

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

Amelia Shoemark, Rahma Mani, Mafalda Gomes, Adrian Gonzales R., Sun Maximo, Claire Hogg, Deborah Morris-Rosendahl, Bernard Maitre, Mahmoud R. Fassad, Myrona Goutaki, et al.

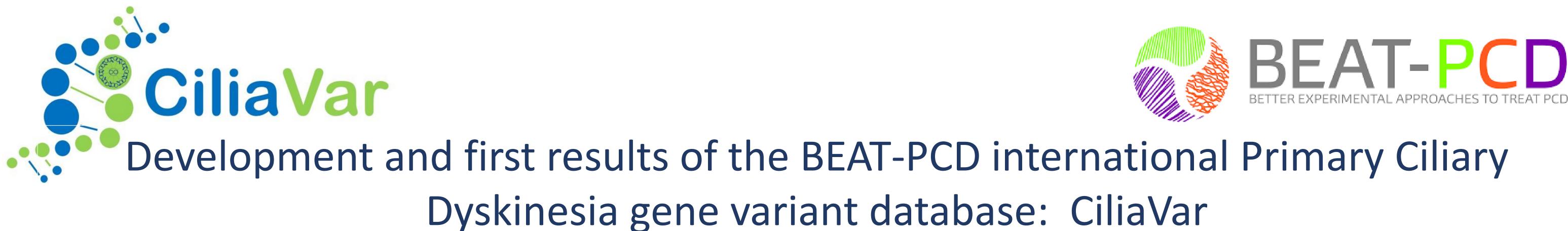
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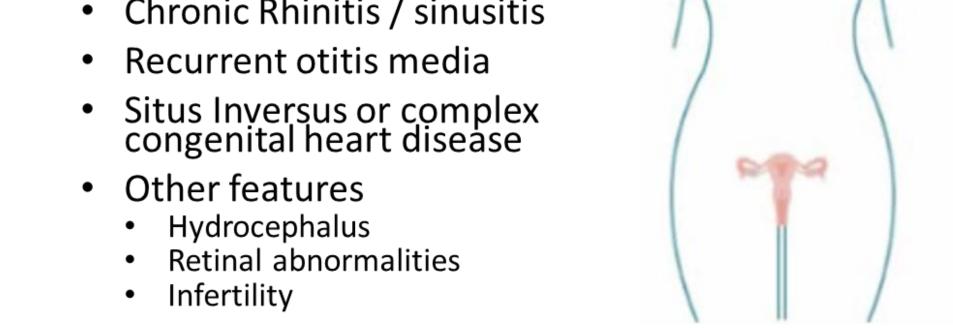
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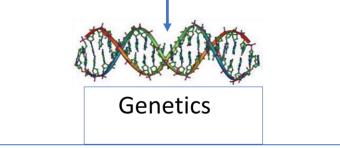
Background		What is PCD?				
<section-header><section-header><section-header><section-header><section-header><image/><text></text></section-header></section-header></section-header></section-header></section-header>	• PCD can be diagnosed by bi-allelic pathogenic mutations in one of >50 ciliary genes. $ \frac{2000}{2006} = 2007 = 2009 = 2012 = 2013 = 2014 = 2015 = 2017 = 2019 = 2021 = 2021 = 2020 $	Dysfunction of multiple motile cilia Incidence ~1:7500 Heterogenous multi-system disorder Symptoms include: • Respiratory • neonatal respiratory distress • Wet/ productive cough				
	DNAH5NME8DNAAF1CCDC103C21orf59RSPH3DNAAF6GAS2L2TP73DNAAF3CCDC65 <td< th=""><th> Recurrent chest infections Bronchiectasis Chronic Phinitic / cinucitic </th><th>KA</th></td<>	 Recurrent chest infections Bronchiectasis Chronic Phinitic / cinucitic 	KA			



DNAI1 RPGR	DNAH11 DNAAF2 RSPH9 RSPH4A DNAI2	CCDC39 CCDC40 DNAL1	DNAAF5 LRRC6 HYDIN	CCDC114 CCDC164 DNAAF4 GAS8 RSPH1 SPAG1 ZMYND10	CCDC151 MCIDAS CCNO	DNAJB13 TTC25	CFAP300 DNAH9 LRRC56 MNS1 OFD1	TTC12 NEK10 CFAP57 CFAP221
				RSPH1 LRRC6		PCD c	ausing genes and	d date of identification



- ~ 60% of patients with an identified genetic cause have private mutations, that have not been previously reported in another patient.
- Electron microscopy



- 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.

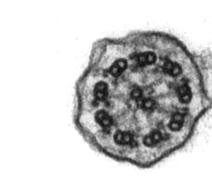
Aim: To establish an online open database registering mutations and specific combinations of mutations causing PCD.

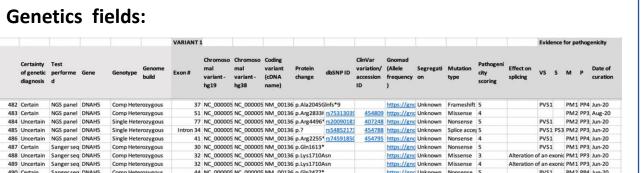
Methods

- 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.

Clinical fields: At point of diagnosis: Age Sex Affected siblings FEV1% pred Neonatal respiratory distress y/n Bronchiectasis y/n

Data collected





• Database curators checked mutation nomenclature and classification of variants was carried out following ACMG guidelines.

	490 Certain	Sanger seq	DNAHS	Comp Heterozygous	44 NC_000005 NC_000005 NM_00136 p.Gin2477*		https://gnc Unknown	Nonsense 5	PVS1	PMZ PP4 Jun-20
	491 Certain	Sanger seq	DNAH5	Comp Heterozygous	50 NC_000005 NC_000005 NM_00136 p.Arg2799Pro		https://gnc Mother is a	Missense c 4	Creation of an exoni	EPM1 PP3, Jun-20
/	492 Uncertain	Sanger seq	DNAH5	Comp Heterozygous	50 NC_000005 NC_000005 NM_00136 p.Glu2814* rs75513623	454808	https://gnc Mother is a	Nonsense 5	PVS1	PM2 PP4, Jun-20
Lobetomy y/n	493 Certain	Sanger seq	DNAH5	Comp Heterozygous	53 NC_000005 NC_000005 NM_00136 p.Gln2963Glu		https://gnc Unknown	Missense c 4	Activation of an exo	nik PM1 PP3, Jun-20
	494 Uncertain	Sanger seq	DNAH5	Single Heterozygous	68 NC_000005 NC_000005 NM_00136 p.Ser3861A rs57609675	381547	https://gnc Unknown	Missense 3		PP3, Jun-20
	495 Uncertain	NGS panel	DNAH5	Comp Heterozygous	6 NC_000005 NC_000005 NM_00136 p.Asp239Glufs*11		https://gnc Unknown	Frameshift 5	PVS1	PM1 PP4 Jun-20
Otitis media y/n	496 Certain	NGS panel	DNAH5	Comp Heterozygous	29 NC_000005 NC_000005 NM_00136 p.Glu1554*		https://gnc Unknown	Nonsense 5	PVS1	PM1 PP3, Jun-20
Ullus media V/m	497 Certain	NGS panel	DNAH5	Comp Heterozygous	34 NC_000005 NC_000005 NM_00136 p.Ile1855A: rs75292505	407241	https://gnc Unknown	Frameshift 5	PVS1	PM2 PP4 Aug-2
	498 Certain	NGS panel	DNAH5	Comp Heterozygous	49 NC_000005 NC_000005 NM_00136 p.Arg2677* rs77594608	238987	https://gnc Unknown	Nonsense 5		PM1 PP3, Jun-20
	499 Certain	WES	DNAH5	Homozygous	28 NC_000005 NC_000005 NM_00136 p.Gln1464*		https://gnc Unknown	Nonsense 5	PVS1	PM1 PP3, Jun-20
Productive/ wet cough $y/n =$	500 Certain		DNAH5	Homozygous	Intron 41 NC_000005 NC_000005 NM_00136 p.? rs10575206	379701	https://gnc Unknown			PM2 PP3, Jun-20
	501 Certain			Comp Heterozygous	19 NC_000005 NC_000005 NM_00136 p.Thr990Asnfs*2		https://gnc Unknown			PM1, PM Jun-20
	502 Certain			Homozygous	31 NC_000005 NC_000005 NM_00136 p.Cys1678*		https://gnc Unknown		PVS1	PM1 PP3 Jun-20
Chronic rhinitis y/n	503 Uncertain			Homozygous	50 NC_000005 NC_000005 NM_00136 p.Trp2774Arg		https://gnc Unknown			PM1 PP3 Jun-20
	504 Uncertain	Sanger seq	DNAH5	Single Heterozygous	45 NC_000005 NC_000005 NM_00136 p.Arg2501F rs78853305	179699	https://gnc Unknown	Missense 3		PP3, Jun-20

Diagnostic fields: Nasal NO (nl/min)

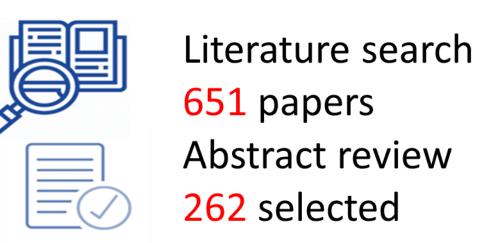
High speed video

Immunofluorescene

TEM (consensus guideline)

PCD +tve/-tve (ERS guideline)

Results



Patients 1551 from literature

466 from 4 diagnostic centres



1648 Mutations

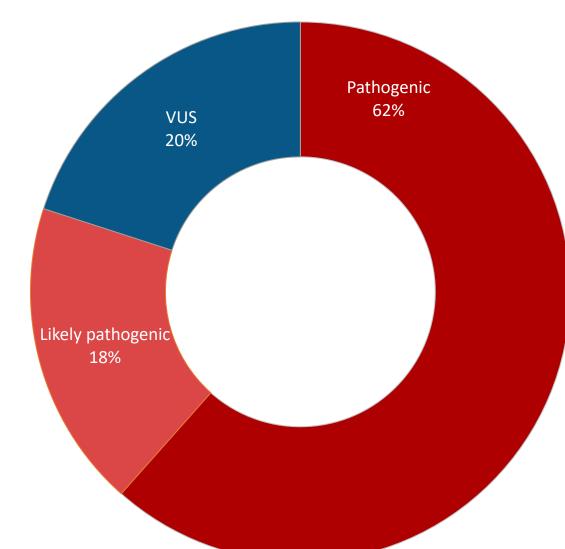
Mutation nomenclature verification and classification following ACMG guidelines

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.



Mutations can be mapped onto genes to look for potential hotspots



Discussion

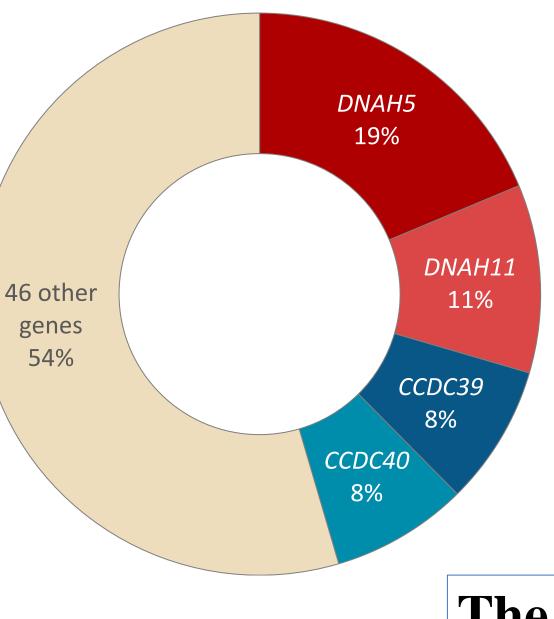
The online open database CiliaVar will go live on 2^{nd} September 2022

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

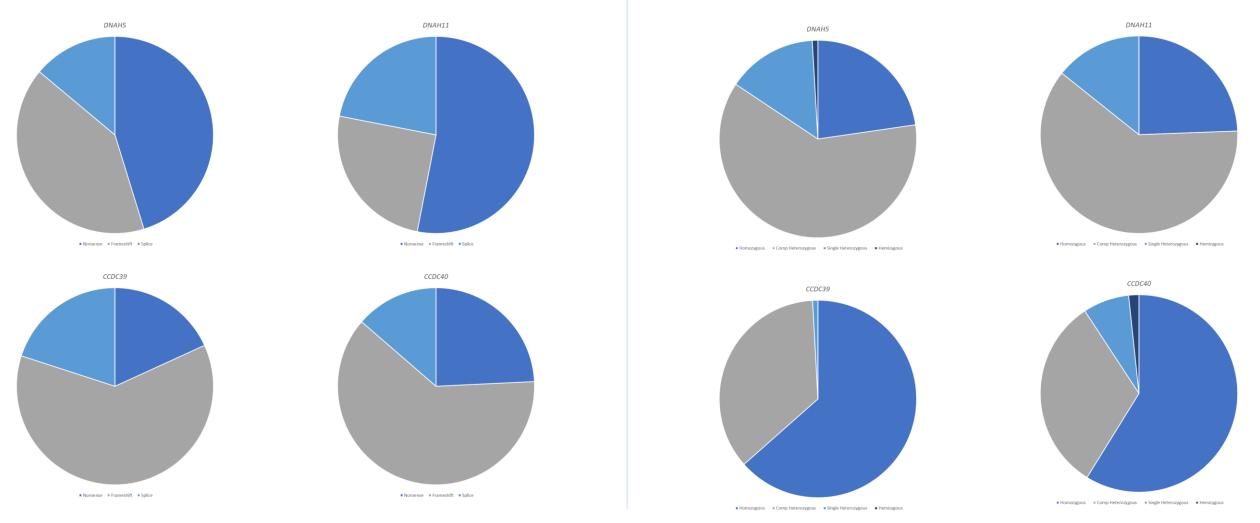
We aim to improve access to PCD variant information and diagnosis of PCD

Acknowledgements

We would like to thank ERS for funding for BEAT-PCD and CFTR France for sharing knowledge on establishing genetic databases Most frequent causative genes in CiliaVar



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



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