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DEVELOPMENT

MAZ mediates urogenital development

Copy number variation (CNV) in *MAZ*, which is located in the 16p11.2 locus and encodes a C2H2 zinc finger transcription factor, contributes considerably to a variety of urogenital birth defects. Discovery of the function of this gene provides a target for the development of therapies for treatment of at-risk pregnancies.

In a new study, retrospective analysis revealed 40 patients who had urogenital defects and 16p11.2 dosage variation. *MAZ* was found to be an excellent candidate gene for involvement in the urogenital phenotypes seen in these patients on assessment of breakpoints of each 16p11.2 CNV. *MAZ* was the only gene within the minimal linear region of maximum CNV overlap when all breakpoints were compared. A prospective genetic screen of 258 patients with urogenital abnormalities and 57 participants with no clinical history of urogenital defects showed that 6% of those with urogenital tract abnormalities harboured *MAZ* CNV alterations, with a bias towards deletions.

In situ hybridization against *Maz* in the developing mouse fetus showed that *Maz* is ubiquitously expressed at embryonic day 14.5. By embryonic day 16.5, during genitourinary tract development, *Maz* is observed at high levels in the cortex of the kidney, lining of the ureters, lining of the urethra of the developing genital tubercle, throughout the bladder, and in the developing testis. Increased *Maz* expression was observed in the cortex of the kidney compared with the medulla, and in the interstitium of the testis compared with the tubules. A quantitative PCR screen of complimentary DNA from spontaneously aborted human fetuses showed that *MAZ* is ubiquitously expressed in developing tissues.

In vitro, knockdown of *MAZ* in human embryonic kidney (HEK)293 cells reduced proliferation and resulted in deregulation of several cell cycle genes in Cyclin A, Cyclin D, and TGFβ families. *MAZ* knockdown also reduced the number of cells entering S phase. WNT pathway expression miniarray analysis showed that *MAZ* knockdown caused altered expression in 20% of tested transcripts including *WNT3A*, *WNT4*, *WNT5B*, *WNT7B*, *WNT8A*, and *WNT11*.

In vivo, deletion of *Maz* caused dose-dependent rates of perinatal lethality, and 31% of *Maz* +/Δ and 89% of *Maz* Δ/Δ pups expired before postnatal day 13. Microdissection of embryonic day 18.5 littermates resulting from timed matings of *Maz* +/Δ mice showed high rates of congenital anomalies of the kidney and urinary tract (CAKUT), including renal agenesis, renal hypoplasia, and hydronephrosis. *Maz* Δ/Δ embryos had at least 65.5% penetrance of grossly observable CAKUTs. Mice homozygous for *Maz* deletion that survived to adulthood had urogenital defects, including unilateral renal agenesis, increased rates of vesicoureteral reflux, cryptorchidism, overt penile malformations, and abrogated bladder capacity.

Overall, these data show that *MAZ* has a role in mediating urogenital development *in utero*. Discovery of therapies targeting *MAZ* would benefit the treatment of at-risk pregnancies.

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> “*Maz* Δ/Δ embryos had at least 65.5% penetrance of grossly observable CAKUTs”

ORIGINAL ARTICLE Haller, M. *et al.* 16p11.2 transcription factor *MAZ* is a dosage-sensitive regulator of genitourinary development. *Proc. Natl. Acad. Soc.* **115**, E1849–E1858 (2018)