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Supplementary Table SI Previously described and novel candidate genes for DFS-MMAF and related sperm phenotypes.

Gene symbol	Synonym	Full gene name	Proposed protein function	Variants in humans	Types of variants described	Absence of homozygous loss of function variation in proven fathers?	Reference
AK7		Adenylate Kinase 7	Phosphotransferase involved in the interconversion of adenine nucleotides. Potentially involved in maintaining motile cilia axoneme stability. Loss of function leads to a spectrum of conditions ranging from pure PCD to severe teratozospermia characterised by poor axoneme elongation and reduced sperm output.	Previously described	Missense	Yes	Lores *et al.* (2018), Fernandez-Gonzalez *et al.* (2009) and Panayiotou *et al.* (2011)
AKAP4		A-Kinase Anchoring Protein 4	Scaffold protein for cAMP-dependent protein kinases and thereby localise sites for protein phosphorylation. Major component of the sperm fibrous sheath. Loss of protein function leads to fibrous sheath disorganisation and compromised glycolysis and thus sperm motility.	Previously described	Missense	Yes	Visser *et al.* (2011) and Miki *et al.* (2002)
ARMC2		Armadillo Repeat Containing 2	Potential involvement in the assembly or stability of the axoneme central microtubule pair. As yet unknown biochemical function. Defects in axoneme and sperm tail accessory structure assembly. Oligozoospermia.	Previously described	LoF and missense	Yes	Coutton *et al.* (2019)
CEP135		Centrosomal Protein 135	A coiled coil domain containing protein involved in microtubule bunding and centriole assembly and stability.	Previously described	Missense	Yes	Sha *et al.* (2017) and Kraatz *et al.* (2016)
CFAP43	*WDR96*	Cilia And Flagella Associated Protein 43	As yet unknown biochemical function. Proposed role in centriole function and axoneme extension from the centriole. Disfunction leads to defects in motile cilia function including hydrocephalus, grossly disorganised sperm axoneme structure and length and associated sperm tail accessory structure defects.	Previously described and described in this study	LoF and missense	Yes	Tang *et al.* (2017), McLachlan and Krausz (2012), Coutton *et al.* (2018), Sha *et al.* (2019b), Coutton *et al.* (2019), Li *et al.* (2019b), Wu *et al.* (2019), Morimoto *et al.* (2019b) This study
CFAP44	*WDR52*	Cilia And Flagella Associated Protein 44	As yet unknown biochemical function. Proposed role in centriole function, axoneme extension and/or stability. Dysfunction leads to grossly disorganised sperm axoneme structure and length and associated sperm tail accessory structure defects.	Previously described	LoF and missense	Yes	Tang *et al.* (2017), Escudier et al. (2009), Coutton *et al.* (2018), Sha *et al.* (2019b), Coutton *et al.* (2019), Li *et al.* (2019b) and Wu *et al.* (2019) This study
CFAP58					LoF	Yes	He *et al.* (2020)

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Supplementary Table SI Continued

Gene symbol	Synonym	Full gene name	Proposed protein function	Variants in humans	Types of variants described	Absence of homozygous loss of function variation in proven fathers?	Reference
		Cilia And Flagella Associated Protein 58	Unknown biochemical function. Localised to motile cilia in the fallopian tube. No available animal models.	Novel candidate gene described in this study			This study
CFAP65	*CCDC108*	Cilia And Flagella Associated Protein 65	Biochemical function unknown. Proposed role in axoneme extension and/or stability. Defects in humans are associated with PCD-like phenotype including respiratory tract disease and MMAF in spermatozoa plus acrosome defects.	Previously described	LoF and missense	Yes	Wang *et al.* (2019), Li *et al.* (2019a), and Zhang *et al.* (2019b)
CFAP69		Cilia And Flagella Associated Protein 69	Biochemical function unknown. Proposed role in axoneme extension/stability and sperm tail organisation. Localised to the mid-piece of normal sperm. Dysfunction leads to PCD symptoms including respiratory disease and MMAF in spermatozoa including the absence of axoneme central microtubule pair.	Previously described	LoF	No, 1/5784 proven fathers carried a homozygous Chr7(GRCh37):g.89906394del; NM_001039706.2(CFAP69):c.992del; p.(Gly331Alafs*6) variant	Dong et al. (2018) and He *et al.* (2019)
CFAP70	*TTC18*	Cilia And Flagella Associated Protein 70	Biochemical function is unknown. Proposed function in protein transport. Associated with the axoneme in motile cilia. Dysfunction of the orthologous protein in trypanosomes leads to the loss of outer dynein arms.	Previously described	LoF and missense	Yes	Beurois *et al.* (2019) and Shamoto *et al.* (2018)
DNAH1		Dynein Axonemal Heavy Chain 1	Inner dynein arm-associated dynein heavy chain. Proposed additional role in axoneme assembly or stability. Dysfunction results in PCD symptoms. In the mouse loss of function leads to sterility associated with sperm clumping and compromised motility.	Previously described	LoF and missense	Yes	Ben Khelifa *et al.* (2014), Wambergue *et al.* (2016), Wang *et al.* (2017), Amiri-Yekta *et al.* (2016), Sha *et al.* (2017), Coutton *et al.* (2018), Sha *et al.* (2019b), Coutton *et al.* (2019), Li *et al.* (2019b), and Hu *et al.* (2019) This study
DNAH2		Dynein Axonemal Heavy Chain 2	Axonemal inner arm dynein heavy chain protein. Proposed additional role in axoneme assembly or stability.	Previously described	LoF and missense	Yes	Li *et al.* (2019b)
DNAH6		Dynein Axonemal Heavy Chain 6	Axonemal dynein heavy chain protein. Proposed role in axoneme assembly or stability. Highly expressed in tissues	Previously described and	LoF and missense	Yes	Tu *et al.* (2019) and Gershoni *et al.* (2017) This study

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Supplementary Table SI Continued

Gene symbol	Synonym	Full gene name	Proposed protein function	Variants in humans	Types of variants described	Absence of homozygous loss of function variation in proven fathers?	Reference
			containing motile cilia and associated with known PCD genes. Evidence of respiratory disease in some patients.	described in this study			
DNAH12		Dynein Axonemal Heavy Chain 12	Dynein heavy chain protein. Its function has not been tested experimentally.	Novel candidate gene described in this study	Unknown	Yes	This study
DNAH17		Dynein Axonemal Heavy Chain 17	Dynein outer dynein arm heavy chain protein. Proposed role in axoneme stability. Its function has not been tested experimentally.	Previously described	LoF and missense	Yes	Whitfield et al. (2019), Zhang et al. (2019a), and Sha et al. (2019a)
DRC1	*CCDC164*	Dynein Regulatory Complex Subunit 1	A component of the nexin-dynein regulatory complex involved in the regulation of dynein motors and coordination between the central microtubule pair and the outer dyein arms within the axoneme. Mutations are associated with PCD symptoms including sinopulmonary disease—male fertility was not explored.	Novel candidate gene described in this study	Unknown	Yes	Keicho et al. (2020), Morimoto et al. (2019a), Wirschell et al. (2013) This study
DZIP1		DAZ Interacting Zinc Finger Protein 1	Associated with centrosomes and ciliogenesis	Previously described	LoF and missense	Yes	Lv et al. (2020)
FSIP2		Fibrous Sheath Interacting Protein 2	AKAP4 binding protein of unknown biochemical function. Fibrous sheath localisation. Proposed role in fibrous sheath assembly and sperm tail stability.	Previously described	LoF	Yes	Martinez et al. (2018), Liu et al. (2019e), Coutton et al. (2019), and Brown et al. (2003)
MAATS1	*CFAP91*	MYCBP Associated And Testis Expressed 1	Axonemal protein with a likely function in the central pair complex	Previously described	LoF and missense	Yes	Martinez et al. (2020)
MDC1		Mediator Of DNA Damage Checkpoint 1	Silencing of sex chromosome and genome stability	Novel candidate gene described in this study	Unknown	Yes	This study
PACRG		Parkin Coregulated	Key component of the junction between the A- And B-tubules within the axoneme and thus ciliary dyein function. Potential role in protein transport into the developing sperm tail.	Novel candidate gene described in this study	Unknown	Yes	This study

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Supplementary Table SI Continued

Gene symbol	Synonym	Full gene name	Proposed protein function	Variants in humans	Types of variants described	Absence of homozygous loss of function variation in proven fathers?	Reference
			Dysfunction leads to compromised inner dynein arm assembly and is associated with PCD including hydrocephalus.				
QRICH2		Glutamine Rich 2	Undefined biochemical function. A potential role in intra-flagella protein transport. Dysfunction leads to sperm tail malformation and instability.	Previously described and described in this study	LoF and missense	Yes	Shen *et al.* (2019) and Kherraf *et al.* (2019) This study
SPEF2		Sperm Flagellar 2	IFT20 interacting protein with a proposed role in intra-manchette protein transport. Dysfunction leads to PCD in humans. Involved in manchette migration, and thus sperm head shaping, in mouse spermatogenesis. Also involved in regulating centriole duplication and formation/stability of the axoneme central microtubule pair.	Previously described	LoF	Yes	Liu *et al.* (2019b), Liu *et al.* (2019d), Sha *et al.* (2019a), and Tu *et al.* (2020)
SPPL2C		Signal Peptide Peptidase Like 2C	A catalytically active GxGD-type intramembrane protease involved in vesicle transport. Proposed role in acrosome formation. Function untested in the context of spermatogenesis.	Novel candidate gene described in this study	Unknown	Yes	This study
TPTE2		Transmembrane Phosphoinositide 3-Phosphatase And Tensin Homolog 2	Transmembrane voltage sensor. Untested role in male fertility.	Novel candidate gene described in this study	Unknown	Yes	This study
TTC29		Tetratricopeptide Repeat Domain 29	Required for delivery of key proteins into the sperm tail via intra-flagellar transport pathway. The loss of *TTC29* in the mouse leads to severely disrupted axoneme and accessory structure formation. The precise biochemical function is unknown.	Previously described	LoF	Yes	Liu *et al.* (2019a) and Lores *et al.* (2019)
TTC21A	*IFT139A*	Tetratricopeptide Repeat Domain 21 A	Proposed role in intra-flagellar transport and sperm tail stability. Dysfunction in humans and mice leads to sperm tail disorganisation including missing central axoneme microtubules, sperm neck/connecting piece defects and short tails.	Previously described	LoF and missense	Yes	Liu et al. (2019c)

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Supplementary Table SI Continued

Gene symbol	Synonym	Full gene name	Proposed protein function	Variants in humans	Types of variants described	Absence of homozygous loss of function variation in proven fathers?	Reference
WDR66	*CFAP251*	WD Repeat Domain 66	An axoneme associated protein with a proposed role in axoneme central pair formation and sperm tail stability. Loss of function lead to sperm tail disorganisation and shortening. Also observed acrosomal defects. Loss of function of the orthologous protein in T.brucei resulted in compromised flagella motility characterised by axoneme disorganisation. The central microtubule pair of the axoneme were notably affected.	Previously described	LoF	Yes	Kherraf *et al.* (2018), Auguste *et al.* (2018), Li *et al.* (2019a), and Coutton *et al.* (2019)

LoF, loss-of-function (nonsense, canonical splice site and frameshift variation).

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