



The University of Manchester



Rare Early Onset Lower Urinary
Tract Disorders - REOLUT

Rare Early Onset Lower Urinary Tract Disorders (REOLUT)

Principle Investigator: Prof. Bill Newman (University of Manchester)

Co Investigator: Prof. David Long (University College London)

Co Investigator: Prof. Adrian Woolf (University of Manchester)

Co Investigator: Dr. Neil Roberts (University of Manchester)

Co Investigator: Dr. Melanie Chan (Imperial College London)

Co Investigator: Prof. Menna Clatworthy (University of Cambridge)

Patient organisation partner group – ERIC – The Children's bowel and bladder charity

Project Background

- Rare lower urinary tract disorders – affecting the bladder and ureters
- Limited research to date
- Building on >10 years discovery work – identification of changes in multiple genes account for ~10% of rare bladder disorders
- Rare conditions provide insight into common urinary tract disorders (affect ~1 million children)
- Huge impact on psychological well being

Project Overview

REOLUT Research Goals 2023-28

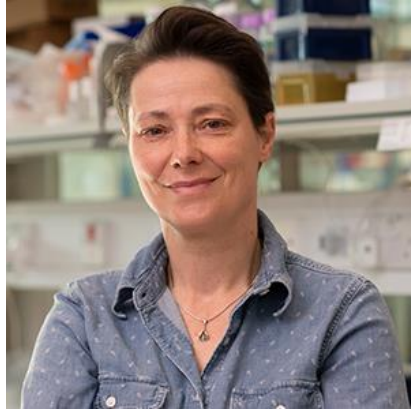
- Encourage junior researchers – clinical/non-clinical research in 3 projects
- Create national infrastructure for REOLUT research – recruitment across multiple clinical centres
- Sustainable resource: REOLUT registry within RaDaR database

Research Project 1 _Genetics



- Rare disease gene analysis (ASW and BN)
- Genomic Architecture of Bladder Exstrophy
- Common disease analysis (MC): GWAS, meta-analysis

Research Project 2 - Expression



- Single cell transcriptomic (RNA) analysis in normal bladder tissue and in BEEC

Research Project 3 - Treatment



- Develop gene therapy for urofacial syndrome – transfer from mouse model to human cell models
- Plans for clinical trials
- Economic analyses

Creating a national network for participant recruitment in REOLUT



★ 10 Open

>200 patients recruited
Target 250 trios

Professional and Patient Resources

 **U.S. National Library of Medicine**
National Center for Biotechnology Information

NLM Citation: Newman WG, Woolf AS, Beaman GM, et al. Urofacial Syndrome. 2013 Aug 22 [Updated 2023 Sep 28]. In: Adam MP, Bick S, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2026.
Bookshelf URL: <https://www.ncbi.nlm.nih.gov/books/>

**GeneReviews**
Clinical Reviews
of Genetic Disorders

Urofacial Syndrome
Synonym: Ochoa Syndrome
William G Newman, MA, PhD, FRCP,¹ Adrian S Woolf, MA, MD,² Glenda M Beaman, PhD,¹ and Neil A Roberts, PhD²
Created: August 22, 2013; Updated: September 28, 2023.

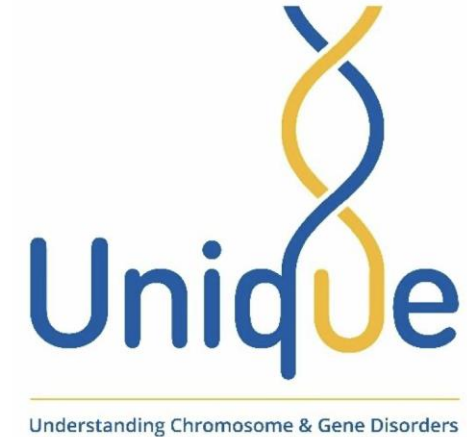
Summary

Clinical characteristics

Urofacial syndrome (UFS; also known as Ochoa syndrome) is characterized by prenatal or childhood onset of urinary bladder voiding dysfunction, abnormal facial movement with expression (resulting from abnormal co-contraction of the corners of the mouth and eyes), and often bowel dysfunction (constipation and/or encopresis). Bladder voiding dysfunction can present before birth as megacystis. In infancy and later childhood, UFS can present with a poor urinary stream and dribbling incontinence; incomplete bladder emptying can lead to urinary infection with progressive kidney failure. Investigations after birth can show abnormal bladder contractility and vesicoureteral reflux of urine into the ureter and renal pelvis. Nocturnal lagophthalmos (incomplete closing of the eyes during sleep) has also been documented.

Diagnosis/testing

The clinical diagnosis of UFS can be established in an individual with urinary tract dysfunction and characteristic facial movement with expression, or the molecular diagnosis can be established in an individual with characteristic features and biallelic pathogenic variants in either *HPSE2* or *LRIG2* identified by molecular genetic testing.



Urofacial syndrome (UFS) (Ochoa syndrome)

What do parents, children and families want?

- Work with VOCAL
- ERIC – Brenda Cheer and Sunni Liston
- Focus groups

VOCAL

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Bringing people and health research together

Vocal creates opportunities for people to find out about, and have a voice in, health research in Greater Manchester. Find out more about our work and how you can get involved.

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Key REOLUT Node Highlights



Journal of Pediatric Urology (xxxx) xxx xxx

Letter to the Editor

Letter to the Editor re: "Myh11 haploinsufficiency recapitulates megacystis and voiding dysfunction in a mouse model of MMIHS"

National Paediatric
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SUBMIT AN ABSTRACT

Whole-genome sequencing characterizes monogenic and polygenic contributions to structural kidney and urinary tract malformations



Cohort



1,052 patients with congenital anomalies of the kidneys and urinary tract (CAKUT)



Whole genome sequencing



Methods

Diagnostic yield

Genome-wide association study (GWAS) with rare and common variants

Heritability analysis

PUV Genomic risk score

Outcomes



4.9% received a genetic diagnosis

- 11.1% of cystic dysplasia
- 7.4% of kidney agenesis/hypodysplasia



Predictors of a positive genetic diagnosis (Odds Ratios and 95% confidence intervals):

- Family history OR: 2.2 (1.1-4.4)
- Consanguinity OR 3.0 (1.2-6.9)
- Extra-renal manifestations OR: 3.1 (1.7-5.7)



Common and low-frequency variants may explain ~23% (95% CI 1-45%) heritability of CAKUT

Chan et al., 2026

CONCLUSIONS:

1. A monogenic diagnosis was identified in a minority of this cohort of CAKUT patients
2. Some of this missing heritability may be attributable to low-frequency and common variants
3. Non-Mendelian genomic factors are likely to be important in the pathogenesis of CAKUT

Developing the next cadre of researchers



Neil Roberts

Lecturer,
University of
Manchester



Nav Johal

Consultant
Paediatric
Urologist, GOSH



Mel Chan

Consultant
Nephrologist
Imperial College,
London

All awarded large MRC grants to develop their research
into rare bladder disorders

Next steps

- Plans for further funding to develop studies – Urology Foundation, MRC, KRUK



- Maintain national network of recruiting sites

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