



## Development and first results of the BEAT PCD international Primary Ciliary Dyskinesia gene variant database: CiliaVar

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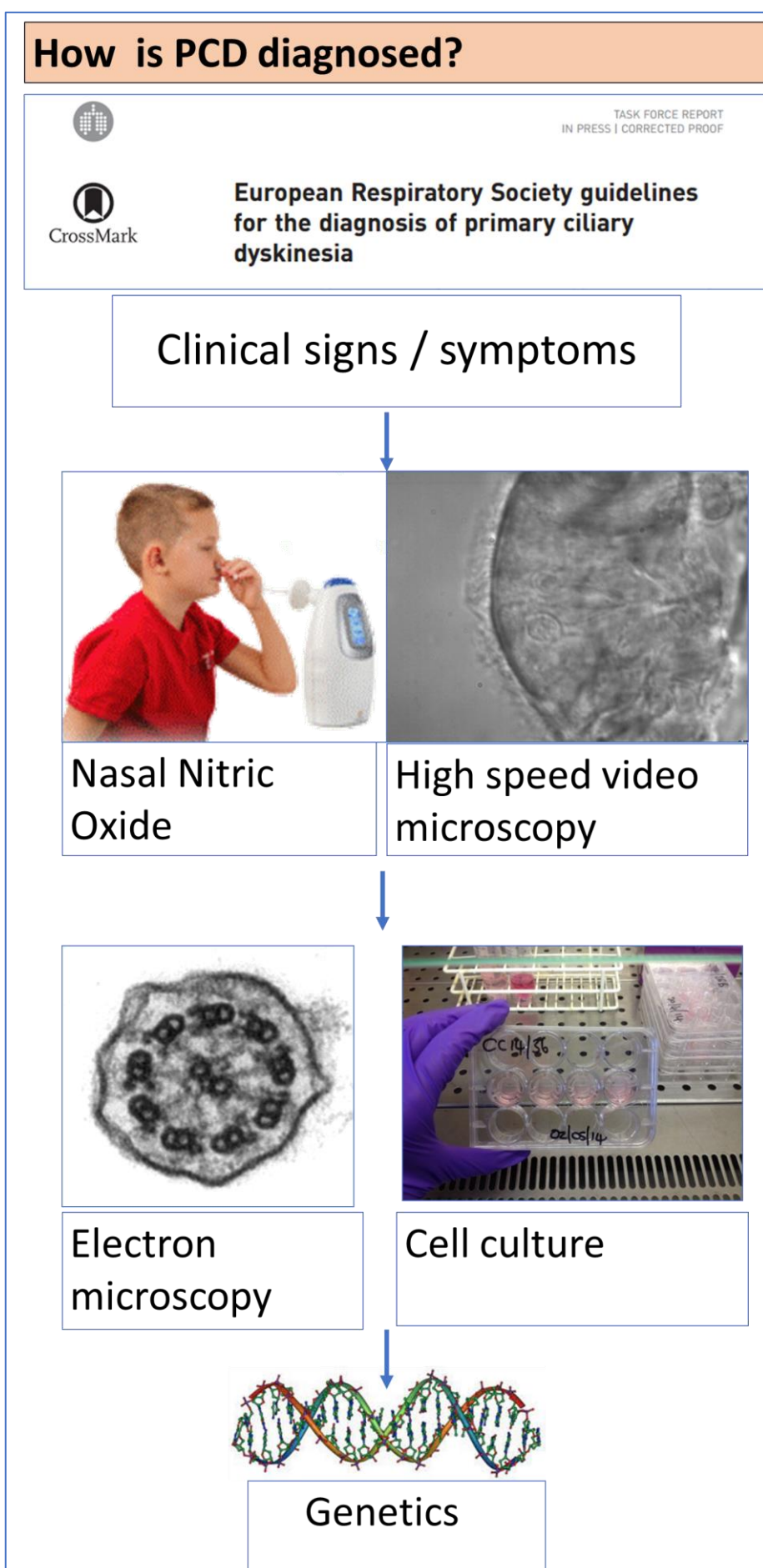
# Development and first results of the BEAT-PCD international Primary Ciliary Dyskinesia gene variant database: CiliaVar

Amelia Shoemark

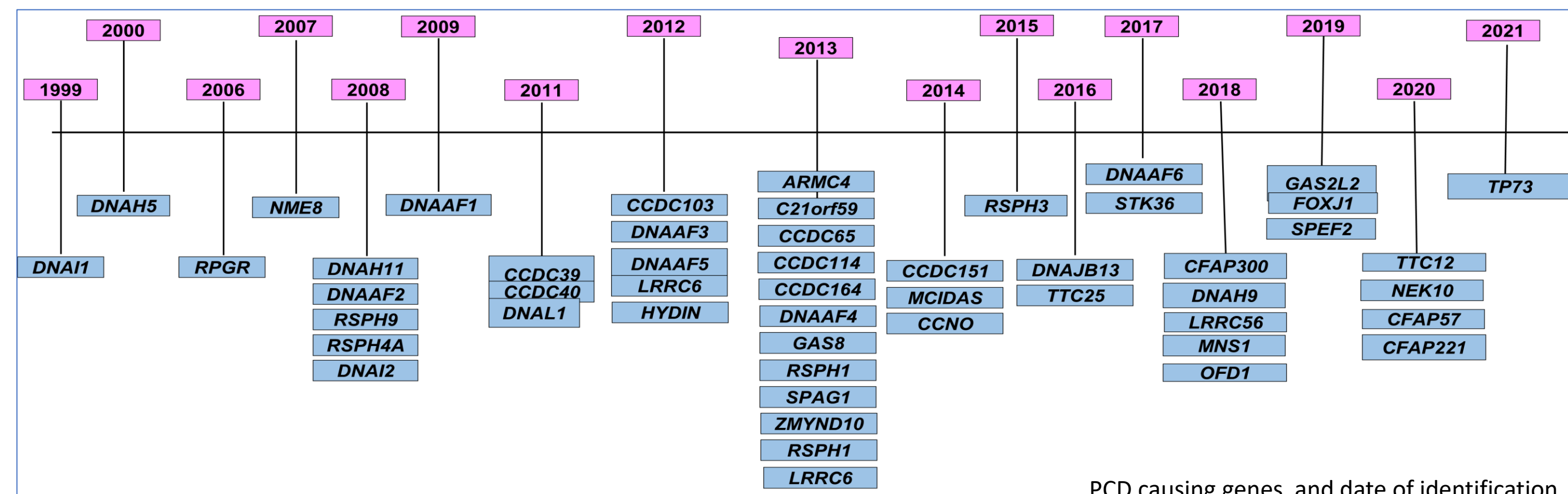
On behalf of BEAT-PCD WP2 CiliaVar team: **Rahma. Mani<sup>1</sup>, Mafalda. Gomes<sup>2</sup>, Adrian . R. González<sup>3</sup>, Sun Maximo<sup>2</sup>, Claire. Hogg<sup>4</sup>, Deborah. Morris-Rosendahl<sup>5</sup>, Bernard. Maitre<sup>6</sup>, Mahmoud. R. Fassad<sup>3</sup>, Myrona. Goutaki<sup>7</sup>, Nisreen Rumman<sup>8</sup>, Jane. S. Lucas<sup>9</sup>, Hannah. M. Mitchison<sup>3</sup>, Marie. Legendre<sup>10</sup>, Suzanne. Crowley<sup>11</sup>**

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## Background



- PCD can be diagnosed by bi-allelic pathogenic mutations in one of >50 ciliary genes.



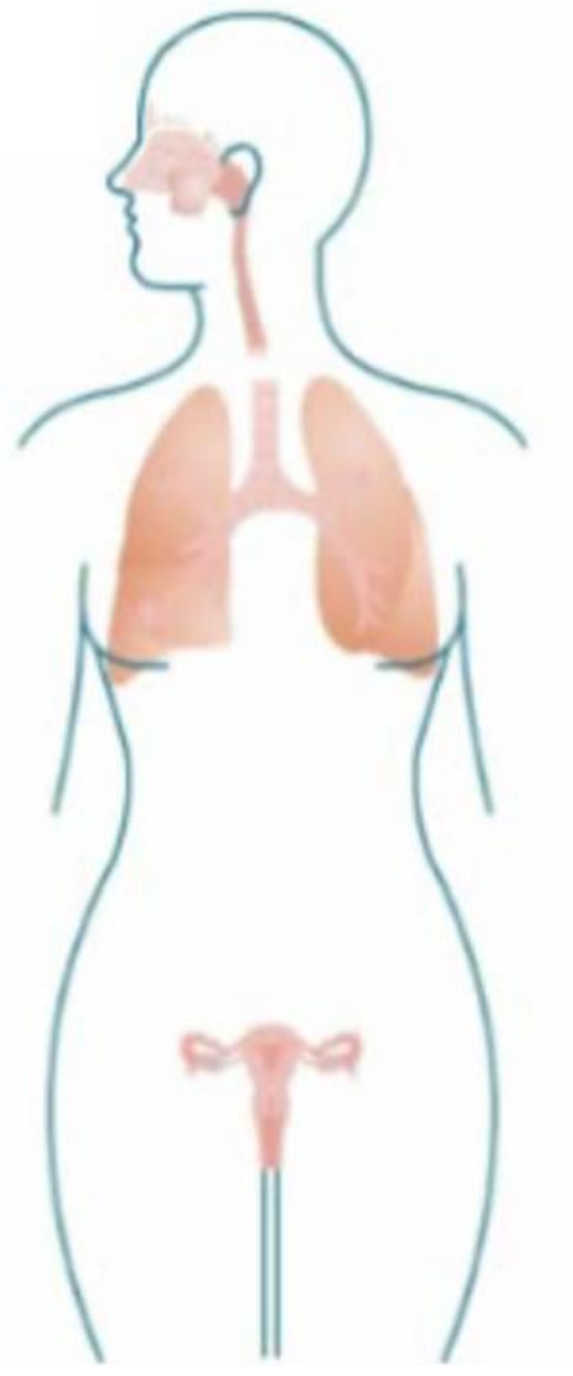
- ~ 60% of patients with an identified genetic cause have private mutations, that have not been previously reported in another patient.
- Increasing numbers of variants of unknown significance (VUS, i.e. unknown if they are pathogenic or non-pathogenic) are identified.
- As clinical genetic testing is increasingly implemented for PCD, there is a need to develop a public access resource to identify if variants have previously been reported to be associated with disease.

## What is PCD?

Dysfunction of multiple motile cilia  
Incidence ~1:7500  
Heterogenous multi-system disorder

### Symptoms include:

- Respiratory
  - neonatal respiratory distress
  - Wet/ productive cough
  - Recurrent chest infections
  - Bronchiectasis**
- Chronic Rhinitis / sinusitis
- Recurrent otitis media
- Situs Inversus or complex congenital heart disease
- Other features
  - Hydrocephalus
  - Retinal abnormalities
  - Infertility



**Aim: To establish an online open database registering mutations and specific combinations of mutations causing PCD.**

## Methods

- A panel of clinicians and geneticists with expertise in PCD identified database fields to link each variant with the associated diagnostic, clinical and genetic evidence supporting pathogenicity.
- A PubMed search was conducted using search terms (“name of the gene” AND “cili\*” NOT “review”) to identify published mutations in PCD genes.
- Database curators checked mutation nomenclature and classification of variants was carried out following ACMG guidelines.

## Data collected


**Clinical fields:**  
At point of diagnosis:  
Age  
Sex  
Affected siblings  
FEV1% pred  
Neonatal respiratory distress y/n  
Bronchiectasis y/n  
Infertility y/n  
Lobectomy y/n  
Otitis media y/n  
Productive/ wet cough y/n  
Chronic rhinitis y/n

**Diagnostic fields:**  
Nasal NO (nl/min)  
TEM (consensus guideline)  
High speed video  
Immunofluorescence  
PCD +tve/-tve (ERS guideline)


### Genetics fields:

Gene	Variant	Variant type	Variant location	Variant description	Variant classification	Variant frequency	Variant pathogenicity	Variant source	Variant date	Variant status	Variant notes
DNAH5	c.248del	Deletion	Exon 1	Deletion of 1 bp	Pathogenic	0.0001	Pathogenic	ERS	2012	Pathogenic	Pathogenic
DNAH5	c.48+2dupT	Duplication	Intron 1	Duplication of 2 bp	Pathogenic	0.0001	Pathogenic	ERS	2012	Pathogenic	Pathogenic
DNAH5	c.1100G>A	Point mutation	Exon 3	G to A transition	VUS	0.0001	VUS	ERS	2012	VUS	VUS
DNAH5	c.1100G>A	Point mutation	Exon 3	G to A transition	VUS	0.0001	VUS	ERS	2012	VUS	VUS
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DNAH5	c.1100G>A	Point mutation	Exon 3	G to A transition	VUS	0.0001	VUS	ERS	2012	VUS	VUS
DNAH5	c.1100G>A	Point mutation	Exon 3	G to A transition	VUS	0.0001	VUS	ERS	2012	VUS	VUS


## Results




Literature search  
**651** papers  
Abstract review  
**262** selected



Patients  
**1551** from literature  
**466** from 4 diagnostic centres



**1648** Mutations



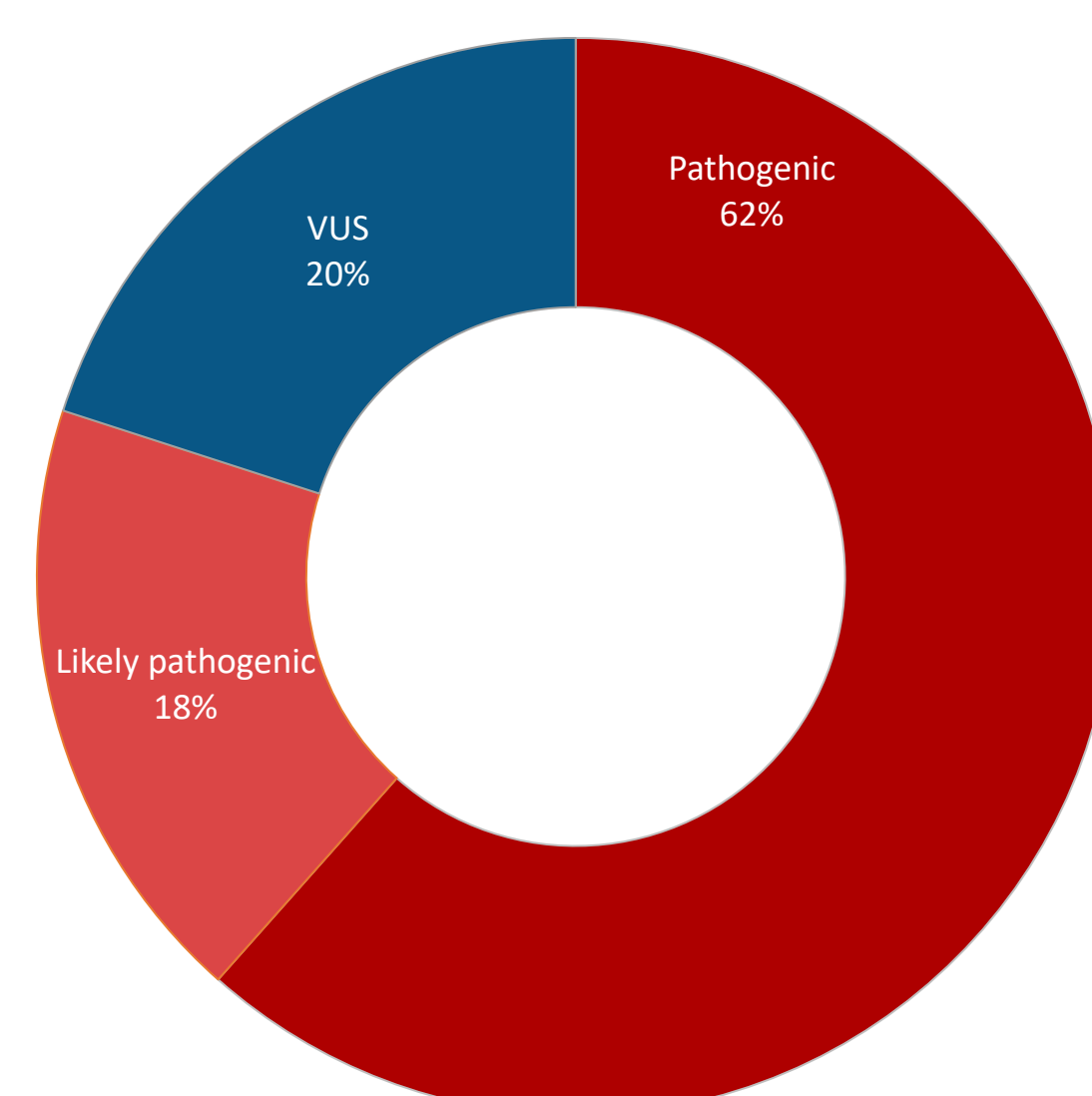
Mutation nomenclature verification and classification following ACMG guidelines

**CiliaVar**

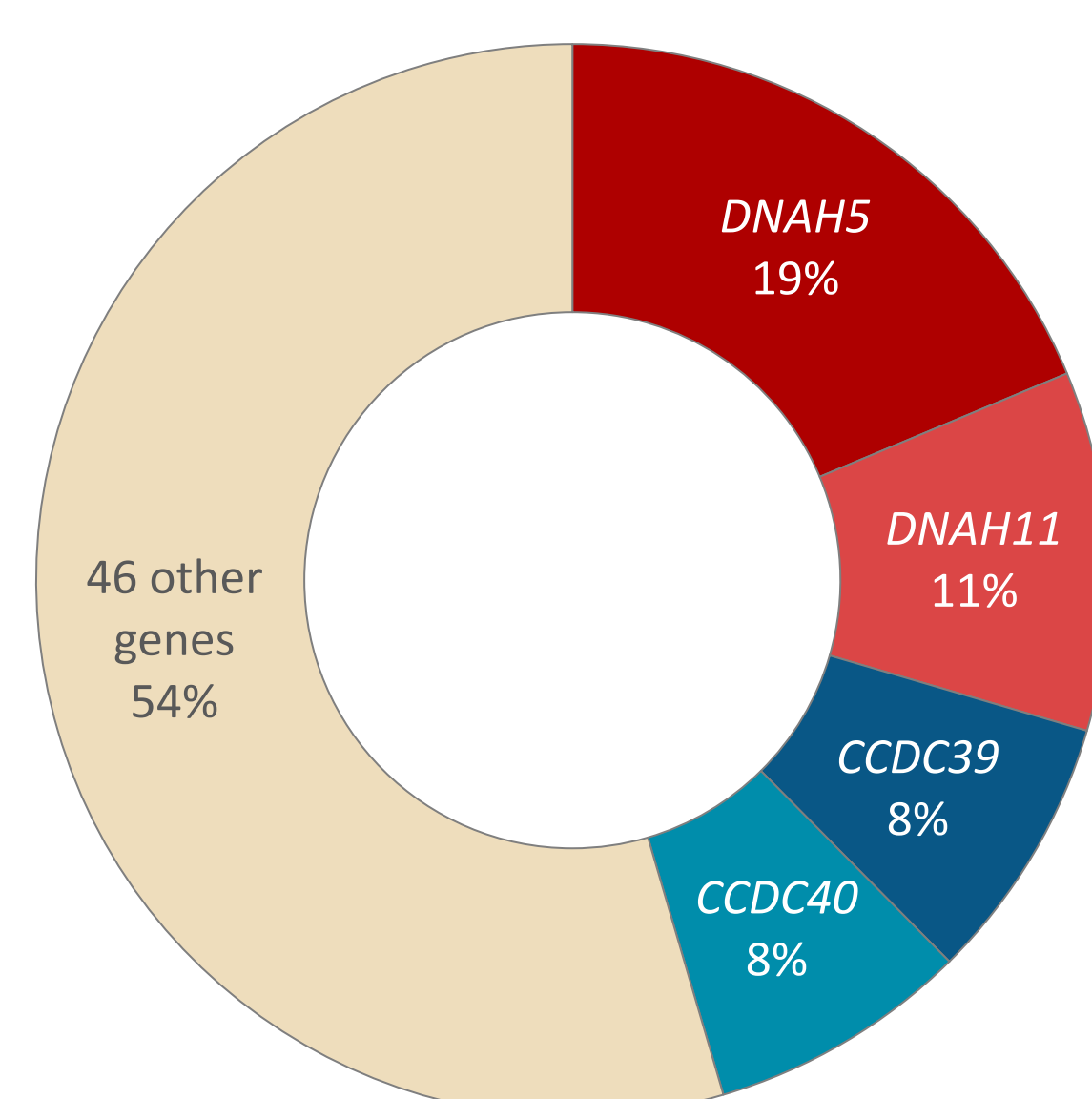
1648 mutations were included in CiliaVar.

The most common variants reported are CCDC40: c.248del (n=41 patients) and DNAI1: c.48+2dupT (n=49).

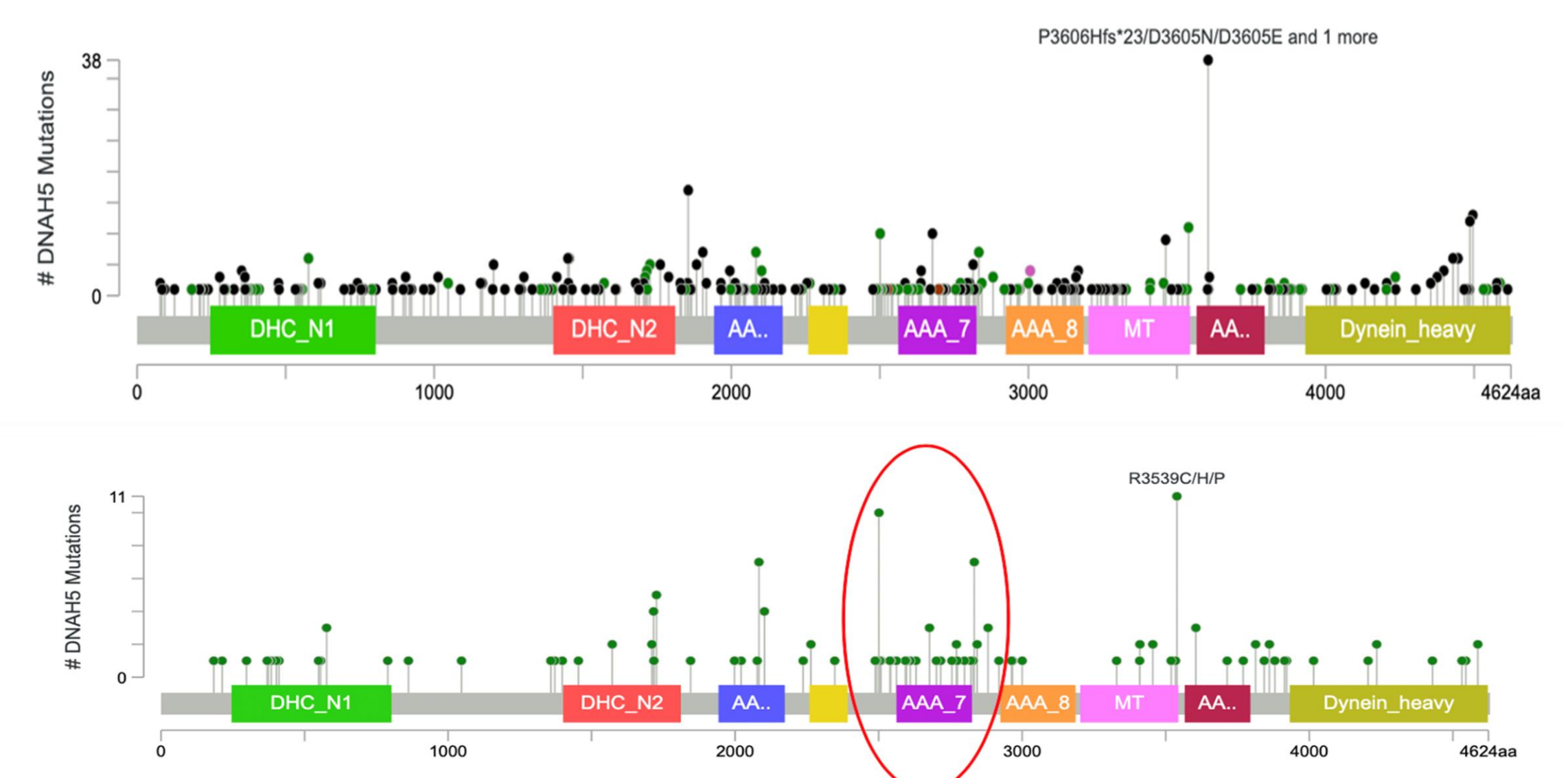
**20%** of the distinct mutations are classified as **VUS** and 93% of those VUS are missense mutations.



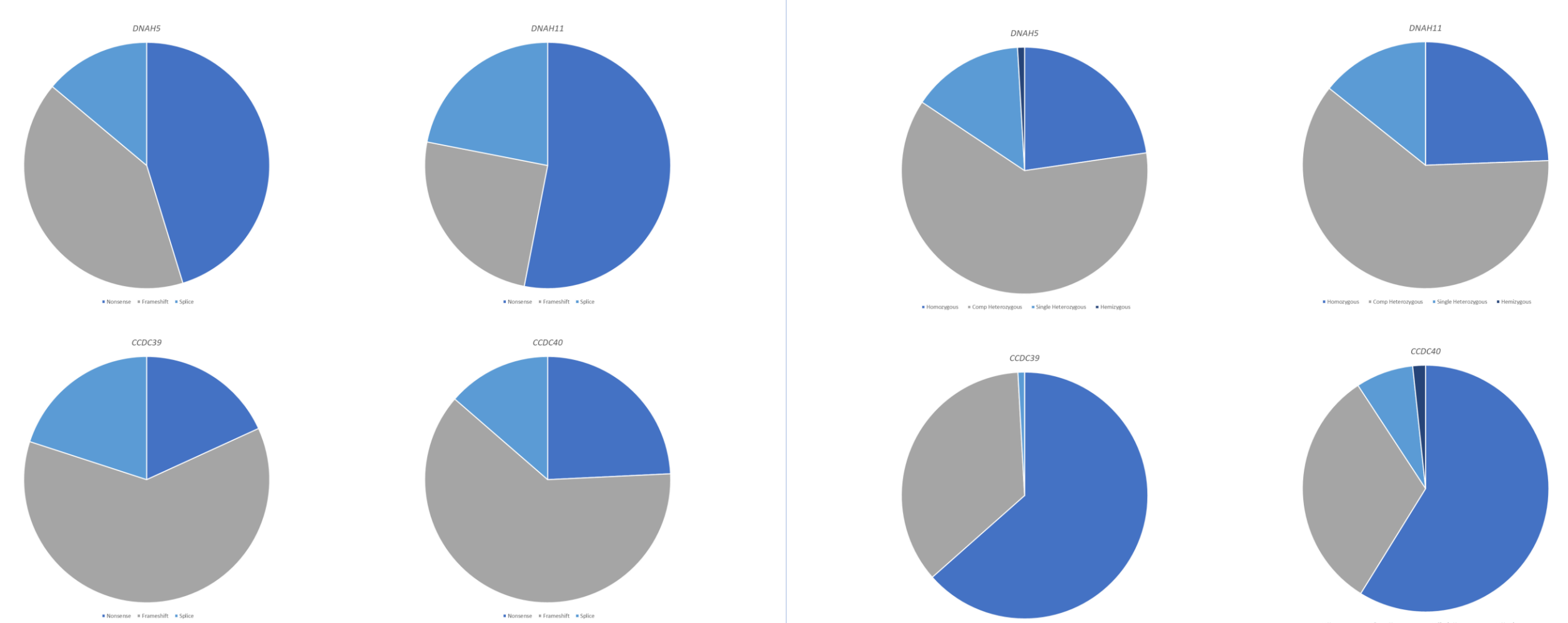
Most frequent causative genes in CiliaVar



Mutations can be mapped onto genes to look for potential hotspots



Genotype – phenotype relationships can be explored  
CCDC39 & CCDC40 more frameshift & homozygous mutations



## Discussion

The online open database CiliaVar will go live on 2<sup>nd</sup> September 2022

Annual updates from published literature and new clinical centres will be added.

We aim to improve access to PCD variant information and diagnosis of PCD

## Acknowledgements

We would like to thank ERS for funding for BEAT-PCD and CFTR France for sharing knowledge on establishing genetic databases

**The online open database CiliaVar will go live on 2<sup>nd</sup> September 2022 to improve access to PCD variant information and diagnosis of PCD.**