NIHR | BioResource

# IMP – Imprinting Disorders Cohort

NIHR BioResource – Rare Diseases study project

**Lead Investigator: Professor Karen Temple**

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**Prof Karen Temple, IMP project Lead**

## Summary

Imprinting Disorders (IDs) are an under-recognised network of medical disorders with at least 10 recognised clinical presentations. They affect growth, development and metabolism, cause considerable morbidity for patients and can be difficult to diagnose.

There are two broad categories of IDs: patients with restricted intrauterine growth who have significant short stature and long term metabolic disturbance such as diabetes; and those with intrauterine overgrowth and predisposition to cancer.

Early treatment and appropriate medical surveillance changes the outcome (final height, metabolic health, cancer survival) and a national collaboration to improve diagnosis and stratification will enhance outcome for patients and provide the opportunity for treatment intervention trials.

There are currently 10 recognised syndromes: Prader Willi, Angelman syndrome, Silver Russell syndrome (SRS), Beckwith Wiedemann syndrome (BWS), Temple Syndrome, Kagami Ogata, Pseudohypoparathyroidism type 1B, Mulchandani-Bhoj-Conlin syndrome (Mat UPD 20), Maternal UPD 6 syndrome and Transient Neonatal Diabetes type 1. They are diagnosed using array CGH and epigenetic analysis at one of 10 imprinted loci followed by specific gene sequencing/ copy number analysis on a case by case basis. This requires a standalone genetic test and medical awareness to prompt testing. The actual incidence of IDs as a group, while rare, is unknown and the lack of a routine screening test in clinical practice means that a focus on these disorders may alert health professionals and patients.

Our project is to build a cohort of patients with IDs to enhance the opportunities for clinical trials, novel diagnostics and studies to understand and improve long term outcomes.

## Recruitment Criteria

### Inclusion

Patients with imprinting disorders have unexplained restrained growth (<-2SD usually) or overgrowth at birth (>+2 SD usually) and the nonspecific medical problems makes them difficult to diagnose particularly in later life.

Post-natally the pattern of growth is maintained in childhood and without intervention results in short or tall stature. Congenital anomalies are usually minor if present, but may include umbilical anomalies (hernia, exomphalos), genital anomalies, heart disease and cleft palate and there maybe body asymmetry. Metabolic disorders such as diabetes, obesity and early puberty are common in the restricted growth disorders and childhood cancers in the overgrowth group, particularly Wilms and hepatoblastoma. Motor and speech delay are common and development in general ranges from normal to significant handicap and can include abnormal behaviour from eating disorders to autism.

Conditions are well described although there is a general lack of awareness that there is such overlap between conditions that a child with a suspected imprinting disorder where the initial test is negative should be tested at all human disease-implicated imprinted loci on chromosomes 6, 7, 11, 14, 15 and 20.

**This study aims to recruit any patient with a confirmed imprinting disorder or a patient who meets the clinical criteria but with a negative test.** While Prader Willi and Angelman syndrome are better characterised (as the genomic cause is predominantly an aberrant copy number at 15q11-13 identified through CGH array), the 8 rarer imprinting conditions (Silver Russell syndrome (SRS), Beckwith Wiedemann syndrome (BWS), Temple Syndrome, Kagami Ogata, Pseudohypoparathyroidism type 1B, Mulchandani-Bhoj-Conlin syndrome (Mat UPD 20), Maternal UPD 6 syndrome and Transient Neonatal Diabetes type 1) ideally require methylation testing followed by specific gene sequencing to confirm.