Title: Primary Ciliary Dyskinesia *GeneReview* – Table 2

Authors: Zariwala MA, Knowles MR, Leigh MW

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Note: The following information is provided by the authors and has not been reviewed by *GeneReviews* staff.

Table 2. Ciliary Ultrastructural Findings by Mutated Gene [0] (See footnotes for details defining relative confidence levels.)

Gene	Locus Name	Ciliary Structure			
		Dynein Arms		Radial spokes/Central Pair	Axonemal Organization/Nexin-Dynein Regulatory Complex
		Outer	Inner		
DNAI1	CILD1	Abnormal [1*]	Normal [1*]	Normal [1]	Normal [1]
DNAAF3	CILD2	Abnormal [2*]	Abnormal [2*]	Normal [2]	Normal [2]
DNAH5	CILD3	Abnormal [3*]	Normal [3*]	Normal [3]	Normal [3]
HYDIN	CILD5	Normal [4*]	Normal [4*]	Normal [4]	Normal [4*]
NME8 (TXNDC3)	CILD6	66% abnormal [5]	Normal [5]	Normal [5]	Normal [5]
DNAH11	CILD7	Normal [6*]	Normal [6]	Normal [6]	Normal [6]
DNAI2	CILD9	Abnormal [7*]	Normal [7*]	Normal [7]	Normal [7]
DNAAF2 (*C14orf104, KTU, PF13*)	CILD10	Abnormal [8*]	Abnormal [8*]	Normal [8]	Normal [8]
RSPH4A	CILD11	Normal [9]	Normal [9]	Defective [9*]	Variable [9]
RSPH9	CILD12	Normal [10]	Normal [10]	Defective [10*]	Variable [10]
DNAAF1 (*LRRC50*)	CILD13	Abnormal [11*]	Abnormal [11*]	Normal [11]	Normal [11]
CCDC39	CILD14	Normal [12*]	Abnormal [12*]	Variable [12]	Abnormal [12*]
CCDC40	CILD15	Normal [13*]	Abnormal [13*]	Variable [13]	Abnormal [13*]
DNAL1	CILD16	Abnormal [14]	Normal [14]	Normal [14]	Normal [14]
CCDC103	CILD17	Abnormal [15*]	Normal [15*]	Normal [15]	Normal [15]
HEATR2	CILD18	Abnormal [16*]	Abnormal [16]	Normal [16]	Normal [16]
LRRC6	CILD19	Abnormal [17*]	Abnormal [17*]	Normal [17]	Normal [17]
CCDC114	CILD20	Abnormal [18*]	Normal [18*]	Normal [18]	Normal [18]
DRC1	CILD21	Normal [19*]	Normal [19*]	undefined	Abnormal [19*]
ZMYND10	CILD22	Abnormal [20*]	Abnormal [20*]	Normal [20]	Normal [20]
ARMC4	CILD23	Abnormal [21*]	Normal [21*]	Normal [21]	Normal [21]
RSPH1	CILD24	Normal [22*]	Normal [22*]	Abnormal [22*]	variable

DYX1C1	CILD25	Abnormal [23*]	Abnormal [23*]	Normal [23]	Normal [23*]
C21orf59	CILD26	Abnormal [24*]	Abnormal [24*]	Normal [24]	Normal [24]
CCDC65	CILD27	Normal [25]	Normal [25]	undefined	Abnormal [25*]
SPAG1	CILD28	Abnormal [26*]	Abnormal [26*]	Normal [26]	Normal [26]
CCNO	CILD29	Normal [27*]	undefined	undefined	Normal [27*]
CCDC151	CILD30	Abnormal [28*]	Normal [28*]	Normal [28]	Normal [28*]
MCIDAS		Abnormal [29*]	undefined	undefined	Abnormal [29*]
RSPH3		Normal [30]	Normal [30*]	Abnormal [30*]	variable
DNAH1 [31]		unknown	unknown	unknown	unknown
DNAH8		unknown	unknown	unknown	unknown

0 listed in order by chromosome locus

* denotes ciliary ultrastructural analysis confirmed by immunofluorescent staining as well.

1. Analysis by ciliary ultrastructure [Hornef et al 2006] and immunofluorescent staining [Fliegauf et al 2005, Loges et al 2008] revealed outer dynein arm defects from persons with biallelic pathogenic variants in *DNAI1*.

2. Analysis by ciliary ultrastructure and immunofluorescent staining revealed outer+inner dynein arm defects from persons with biallelic pathogenic variants in *DNAAF3* [Mitchison et al 2012].

3. Analysis by ciliary ultrastructure and immunofluorescent staining revealed outer dynein arm defects from persons with biallelic pathogenic variants in *DNAH5* [Fliegauf et al 2005, Hornef et al 2006].

4. Persons with biallelic pathogenic variants in *HYDIN* have defective C2b projections of central pair that is not detectable using routine ciliary ultrastructure analysis; thus, they exhibit normal cilia on cross-section analysis with a very rare occurrence of 9+0 or 8+1 central microtubular structure. Immunofluorescent staining confirmed normal ciliary ultrastructure [Olbrich et al 2012].

5. Only one patient with pathogenic variant identified who had heterogeneous ultrastructure including normal cilia and two thirds of cilia with defective ODA

6. Although *DNAH11* encodes an outer dynein arm protein, individuals with biallelic pathogenic variants have normal dynein arms on ultrastructural examination [Bartoloni et al 2002, Schwabe et al 2008, Knowles et al 2012].

7. Analysis by ciliary ultrastructure and immunofluorescent staining revealed outer dynein arm defects from persons with biallelic pathogenic variants in *DNAI2* [Loges et al 2008].

8. Analysis by ciliary ultrastructure and immunofluorescent staining revealed outer+inner dynein arm defects from persons with biallelic pathogenic variants in *DNAAF2* [Omran et al 2008].

9. Analysis by ciliary ultrastructure from persons with biallelic pathogenic variants in *RSPH4A* revealed central pair defects characterized by absence of one or both central pair, supernumerary central pair, off-center central pair, translocation of outer doublet to the center, eccentric outer doublet, and extra microtubules outside the doublet ring [Castleman et al 2009, Daniels et al 2013]. Immunofluorescent staining revealed absence of radial spoke head, but presence of radial spoke stalk [Frommer et al 2015]. The prevalence of normal axonemal organization varies greatly on electron micrographs.

10. Analysis of ciliary ultrastructure from a person with biallelic pathogenic variants in *RSPH9* revealed central pair abnormalities, but in another case cilia appeared to be normal [Castleman et al 2009]. Immunofluorescent staining revealed absence of radial spoke head, but presence of radial spoke stalk [Frommer et al 2015]. The prevalence of normal axonemal organization varies greatly on electron micrographs.

11. Analysis by ciliary ultrastructure and immunofluorescent staining revealed outer+inner dynein arm defects from persons with biallelic pathogenic variants in *DNAAF1* [Loges et al 2009].

12. Analysis by ciliary ultrastructure and immunofluorescent staining [Merveille et al 2011] revealed inner dynein arm defects with axonemal disorganization from persons with biallelic pathogenic variants in *CCDC39*. Axonemal disorganization includes eccentric central pair, abnormal radial spokes and nexin links, reduced number of inner dynein arms, and displacement of the outer doublet [Merveille et al 2011, Blanchon et al 2012, Antony et al 2013]. The prevalence of central pair/radial spokes varies greatly on electron micrographs.

13. Analysis by ciliary ultrastructure and immunofluorescent staining revealed inner dynein arm defects with axonemal disorganization from persons with biallelic pathogenic variants in *CCDC40*. Axonemal disorganization includes eccentric central pair, abnormal radial spokes and nexin links, reduced number of inner dynein arms, and displacement of the outer doublet [Becker-Heck et al 2011, Blanchon et al 2012, Antony et al 2013]. The prevalence of central pair/radial spokes varies greatly on electron micrographs.

14. Analysis by ciliary ultrastructure from a person with biallelic pathogenic variants in *DNAL1* showed defective outer dynein arm, and other ciliary structures appeared normal [Mazor et al 2011]. Immunofluorescent data not available.

15. Ciliary ultrastructure analysis revealed outer+inner dynein arm defects from persons with biallelic pathogenic variants in *CCDC103* [Panizzi et al 2012]; however, other cases showed outer dynein arm defects. Immunofluorescent staining using antibodies specific for outer dynein arms confirmed outer dyenin arms defects, but antibodies specific for inner dynein arm showed presence of inner dynein arms in persons with biallelic pathogenic variants [Panizzi et al 2012].

16. Ciliary ultrastructure analysis shows outer+inner dynein arm defects from a person with biallelic pathogenic variants in *HEATR2.* Immunofluorescent staining using antibodies specific for outer dynein arms confirmed outer dynein arms defects [Horani et al 2012]. However, inner dynein arm specific antibody showed presence of staining, suggesting either inner dynein arms is partially present or the protein is mislocalized [Horani et al 2012].

17. Analysis by ciliary ultrastructure analysis and immunofluorescent staining revealed outer+inner dynein arm defects from persons with biallelic pathogenic variants in *LRRC6* [Kott et al 2012, Zariwala et al 2013].

18. Analysis by ciliary ultrastructure and immunofluorescent staining revealed outer dynein arm defects from persons with biallelic pathogenic variants in *CCDC114* [Knowles et al 2013b, Onoufriadis et al 2013].

19. Ultrastructural analysis revealed most cilia appeared normal but in depth observations showed subtle alternation of nexin-dynein regulatory complex which was confirmed by immunofluorescent staining from a person with biallelic pathogenic variant in *DRC1* [Wirschell et al 2013].

20. Analysis by ciliary ultrastructure and immunofluorescent staining revealed outer+inner dynein arm defects from persons with biallelic pathogenic variants in *ZMYND10* [Zariwala et al 2013, Moore et al 2013].

21. Analysis by ciliary ultrastructure and immunofluorescent staining revealed outer dynein arm defects from persons with biallelic pathogenic variants in *ARMC4* [Hjeij et al 2013].

22. Analysis of ciliary ultrastructure from persons with biallelic pathogenic variants in *RSPH1* revealed normal cilia in some sections but central pair abnormalities in others [Kott et al 2013, Knowles et al 2014]. Immunofluorescent staining revealed absence of radial spoke head but, presence of radial spoke stalk [Frommer et al 2015]. The prevalence of normal axonemal organization varies greatly on electron micrographs.

23. Analysis by ciliary ultrastructure and immunofluorescent staining revealed outer+inner dynein arm defects from person with biallelic pathogenic variants in *DYX1C1* [Moore et al 2013, Zariwala et al 2013].

24. Analysis by ciliary ultrastructure and immunofluorescent staining revealed outer+inner dynein arm defects from persons with biallelic pathogenic variants in *C21orf59* [Austin-Tse et al 2013].

25. Ultrastructural analysis [Austin-Tse et al 2013] revealed most cilia appeared normal but 5-15% had microtubular disorganization from person with biallelic pathogenic variants in *CCDC65*. Additionally, immunofluorescent staining [Horani et al 2013] revealed nexin-dynein regulatory complex defects from a person with biallelic pathogenic variant in *CCDC65*.

26. Analysis by ciliary ultrastructure and immunofluorescent staining revealed outer+inner dynein arm defects from persons with biallelic pathogenic variants in *SPAG1* [Knowles et al 2013c].

27. Persons harboring biallelic pathogenic variants in *CCNO* had reduced number of multiple motile cilia. Immunofluorescent staining for the remaining residual cilia revealed structurally normal outer dynein arm and dynein regulatory complex [Wallmeier et al 2014].

28. Analysis by ciliary ultrastructure and immunofluorescent staining revealed outer dynein arm defects from persons with biallelic pathogenic variants in *CCDC151* [Hjeij et al 2014].

29. Pathogenic variants in *MCIDAS* lead to reduced generation of multiple motile cilia by transmission electron microscopic and/or immunofluorescent analysis. This was confirmed by in vitro ciliogenesis. Immunofluorescent analysis of the residual respiratory cilia from affected individuals, revealed absence of multicilin from differentiated and undifferentiated cells, as well as absence of motility-related proteins (DNAH5 and CCDC39); thus, residual cilia are predicted to be dysfunctional. Similarly, staining was also reduced/absent for CCNO (required for centriole amplification and localization and associated with PCD) and FoxJ1 (protein for the transcriptional control of motility

protein) suggesting that multicilin, CCNO, and FoxJ1 are on the same pathway and that multicilin acts upstream of CCNO and FoxJ1 [Boon et al 2014].

30. Analysis of ciliary ultrastructure from persons with biallelic pathogenic variants in RSPH3 revealed normal cilia in some sections but central pair abnormalities in others. Immunofluorescent staining revealed presence of the spoke head and neck, and absence of the spoke stalk [Jeanson et al 2015].

31. Ciliary ultrastructure analysis was not performed in persons with PCD with biallelic missense variants in *DNAH1* [Imtiaz et al 2015]. However, analysis of sperm flagella from males with homozygous DNAH1 pathogenic variants and non-syndromic infertility (but not PCD) by ultrastructure and immunofluorescent staining revealed inner dynein arm defects with axonemal disorganization [Ben Khelifa et al 2014]. Axonemal disorganization includes eccentric central pair, abnormal radial spokes and nexin links, reduced number of inner dynein arms, and displacement of the outer doublet.

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