UW-Madison Summer Program for Undergraduate Urology Research

EXAMINATION OF GENE MARKERS OF URETHRAL DEVELOPMENT IN SONIC HEDGEHOG SIGNALING DEFICIENT MICE

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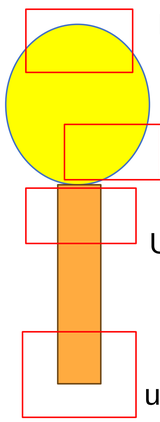
BACKGROUND AND HYPOTHESIS

- Genitourinary malformations and incontinence in humans impose significant healthcare costs.
- GU malformations and disorders in humans have been linked to sonic hedgehog (Shh) mutations and mutations in the downstream Gli transcription factors.
- The Gli mutant mouse model (Gli2+/-; Gli3Δ699/+), a Shh signaling deficient mouse model, has GU malformations and incontinence (Yadav *et al*., 2022).
- ***We predict that mice with hypomorphic Shh signaling fail to form a distinct boundary between the bladder and urethra.***
- ***Therefore, we expect to observe inappropriately expressed gene markers in the epithelium of the bladder and urethra.***

MATERIALS AND METHODS

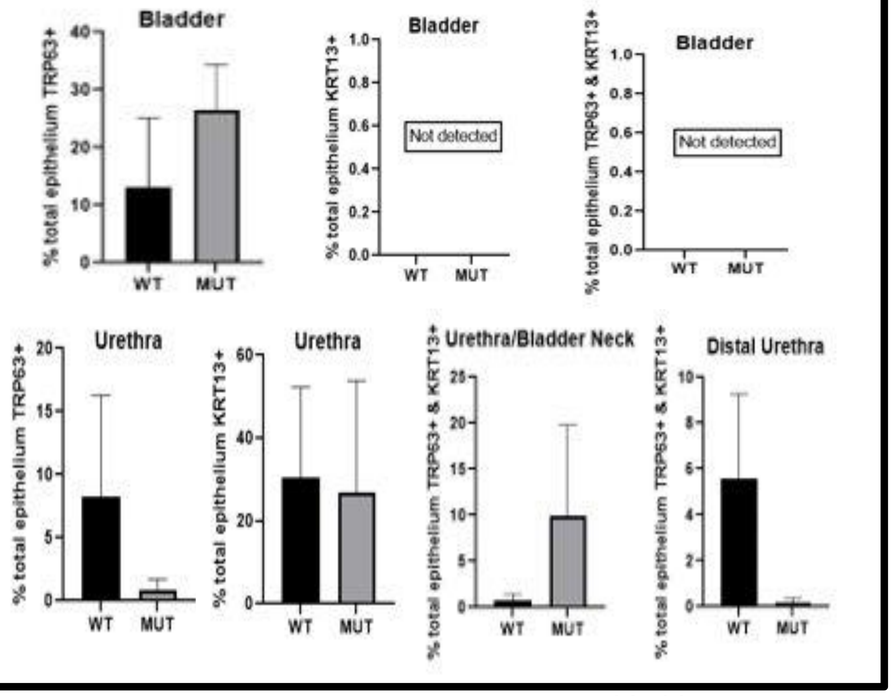
- Adult Gli mutant female mice and wild type controls were sacrificed and the lower urinary tracts, including the bladder and urethra, were dissected and embedded in paraffin.
- The tissue blocks were sectioned, and immunohistochemistry was performed using antibodies targeting cytokeratin 13 (KRT13) and transformation related protein 63 (TRP63).
- Statistics were calculated using Prism software.



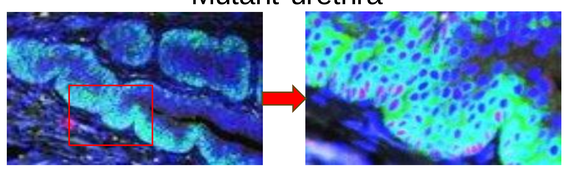
- **KRT13 (green) stains superficial and intermediate urethral epithelium.**
- **TRP63 (red) stains intermediate and basal epithelium of both urethra and bladder.**

RESULTS

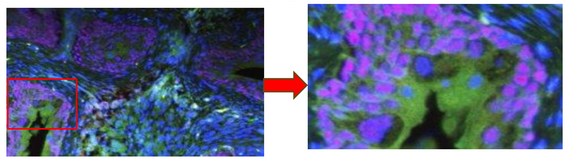
- Preliminary results indicate no significant differences with the current sample size.
- However, trending differences were observed.
- The mutant bladders showed higher percentages of TRP63 positive epithelium than wild type controls.
- The mutant urethras showed lower percentages of TRP63 positive epithelium, higher percentages of double positive epithelium in the bladder neck region, and lower percentages of double positive epithelium in distal urethra than wild type controls.



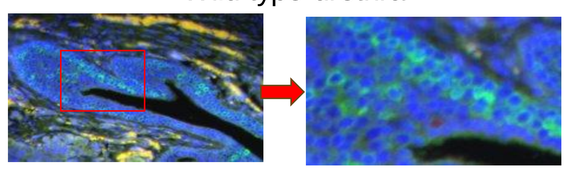
Mutant urethra



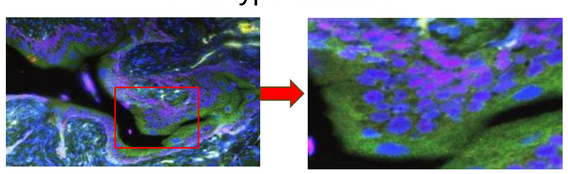
Mutant bladder



Wild type urethra



Wild type bladder



CONCLUSION

- Our data indicate that there are trends toward differences in the differentiation of the epithelium of the urethra and bladder between Gli mutant mice and wild-type controls.
- This would indicate that mutations leading to reduced Shh signaling result in abnormal differentiation of the urethral epithelium, which could lead to reduced ability for the urethra to function, leading to incontinence.

RELEVANCE

- People that suffer from genital malformations or genetically based incontinence often have Gli mutations.
- Better understanding the impact of Gli mutations on urinary tract physiology can lead to better treatment and quality of life outcomes.

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