Rare Early Onset Lower Urinary Tract Disorders (REOLUT)

Rare Disease Research UK.
Rare Early Onset Lower Urinary Tract Disorders - REOLUT

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Charity Partners: ERIC The Children's Bowel and Bladder Charity, The Urology Foundation, VOCAL, Unique

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Background & aims

Rare Early Onset disorders of the Lower Urinary Tract (REOLUT) are the most common cause of kidney failure in children in the UK. Such disorders have negative impacts on children's self-esteem, education and socialisation. They have been greatly understudied compared with kidney diseases and thus very little is known about the genetics and biology of these disorders. The REOLUT Node will improve the diagnosis and care of patients with rare LUT disorders via four work packages (WP1-4):

WP 1. Determine novel genetic causes of rare LUT disorders.
WP 2. Understand cellular & molecular mechanisms of LUT disorders.
WP 3. Optimise and develop novel treatment approaches.
WP 4a. & 4b. Build network of patients, researchers & clinicians in rare LUT disorder research.

Upcoming Events

Scan QR code above for more details - https://rd-research.org.uk/node/reolut/

3rd REOLUT Conference
Thursday 9th July 26
London, UK

European Nephrogenesis Workshop
Friday 10th July 26
London, UK

Node highlights

- Additional leveraged funding of £3,465,534.98.
- 15 MRC-NIHR acknowledged publications (29 REOLUT publications in total).
- Co-development of Urofacial Syndrome (UFS) patient information resource with Unique.

WP 1: Genomic discovery in REOLUT disorders

Uncovering the missing genetic causes of REOLUT disorders is essential to improving diagnosis and enabling targeted therapies. Fewer than 10% of patients have a known genetic cause for their condition, underscoring the need for expanded cohorts (via the GenRALT study) and more powerful gene discovery approaches.

Key progress:

- **~151 participants** have been recruited to the GenRALT study (target of 250 parent-child trios).
- **Active recruitment at eight UK centres** (Figure 1A).
- **Congenital anomalies of the kidney and urinary tract (CAKUT) rare disease group approved within UK Kidney Association RaDaR registry.**
- **566 patients included**, forming one of the most deeply phenotyped posterior urethral valve (PUV) datasets internationally (Figure 1B).
- One novel molecular diagnosis has been achieved in a **de novo SETBP1 mutation causing Schinzel–Giedion syndrome** (1).
- GWAS meta-analysis in PUV and bladder exstrophy (BE) in progress, comprising **1,100 cases and 15,000 controls** from international cohorts across Europe and the USA.
- **Pilot DNA methylation study in BE** is in progress with collaboration from EpiGenRare.

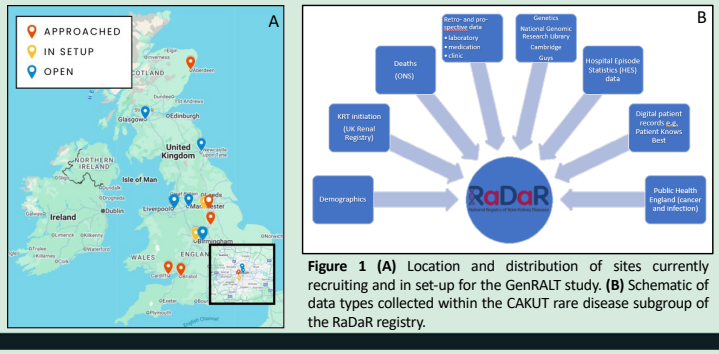

Figure 1 (A) Location and distribution of sites currently recruiting and in set-up for the GenRALT study. **(B)** Schematic of data types collected within the CAKUT rare disease subgroup of the RaDaR registry.

WP4a: Networking activities

The REOLUT Node has established a strong global network through:

- **Two annual conferences and two Scientific Advisory Board (SAB)** meetings.
- **33 invited international talks and workshops**, at meetings and institutions in genetics, nephrology, and urology.
- **Partnerships have been developed:18 higher education institution partners, 17 healthcare partners, and 7 charity partners** (Figure 2), with strong links to existing infrastructure such as BRCs and other RDRUK Nodes.

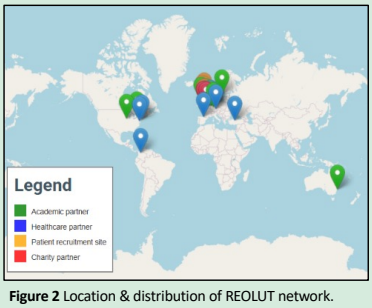

Figure 2 Location & distribution of REOLUT network.

WP 2: Understand mechanisms of LUT disorders

The biological mechanisms underlying LUT health and disease remain poorly understood. This project will build a comprehensive cellular and molecular atlas of BE and healthy tissues to inform the development of novel therapies.

Key progress:

- **120 BE and normal bladder specimens collected** & stored for future analysis.
- BE fibrosis has been characterised at genetic, histological and physiological level (Figure 3A).
- **Spatial transcriptomics** comparing BE, PUV, and normal bladder tissue in progress.
- **Surgically induced bladder fibrosis mouse model** recapitulating key features of PUV-like obstruction established (manuscript in preparation, Figure 3B).
- Novel therapeutic intervention in this model prevented bladder and kidney fibrosis.
- **Single-cell transcriptomic atlas of normal and fibrotic murine bladder generated** (Figure 3C).
- **New patient-derived experimental platforms** have been developed, including isolation of bladder urinary cells using the Cell Catcher device, multilayer urothelial culture systems, and urothelial and smooth muscle iPSCs.
- **3D imaging of bladder lymphatics** applied to human and mouse tissues (Figure 3D).
- **Pre-clinical lymphatic-modulating gene therapy trial** underway.

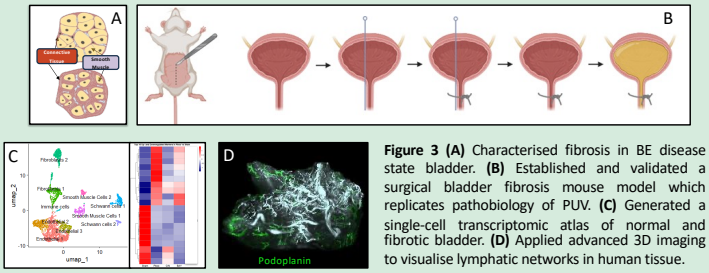

Figure 3 (A) Characterised fibrosis in BE disease state bladder. **(B)** Established and validated a surgical bladder fibrosis mouse model which replicates pathobiology of PUV. **(C)** Generated a single-cell transcriptomic atlas of normal and fibrotic bladder. **(D)** Applied advanced 3D imaging to visualise lymphatic networks in human tissue.

WP 3: Develop novel treatments

Current clinical management of REOLUT disorders does not address the underlying biological mechanisms driving disease. This project aims to take the first steps towards human therapeutic translation by setting up a novel *in vitro* human neuronal-smooth muscle model and optimising gene transfer into human LUT cells.

Key progress:

- **Co-culture system of human bladder smooth muscle and neuronal cells developed**, with early evidence of neurite–smooth muscle interaction (Figure 4A).
- More sophisticated **microfluidic co-culture** systems are being optimised (Figure 4 B, C and D).
- **AAV vector panel has identified a vector targeting** bladder muscle cells (Figure 4E).
- Novel therapeutic intervention for UFS restores bladder function in mouse models.
- **RNA sequencing identified downstream neuronal effectors** on axonal guidance on neuronal cells transduced with AAV9_CAG_ *HPSE2*.

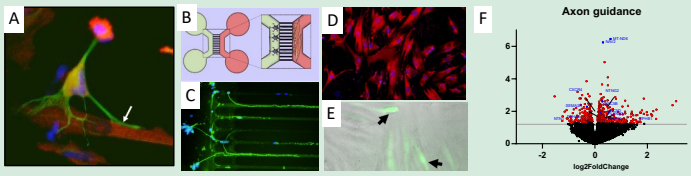

Figure 4 (A) Human bladder smooth muscle cell (red) and neuronal cell (green) co-culture with potential neuromuscular innervation (arrow). **(B)** Depiction of microfluidic co-culture devices. **(C)** Human neuronal cells (green) growing on microfluidic devices. **(D)** Human bladder smooth muscle cells growing on microfluidic devices. **(E)** Human bladder smooth muscle cells transduced with AAV-GFP. **(F)** Volcano plot showing up regulated and downregulated genes on neuronal cells transduced with AAV9_CAG_ *HPSE2* .

WP4b. Patient public involvement & engagement

Through strong partnerships with patient organisations, including **ERIC (The Children's Bowel and Bladder Charity), The Urology Foundation, and VOCAL**, we have achieved:

- **Two online patient forums** co-chaired by ERIC and VOCAL to enable structured feedback on research priorities, with one session dedicated to young people.
- Patient and charity partners **regularly participate in REOLUT meetings and conferences**.
- Co-development of a **UFS clinical guideline** (3).
- **Online patient resources** are also in development for UFS.
- **Media coverage, patient-facing publications, and parliamentary engagement** via a House of Commons reception, ensuring broad dissemination and meaningful impact beyond academia.

References

Scan QR code above for full list of publications

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(3) Newman, W. G., Woolf, A. S., Beaman, G. M. & Roberts, N. A. 1993. Urofacial Syndrome. In: Adam, M. P., Feldman, J., Mirzaa, G. M., Pagon, R. A., Wallace, S. E. & Amemiya, A. (Eds.) Genereviews(®). Seattle (Wa): University Of Washington, Seattle.

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