Supplementary methods

Ethics

Local and national research and ethical approvals were obtained and adhered to (NRES Committee South Central Hampshire Ethics 06/Q1702/109, London Bloomsbury Research Ethics Committee 08/H0713/82 and Ile-de-France Ethics Committee CPP07729).

Genetics

Patients were screened by the next generation and Sanger sequencing methods summarised. Genetic analysis was evaluated by geneticists and clinicians specialised in PCD, with a confirmed genetic diagnosis defined as the presence of autosomal bi-allelic or single X-linked hemizygous variants classified as pathogenic according to international guidelines [1, 2]. Of 292 genetically screened patients in the discovery cohort, using these criteria we confirmed a genetic diagnosis in 199 patients. We excluded 93 patients carrying variants judged to be of uncertain significance, which included single variants in PCD genes predicted pathogenic/likely pathogenic but without a second variant identified; variants identified in candidate rather than known PCD genes; and variants of uncertain pathogenic effect for example if TEM data inconsistent.

Discovery and validation cohorts

The discovery group consisted of PCD patients from University Hospital Southampton (UHS) and the Royal Brompton Hospital (RBH), London, genotyped at University College London (UCL). Clinical and diagnostic data were collected retrospectively from electronic and paper-based medical records for all patients with a conclusive genetic result available up to July 2017. The

validation group consisted of patients genotyped from UHS and RBH between July 2017 and May 2019, and at Trousseau, Cochin and Creteil hospitals in France and Emma Children's Hospital in the Netherlands up to May 2019. Study data were collected applying the definitions according to the study coding protocol. Ciliary beat pattern and TEM were reviewed by specialists, blinded to all genetic data.

The phenotypic data collected from both validation and discovery cohorts and used for clustering were based upon 12 clinical and diagnostic variables: BMI, FEV_1 z-score, FVC z-score, NRDS, wet cough, rhinitis, glue ear, cardiac situs, CHD, nNO, CBP and TEM, as described in the main manuscript. Data found not to shape the model during development were excluded; this include age at diagnosis, height, weight, mutation type and ethnicity. Additional data were collected on clinical and diagnostic characteristics (see Table E1) but were not included in the modelling; these were used to explore the model. Each variable was used to colour the nodes by the categories detailed in Table E1 to further explore potential clusters of phenotypic data.

Ciliary beat pattern was described and categorised according to the predominant finding from the following terms: normal, completely immotile, weak residual movement, stiff, rotating, staggered beat, lack of cilia. Transmission electron microscopy was categorised as one of the following terms: non diagnostic, isolated ODA defect, ODA & IDA defect, MTD & IDA defect or isolated IDA defect, CC defect or lack of cilia.

Topological data analysis (TDA)

Topology is a branch of applied mathematics that is primarily concerned with the study of shape of data and is specifically designed to identify structural characteristics of high-dimensional

datasets. TDA [3] consists of a set of techniques for data analyses based on the reproduction of the structure of complex datasets into a geometric shape, that captures the essential features similarly to how a topographical map captures features of a landscape. It does so by dividing (or binning) the dataset through the application of a distance metric (e.g. a similarity measure) and then performing clustering within each of those separate segments. These are then visually represented as nodes of a network, each of which correspond to a collection of datapoints. TDA does not produce distinct clusters as traditional clustering techniques do but rather a network where points are connected depending on (dis)similarity between combination of the features of variables included in the model. In Symphony AyasdiAI, a user-friendly software that combines TDA with machine learning, different colours can be applied to the nodes of the network using any of the metrics or variables in the dataset, in order to inspect the data for patterns and hotspots.

TDA is an unsupervised data-driven technique, with no prior hypothesis needed. The outcome of interest should not be included in the clustering, which in this study were the genetic data. After the models were developed, we inspected the data by colouring the nodes by the different genes in order to identify any clusters or hotspots that would require further interrogation.

Machine learning was used in the lenses that were applied to our model. These lenses only provide the visualisation of the network through the application of a layout algorithm and therefore do not influence the clustering itself. In order to construct the topological models, we applied a variety of lenses. Lenses can be derived from statistical measures such as mean, from geometry such as centrality, from dimensionality-reduction techniques such as principal component analysis (PCA), or even from a variable in the dataset. After exploring several different lenses, we selected locally linear embedding (LLE) lenses as the most relevant to our dataset because they showed distinct clusters for further exploration. Similarly, we selected correlation as a metric after evaluating other

metrics. Correlation seemed an appropriate choice due to the differences of variance between variables, and the various categorical variables included in our dataset.

TDA deals with missing values individually; where they are missing, the TDA network will be mapped without that data point for that individual for that specific variable. The individual will still be plotted into the network according to similarities in variables for which there are data. For example, if an individual has values for BMI, NRDS, wet cough, rhinitis, glue ear, cardiac situs, CHD, nNO, CBP and TEM but data were missing for FEV_1 and FVC due to the age of the patient, this patient would be clustered in the TDA network according to similarities in the other ten variables for which we had measurements. This will have no effect on whether a patient clusters with patients that have similar values for these ten variables, they simply will not be clustered according to FEV_1 and FVC.

Additionally, TDA is highly robust in handling missing data, as has been shown in the literature [see references quoted in main paper] and also in a white paper by Glushakov et al [4]. In their study, the authors intentionally deleted values from their dataset in order to test the robustness of the TDA approach and found that the topological models were geometrically stable even when 90% of data were missing. We are therefore confident that missing data in our datasets did not affect the shape or clustering in the topological models.

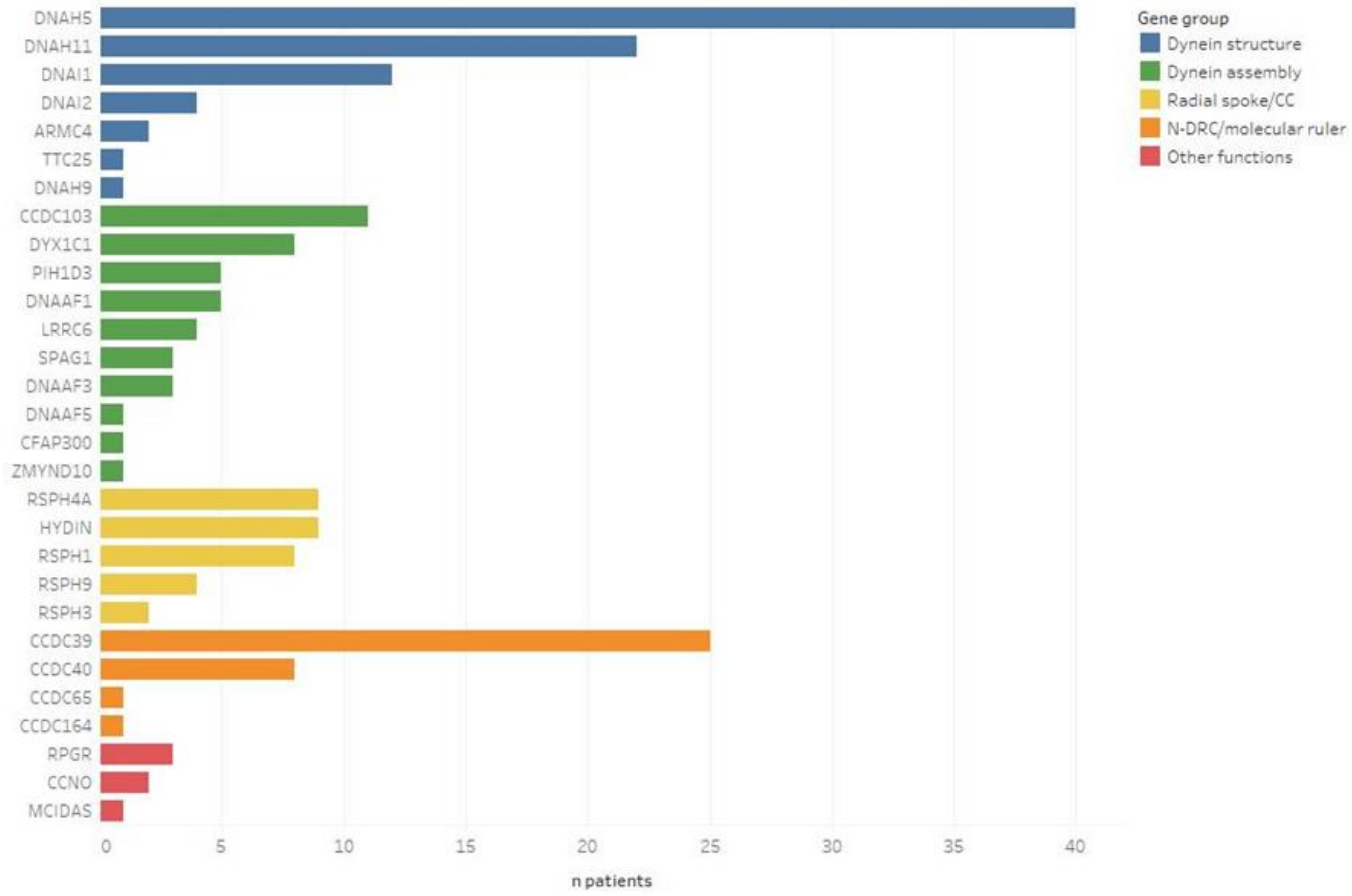
Summary of clinical diagnostic methods by group

Method	University Hospital Southampton	Royal Brompton London	Hôpital Trousseau, Paris	Hôpital Intercommunal Créteil	Hôpital Kremlin-Bicêtre, Le Kremlin-Bicêtre	Hôpital Cochin, Paris	Amsterdam UMC
Genotyping	**Discovery group:** DNA extracted from blood using salting out technique and stored in -20 until further use. Next-generation sequencing performed as previously described [5], either by whole exome sequencing (WES) or targeted gene panel sequencing (Illumina TruSeq Custom Amplicon, Agilent SureSelect Focused Exome or SureSelectXT custom panel), including all known PCD genes and other candidate genes, on an Illumina platform. Variant analysis used an in-house bioinformatics pipeline similar to [6] with variant confirmation by Sanger sequencing with parental segregation. **Validation Group:** Wessex Clinical Exome analysis using the llumina TruSight One Sequencing Panel; 29 PCD gene panel applied to NGS sequence data. Confirmation by Sanger sequencing with parental segregation.	DNA extracted from blood using salting out technique and stored in -20 until further use. Next-generation sequencing performed as previously described [5], either by whole exome sequencing (WES) or targeted gene panel sequencing (Illumina TruSeq Custom Amplicon, Agilent SureSelect Focused Exome or SureSelectXT custom panel), including all known PCD genes and other candidate genes, on an Illumina platform. Variant analysis used an in-house bioinformatics pipeline similar to [6] with variant confirmation by Sanger sequencing with parental segregation. For a number of patients, variants were identified by candidate gene Sanger sequencing.	Genomic DNA was extracted from whole blood (EDTA sampling) either with the Maxwell 16 IVD device (Promega) or with a FlexiGene kit (Qiagen). DNA was analysed by a targeted capture panel (SeqCap EZ Choice, Roche Diagnostics) including all the known PCD genes and candidate genes. Librairies were sequenced on a MiSeq sequencer (Illumina). Data was analysed with a in-house double pipeline base on Bwa and Bowtie. Sequencing depth of the regions of interest was over 50X. DNA from relatives and control samples from the probands were analysed by Sanger sequencing (BigDye v3.1, Life Technologies) on a 3130XL sequencer (Life Technologies).	Performed in Hôpital Trousseau, Paris	Performed in Hôpital Trousseau, Paris	Performed in Hôpital Trousseau, Paris	DNA extracted from blood using a Chemogen robot and stored in -20 until further use. DNA sequencing was done using whole exome sequencing with targeted analysis, including all known PCD genes. Enriched libraries were sequenced with the HiSeq or Nextseq platforms (Illumina, San Diego, CA) as paired-end 100 bp reads. Sequencing reads were cleaned by 5′-end quality trimming and Illumina-adapter clipping by Trimmomatic. Prealignment quality control of the cleaned sequencing reads was done with FastQC. Clean reads were mapped to reference genome hg19 (GRCh37) using BWA-MEM. The genome analysis toolkit was used for recalibrating quality scores, realignment around indels, marking PCR duplicates, and variant calling and variants were annotated with ANNOVAR. All

							mutations were confirmed by Sanger sequencing. The analysis of the sequencing data was done using in-house bioinformatics pipeline. Sequencing and data analysis done at the Department of Clinical Genetics, Amsterdam UMC, Vrije Universiteit Amsterdam.
Nasal nitric oxide analysis	Ecomedics CLD 88 Exhalyzer; exhalation against resistance; sampling 0.33 l/min	Logan LR5000 Chemiluminscence Analyser (Rochester Kent); breath hold sampling 0.25 l/min	NIOX Flex up to 2014 ; From 2014 up to now CLD 88 sp Ecophysics chemiluminescence NO analyser ; sampling flow rate of 0.3 $L.min^{-1}$; measurements during breathhold, expiration against resistance and tidal breathing	EVA4000 chemiluminescent analyzer (Seres, France) ; breath hold sampling 1.3 l/min followed ATS/ERS standards	FeNO+ medisoft biochemical analyser (Sorinnes, Belgium), NO nasal at a sample flow rate of 100ml/s through a nasal catheter, breathing through resistance for velum closing	Chemiluminescence Analyser (EndoNO 8000®, SERES, Aix-en-Provence, France), breath hold analysis 1.3 l/min	Niox vero, exhalation against resistance, sampling 0.33l/min
Electron microscope	60,000x magnification (minimum) by Hitachi H7000; 100-300 cilia were imaged in transverse section for assessment of axonemal structure. Quantitative analysis determined ciliary ultrastructure.	60,000x magnification (minimum) by Hitachi H7000; 100-300 cilia were imaged in transverse section for assessment of axonemal structure. Quantitative analysis determined ciliary ultrastructure.	Performed in Hôpital Intercommunal Créteil	Analyses were carried out in the Pathology Department, in collaboration with the ICM-QUANT platform (Institut du Cerveau et de la Moelle Epinière, Paris). 80,000x magnification (minimum) by Hitachi HT7700; at least 100 cilia were imaged in transverse section for assessment of axonemal structure. Quantitative analysis determined ciliary ultrastructure.	Performed in Hôpital Intercommunal Créteil	Performed in Hôpital Intercommunal Créteil	The samples were screened by using a transmission electron microscope (Tecnai $12G^2$, FEI Company) and minimal 20 images of representative cross-sections were taken with a VELETA side-entry camera at a magnification of at least x60.000.
High-speed video microscopy equipment	0.5 mm coverwell imaging chamber (Sigma-Aldrich, Poole, UK) mounted onto a glass slide; Olympus IX71 inverted microscope and	0.5 mm coverwell imaging chamber (Sigma-Aldrich, Poole, UK) mounted onto a glass slide; Leica DM-LB upright microscope with x100 oil plan	Glass slide with coverslip; Nikon Eclipse Ci upright microscope with x100 oil plan objective lens; room temperature; PL-A741 high-speed video	Performed in Hôpital Trousseau, Paris	Performed in Hôpital Trousseau, Paris	Performed in Hôpital Trousseau, Paris	0.5 mm coverwell imaging chamber (Sigma-Aldrich, Poole, UK) mounted onto a glass slide; Zeiss AX10 Observer.A1 inverted microscope and

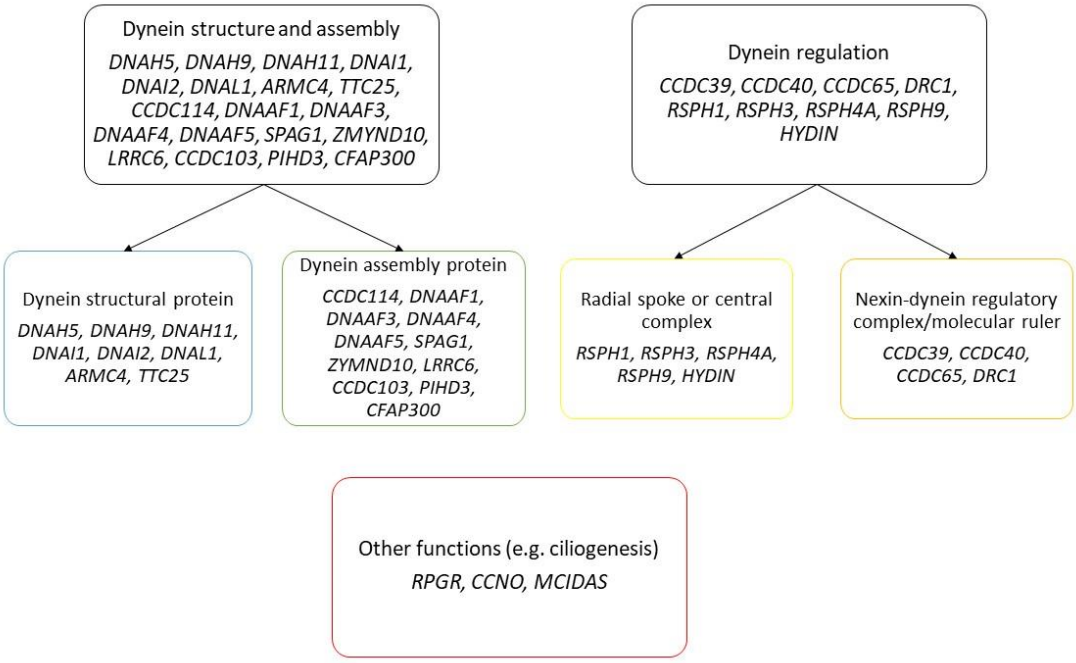
	condenser;x100 UPlan wide aperture oil objective; 37ºC heated environmental chamber (Solent Scientific, Southampton, UK); Photron FASTCAM MC2 high-speed video digital camera and Photron software.	objective lens; 37ºC heated stage; anti-vibration table (Wentworth Laboratories Ltd, Sandy, UK); Troubleshooter TS-5 Fastec imaging.	digital camera (PixeLINK, Ottawa, Canada).				condenser;Basler aVA1000 High-speed video digital camera and Strempix software.
High-speed video microscopy analyses	Images were digitally recorded using a high-speed camera at a rate of 500 frames per second (fps) and reviewed at reduced frame rates (30-60 fps) for analysis of ciliary beat pattern (CBP) and ciliary beat frequency (CBF).	Images were digitally recorded using a high-speed camera at a rate of 500 frames per second (fps) and reviewed at reduced frame rates (30-60 fps) for analysis of ciliary beat pattern (CBP) and ciliary beat frequency (CBF).	Images were digitally recorded using a high-speed camera at a rate of 355 frames per second (fps). Each movie was composed of 1,800 frames with a definition of 256 x 192 pixels (pixel size: 0.13 x 0.13 μm^2); twenty distinct areas containing intact undisrupted ciliated epithelial edges greater than 50 µm were recorded for analysis of ciliary beat pattern (CBP) and ciliary beat frequency (CBF).	Performed in Hôpital Trousseau, Paris	Performed in Hôpital Trousseau, Paris	Performed in Hôpital Trousseau, Paris	Images were digitally recorded using a high-speed camera at a rate of 120 frames per second (fps) and reviewed at reduced frame rates (10-20 fps) for analysis of ciliary beat pattern (CBP) and ciliary beat frequency (CBF).
Spirometry	FEV_1 on day of diagnostic testing, or first available result. Followed ATS/ERS Standards.	FEV_1 on day of diagnostic testing, or first available result. Followed ATS/ERS Standards.	FEV_1 on day of diagnostic testing, or first available result. Followed ATS/ERS Standards.	FEV_1 on day of diagnostic testing, or first available result. Followed ATS/ERS Standards.	FEV_1 on day of diagnostic testing, or first available result. Followed ATS/ERS Standards.	FEV_1 on day of diagnostic testing, or first available result. Followed ATS/ERS Standards. Jaeger MasterScreen Body (CAREFUSION, Hoechberg, Germany).	FEV_1 on day of diagnostic testing, or first available result. Followed ATS/ERS Standards.

Figure E1. Genetic results in 197 PCD patients from the *validation* group.



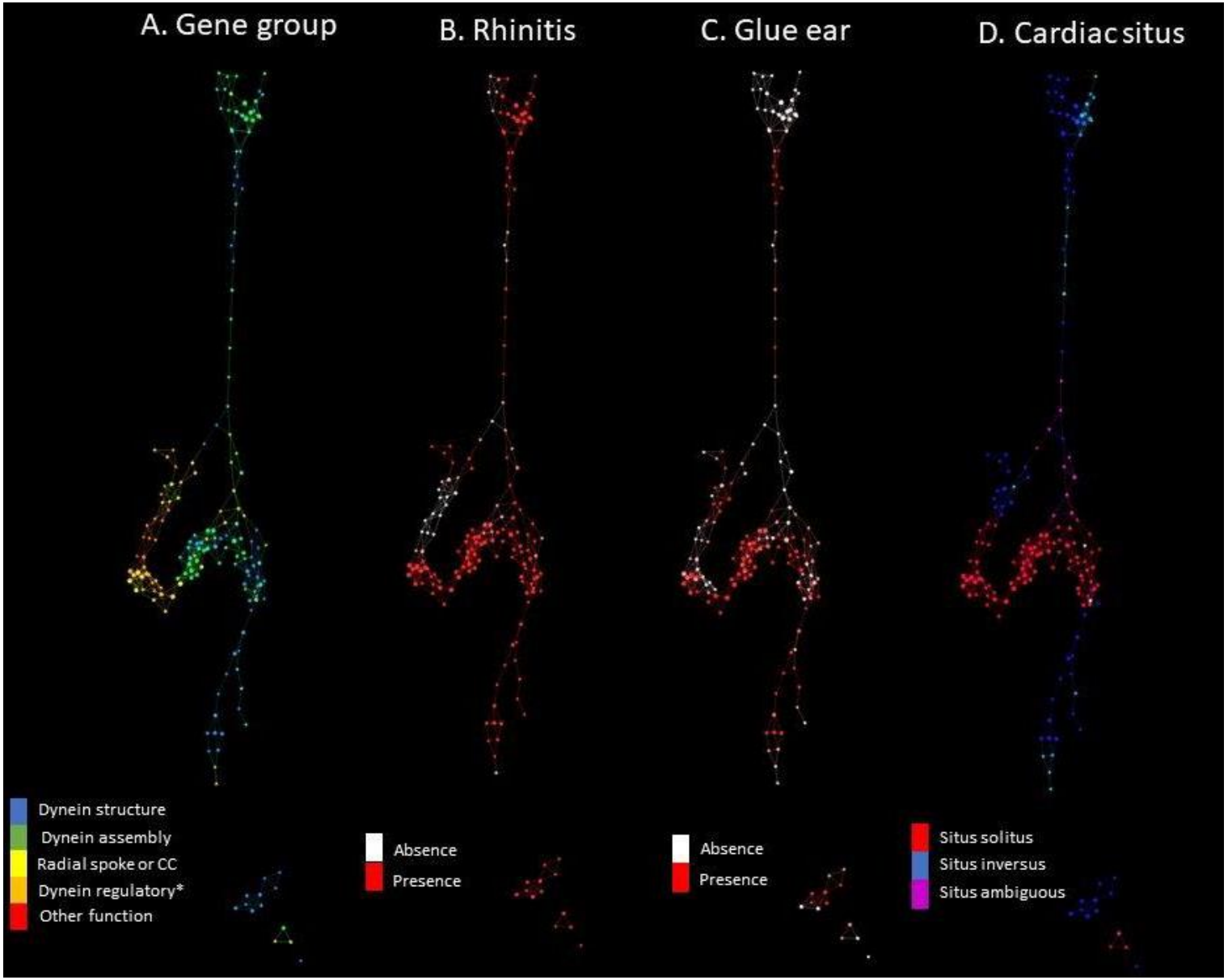
Patients in the validation cohort all had a confirmed clinical genetic diagnosis based upon PCD clinical experts identifying pathogenic or likely pathogenic variants, using identical diagnostic criteria for variant classification to that used for the discovery cohort (data not shown).

Figure E2. Stratification of all 31 PCD-causative genes in the overall study cohorts, placed into functional gene groups according to the ciliary components they encode.



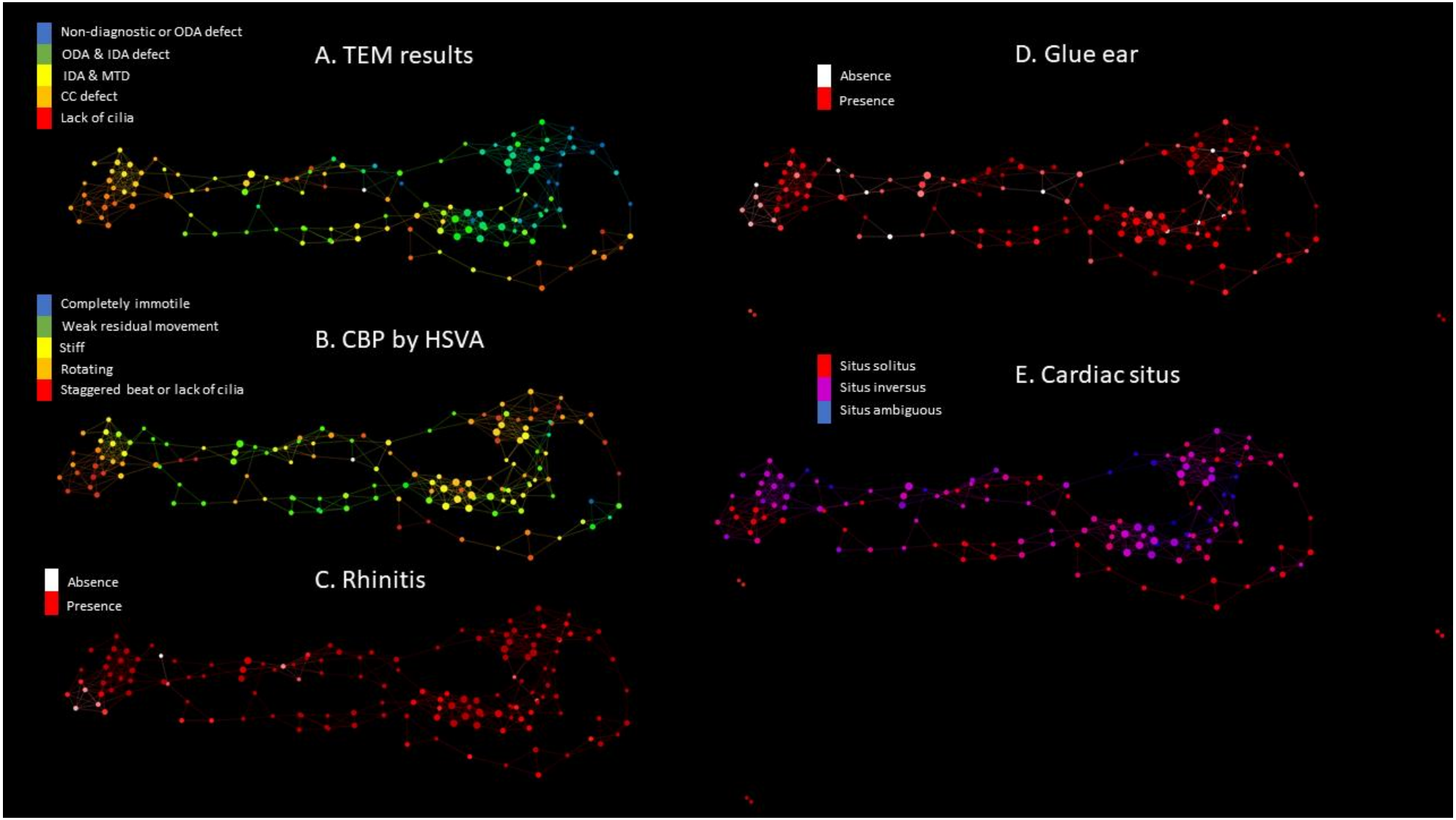
Each box defines a group: dynein structural protein, dynein assembly protein, radial spoke or central complex, dynein regulatory/molecular ruler, and other functions. Colours represent the gene groups: blue for genes involved in dynein structure, green in dynein assembly, yellow in radial spoke and central complex, orange in nexin-dynein regulatory complex/molecular ruler, and red in other functions.

Figure E3. Topological discovery model.



Models A-D are coloured by the following features: A. Gene group; B. History of rhinitis; C. History of glue ear; D. Cardiac situs. Node size represents the number of subjects. Each node represents combinations of features, connections represent that there are patients shared between the two nodes.

Figure E4. Topological validation model.



Models A-E are coloured by the following features: A. Transmission electron microscopy (TEM) findings; B. Ciliary beat pattern (CBP) by high-speed video analysis (HSVA); C. Rhinitis; D. Glue ear; E. Cardiac situs. Node size represents the number of subjects. Each node represents combinations of features, connections represent that there are patients shared between the two nodes.

Table E1. Description of data coding for clinical characteristics included in the study

Clinical characteristic	Description
Study ID	Unique ID (e.g. 0X-XXX)
DOB	
Date of LF (lung function) test	Closest to age at diagnosis Date format (e.g. DD-MM-YYYY)
Gender	Male = 1 Female = 2
Consanguinity	Up to 3rd degree cousins No = 0 Yes = 1
Number of siblings with PCD	Siblings with confirmed PCD
Ethnicity	Global Lung Function Initiative categories [7]
Weight	in kg
Height	in cm
BMI	Calculate BMI z-scores [8]
FEV_1	in litres. Calculate FEV_1 z-scores [7]
FVC	in litres
Date of diagnosis	Date format (e.g. DD-MM-YYYY)
Age at diagnosis	in years (1 decimal point)
Neonatal respiratory distress syndrome	Present Absent Unknown
History of wet cough	Present Absent Unknown
History of rhinitis	Present Absent Unknown
History of glue ear	Present Absent Unknown
Cardiac situs	Levocardia Dextrocardia Not applicable
Situs inversus totalis	Yes No Unknown
Echo done?	Yes No
Echo normal?	Yes No
Cardiac anatomy normal according to investigations?	Yes No Not applicable
Echo details, if abnormal	Free text
Abd USG	Performed Not performed
Abd USG normal?	Yes No Not applicable
nNO	in nL/min

Gene	Free text
Mutation	Free text
Transmission electron microscopy	
n cilia counted for arms	Calculate % of cilia with dynein arms
n cilia counted for microtubules	Calculate % of cilia with microtubules present
Both arms present	Calculate %
Inner arms missing	Calculate %
Outer arms missing	Calculate %
Both arms missing	Calculate %
Microtubular arrangement normal 9+2	Calculate %
Microtubules dis-arranged	Calculate %
Extra tubule	Calculate %
Single tubule	Calculate %
Central pair transposition	Calculate %
One of the central pair missing	Calculate %
Both central pair missing	Calculate %
Compound	Calculate %
TEM defect	Normal ODA IDA I&ODA IDA&MTD MTD Central complex defect Lack of cilia Inconclusive Note done
If ODA or I&ODA only please select if ODA is predominantly	Present Truncated Absent
If ODA or I&ODA only please select if ODA is present but not predominant	Present Truncated Absent
If ODA or I&ODA only please select if ODA is present but not predominant	Present Truncated Absent
High-speed video analysis	
CBP side view predominant finding	Normal Completely immotile Weak residual movement Stiff Rotating Staggered beat Long with bulbous tips Lack of cilia Not done
CBP present but not predominant 1	Normal Completely immotile Weak residual movement Stiff Rotating Staggered beat Long with bulbous tips Lack of cilia Not done
CBP present but not predominant 2	Normal Completely immotile

	Weak residual movement Stiff Rotating Staggered beat Long with bulbous tips Lack of cilia Not done
CBP present but not predominant 3	Normal Completely immotile Weak residual movement Stiff Rotating Staggered beat Long with bulbous tips Lack of cilia Not done
CBP present but not predominant 4	Normal Completely immotile Weak residual movement Stiff Rotating Staggered beat Long with bulbous tips Lack of cilia Not done
CBP present but not predominant 5	Normal Completely immotile Weak residual movement Stiff Rotating Staggered beat Long with bulbous tips Lack of cilia Not done
CBP present but not predominant 6	Normal Completely immotile Weak residual movement Stiff Rotating Staggered beat Long with bulbous tips Lack of cilia Not done
CBP top view predominant finding	Normal Completely immotile Weak residual movement Stiff Rotating Staggered beat Long with bulbous tips Lack of cilia Not done
CBP top present but not predominant 1	Normal Completely immotile Weak residual movement Stiff Rotating

	Staggered beat Long with bulbous tips Lack of cilia Not done
If stiff report location	Apical Basal Global
Syncronisation of CBP present	Yes No Not applicable
CBF	in Hz/min
Comments	Free text

Table E2. Diagnostic characteristics of patients in the *discovery* group, stratified by predefined gene groups. Genes are ordered according to gene distribution in the study population.

Diagnostic characteristic	**Dynein structure** (*DNAH5, DNAH11, DNAI1, ARMC4, DNAI2, DNAL1*) (n=89)	**Dynein assembly** (*CCDC103, DNAAF3, LRRC6, DNAAF4, SPAG1, ZYMND10, DNAAF1, CCDC114, PIHD3)* (n=52)	**Radial spoke or central complex** *(RSPH4A, RSPH9, RSPH1, HYDIN)* (n=18)	**N-RC/molecular ruler** *(CCDC40, CCDC39, DRC1, CCDC164)* (n=33)	**Other functions** *(RPGR, CCNO, MCIDAS)* (n=7)	**All**	**p-value**
Median nNO level in nL/min (IQR); n=149	11.0 (6.8 to 18.8)*	17.8 (7.8 to 33.6)	23.0 (11.0 to 34.2)	12.6 (5.4 to 18.8)	39.9 (15.3 to 96.9)*	13.0 (7.4 to 24.0)	**0.0071**
TEM findings, n=187							
Non-diagnostic TEM (%)	25 (30.1)	4 (7.7)	4 (23.5)	2 (6.9)	2 (33.3)	37 (19.8)	
Isolated ODA defect (%)	51 (61.5)	9 (17.3)	0	0	0	60 (32.1)	
ODA & IDA defect (%)	6 (7.2)	34 (65.4)	0	0	0	40 (21.4)	
MTD & IDA defect or isolated IDA defect (%)	0	4 (7.7)	0	27 (93.1)	0	31 (16.6)	
CC defect (%)	0	0	13 (76.5)	0	0	13 (7.0)	
Lack of cilia (%)	1 (1.2)	1 (1.9)	0	0	4 (66.7)	6 (3.2)	
CBP predominant side view, n=133							
Normal (%)	0	3 (8.8)	0	0	0	3 (2.7)	
Completely immotile (%)	35 (58.3)	25 (73.5)	0	5 (22.7)	3 (42.9)	68 (51.1)	
Weak residual movement (%)	8 (13.3)	0	0	1 (4.6)	0	9 (6.8)	
Stiff (%)	16 (26.7)	6 (17.7)	3 (30.0)	11 (50.0)	2 (28.6)	38 (28.6%	
Rotating (%)	0	0	7 (70.0)	0	0	7 (5.3)	
Staggered beat (%)	0	0	0	5 (22.7)	0	5 (3.8)	
Lack of cilia (%)	1 (1.7)	0	0	0	2 (28.6)	3 (2.3)	

*nNO= nasal nitric oxide (normal levels <77nl/min), TEM = Transmission electron microscopy, ODA= outer dynein arm, IDA = inner dynein arm, CC = central complex, CBP= ciliary beat pattern, ODA= outer dynein arm, IDA= inner dynein arm, MTD= microtubular disorganisation; * = significant difference between the pairs, Dunn's pairwise comparison with Holm-Sidak adjustment. P values $\leq$0.05 highlighted.

Table E3. Clinical characteristics of patients in the *discovery* group, stratified by predefined gene groups. Genes are ordered according to gene distribution in the study population.

Clinical characteristic	**Dynein structure** *(DNAH5, DNAH11, DNAI1, ARMC4, DNAI2, DNAL1)* (n=89)	**Dynein assembly** *(CCDC103, DNAAF3, LRRC6, DNAAF4, SPAG1, ZYMND10, DNAAF1, CCDC114 PIHD3)* (n=52)	**Radial spoke/ central complex** *(RSPH4A, RSPH9, RSPH1, HYDIN)* (n=18)	**N-DRC/molecular ruler** *(CCDC40, CCDC39, CCDC65, DRC1)* (n=33)	**Other functions** *(RPGR, CCNO, MCIDAS)* (n=7)	**All**	**p-value**
Male (%)	34 (38.2)	27 (51.9)	9 (50.0)	12 (36.4)	5 (71.4)	87 (43.7)	0.226
Ethnicity (n=191)							
White-British (%)	50 (58.1)	7 (13.5)	3 (16.7)	14 (50.0)	1 (14.3)	75 (39.3)	
White Irish (%)	0	5 (9.6)	3 (16.7)	1 (3.6)	4 (57.1)	13 (6.8)	
White-other (%)	10 (11.6)	4 (7.7)	1 (1.6)	5 (17.9)	1 (14.3)	21 (11.0)	
Indian (%)	4 (4.7)	5 (9.6)	0	1 (3.6)	0	10 (5.3)	
Pakistani (%)	6 (7.0)	18 (34.6)	3 (16.7)	2 (7.1)	0	29 (15.2)	
Bangladeshi (%)	0	2 (3.9)	1 (5.6)	0	0	3 (1.6)	
Sri Lankan (%)	3 (3.5)	2 (3.9)	0	0	0	5 (2.6)	
Middle East (%)	1 (1.2)	1 (1.9)	5 (27.8)	1 (3.6)	0	8 (4.2)	
Black (%)	7 (8.1)	0	1 (5.6)	1 (3.6)	0	9 (4.7)	
Chinese (%)	0	3 (5.8)	0	0	0	3 (1.6)	
Mixed (%)	1 (1.2)	1 (1.9)	0	1 (3.6)	0	3 (1.6)	
Other (%)	4 (4.7)	4 (7.9)	1 (5.6)	2 (7.1)	1 (14.3)	12 (6.3)	
Mean FEV_1 z-scores (SD), n=138	-1.4 (1.4) $^{+}$	-1.9 (1.4)	-1.7 (2.1)	-2.7 (1.6)$^{+}$	-2.7 (2.7)	-1.8 (1.6)	**0.0069**
Median age at diagnosis (IQR) n=184	9.1 (2.0 to 23.2)	7.3 (2.3 to 12.5)	9.5 (8.4 to 15.4)	7.5 2.0 to 13.8)	10.2 (5.8 to 12.7)	9.0 (2.9 to 15.4)	0.667
Neonatal respiratory distress (%)	31 (54.4)	31 (88.6)	7 (63.6)	15 (65.2)	3 (42.9)	87 (65.4)	**0.006**
Wet cough (%)	66 (94.3)	40 (100)	14 (100)	25 (96.2)	5 (71.4)	150 (95.5)	**0.042**
Rhinitis (%)	65 (91.6)	38 (95.0)	11 (91.7)	18 (72.0)	5 (71.4)	137 (88.4)	**0.027**
Glue ear (%)	38 (57.6)	19 (51.4)	9 (81.8)	9 (39.1)	4 (57.1)	79 (54.9)	0.206
Situs solitus (%)	31 (37.8)	19 (37.3)	18 (100)	18 (58.1)	7 (100%)	93 (49.2)	**<0.001**

$^{+}$ difference between groups was statistically significant (ANOVA followed by Tukey for pairwise comparisons). P values $\leq$0.05 highlighted.

Table E4. Variants defined in 199 PCD patients from the *discovery* cohort.

Pt ID	Gene	Allele 1	Allele 2	Variant classification		Reference	
				Allele 1	Allele 2	A1	A2
01-205	*ARMC4 (NM_001290020.1)*	c.1233_1234delinsT, p.Leu411Phefs*48	c.1969C>T, p.Gln657*	Frameshift (5)	Nonsense (5)	NA	[9]
01-214	*ARMC4 (NM_001290020.1)*	c.1283C>G, p.Ser428*	c.1283C>G, p.Ser428*	Nonsense (5)	Nonsense (5)	NA	NA
01-072	*ARMC4 (NM_001290020.1)*	c.2675C>A, p.Ser892*	c.2675C>A, p.Ser892*	Nonsense (5)	Nonsense (5)	[10]	[10]
01-073	*ARMC4 (NM_001290020.1)*	c.2675C>A, p.Ser892*	c.2675C>A, p.Ser892*	Nonsense (5)	Nonsense (5)	[10]	[10]
01-098	*CCDC103 (NM_001258395.1)*	c.461A>C, p.His154Pro	c.461A>C, p.His154Pro	Missense (5)	Missense (5)	[11-13]	[11-13]
01-099	*CCDC103 (NM_001258395.1)*	c.461A>C, p.His154Pro	c.461A>C, p.His154Pro	Missense (5)	Missense (5)	[11-13]	[11-13]
01-100	*CCDC103 (NM_001258395.1)*	c.461A>C, p.His154Pro	c.461A>C, p.His154Pro	Missense (5)	Missense (5)	[11-13]	[11-13]
01-103	*CCDC103 (NM_001258395.1)*	c.461A>C, p.His154Pro	c.461A>C, p.His154Pro	Missense (5)	Missense (5)	[11-13]	[11-13]
01-123	*CCDC103 (NM_001258395.1)*	c.461A>C, p.His154Pro	c.461A>C, p.His154Pro	Missense (5)	Missense (5)	[11-13]	[11-13]
01-124	*CCDC103 (NM_001258395.1)*	c.461A>C, p.His154Pro	c.461A>C, p.His154Pro	Missense (5)	Missense (5)	[11-13]	[11-13]
01-156	*CCDC103 (NM_001258395.1)*	c.461A>C, p.His154Pro	c.461A>C, p.His154Pro	Missense (5)	Missense (5)	[11-13]	[11-13]
01-170	*CCDC103 (NM_001258395.1)*	c.461A>C, p.His154Pro	c.461A>C, p.His154Pro	Missense (5)	Missense (5)	[11-13]	[11-13]
01-201	*CCDC103 (NM_001258395.1)*	c.461A>C, p.His154Pro	c.461A>C, p.His154Pro	Missense (5)	Missense (5)	[11-13]	[11-13]
02-051	*CCDC103 (NM_001258395.1)*	c.461A>C, p.His154Pro	c.461A>C, p.His154Pro	Missense (5)	Missense (5)	[11-13]	[11-13]
02-018	*CCDC103 (NM_001258395.1)*	c.461A>C, p.His154Pro	c.461A>C, p.His154Pro	Missense (5)	Missense (5)	[11-13]	[11-13]
02-033	*CCDC103 (NM_001258395.1)*	c.461A>C, p.His154Pro	c.461A>C, p.His154Pro	Missense (5)	Missense (5)	[11-13]	[11-13]
02-034	*CCDC103 (NM_001258395.1)*	c.461A>C, p.His154Pro	c.461A>C, p.His154Pro	Missense (5)	Missense (5)	[11-13]	[11-13]
01-079	*CCDC114 (NM_144577.3)*	c.287del, p.Lys96Argfs*23	c.287del, p.Lys96Argfs*23	Frameshift (5)	Frameshift (5)	NA	NA
01-029	*CCDC114 (NM_144577.3)*	c.486+1G>A	c.486+1G>A	Essential splice (5)	Essential splice (5)	[14]	[14]
01-074	*CCDC39 (NM_181426.1)*	c.1315A>T, p.Lys439*	c.1315A>T, p.Lys439*	Nonsense (5)	Nonsense (5)	NA	NA
01-064	*CCDC39 (NM_181426.1)*	c.1450del, p.Ile484Leufs*47	c.357+1G>C	Frameshift (5)	Essential splice (5)	[15]	[16]
01-030	*CCDC39 (NM_181426.1)*	c.1795C>T, p.Arg599*	c.1795C>T, p.Arg599*	Nonsense (5)	Nonsense (5)	[15]	[16]
01-045	*CCDC39 (NM_181426.1)*	c.2039_2040del, p.Cys680Phefs*9	c.526_527del, p.Leu176Alafs10*	Frameshift (5)	Frameshift (5)	[17]	NA
01-093	*CCDC39 (NM_181426.1)*	c.2040_2043del, p.Cys680Trpfs*15	c.440T>G, p.Leu147*	Frameshift (5)	Nonsense (5)	[17]	NA
01-063	*CCDC39 (NM_181426.1)*	c.2245G>T, p.Glu749*	c.2245G>T, p.Glu749*	Nonsense (5)	Nonsense (5)	[15]	[15]
01-016	*CCDC39 (NM_181426.1)*	c.2596G>T, p.Glu866*	c.2596G>T, p.Glu866*	Nonsense (5)	Nonsense (5)	[15]	[15]
02-028	*CCDC39 (NM_181426.1)*	c.664G>T, p.Glu222*	c.526_527del, p.Leu176Alafs10*	Nonsense (5)	Frameshift (5)	[15]	[15]
01-086	*CCDC39 (NM_181426.1)*	c.669_670insTA	c.610-2A>G	Frameshift (5)	Essential splice (5)	NA	[16]
01-200	*CCDC39 (NM_181426.1)*	c.830_831delCA, p.Asn276Lysfs*4	c.830_831delCA, p.Asn276Lysfs*4	Frameshift (5)	Frameshift (5)	[15]	[15]
01-102	*CCDC40 (NM_017950.3)*	c.1414del, p.Arg472Glyfs*3	c.3097A>T, p.Lys1033*	Frameshift (5)	Nonsense (5)	NA	[18]
01-179	*CCDC40 (NM_017950.3)*	c.1415delC, p.Arg472fs3*	c.1415delC, p.Arg472fs3*	Frameshift (5)	Frameshift (5)	[15]	[15]
02-049	*CCDC40 (NM_017950.3)*	c.1819_1823delinsT, p.Leu607Trpfs*33	c.1819_1823delinsT, p.Leu607Trpfs*33	Frameshift (5)	Frameshift (5)	NA	NA
01-138	*CCDC40 (NM_017950.3)*	c.248del, p.Ala83Valfs*84	c.552+6T>A	Frameshift (5)	Splice site (4)	[15, 19, 20]	[15, 19, 20]
01-054	*CCDC40 (NM_017950.3)*	c.248del, p.Ala83Valfs*84	c.248del, p.Ala83Valfs*84	Frameshift (5)	Frameshift (5)	[15, 19, 20]	[15, 19, 20]
01-068	*CCDC40 (NM_017950.3)*	c.248del, p.Ala83Valfs*84	c.248del, p.Ala83Valfs*84	Frameshift (5)	Frameshift (5)	[15, 19, 20]	[15, 19, 20]
02-045	*CCDC40 (NM_017950.3)*	c.248del, p.Ala83Valfs*84	c.248del, p.Ala83Valfs*84	Frameshift (5)	Frameshift (5)	[15, 19, 20]	[15, 19, 20]
02-067	*CCDC40 (NM_017950.3)*	c.248del, p.Ala83Valfs*84	c.748C>T, p.Glu250*	Frameshift (5)	Nonsense (5)	[15, 19, 20]	[15, 19, 20]
01-216	*CCDC40 (NM_017950.3)*	c.248del, p.Ala83Valfs*84	c.2450-2A>G	Frameshift (5)	Essential splice (5)	[15, 19, 20]	[15, 19, 20]
01-187	*CCDC40 (NM_017950.3)*	c.248del, p.Ala83Valfs*84	c.248del, p.Ala83Valfs*84	Frameshift (5)	Frameshift (5)	[15, 19, 20]	[15]
01-005	*CCDC40 (NM_017950.3)*	c.2712-1G>T	c.2712-1G>T	Essential splice (5)	Essential splice (5)	[15]	[15]
01-031	*CCDC40 (NM_017950.3)*	c.2712-1G>T	c.2712-1G>T	Essential splice (5)	Essential splice (5)	[15]	[15]
02-021	*CCDC40 (NM_017950.3)*	c.2712-1G>T	c.2712-1G>T	Essential splice (5)	Essential splice (5)	[15]	[15]
01-111	*CCDC40 (NM_017950.3)*	c.2712-1G>T	c.248del, p.Ala83Valfs*84	Essential splice (5)	Frameshift (5)	[15]	[15]
01-092	*CCDC40 (NM_017950.3)*	c.3181-3C>G	c.3181-3C>G	Splice site (3)	Splice site (3)	NA	NA
01-215	*CCDC40 (NM_017950.3)*	c.712G>T, p.Glu238*	c.940-2A>G	Nonsense (5)	Essential splice (5)	NA	[15]
01-137	*CCDC40 (NM_017950.3)*	c.940-2A>G	c.248del, p.Ala83Valfs*84	Essential splice (5)	Frameshift (5)	[15]	[15, 19, 20]
01-160	*CCDC65 (NM_033124.4)*	c.658G>T, p.Glu220*	c.658G>T, p.Glu220*	Nonsense (5)	Nonsense (5)	NA	NA
01-161	*CCDC65 (NM_033124.4)*	c.658G>T, p.Glu220*	c.658G>T, p.Glu220*	Nonsense (5)	Nonsense (5)	NA	NA

01-122	*CCDC65 (NM_033124.4)*	c.877_878del, p.Ile293Profs*2	c.877_878del, p.Ile293Profs*2	Frameshift (5)	Frameshift (5)	[21]	[21]
01-109	*CCDC65 (NM_033124.4)*	c.913C>T, p.Arg305*	c.913C>T, p.Arg305*	Nonsense (5)	Nonsense (5)	NA	NA
01-139	*CCNO (NM_021147.3)*	c.258_262dup, p.Gln88Argfs*8	c.258_262dup, p.Gln88Argfs*8	Frameshift (5)	Frameshift (5)	[22]	[22]
02-017	*CCNO (NM_021147.3)*	c.538dupC, p.Val180Glyfs*55	c.538dupC, p.Val180Glyfs*55	Frameshift (5)	Frameshift (5)	NA	NA
01-126	*DNAAF1 (NM_178452.5)*	c.285del, p.Lys95Asnfs*14	c.1484del, p.Pro495Glnfs*40	Frameshift (5)	Frameshift (5)	NA	[23]
01-127	*DNAAF1 (NM_178452.5)*	c.285del, p.Lys95Asnfs*14	c.1484del, p.Pro495Glnfs*40	Frameshift (5)	Frameshift (5)	NA	[23]
01-128	*DNAAF1 (NM_178452.5)*	c.285del, p.Lys95Asnfs*14	c.1484del, p.Pro495Glnfs*40	Frameshift (5)	Frameshift (5)	NA	[23]
01-223	*DNAAF1 (NM_178452.6)*	Deletion of exons 1-3	Deletion of exons 1-3	CNV (5)	CNV (5)	NA	NA
01-186	*DNAAF3 (NM_001256715.1)*	c.1030_1031delinsG, p.Pro344Glyfs*64	c.1273G>T, p.Gly425*	Frameshift (5)	Nonsense (5)	NA	NA
01-113	*DNAAF3 (NM_001256715.1)*	c.162_164delinsG, p.Val55Glyfs*28	c.162_164delinsG, p.Val55Glyfs*28	Frameshift (5)	Frameshift (5)	NA	NA
01-185	*DNAAF3 (NM_001256715.1)*	c.228+5G>C	c.228+5G>C	Splice site (3)	Splice site (3)	NA	NA
01-112	*DNAAF3 (NM_001256715.1)*	c.481-1G>A	c.481-1G>A	Essential splice (5)	Essential splice (5)	NA	NA
01-047	*DNAAF3 (NM_001256715.1)*	c.609_610delinsTGGGA, p.Ala272delinsGlyThr	c.296del, p.Glu167Glyfs*88	Inframe delins (5)	Frameshift (5)	NA	NA
01-089	*DNAAF3 (NM_001256715.1)*	c.621dupT, p.Val208Cysfs*12	c.621dupT, p.Val208Cysfs*12	Frameshift (5)	Frameshift (5)	[24]	[24]
01-090	*DNAAF3 (NM_001256715.1)*	c.621dupT, p.Val208Cysfs*12	c.621dupT, p.Val208Cysfs*12	Frameshift (5)	Frameshift (5)	[24]	[24]
01-174	*DNAAF3 (NM_001256715.1)*	c.621dupT, p.Val208Cysfs*12	c.621dupT, p.Val208Cysfs*12	Frameshift (5)	Frameshift (5)	[24]	[24]
01-131	*DNAAF3 (NM_001256715.1)*	c.901C>T, p.Gln301*	c.901C>T, p.Gln301*	Nonsense (5)	Nonsense (5)	NA	NA
01-070	*DNAAF3 (NM_001256715.1)*	c.997dup, p.Asp333Glyfs*64	c.570G>A, p.Trp190*	Frameshift (5)	Nonsense (5)	NA	NA
01-088	*DNAAF4 (NM_130810.3)*	3.5 kb deletion of exon 7	3.5 kb deletion of exon 7	CNV (5)	CNV (5)	[25]	[25]
01-232	*DNAAF4 (NM_130810.3)*	3.5 kb deletion of exon 7	3.5 kb deletion of exon 7	CNV (5)	CNV (5)	[25]	[25]
02-022	*DNAAF4 (NM_130810.3)*	3.5 kb deletion of exon 7	3.5 kb deletion of exon 7	CNV (5)	CNV (5)	[25]	[25]
02-010	*DNAAF4 (NM_130810.3)*	3.5 kb deletion of exon 7	3.5 kb deletion of exon 7	CNV (5)	CNV (5)	[25]	[25]
02-019	*DNAAF4 (NM_130810.3)*	3.5 kb deletion of exon 7	3.5 kb deletion of exon 7	CNV (5)	CNV (5)	[25]	[25]
01-085	*DNAAF4 (NM_130810.3)*	c.390_393del, p.Val132*	c.390_393del, p.Val132*	Nonsense (5)	Nonsense (5)	[25]	[25]
01-136	*DNAAF4 (NM_130810.3)*	c.808C>T, p.Arg270*	c.808C>T, p.Arg270*	Nonsense (5)	Nonsense (5)	[25]	[25]
01-176	*DNAH11 (NM_001277115.1)*	c.13040T>C, p.Leu4347Pro	Deletion of exons 68-75	Missense (3)	CNV (5)	NA	NA
02-073	*DNAH11 (NM_001277115.1)*	c.13270G>T, p.Glu4424*	c.13373C>T, p.Pro4458Leu	Nonsense (5)	Missense (5)	NA	[26]
01-040	*DNAH11 (NM_001277115.1)*	c.13531_13532ins13, p.Ala4511Valfs*13	c.3727G>T, p.Glu1243*	Frameshift (5)	Nonsense (5)	[27]	[27]
01-041	*DNAH11 (NM_001277115.1)*	c.13531_13532ins13, p.Ala4511Valfs*13	c.3727G>T, p.Glu1243*	Frameshift (5)	Nonsense (5)	[27]	[27]
01-042	*DNAH11 (NM_001277115.1)*	c.13531_13532ins13, p.Ala4511Valfs*13	c.3727G>T, p.Glu1243*	Frameshift (5)	Nonsense (5)	[27]	[27]
01-043	*DNAH11 (NM_001277115.1)*	c.13531_13532ins13, p.Ala4511Valfs*13	c.3727G>T, p.Glu1243*	Frameshift (5)	Nonsense (5)	[27]	[27]
01-095	*DNAH11 (NM_001277115.1)*	c.2832dup, p.Gln945Serfs*10	c.13240dup, p.Thr4414Asnfs*34	Frameshift (5)	Frameshift (5)	[27]	[27]
01-133	*DNAH11 (NM_001277115.1)*	c.3220G>T, p.Glu1074*	c.13069C>T, p.Arg4357*	Nonsense (5)	Nonsense (5)	[27]	[27]
01-147	*DNAH11 (NM_001277115.1)*	c.3380G>A, p.Trp1127*	c.3380G>A, p.Trp1127*	Nonsense (5)	Nonsense (5)	NA	NA
01-157	*DNAH11 (NM_001277115.1)*	c.3544C>T, p.Arg1182*	c.8798-5G>A	Nonsense (5)	Splice site (3)	[27]	[27]
02-063	*DNAH11 (NM_001277115.1)*	c.4333C>T, p.Arg1445*	c.9783G>C, p.Glu3261Asp	Nonsense (5)	Missense (3)	[26]	NA
02-062	*DNAH11 (NM_001277115.1)*	c.4333C>T, p.Arg1445*	c.4333C>T, p.Arg1445*	Nonsense (5)	Nonsense (5)	[26]	[26]
02-068	*DNAH11 (NM_001277115.1)*	c.4333C>T, p.Arg1445*	c.8698C>T, p.Arg2900*	Nonsense (5)	Nonsense (5)	[26]	[28]
02-038	*DNAH11 (NM_001277115.1)*	c.4333C>T, p.Arg1445*	c.13171C>T, p.Gln4391*	Nonsense (5)	Nonsense (5)	[26]	NA
01-065	*DNAH11 (NM_001277115.1)*	c.4410_4413del	c.7663C>T, p.Gln2555*	Frameshift (5)	Nonsense (5)	[27]	[27]
01-163	*DNAH11 (NM_001277115.1)*	c.4552C>T, p.Gln1518*	c.5778+1G>A, p.Val1821Thrfs*7	Nonsense (5)	Essential splice (5)	NA	[26]
01-084	*DNAH11 (NM_001277115.1)*	c.5506C>T, p.Arg1836*	c.5636T>A, p.Leu1879*	Nonsense (5)	Nonsense (5)	[27]	[27]
02-079	*DNAH11 (NM_001277115.1)*	c.5593C>T, p.Arg1865*	c.5593C>T, p.Arg1865*	Nonsense (5)	Nonsense (5)	NA	NA
01-158	*DNAH11 (NM_001277115.1)*	c.5924+1G>C	c.5924+1G>C	Essential splice (5)	Essential splice (5)	NA	NA
01-082	*DNAH11 (NM_001277115.1)*	c.6506C>T, p.Ser2169Leu	c.6506C>T, p.Ser2169Leu	Missense (3)	Missense (3)	[28]	[28]
01-083	*DNAH11 (NM_001277115.1)*	c.6506C>T, p.Ser2169Leu	c.6506C>T, p.Ser2169Leu	Missense (3)	Missense (3)	[28]	[28]
02-016	*DNAH11 (NM_001277115.1)*	c.6664C>T, p.Arg2222*	c.6682A>T, p.Lys2228*	Nonsense (5)	Nonsense (5)	NA	NA
01-221	*DNAH11 (NM_001277115.1)*	c.7472G>C, p.Arg2491Pro	c.6565C>T, p.Arg2189*	Missense (5)	Nonsense (5)	NA	NA
02-050	*DNAH11 (NM_001277115.1)*	c.8719C>T, p.Arg2907*	c.8719C>T, p.Arg2907*	Nonsense (5)	Nonsense (5)	[28]	[28]
01-169	*DNAH11 (NM_001277115.1)*	c.8932C>T, p.Gln2978*	c.853_857delinsG, p.Arg285Glufs*22	Nonsense (5)	Frameshift (5)	NA	NA
01-220	*DNAH11 (NM_001277115.1)*	c.9581_9582del, p.Leu3194Glnfs*10	c.4333C>T, p.Arg1445*	Frameshift (5)	Nonsense (5)	NA	[26]
01-178	*DNAH5 (NM_001369.2)*	c.10601T>C, p.Phe3534Ser	c.13458_13459insT, p.Asn4487fs*1	Missense (4)	Frameshift (5)	NA	[29, 30]
01-062	*DNAH5 (NM_001369.2)*	c.10616G>C, p.Arg3539Pro	c.7915C>T, p.Arg2639*	Missense (5)	Nonsense (5)	[31]	[32]

02-053	*DNAH5 (NM_001369.2)*	c.10815del, p.Pro3606Hisfs*22	c.6070-6071delAC, p.Gln2024Valfs*8	Frameshift (5)	Frameshift (5)	[20, 33, 34]	NA
02-054	*DNAH5 (NM_001369.2)*	c.10815del, p.Pro3606Hisfs*22	c.6070-6071delAC, p.Gln2024Valfs*8	Frameshift (5)	Frameshift (5)	[20, 33, 34]	NA
02-072	*DNAH5 (NM_001369.2)*	c.10815del, p.Pro3606Hisfs*22	c.5537T>C, p.Leu1846Pro	Frameshift (5)	Missense (5)	[20, 33, 34]	NA
02-048	*DNAH5 (NM_001369.2)*	c.10815del, p.Pro3606Hisfs*22	c.10616C>T, p.Arg3539Cys	Frameshift (5)	Missense (5)	[20, 33, 34]	[33]
02-023	*DNAH5 (NM_001369.2)*	c.10815del, p.Pro3606Hisfs*22	c.9720+5G>A	Frameshift (5)	Splice site (4)	[34]	NA
01-175	*DNAH5 (NM_001369.2)*	c.10815del, p.Pro3606Hisfs*22	c.13458_13459insT, p.Asn4487fs*1	Frameshift (5)	Frameshift (5)	[34]	[29, 30]
01-211	*DNAH5 (NM_001369.2)*	c.10815del, p.Pro3606Hisfs*22	c.10815del, p.Pro3606Hisfs*22	Frameshift (5)	Frameshift (5)	[33]	[33]
01-230	*DNAH5 (NM_001369.2)*	c.10815del, p.Pro3606Hisfs*22	c.2410G>T, p.Glu804*	Frameshift (5)	Nonsense (5)	[34]	NA
01-145	*DNAH5 (NM_001369.2)*	c.10825C>T, p.Gln3609*	c.3466del, p.Ile1156Leufs*24	Nonsense (5)	Frameshift (5)	NA	NA
01-146	*DNAH5 (NM_001369.2)*	c.10825C>T, p.Gln3609*	c.3466del, p.Ile1156Leufs*24	Nonsense (5)	Frameshift (5)	NA	NA
01-120	*DNAH5 (NM_001369.2)*	c.12705+1del	c.6249G>A, p.Met2083Ile	Essential splice (5)	Missense (5)	NA	[35]
01-191	*DNAH5 (NM_001369.2)*	c.13285C>T, p.Arg4429*	c.8642C>G, p.Ala2881Gly	Nonsense (5)	Missense (5)	NA	[34]
01-134	*DNAH5 (NM_001369.2)*	c.13285C>T, p.Arg4429*	c.13285C>T, p.Arg4429*	Nonsense (5)	Nonsense (5)	NA	NA
01-135	*DNAH5 (NM_001369.2)*	c.13285C>T, p.Arg4429*	c.13285C>T, p.Arg4429*	Nonsense (5)	Nonsense (5)	NA	NA
01-143	*DNAH5 (NM_001369.2)*	c.13338+1G>C	c.11437C>T, p.Arg3813Trp	Essential splice (5)	Missense (5)	NA	[18]
01-116	*DNAH5 (NM_001369.2)*	c.13399C>T, p.Gln4467*	c.13399C>T, p.Gln4467*	Nonsense (5)	Nonsense (5)	NA	NA
02-039	*DNAH5 (NM_001369.2)*	c.13458_13459insT, p.Asn4487fs*1	c.13338+1G>C	Frameshift (5)	Essential splice (5)	[29, 30]	NA
02-009	*DNAH5 (NM_001369.2)*	c.13458_13459insT, p.Asn4487fs*1	c.6930_6934delinsG, p.Asn2310Lysfs*15	Frameshift (5)	Frameshift (5)	[29, 30]	NA
01-048	*DNAH5 (NM_001369.2)*	c.13486C>T, p.Arg4496*	c.13458_13459insT, p.Asn4487fs*1	Nonsense (5)	Frameshift (5)	[29, 36, 37]	[29, 30]
02-024	*DNAH5 (NM_001369.2)*	c.13836G>A, p.Trp4612*	c.5710-2A>G, p.Cys1904-Lys1909del	Nonsense (5)	Essential splice (5)	NA	[33]
01-144	*DNAH5 (NM_001369.2)*	c.1828C>T, p.Gln610*	c.5563dup, p.Ile1855Asnfs*6	Nonsense (5)	Frameshift (5)	[32]	NA
01-189	*DNAH5 (NM_001369.2)*	c.232C>T, p.Arg78*	c.10815del, p.Pro3606Hisfs*22	Nonsense (5)	Frameshift (5)	[29, 36]	[34]
01-181	*DNAH5 (NM_001369.2)*	c.2710G>T, p.Glu904*	c.2710G>T, p.Glu904*	Nonsense (4)	Nonsense (4)	NA	NA
01-051	*DNAH5 (NM_001369.2)*	c.2893C>T, p.Gln965*	c.975-2A>G	Nonsense (5)	Essential splice (5)	NA	NA
01-206	*DNAH5 (NM_001369.2)*	c.5177T>C, p.Leu1726Pro	c.1730G>C, p.Arg577Thr	Missense (5)	Missense (5)	[31]	[29]
01-207	*DNAH5 (NM_001369.2)*	c.5177T>C, p.Leu1726Pro	c.1730G>C, p.Arg577Thr	Missense (5)	Missense (5)	[31]	[29]
02-029	*DNAH5 (NM_001369.2)*	c.5710-2A>G, p.Cys1904-Lys1909del	c.5710-2A>G, p.Cys1904-Lys1909del	Essential splice (5)	Essential splice (5)	[33]	[33]
01-190	*DNAH5 (NM_001369.2)*	c.5890_5894dup, p.Leu1966Serfs*9	c.6791G>A, p.Ser2264Asn	Frameshift (5)	Missense (5)	NA	[29]
02-011	*DNAH5 (NM_001369.2)*	c.6261T>G, p.Tyr2087*	c.6261T>G, p.Tyr2087*	Nonsense (5)	Nonsense (5)	NA	NA
02-026	*DNAH5 (NM_001369.2)*	c.6304C>T, p.Arg2102Cys	c.2052+1G>T	Missense (3)	Essential splice (5)	NA	NA
01-196	*DNAH5 (NM_001369.2)*	c.6763C>T, p.Arg2255*	c.9480T>A, p.Cys3160*	Nonsense (5)	Nonsense (5)	NA	NA
01-132	*DNAH5 (NM_001369.2)*	c.8383C>T, p.Arg2795*	c.5484+1G>A	Nonsense (5)	Essential splice (5)	NA	NA
01-209	*DNAH5 (NM_001369.2)*	c.8404C>T, p.Gln2802*	c.6249G>A, p.Met2083Ile	Nonsense (5)	Missense (5)	[29, 36]	NA
01-015	*DNAH5 (NM_001369.2)*	c.9516dup, p.Val3173Argfs*14	c.9516dup, p.Val3173Argfs*14	Frameshift (5)	Frameshift (5)	NA	NA
01-115	*DNAH5 (NM_001369.2)*	c.9694C>T, p.Gln3232*	c.9694C>T, p.Gln3232*	Nonsense (5)	Nonsense (5)	NA	NA
02-046	*DNAI1 (NM_012144.3)*	c.1490G>A, p.Gly497Asp	c.48+2dup, p.Ser17Valfs*12	Missense (5)	Essential splice (5)	[38]	[38]
01-044	*DNAI1 (NM_012144.3)*	c.1603del, p.Thr535Profs*31	c.1603del, p.Thr535Profs*31	Frameshift (5)	Frameshift (5)	NA	NA
01-069	*DNAI1 (NM_012144.3)*	c.1603del, p.Thr535Profs*31	c.1603del, p.Thr535Profs*31	Frameshift (5)	Frameshift (5)	NA	NA
01-087	*DNAI1 (NM_012144.3)*	c.1603del, p.Thr535Profs*31	c.1603del, p.Thr535Profs*31	Frameshift (5)	Frameshift (5)	NA	NA
02-013	*DNAI1 (NM_012144.3)*	c.1612G>A, p.Ala538Thr	c.1612G>A, p.Ala538Thr	Missense (5)	Missense (5)	[38]	[38]
02-031	*DNAI1 (NM_012144.3)*	c.1612G>A, p.Ala538Thr	c.1612G>A, p.Ala538Thr	Missense (5)	Missense (5)	[38]	[38]
01-021	*DNAI1 (NM_012144.3)*	c.48+2dup, p.Ser17Valfs*12	c.48+2dup, p.Ser17Valfs*12	Essential splice (5)	Essential splice (5)	[38]	[38]
01-022	*DNAI1 (NM_012144.3)*	c.48+2dup, p.Ser17Valfs*12	c.48+2dup, p.Ser17Valfs*12	Essential splice (5)	Essential splice (5)	[38]	[38]
01-140	*DNAI1 (NM_012144.3)*	c.48+2dup, p.Ser17Valfs*12	c.48+2dup, p.Ser17Valfs*12	Essential splice (5)	Essential splice (5)	[38]	[38]
02-006	*DNAI1 (NM_012144.3)*	c.48+2dup, p.Ser17Valfs*12	c.48+2dup, p.Ser17Valfs*12	Essential splice (5)	Essential splice (5)	[38]	[38]
02-058	*DNAI1 (NM_012144.3)*	c.48+2dup, p.Ser17Valfs*12	c.48+2dup, p.Ser17Valfs*12	Essential splice (5)	Essential splice (5)	[38]	[38]
02-059	*DNAI1 (NM_012144.3)*	c.48+2dup, p.Ser17Valfs*12	c.48+2dup, p.Ser17Valfs*12	Essential splice (5)	Essential splice (5)	[38]	[38]
02-069	*DNAI1 (NM_012144.3)*	c.48+2dup, p.Ser17Valfs*12	c.48+2dup, p.Ser17Valfs*12	Essential splice (5)	Essential splice (5)	[38]	[38]
01-001	*DNAI1 (NM_012144.3)*	c.48+2dup, p.Ser17Valfs*12	c.1612G>A, p.Ala538Thr	Essential splice (5)	Missense (5)	[38]	[38]
02-061	*DNAI1 (NM_012144.3)*	c.48+2dup, p.Ser17Valfs*12	c.1612G>A, p.Ala538Thr	Essential splice (5)	Missense (5)	[38]	[38]
01-028	*DNAI2 (NM_023036.4)*	c.1304G>A, p.Trp435*	c.1304G>A, p.Trp435*	Nonsense (5)	Nonsense (5)	[35]	[35]
01-101	*DNAI2 (NM_023036.4)*	c.1304G>A, p.Trp435*	c.1304G>A, p.Trp435*	Nonsense (5)	Nonsense (5)	[35]	[35]
01-229	*DNAI2 (NM_023036.4)*	c.883C>T, p.Arg295*	c.883C>T, p.Arg295*	Nonsense (5)	Nonsense (5)	NA	NA

01-097	*DNAL1 (NM_031427.3)*	c.225_229del, p.Leu75Phefs*30	c.225_229del, p.Leu75Phefs*30	Frameshift (5)	Frameshift (5)	NA	NA
01-055	*DRC1 (NM_145038.2)*	c.352C>T, p.Gln118*	c.2020C>T, p.Gln674*	Nonsense (5)	Nonsense (5)	[39]	NA
01-056	*DRC1 (NM_145038.2)*	c.352C>T, p.Gln118*	c.2020C>T, p.Gln674*	Nonsense (5)	Nonsense (5)	[39]	NA
01-119	*HYDIN (NM_001270974.2)*	c.13709del, p.Pro4570Leufs*22	c.13709del, p.Pro4570Leufs*22	Frameshift (5)	Frameshift (5)	NA	NA
01-121	*HYDIN (NM_001270974.2)*	c.2194dup, p.Tyr732Leufs*2	c.2194dup, p.Tyr732Leufs*2	Frameshift (5)	Frameshift (5)	NA	NA
02-027	*LRRC6 (NM_012472.4)*	c.299T>C, p.Ile100Thr	c.630del, p.Trp210Cysfs*12	Missense (5)	Frameshift (5)	[37]	[20]
01-057	*LRRC6 (NM_012472.4)*	c.630del, p.Trp210Cysfs*12	c.630del, p.Trp210Cysfs*12	Frameshift (5)	Frameshift (5)	[20]	[20]
01-094	*LRRC6 (NM_012472.4)*	c.630del, p.Trp210Cysfs*12	c.630del, p.Trp210Cysfs*12	Frameshift (5)	Frameshift (5)	[20]	[20]
01-129	*LRRC6 (NM_012472.4)*	c.630del, p.Trp210Cysfs*12	c.630del, p.Trp210Cysfs*12	Frameshift (5)	Frameshift (5)	[20]	[20]
01-130	*LRRC6 (NM_012472.4)*	c.630del, p.Trp210Cysfs*12	c.630del, p.Trp210Cysfs*12	Frameshift (5)	Frameshift (5)	[20]	[20]
01-184	*LRRC6 (NM_012472.4)*	c.630del, p.Trp210Cysfs*12	c.630del, p.Trp210Cysfs*12	Frameshift (5)	Frameshift (5)	[20]	[20]
01-204	*LRRC6 (NM_012472.4)*	c.630del, p.Trp210Cysfs*12	c.630del, p.Trp210Cysfs*12	Frameshift (5)	Frameshift (5)	[20]	[20]
01-218	*LRRC6 (NM_012472.4)*	c.630del, p.Trp210Cysfs*12	c.630del, p.Trp210Cysfs*12	Frameshift (5)	Frameshift (5)	[20]	[20]
01-010	*LRRC6 (NM_012472.4)*	c.183T>G, p.Asn61Lys	c.179-1G>A	Missense (4)	Essential splice (5)	NA	NA
01-011	*LRRC6 (NM_012472.4)*	c.183T>G, p.Asn61Lys	c.179-1G>A	Missense (4)	Essential splice (5)	NA	NA
01-142	*LRRC6 (NM_012472.4)*	c.793del, p.Arg266Aspfs*13	c.239_243del, p.Lys80Argfs*7	Frameshift (5)	Frameshift (5)	NA	NA
01-203	*MCIDAS (NM_001190787.1)*	c.332_333delinsG, p.Ala111Glyfs*22	c.332_333delinsG, p.Ala111Glyfs*22	Frameshift (5)	Frameshift (5)	NA	NA
01-007	*PIH1D3 (NM_001169154.1)*	c.127G>T, p.Glu43*	X-linked hemizygous	Nonsense (5)	-	[40]	-
01-164	*PIH1D3 (NM_001169154.1)*	c.266G>A, p.Trp89*	X-linked hemizygous	Nonsense (5)	-	[40]	-
01-075	*RPGR (NM_001034853.1)*	c.633del, p.Tyr212Metfs*11	X-linked hemizygous	Frameshift (5)	-	NA	-
02-007	*RPGR (NM_001034853.1)*	c.646G>T, p.Glu216*	X-linked hemizygous	Nonsense (5)	-	NA	-
02-012	*RPGR (NM_001034853.1)*	c.646G>T, p.Glu216*	X-linked hemizygous	Nonsense (5)	-	NA	-
02-037	*RPGR (NM_001034853.1)*	c.706C>T, p.Gln236*	X-linked hemizygous	Nonsense (5)	-	NA	-
01-208	*RSPH1 (NM_080860.3)*	c.275-2A>C, p.Gly92Alafs*10	c.275-2A>C, p.Gly92Alafs*10	Essential splice (5)	Essential splice (5)	[41]	[41]
02-005	*RSPH1 (NM_080860.3)*	c.275-2A>C, p.Gly92Alafs*10	c.275-2A>C, p.Gly92Alafs*10	Essential splice (5)	Essential splice (5)	[41]	[41]
02-008	*RSPH1 (NM_080860.3)*	c.275-2A>C, p.Gly92Alafs*10	c.275-2A>C, p.Gly92Alafs*10	Essential splice (5)	Essential splice (5)	[41]	[41]
01-199	*RSPH4A (NM_001010892.2)*	c.1351C>T, p.Gln451*	c.116C>A, p.Ser39*	Nonsense (5)	Nonsense (5)	NA	[42]
01-173	*RSPH4A (NM_001010892.2)*	c.1962_1966delinsC, p.Asp655Ilefs*83	c.1962_1966delinsC, p.Asp655Ilefs*83	Frameshift (5)	Frameshift (5)	NA	NA
01-026	*RSPH4A (NM_001010892.2)*	c.325C>T, p.Gln109*	c.1468C>T, p.Arg490*	Nonsense (5)	Nonsense (5)	[43]	[43]
01-037	*RSPH4A (NM_001010892.2)*	c.460C>T, p.Gln154*	c.460C>T, p.Gln154*	Nonsense (5)	Nonsense (5)	[43]	[43]
01-038	*RSPH4A (NM_001010892.2)*	c.460C>T, p.Gln154*	c.460C>T, p.Gln154*	Nonsense (5)	Nonsense (5)	[43]	[43]
01-039	*RSPH4A (NM_001010892.2)*	c.460C>T, p.Gln154*	c.460C>T, p.Gln154*	Nonsense (5)	Nonsense (5)	[43]	[43]
01-081	*RSPH4A (NM_001010892.2)*	c.460C>T, p.Gln154*	c.460C>T, p.Gln154*	Nonsense (5)	Nonsense (5)	[43]	[43]
02-057	*RSPH4A (NM_001010892.2)*	c.166dup, p.Arg56Profs*11	c.166dup, p.Arg56Profs*11	Frameshift (5)	Frameshift (5)	[12]	[12]
01-033	*RSPH9 (NM_001193341.1)*	c.801_803delGAA, p.Lys268del	c.801_803delGAA, p.Lys268del	Inframe AA del (5)	Inframe AA del (5)	[43]	[43]
01-034	*RSPH9 (NM_001193341.1)*	c.801_803delGAA, p.Lys268del	c.801_803delGAA, p.Lys268del	Inframe AA del (5)	Inframe AA del (5)	[43]	[43]
01-035	*RSPH9 (NM_001193341.1)*	c.801_803delGAA, p.Lys268del	c.801_803delGAA, p.Lys268del	Inframe AA del (5)	Inframe AA del (5)	[43]	[43]
01-036	*RSPH9 (NM_001193341.1)*	c.801_803delGAA, p.Lys268del	c.801_803delGAA, p.Lys268del	Inframe AA del (5)	Inframe AA del (5)	[43]	[43]
01-071	*RSPH9 (NM_001193341.1)*	c.801_803delGAA, p.Lys268del	c.801_803delGAA, p.Lys268del	Inframe AA del (5)	Inframe AA del (5)	[43]	[43]
01-194	*SPAG1 (NM_003114.4)*	c.1519dupA, p.Ile507Asnfs*5	c.1519dupA, p.Ile507Asnfs*5	Frameshift (5)	Frameshift (5)	[44]	[44]
01-195	*SPAG1 (NM_003114.4)*	c.1519dupA, p.Ile507Asnfs*5	c.1519dupA, p.Ile507Asnfs*5	Frameshift (5)	Frameshift (5)	[44]	[44]
01-025	*ZMYND10 (NM_015896.2)*	c.47T>G, p.Val16Gly	c.593_594del, p.Val198Glyfs*13	Missense (5)	Frameshift (5)	[45]	[45]
01-077	*ZMYND10 (NM_015896.2)*	c.65del, p.Phe22Serfs*21	c.65del, p.Phe22Serfs*21	Frameshift (5)	Frameshift (5)	[45]	[45]
01-078	*ZMYND10 (NM_015896.2)*	c.65del, p.Phe22Serfs*21	c.65del, p.Phe22Serfs*21	Frameshift (5)	Frameshift (5)	[45]	[45]
02-060	*ZMYND10 (NM_015896.2)*	c.47T>G, p.Val16Gly	c.47T>G, p.Val16Gly	Missense (5)	Missense (5)	[20, 45]	[20, 45]

Variants pathogenicity classified according to ACMG guidelines as Class 5 (pathogenic), Class 4 (likely pathogenic) or Class 3 (variant of uncertain significance, VUS) [2]. Class 3 variants (n=8) were included if variant present in combination with a Class 5 variant in the patient, or additional phenotypes suggested the Class 3 variant was highly likely causal although unpublished.

Table E5. Diagnostic characteristics of patients in the *validation* group, stratified by predefined gene groups. Genes are ordered according to gene distribution in the study population.

Diagnostic characteristic	**Dynein structure** *(DNAH5, DNAH11, DNAI1, DNAI2, ARMC4, DNAH9, TTC25)* (n=82)	**Dynein assembly** *(CCDC103, DNAAF4, PIHD3, DNAAF1, LRRC6, DNAAF3, SPAG1, DNAAF5, ZYMND10, CFAP300)* (n=42)	**Radial spoke/ central complex** *(RSPH4A, HYDIN, RSPH1, RSPH9, RSPH3)* (n=32)	**N-DRC/molecular ruler** *(CCDC39, CCDC40, CCDC65, DRC1)* (n=35)	**Other functions** *(RPGR, CCNO, MCIDAS)* (n=6)	**All**	**p-value**
Median nNO level in nL/min (IQR); n=138	16 (8.1 to 23.6)	14.4 (8 to 25)	22.9 (7.6 to 40.5)	13 (9.9 to 23)	35 (15.9 to 54)	16.3 (8.4 to 28)	0.7038
TEM findings, n=178							
Non-diagnostic TEM (%)	21 (28.4)	3 (8.3)	7 (22.6)	1 (2.9)	0	32 (18)	
Isolated ODA defect (%)	38 (51.4)	1 (2.8)	0	0	0	39 (21.9)	
ODA & IDA defect (%)	14 (18.9)	31 (86.1)	0	1 (2.9)	2 (66.7)	48 (27)	
MTD & IDA defect or isolated IDA defect (%)	0	1 (2.8)	1 (3.2)	32 (94.1)	0	34 (19.1)	
CC defect (%)	0	0	22 (71)	0	0	22 (12.4)	
Lack of cilia (%)	1 (1.4)	0	1 (3.2)	0	1 (33.3)	3 (1.7)	
CBP predominant side view, n=133							
Normal (%)	2 (2.6)	3 (9.1)	6 (20.7)	0	2 (40)	13 (7.4)	
Completely immotile (%)	34 (44.7)	27 (81.8)	1 (3.5)	14 (42.4)	1 (20)	77 (43.8)	
Weak residual movement (%)	29 (38.2)	3 (9.1)	6 (20.7)	12 (36.4)	0	50 (28.4)	
Stiff (%)	11 (14.5)	0	6 (20.7)	7 (21.2)	0	24 (13.6)	
Rotating (%)	0	0	10 (34.5)	0	0	10 (5.7)	
Staggered beat (%)	0	0	0	0	2 (40)	2 (1.1)	
Lack of cilia (%)	0	0	0	0	0	0	

*nNO= nasal nitric oxide (normal levels <77nl/min), TEM = Transmission electron microscopy, ODA= outer dynein arm, IDA = inner dynein arm, CC = central complex, CBP= ciliary beat pattern, ODA= outer dynein arm, IDA= inner dynein arm, MTD= microtubular disorganisation.

Table E6. Clinical characteristics of patients in the *validation* group, stratified by predefined gene groups. Genes are ordered according to gene distribution in the study population.

Clinical characteristic	**Dynein structure** *(DNAH5, DNAH11, DNAI1, DNAI2, ARMC4, DNAH9, TTC25)* (n=82)	**Dynein assembly** *(CCDC103, DNAAF4, PIHD3, DNAAF1, LRRC6, DNAAF3, SPAG1, DNAAF5, ZYMND10, CFAP300)* (n=42)	**Radial spoke/ central complex** *(RSPH4A, HYDIN, RSPH1, RSPH9, RSPH3)* (n=32)	**N-DRC/molecular ruler** *(CCDC39, CCDC40, CCDC65, DRC1)* (n=35)	**Other functions** *(RPGR, CCNO, MCIDAS)* (n=6)	**All**	**p-value**
Male (%)	41 (50)	22 (52.4)	14 (43.8)	23 (65.7)	4 (66.7)	104 (52.8)	0.393
Ethnicity, n=185							
White-British (%)	15 (20.0)	4 (11.1)	3 (9.4)	3 (9.4)	0	25 (13.5)	
White-Irish (%)	0	2 (5.6)	4 (12.5)	0	0	6 (3.2)	
White-other (%)	33 (41.8)	10 (27.8)	13 (40.6)	10 (31.3)	4 (66.7)	70 (37.8)	
Indian (%)	1 (1.3)	0	1 (3.1)	1 (3.1)	0	3 (1.6)	
Pakistani (%)	1 (1.3)	5 (13.9)	1 (3.1)	2 (6.3)	1 (16.7)	10 (5.4)	
Bangladeshi (%)	1 (1.3)	0	0	0	0	1 (0.5)	
Black (%)	2 (2.5)	3 (8.3)	1 (3.1)	1 (3.1)	0	7 (3.8)	
Chinese (%)	1 (1.3)	0	0	0	0	1 (0.5)	
Mixed (%)	5 (6.3)	0	0	1 (3.1)	0	6 (3.2)	
Other (%)	20 (25.3)	12 (33.3)	9 (28.1)	14 (43.8)	1 (16.7)	56 (30.3)	
Median FEV_1 z-scores (IQR), n=169	-1.3 (1.5)$^+$	-1.5 (1.6)	-2.1 (1.8)	-2.6 (1.5)$^+$	-2.6 (1.7)	-1.8 (1.6)	**0.0008**
Median age at diagnosis (IQR) n=184	14 (4.9 to 17.8)	14.3 (5.5 to 19.1)	15.9 (7.2 to 21.9)	13.9 (3.5 to 21.5)	20.4 (6.1 to 36)	14.5 (6 to 19.5)	0.435
Neonatal respiratory distress (%)	41 (56.9)	21 (60)	14 (50)	20 (69)	3 (50)	99 (58.2)	0.650
Wet cough (%)	78 (96.3)	38 (95)	29 (93.6)	31 (91.2)	5 (83.3)	181 (94.3)	0.431
Rhinitis (%)	77 (96.3)	37 (90.2)	26 (83.9)	31 (91.2)	5 (83.3)	176 (91.7)	0.150
Glue ear (%)	55 (69.6)	26 (66.7)	25 (83.3)	23 (69.7)	4 (66.7)	133 (71.1)	0.574
Situs solitus (%)	38 (48.1)	17 (41.5)	30 (100)	22 (62.9)	6 (100)	113 (59.2)	**<0.001**

$^+$ difference between groups was statistically significant (ANOVA followed by Tukey for pairwise comparisons). P values $\leq$0.05 highlighted. IQR: interquartile range, NRDS: neonatal respiratory distress syndrome, CHD: congenital heart defect.

Table E7. Summary of diagnostic test results for all patients included in the study, stratified by gene group. Genes are ordered according to gene distribution in the study population.

Diagnostic test	**Dynein structure** *(DNAH5, DNAH11, DNAI1, DNAI2, ARMC4, DNAL1, DNAH9, TTC25)*, (n=171)	**Dynein assembly** *(CCDC103, DNAAF4, LRRC6, DNAAF3, DNAAF1, PIHD3, SPAG1, ZYMND10, CCDC114, DNAAF5, CFAP300)*, (n=94)	**Radial spoke/ central complex** *(RSPH4A, RSPH1, HYDIN, RSPH9, RSPH3)*, (n=50)	**N-DRC/molecular ruler** *(CCDC39, CCDC40, CCDC65, DRC1)*, (n=68)	**Other function** *(RPGR, CCNO, MCIDAS)*, (n=13)	**All**
nNO findings (%), n=287						
Median nNO level in nL/min [IQR]; n=287	12.1 [7.2 to 21.3]	15.3 [7.9 to 30.4]	23 [9.8 to 36]	12.8 [7.5 to 20]	39.9 [15.6 to 75.5]	14.4 [8.0 to 26.0]
n patients with nNO<77 nL/min (%)	120 (95.2)	53 (88.3)	34 (89.5)	54 (98.2)	6 (75)	267 (93.0)
TEM findings (%), n=365						
Non-diagnostic TEM	46 (29.3)	7 (8.0)	10 (20.8)	3 (4.8)	2 (22.2)	68 (18.6)
Isolated ODA defect	89 (56.7)	10 (11.4)	0	0	0	99 (27.1)
ODA & IDA defect	20 (12.7)	65 (73.9)	0	1 (1.6)	(22.2)	88 (24.1)
MTD & IDA defect or isolated IDA defect	0	5 (5.7)	1 (2.1)	59 (93.7)	0	65 (17.8)
CC defect	0	0	35 (72.9)	0	0	35 (9.6)
Lack of cilia	2 (1.3)	1 (1.1)	2 (4.2)	0	5 (55.6)	10 (2.7)
CBP predominant side view (%), n=309						
Normal	2 (1.5)	6 (9.0)	6 (15.4)	0	2 (16.7)	16 (5.2)
Completely immotile	69 (50.7)	52 (77.6)	1 (2.6)	19 (34.6)	4 (33.3)	145 (46.9)
Weak residual movement	37 (27.2)	3 (4.5)	6 (15.4)	13 (23.6)	0	59 (19.1)
Stiff	27 (19.9)	6 (9.0)	9 (23.1)	18 (32.7)	2 (16.7)	62 (20.1)
Rotating	0	0	16 (41.0)	0	0	16 (5.2)
Staggered beat	0	0	1 (2.6)	5 (9.1)	2 (16.7)	8 (2.6)
Lack of cilia	1 (0.7)	0	0	0	2 (16.7)	3 (1.0)

N-DRC = nexin-dynein regulatory complex, nNO = nasal nitric oxide (normal levels <77nl/min), IQR = interquartile range, TEM = Transmission electron microscopy, ODA= outer dynein arm, IDA = inner dynein arm, CC = central complex, MTD = microtubular disorganisation, CBP= ciliary beat pattern.

Table E8. Summary of clinical characteristics for all patients included in the study, stratified by gene group. Genes are ordered according to gene distribution in the study population.

Clinical characteristic	**Dynein structure** *(DNAH5, DNAH11, DNAI1, DNAI2, ARMC4, DNAL1, DNAH9, TTC25)*, (n=171)	**Dynein assembly** *(CCDC103, DNAAF4, LRRC6, DNAAF3, DNAAF1, PIHD3, SPAG1, ZYMND10, CCDC114, DNAAF5, CFAP300)*, (n=94)	**Radial spoke/ central complex** *(RSPH4A, RSPH1, HYDIN, RSPH9, RSPH3)*, (n=50)	**N-DRC/ molecular ruler** *(CCDC39, CCDC40, CCDC65, DRC1)*, (n=68)	**Other function** *(RPGR, CCNO, MCIDAS)*, (n=13)	**All**	**p-value**
Male (%), n=396	75 (43.9)	49 (52.1)	23 (46.0)	35 (51.5)	9 (69.2)	191 (48.2)	0.226
Mean FEV_1 z-scores (SD), n=275	-1.3 (1.4)$^{+}$	-1.7 (1.5)$^{\#}$	-1.7 (1.9)	-2.5 (1.5)$^{+\#}$	-2.8 (2.2)	-1.7 (1.6)	**<0.001**
Median age at diagnosis (IQR) n=353	12 (3 to 20)	9.6 (3.1 to 16.3)	14.6 (7.8 to 18.7)	10.9 (2.2 to 15.4)	12.1 (6 to 20.4)	11.1 (4.2 to 17.8)	0.235
Neonatal respiratory distress syndrome (%), n=305	72 (55.8)	52 (73.2)	21 (52.5)	35 (67.3)	6 (46.2)	186 (61.0)	0.056
Wet cough (%), n=351	144 (95.4)	78 (95.3)	43 (93.5)	56 (93.3)	10 (76.9)	331 (94.3)	0.165
Rhinitis (%), n=349	142 (94.0)	75 (91.5)	37 (84.1)	49 (83.1)	10 (76.9)	313 (89.7)	**0.028**
Glue ear (%), n=333	93 (64.1)	45 (58.4)	34 (81.0)	32 (57.1)	8 (61.5)	214 (63.7)	0.099
Situs solitus (%), n=380	69 (42.9)	36 (39.1)	48 (100)	40 (60.6)	13 (100)	206 (54.2)	**<0.001**

N-DRC = nexin-dynein regulatory complex; SD = standard deviation; IQR = interquartile range; + # difference between groups was statistically significant (ANOVA followed by Tukey for pairwise comparisons).

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