Ciliopathies Gene Panel

Contact details

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Samples required

- 5ml venous blood in plastic EDTA bottles (>1ml from neonates)
- Prenatal testing must be arranged in advance, through a Clinical Genetics department if possible.
- Amniotic fluid or CV samples should be sent to Cytogenetics for dissecting and culturing, with instructions to forward the sample to the Regional Molecular Genetics laboratory for analysis
- A completed DNA request form should accompany all samples

Patient details

To facilitate accurate testing and reporting please provide patient demographic details (full name, date of birth, address and ethnic origin), details of any relevant family history and full contact details for the referring clinician

Introduction

The ciliopathies are a heterogeneous group of conditions with considerable phenotypic overlap. These inherited diseases are caused by defects in cilia; hair-like projections present on most cells, with roles in key human developmental processes via their motility and signalling functions. Ciliopathies are often lethal and multiple organ systems are affected. Ciliopathies are united in being genetically heterogeneous conditions and the different subtypes can share many clinical features, predominantly cystic kidney disease, but also retinal, respiratory, skeletal, hepatic and neurological defects in addition to metabolic defects, laterality defects and polydactyly. Their clinical variability can make ciliopathies hard to recognise, reflecting the ubiquity of cilia. Gene panels currently offer the best solution to tackling mutational analysis of genetically heterogeneous conditions such as the ciliopathies. Ciliopathies affect approximately 1:2,000 births.

Ciliopathies are generally inherited in an autosomal recessive manner, with some autosomal dominant and X-linked exceptions.

Referrals

- Patients presenting with a ciliopathy; due to the phenotypic variability this could be a diverse set of features. For guidance contact the laboratory or Dr Hannah Mitchison (h.mitchison@ucl.ac.uk) / Prof Phil Beales (p.beales@ucl.ac.uk)
- Referrals will be accepted from clinical geneticists and consultants in nephrology, metabolic, respiratory and retinal diseases.
- Testing for Bardet-Biedl syndrome is NCG-funded for patients resident in England and Scotland.

Prenatal testing

Prenatal diagnosis may be offered as appropriate where pathogenic mutations have been identified in accordance with expected inheritance pattern and where appropriate parental testing and counselling has been conducted.

Service offered

Analysis of coding regions and intron/exon boundaries of up to 125 genes. Analysis may be based on a sub-panel appropriate to the presentation (preferable), or if diagnosis is unclear, analysis of the entire panel may be requested.

Sub-panels:

- Primary ciliary dyskinesia (PCD) and reduced generation of multiple motile cilia (RGMC) syndrome.
- Bardet Biedl syndrome (BBS)
- Visceral Heterotaxy
- Orofaciodigital syndrome (OFDS)
- Alstrom syndrome
- Meckel syndrome
- Skeletal ciliopathies
- Polycystic kidney disease, nephronophthisis and related disorders
- Joubert syndrome and Senior Loken syndrome

For gene lists see below.

Technical

Mutation screening is carried out by next generation sequencing with library preparation using the Agilent focused clinical exome +1 kit followed by sequencing on the Illumina platforms. Data is analysed using an in-house pipeline with all mutations confirmed by Sanger sequencing.

Target reporting time

4 months for next generation sequencing screening in an index case. 2 weeks for familial mutation testing. Please contact the laboratory for urgent cases.

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Full gene list (CILIA_v2):

ACVR2B, AHI1, ALMS1, ANKS6, ARL6, ARL13B, ARMC4, B9D1, B9D2, BBIP1, BBS1, BBS2, BBS4, BBS5, BBS7, BBS9, BBS10, BBS12, C21ORF59, C2CD3, C5ORF42, CC2D2A, CCDC28B, CCDC39, CCDC40, CCDC65, CCDC103, CCDC114, CCDC151, CCNO, CEP41, CEP83, CEP120, CEP164, CEP290, CFAP53, CFC1, CRELD1, CSPP1, DCDC2, DDX59, DNAAF1, DNAAF2, DNAAF3, DNAAF5, DNAH5, DNAH11, DNAI1, DNAI2, DNAL1, DRC1, DYNC2H1, DYX1C1, EVC, EVC2, GAS8, GDF1, GLI3, GLIS2, HNF1B, HYDIN, HYLS1, IFT27, IFT43, IFT80, IFT122, IFT140, IFT172, INPP5E, INVS, IQCB1, KIAA0586, KIF7, LBR, LRRC6, LZTFL1, MCIDAS, MKKS, MKS1, MUC1, NEK1, NEK8, NME8, NODAL, NPHP1, NPHP3, NPHP4, OFD1, PDE6D, PKD1*, PKD2, PKHD1, POC1B, PRKCSH, RPGR*, RPGRIP1L, RSPH1, RSPH4A, RSPH9, SBDS, SCLT1, SDCCAG8, SEC63, SPAG1, TBC1D32, TCTN1, TCTN2, TCTN3, TMEM67, TMEM138, TMEM216, TMEM231, TMEM237, TRIM32, TTC21B, TTC8, UMOD, WDPCP, WDR19, WDR34, WDR35, WDR60, ZIC3, ZMYND10, ZNF423*

Primary ciliary dyskinesia (PCD) and reduced generation of multiple motile cilia (RGMC) syndrome (PCD_v2)

ARMC4, C21ORF59, CCDC39, CCDC40, CCDC65, CCDC103, CCDC114, CCDC151, CCNO, DNAAF1, DNAAF2, DNAAF3, DNAAF5, DNAH11, DNAH5, DNAI1, DNAI2, DNAL1, DRC1, DYX1C1, GAS8, HYDIN, LRRC6, MCIDAS, NME8, OFD1, RPGR, RSPH1, RSPH4A, RSPH9, SPAG1, ZMYND10*

Bardet Biedl syndrome (BBS)

ARL6, BBIP1, BBS1, BBS2, BBS4, BBS5, BBS7, BBS9, BBS10, BBS12, CCDC28B, CEP290, IFT27, LZTFL1, MKKS, MKS1, SDCCAG8, TRIM32, TTC8, WDPCP

Visceral Heterotaxy (HETEROTAXY_v2)

ACVR2B, CFAP53, CFC1, CRELD1, GDF1, NODAL, ZIC3*

Orofaciodigital syndrome (OFDS_v2)

C2CD3, C5ORF42, DDX59, OFD1, SCLT1, TBC1D32, TCTN3

Alstrom syndrome (ALMS)

ALMS1

Meckel syndrome (MECKEL)

B9D1, B9D2, CEP290, HYLS1, MKS1, NPHP3, TCTN2, TMEM216, TMEM67

Skeletal ciliopathies (SKELCIL)

C5orf42, CEP120, CSPP1, DDX59, DYNC2H1, EVC, EVC2, IFT43, IFT80, IFT122, IFT140, IFT172, LBR, NEK1, OFD1, SBDS, TCTN3, TMEM216, TTC21B, WDR19, WDR34, WDR35, WDR60

Polycystic kidney disease, nephronophthisis and related disorders (PKDNEPH_v2)

ANKS6, CEP164, CEP83, DCDC2, GLIS2, HNF1B, IFT43, INVS, MUC1, NEK8, NPHP1, NPHP3, NPHP4, PKD1, PKD2, PKHD1, PRKCSH, SEC63, TMEM67, TTC21B, UMOD, WDR19, ZNF423*

Joubert syndrome and Senior Loken syndrome (JOUBERT_v2)

AHI1, ARL13B, C5ORF42, CC2D2A, CEP41, CSPP1, GLI3, INPP5E, IQCB1, KIAA0586, KIF7, NPHP4, OFD1, PDE6D, POC1B, RPGRIP1L, SDCCAG8, TCTN1, TCTN3, TMEM138, TMEM216, TMEM231, TMEM237, WDR19, ZNF423

*Genes marked with an asterisk have low (<90%) horizontal coverage due to sequence context and/or the presence of highly homologous regions in the genome.