

Supplemental Data

Mutations of the Transcriptional Corepressor

ZMYM2 Cause Syndromic

Urinary Tract Malformations

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Supplemental Data

Supplementary Text

Since the nuclear localization site (NLS) usually consists of one or more short sequences of positively charged lysines or arginines exposed on the protein surface, we hypothesized that a new NLS should be located in p.718-p723. To test this hypothesis, we employed immunofluorescence of wild type and three missense mutated ZMYM2 proteins (Arg. in p.718, p.719 and p.723 mutated to Ala). The missense mutant protein (p.Arg718Ala) showed the same expression pattern as wild type in all cells with a nuclear signal, while the other two missense mutant proteins (p.Arg719Ala and p.Arg723Ala) have a mainly cytoplasmic pattern in all cells with partially nuclear signal in some cells. We therefore conclude that Arg in p.719 or p.723 mutated to Ala is sufficient to influence the nuclear localization of ZMYM2, which suggests that p.719-p723 (RLGLR) is the region of this new functional NLS.

Acknowledgements

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of Medicine & Dentistry at Western University, London, Ontario, Canada.

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N.M. is supported by funding from the National Institute of Health (T32-DK007726-33) grant at Boston Children's Hospital.

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I.O. is supported by the German National Academic Scholarship Foundation (Studienstiftung des deutschen Volkes) and German Academic Exchange Service (DAAD). C.-H.W.W. is supported by funding from the National Institute of Health (Grant T32-GM007748).

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This research was supported by grants from the National Institutes of Health to R.P.L and to F.H. (DK088767).

Figure S1. Confocal microscope analysis of ZMYM2 following MYC tagged ZMYM2 transfection with wild type or mutant.

(A) Location of Myc-ZMYM2 wild type and mutant proteins in Hek293 cells.

ZMYM2 wild type (wt) and missense mutant protein were diffusely nuclear localized. The **truncated** proteins (p.Gly257fs*, p.Gln398, p.Arg540*) showed cytoplasmic pattern in all cells. However, in some cells the locations of some **truncated** proteins (p.Tyr763Glnfs*6, p.Cys812Aspfs*18, p.Asp997del, p.Cys823*, p.Gly1045Argfs*33) were partially nuclear, suggesting that the early repetitive Nuclear Localization Signal (NLS) (p.1038-1049 and p.1250-1284) greatly affected the location of ZMYM2 protein, while, there should be another functional NLS between p.540 and p.763. (White bar = 15µm)

Figure S2 *zmym2* Expression and Depletion in *Xenopus*

A Figure depicting expression of *zmym2* (referred to as *zfp198*) in *Xenopus laevis* embryos at a variety of stages (Adapted from Nielson *et al.* Dev Dyn 2010).

B Figure deposited in Xenbase by the Papalopulu lab depicting expression of *zmym2* in a stage 28 *Xenopus tropicalis* embryos.

C Expression of *zmym2* in a stage 34 *Xenopus tropicalis* embryo with sense control shown for comparison. Arrows indicate enrichment of expression in pronephros and pronephric tubule.

D Agarose gel confirming splice blocking achieved by MO injection. Upper arrowhead indicates full length product of PCR flanking exon 3 from cDNA while lower arrowhead indicated splice blocked product seen only in splice blocking MO injected embryo cDNA.

Figure S3 Sanger confirmation with segregation (if available) for each of the heterozygous mutations identified in families.

Figure S4. Luciferase reporter assay, driven by a LexA-VP16 fusion protein, to test if Gal4-ZMYM2 fusion protein for the missense mutants could repress transcription.

Lex-VP16 is transfected to activate the reporter, and then either 5 or 50ng of GAL-ZMYM2 (wild-type or mutants as indicated) are added. The transcriptional repressive activity is retained in both the wild type and missense mutant proteins.

Figure S5 Expression of *ZMYM2* and patient variant sequences in *zmym2* morphant *Xenopus* embryos identifies variants with loss of function in pronephric development.

Xenopus embryos were injected with MO at the one-cell stage. mRNA derived from either wildtype or variant *ZMYM2* was then injected at the 2-cell stage. Proximal pronephric area was scored at stage 34. MO only and MO + mRNA injected sides of embryos receiving wildtype or variant mRNA. Scale bars depict 500 μ m.

Figure S6. Additional data on Zmym2 heterozygous mutant mouse model.

A. Frameshift mutation in ZMYM2^{+/-} mouse models mutation found in individual GM1-21 (c 766_767 GT nucleotide duplication).

B. Curve of non-refluxing animals relative to pressure (centimeters representing the height of dye reservoir; bladder level= 0 cm) for wild-type (n = 25) and ZMYM2^{+/-} (n = 20) **p-value of 0.0039 was calculated using the Gehan-Breslow-Wilcoxon test for survival curves. Grey dotted area represents the average pressure at which the urethra voids ^{+/-} 1 SD.

C. Urethral voiding pressures is unaffected in ZMYM2^{+/-} mice (student t-test).

Figure S7. Zmym2 expression in the developing mouse urinary tract

A. Immunohistofluorescence analysis of wildtype E18.5 kidneys shows low and widespread expression of Zmym2. Cytokeratin 8/18 expression highlights tissue structure. Structures labeled include: UT: ureter tip, RPC: renal progenitor cells, CD: collecting duct, PT: proximal tubules, DT: distal tubules, G: glomerulus. Yellow foci come from autofluorescent blood cells.

B. In situ hybridization of *Zmym2* in E15.5 urogenital systems of female (top) and male (bottom) mice. Images taken from GUDMAP database, Specimens: N-H79Y,N-H7CR.

This study used data from the GUDMAP database, <http://www.gudmap.org> on May 26, 2020, including in situ data generated by McMahon, A. in correspondence with the following publication: Brunskill EW, Park JS, Chung E, Chen F, Magella B, Potter SS. Single cell dissection of early kidney development: multilineage priming. *Development*. 2014;141(15):3093-3101. <https://doi.org/10.1242/dev.074005>

C. Expression levels of Zmym2, Pax2 and Six2 in developing kidney tissues. Note: Mean values of similar samples are presented for E15.5 collecting duct (GSM1585035, GSM1585037, GSM1585042), E15.5 podocytes (GSM1585039, GSM1585036) and E15.5 proximal tubules (GSM1585040, GSM1585034), where error bars show SD. This graph was generated using RNA sequencing data of micro-dissected and FACS-sorted developing tissues, dataset ID: GSE64959.

Figure S8 Identification of a new ZMYM2 Nuclear Localization Signal or Sequence (NLS) site.

- A. Yellow highlights the positively charged lysines or arginines NLS characteristic of NLS. Green numbers indicated the 6 potential NLS are located in the region p.540 – p.763.
- B. Immunofluorescence of wild type (Wt) and the truncated ZMYM2 proteins.
- C. Immunofluorescence of wild type and three missense, mutated ZMYM2 proteins which suggests that p.719-p723 (RLGLR) is the region of this new functional NLS.

Figure S9

A) Bioluminescence Resonance Energy Transfer (BRET) assays to measure effects of ZMYM2 protein truncations on interactions with FOXP1, FOXP2 and wild-type ZMYM2.

Wild-type ZMYM2 and three different truncated constructs of ZMYM2 (pGly257*, pGln398*, pArg540*) were overexpressed as fusion proteins with YFP, and function as acceptor constructs in these assays (X-axis). Co-expressed donor constructs were either NLS (a negative control with nuclear localization signal only), FOXP1, FOXP2 or wild-type ZMYM2 constructs, in each case overexpressed as a fusion protein with Renilla

luciferase (rLuc). Bars represent the corrected mean BRET ratio \pm standard deviation of three independent experiments performed in triplicate (see Methods for details). All three truncated ZMYM2 constructs showed impaired interaction with FOXP1 and FOXP2, compared with wild-type ZMYM2 interaction capacities.

B) Immunoblot analysis of constructs used in BRET assays

Western blot with whole-cell lysates expressing seven different YFP-tagged ZMYM2 constructs, probed with an anti-EGFP antibody. These constructs included wild-type, three missense variants and three stop-gain variants. Lane 1: untransfected cells; Lane 2: wild-type; lane 3: pLys649Arg; lane 4: pTyr763His; lane 5: pAsp997del; lane 6: pGly257*; lane 7: pGln398*; lane 8: pArg540*. This blot demonstrates that all ZMYM2-YFP-fusion proteins used for the BRET assays (wild-type, pGly257*, pGln398*, pArg540*) are expressed at the expected molecular weights.

Figure S10. Proximity-dependent biotin identification demonstrating the ZMYM2 protein interaction landscape or ZMYM2 interactome

The interactome shows that ZMYM2 is significantly enriched in DNA binding transcription factors, transcriptional co-repressors, and proteins linked to chromatin regulation, chromatin organization and SUMO ligase activity ($p=6.7 \times 10^{-5}$). The majority of the components involved multiple previously reported ZMYM2 interactors²⁶: LSD1(KDM1A)-CoREST (Corum complexes 633 and 1492)²⁷, HDAC128 and HDAC2 (Corum 632). IP-MS (immunoprecipitation coupled with mass spectrometry) analyses were identified in our ZMYM2 BioID analysis (HDAC1, HDAC2, KDM1A/LSD1, GTF2I, GSE1/KIAA0182, PHF21A/BHC80, RCOR1, RCOR2, RCOR3, ZNF217, ZMYM3 and ZMYM4)

Figure S11 ZMYM2 truncation mutant BioID Heat Map

Table S1. List of mutagenesis primers used to generate clones representing the variants identified in each family

Table S2. Twelve non-pathogenic missense heterozygous mutations in *ZMYM2* in 13 individuals from 12 families with congenital anomalies of the kidney and urinary tract.

Table S3. List of truncating heterozygous variants of *ZMYM2* that exist in gnomAD.

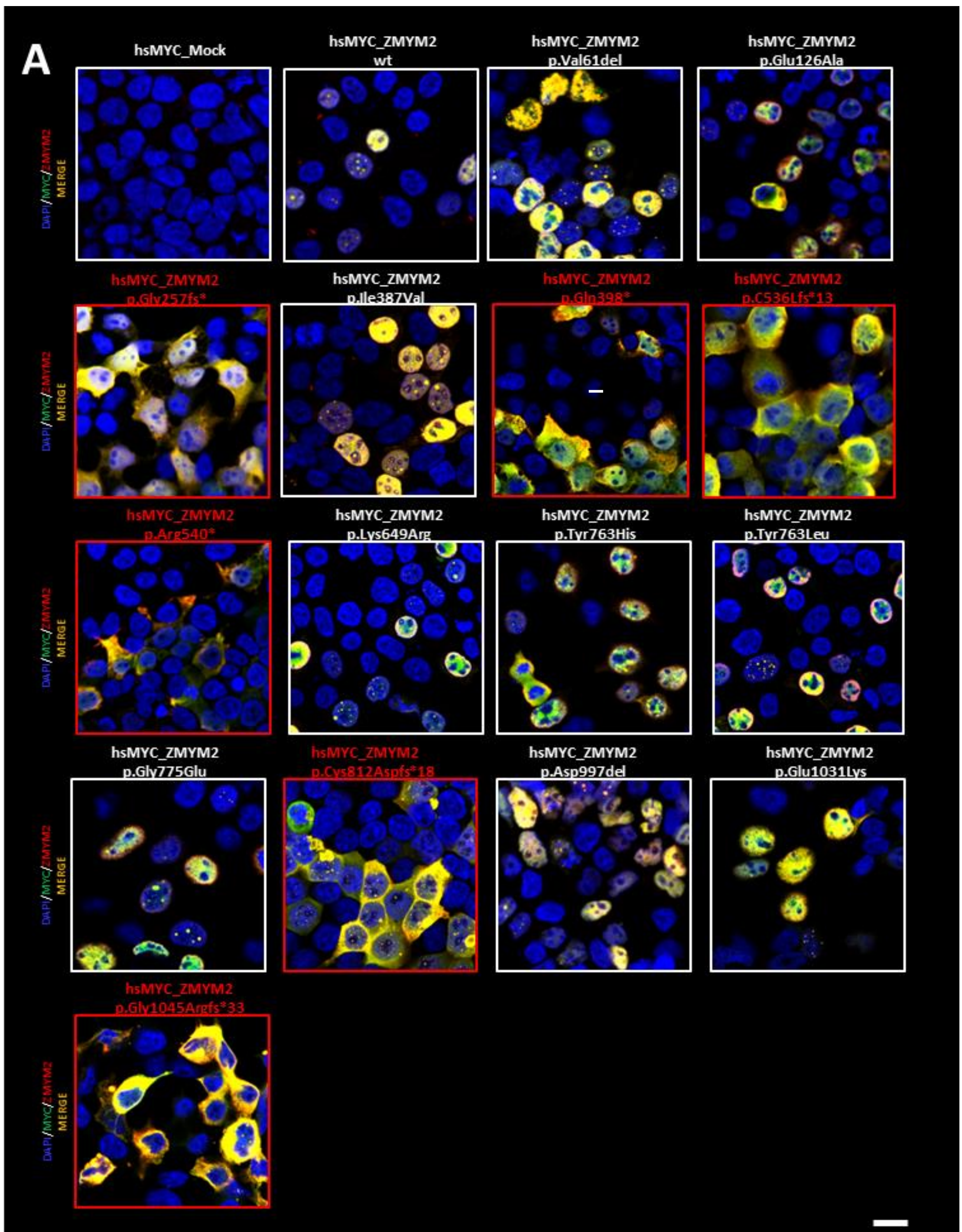
Table S4A. Overview of *ZMYM2* variants identified in two control cohorts of 100 families with steroid resistant nephrotic syndrome and 238 families with nephronophthisis.

Table S4B. Overview of monogenic causes identified in a cohort of 100 patients with steroid resistant nephrotic syndrome.

Table S5. Proximity-dependent biotin identification (BioID) characterizing the *ZMYM2* protein interaction landscape.

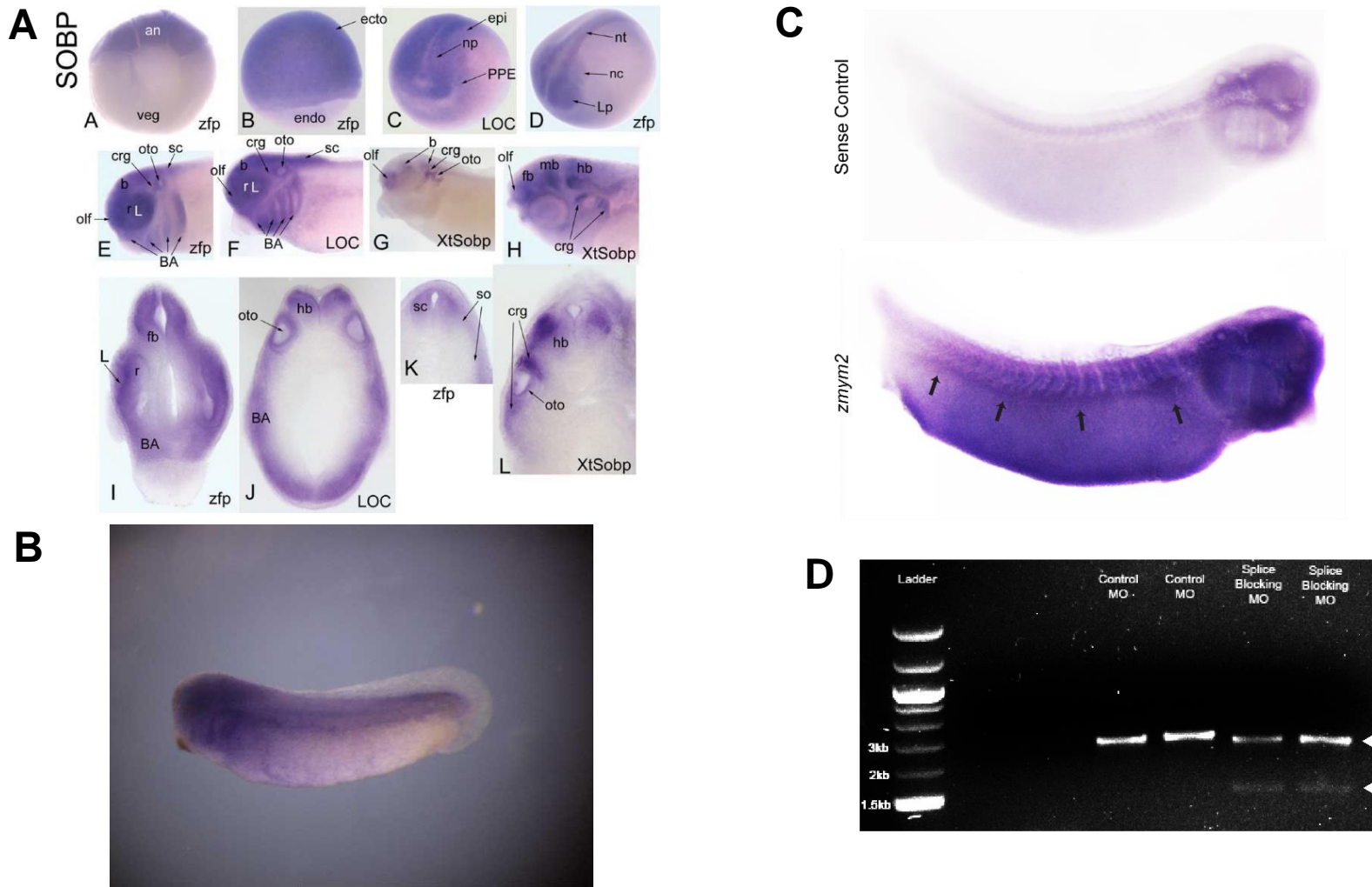
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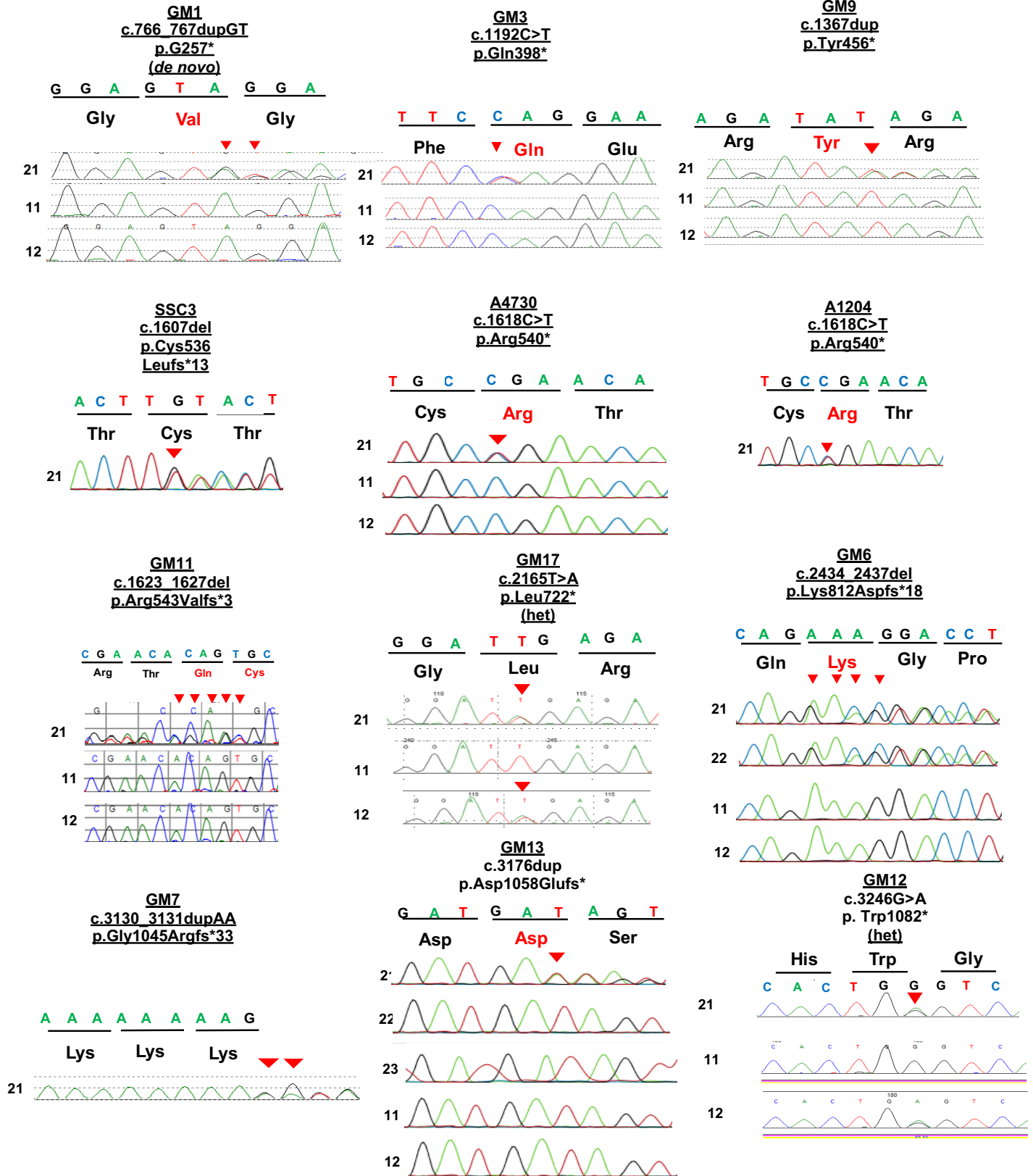
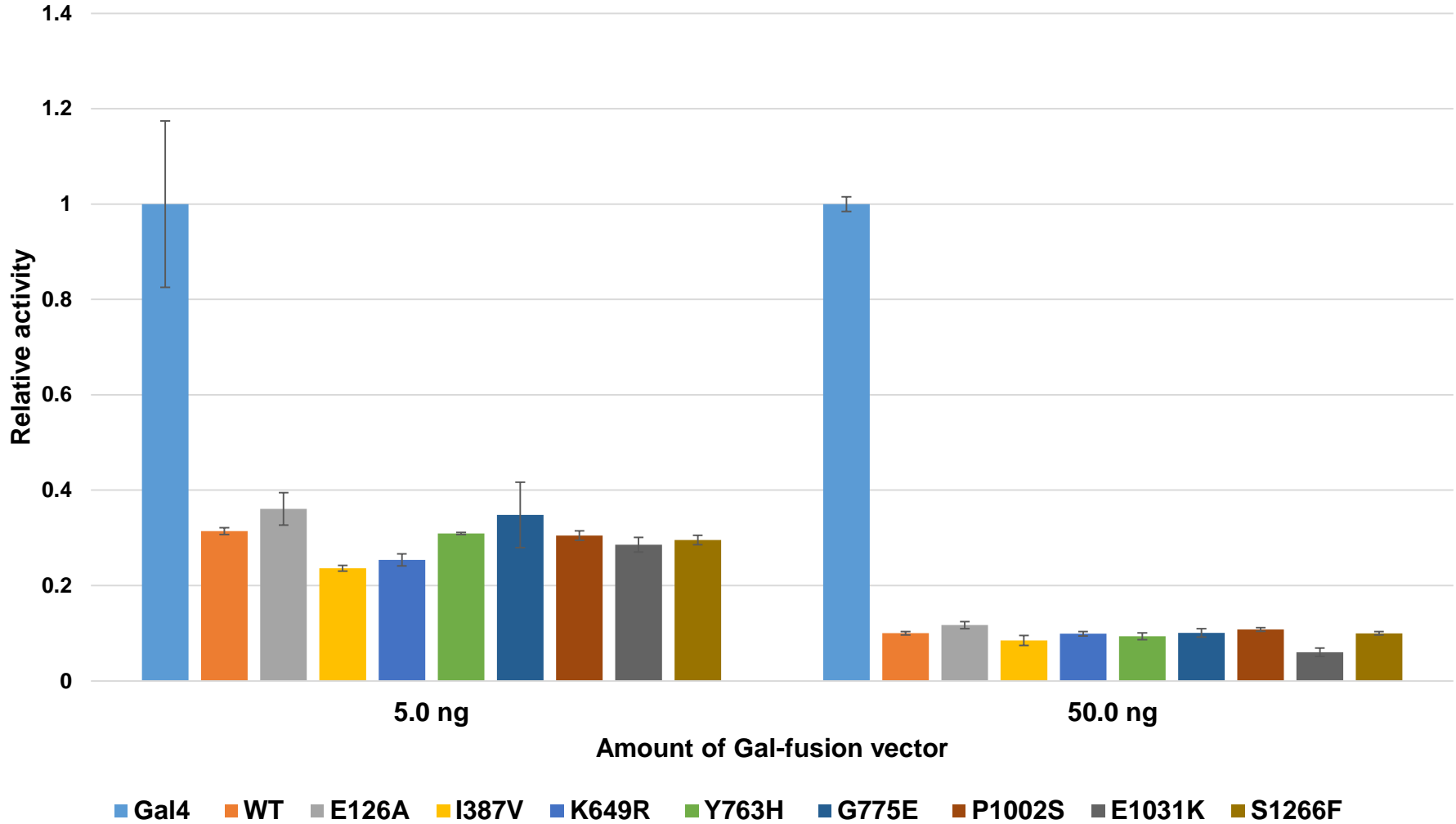


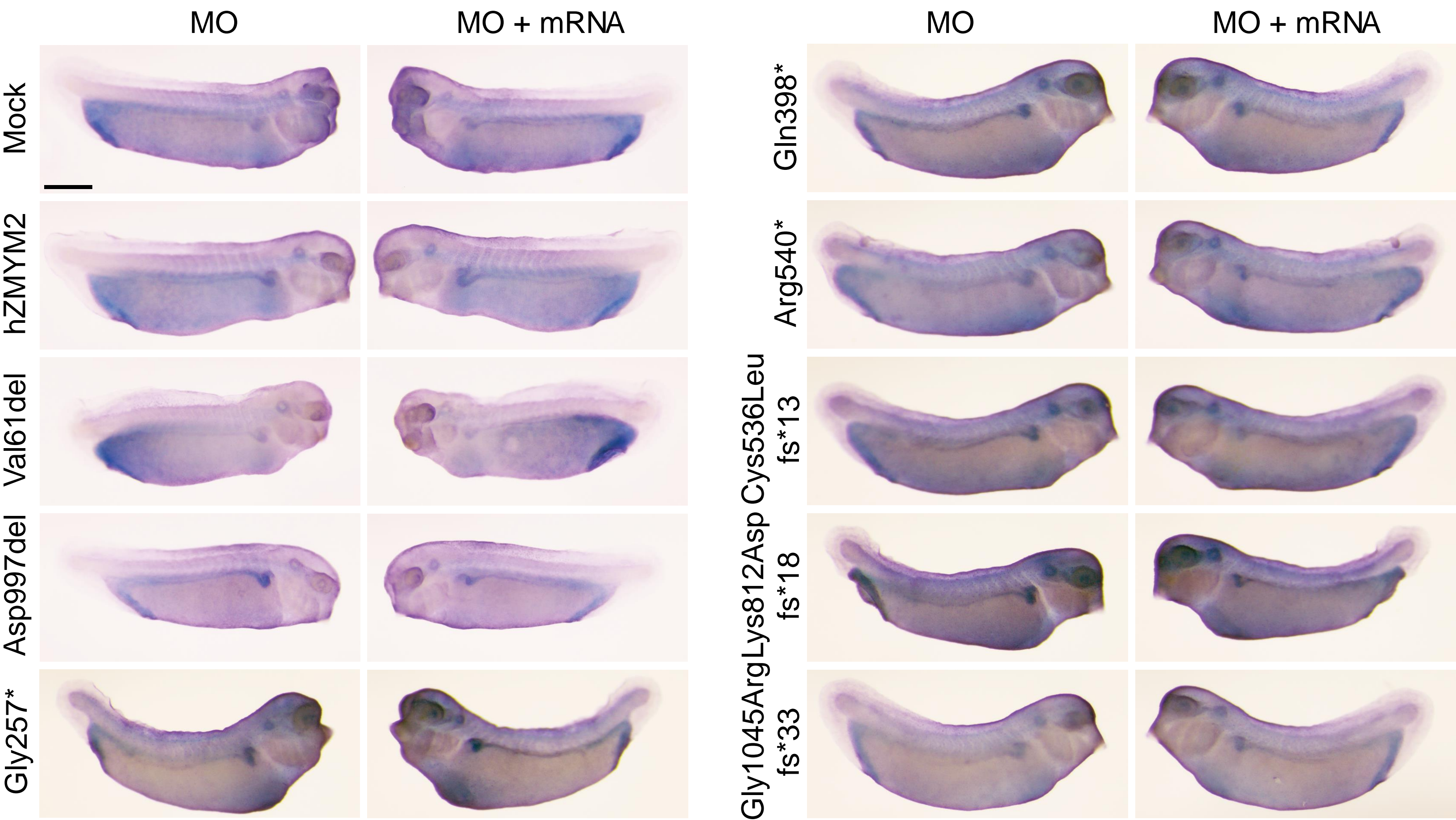
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Scale bars depict 500 μ m.

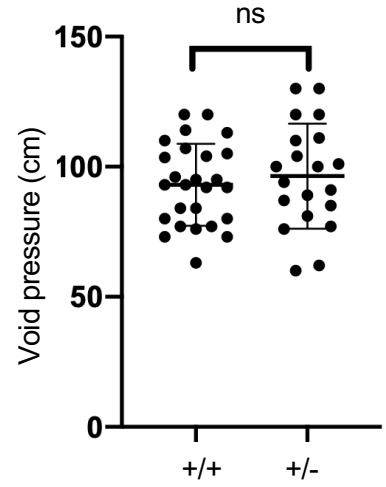
Figure S6. Additional data on Zmym2 heterozygous mutant mouse model.

A

| Human | |
|--------|---|
| WT | 180 E I Q I A N V T T L E T G V S S V N D G Q L E N 205 |
| GT dup | 180 E I Q I A N V T T L E T G V * 194 |
| Mouse | |
| WT | 180 E I Q I A N V T T L E T G V S S V S D G Q L E S 205 |
| GT dup | 180 E I Q I A N V T T L E T G V * 194 |
| Δ1bp | 180 E I Q I A N V T T : L E Q A * 193 |

CRISPR Cas9 cut site

B



C

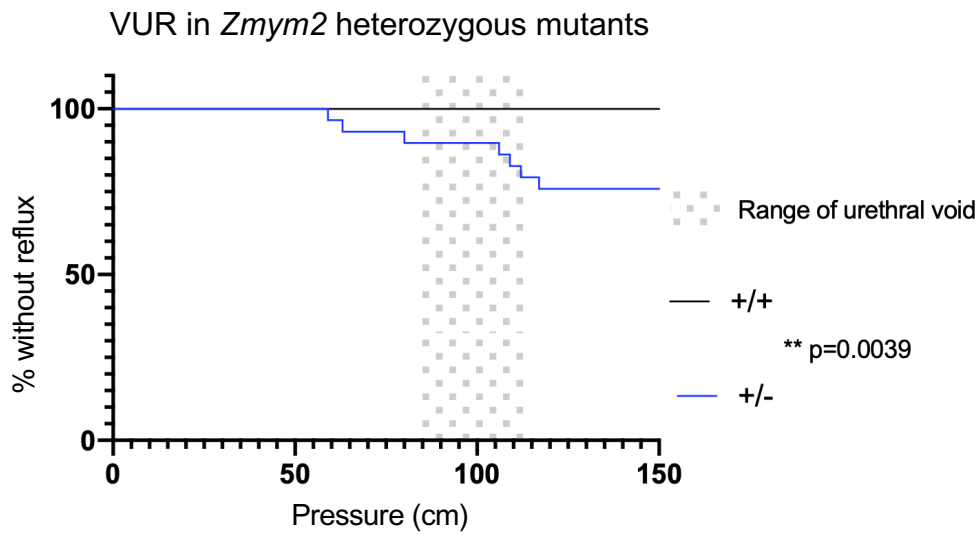
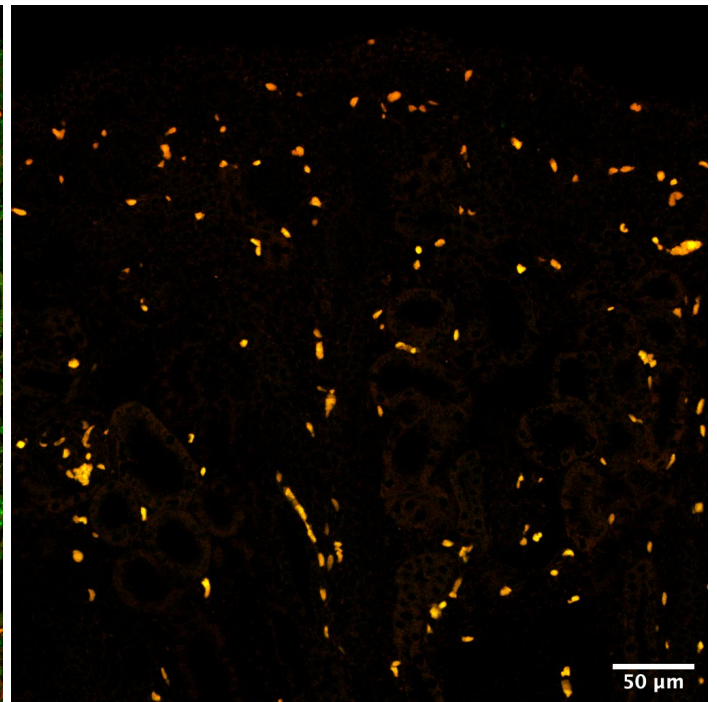
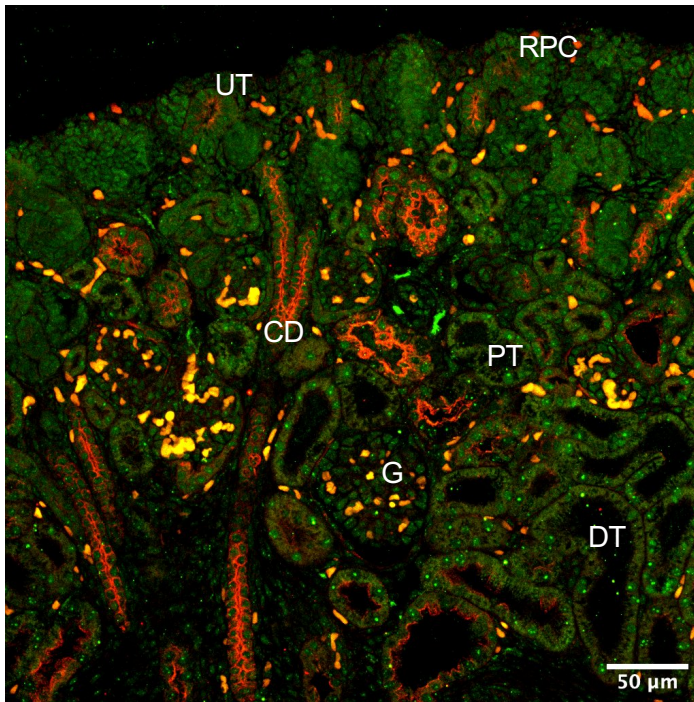


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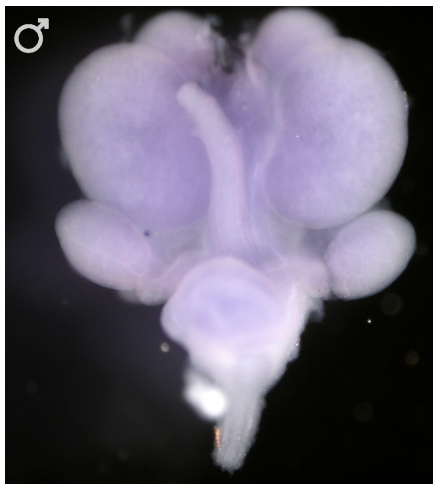
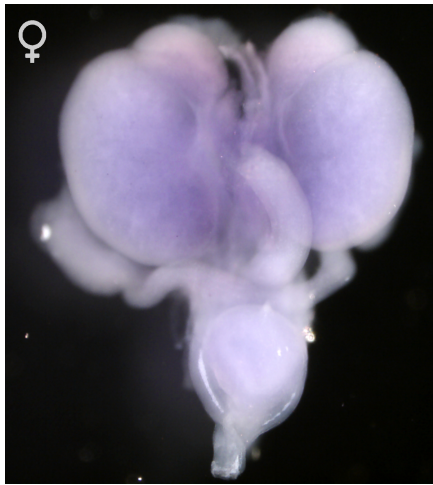
A

Zmym2 ; CK8/18

No primary control



B



C

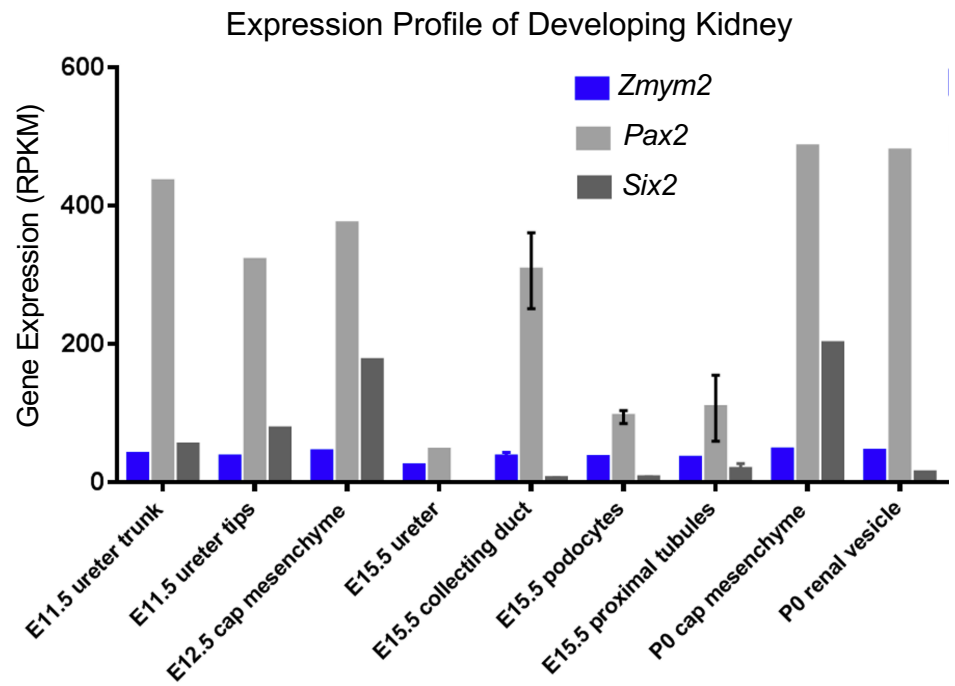
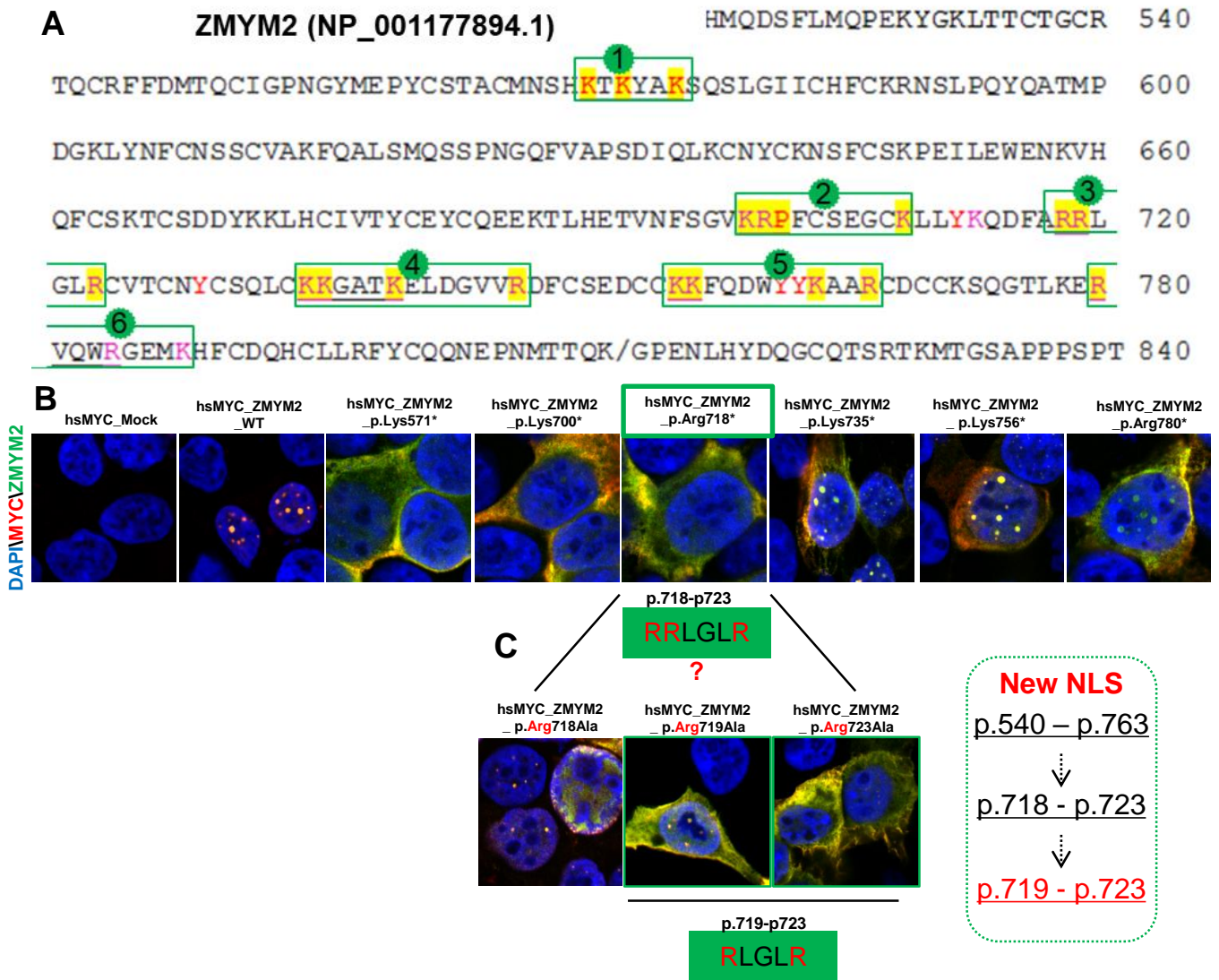
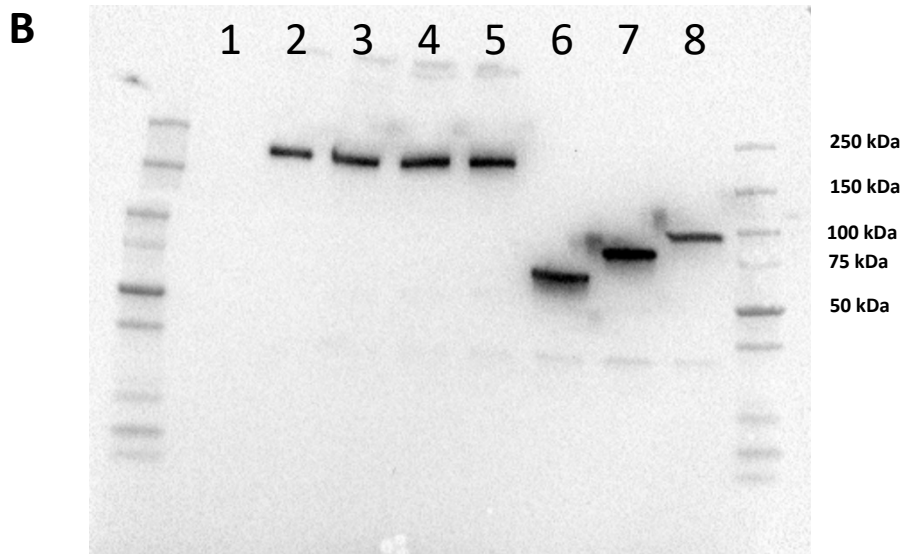
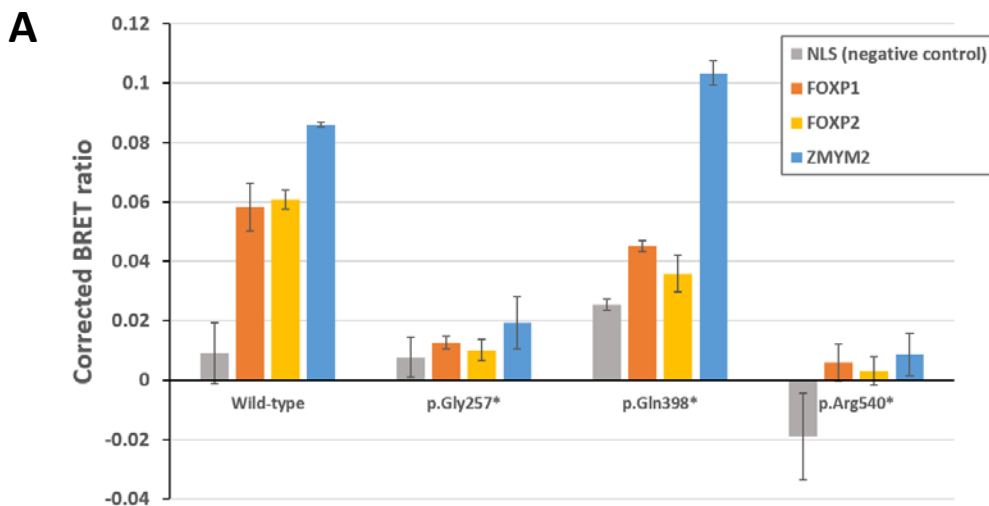


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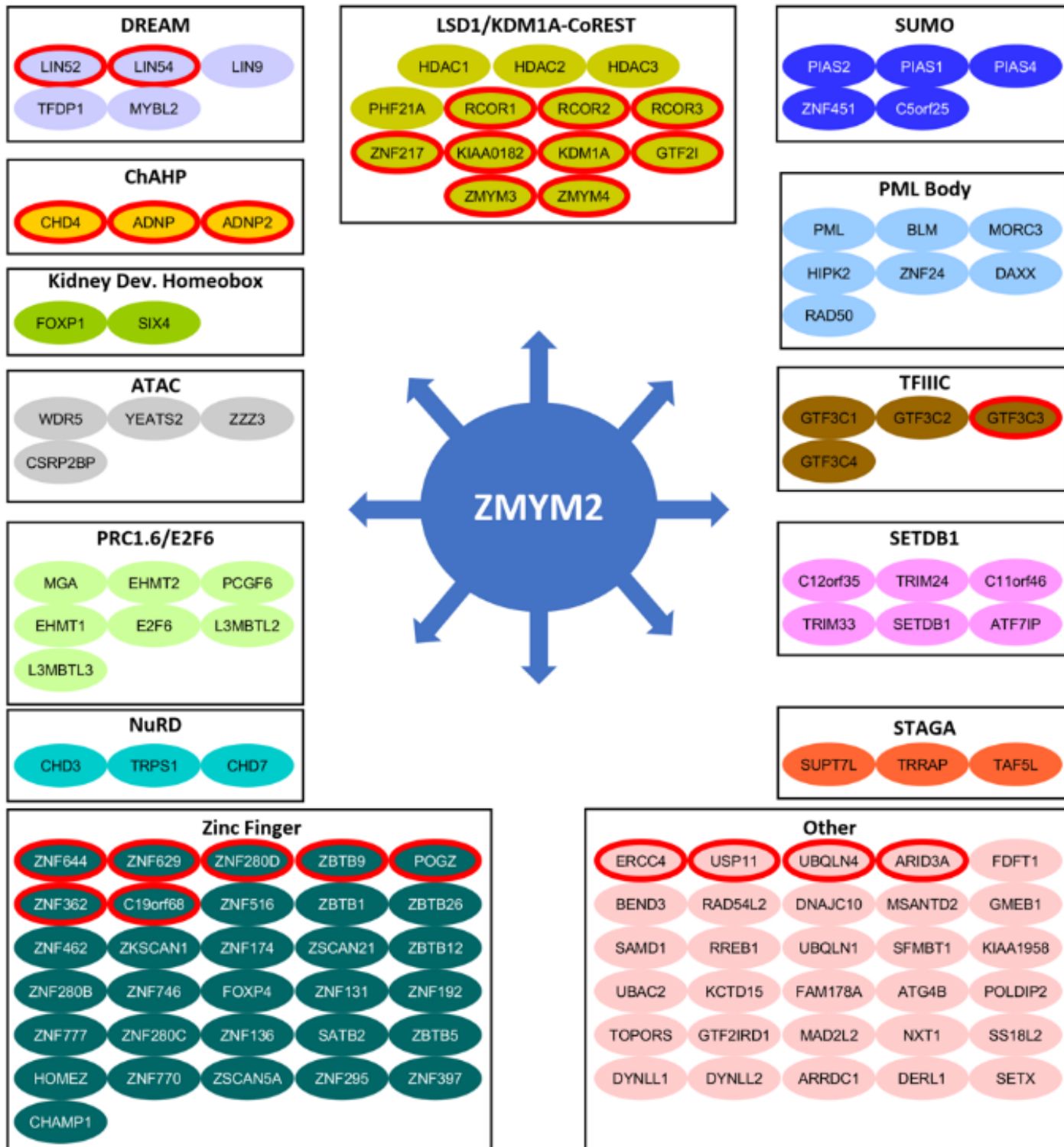
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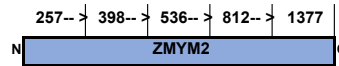
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Figure S11 ZMYM2 truncation mutant BioID Heat Map



| Protein | HGNC | Full name | ZMYM2 | | | | | Full length | Legend | |
|----------|----------|--|---------|---------|---------|---------|----------|-------------|------------|-----|
| | | | 1-- 257 | 1-- 398 | 1-- 536 | 1-- 812 | 1-- 1377 | | quartile | %WT |
| ZBTB5 | ZBTB5 | zinc finger and BTB domain containing 5 | Red | Red | Red | Red | Green | 1 | 0-- 24 | |
| L3MBTL3 | L3MBTL3 | L3MBTL histone methyl--lysine binding protein 3 | Red | Red | Red | Red | Green | 2 | 25-- 49 | |
| GTF2IRD1 | GTF2IRD1 | GTF2I repeat domain containing 1 | Red | Red | Red | Red | Green | 3 | 50-- 74 | |
| ZSCAN5A | ZSCAN5A | zinc finger and SCAN domain containing 5A | Red | Red | Red | Red | Green | 4 | 75-- 100 | |
| MAD2L2 | MAD2L2 | mitotic arrest deficient 2 like 2 | Red | Red | Red | Red | Green | | | |
| HIPK2 | HIPK2 | homeodomain interacting protein kinase 2 | Red | Red | Red | Red | Green | | | |
| ZNF217 | ZNF217 | zinc finger protein 217 | Red | Red | Red | Red | Green | | | |
| FDFT1 | FDFT1 | farnesyl--diphosphate farnesyltransferase 1 | Red | Red | Red | Red | Green | | | |
| TRPS1 | TRPS1 | transcriptional repressor GATA binding 1 | Red | Red | Red | Red | Green | | | |
| UBQLN4 | UBQLN4 | ubiquilin 4 | Red | Red | Red | Red | Green | | | |
| ZNF280D | ZNF280D | zinc finger protein 280D | Red | Red | Red | Red | Green | | | |
| DYNLL1 | DYNLL1 | dynein light chain LC8--type 1 | Red | Red | Red | Red | Green | | | |
| HOMEZ | HOMEZ | homeobox and leucine zipper encoding | Red | Red | Red | Red | Green | | | |
| ZNF451 | ZNF451 | zinc finger protein 451 | Red | Red | Red | Red | Green | | | |
| RCOR2 | RCOR2 | REST corepressor 2 | Red | Red | Red | Red | Green | | | |
| ZBTB1 | ZBTB1 | zinc finger and BTB domain containing 1 | Red | Red | Red | Red | Green | | | |
| KIAA1958 | KIAA1958 | KIAA1958 | Red | Red | Red | Red | Green | | | |
| RCOR3 | RCOR3 | REST corepressor 3 | Red | Red | Red | Red | Green | | | |
| DAXX | DAXX | death domain associated protein | Red | Red | Red | Red | Green | | | |
| RCOR1 | RCOR1 | REST corepressor 1 | Red | Red | Red | Red | Green | | | |
| ZNF777 | ZNF777 | zinc finger protein 777 | Red | Red | Red | Red | Green | | | |
| ZNF192 | ZKSCAN8 | | Red | Red | Red | Red | Green | | | |
| PIAS1 | PIAS1 | protein inhibitor of activated STAT 1 | Red | Red | Red | Red | Green | | | |
| KDM1A | KDM1A | lysine demethylase 1A | Red | Red | Red | Yellow | Green | | | |
| DYNLL2 | DYNLL2 | dynein light chain LC8--type 2 | Red | Red | Red | Yellow | Green | | | |
| TOP3A | TOP3A | DNA topoisomerase III alpha | Red | Red | Red | Green | Green | | | |
| MORC3 | MORC3 | MORC family CW--type zinc finger 3 | Red | Red | Red | Green | Green | | | |
| ZNF516 | ZNF516 | zinc finger protein 516 | Red | Red | Red | Green | Green | | | |
| ZBTB12 | ZBTB12 | zinc finger and BTB domain containing 12 | Red | Red | Red | Green | Green | | | |
| KIAA0182 | GSE1 | Gse1 coiled--coil protein | Red | Red | Red | Green | Green | | | |
| HDAC1 | HDAC1 | histone deacetylase 1 | Red | Red | Red | Yellow | Green | | HDACs | |
| HDAC2 | HDAC2 | histone deacetylase 2 | Red | Red | Red | Yellow | Green | | HDACs | |
| POGZ | POGZ | pogo transposable element derived with ZNF domain | Red | Red | Red | Yellow | Green | | | |
| ZMYM3 | ZMYM3 | zinc finger MYM--type containing 3 | Red | Red | Red | Yellow | Green | | | |
| C19orf68 | ZSWIM9 | zinc finger SWIM--type containing 9 | Red | Red | Red | Yellow | Green | | | |
| MSANTD2 | MSANTD2 | Myb/SANT DNA binding domain containing 2 | Red | Red | Red | Yellow | Green | | | |
| CHAMP1 | CHAMP1 | chromosome alignment maintaining phosphoprotein 1 | Red | Red | Red | Yellow | Green | | | |
| BEND3 | BEND3 | BEN domain containing 3 | Red | Red | Red | Yellow | Green | | | |
| MYBL2 | MYBL2 | MYB proto--oncogene like 2 | Red | Red | Red | Yellow | Green | | | |
| CBX1 | CBX1 | chromobox 1 | Red | Red | Red | Yellow | Green | | | |
| SETDB1 | SETDB1 | SET domain bifurcated histone lysine methyltransferase 1 | Red | Red | Red | Yellow | Green | | ATF7-- SET | |
| ATF7IP | ATF7IP | activating transcription factor 7 interacting protein | Red | Red | Red | Yellow | Green | | ATF7-- SET | |
| ZNF644 | ZNF644 | zinc finger protein 644 | Red | Red | Red | Yellow | Green | | | |
| RAD54L2 | RAD54L2 | RAD54 like 2 | Red | Red | Red | Yellow | Green | | | |
| LIN52 | LIN52 | lin--52 DREAM MuvB core complex component | Red | Red | Red | Yellow | Green | | DREAM MuvB | |
| LIN9 | LIN9 | lin--9 DREAM MuvB core complex component | Red | Red | Red | Yellow | Green | | DREAM MuvB | |
| TRRAP | TRRAP | transformation/transcription domain associated protein | Red | Red | Red | Yellow | Green | | | |
| ZMYM4 | ZMYM4 | zinc finger MYM--type containing 4 | Red | Red | Red | Yellow | Green | | | |
| C11orf46 | ARL14EP | ADP ribosylation factor like GTPase 14 effector protein | Red | Red | Red | Yellow | Green | | | |
| ZNF174 | ZNF174 | zinc finger protein 174 | Red | Red | Red | Yellow | Green | | | |
| LIN54 | LIN54 | lin--54 DREAM MuvB core complex component | Red | Red | Red | Yellow | Green | | | |
| TRIM24 | TRIM24 | tripartite motif containing 24 | Red | Red | Red | Yellow | Green | | | |
| PCGF6 | PCGF6 | polycomb group ring finger 6 | Red | Red | Red | Yellow | Green | | | |
| SS18L2 | SS18L2 | SS18 like 2 | Red | Red | Red | Yellow | Green | | | |
| ADNP | ADNP | activity dependent neuroprotector homeobox | Red | Red | Red | Yellow | Green | | | |
| ADNP2 | ADNP2 | ADNP homeobox 2 | Red | Red | Red | Yellow | Green | | ChAUP | |
| CHD4 | CHD4 | chromodomain helicase DNA binding protein 4 | Red | Red | Red | Yellow | Green | | ChAUP | |
| GTF3C1 | GTF3C1 | general transcription factor IIIC subunit 1 | Red | Red | Red | Yellow | Green | | GTF3C | |
| GTF3C2 | GTF3C2 | general transcription factor IIIC subunit 2 | Red | Red | Red | Yellow | Green | | GTF3C | |
| GTF3C3 | GTF3C3 | general transcription factor IIIC subunit 3 | Red | Red | Red | Yellow | Green | | GTF3C | |
| MGA | MGA | MAX dimerization protein MGA | Red | Red | Red | Yellow | Green | | | |
| CBX3 | CBX3 | chromobox 3 | Red | Red | Red | Yellow | Green | | | |
| ZNF295 | ZBTB21 | zinc finger and BTB domain containing 21 | Red | Red | Red | Yellow | Green | | | |
| GTF2I | GTF2I | general transcription factor III | Red | Red | Red | Yellow | Green | | | |
| ZBTB9 | ZBTB9 | zinc finger and BTB domain containing 9 | Red | Red | Red | Yellow | Green | | | |
| ZBTB33 | ZBTB33 | zinc finger and BTB domain containing 33 | Red | Red | Red | Yellow | Green | | | |

Table S1. List of mutagenesis primers used to generate clones representing the variants identified in each family

| Family | Nucleotide change | Amino acid change | F: Forward primer R: Reverse primer |
|------------------------------|----------------------------|--------------------------|---|
| SSC1 | c.181_183del | p.Val61del | F: aggtgtacaggttcgataaaaacatcatcatctccac R: gtggaagatgatgatgatggtttatcgaacctgacaacct |
| A781 | c.377A>C | p.Glu126Ala | F: ctctgcccttgattgttgccatgtcctctcatcatc R: gatgatgaagaggacatggcaacaaatcaagggcaagag |
| GM10 | c.622C>T | p. Arg208* | Not tested |
| GM1 | c.766_767dupGT | p. Gly257* | F: gattaaaggctcactactccagctctggctgtgaagtaa R: ttaactcacagaccaagactggaggttaggacctttaatc |
| SSC2 | c.1159A>G | p.Ile387Val | F: ctggaatccacttgagcaacaacggtcctttcattgtagtata R: tataactacaatgaaaggaaccgtgttgctcaagtgattcaag |
| GM3 | c.1192C>T | p. Gln398* | F: gatgtactacagaattcctagaaggactcactgaaatcc R: ggattcaagtgagtcctcttaggaattctgtagtacac |
| GM16 | c.1351C>T | p.His451Tyr | Not tested |
| GM15 | c.1654A>G | p.I552V | Not tested |
| GM9 | c.1367dup | p.Tyr456* | Not tested |
| SSC3 | c.1607del | p.Cys536Leufs*1 3 | F: tgttcggcaaccagtaaagttgcagtttccatatttctc R: gagaaatatggaaaactgacaacttactggtgccgaaca |
| A4730 A1204 | c.1618C>T | p. Arg540* | F: aaacctgcactgtgttcagcaaccagtacaagttg R: caactgtactggttctgaacacagtcaggttt |
| GM11 | c.1623_1627del | p.Cys543Valfs*3 | Not tested |
| A3928 | c.1946A>G | p.Lys649Arg | F: tccaggatttctggtctgaacaaaaggaatcttgcagtagttg R: caactactgcaaaaattcctttgttcaagaccagaaatcctgga |
| GM17 | c.2165T>A | p. Leu722* | Not tested |
| B1410 | c.2287T>C | p.Tyr763His | F: cacacctgcagccttggtaccaatcctgaaattt R: aaatttcaggattggtaccacaaggctgcaaggtgtg |
| A663/ A3135 | c.2287_2288 delinsTA>CT | p.Tyr763Leu | F: cagtcacacctgcagccttgaggtaccaatcctgaaattttt R: aaaaaattcaggattggtacctcaaggctgcaaggtgtgactg |

| | | | |
|-------------|----------------------|-----------------------|---|
| B960 | c.2324G>A | p.Gly775Glu | F: tgaactcgctctttaagagtttcttgagatttacaacagtcac R: gtgactgttgtaaactcaagaaactctaaagagcgagtca |
| GM19 | c.2338C>T | p.Arg780* | Not tested |
| GM6 | c.2434_2437del | p.Lys812Aspfs*1 8 | F: gcccaacatgacaactcaggacctgaaaacttacatta R: taatgtaagtttcaggctctgagttgtcatgttgggc |
| GM18 | c.2494-1 G>A | IVS15-1 G>A | Not tested |
| SSC4 | c.2990_2992 del | p.Asp997del | F: atctggttcatatggtacaggcatgctggactgt R: acagtccagcatgcctgtacatgaaccagat |
| SSC5 | c.3091G>A | p.Glu1031Lys | F: ggctgttcctcatattcttgccaaaaaacagggtggaat R: attaccacctgttttgcaaagaatatgaggaacagcc |
| GM7 | c.3130_3131dup AA | p.Gly1045 Argfs*33 | F: cccagacctcgatctaaaaaaaaaaggagccaagag R: ctctggctcccttttttttagatcgagggtctggg |
| GM13 | c.3176dup | p.Asp1059 Glufs*2 | Not tested |
| GM12 | c.3246G>A | p. Trp1082* | Not tested |

Table S2. Twelve non-pathogenic missense heterozygous mutations in *ZMYM2* in 13 individuals from 12 families with congenital anomalies of the kidney and urinary tract

| Family-Individual | Nucleotide change | Amino acid change ^{a, b} | Exon (Segregation) | Poly 2 SIFT MT | Amino acid conservation to species | gnomAD allele frequency ^a | Ethnicity Gender | CAKUT (sidedness ^a) | Extra-renal manifestation | Neurologic involvement |
|-------------------|-------------------------|-----------------------------------|------------------------------------|-------------------|------------------------------------|--------------------------------------|------------------|--|--|--|
| SSC1-21 | c.181_183del | p.Val61del | 3 <i>de novo</i> | / / | / | / | Poland M | <u>UUT</u> : Renal Agenesis (L) | <u>Heart</u> : ASD | - |
| A781-21 | c.377A>C | p.Glu126Ala | 3 (ND) | 0.16 Tol. / | <i>A.platyrhynchos</i> | / | Macedonia F | <u>UUT</u> : Duplex kidney (BL) <u>LUT</u> : Ureterocele (L) | <u>Skeleton</u> : Facial dysmorphism ¹ Congenital hip dysplasia | - |
| SSC2-21 | c.1159A>G | p.Ile387Val | 5 <i>de novo</i> | 0.48 Tol. / | <i>D. rerio</i> | / | Italy M | <u>UUT</u> : UPJO (L) | <u>Heart</u> : WPW syndrome | - |
| GM16-21 | c.1351C>T | p.His451Tyr | 8 p het m WT (imprinting) | 0.81 Tol / | <i>D. rerio</i> | 0/1/238682 | ? | - | <u>Skeletal</u> : Excessive femoral anteversion, gait disturbance <u>Skin</u> : Alopecia, Ectodermal dysplasia, , <u>Other</u> : Hyponatremia, Hypothyroidism, Ichthyosis, Neutropenia, Photophobia, Recurrent infections, Abnormal thrombosis, Thrombocytopenia | Global DD, Mild ID, Rotary nystagmus, Seizures |
| GM15-21 | c.1654A>G | p.I552V | 10 <i>de novo</i> | 0.103 Tol / | <i>D. rerio</i> | / | ? | <u>NA</u> | <u>Skeletal</u> : Scoliosis | Macrocephaly, hypotonia, DD |
| A3928-21 | c.1946A>G | p.Lys649Arg | 10 (ND) | 0.98 Tol. / | <i>D. rerio</i> | / | Indian M | <u>UUT</u> : Renomegaly (BL) | - | - |
| B1410-21 | c.2287T>C | p.Tyr763His | 12 p het m WT | 0.90 Tol. / | <i>D. rerio</i> | 0/10/240,574 | Macedonia M | <u>UUT</u> : Hypoplastic pelvic kidney (L) <u>LUT</u> : Cryptorchidism (BL) | - | - |
| -11 | c.2287T>C | p.Tyr763His | 12 p het m WT | 0.90 Tol. / | <i>D. rerio</i> | 0/10/240,574 | Macedonia M | RUS-N <u>LUT</u> : Cryptorchidism (BL) | - | - |
| A663-21 | c.2287_2288 delinsTA>CT | <u>p.Tyr763Leu^b</u> | 12 (ND) | 0.21 Tol / | <i>D. rerio</i> | 0/10/237,916 | Kuwait F | <u>UUT</u> : Horseshoe kidney, UPJO (L) | - | - |
| A3135-21 | c.2287_2288 delinsTA>CT | <u>p.Tyr763Leu^b</u> | 12 (ND) | 0.21 Tol / | <i>D. rerio</i> | 0/10/237,916 | Kuwait M | <u>UUT</u> : Horseshoe kidney, renal calculi | - | - |
| B960-21 | c.2324G>A | p.Gly775Glu | 13 (p NA m WT) | 1.00 Del / | <i>D. rerio</i> | 0/1/245,306 | Caucasian F | <u>UUT</u> : UPJO (BL), renal calculi | - | - |
| SSC4-21 | c.2990_2992 del | p.Asp997del | 18 <i>de novo</i> | / / | / | / | Netherlands M | <u>UUT</u> : Renal agenesis (L) <u>LUT</u> : Duplex urethra | <u>Skeleton</u> : Club hand, hemi-vertebrae (VACTERL) | - |

| | | | | | | | | | | |
|----------------|-----------|--------------|---------------|-------------------|-----------------|-------------|----------------|-----------------------|---|---|
| SSC5-21 | c.3091G>A | p.Glu1031Lys | 19 de novo | 0.07 Tol. / | <i>D. rerio</i> | 0/0/225,618 | Macedonia F | <u>UUT</u> : UVJO (R) | - | - |
|----------------|-----------|--------------|---------------|-------------------|-----------------|-------------|----------------|-----------------------|---|---|

Transcript accession number for *ZMYM2* **NM_001190965.2** a sidedness of CAKUT phenotype given in parentheses; ND denotes not done. ? denotes unknown.

ASD, atrial septal defect; **BL**, bilateral; **DD**, developmental delay; **Del**, deleterious; **F**, female; **het**, heterozygous; **ID**, intellectual disability; **L**, left; **LUT**, lower urinary tract; **m**, maternal; **M**, male; **N**, normal; **NA**, not available; **p**, paternal; **PPH2 score**, HumVar PolyPhen-2 prediction score; **R**, right; **RUS-N**, renal ultrasound normal; **SIFT**, sorting tolerant from intolerant; **Tol.**, tolerated; **UUT**, upper urinary tract; **UPJO**, ureteropelvic junction obstruction; **RUS**, renal ultrasound; **VACTERL**, vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities.

Table S3. List of truncating heterozygous variants of *ZMYM2* that exist in gnomAD.

Note: In 31 truncating variants present in gnomAD 27 are only reported once heterozygously and never homozygously (see last column). This is consistent with the hypothesis that the *CAKUT* causing mutations outlined in Table 1 occurred *de novo* and with reduced transmission of truncating alleles due to a sub-fertility phenotype.

| Gene | hg19 position | Type of mutation | Exon | Zygoty | c.change | p.change | SNP ID | Present in 1000-genomes | EVS | gnomAD (hom/het/allele count) |
|--------------|----------------------------|------------------------|-----------|--------|-------------------------|-------------------------|--------------|-------------------------|-----|-------------------------------|
| <i>ZMYM2</i> | chr13:20567212CA>C | 5' UTR deletion (1 bp) | 3 of 25 | het | c.-1del | p.Met1? | rs769561518 | / | / | 0/4/230248 |
| <i>ZMYM2</i> | chr13:20567337T>A | stop gained | 3 of 25 | het | c.125T>A | p.Leu42Ter | | / | / | 0/1/249444 |
| <i>ZMYM2</i> | chr13:20567613AT>A | frameshift | 3 of 25 | het | c.403del | p.Ser135 ProfsTer31 | rs767307088 | / | / | 0/1/249650 |
| <i>ZMYM2</i> | chr13:20567936C>T | stop gained | 3 of 25 | het | c.724C>T | p.Gln242Ter | | | | 0/1/251188 |
| <i>ZMYM2</i> | chr13:20580624T>A | stop gained | 6 of 25 | het | c.1410T>A | p.Cys470Ter | rs754728724 | / | / | 0/1/248728 |
| <i>ZMYM2</i> | chr13:20580727G>A | splice donor | Intron 6 | het | c.1512+1G>A | 100% ESS | | | | 0/1/ 247968 |
| <i>ZMYM2</i> | chr13:20580727G>T | splice donor | Intron 6 | het | c.1512+1G>T | 100% ESS | | | | 0/1/247968 |
| <i>ZMYM2</i> | chr13:20593759G>A | splice donor | Intron 7 | het | c.1584+1G>A | 100% ESS | | / | / | 0/1/31384 |
| <i>ZMYM2</i> | chr13:20608479_20608480del | frameshift | 11 of 25 | het | c.2054_2055del | p.Gln685 ArgfsTer7 | rs1241090598 | | | 0/1/31396 |
| <i>ZMYM2</i> | chr13:20608493_20608494del | frameshift | 11 of 25 | het | c.2068_2069del | p.Leu690 SerfsTer2 | rs1474114489 | | | 0/1/245312 |
| <i>ZMYM2</i> | chr13:20632845G>A | splice donor | Intron 15 | het | c.2623+1G>A | 100% ESS | rs766769611 | / | / | 0/1/248444 |
| <i>ZMYM2</i> | chr13:20632988G>T | splice acceptor | Intron 15 | het | c.1070-1G>T | | | | | 0/1/226006 |
| <i>ZMYM2</i> | chr13:20632998G>A | stop gained | Intron 15 | het | intronic | p.Trp360Ter | | / | / | 0/2/220922 |
| <i>ZMYM2</i> | chr13:20633039CTG>C | frameshift | Intron 15 | het | intronic | p.Leu374His fsTer12 | | / | / | 0/1/176838 |
| <i>ZMYM2</i> | chr13:20635344C>CA | frameshift | 17 of 25 | het | c.2892dup | p.Glu965 ArgfsTer11 | | / | / | 0/1/248630 |
| <i>ZMYM2</i> | chr13:20641009G>GT | frameshift | 20 of 25 | het | c.3152dup | p.Ser1052 IlefsTer7 | rs778985497 | / | / | 0/1/236934 |
| <i>ZMYM2</i> | chr13:20641049C>A | stop gained | 20 of 25 | het | c.3191C>A | p.Ser1064 Ter | rs769681794 | / | / | 0/1/248184 |
| <i>ZMYM2</i> | chr13:20641051GA>G | frameshift | 20 of 25 | het | c.3195del | p.Glu1065 AspfsTer12 | | / | / | 0/1/248352 |
| <i>ZMYM2</i> | chr13:20641151T>G | stop gained | 20 of 25 | het | c.3293T>G | p.Leu1098 Ter | rs756477730 | / | / | 0/1/237798 |
| <i>ZMYM2</i> | chr13:20641159TGTAAT | splice donor | Intron 20 | het | c.3301+3_3301+6delAA... | -79.4% SS | rs745854601 | / | / | 0/1/230760 |
| <i>ZMYM2</i> | chr13:20641160G>C | splice donor | Intron 20 | het | c.3301+1G>C | 100% ESS | | / | / | 0/1/230574 |

| Gene | hg19 | Type | Exon | Zygos-ity | c.change | p.change | SNP ID | In '1000-genomes'? | EVS | gnomAD (hom/het/allele count) |
|--------------|-----------------------------|-----------------|----------|-----------|---------------------|---------------------|--------------|--------------------|-----|-------------------------------|
| ZMYM2 | chr13:20641465C>T | stop gained | 21 of 25 | het | c.3388C>T | p.Arg1130 Ter | rs1299725201 | | | 0/1/242044 |
| ZMYM2 | chr13:20656154_20656155del | splice acceptor | 21 of 25 | het | c.34542_3454-1delAG | 100% ESS | rs1176659089 | / | / | 0/4/191222 |
| ZMYM2 | chr13:20656154A>T | splice acceptor | 21 of 25 | het | c.3454-2A>T | 100% ESS | rs1408869997 | | | 0/18/198980 |
| ZMYM2 | chr13:20656155G>T | splice acceptor | 21 of 25 | het | c.3454-1G>T | 100% ESS | rs1421349760 | | | 0/21/213812 |
| ZMYM2 | chr13:20657015C>CT | frameshift | 23 of 25 | het | c.3666dup | p.Asn1223 Ter | | / | / | 0/1/249220 |
| ZMYM2 | chr13:20657101AT>A | frameshift | 23 of 25 | het | c.3750del | p.Pro1251 LeufsTer2 | | / | / | 0/1/31406 |
| ZMYM2 | chr13:20657133C>T | stop gained | 23 of 25 | het | c.3781C>T | p.Arg1261 Ter | rs773436243 | / | / | 0/1/248642 |
| ZMYM2 | chr13:20657897G>T | stop gained | 24 of 24 | het | c.3922G>T | p.Glu1308 Ter | rs1241191383 | / | / | 0/1/233828 |
| ZMYM2 | chr13:20660054C>G | stop gained | 25 of 25 | het | c.4034C>G | p.Ser1345 Ter | rs1429293566 | | | 0/1/249166 |
| ZMYM2 | chr13:20660104_20660105insG | frameshift | 25 of 25 | het | c.4084_4085 insG | p.Lys1362 ArgfsTer5 | rs774438077 | | | 0/1/249016 |

bp, base pair; Del, deletion; ESS, essential splice site; EVS, exome variant server; het, heterozygous; hom, homozygous; ins, insertion; SNP, single nucleotide polymorphism; UTR, untranslated region.

Table S4A. Overview of *ZMYM2* variants identified in two control cohorts of 100 families with steroid resistant nephrotic syndrome and 238 families with nephronophthisis.

| COHORT | TRUNCATING VARIANTS | MISSENSE VARIANTS | INFRAME VARIANTS |
|------------------------------|----------------------------|--------------------------|-------------------------|
| SRNS solved (n=100) | 0 | 2 | 0 |
| NPHP unsolved (n=238) | 0 | 2 | 0 |

SRNS, steroid resistant nephrotic syndrome; NPHP, nephronophthisis.

Table S4B. Overview of monogenic causes identified in a cohort of 100 patients with steroid resistant nephrotic syndrome.

| Gene | OMIM ID | Mode of inheritance | Percentage of patients (%) |
|-----------------|----------------|----------------------------|-----------------------------------|
| <i>ADCK4</i> | #615567 | AR | 3 |
| <i>AGXT</i> | #604285 | AR | 2 |
| <i>CLCN5</i> | #300008 | XL | 1 |
| <i>COL4A3</i> | #120070 | AR, AD | 7 |
| <i>COL4A4</i> | #120131 | AR, AD | 2 |
| <i>COL4A5</i> | #303630 | XL | 3 |
| <i>COQ2</i> | #609825 | AR | 1 |
| <i>CTNS</i> | #219800 | AR | 1 |
| <i>DGKE</i> | #601440 | AR | 1 |
| <i>GLA</i> | #300644 | XL | 1 |
| <i>INF2</i> | #610982 | AD | 2 |
| <i>ITGA3</i> | #605025 | AR | 1 |
| <i>KANK4</i> | #614612 | ?AR | 1 |
| <i>LAMB2</i> | #150325 | AR | 6 |
| <i>LMX1B</i> | #602575 | AD | 2 |
| <i>MYO1E</i> | #601479 | AR | 3 |
| <i>NPHS1</i> | #256300 | AR | 12 |
| <i>NPHS2</i> | #600995 | AR | 12 |
| <i>NUP107</i> | #607617 | AR | 1 |
| <i>NUP205</i> | #614352 | AR | 2 |
| <i>NUP93</i> | #614351 | AR | 3 |
| <i>OSGEP</i> | #610107 | AR | 3 |
| <i>PDSS2</i> | #610564 | AR | 1 |
| <i>PLCE1</i> | #608414 | AR | 10 |
| <i>RPL15</i> | #604174 | AD | 1 |
| <i>SGPL1</i> | #603729 | AR | 3 |
| <i>SMARCAL1</i> | #606622 | AR | 7 |
| <i>TRPC6</i> | #603652 | AD | 1 |
| <i>TTC21B</i> | #612014 | AR, AD | 2 |
| <i>WDR73</i> | #616144 | AR | 3 |
| <i>WT1</i> | #607102 | AD | 2 |

AR, autosomal recessive; AD, autosomal dominant; XL; X-linked