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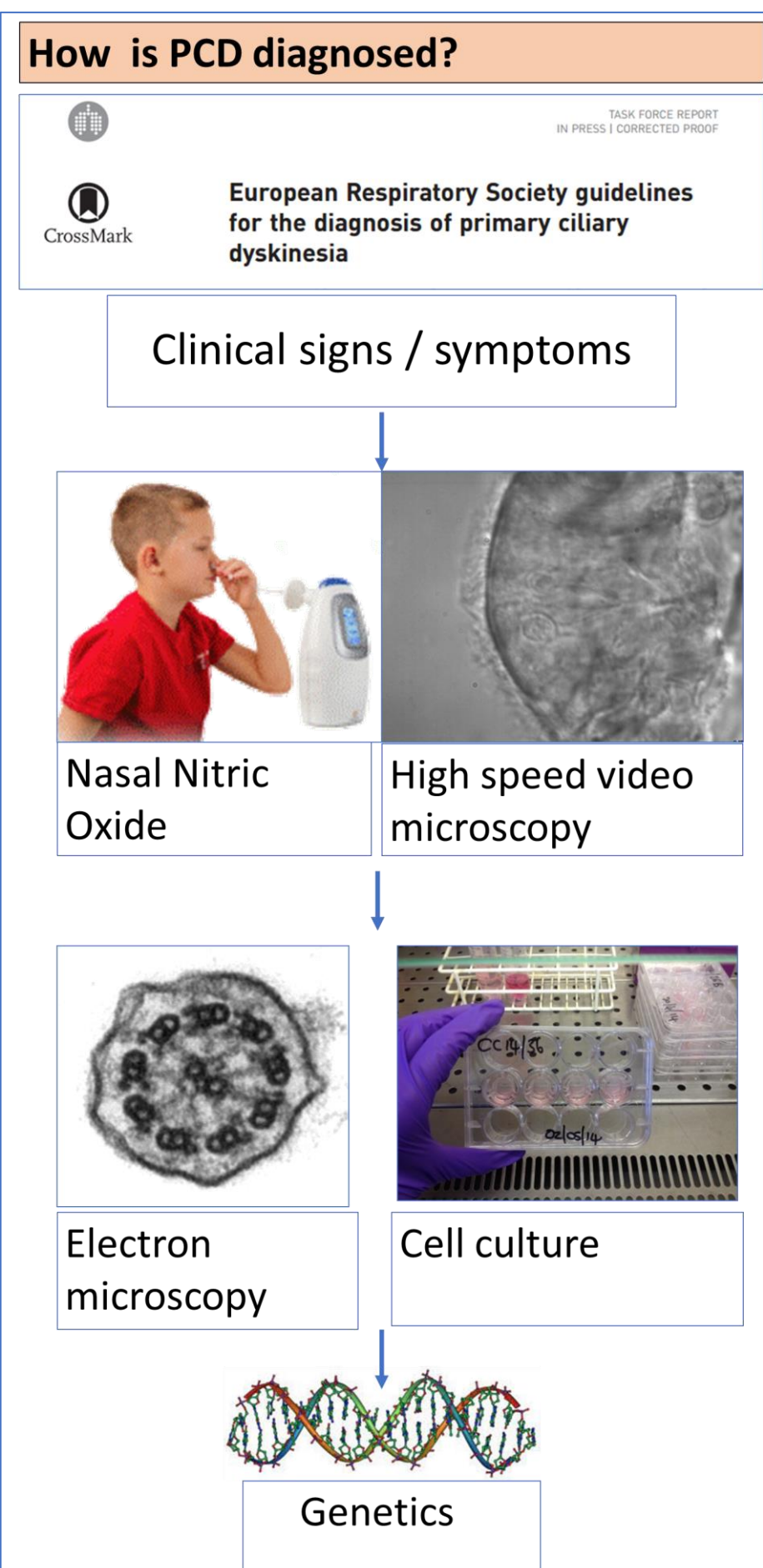
Development and first results of the BEAT-PCD international Primary Ciliary Dyskinesia gene variant database: CiliaVar

Amelia Shoemark

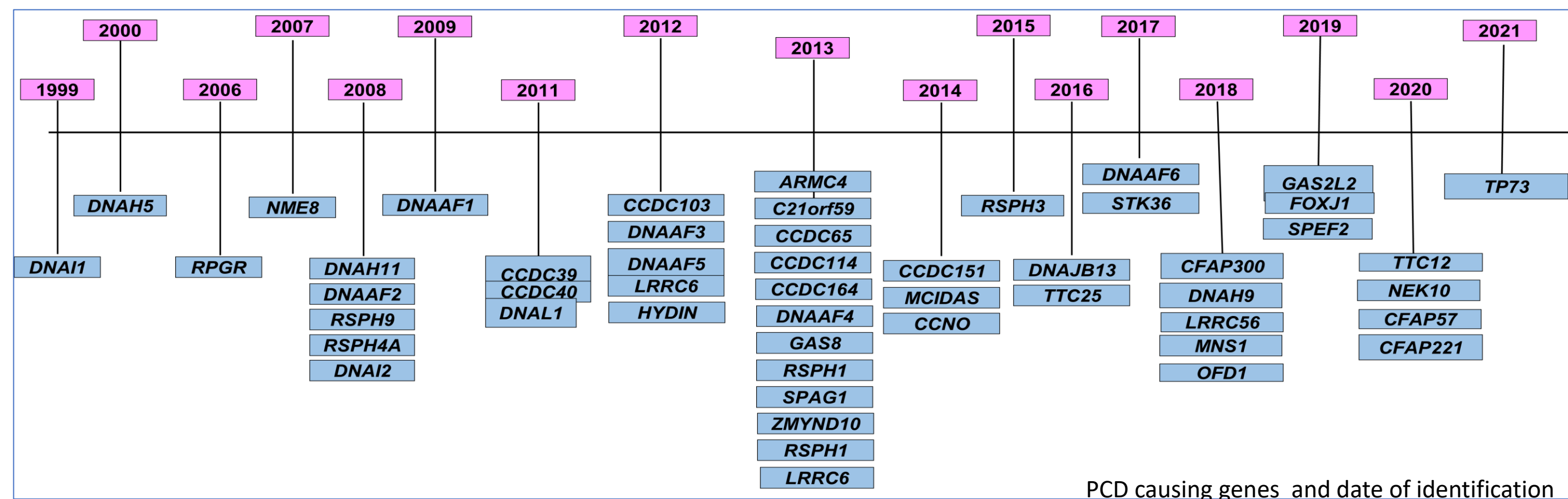
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Background



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.

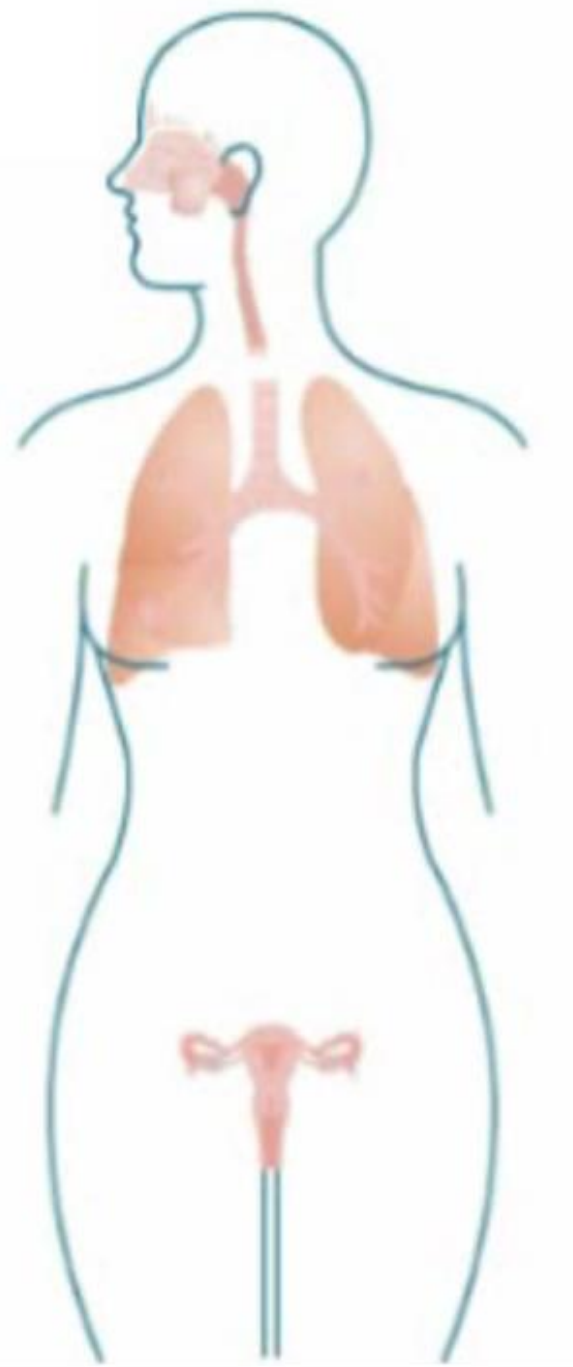
As clinical genetic testing is increasingly implemented for PCD, there is a need to develop a public access resource to identify if variants have previously been reported to be associated with disease.

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

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

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

Genetics fields:

Gene	Variant	Classification	Pathogenicity
DNAI1	c.48+2dupT	VUS	Pathogenic
CCDC40	c.248del	VUS	Pathogenic

Results

Literature search
651 papers
Abstract review
262 selected

Patients
1551 from literature
466 from 4 diagnostic centres

1648 Mutations

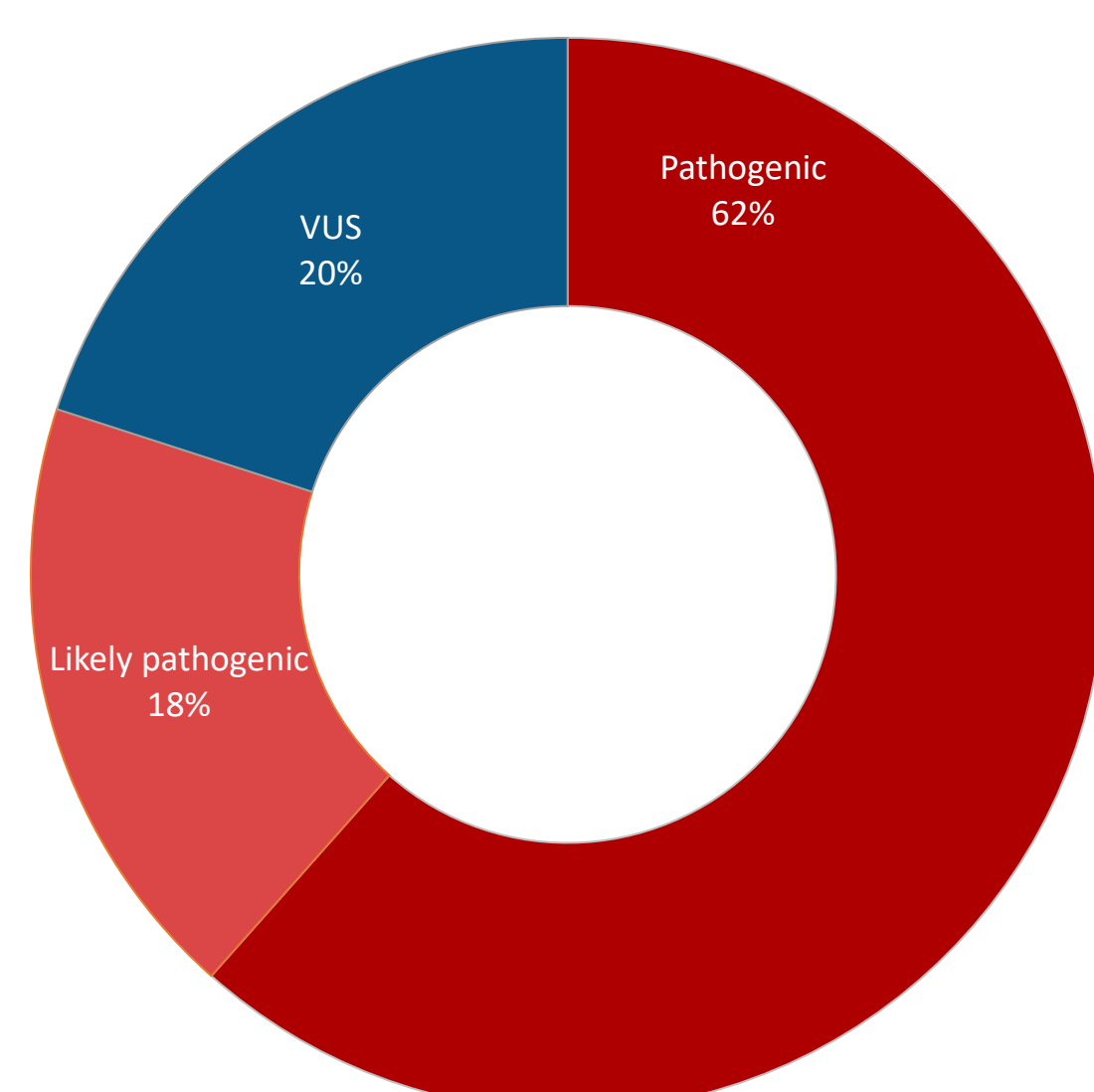
Mutation nomenclature verification and classification following ACMG guidelines

CiliaVar

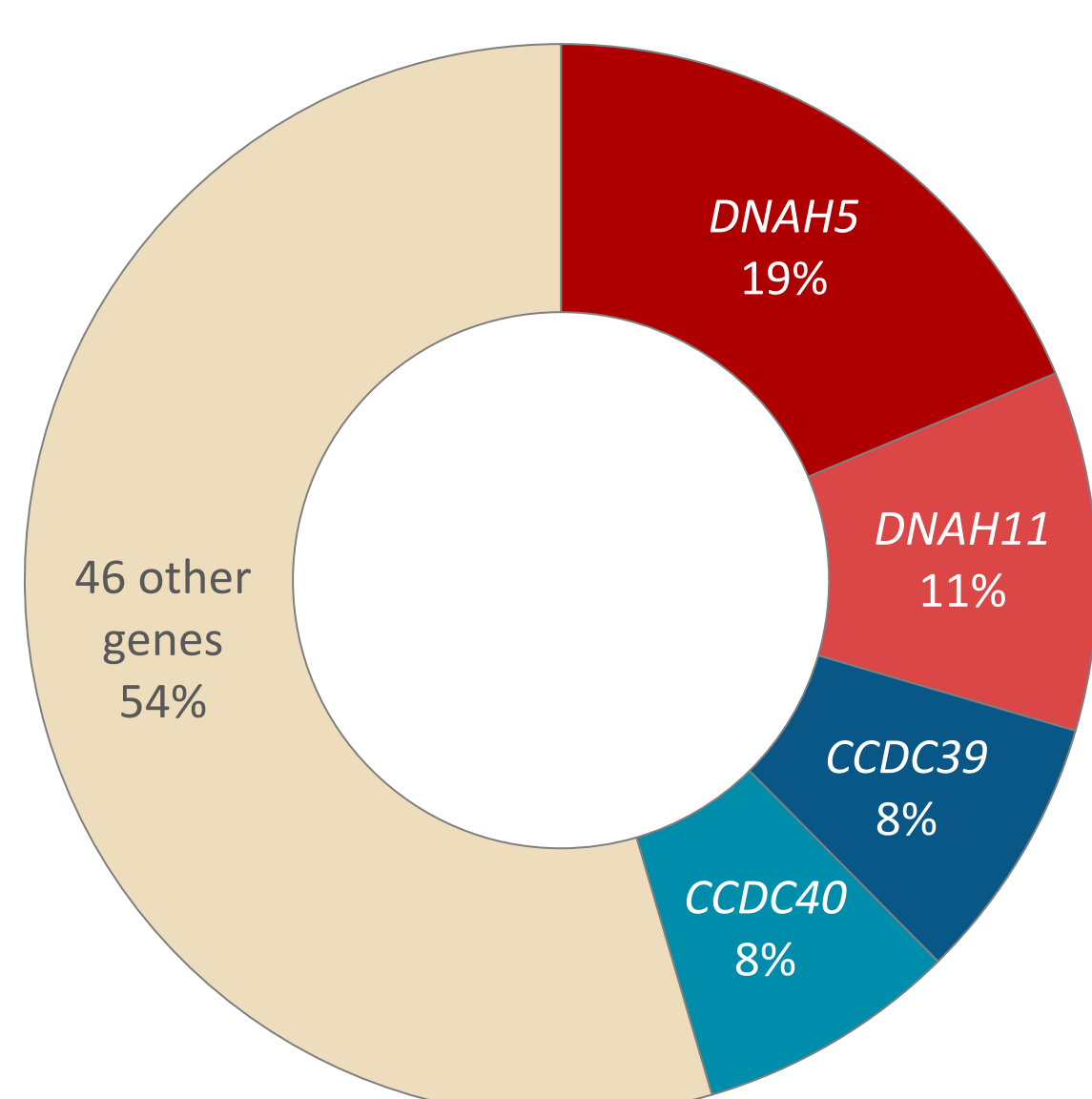
1648 mutations were included in CiliaVar.

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.



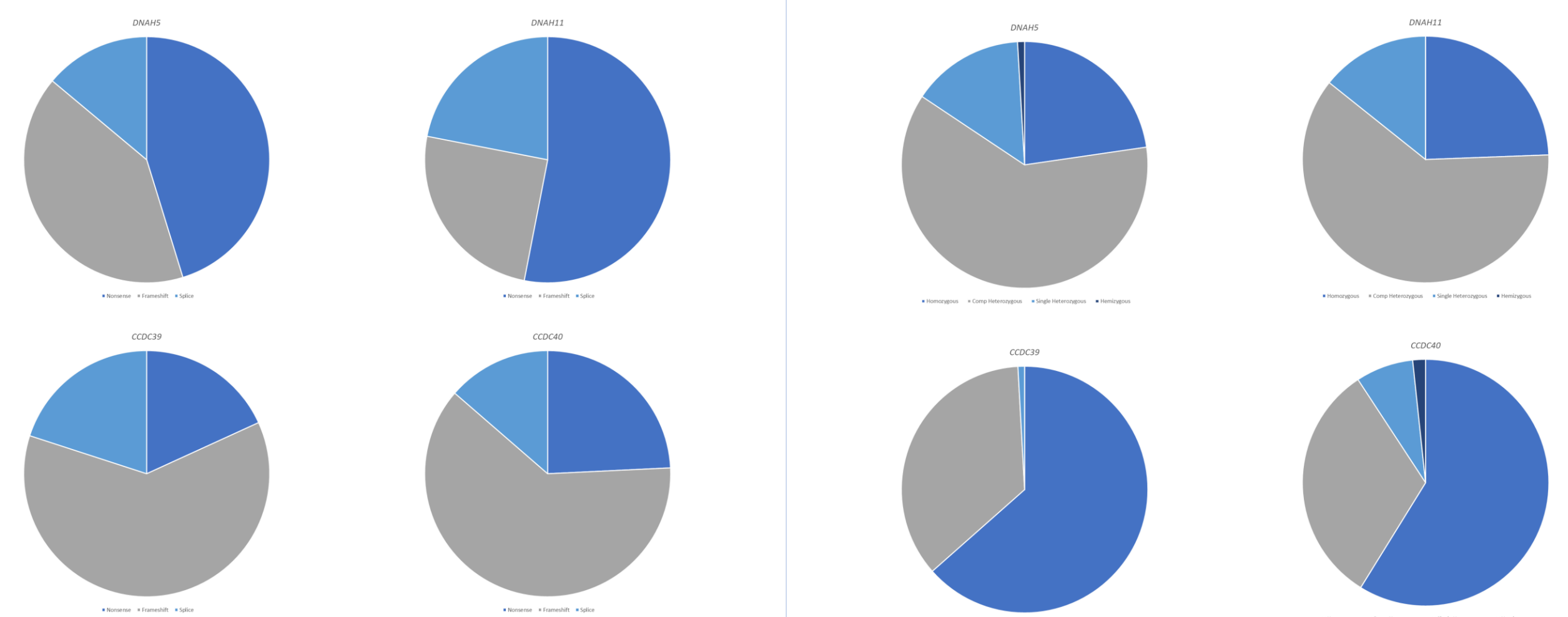
Most frequent causative genes in CiliaVar



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 2nd 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 2nd September 2022 to improve access to PCD variant information and diagnosis of PCD.