Title: Primary Ciliary Dyskinesia *GeneReview* – Less Commonly Mutated Genes

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

Details on the less commonly mutated genes (i.e., account for <1% of PCD) from Table 1B. Note: Genes are ordered by locus name.

DNAAF3 (CILD2)

Gene structure. *DNAAF3* comprises 12 exons.

Pathogenic variants. See Table 20. Three pathogenic variants have been reported in *DNAAF3*. All are homozygous and found in families of either Pakistani or Arab ancestry [Mitchison et al 2012].

Table 20. *DNAAF3* Variants

DNA Nucleotide Change (Alias) [1]	Protein Amino Acid Change (Alias) [1]	Reference Sequences
c.386T>C (323T>C)	p.Leu120Pro (Leu108Pro)	NM_001256714.1 NP_001243643.1
c.469C>T (406C>T)	p.Arg157Ter (Arg136Ter)	
c.825dupT (762_763insT)	p.Val276CysfsTer12 (Val255CysfsTer12)	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

Normal gene product. *DNAAF3* encodes dynein axonemal assembly factor 3, a protein of 588-amino acids. It does not have any characterized structural motifs or similarities to the known protein families and is predicted to function in axonemal dynein assembly [Mitchison et al 2012].

Abnormal gene product. Pathogenic variants in *DNAAF3* lead to defective outer+inner dynein arms [Mitchison et al 2012].

HYDIN (CILD5)

Gene structure. *HYDIN* comprises 86 exons.

Intrachromosomal duplication during human evolution led to *HYDIN2*, a pseudogene at chromosomal locus 1q21.1 that has identical intron-exon structure consisting of exons 6-83 complicating molecular testing [Olbrich et al 2012].

Pathogenic variants. See Table 21. Two truncating *HYDIN* pathogenic variants are described: a nonsense pathogenic variant from a kindred with PCD from the Faroe Islands and the splice acceptor-site pathogenic variant c.3985G>T in a German family.

Expression analysis of the c.3985G>T splice site pathogenic variant revealed insertion of 47 bp from the 3'end of intron 26 between exons 26 and 27 (r.3985-47_3985-1ins) resulting in premature protein truncation [Olbrich et al 2012].

Table 21. *HYDIN* Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.922A>T	p.Lys308Ter	NM_001270974.1 NP_001257903.1
c.3985G>T r.3985-47_3985-1ins	--	

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Normal gene product. *HYDIN* encodes the 5121 amino acid hydrocephalus-inducing protein.

Abnormal gene product. Pathogenic variants in *HYDIN* lead to defective C2b projection in the central microtubule pair that cannot be detected by routine ciliary ultrastructure analysis [Olbrich et al 2012].

NME8 (previously *TXNDC3*) (CILD6)

Gene structure. *NME8* has a full-length transcript of 2327 nucleotides and 18 exons.

Pathogenic variants. See Table 22. One person with *NME8*-related PCD has been reported. Duriez et al [2007] identified a heterozygous nonsense pathogenic variant (p.Leu426Ter) in *trans* configuration with an intronic c.271-27C>T variant which is found in 1% of the general population.

The c.271-27C>T variant affects splicing and alters the ratio of the full-length transcript and a shorter variant isoform (with an in-frame deletion of exon 7, termed variant TXNDC3d7) [Duriez et al 2007]. The TXNDC3d7 allele (see **Abnormal gene product**) is considered pathogenic in the presence of the nonsense pathogenic variant on the other allele.

Table 22. *NME8* Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.1277T>A	p.Leu426Ter	NM_016616.4 NP_057700.3
c.271-27C>T	--	

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Normal gene product. Thioredoxin domain-containing protein 3 is a member of the large family of thioedoxins, enzymatic proteins that function as disulfide reductases. The full-length transcript of *NME8* encodes a protein of 588 amino acid residues. About 1% of *NME8* alleles encode a shorter isoform resulting from the in-frame deletion of exon 7 in the transcript variant TXNDC3d7 [Duriez et al 2007].

Abnormal gene product. The TXNDC3d7 isoform lacks part of the thioredoxin domain, rendering it nonfunctional. However, this isoform showed slightly stronger binding to microtubules compared to the full-length isoform, suggesting functional significance. Ultrastructural analysis of respiratory cilia from the affected individual with the nonsense pathogenic variant and the c.271-27C>T intronic variant revealed a combination of normal dynein arms and defective outer dynein arms [Duriez et al 2007].

RSPH9 (CILD12)

Gene structure. *RSPH9* comprises five exons.

Pathogenic variants. See Table 23. At least five pathogenic variants in *RSPH9* have been described. One pathogenic variant, p.Lys268del, caused an in-frame deletion of one amino acid in two unrelated Bedouin families [Castleman et al 2009].

Table 23. *RSPH9* Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.804_806delGAA	p.Lys268del	NM_152732.3 NP_689945.2

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Normal gene product. *RSPH9* encodes radial spoke head protein 9 homolog, a 276-amino acid protein which regulates dynein-induced motility and governs axonemal waveform motion [Castleman et al 2009].

Abnormal gene product. Ultrastructural analysis from one family with PCD revealed a mixture of 9+2 and 9+0 microtubular configuration, while the other family had normal dynein arm structure [Castleman et al 2009].

DNAL1 (CILD16)

Gene structure. *DNAL1* comprises eight exons.

Pathogenic variants. See Table 24. The missense pathogenic variant p.Asn150Ser was identified in two unrelated Bedouin families. The parents of the probands were carriers. The allele frequency in control chromosome from Bedouins was 0.004 (1 of 248 chromosomes analyzed) [Mazor et al 2011].

Table 24. *DNAL1* Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.449A>G	p.Asn150Ser	NM_031427.3 NP_113615.2

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Normal gene product. *DNAL1* encodes the dynein axonemal light chain 1 protein of outer dynein arms. It is a 190-amino acid protein. It is a member of leucine-rich-repeat (LRR) subclass defined by SDS22+ (which contains 22 residue repeats). Co-immunoprecipitation assay showed that DNAL1 interacts with DNAH5 [Horvath et al 2005].

Abnormal gene product. The p.Asn150Ser pathogenic variant in *DNAL1* causes outer dynein arm defects, as well as instability and reduced levels of the mutant DNAL1 protein [Mazor et al 2011].

HEATR2 (CILD18)

Gene structure. *HEATR2* comprises 13 exons.

Pathogenic variants. See Table 25. One missense *HEATR2* pathogenic variant is described in an Amish kindred [Horani et al 2012].

Table 25. *HEATR2* Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.2384T>C	p.Leu795Pro	NM_017802.3 NP_060272.3

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Normal gene product. *HEATR2* encodes heat repeat-containing 2, a protein of 855 amino acids that belongs to a family of ten uncharacterized proteins. The HEAT repeat is related to the armadillo/beta-catenin-like repeats found in many eukaryotes and prokaryotes. In addition, immunofluorescent analysis from a healthy person showed that HEATR2 is present in the cytoplasm of ciliated cells [Kott et al 2012].

Abnormal gene product. Biallelic pathogenic variants in *HEATR2* lead to defective outer and inner dynein arms detected by ciliary ultrastructural analysis. In addition HEATR2 protein is absent from the cytoplasm of ciliated cells from affected individuals [Kott et al 2012].

DRC1 (CILD21)

Gene structure. *DRC1* comprises 17 exons.

Pathogenic variants. See Table 26. Two homozygous nonsense variants p.Lys686Ter (one family) and p.Gln118Ter (two families) have been reported in *DRC1* (*CCDC164*) [Wirschell et al 2013].

Table 26. *DRC1* Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.352C>T	p.Lys686Ter	NM_145038.2 NP_659475.2
c.2056A>T	p.Gln118Ter	

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Normal gene product. *DRC1* encodes the 740-amino acid protein containing a C terminus coiled-coil domain and 3 additional coiled-coil domains at N terminus. The assembly of nexin-dynein regulatory complex is dependent on the DRC1 subunit [Wirschell et al 2013].

Abnormal gene product. The majority of cilia from individuals with pathogenic variants in *DRC1* had normal ultrastructure by electron microscopy; however, a few cilia showed subtle defects of the nexin-dynein regulatory complex as well as beat frequency but reduced bending amplitude [Wirschell et al 2013].

DNAAF4 (previously *DYX1C1*) (CILD25)

Gene structure. *DNAAF4* comprises ten exons.

Pathogenic variants. Pathogenic variants in *DNAAF4* were found in 10 of 106 unrelated families in which the cilia had defective outer plus inner dynein arms. Total of nine pathogenic alleles were observed comprising eight truncating (four nonsense, three frameshift, and one splice site) variants and one large 3549-bp deletion that includes exon 7. This deletion was also observed in an affected individual of Irish Traveller ancestry [Casey et al 2015].

Normal gene product. *DNAAF4* encodes the 420-amino acid cytoplasmic protein dyslexia susceptibility 1 candidate gene 1 protein, with three tetratricopeptide repeat (TPR) domains; it interacts with another cytoplasmic dynein pre-assembly factor, DNAAF2 [Tarkar et al 2013].

Abnormal gene product. Pathogenic variants in *DNAAF4* lead to defective outer and inner dynein arms and immotile cilia [Tarkar et al 2013].

C21orf59 (CILD26)

Gene structure. *C21orf59* comprises seven exons.

Pathogenic variants. See Table 27. Three truncating pathogenic variants in *C21orf59* have been reported (p.Tyr245Ter, p.Arg98Ter and c.792_795delTTTA). p.Tyr245Ter was identified in three of four families studied, two of whom were of Ashkenazi Jewish

descent [Austin-Tse et al 2013]. The carrier frequency of this variant was found to be 0.48% in controls of Ashkenazi Jewish descent [Fedick et al 2015].

Table 27. *C21orf59* Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.292C>T	p.Arg98Ter	NM_021254.2 NP_067077.1
c.735C>G	p.Tyr245Ter	
c.792_795delTTTA	p.Tyr264Ter	

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Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *C21orf59* encodes a 290-amino acid protein that contains coiled-coiled and DUF2870 domains. C21ORF59 was shown to be a flagellar matrix protein by biochemical analysis of FBB18 (ortholog of C21orf59) in *Chlamydomonas* [Austin-Tse et al 2013].

Abnormal gene product. Pathogenic variants in *C21orf59* lead to outer plus inner dynein arm defects and immotile cilia. Knock-down of c21orf59 in zebrafish and planaria blocked outer dynein arm assembly [Austin-Tse et al 2013].

CCDC65 (CILD27)

Gene structure. *CCDC65* comprises eight exons.

Pathogenic variants. A c.876_877delAT (p.Ile293ProfsTer2) pathogenic variant has been identified in multiple individuals of Ashkenazi Jewish descent [Austin-Tse et al 2013, Horani et al 2013]. Carrier frequency of this variant was found to be 0.29% in controls of Ashkenazi Jewish descent [Fedick et al 2015].

Table 28. *CCDC65* Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.876_877delAT	p.Ile293ProfsTer2	NM_033124.4 NP_149115.2

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *CCDC65* encodes the 484-amino acid protein containing coiled-coil domain and motifs containing phosphorylation, N-glycosylation and N-myristoylation sites [Horani et al 2013]. CCDC65 is expressed in the cytoplasm and axoneme of airway epithelial cells [Horani et al 2013]. CCDC65 is a part of the nexin dynein regulatory complex (N-DRC) that is important for regulating dynein activity and maintaining outer doublet alignment and microtubule bending.

Abnormal gene product. Pathogenic variants in *CCDC65* lead to very subtle changes in ciliary ultrastructure which may be scored as normal; however, the cilia are

hyperkinetic but stiff [Austin-Tse et al 2013, Horani et al 2013]. GAS8 (an integral part of N-DRC) is absent from airway epithelial cells in affected individuals [Horani et al 2013].

CCNO (CILD29)

Gene structure. *CCNO* comprises three exons.

Pathogenic variants. See Table 29. Pathogenic variants in *CCNO* were found in 10 of 54 unrelated families with inadequate cilia on biopsy. None of the affected individuals displayed situs abnormalities. A total of seven pathogenic variants were observed which included six truncating alleles (c.248_252dup, c.258_262dup, c.263_267dup, c.481_482delCT, c.926delC, p.Gln321Ter) and one missense allele (p.His239Arg) [Wallmeier et al 2014]. The c.258-262dup was identified in an affected sib-pair of Irish Traveller ancestry [Casey et al 2015].

Table 29. *CCNO* Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.248_252dupTGCCC	p.Gly85CysfsTer11	NM_021147.3 NP_066970.3
c.258_262dupGGCCC	p.Gln88ArgfsTer8	
c.263_267dupAGCCC	p.Val90SerfsTer6	
c.481_482delCT	p.Leu161GlyfsTer73	
c.716A>G	p.His239Arg	
c.926delC	p.Pro309ArgfsTer18	
c.961C>T	p.Gln321Ter	

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Normal gene product. *CCNO* encodes the 350-amino acid protein containing two cyclin binding domains. It is localized to the apical cytoplasm and has a role in mother centriole amplification that acts as a template for the generation of multiple motile cilia. It acts downstream of multicilin (required for multiciliated cell differentiation) that is associated with PCD.

Abnormal gene product. Pathogenic variants in *CCDC65* lead to basal body amplification defects resulting in the reduced generation of multiple motile cilia and, occasionally, a basal body migration defect. Residual cilia had a normal ciliary beat with correct localization of axonemal proteins (DNAH5 and CCDC39) [Wallmeier et al 2014].

DNAH1

Gene structure. *DNAH1* comprises 78 exons.

Pathogenic variants. See Table 30. One pathogenic variant (p.Lys11564Gln) associated with PCD was described in two sibs from Saudi Arabia [Imtiaz et al 2015].

Additionally, four pathogenic variants have been described in *DNAH1* that are associated with nonsyndromic male infertility [Ben Khelifa et al 2014] (see Genetically Related Disorders).

Table 30. *DNAH1* Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.3460A>C	p.Lys1154Gln	NM_015512.4 NP_056327.4

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Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. Ciliary dynein axonemal heavy chain 1 is 4,264-amino acid protein of inner dynein arms that functions as a microtubule-dependent motor ATPase involved in axonemal motility. *DNAH1* expression is higher (8x) in testis compared to trachea. DNAH1 is localized to the entire length of sperm flagella [Ben Khelifa et al 2014].

Abnormal gene product. Functional consequences of the PCD-associated variant of DNAH1 have not been studied [Imtiaz et al 2015]. However, immunofluorescence analysis revealed absence of DNAH1 from the sperm flagella of an individual with non-syndromic male infertility with biallelic pathogenic variants in DNAH1. Additionally, inner dynein arms defects of sperm flagella were ascertained by the absence of DNALI1 (marker for inner dynein arms) staining; whereas, outer dynein arms appeared normal with DNAI2 (marker for outer dynein arms) staining [Ben Khelifa et al 2014].

DNAH8

Gene structure. *DNAH8* comprises 92 exons.

Pathogenic variants. See Table 31. A homozygous pathogenic variant (p.Arg590Ter) in *DNAH8* was identified in an individual with primary ciliary dyskinesia [Watson et al 2014].

Table 31*. DNAH8* Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.2419C>T	p.Arg807Ter	NM_001206927.1 NP_001193856.1

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Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. *DNAH8* encodes the 4707-amino acid axonemal dynein heavy chain protein that is paralogous to *DNAH5*. DNAH8 is involved in azxonemal motility by generating force using ATPase activity and binding to microtubules.

Abnormal gene product. Studies are needed to decipher the role of mutated protein.

MCIDAS

Gene structure. *MCIDAS* comprises seven exons.

Pathogenic variants. See Table 32. Pathogenic variants in *MCIDAS* were found in four of 60 unrelated families with reduced cilia on electron microscopic and/or immunofluorescent analysis on tissue obtained by nasal brushing and absence or reduced cilia on in vitro ciliogenesis. None of the eight affected individuals (from the four families) displayed situs abnormalities. A total of three pathogenic variants were observed: one truncating allele (p.Cys147Ter) and two missense alleles (p.Gly366Asp and p.Arg381His) [Boon et al 2014].

Table 32. *MCIDAS* Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.441C>A	p.Cys147Ter	NM_001190787.1 NP_001177716.1
c.1097G>A	p.Gly366Asp	
c.1142G>A	p.Arg381His	

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Normal gene product. *MCIDAS* encodes the 385-amino acid nuclear protein called multicilin containing coiled-coil domains. It induces gene expression in epithelial progenitor cells that is necessary and sufficient for multiciliated cell differentiation.

Abnormal gene product. The missense variants p.Arg381His and p.Gly366Asp induced a reduced number of multiciliated cells compared to wild-type in Xenopus skin fibroblasts.

Pathogenic variants in *MCIDAS* lead to a reduced number of multiple motile cilia with abnormal structure of the outer dynein arm and dynein regulatory complex [Boon et al 2014].

RSPH3

Gene structure. *RSPH3* comprises eight exons.

Pathogenic variants. See Table 33. At least five pathogenic variants in *RSPH3* have been described of which four were private and one – a pathogenic splice variant (c.631-2A>G) - was identified in two unrelated families [Jeanson et al 2015].

Table 33. *RSPH3* Variants

DNA Nucleotide Change	Protein Amino Acid Change	Reference Sequences
c.631-2A>G	Not determined	NM_031924.4 NP_114130.3

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Normal gene product. *RSPH3* encodes radial spoke protein 3 homolog, a 560-amino acid protein with a radial spoke 3 domain (RS3D) containing an RIIa-domain-binding-amphipathic helix (AH_R) and two coiled-coil domains, which plays a role in microtubule sliding by anchoring and modifying dynein motor activity. The protein product localizes to the cilia of the respiratory epithelial cells [Jeanson et al 2015].

Abnormal gene product. In most cilia pathogenic variants in *RSPH3* cause defects of the ciliary central microtubule doublets; however, some cilia are intact resulting in the coexistence of immotile and motile cilia with reduced amplitude. Radial spokes were rarely present. RSPH3 protein product is lacking from the respiratory epithelial cells of individuals harboring pathogenic variants. Immunofluorescence analysis revealed that absence of RSPH3 from the cilia of individuals harboring pathogenic variants resulted in the absence of another radial spoke stalk protein RSPH11, but did not affect either the radial spoke head proteins (RSPH1 and RSPH4a), or radial spoke neck protein (RSPH23), or inner dynein arm light chain protein (DNALI1) [Jeanson et al 2015].

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