**The genetic and molecular defects in severe bladder malformations in the T30H experimental model**

Obstructive uropathies account for up to 20% of paediatric end stage renal failure, with irreparable damage often occurring to the kidneys before surgical correction of obstruction is possible. Moreover, problems such as abnormal voiding and urinary incontinence with increased risk of urinary tract infections can persist throughout life. Animal models are useful tools in investigating developmental disorders, but most uropathy models rely on surgery to generate obstruction which can only be performed at later stages of development. The T30 Homozygote (T30H) mouse was developed in the 1950s in chemical mutagenesis experiments investigating imprinting genes. This created a balanced chromosomal translocation that specifically compromised smooth muscle development in the bladder from the onset of development, without overt defects in other organs. This lack of smooth muscle means that T30H mice are unable to void the bladder during gestation, and is associated with hydronephrosis and reduced nephron numbers.

While cytogenetics demonstrated the translocation between chromosomes 2 and 11 nearly 70 years ago, the exact translocation point and the genes affected were unknown. Here we utilised next generation sequencing to identify the translocation; sequences were detected that originated on chromosome 2 and ended on 11, and vice versa. The breakpoint does not span any recognised genes but it is upstream of myocardin, a gene strongly implicated in smooth muscle development in diverse organs.

The model has also been further characterised by investigating the expression of a variety of muscle and renal specific antibody markers using histology. Markers specific to the urothelium remain unchanged, whereas smooth muscle specific markers are either absent in the bladder or show very limited expression. Conversely, smooth muscle specific markers exhibit normal expression in other organs such as the heart and gut. This raises the possibility that the phenotype is caused by bladder-specific changes in myocardin expression. To further investigate the role of myocardin in smooth muscle expression in the bladder, we have carried out RT-PCR analysis to compare the splice variants present in both T30 and wild type postnatal day 1 mouse organs. Alternate splice variants are found in the bladder compared with other organs in both data sets, and it will be interesting in further study to analyse the ratio of these splice variants to each other, as this may be causative of the phenotype observed.

A greater understanding of the regulation of smooth muscle in the bladder will enable us to both better understand the development of the urinary tract, and to develop more informed therapies for treatment of smooth muscle complications arising from congenital urinary tract malformations.