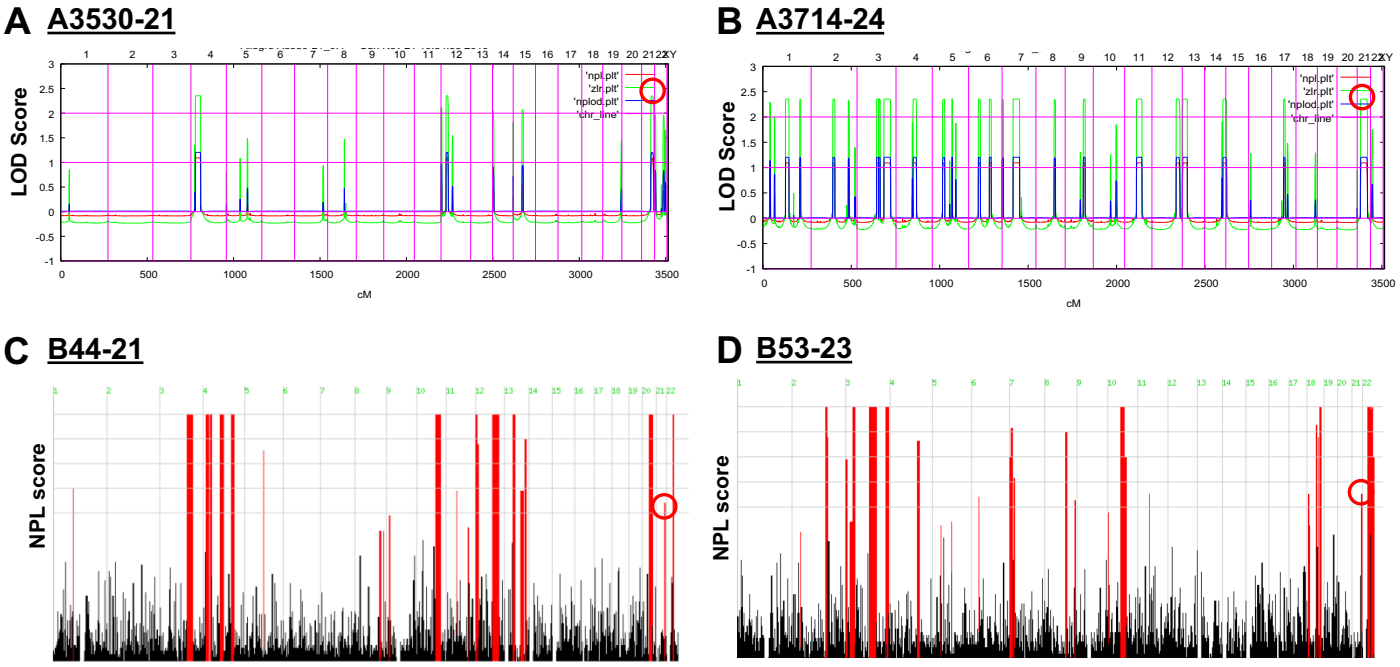
Supplemental Figure 1. Generation of *PRDM15* CRISPR/Cas9 knock-out cell lines (C7 and D12) in human podocytes.

(**A**) Two CRISPR gRNAs were designed to generate two stable knock-out cell lines: **C7** (*PRDM15*-gRNA2) and **D12** (*PRDM15*-gRNA4).

(**B**) Sanger sequencing confirms a 34-bp deletion in the D12 cell line. Sequences in blue denote the PAM sequence and the sequences in red denote the sequence of gRNA4.

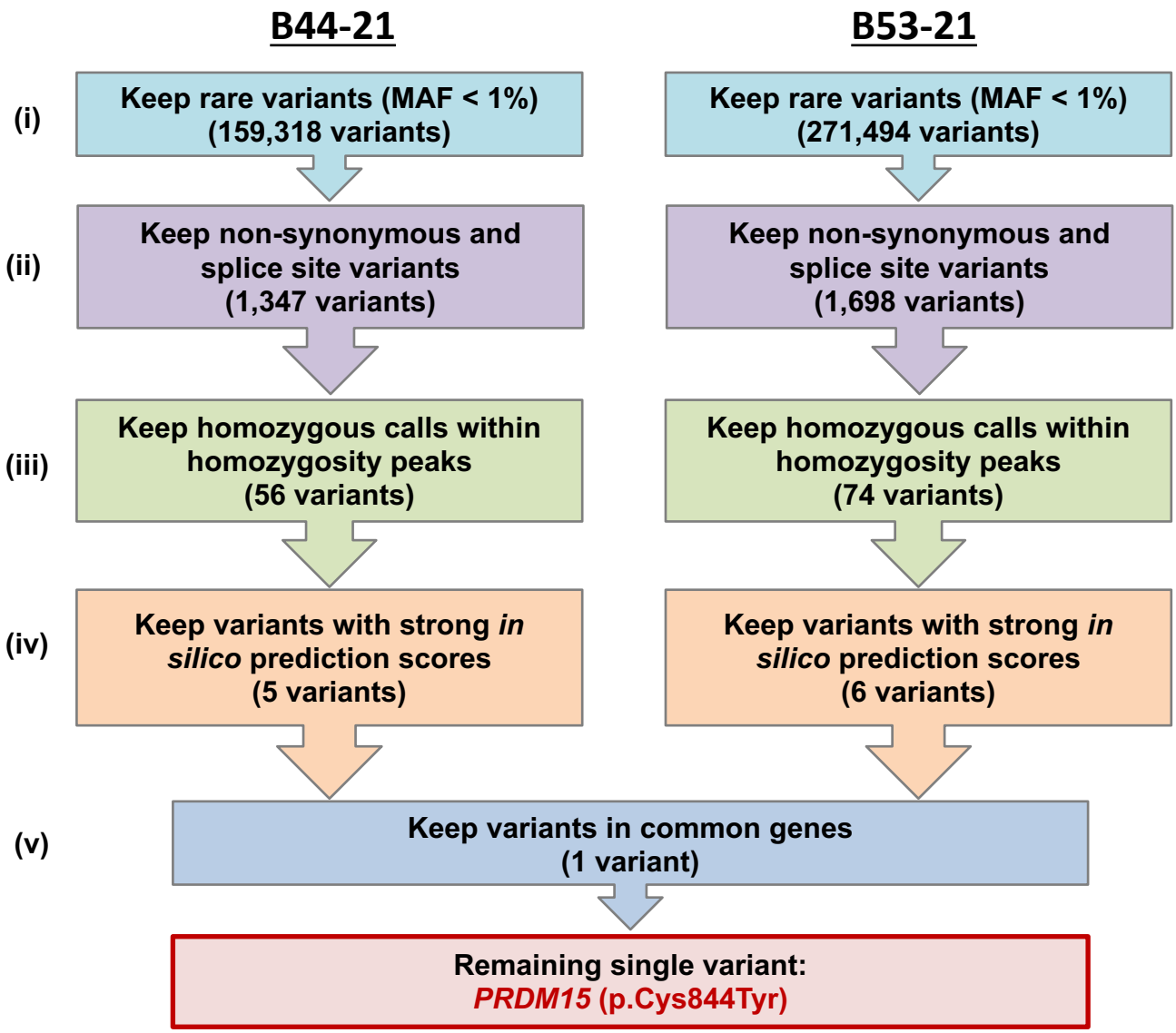
(**C**) Western blot confirming the knockout of PRDM15 for both the C7 and D12 stable cell lines.

(**D**) Immunofluorescence staining demonstrates PRDM15 localization to discrete nuclear domains in the control A6 cells. No nuclear staining is seen in the C7 and D12 *PRDM15* knock-out cell lines.



Supplemental Figure 2. Homozygosity mapping in four families identifies a recessive candidate locus on chromosome 21q containing the *PRDM15* locus.

In four individuals with either isolated nephrotic syndrome or GAMOS-Mildenberger type, A3530-21 (**A**), A3714-24 (**B**), B44-21 (**C**) and B53-21 (**D**), nonparametric LOD scores (NPL) were calculated and plotted across the human genome. The *x*-axis shows Affymetrix 250K *StyI* array SNP positions on human chromosomes concatenated from the p terminus (left) to the q terminus (right). Genetic distance is given in cM. Maximum NPL peaks indicate candidate regions of homozygosity by descent. The *PRDM15* locus (red circle) is positioned within one of the NPL peaks on chromosome 21q.



Supplemental Figure 3. Variant filtering process from whole exome sequencing data for affected individuals B44-21 and B53-21.

i) Keep rare variants that are present with a minor allele frequency (MAF) <1% in healthy control cohorts (Genome Aggregation Database, gnomAD).

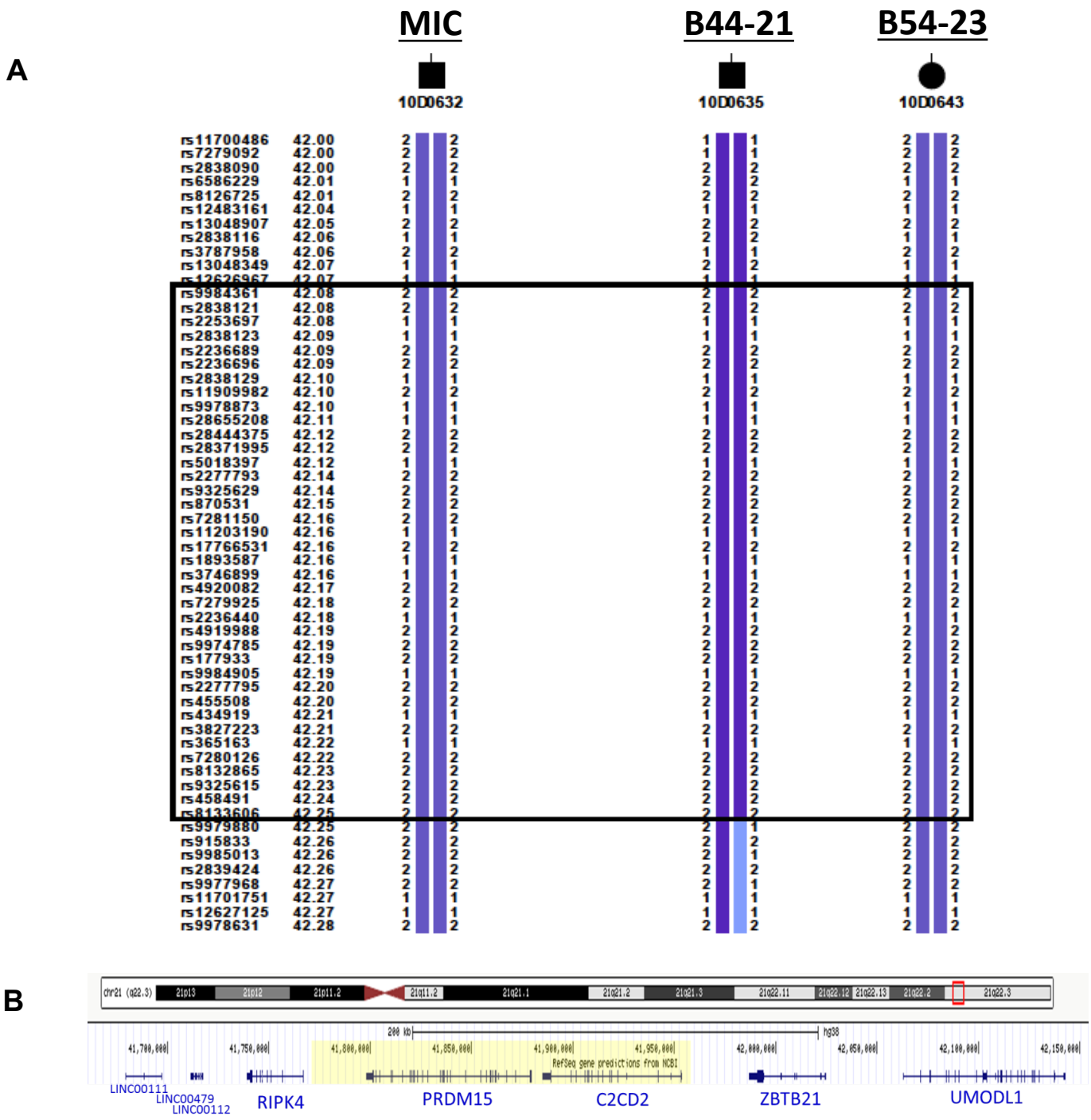
ii) Keep non-synonymous variants and intronic variants that are located within splice sites.

iii) Due to presence of consanguinity, apply an autosomal recessive hypothesis and overlap surviving variants with the homozygosity mapping. Keep all homozygous calls within the regions of homozygosity by descent.

iv) Rank remaining variants based on their predicted likelihoods of being deleterious for the function of the encoded protein. Keep variants that are protein-truncating (i.e. nonsense, frameshift, obligatory splice, or loss of start or stop codons) or that are highly conserved across phylogeny and predicted to be deleterious based on at least two of three prediction programs (PoyPhen2, SIFT, and MutationTaster).

v) Keep variants in common genes in families B44-21 and B53-21

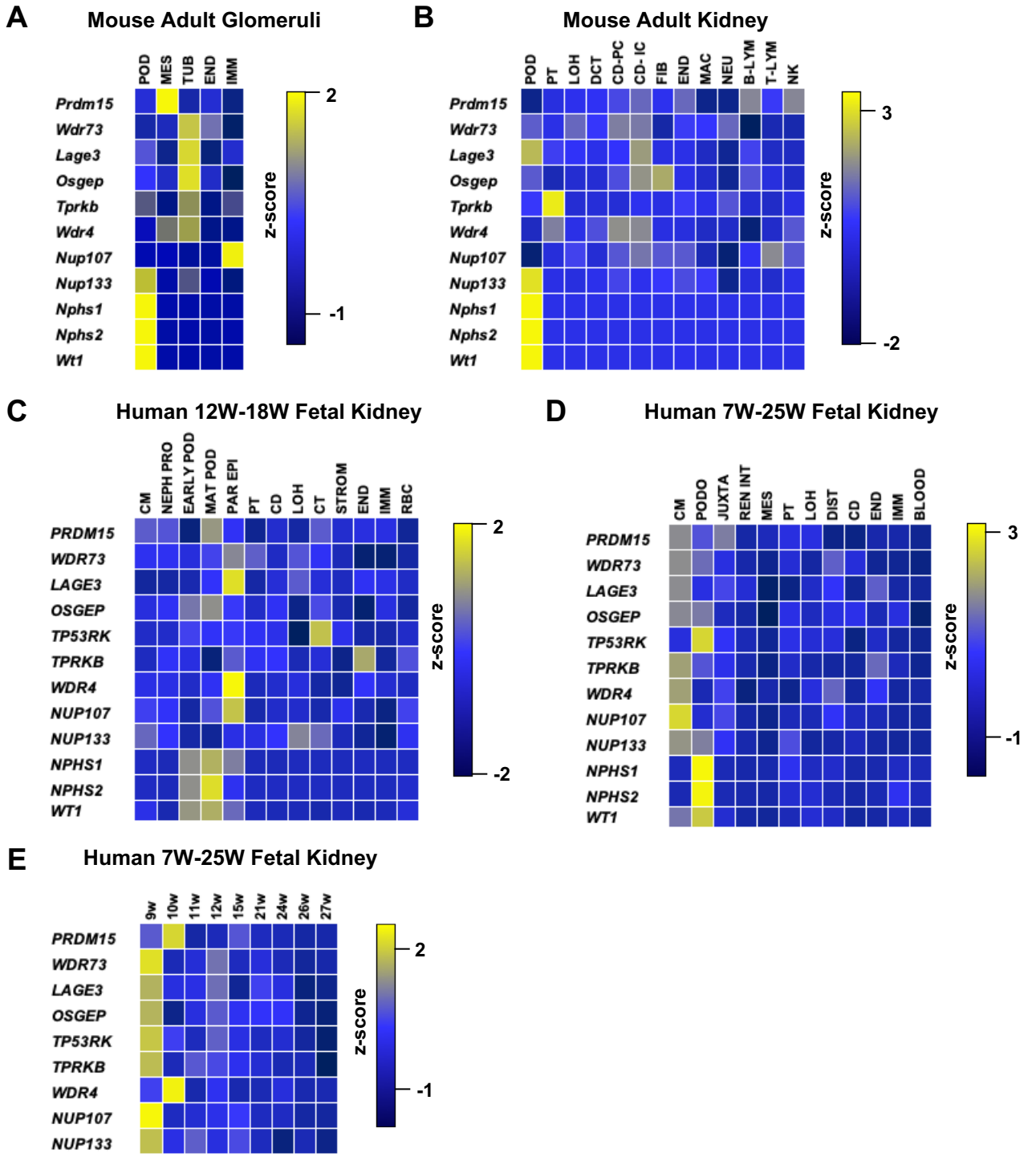
The only remaining variant following this process was a homozygous mutation in *PRDM15* (p.Cys844Tyr).



Supplemental Figure 4. Genome-wide linkage analysis for families MIC, B44, and B54 assuming a common ancestor.

(A) Linkage analysis demonstrates a common haplotype that was homozygous in individuals MIC-21, B44-21, and B54-23 of approximately 183kb, flanked by the SNPs rs13048349 and rs9979880 (chr21:41,774,299-41,957,463).

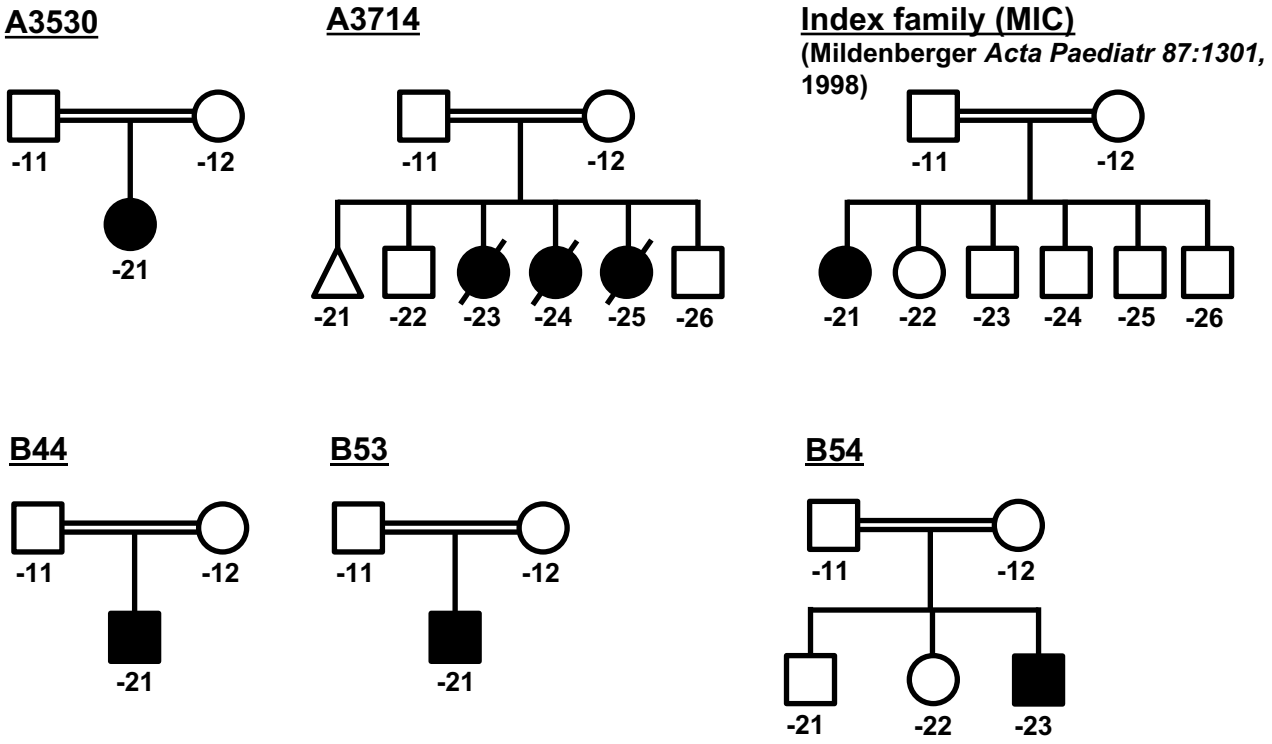
(**B**) The extension of a shared ancestral haplotype in families MIC, B44, and B54 is highlighted in yellow. This interval of 183kb contains only two genes, *PRDM15* and *C2CD2*.



Supplemental Figure 5. *PRDM15* expression in adult and developing kidneys.

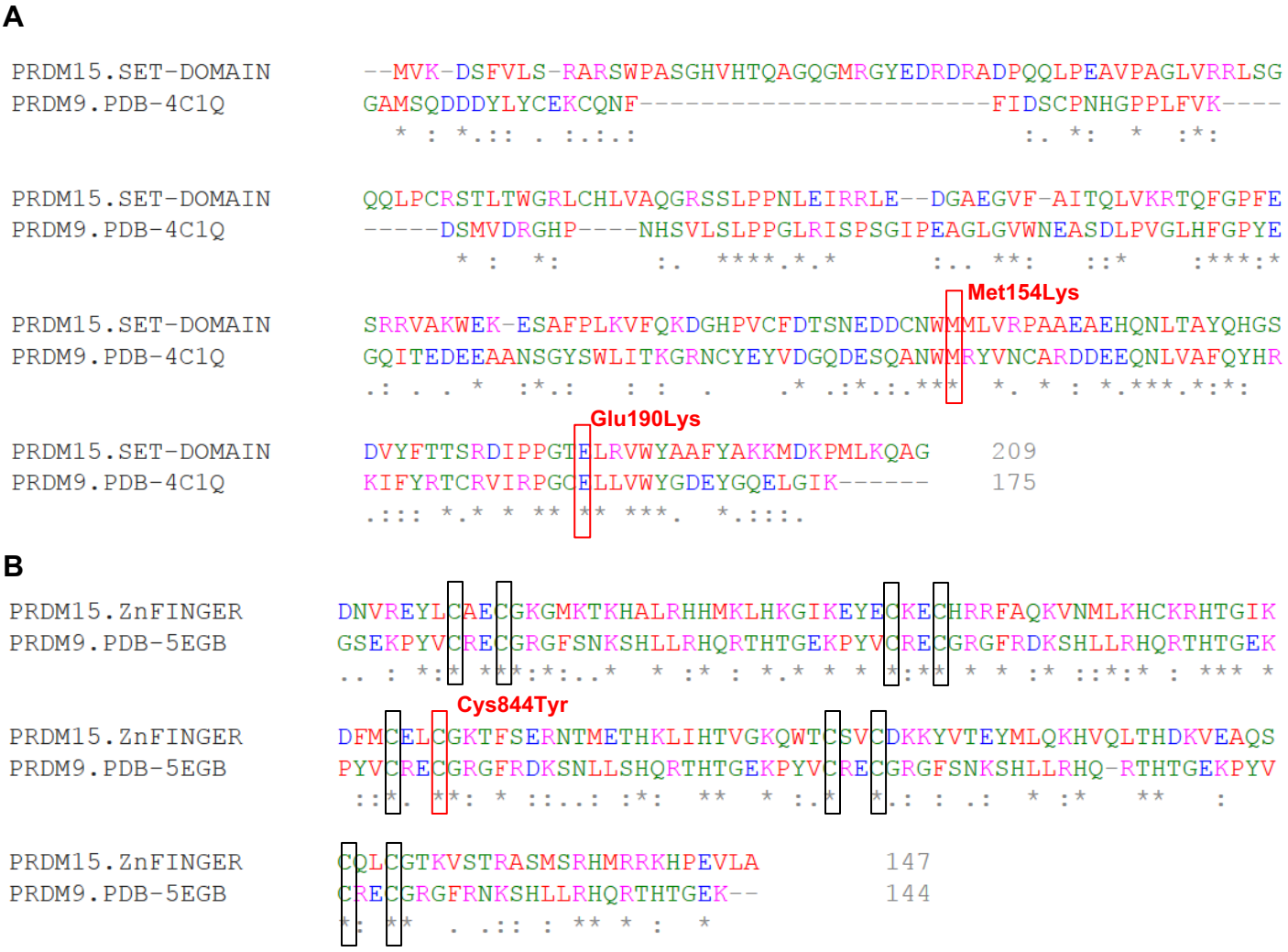
Expression of *PRDM15* and other genetic causes of Galloway Mowat Syndrome and isolated nephrotic syndrome based on previously published single cell RNAseq data from **(A)** mouse adult glomeruli (Karaiskos *JASN* 29:2060, 2018), (**B**) mouse adult kidneys (Park *Science* 360:758, 2018), (**C**) human fetal kidneys (12-18 weeks gestation) (Menon *Development* 145, 2018), and (**D**) human fetal kidneys (7-25 weeks gestation) (Wang *Cell Rep* 24:3554, 2018). *PRDM15* is expressed in the cap mesenchyme and podocytes in developing kidneys. (**E**) *PRDM15* expression based on human fetal gestational age (Wang *Cell Rep* 24:3554, 2018). Z scores are based on percentage of cells expressing *PRDM15* and expression level within cells.

CD, collecting duct; CM, cap mesenchyme; CT, collecting tubule; DCT, distal collecting tubule; End, endothelial; Fib, fibroblast; Imm, immune cell; LOH, loop of henle; Lym, lymphocyte; Mac, macrophage; Mes, mesenchyme; NK, natural killer; Neph Pro, nephron progenitor; Neu, neutrophil; Par Epi, parietal epithelial; Pod, podocyte; PT, proximal tubule; RBC, red blood cell; Strom, stromal cells; Tub, tubule



Supplemental Figure 6. Pedigrees of families with biallelic *PRDM15* mutations.

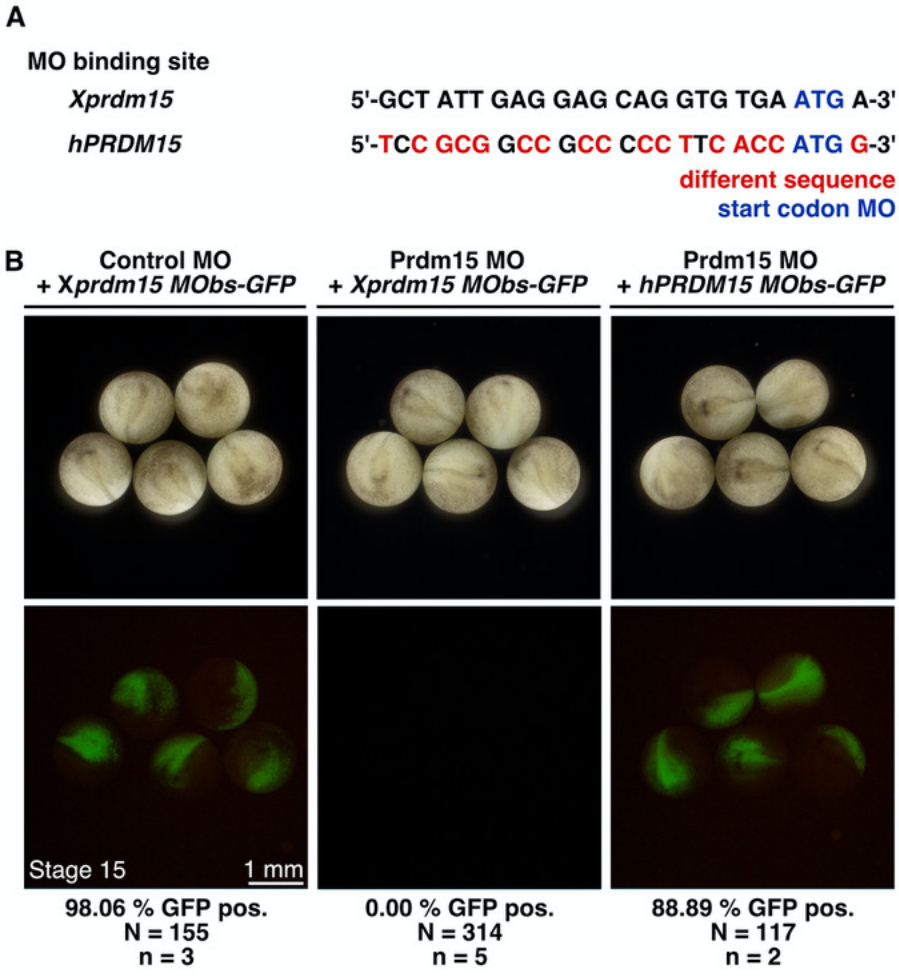
Squares indicate male family members and circles indicate females. Slashes indicate deceased individuals and solid symbols represent affected family members. Double horizontal bars indicate consanguinity. The numbers below each circle and square indicate generation and sibling number. The index family (MIC) has been described in **Mildenberger *Acta Paediatr* 87:1301, 1998.**



Supplemental Figure 7. Amino acid sequence alignment of the SET and zinc finger (ZNF) domains of human PRDM15 and its paralog PRDM9.

(**A**) Alignment of the sequences from the SET domains of human PRDM15 and mouse PRDM9 (PDB 4C1Q) shows ~31% amino acid sequence identity. Red boxes denote the two different PRDM15 mutations, Met154Lys and Glu190Lys, identified in individuals A3530-21 and A3714-24, respectively.

(**B**) Alignment of the sequences from the ZNF domains of human PRDM15 and human PRDM9 (PDB 5EGB) shows ~34% amino acid sequence identity. The red box denotes the PRDM15 mutation, Cys844Tyr, identified in the individuals with GAMOS. Black boxes denote the other zinc complexing amino acid residues in the ZNF domain.

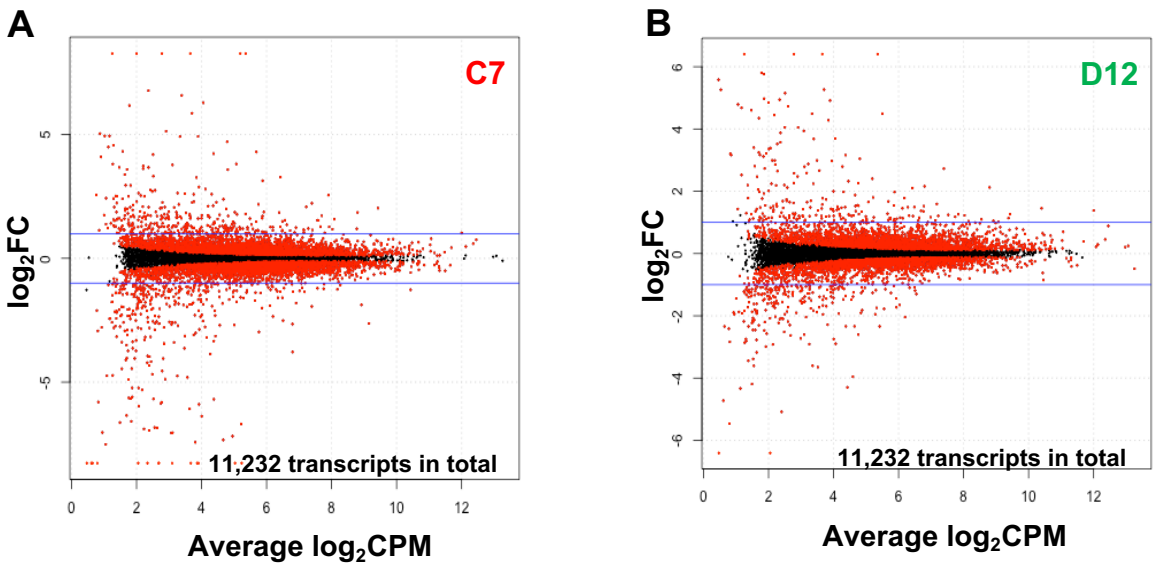


Supplemental Figure 8. Prdm15 MO specifically binds *Xenopus prdm15* RNA.

(**A**) MO binding sites (bs) of *Xenopus prdm15* (*Xprdm15*) and human *PRDM15* (*hPRDM15*) are indicated. The ATG start codon is highlighted in blue and the different bases in the *hPRDM15* binding site are shown in red.

(**B**) MO binding sites were cloned in front of and in frame with *GFP.* The GFP fusion constructs were co-injected together with Prdm15 or Control MO at the 2 cell stage and monitored in stage 15. Prdm15 MO but not Control MO specifically blocks the translation of the *Xenopus prdm15 Mobs-GFP*. The *hPrdm15 Mobs-GFP* construct was not targeted by the Prdm15 MO. The percentage of GFP-positive embryos are given.

n, number of independent experiments. N, number of analyzed embryos in total.



Supplemental Figure 9. Volcano plots of differentially regulated genes in *PRDM15* CRISPR/Cas9 knock-out cell lines.

Volcano plots of differentially regulated genes in two *PRDM15* CRISPR/Cas9 knock-out cell lines, **(A)** C7 and **(B)** D12. Genes that are differentially regulated (adjusted p-value < 0.05) are depicted as red dots, and those whose differential expression does not reach statistical significance are depicted in black.