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CIL. Ciliopathies – Bardet Biedl Syndrome & Alström Syndrome

NIHR BioResource – Rare Diseases study project

Lead Investigators:
Professor Phil Beales; Professor Tim Barrett

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Prof. Phil Beales, CIL project lead

Summary

Ciliopathy diseases are a group of rare conditions that currently have no treatment. For two of them, Alström syndrome and Bardet Biedl syndrome, there are NHS England national multidisciplinary services, but these only provide supportive treatments.

Bardet Biedl syndrome affects about 1 in 300,000 children, causing vision loss, obesity and kidney problems. Alström syndrome affects 1 in a million children, and causes vision and hearing loss, heart, obesity and kidney problems.
There is already industry interest in treatments for these conditions. The overall objective of this cohort is to characterise children and adults with Bardet Biedl syndrome and Alström Syndrome. This will include baseline and repeated assessments over time of the growth, kidney, heart, chest and metabolism of these children and adults, together with genetic testing and collection of tissue in order to:

1. describe the natural histories these diseases and their complications in a multiethnic cohort of UK children and adults
2. identify bio-markers which will predict progression of the syndromes and effectiveness of future treatments to prevent or delay the progression of the syndrome
3. generate a tissue resource for basic science studies into the biology of the syndromes.

Recruitment Criteria

Please refer to the following two pages for inclusion criteria for Bardet Biedl syndrome and Alström syndrome.

Inclusion – Bardet Biedl Syndrome

Beales[1] et al (1999; 2001) have suggested that the presence of 4 primary features or 3 primary features plus 2 secondary features are necessary for the diagnosis. Primary and secondary features are listed in the below table.

Note: The diagnosis is established in individuals of all ages in whom two pathological mutations in the same gene are identified.

Primary Features	**Secondary Features**
• **Rod-cone dystrophy** (76%, 72%) • **Postaxial polydactyly** (80%, 79%) • **Truncal obesity** (80%, 77%) • **Learning disabilities** (24%, 30%) • **Hypogonadism** in male or **genital abnormalities** in females (4%, 4%) • **Renal disease** (9%, 10%)	• **Speech delay/disorder** (2%, 2%) • **Developmental delay** (9%, 5%) • **Behavioral abnormalities** (9%, 7%) • **Eye abnormalities** include strabismus, cataracts, and astigmatism (17%, 26%) • **Brachydactyly/syndactyly** (4%, 3%) • **Ataxia/poor coordination/imbalance** (0%, 0%) • **Mild hypertonia** (especially lower limbs) (0%, 0%) • **Diabetes mellitus** (4%, 6%) • **Orodental abnormalities** (2%, 2%) • **Cardiovascular anomalies** (6%, 10%) • **Hepatic involvement** (0%, 5%) • **Craniofacial dysmorphism** (0%, 1%) • **Hirschsprung disease** (2%, 1%) • **Anosmia** (0%, 0%)

Percentages in parentheses for each feature are based on prevalence in a cohort of 96 BBS patients (46 with molecular genetic diagnosis) participating in the EURO-WABB registry (% in those with genetic diagnosis, % overall).

[1]Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet-Biedl syndrome: results of a population survey. J Med Genet. 1999;36:437–46.

Inclusion – Alström Syndrome

The diagnosis is established in individuals of all ages in whom two pathological *ALMS1* mutations are identified.

Diagnostic Criteria by Age (from Marshall[1] et al. 2013).

Age Range	Major	Minor	Minimum Required	Other Variable Supportive Evidence
Birth – 2 yrs	• Loss of function mutation in 1 allele of *ALMS1* AND/OR • Family history of Alström syndrome • Vision (nystagmus/photophobia)	• Obesity • dilated cardiomyopathy (DCM)/congestive heart failure (CHF)	2 major criteria OR 1 major + 2 minor criteria	• Recurrent pulmonary infections • Normal digits • (History of) delayed developmental milestones
3-14 yrs	• Loss of function *ALMS1* mutation in 1 allele AND/OR • Family history of Alström syndrome • Vision (nystagmus, photophobia, diminished acuity, if old enough for testing: cone dystrophy by ERG)	• Obesity and/or insulin resistance and/or T2DM • DCM/CHF • Hearing loss • Hepatic dysfunction • Renal failure • Advanced bone age • DCM/CHF	2 major criteria OR 1 major + 3 minor criteria	• Recurrent pulmonary infections • Normal digits •(History of) delayed developmental milestones • Hypertriglyceridaemia • Scoliosis • Flat wide feet • Hypothyroidism • Hypertension • Growth hormone deficiency • Recurrent UTI
15 yrs - adult	• Loss of function *ALMS1* mutation in 1 allele AND/OR • Family history of Alström syndrome • Vision (history of nystagmus in infancy/childhood, legal blindness, cone and rod dystrophy by ERG)	• Obesity and/or insulin resistance and/or T2DM • DCM/CHF • Hearing loss •Hepatic dysfunction • Renal failure • Short stature • Males: hypogonadism • Females: irregular menses and/or hyperandrogenism	2 major + 2 minor criteria OR 1 major + 4 minor criteria	• Recurrent pulmonary infections • Normal digits • (History of) delayed developmental milestones • Hypertriglyceridaemia • Kypho-scoliosis • Flat wide feet • Hypothyroidism • Hypertension • Growth hormone deficiency • Recurrent UTI / urinary dysfunction • Alopecia

Figures in parentheses relate to prevalence in EURO-WABB Registry participants with confirmed molecular genetic diagnoses: n=13 aged birth-2yrs; n=24 aged 3-14yrs; n=13 aged ≥15 yrs.
ERG = electroretinogram ; T2DM = type 2 diabetes mellitus ; DCM/CHF = dilated cardiomyopathy with congestive heart failure ; UTI = urinary tract infections.

[1]*Marshall JD, Maffei P, Beck S, Barrett TG, Paisey RB, Naggert JK. Clinical utility gene card for: Alström syndrome – update 2013. Eur J Hum Genet 2013 Apr 24th*.