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Evaluating Gene-Disease Relationships in Motile Ciliopathies: an international ClinGen - BEAT-PCD ERS CRC collaboration

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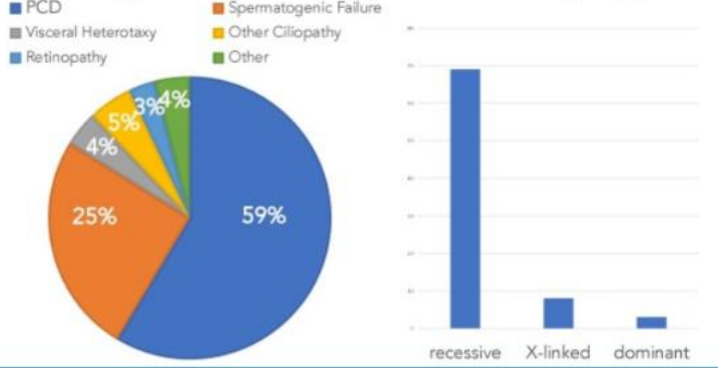


Introduction

Genetic diagnosis of motile ciliopathies is conducted by healthcare, commercial and private laboratories. 86 causative genes have been implicated in motile ciliopathies (PCD, male infertility and associated disorders including retinopathy and hydrocephalus). Gene-disease relationships are uncertain where evidence is limited, thus risking inaccurate reporting and diagnosis.

The ClinGen Motile Ciliopathy Gene Curation Expert Panel (GCEP) was established in collaboration with BEAT-PCD ERS CRC in 2021. The GCEP comprises geneticists, pulmonologists and biocurators from Canada, France, Germany, Norway, Poland, Tunisia, UK and USA, all tasked with classifying the clinical validity of gene-disease relationships in motile ciliopathies to aid interpretation of genetic results. As part of the curation process, the GCEP established guidelines to capture the critical details of motile ciliopathy cases and to score genetics and experimental evidence conservatively and consistently. The GCEP meets monthly and to date has curated 43 gene-disease relationships involving 39 genes (list at <https://clinicalgenome.org/affiliation/40102/>).

99 phenotypes associated with 86 putative motile ciliopathy genes



Definitions of clinical and diagnostic criteria for gene curation

Necessitated by the phenotypic and genetic heterogeneity of PCD, with emphasis on lumping and splitting of disease features to precisely define phenotypes.

Must include a chronic, persistent year-round wet cough from birth or early childhood and one of the following (combined ATS and ERS criteria):

- Chronic year-round nasal congestion from birth or early childhood.
- Unexplained neonatal respiratory distress in a term infant.
- An organ laterality defect.
- Most adults will have developed bronchiectasis.

Confirmatory diagnostic investigation in someone with typical clinical features should include:

Class 1 TEM defect (ODA, IDA +ODA, IDA+MTD) OR:
2 of the following - these should be concordant with gene function and one another:

- Low nasal nitric oxide (<77nl/min) – measured by chemiluminescence analyser

Respiratory epithelial cells demonstrating concordant evidence:

- Absent axonemal protein on IF, either the mutated protein or a marker of an associated structure.
- Recognised HSVM defect of beat pattern (immotile, rotating, hyper-frequent).
- Class 2 TEM defect (MTD, RGMC, central pair defect, partial ODA or ODA+IDA defect).
- Reduced CBF or MCC following epithelial culture/fresh primary sample, noting that for *DNAH11* mutation, the cilia can appear hyper-frequent.

TEM: transmission electron microscopy, IDA+ODA: inner + outer dynein arms, MTD: microtubular doublet, IF: immunofluorescence, HSVM: high speed video microscopy, MTD: microtubular disorganisation, RGMC: reduced generation of multiple motile cilia, CBF: cilia beat frequency, MCC: mucociliary clearance

Results of 43 gene-disease curations based on genetic and experimental evidence

• PCD, 35 genes

| Classification | Gene |
|----------------|---|
| Definitive | CCDC103, CCDC39, CCDC40, CCNO, CFAP300, DNAAF1, DNAAF3, DNAH11, DNAH5, DNAI1, DNAI2, HYDIN, MCIDAS, ODAD1, ODAD2, ODAD3, ODAD4, RSPH1, RSPH4A, SPAG1, ZMYND10 |
| Strong | FOXJ1 |
| Moderate | CFAP221, CFAP298 |
| Limited | CFAP57, *DNAH1, DNAL1, GAS2L2, NME8 |
| Disputed | *AK7, BRWD1, *CFAP43, *DNAH8, MNS1 |

• Infertility (spermato-genetic failure), 7 genes

| Classification | Gene |
|----------------|-------------------------------|
| Definitive | ARMC2, CFAP43, *DNAH1, DNAH17 |
| Strong | *DNAH8 |
| Limited | *AK7, CFAP47 |

• Normal pressure hydrocephalus, 1 gene

| Classification | Gene |
|----------------|---------|
| Limited | *CFAP43 |

*indicates a gene curated for more than one disease, i.e. an example of splitting

Conclusions: These efforts provide a basis for future classifications of gene-disease relationships. The goal of the Motile Ciliopathy CGEP is to leverage emerging research to enhance the reliability of genetic testing for improved clinical detection and diagnosis of PCD and other motile ciliopathies worldwide.



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