A Study on the Genetics of Primary Ciliary Dyskinesia

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SUPPLEMENTARY MATERIALS

Table S1. PCD genes covered by the Centogene® comprehensive pulmonary disease panel (Source: https://www.centogene.com/science/centopedia/ comprehensive-pulmonary-disease-panel.html; accessed 17 September 2021)

Gene	OMIM (Gene)	Associated diseases (OMIM)
CCDC39	613798	Ciliary dyskinesia, primary, 14
CCDC40	613799	Ciliary dyskinesia, primary, 15
DNAAF1	613190	Ciliary dyskinesia, primary, 13
DNAAF2	612517	Ciliary dyskinesia, primary, 10
DNAH11	603339	Primary ciliary dyskinesia type 7, with or without situs inversus
DNAH5	603335	Primary ciliary dyskinesia type 3, with or without situs inversus
DNAH9	603330	
DNAI1	604366	Primary ciliary dyskinesia type 1, with or without situs inversus
DNAI2	605483	Primary ciliary dyskinesia type 9, with or without situs inversus
DNAL1	610062	Ciliary dyskinesia, primary, 16
NME8	607421	Ciliary dyskinesia, primary, 6
RSPH1	609314	Primary ciliary dyskinesia, 24
RSPH4A	612647	Ciliary dyskinesia, primary, 11
RSPH9	612648	Ciliary dyskinesia, primary, 12

Table S2. Details of genetic tests done

Patient	Comprehensive pulmonary disease panel	Whole (diagnostic) exome sequencing	Chromosomal Microarray	Targeted deletion/ duplication analysis	Single gene sequencing
1	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test done for DNAH1; negative result	Test not done
2	Test not done	Test done, variant in PCD-related gene detected	Test done, abnormalities in PCD-related genes not found	Test not done	Test not done
3	Test not done	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done
4	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
5	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
6	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
7	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
8	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
9	Test done, variant in PCD-related gene detected	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done
10	Test not done	Test not done	Test not done	Test not done	Test done, variant in *DNAH5* detected
11	Test done, variant in PCD-related gene detected	Test not done	Test done, duplication of exons 1-47 of *DNAH5* found	Test done for *DNAH5*; negative result	Test not done
12	Test done, variant in PCD-related gene detected	Test not done		Test not done	Test not done
13	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
14	Test done, variant in PCD-related gene detected	Test not done	Test done, abnormalities in PCD-related genes not found	Test not done	Test not done
15	Test not done	Test done, variant in PCD-related gene detected	Test done, abnormalities in PCD-related genes not found	Test not done	Test not done

16	Test not done	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test done, two variants in *DRC1* detected
17	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
18	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test done for DNAH5; negative result	Test not done
19	Test done, variant in PCD-related gene detected	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done
20	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
21	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
22	Test not done	Test not done	Test not done	Test not done	Test done, variant in *CCDC39* and variant in *DNAH5* detected
23	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
24	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
25	Test done, variant in PCD-related gene detected	Test not done	Test done, abnormalities in PCD-related genes not found	Test not done	Test not done
26	Test done, variant in PCD-related gene detected	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done
27	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
28	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
29	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
30	Test not done	Test not done	Test not done	Test not done	Test done, variant in *DNAH5* detected
31	Test not done	Test not done	Test not done	Test not done	Test done, variant in *DNAH5* detected

32	Test not done	Test not done	Test not done	Test not done	Test done, variant in *DNAH5* detected
33	Test not done	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done
34	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
35	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
36	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test done for DNAI1; negative result	Test not done
37	Test not done	Test done, variant in PCD-related gene detected	Test done, abnormalities in PCD-related genes not found	Test not done	Test not done
38	Test not done	Test not done	Test not done	Test not done	Test done, variant in *DNAH11* detected
39	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
40	Test not done	Test done, variant in PCD-related gene detected	Test done, abnormalities in PCD-related genes not found	Test not done	Test not done
41	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
42	Test not done	Test done, variant in PCD-related gene detected	Test done, abnormalities in PCD-related genes not found	Test not done	Test not done
43	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
44	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
45	Test done, variant in PCD-related gene detected	Test not done	Test done, duplication of exons 1-47 of DNAH5 found	Test not done	Test not done
46	Test not done	Test done, variant in PCD-related gene detected	Test done, abnormalities in PCD-related genes not found	Test not done	Test not done

47	Test done, variant in PCD-related gene detected	Test done, variant in PCD-related gene *not* detected	Test done, abnormalities in PCD-related genes not found	Test not done	Test not done
48	Test done, variant in PCD-related gene detected	Test done, variant in PCD-related gene *not* detected	Test not done	Test not done	Test not done
49	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
50	Test not done	Test done, varaints in PCD-related genes *not* detected	Test done, duplication of exons 1-47 of DNAH5 found	Test not done	Test not done
51	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
52	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
53	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
54	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
55	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
56	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test done for DNAH5; negative result	Test not done
57	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
58	Test done, variant in PCD-related gene detected	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done
59	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
60	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
61	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done
62	Test not done	Test not done	Test done, duplication of exons 1-47 of DNAH5 found	Test not done	Test done, variant in *DNAH5* detected
63	Test not done	Test not done	Test done, duplication of exons 1-47 of DNAH5 found	Test not done	Test not done

64	Test done, variant in PCD-related gene detected	Test not done		Test not done	Test not done
65	Test done, variant in PCD-related gene detected	Test not done	Test done, abnormalities in PCD-related genes not found	Test not done	Test not done
66	Test done, variant in PCD-related gene detected	Test not done	Test not done	Test not done	Test not done

Table S3. NCBI RefSeq accession of protein sequences used for multiple sequence alignment

Protein	Human	Chimpanzee	Mouse	Rat	Dog	Horse	Bovine	Frog	Chicken	Zebrafish
ARMC4	NP_060546.2	XP_016818326.2	XP_030106482.1	XP_008770032.1	XP_535146.3	XP_023488011.1	XP_024856406.1	XP_017950189.1	XP_003640684.3	XP_005156286.1
C1orf127	NP_001164225.1	XP_016809392.1	NP_001355764.1	XP_017449424.1	-	XP_023484158.1	-	XP_017951136.1	-	XP_021325672.1
CCDC39	NP_852091.1	XP_016797828.1	NP_080498.1	NP_001101137.1	XP_545213.3	XP_023479118.1	NP_001192985.1	NP_001072342.1	XP_422777.4	XP_001344625.2
CCDC40	NP_060420.2	XP_009431725.2	NP_001351696.1	NP_001128160.1	XP_005624081.1	XP_023507634.1	XP_010814878.1	XP_002937644.2	XP_024997485.1	NP_001258742.1
CCDC65	NP_149115.2	NP_001233475.1	NP_705738.1	NP_001014225.1	XP_534816.1	XP_001504180.1	NP_001033255.1	XP_012813228.3	XP_025001449.1	XP_005165756.1
CEP104	NP_055519.1	XP_016808323.1	NP_808341.1	NP_659550.2	XP_022274677.1	XP_023491684.1	XP_015330669.1	XP_012822790.2	XP_004947417.1	XP_005167010.1
CFAP298	NP_067077.1	NP_001337257.1	NP_080778.2	NP_001008289.1	XP_848523.1	XP_001498633.1	NP_001039872.1	NP_001086851.1	NP_001006258.1	NP_956382.1
DNAAF1	NP_848547.4	XP_016785762.2	NP_080924.1	NP_001014176.1	XP_536764.3	XP_023493171 .1	NP_001030422.2	XP_004913593.2	-	NP_001306060.1
DNAAF2	NP_060609.2	XP_509930.3	NP_081545.3	NP_001014219.3	XP_005623972.1	XP_023480449.1	NP_001069492.2	NP_001072474.1	XP_421456.5	NP_001028272.1
DNAAF3	NP_001243643.1	XP_016789630.1	NP_001028720.1	NP_001258044.1	XP_005616232.1	XP_014586276.1	XP_005219742.3	XP_012822876.2		XP_021326065.1
DNAAF5	NP_060272.3	XP_024213446.1	NP_001074734.1	NP_001128329.1	XP_548719.2	XP_023510815.1	XP_010818002.2	XP_002941855.1	XP_414755.2	XP_009302392.3
DNAH1	NP_056327.4	XP_016796718.2	NP_001028840.1	NP_001028827.2	XP_022262349.1	XP_023476087.1	XP_024839013.1	XP_012816961.1	XP_025010454.1	XP_009304459.3
DNAH11	NP_001264044.1	XP_024213530.1	NP_034190.3	XP_017458807.1	XP_022283175.1	XP_023495115.1	XP_027395750.1	XP_017950422.1	XP_025003205.1	XP_009290539.1
DNAH5	NP_001360.1	XP_016808445.2	NP_579943.3	XP_008773325.1	XP_022269819.1	XP_023481602.1	XP_015314607.2	XP_012820905.1	XP_025003476.1	XP_021322524.1
DNAH6	NP_001361.1	XP_515578.5	NP_001158141.1	XP_017448573.1	XP_022260075.1	XP_001916921.2	XP_024855197.1	XP_012811375.1	-	XP_021326862.1
DNAH8	NP_001193856.1	XP_016810881.2	NP_038839.2	XP_008773178.1	XP_022281494.1	XP_023480644.1	XP_024839646.1	-	XP_025004702.1	-
DNAI1	NP_036276.1	XP_016816249.1	NP_780347.2	NP_001019513.1	XP_022281224.1	XP_023483256.1	NP_001033231.1	-	XP_003643013.1	-
DNAI2	NP_075462.3	XP_003953226.2	NP_001030050.2	NP_001007727.1	XP_540403.3	XP_014594482.1	XP_002696267.2	XP_002935429.1	XP_415701.2	XP_005156459.1
DRC1	NP_659475.2	NP_001233391.1	NP_001028632.1	NP_001007010 .1	XP_532897.3	XP_014586742.2	NP_001032680.1	XP_002938220.2	XP_420016.3	NP_001120940.1
HYDIN	NP_001257903.1	XP_009429461.3	NP_766504.3	XP_017443416.1	XP_022274932.1	XP_023493062.1	XP_024834777.1	XP_012817094.1	NP_001152843.1	XP_017207419.1
NME8	NP_057700.3	XP_009451181.2	NP_853622.2	XP_006254150.1	XP_013976321.1	XP_001492951.3	XP_005205470.1	-	XP_426021.3	XP_021334262.1
OFD1	NP_003602.1	XP_024209005.1	NP_803178.2	NP_001100431.1	XP_537958.3	XP_023489673.1	NP_001179566.2	XP_002933857.3	XP_416831.2	NP_001306137.1
RSPH1	NP_543136.1	XP_009434401.3	NP_079566.1	NP_001012176.1	XP_022268910.1	XP_001491109.1	XP_005202079.1	NP_001088789.1	XP_416745.1	-
RSPH4A	NP_001010892.1	XP_016811695.1	NP_001156429.1	NP_001101099.2	XP_541210.2	XP_001504187.1	XP_002690133.2	-	-	-
RSPH9	NP_689945.2	XP_016811076.1	NP_083614.1	XP_006244600.1	XP_005627453.1	XP_023480767.1	NP_001039732.1	NP_001005021.1	XP_015139198.1	NP_001025284.1
ZMYND10	NP_056980.2	NP_001233432.1	XP_017168594.1	NP_001004284.1	XP_533818.1	XP_023476145.1	NP_001035638.1	XP_018112468.1	XP_015148255.1	NP_956691.1

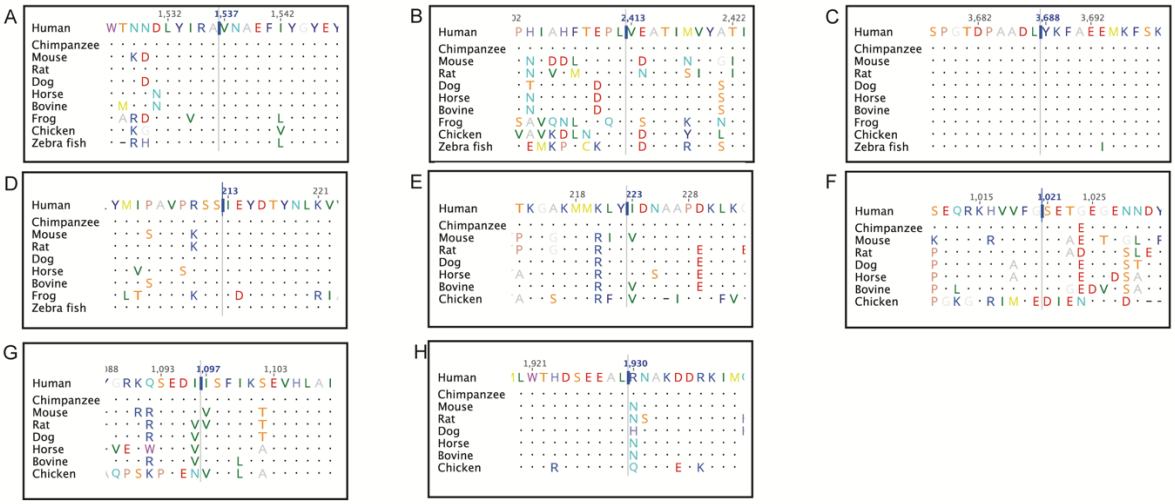

Figure S1. Twenty-one amino acid regions, centered around missense/nonsense variations, obtained from a multiple sequence alignment of dynein axonemal heavy chain proteins (other than DNAH5 and DNAH11). DNAH1 protein alignment from human, chimpanzee, mouse, rat, dog, horse, bovine, frog, and zebra fish are shown in A-C – **A**) V1537M (c.4609G>A); **B**) Vl2413A (c.7238T>C); **C**) Y3688C (c.11063A>G). **D**) DNAH6 protein alignment from human, chimpanzee, mouse, rat, dog, horse, bovine, frog, and zebra fish for I213V (c.637A>G). DNAH8 protein alignment from human, chimpanzee, mouse, rat, dog, horse, bovine, frog, and chicken are shown in E-I – **E**) I223T (c.668T>C); **F**) S1021G (c.3061A>G); **G**) I1097V (c.3289A>G); **H**) R1930H (c.5789G>A).

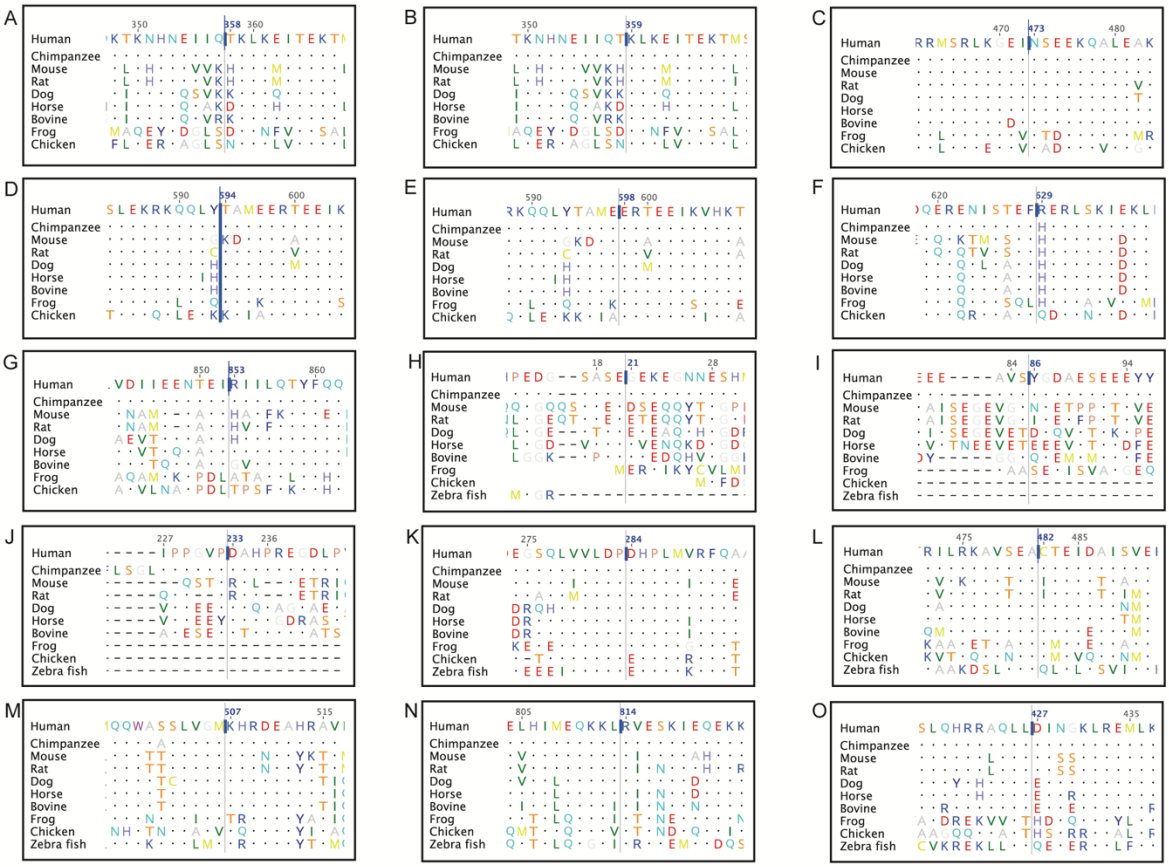

Figure S2. Twenty-one amino acid regions, centered around missense/nonsense variations, obtained from a multiple sequence alignment of coiled-coil domain-containing (CCDC) proteins. CCDC39 protein alignment from human, chimpanzee, mouse, rat, dog, horse, bovine, frog, and chicken are shown in A-G – **A**) T358I (c.1073C>T); **B**) K359T (c.1076A>C); **C**) N473D (c.1417A>G); **D**) T594I (c.1781C>T); **E**) E598Ter (c.1792G>T); **F**) R629C (c.1885C>T); **G**) R853C (c.2557C>T). CCDC40 protein alignment from human, chimpanzee, mouse, rat, dog, horse, bovine, frog, chicken, and zebra fish are shown in H-N – **H**) G21V (c.62G>T); **I**) Y86C (c.257A>G); **J**) D233N (c.697G>A); **K**) D284H (c.850G>C); **L**) C482Y (c.1445G>A); **M**) K507M (c.1520A>T); **N**) R814Ter (c.2440C>T). CCDC65 protein alignment from human, chimpanzee, mouse, rat, dog, horse, bovine, frog, chicken, and zebra fish are shown in O – **O**) D427G (c.1280A>G).

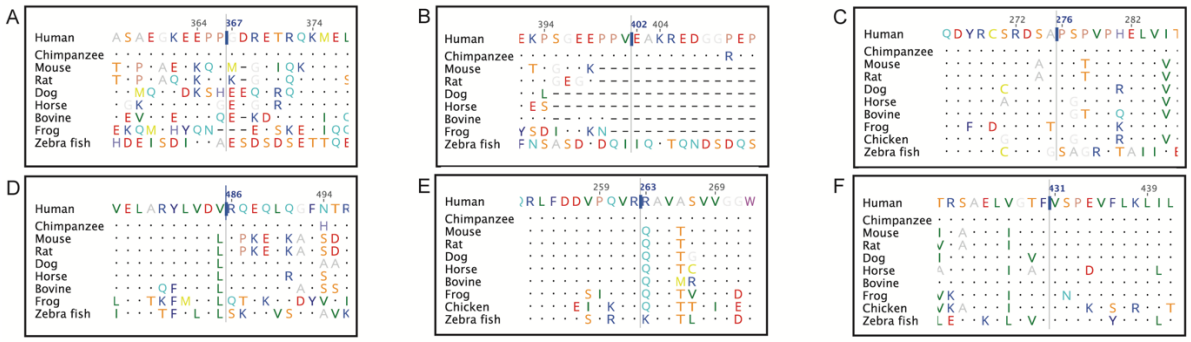

Figure S3. Twenty-one amino acid regions, centered around missense/nonsense variations, obtained from a multiple sequence alignment of dynein axonemal assembly factor (DNAAF) proteins. Protein alignment performed using sequences from human, chimpanzee, mouse, rat, dog, horse, bovine, frog, chicken, and zebra fish, where available. **A**) DNAAF1, G367R (c.1099G>A); **B**) DNAAF1, E402V (c.1205A>T); **C**) DNAAF2, P276R (c.827C>G); **D**) DNAAF3, R486W (c.1456C>T); **E**) DNAAF5, R263Q (c.788G>A); **F**) DNAAF5, V431A (c.1292T>C).

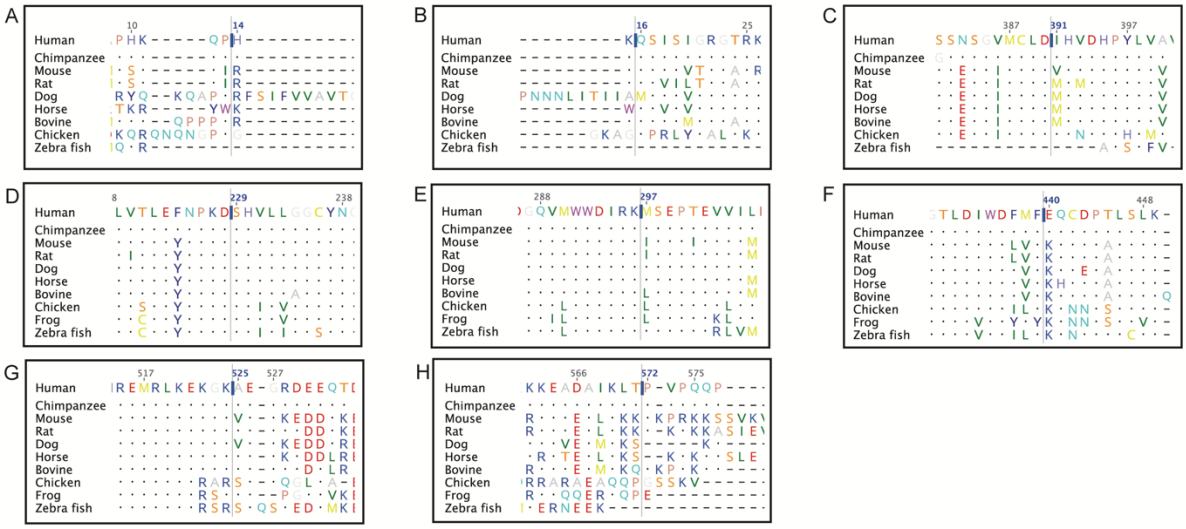

Figure S4. Twenty-one amino acid regions, centered around missense/nonsense variations, obtained from a multiple sequence alignment of dynein axonemal intermediate chain (DNAI) proteins. DNAI1 protein alignment from human, chimpanzee, mouse, rat, dog, horse, bovine, chicken, and zebra fish are shown in A-C – **A**) H14Y (c.40C>T); **B**) Q16R (c.47A>G); **C**) I391M (c.1173C>G). DNAI2 protein alignment from human, chimpanzee, mouse, rat, dog, horse, bovine, frog, chicken, and zebra fish are shown in D-H – **D**) S229A (c.685T>G); **E**) M297I (c.891G>A); **F**) E440Q (c.1318G>C); **G**) A525V (c.1574C>T); **H**) P572L (c.1715C>T).

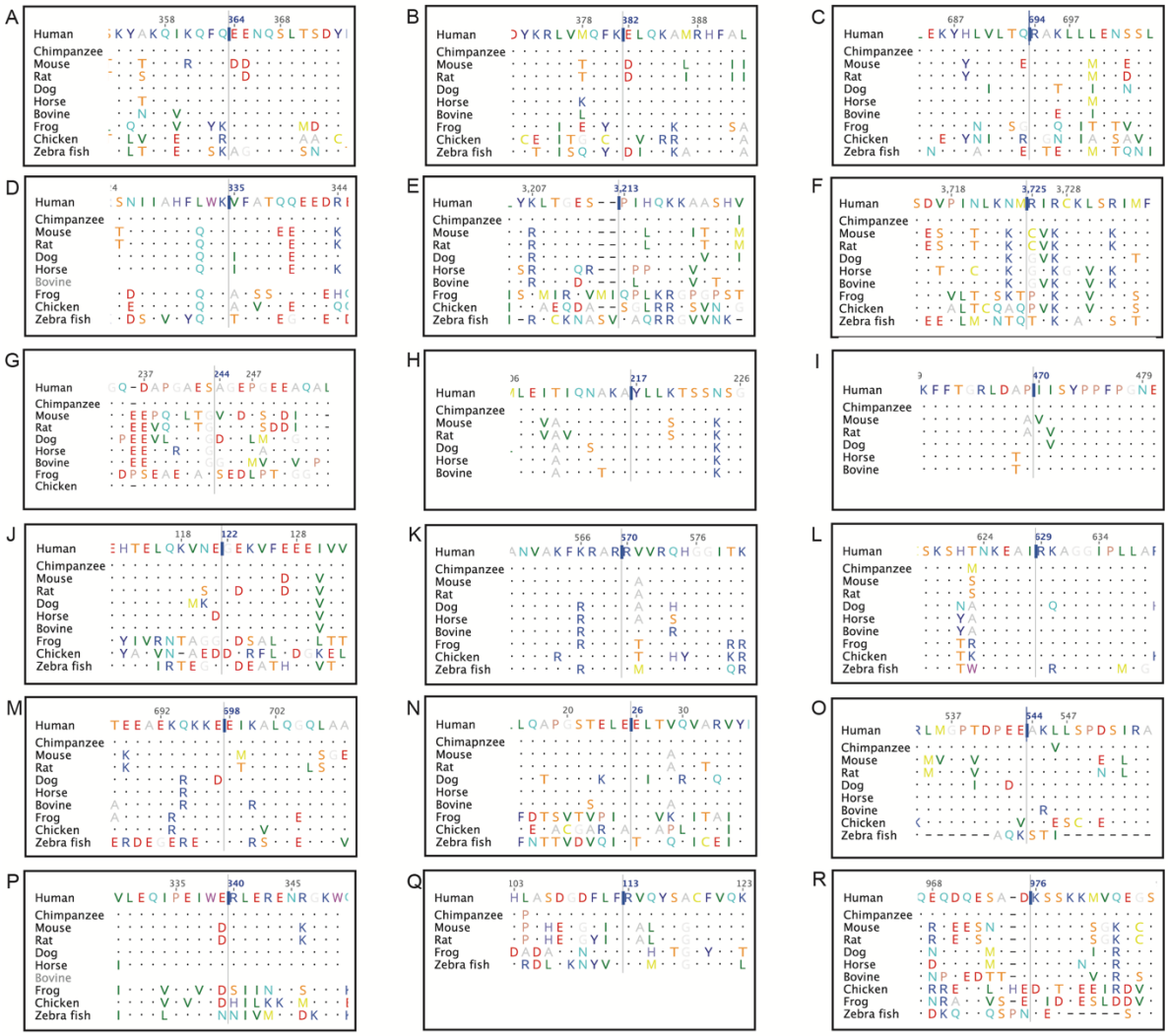

Figure S5. Twenty-one amino acid regions, centered around missense/nonsense variations, obtained from a multiple sequence alignment of proteins from human, chimpanzee, mouse, rat, dog, horse, bovine, frog, chicken, and zebra fish, where available. **A**) DRC1, E364K (c.1090G>A); **B**) DRC1, E382D (c.1146G>C); **C**) DRC1, R694T (c.2081G>C); **D**) HYDIN, V335L (c.1003G>T); **E**) HYDIN, P3213R (c.9638C>G); **F**) HYDIN, R3725W (c.11173C>T); **G**) RSPH1, A244T (c.730G>A); **H**) RSPH4A, Y217S (c.650A>C); **I**) RSPH4A, I470M (c.1410C>G); **J**) RSPH9, G122D (c.365G>A); **K**) ARMC4, R570Q (c.1709G>A); **L**) ARMC4, R629H (c.1886G>A); **M**) CEP104, E698K (c.2092G>A); **N**) CFAP298, E26A (c.77A>C); **O**) NME8, A544T (c.1630G>A); **P**) ZYMND10, R340Q (c.1019G>A); **Q**) C1orf127, R113Ter (c.337C>T).