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WD40-Repeat Proteins in Ciliopathies and Congenital Disorders of Endocrine System

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WD40-repeat (WDR)-containing proteins constitute an evolutionarily conserved large protein family with a broad range of biological functions. In human proteome, WDR makes up one of the most abundant protein-protein interaction domains. Members of the WDR protein family play important roles in nearly all major cellular signalling pathways. Mutations of WDR proteins have been associated with various human pathologies including neurological disorders, cancer, obesity, ciliopathies and endocrine disorders. This review provides an updated overview of the biological functions of WDR proteins and their mutations found in congenital disorders. We also highlight the significant role of WDR proteins in ciliopathies and endocrine disorders. The new insights may help develop therapeutic approaches targeting WDR motifs.

Keywords: WDR proteins; Ciliopathies; Congenital, hereditary, and neonatal diseases and abnormalities; Neuroendocrine; Kallmann syndrome

INTRODUCTION

WD40-repeat (WDR) refers to a series of loosely conserved structural motifs comprised of approximately 40 amino acids, often terminating in tryptophan (W)-aspartic acid (D). WDR protein family is a large group of proteins commonly possessing the WDR motifs, that are involved in a wide range of important biological processes. Inherited or acquired defects in WDR proteins result in numerous health problems including neurological diseases, ciliopathies, and cancers. In this review, we provide a unique overview and discussion on the molecular mechanisms and functions of WDR proteins, especially focusing on those that have been associated with human congenital disorders and endocrine diseases. Many of the WDR proteins are called different names mainly due to historical reasons. The official gene nomenclature along with full and alternative names of WDR proteins (based on UniProt) discussed in this review are summarised in the Supplemental Table S1. WDR proteins associated with pathological conditions that are not discussed in the main text in detail are summarised in the Supplemental Table S2.

MOLECULAR STRUCTURE OF WDR PROTEINS

WDR motif was first described in the β-subunit of a GTP-binding protein transducin complex as a sequence of repeats of 40 to 60 amino acids that begin with glycine and histidine (GH) and end with tryptophan and aspartic acid (WD) dipeptides [1]. WDR is an evolutionarily conserved and highly abundant domain in eukaryotes with nearly 1% of human proteomes consisting of WDR-containing proteins [2]. Most recent protein domain database (SMART, http://smart.embl.de/) predicts that 921 WDR proteins are encoded in humans, 591 in *Mus musculus*

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and 212 in *Drosophila melanogaster*. WDR proteins are rarely present in prokaryotes [2]. Each WDR protein can have 4 to 16 copies of WDRs forming seven or more bladed beta-propeller folds [3], which can provide three structural surfaces (top, side, and bottom region of propeller) available to interact with other binding partners [2]. Based on these structural features, it is suggested that WDR proteins could serve as a scaffold that mediates protein-protein or protein-DNA interaction [4]. Since WDRs do not possess any catalytic activity themselves, functional diversity is likely achieved by coordination of multiple binding partners. Mutations in WDR proteins have been reported in several human diseases. Notably, clinically identified mutations of WDR are mostly found on the surface of the protein, presumably interfering their binding interactions with other proteins [1,2,4].

BIOLOGICAL FUNCTIONS OF WDR PROTEINS

WDR proteins can be primarily defined by their sequence similarity in the WD40-repeat domain. However, a wide range of sequence variation has been found in WD40-repeats, resulting in variable numbers of beta-propeller structures. Variations outside of the WD-repeat domain can also contribute to the multi-domain contexts [5]. In fact, although all WDR proteins are structurally related, their molecular functions can be quite distinct. This functional diversity is usually acquired from the additional domains present in the respective WDR proteins. Currently, more than 360 additional domains are reported in WDR proteins [6]. The most commonly found additional domains are shown to be functionally involved with ubiquitylation (e.g., F-box [7], SOCS-box [8], RING-finger [9]), microtubule dynamics (e.g., CTLH domain [10]), phospholipid-binding (e.g., FYVE domain [11]) and endocytic vesicle coating (e.g., clathrin terminal domain [12]). WDR domains are also identified in essential subunits of multiprotein complexes that participate in various signalling pathways regulating DNA repair [13-15], protein degradation [16,17], cell cycle control [18,19], mRNA translation [20,21], cilia assembly and maintenance [22,23], and hormone biosynthesis [24]. Therefore, it is not surprising that WDR proteins play important roles in fundamental cellular functions, such as signal transduction, gene expression, RNA processing, protein synthesis, homeostasis, proliferation, apoptosis, intracellular vesicle trafficking, and cargo recognition [2,25-29].

WDR PROTEINS IN HUMAN DISEASE

According to the Online Mendelian Inheritance in Man (OMIM) database (https://omim.org/), there is a significant correlation between WDR protein dysfunction and human diseases (Fig. 1). Among 360 WDR genes we assessed, 79 genes were reported to be associated with human pathologies which include neurological disorders (40.5%), ciliopathies (21.5%), immune diseases (8.9%), eye problems (7.6%), skeletal anomalies (3.8%), cancers (3.8%), endocrine disorders (2.5%), inflammation (2.5%), and others including preimplantation embryonic lethality (8.9%).

Notably, a significant number of WDR proteins have been associated with ciliopathies, a group of genetic disorders resulting from defects in the structure or function of cilia. Cilia are highly conserved microtubule-based hair-like organelles that extend from the plasma membrane of most vertebrate cells. Cilia can broadly be classified into two types, motile and non-motile (primary) cilia that share the principal axoneme structures [30,31]. The axoneme consists of a circular arrangement of nine pairs of microtubules called outer doublets. In addition to the outer doublets, motile cilia contain a pair of microtubules in the centre called inner doublets [32]. This central pair of microtubules is the scaffold of the central pair complex including radial spokes, inner and outer dynein arms and nexin links [33]. The intraflagellar transport (IFT) particles assemble and maintain the cilium by trafficking ciliary proteins within the cilium [22,23]. Two

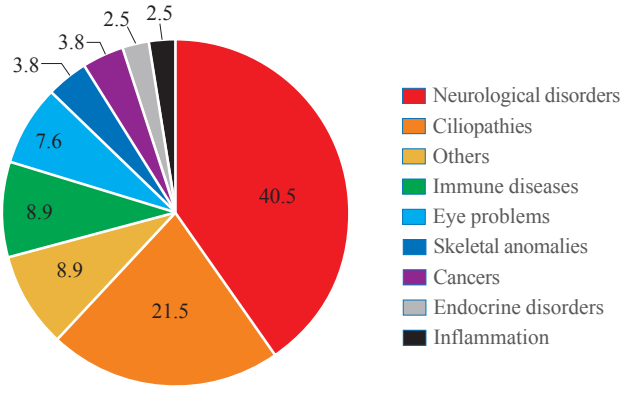

Fig. 1. A chart indicating the relevant prevalence of human diseases associated with WD40-repeat (WDR) proteins. The data are based on the entries in Online Mendelian Inheritance in Man (OMIM). Total 79 out of 360 WDR proteins have been linked with disease categories as indicated. The 'others' category includes multi-organ defects, liver failure, cardiovascular defects and embryonic lethality. The full list of WDR proteins assessed are included in Supplementary Table S1.

subcomplexes IFT-A and IFT-B, consisting of at least 6 and 13 proteins, respectively, move along the cilium bidirectionally via retrograde (IFT-A) and anterograde (IFT-B) transport. In retrograde transport (from the ciliary tip to the base), IFT-A uses dynein-2 as a motor, whereas IFT-B is powered by kinesin-2 for anterograde movement [34,35]. Many IFT proteins contain protein-protein interaction motifs including WDRs, tetratricopeptide repeats and coiled coils motifs [22], facilitating the interaction and transport of multiple cargos such as tubulin and dynein components [22,36,37]. Primary cilium serves as a regulatory platform and organising centre for many cellular signalling pathways [38] such as Hedgehog [39], receptor tyrosine kinases [40], and G protein-coupled receptors [41], playing critical roles in normal embryonic development and adult homeostasis [42]. Therefore, defects in the formation and function of primary cilia lead to a wide range of health problems [43], including renal dysfunction, retina degeneration, hypogonadism, diabetes, obesity, hearing impairment, craniofacial/skeletal anomalies, cardiovascular defects, and brain malformations [30,44-46], which are collectively termed as ciliopathies.

WDR proteins associated with neurological disorders

Mutations of WDR proteins are most frequently associated with neurological disorders (see Table 1 for the full list). PAFAH1B1 (LIS1) is the first WDR protein identified in severe brain malformation called lissencephaly type 1 (also known as classic lissencephaly) characterized by the absence or incomplete development of the cerebral cortex, causing unusually smooth brain surface. Lissencephaly can occur in association with other syndromes such as Miller-Dieker syndrome (MDS) [47,48] or as an isolated lissencephaly sequence (ILS) [49,50]. *PAFAH1B1* gene is located in 17p 13.3 which is the most frequently deleted chromosomal region in MDS and ILS patients [51]. So far, it is estimated that 65% of ILS patients have deletions or intragenic mutations of *PAFAH1B1* [50]. PAFAH1B1 is a microtubule-associated phosphoprotein and its direct interaction with cytoplasmic dynein heavy change is important for neuronal migration, disruptions of which result in lissencephaly [52,53].

Mutations in *KATNB1* (*LIS6*) are associated with complex cerebral malformations known as lissencephaly 6 (microcephaly co-existing with lissencephaly) [54,55]. *KATNB1* encodes the p80 subunit of katanin, a microtubule-associated ATPase [56,57] which consists of two subunits [56]. While p60 subunit provides the catalytic function, p80 subunit is the regulatory element that targets this protein to centrosomes and maintains the length of microtubules in developing neurons [58,59].

Mutations in *LRRK2* are the most common cause of autosomal dominant Parkinson's disease [60,61]. To date, more than a hundred mutations of *LRRK2* have been identified and six of them are confirmed to be pathogenic [62]. LRRK2 protein binds to the synaptic vesicles and regulates vesicular trafficking by interacting with pre-synaptic proteins such as actin and synapsin [63]. The sequence variation of glycine to arginine at residue 238 (G2385R) which is located between the 5th and 6th WDR domain has been confirmed as a risk factor in the Asian population [64-66]. This mutation modifies LRRK2 protein structure, likely altering its binding affinity to synaptic vesicles and other interactors required for vesicle trafficking [67].

Cockayne syndrome type A (CSA) is a rare neurodegenerative disorder characterized by complex phenotypes including a growth delay, optic atrophy, deafness, abnormalities in limb and digits, and mental disability [15,68]. According to the Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=ERCC8), up to 70 mutations of the *ERCC8* gene have been reported in CSA so far. ERCC8 is a subunit of E3 ubiquitin ligase complex [13,14] and interacts with ERCC6 during transcription-coupled nucleotide excision repair [13]. ERCC6, a putative helicase, is recruited by stalled RNA polymerase 2 on the DNA damage site and initiates DNA repair by attracting repair proteins including ERCC8 to the lesion [13,15].

Triple-A syndrome (AAAS) is a rare autosomal recessive disorder and patients suffer from adrenal insufficiency, achalasia of the oesophagal cardia, alacrimia, and neurological abnormalities affecting the central, peripheral, and autonomic nervous systems [69,70]. Mutations of *ALADIN* have been found in all AAAS patients, which results in a truncated protein with loss of function [71]. ALADIN protein is normally localised within nuclear pore complexes [18] but mutants of ALADIN are shown to be sequestered in the cytoplasm [72], leading to impaired nuclear transport of proteins that are required to protect the nucleus from oxidative damage [73,74].

Mutations in *WDR4* are reported in patients with microcephaly with severe growth deficiency, seizures, and brain malformations [75,76]. Recent whole-exome sequencing analyses of a family with Galloway-Mowat syndrome (GAMOS) identified a novel mutation of WDR4 [77]. GAMOS present clinically heterogeneous phenotypes which combine renal failure and brain anomalies [78], with additionally associated features including facial dysmorphism, growth retardation and skeletal anomalies [79]. Fibroblast cells derived from patients with GAMOS show defective growth and altered microtubule networks [80]. WDR4 is the human ortholog of yeast Trm82p and forms a complex

Table 1. List of WDR Proteins Associated with Neurological Disorders

WDR protein	Associated diseases	MIM number	Mode of inheritance
LRRK2	Parkinson disease	607060	AD
PPP2R2B	Spinocerebellar ataxia	604326	AD
TBL1XR1	Mental retardation	616944	AD
	Pierpont syndrome	602342	AD
ERCC8	Cockayne syndrome, type A	216400	AR
	UV-sensitive syndrome	614621	AR
PAFAH1B1 (LIS1)	Lissencephaly	607432	AD
	Subcortical laminar heterotopia	607432	AD
WDR26	Skraban-Deardorff syndrome	617616	AD
WIPI2	Intellectual developmental disorder with short stature and variable skeletal anomalies	618453	AR
COPB2	Primary microcephaly	617800	AR
DYNC1I2	Neurodevelopmental disorder with microcephaly and structural brain anomalies	618492	AR
ELP2	Mental disability	617270	AR
GNB4	Charcot-Marie-Tooth disease	615185	AD
SEC31A	Neurodevelopmental disorder with spastic quadriplegia, optic atrophy, seizures, and structural brain anomalies	618651	AR
DCAF8	Giant axonal neuropathy	610100	AD
DMXL2	Deafness	617605	AD
	Polyendocrine-polyneuropathy syndrome	616113	AR
	Early infantile epileptic encephalopathy	618663	AR
EML1	Band heterotopia	600348	AR
PHIP	Chung-Jansen syndrome	617991	AD
PLAA	Neurodevelopmental disorder with progressive microcephaly, spasticity, and brain anomalies	617527	AR
WDFY3	Primary microcephaly	617520	AD
WDR62	Primary microcephaly, with or without cortical malformations	604317	AR
AAAS	Achalasia-addisonianism-alacrimia syndrome	231550	AR
BRWD3	X-linked mental disability	300659	XLR
GNB5	Intellectual developmental disorder with cardiac arrhythmia	617173	AR
	Language delay and ADHD/cognitive impairment with or without cardiac arrhythmia	617182	AR
HERC1	Macrocephaly, dysmorphic faces, and psychomotor retardation	617011	AR
KATNB1	Lissencephaly, with microcephaly	616212	AR
RIC1	CATIFA syndrome	618761	AR
THOC6	Beaulieu-Boycott-Innes syndrome	613680	AR
WDR45	Neurodegeneration with brain iron accumulation	300894	XLD
WDR45B	Neurodevelopmental disorder with spastic quadriplegia and brain abnormalities with or without seizures	617977	AR
NUP37	Primary microcephaly	618179	AR
WDR37	Neuro-oculo-cardio-genitourinary syndrome	618652	AD
WDR4	Galloway-Mowat syndrome	618347	AR
	Microcephaly, growth deficiency, seizures, and brain malformations	618346	AR
WDR73	Galloway-Mowat syndrome	251300	AR

WDR, WD40-repeat; MIM, Mendelian Inheritance in Man; AD, autosomal dominant; AR, autosomal recessive; UV, ultraviolet light; XLR, X-linked recessive; ADHD, attention deficit hyperactivity disorder; CATIFA, cleft lip, cataract, tooth abnormality, impaired intellectual development, facial dysmorphism, attention-deficit hyperactivity; XLD, X-linked dominant.

with N7-methylguanosine tRNA methyltransferase and METTL1, which is essentially required for mRNA translation and stem cell self-renewal and differentiation [20,21]. WDR73 is another WDR protein related to GAMOS [81]. WDR73 is concentrated in the microtubule and interacts with several proteins critical to cell cycle and survival, such as tubulins α/β/γ and Hsp70/ 90 [81].

WDR proteins and cancer predisposition

WDR protein PALB2 is a breast and pancreatic cancer susceptibility factor that interacts with BRCA2 and RAD51C [17,37] facilitating their DNA repair function [82]. Cancer-associated PALB2 mutations cause the loss of its binding ability to BRCA2/RAD51C and biallelic mutations of PALB2 are associated with an increased occurrence of childhood cancers [82].

Another WDR protein FBXW7 is a ubiquitin ligase substrate receptor and the most commonly deregulated ubiquitin/proteasome system (UPS) protein in human cancer [16]. FBXW7 is a tumour suppressor protein that binds to the phosphorylated cyclin E and mediates its degradation by ubiquitination [16,17]. Loss-of-function mutations of FBXW7 result in inappropriate accumulation of cyclin E [17], which is observed in 18% of colorectal cancers, 15% of uterine endometrial carcinoma and 40% of uterine carcinosarcoma [16,17].

WDR proteins associated with ciliopathies

To date, mutations in at least 17 different WDR proteins have been identified in ciliopathies (see below and Table 2). Mutations in all components of IFT-A complex—WDR10/IFT122 [83], WDR19/IFT144 [84], WDR35/IFT121 [85], IFT43 [86],

Table 2. List of WDR Proteins Associated with Ciliopathies

WDR protein	Associated ciliopathy phenotypes	MIM number	Mode of inheritance
AHI1	Joubert syndrome	608629	AR
WDR19	Cranioectodermal dysplasia	614378	AR
	Short-rib thoracic dysplasia with or without polydactyly	614376	AR
	Nephronophthisis	614377	AR
	Senior-Loken syndrome	616307	AR
MAPKBP1	Nephronophthisis	617271	AR
WDR35	Cranioectodermal dysplasia	613610	AR
	Short-rib thoracic dysplasia with or without polydactyly	614091	AR
WDR66	Spermatogenic failure	618152	AR
WDR81	Cerebellar ataxia, mental retardation, and dysequilibrium syndrome	610185	AR
	Congenital hydrocephalus with brain anomalies	617967	AR
CFAP43	Hydrocephalus (normal pressure)	236690	AD
	Spermatogenic failure	617592	AR
CFAP44	Spermatogenic failure	617593	AR
DNAI1	Primary ciliary dyskinesia, with or without situs inversus	244400	AR
DNAI2	Primary ciliary dyskinesia, with or without situs inversus	612444	
IFT122	Cranioectodermal dysplasia	218330	AR
IFT140	Retinitis pigmentosa	617781	AR
	Short-rib thoracic dysplasia, with or without polydactyly	266920	AR
IFT172	Retinitis pigmentosa	616394	AR
	Short-rib thoracic dysplasia, with or without polydactyly	615630	AR
IFT80	Short-rib thoracic dysplasia, with or without polydactyly	611263	AR
WDPCP	Bardet-Biedl syndrome	615992	AR
	Congenital heart defects, hamartomas of tongue, and polysyndactyly	217085	AR
WDR34	Short-rib thoracic dysplasia, with or without polydactyly	615633	AR
WDR60	Short-rib thoracic dysplasia, with or without polydactyly	615503	AR

WDR, WD40-repeat; MIM, Mendelian Inheritance in Man; AR, autosomal recessive; AD, autosomal dominant.

IFT140 [87], TTC21B [88]—and a subset of proteins in IFT-B complex—WDR56/IFT80 [89], IFT172 [90], IFT52 [91], IFT81 [92]—have been identified in skeletal ciliopathies. Cranio-ectodermal dysplasia (CED), also known as Sensenbrenner syndrome, is a ciliopathy characterized by craniofacial and skeletal anomalies [93]. So far, four IFT-A proteins are reported to be mutated in CED, namely, WDR10/IFT122, WDR19/IFT144, WDR35/IFT121, and IFT43 [87,94-97]. Mutations in WDR19/IFT144 have also been identified in patients with Jeune syndrome, also known as asphyxiating thoracic dystrophy (ATD), presenting short stature, short digits (brachydactyly), and respiratory distress due to insufficient rib bone growth [84]. WDR35/IFT121 mutations are found in both Jeune syndrome and Short-Rib-Polydactyly syndrome (SRPS) [98]. Mutations in WDR34 and WDR60 are also associated with ATD and SRPS [98,99]. WDR34 and WDR60 are subunits of the dynein-2 complex, comprising the two intermediate chains of dynein-2 which mediates retrograde ciliary transport via IFT-A [100,101]. In addition to WDR34 and WDR60, disruptions in other dynein-2 subunits are also common causes of ATD and SRPS [89-91]. Therefore, patients with CED, ATD, and SRPS share clinical and genetic features [102] and can also be affected in non-skeletal organs including kidney, eye, liver, and heart [99].

AHI1 encodes a protein called Jouberin which contains seven WDR domains [103]. Recessive mutations of AHI1 underlie Joubert syndrome (JS) characterized by abnormal development of brain structures, including the cerebellar vermis and the brainstem, which resemble the cross-section of a molar tooth in MRI, thus nicknamed as 'molar tooth malformation' [103,104]. JS patients show additional distinctive features including ocular coloboma, polycystic kidney and polydactyly, which are collectively referred to as JS-related disorders (JSRD) [105,106]. AHI1 mutation is also associated with a broad range of neurological disorders including schizophrenia [107] and autism [108]. Recent mouse model studies have revealed that *Ahi1* is highly expressed in the postnatal brain and interacts with other proteins crucial for neuronal differentiation [109,110].

WDR proteins in endocrine disorders

Table 3 lists the WDR proteins involved in endocrine disorders, many of which are often presented as a part of a ciliopathy. Several signalling receptors important in neuro-endocrine functions are shown to localise to primary cilia [111]. They include kisspeptin receptor (KISS1R) [112], type 1 dopaminergic receptor (D1R), beta-2 adrenergic receptor (B2AR) [113], serotonin receptor 6 (5-HT6) [114], and insulin-like growth factor 1 receptor (IGF1R) [115]. It has been suggested that the spatio-temporal distribution and concentration of these receptors on the ciliary membrane surface may provide an additional level of regulation for the signal capacity and specificity of these receptors [116]. Shortening of cilia length and alteration in ciliation frequency can indicate functional disruption of cilia-dependent receptor signalling and protein trafficking, involved in endocrine functions.

WDR11 is a scaffolding protein required for normal ciliogenesis. Mutations of WDR11 have been identified in congenital isolated hypogonadotropic hypogonadism (CHH), septo-optic dysplasia (SOD), combined pituitary hormone deficiency (CPHD), and pituitary stalk interruption syndrome [117-120]. CHH is defined by the absent or delayed puberty due to defective gonadotrophin-releasing hormone secretion or action. CHH can present with a normal sense of smell (normosmic CHH) or defective sense of smell (hyposmic/anosmic CHH or Kallmann syndrome) [121,122]. CHH patients often show other associated

Table 3. List of WDR Proteins Associated with Endocrine Disorders

WDR protein	Disease name	Endocrine-related phenotypes	MIM number	Mode of inheritance
TBL1X	Congenital non-goitrous hypothyroidism	Hypothyroidism	301033	XL
WDR11	Kallmann syndrome	Hypogonadotropic hypogonadism with or without anosmia	614858	AD
AHI1	Joubert syndrome	Isolated growth hormone deficiency micropenis	608629	AR
WDPCP	Bardet-Biedl syndrome	Obesity Hypogonadism in males	615992	AR
DMXL2	Polyendocrine-polyneuropathy syndrome	Hypothyroidism	616113	AR
AAAS	Achalasia-addisonianism-alacrimia syndrome	Multisystem disorder wiwth endocrine, gastrointestinal, ocular, and neurologic manifestations.	231550	AR

WDR, WD40-repeat; MIM, Mendelian Inheritance in Man; XL, X-linked; AD, autosomal dominant; AR, autosomal recessive.

features such as midline defects (cleft lip or palate), deformity of hands and feet, neurosensory hearing loss, and ocular motor abnormalities [123-125]. Previous studies have suggested that CHH, SOD, and CPHD are genetically overlapping conditions [120]. Clinically identified mutations of WDR11 caused defective cilia formation, and targeted disruption of WDR11 in animal models resulted in dysgenesis of multiple organs affected in CHH and Kallmann syndrome [126]. Hedgehog signalling pathway which depends on the normal function of primary cilia is also shown to be disrupted by the loss of WDR11. Based on these findings, it was suggested that CHH and Kallmann syndrome could be considered as a ciliopathy [126]. The endocrine feature is also common in other ciliopathies such as JS and JSRD. Some JS/JSRD patients show growth hormone or thyroid hormone deficiency [127], CPHD [128], and micropenis [129].

WDR proteins have been associated with obesity. GNB3 is related to childhood obesity and polymorphism of GNB3 is associated with obesity, hypertension, and diabetes type 2 [130-132]. A genome-wide association study identified WDR11 as a novel genetic locus associated with childhood obesity [133]. Siblings sharing a rare variant of WDR11 gene showed obesity with attention deficit hyperactivity disorder [126]. Obesity is, in fact, one of the main features of Bardet-Biedl syndrome (BBS) [134]. BBS is a ciliopathy with a wide spectrum of clinical features including rod-cone dystrophy, polydactyly, hypogonadism in male and renal abnormalities [135]. Homozygous mutation in WDPCP (also called BBS15) is identified in BBS patients with obesity and male hypogonadism [136]. WDPCP is involved in planar polarity effectors (CPLANE) complex required for recruitment of IFT-A proteins during ciliogenesis [137].

Mutations of TBL1X have been identified in isolated congenital central hypothyroidism [138]. Congenital hypothyroidism (CH) is a thyroid hormone deficiency at birth caused by the impaired function of the thyroid itself (primary CH) or defective stimulation of thyroid gland by a thyroid-stimulating hormone (central or secondary CH) [139]. Central CH can be categorized into two subtypes—isolated thyroid hormone deficiency and CPHD [139]. Isolated thyroid hormone deficiency accounts for 40% of central CH cases [140] and can be caused by mutations in four genes that regulate the thyroid-stimulating hormone biosynthesis, including β subunit of thyroid-stimulating hormone (TSHβ), receptor for thyrotropin-releasing hormone (TRHR), IGSF1 (the regulator for TRHR expression in the pituitary) and TBL1X (an essential subunit of the thyroid hormone receptor corepressor complex) [24,138].

Although AAAS was described as a neurological disorder previously, the adrenal glands are one of the primarily affected organs [71,141]. About 85% of AAAS patients show adrenocorticotropin hormone resistant adrenal insufficiency due to impaired glucocorticoid secretion [142] and a subsequence adrenal androgen deficiency is also observed [143]. Homozygous deletion of DMXL2 is identified in patients with the polyendocrine-polyneuropathy syndrome (PEPNS) [144]. PEPNS refers to a combined symptom including CHH with hypothyroidism, hypoglycemia, peripheral polyneuropathy, and mental disability [143]. A recent study has shown that gonad specific DMXL2 deletion causes impaired spermatogenesis in males [145].

CONCLUSIONS

WDR proteins are widely expressed in human tissues and highly conserved in vertebrates (https://www.proteinatlas.org/search/wdr). Thanks to the recent advancements in genome sequencing analysis, many potentially pathogenic variants of WDR proteins have been identified, which can prove to be powerful tools for assigning new functions to the WDR motifs and associated domains. It is possible that WDR proteins with very similar surfaces have common binding partners or similar functions. Mutations in WDR proteins underlie a broad spectrum of human pathologies including neurological disorders, cancer, ciliopathies, and endocrine disorders. These are complex disorders, thus a clear understanding of the clinical phenotypes and comprehensive diagnosis are often challenging. Molecular mechanisms through which WDR proteins are involved in these diverse conditions remain largely unknown. A better understanding of WDR proteins and their interacting partners may offer some clues. The new insights for WDR-related diseases and their underlying mechanisms as provided in this review may help develop therapeutic approaches targeting the common WDR motifs involved.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

1. Li D, Roberts R. WD-repeat proteins: structure characteristics, biological function, and their involvement in human diseases. Cell Mol Life Sci 2001;58:2085-97.
2. Stirnimann CU, Petsalaki E, Russell RB, Muller CW. WD40 proteins propel cellular networks. Trends Biochem Sci 2010;35:565-74.
3. Wall MA, Coleman DE, Lee E, Iniguez-Lluhi JA, Posner BA, Gilman AG, et al. The structure of the G protein heterotrimer Gi alpha 1 beta 1 gamma 2. Cell 1995;83:1047-58.
4. Jain BP, Pandey S. WD40 repeat proteins: signalling scaffold with diverse functions. Protein J 2018;37:391-406.
5. Yu L, Gaitatzes C, Neer E, Smith TF. Thirty-plus functional families from a single motif. Protein Sci 2000;9:2470-6.
6. Schapira M, Tyers M, Torrent M, Arrowsmith CH. WD40 repeat domain proteins: a novel target class? Nat Rev Drug Discov 2017;16:773-86.
7. Pashkova N, Gakhar L, Winistorfer SC, Yu L, Ramaswamy S, Piper RC. WD40 repeat propellers define a ubiquitin-binding domain that regulates turnover of F box proteins. Mol Cell 2010;40:433-43.
8. Linossi EM, Nicholson SE. The SOCS box-adapting proteins for ubiquitination and proteasomal degradation. IUBMB Life 2012;64:316-23.
9. Wu G, Xu G, Schulman BA, Jeffrey PD, Harper JW, Pavletich NP. Structure of a beta-TrCP1-Skp1-beta-catenin complex: destruction motif binding and lysine specificity of the SCF(beta-TrCP1) ubiquitin ligase. Mol Cell 2003;11:1445-56.
10. Kannan M, Bayam E, Wagner C, Rinaldi B, Kretz PF, Tilly P, et al. WD40-repeat 47, a microtubule-associated protein, is essential for brain development and autophagy. Proc Natl Acad Sci U S A 2017;114:E9308-17.
11. Lystad AH, Simonsen A. Phosphoinositide-binding proteins in autophagy. FEBS Lett 2016;590:2454-68.
12. von Kleist L, Stahlschmidt W, Bulut H, Gromova K, Puchkov D, Robertson MJ, et al. Role of the clathrin terminal domain in regulating coated pit dynamics revealed by small molecule inhibition. Cell 2011;146:471-84.
13. Wang X, Huang Y, Yan M, Li J, Ding C, Jin H, et al. Molecular spectrum of excision repair cross-complementation group 8 gene defects in Chinese patients with Cockayne syndrome type A. Sci Rep 2017;7:13686.
14. Groisman R, Kuraoka I, Chevallier O, Gaye N, Magnaldo T, Tanaka K, et al. CSA-dependent degradation of CSB by the ubiquitin-proteasome pathway establishes a link between complementation factors of the Cockayne syndrome. Genes Dev 2006;20:1429-34.
15. van der Weegen Y, Golan-Berman H, Mevissen TET, Apelt K, Gonzalez-Prieto R, Goedhart J, et al. The cooperative action of CSB, CSA, and UVSSA target TFIIH to DNA damage-stalled RNA polymerase II. Nat Commun 2020;11:2104.
16. Davis RJ, Welcker M, Clurman BE. Tumor suppression by the Fbw7 ubiquitin ligase: mechanisms and opportunities. Cancer Cell 2014;26:455-64.
17. Siu KT, Rosner MR, Minella AC. An integrated view of cyclin E function and regulation. Cell Cycle 2012;11:57-64.
18. Cronshaw JM, Matunis MJ. The nuclear pore complex protein ALADIN is mislocalized in triple A syndrome. Proc Natl Acad Sci U S A 2003;100:5823-7.
19. Kumar A, Sharma P, Gomar-Alba M, Shcheprova Z, Daulny A, Sanmartin T, et al. Daughter-cell-specific modulation of nuclear pore complexes controls cell cycle entry during asymmetric division. Nat Cell Biol 2018;20:432-42.
20. Alexandrov A, Martzen MR, Phizicky EM. Two proteins that form a complex are required for 7-methylguanosine modification of yeast tRNA. RNA 2002;8:1253-66.
21. Lin S, Liu Q, Lelyveld VS, Choe J, Szostak JW, Gregory RI. Mettl1/Wdr4-mediated m7G tRNA methylome is required for normal mRNA translation and embryonic stem cell self-renewal and differentiation. Mol Cell 2018;71:244-55.
22. Cole DG. The intraflagellar transport machinery of Chlamydomonas reinhardtii. Traffic 2003;4:435-42.
23. Hao L, Scholey JM. Intraflagellar transport at a glance. J Cell Sci 2009;122(Pt 7):889-92.
24. Schoenmakers N, Alatzoglou KS, Chatterjee VK, Dattani MT. Recent advances in central congenital hypothyroidism. J Endocrinol 2015;227:R51-71.
25. van Nocker S, Ludwig P. The WD-repeat protein superfamily in Arabidopsis: conservation and divergence in structure and function. BMC Genomics 2003;4:50.
26. Feng Y, Zhang C, Luo Q, Wei X, Jiang B, Zhu H, et al. A novel WD-repeat protein, WDR26, inhibits apoptosis of cardiomyocytes induced by oxidative stress. Free Radic Res 2012;46:777-84.
27. Avidor-Reiss T, Maer AM, Koundakjian E, Polyanovsky A,

Keil T, Subramaniam S, et al. Decoding cilia function: defining specialized genes required for compartmentalized cilia biogenesis. Cell 2004;117:527-39.
28. Van Roosbroeck K, Cox L, Tousseyn T, Lahortiga I, Gielen O, Cauwelier B, et al. JAK2 rearrangements, including the novel SEC31A-JAK2 fusion, are recurrent in classical Hodgkin lymphoma. Blood 2011;117:4056-64.
29. Proikas-Cezanne T, Takacs Z, Donnes P, Kohlbacher O. WIPI proteins: essential PtdIns3P effectors at the nascent autophagosome. J Cell Sci 2015;128:207-17.
30. Fliegauf M, Benzing T, Omran H. When cilia go bad: cilia defects and ciliopathies. Nat Rev Mol Cell Biol 2007;8:880-93.
31. Malicki JJ, Johnson CA. The cilium: cellular antenna and central processing unit. Trends Cell Biol 2017;27:126-40.
32. Wemmer KA, Marshall WF. Flagellar motility: all pull together. Curr Biol 2004;14:R992-3.
33. Smith EF, Yang P. The radial spokes and central apparatus: mechano-chemical transducers that regulate flagellar motility. Cell Motil Cytoskeleton 2004;57:8-17.
34. Sung CH, Leroux MR. The roles of evolutionarily conserved functional modules in cilia-related trafficking. Nat Cell Biol 2013;15:1387-97.
35. Taschner M, Lorentzen E. The intraflagellar transport machinery. Cold Spring Harb Perspect Biol 2016;8:a028092.
36. Rosenbaum JL, Witman GB. Intraflagellar transport. Nat Rev Mol Cell Biol 2002;3:813-25.
37. Scholey JM. Intraflagellar transport. Annu Rev Cell Dev Biol 2003;19:423-43.
38. Singla V, Reiter JF. The primary cilium as the cell's antenna: signaling at a sensory organelle. Science 2006;313:629-33.
39. Han YG, Spassky N, Romaguera-Ros M, Garcia-Verdugo JM, Aguilar A, Schneider-Maunoury S, et al. Hedgehog signaling and primary cilia are required for the formation of adult neural stem cells. Nat Neurosci 2008;11:277-84.
40. Christensen ST, Clement CA, Satir P, Pedersen LB. Primary cilia and coordination of receptor tyrosine kinase (RTK) signalling. J Pathol 2012;226:172-84.
41. Schou KB, Pedersen LB, Christensen ST. Ins and outs of GPCR signaling in primary cilia. EMBO Rep 2015;16:1099-113.
42. Goetz SC, Anderson KV. The primary cilium: a signalling centre during vertebrate development. Nat Rev Genet 2010;11:331-44.
43. Wheway G, Nazlamova L, Hancock JT. Signaling through the primary cilium. Front Cell Dev Biol 2018;6:8.
44. Baker K, Beales PL. Making sense of cilia in disease: the human ciliopathies. Am J Med Genet C Semin Med Genet 2009;151C:281-95.
45. Waters AM, Beales PL. Ciliopathies: an expanding disease spectrum. Pediatr Nephrol 2011;26:1039-56.
46. Hildebrandt F, Benzing T, Katsanis N. Ciliopathies. N Engl J Med 2011;364:1533-43.
47. Dobyns WB, Curry CJ, Hoyme HE, Turlington L, Ledbetter DH. Clinical and molecular diagnosis of Miller-Dieker syndrome. Am J Hum Genet 1991;48:584-94.
48. Cardoso C, Leventer RJ, Ward HL, Toyo-Oka K, Chung J, Gross A, et al. Refinement of a 400-kb critical region allows genotypic differentiation between isolated lissencephaly, Miller-Dieker syndrome, and other phenotypes secondary to deletions of 17p13.3. Am J Hum Genet 2003;72:918-30.
49. Lo Nigro C, Chong CS, Smith AC, Dobyns WB, Carrozzo R, Ledbetter DH. Point mutations and an intragenic deletion in LIS1, the lissencephaly causative gene in isolated lissencephaly sequence and Miller-Dieker syndrome. Hum Mol Genet 1997;6:157-64.
50. Cardoso C, Leventer RJ, Matsumoto N, Kuc JA, Ramocki MB, Mewborn SK, et al. The location and type of mutation predict malformation severity in isolated lissencephaly caused by abnormalities within the LIS1 gene. Hum Mol Genet 2000;9:3019-28.
51. Dobyns WB, Reiner O, Carrozzo R, Ledbetter DH. Lissencephaly. A human brain malformation associated with deletion of the LIS1 gene located at chromosome 17p13. JAMA 1993;270:2838-42.
52. Sapir T, Cahana A, Seger R, Nekhai S, Reiner O. LIS1 is a microtubule-associated phosphoprotein. Eur J Biochem 1999;265:181-8.
53. Jimenez-Mateos EM, Wandosell F, Reiner O, Avila J, Gonzalez-Billault C. Binding of microtubule-associated protein 1B to LIS1 affects the interaction between dynein and LIS1. Biochem J 2005;389(Pt 2):333-41.
54. Yigit G, Wieczorek D, Bogershausen N, Beleggia F, Moller-Hartmann C, Altmuller J, et al. A syndrome of microcephaly, short stature, polysyndactyly, and dental anomalies caused by a homozygous KATNB1 mutation. Am J Med Genet A 2016;170:728-33.
55. Mishra-Gorur K, Caglayan AO, Schaffer AE, Chabu C, Henegariu O, Vonhoff F, et al. Mutations in KATNB1 cause complex cerebral malformations by disrupting asymmetrically dividing neural progenitors. Neuron 2014;84:1226-39.
56. McNally KP, Bazirgan OA, McNally FJ. Two domains of

p80 katanin regulate microtubule severing and spindle pole targeting by p60 katanin. J Cell Sci 2000;113(Pt 9):1623-33.
57. McNally FJ, Okawa K, Iwamatsu A, Vale RD. Katanin, the microtubule-severing ATPase, is concentrated at centrosomes. J Cell Sci 1996;109(Pt 3):561-7.
58. Hartman JJ, Mahr J, McNally K, Okawa K, Iwamatsu A, Thomas S, et al. Katanin, a microtubule-severing protein, is a novel AAA ATPase that targets to the centrosome using a WD40-containing subunit. Cell 1998;93:277-87.
59. Ahmad FJ, Yu W, McNally FJ, Baas PW. An essential role for katanin in severing microtubules in the neuron. J Cell Biol 1999;145:305-15.
60. Gandhi PN, Wang X, Zhu X, Chen SG, Wilson-Delfosse AL. The Roc domain of leucine-rich repeat kinase 2 is sufficient for interaction with microtubules. J Neurosci Res 2008;86:1711-20.
61. Liu GH, Qu J, Suzuki K, Nivet E, Li M, Montserrat N, et al. Progressive degeneration of human neural stem cells caused by pathogenic LRRK2. Nature 2012;491:603-7.
62. Kluss JH, Mamais A, Cookson MR. LRRK2 links genetic and sporadic Parkinson's disease. Biochem Soc Trans 2019;47:651-61.
63. Cirnaru MD, Marte A, Belluzzi E, Russo I, Gabrielli M, Longo F, et al. LRRK2 kinase activity regulates synaptic vesicle trafficking and neurotransmitter release through modulation of LRRK2 macro-molecular complex. Front Mol Neurosci 2014;7:49.
64. Farrer MJ, Stone JT, Lin CH, Dachsel JC, Hulihan MM, Haugarvoll K, et al. Lrrk2 G2385R is an ancestral risk factor for Parkinson's disease in Asia. Parkinsonism Relat Disord 2007;13:89-92.
65. Funayama M, Li Y, Tomiyama H, Yoshino H, Imamichi Y, Yamamoto M, et al. Leucine-rich repeat kinase 2 G2385R variant is a risk factor for Parkinson disease in Asian population. Neuroreport 2007;18:273-5.
66. Tan EK, Zhao Y, Skipper L, Tan MG, Di Fonzo A, Sun L, et al. The LRRK2 Gly2385Arg variant is associated with Parkinson's disease: genetic and functional evidence. Hum Genet 2007;120:857-63.
67. Carrion MDP, Marsicano S, Daniele F, Marte A, Pischedda F, Di Cairano E, et al. The LRRK2 G2385R variant is a partial loss-of-function mutation that affects synaptic vesicle trafficking through altered protein interactions. Sci Rep 2017;7:5377.
68. Scheibye-Knudsen M, Tseng A, Borch Jensen M, Scheibye-Alsing K, Fang EF, Iyama T, et al. Cockayne syndrome group A and B proteins converge on transcription-linked resolution of non-B DNA. Proc Natl Acad Sci U S A 2016;113:12502-7.
69. Allgrove J, Clayden GS, Grant DB, Macaulay JC. Familial glucocorticoid deficiency with achalasia of the cardia and deficient tear production. Lancet 1978;1:1284-6.
70. Grant DB, Barnes ND, Dumic M, Ginalska-Malinowska M, Milla PJ, von Petrykowski W, et al. Neurological and adrenal dysfunction in the adrenal insufficiency/alacrima/achalasia (3A) syndrome. Arch Dis Child 1993;68:779-82.
71. Handschug K, Sperling S, Yoon SJ, Hennig S, Clark AJ, Huebner A. Triple A syndrome is caused by mutations in AAAS, a new WD-repeat protein gene. Hum Mol Genet 2001;10:283-90.
72. Huebner A, Kaindl AM, Knobeloch KP, Petzold H, Mann P, Koehler K. The triple A syndrome is due to mutations in ALADIN, a novel member of the nuclear pore complex. Endocr Res 2004;30:891-9.
73. Hirano M, Furiya Y, Asai H, Yasui A, Ueno S. ALADINI482S causes selective failure of nuclear protein import and hypersensitivity to oxidative stress in triple A syndrome. Proc Natl Acad Sci U S A 2006;103:2298-303.
74. Storr HL, Kind B, Parfitt DA, Chapple JP, Lorenz M, Koehler K, et al. Deficiency of ferritin heavy-chain nuclear import in triple a syndrome implies nuclear oxidative damage as the primary disease mechanism. Mol Endocrinol 2009;23:2086-94.
75. Shaheen R, Abdel-Salam GM, Guy MP, Alomar R, Abdel-Hamid MS, Afifi HH, et al. Mutation in WDR4 impairs tRNA m(7)G46 methylation and causes a distinct form of microcephalic primordial dwarfism. Genome Biol 2015;16:210.
76. Trimouille A, Lasseaux E, Barat P, Deiller C, Drunat S, Rooryck C, et al. Further delineation of the phenotype caused by biallelic variants in the WDR4 gene. Clin Genet 2018;93:374-7.
77. Braun DA, Shril S, Sinha A, Schneider R, Tan W, Ashraf S, et al. Mutations in WDR4 as a new cause of Galloway-Mowat syndrome. Am J Med Genet A 2018;176:2460-5.
78. Pezzella M, Yeghiazaryan NS, Veggiotti P, Bettinelli A, Giudizioso G, Zara F, et al. Galloway-Mowat syndrome: an early-onset progressive encephalopathy with intractable epilepsy associated to renal impairment. Two novel cases and review of literature. Seizure 2010;19:132-5.
79. Krishnamurthy S, Rajesh NG, Ramesh A, Zenker M. Infantile nephrotic syndrome with microcephaly and global developmental delay: the Galloway Mowat Syndrome. Indian

J Pediatr 2012;79:1087-90.
80. Jinks RN, Puffenberger EG, Baple E, Harding B, Crino P, Fogo AB, et al. Recessive nephrocerebellar syndrome on the Galloway-Mowat syndrome spectrum is caused by homozygous protein-truncating mutations of WDR73. Brain 2015; 138(Pt 8):2173-90.
81. Colin E, Huynh Cong E, Mollet G, Guichet A, Gribouval O, Arrondel C, et al. Loss-of-function mutations in WDR73 are responsible for microcephaly and steroid-resistant nephrotic syndrome: Galloway-Mowat syndrome. Am J Hum Genet 2014;95:637-48.
82. Reid S, Schindler D, Hanenberg H, Barker K, Hanks S, Kalb R, et al. Biallelic mutations in PALB2 cause Fanconi anemia subtype FA-N and predispose to childhood cancer. Nat Genet 2007;39:162-4.
83. Cortellino S, Wang C, Wang B, Bassi MR, Caretti E, Champeval D, et al. Defective ciliogenesis, embryonic lethality and severe impairment of the Sonic Hedgehog pathway caused by inactivation of the mouse complex A intraflagellar transport gene Ift122/Wdr10, partially overlapping with the DNA repair gene Med1/Mbd4. Dev Biol 2009;325:225-37.
84. Bredrup C, Saunier S, Oud MM, Fiskerstrand T, Hoischen A, Brackman D, et al. Ciliopathies with skeletal anomalies and renal insufficiency due to mutations in the IFT-A gene WDR19. Am J Hum Genet 2011;89:634-43.
85. Mill P, Lockhart PJ, Fitzpatrick E, Mountford HS, Hall EA, Reijns MA, et al. Human and mouse mutations in WDR35 cause short-rib polydactyly syndromes due to abnormal ciliogenesis. Am J Hum Genet 2011;88:508-15.
86. Arts HH, Bongers EM, Mans DA, van Beersum SE, Oud MM, Bolat E, et al. C14ORF179 encoding IFT43 is mutated in Sensenbrenner syndrome. J Med Genet 2011;48:390-5.
87. Schmidts M, Frank V, Eisenberger T, Al Turki S, Bizet AA, Antony D, et al. Combined NGS approaches identify mutations in the intraflagellar transport gene IFT140 in skeletal ciliopathies with early progressive kidney disease. Hum Mutat 2013;34:714-24.
88. Davis EE, Zhang Q, Liu Q, Diplas BH, Davey LM, Hartley J, et al. TTC21B contributes both causal and modifying alleles across the ciliopathy spectrum. Nat Genet 2011;43:189-96.
89. Cavalcanti DP, Huber C, Sang KH, Baujat G, Collins F, Delezoide AL, et al. Mutation in IFT80 in a fetus with the phenotype of Verma-Naumoff provides molecular evidence for Jeune-Verma-Naumoff dysplasia spectrum. J Med Genet 2011; 48:88-92.
90. Halbritter J, Bizet AA, Schmidts M, Porath JD, Braun DA, Gee HY, et al. Defects in the IFT-B component IFT172 cause Jeune and Mainzer-Saldino syndromes in humans. Am J Hum Genet 2013;93:915-25.
91. Zhang W, Taylor SP, Nevarez L, Lachman RS, Nickerson DA, Bamshad M, et al. IFT52 mutations destabilize anterograde complex assembly, disrupt ciliogenesis and result in short rib polydactyly syndrome. Hum Mol Genet 2016;25: 4012-20.
92. Duran I, Taylor SP, Zhang W, Martin J, Forlenza KN, Spiro RP, et al. Destabilization of the IFT-B cilia core complex due to mutations in IFT81 causes a spectrum of short-rib polydactyly syndrome. Sci Rep 2016;6:34232.
93. Konstantinidou AE, Fryssira H, Sifakis S, Karadimas C, Kaminopetros P, Agrogiannis G, et al. Cranioectodermal dysplasia: a probable ciliopathy. Am J Med Genet A 2009;149A: 2206-11.
94. Levin LS, Perrin JC, Ose L, Dorst JP, Miller JD, McKusick VA. A heritable syndrome of craniosynostosis, short thin hair, dental abnormalities, and short limbs: cranioectodermal dysplasia. J Pediatr 1977;90:55-61.
95. Fry AE, Klingenberg C, Matthes J, Heimdal K, Hennekam RC, Pilz DT. Connective tissue involvement in two patients with features of cranioectodermal dysplasia. Am J Med Genet A 2009;149A:2212-5.
96. Gilissen C, Arts HH, Hoischen A, Spruijt L, Mans DA, Arts P, et al. Exome sequencing identifies WDR35 variants involved in Sensenbrenner syndrome. Am J Hum Genet 2010; 87:418-23.
97. Walczak-Sztulpa J, Eggenschwiler J, Osborn D, Brown DA, Emma F, Klingenberg C, et al. Cranioectodermal dysplasia, Sensenbrenner syndrome, is a ciliopathy caused by mutations in the IFT122 gene. Am J Hum Genet 2010;86:949-56.
98. Huber C, Wu S, Kim AS, Sigaudy S, Sarukhanov A, Serre V, et al. WDR34 mutations that cause short-rib polydactyly syndrome type III/severe asphyxiating thoracic dysplasia reveal a role for the NF-κB pathway in cilia. Am J Hum Genet 2013; 93:926-31.
99. McInerney-Leo AM, Schmidts M, Cortes CR, Leo PJ, Gener B, Courtney AD, et al. Short-rib polydactyly and Jeune syndromes are caused by mutations in WDR60. Am J Hum Genet 2013;93:515-23.
100. Tsurumi Y, Hamada Y, Katoh Y, Nakayama K. Interactions of the dynein-2 intermediate chain WDR34 with the light chains are required for ciliary retrograde protein trafficking. Mol Biol Cell 2019;30:658-70.
101. Asante D, Stevenson NL, Stephens DJ. Subunit composi-

tion of the human cytoplasmic dynein-2 complex. J Cell Sci 2014;127(Pt 21):4774-87.
102. Zhang W, Taylor SP, Ennis HA, Forlenza KN, Duran I, Li B, et al. Expanding the genetic architecture and phenotypic spectrum in the skeletal ciliopathies. Hum Mutat 2018;39:152-66.
103. Dixon-Salazar T, Silhavy JL, Marsh SE, Louie CM, Scott LC, Gururaj A, et al. Mutations in the AHI1 gene, encoding jouberin, cause Joubert syndrome with cortical polymicrogyria. Am J Hum Genet 2004;75:979-87.
104. Romani M, Micalizzi A, Valente EM. Joubert syndrome: congenital cerebellar ataxia with the molar tooth. Lancet Neurol 2013;12:894-905.
105. Parisi MA. Clinical and molecular features of Joubert syndrome and related disorders. Am J Med Genet C Semin Med Genet 2009;151C:326-40.
106. Gleeson JG, Keeler LC, Parisi MA, Marsh SE, Chance PF, Glass IA, et al. Molar tooth sign of the midbrain-hindbrain junction: occurrence in multiple distinct syndromes. Am J Med Genet A 2004;125A:125-34.
107. Rivero O, Reif A, Sanjuan J, Molto MD, Kittel-Schneider S, Najera C, et al. Impact of the AHI1 gene on the vulnerability to schizophrenia: a case-control association study. PLoS One 2010;5:e12254.
108. Alvarez Retuerto AI, Cantor RM, Gleeson JG, Ustaszewska A, Schackwitz WS, Pennacchio LA, et al. Association of common variants in the Joubert syndrome gene (AHI1) with autism. Hum Mol Genet 2008;17:3887-96.
109. Weng L, Lin YF, Li AL, Wang CE, Yan S, Sun M, et al. Loss of Ahi1 affects early development by impairing BM88/Cend1-mediated neuronal differentiation. J Neurosci 2013;33:8172-84.
110. Xu X, Yang H, Lin YF, Li X, Cape A, Ressler KJ, et al. Neuronal Abelson helper integration site-1 (Ahi1) deficiency in mice alters TrkB signaling with a depressive phenotype. Proc Natl Acad Sci U S A 2010;107:19126-31.
111. Hilgendorf KI, Johnson CT, Jackson PK. The primary cilium as a cellular receiver: organizing ciliary GPCR signaling. Curr Opin Cell Biol 2016;39:84-92.
112. Koemeter-Cox AI, Sherwood TW, Green JA, Steiner RA, Berbari NF, Yoder BK, et al. Primary cilia enhance kisspeptin receptor signaling on gonadotropin-releasing hormone neurons. Proc Natl Acad Sci U S A 2014;111:10335-40.
113. Leaf A, Von Zastrow M. Dopamine receptors reveal an essential role of IFT-B, KIF17, and Rab23 in delivering specific receptors to primary cilia. Elife 2015;4:e06996.
114. Brailov I, Bancila M, Brisorgueil MJ, Miquel MC, Hamon M, Verge D. Localization of 5-HT(6) receptors at the plasma membrane of neuronal cilia in the rat brain. Brain Res 2000;872:271-5.
115. Higginbotham H, Guo J, Yokota Y, Umberger NL, Su CY, Li J, et al. Arl13b-regulated cilia activities are essential for polarized radial glial scaffold formation. Nat Neurosci 2013;16:1000-7.
116. Nauli SM, Jin X, Hierck BP. The mechanosensory role of primary cilia in vascular hypertension. Int J Vasc Med 2011;2011:376281.
117. McCormack SE, Li D, Kim YJ, Lee JY, Kim SH, Rapaport R, et al. Digenic inheritance of PROKR2 and WDR11 mutations in pituitary stalk interruption syndrome. J Clin Endocrinol Metab 2017;102:2501-7.
118. Kim HG, Ahn JW, Kurth I, Ullmann R, Kim HT, Kulharya A, et al. WDR11, a WD protein that interacts with transcription factor EMX1, is mutated in idiopathic hypogonadotropic hypogonadism and Kallmann syndrome. Am J Hum Genet 2010;87:465-79.
119. Izumi Y, Suzuki E, Kanzaki S, Yatsuga S, Kinjo S, Igarashi M, et al. Genome-wide copy number analysis and systematic mutation screening in 58 patients with hypogonadotropic hypogonadism. Fertil Steril 2014;102:1130-6.
120. Raivio T, Avbelj M, McCabe MJ, Romero CJ, Dwyer AA, Tommiska J, et al. Genetic overlap in Kallmann syndrome, combined pituitary hormone deficiency, and septo-optic dysplasia. J Clin Endocrinol Metab 2012;97:E694-9.
121. Kim SH. Congenital hypogonadotropic hypogonadism and Kallmann syndrome: past, present, and future. Endocrinol Metab (Seoul) 2015;30:456-66.
122. Fraietta R, Zylberstejn DS, Esteves SC. Hypogonadotropic hypogonadism revisited. Clinics (Sao Paulo) 2013;68 Suppl 1(Suppl 1):81-8.
123. Boehm U, Bouloux PM, Dattani MT, de Roux N, Dode C, Dunkel L, et al. Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism. Pathogenesis, diagnosis and treatment. Nat Rev Endocrinol 2015;11:547-64.
124. Bonomi M, Libri DV, Guizzardi F, Guarducci E, Maiolo E, Pignatti E, et al. New understandings of the genetic basis of isolated idiopathic central hypogonadism. Asian J Androl 2012;14:49-56.
125. Brioude F, Bouligand J, Trabado S, Francou B, Salenave S, Kamenicky P, et al. Non-syndromic congenital hypogonad-

otropic hypogonadism: clinical presentation and genotype-phenotype relationships. Eur J Endocrinol 2010;162:835-51.
126. Kim YJ, Osborn DP, Lee JY, Araki M, Araki K, Mohun T, et al. WDR11-mediated Hedgehog signaling defects underlie a new ciliopathy related to Kallmann syndrome. EMBO Rep 2018;19:269-89.
127. Wolf MT, Saunier S, O'Toole JF, Wanner N, Groshong T, Attanasio M, et al. Mutational analysis of the RPGRIP1L gene in patients with Joubert syndrome and nephronophthisis. Kidney Int 2007;72:1520-6.
128. Akcan N, Bas F, Poyrazoglu S, Bundak R. Joubert syndrome with multiple pituitary hormone deficiency. BMJ Case Rep 2019;12:e229016.
129. Niceta M, Dentici ML, Ciolfi A, Marini R, Barresi S, Lepri FR, et al. Co-occurrence of mutations in KIF7 and KIAA0556 in Joubert syndrome with ocular coloboma, pituitary malformation and growth hormone deficiency: a case report and literature review. BMC Pediatr 2020;20:120.
130. Li HL, Zhang YJ, Chen XP, Luo JQ, Liu SY, Zhang ZL. Association between GNB3 c.825C > T polymorphism and the risk of overweight and obesity: a meta-analysis. Meta Gene 2016;9:18-25.
131. Rizvi S, Raza ST, Rahman Q, Mahdi F. Role of GNB3, NET, KCNJ11, TCF7L2 and GRL genes single nucleotide polymorphism in the risk prediction of type 2 diabetes mellitus. 3 Biotech 2016;6:255.
132. Klenke S, Kussmann M, Siffert W. The GNB3 C825T polymorphism as a pharmacogenetic marker in the treatment of hypertension, obesity, and depression. Pharmacogenet Genomics 2011;21:594-606.
133. Comuzzie AG, Cole SA, Laston SL, Voruganti VS, Haack K, Gibbs RA, et al. Novel genetic loci identified for the pathophysiology of childhood obesity in the Hispanic population. PLoS One 2012;7:e51954.
134. Green JS, Parfrey PS, Harnett JD, Farid NR, Cramer BC, Johnson G, et al. The cardinal manifestations of Bardet-Biedl syndrome, a form of Laurence-Moon-Biedl syndrome. N Engl J Med 1989;321:1002-9.
135. Adam MP, Ardinger HH, Pagon RA, Wallace SE. GeneReviews. Seattle: University of Washington, Seattle; 1993-2020. Chapter, Bardet-Biedl syndrome [cited 2020 Jul 28]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1363.
136. Kim SK, Shindo A, Park TJ, Oh EC, Ghosh S, Gray RS, et al. Planar cell polarity acts through septins to control collective cell movement and ciliogenesis. Science 2010;329:1337-40.
137. Toriyama M, Lee C, Taylor SP, Duran I, Cohn DH, Bruel AL, et al. The ciliopathy-associated CPLANE proteins direct basal body recruitment of intraflagellar transport machinery. Nat Genet 2016;48:648-56.
138. Heinen CA, Losekoot M, Sun Y, Watson PJ, Fairall L, Joustra SD, et al. Mutations in TBL1X are associated with central hypothyroidism. J Clin Endocrinol Metab 2016;101:4564-73.
139. Sugisawa C, Takamizawa T, Abe K, Hasegawa T, Shiga K, Sugawara H, et al. Genetics of congenital isolated TSH deficiency: mutation screening of the known causative genes and a literature review. J Clin Endocrinol Metab 2019;104:6229-37.
140. Zwaveling-Soonawala N, Naafs JC, Verkerk PH, van Trotsenburg ASP. Mortality in children with early-detected congenital central hypothyroidism. J Clin Endocrinol Metab 2018;103:3078-82.
141. Brooks BP, Kleta R, Caruso RC, Stuart C, Ludlow J, Stratakis CA. Triple-A syndrome with prominent ophthalmic features and a novel mutation in the AAAS gene: a case report. BMC Ophthalmol 2004;4:7.
142. Clark AJ, Weber A. Adrenocorticotropin insensitivity syndromes. Endocr Rev 1998;19:828-43.
143. Roucher-Boulez F, Brac de la Perriere A, Jacquez A, Chau D, Guignat L, Vial C, et al. Triple-A syndrome: a wide spectrum of adrenal dysfunction. Eur J Endocrinol 2018;178:199-207.
144. Tata B, Huijbregts L, Jacquier S, Csaba Z, Genin E, Meyer V, et al. Haploinsufficiency of Dmxl2, encoding a synaptic protein, causes infertility associated with a loss of GnRH neurons in mouse. PLoS Biol 2014;12:e1001952.
145. Gobe C, Elzaiat M, Meunier N, Andre M, Sellem E, Congar P, et al. Dual role of DMXL2 in olfactory information transmission and the first wave of spermatogenesis. PLoS Genet 2019;15:e1007909.

Supplemental Table S1. Full List of WDR Proteins Accessed

Gene name	Full name of the protein	Alternative name of the gene	Gene ID from NCBI RefSeq
A6NM71	PRA1 family protein		10567
A6P4T4	Tyrosine-protein kinase receptor		
A6P4V4	Tyrosine-protein kinase receptor		
A8MWR8	Highly similar to SEC13-related protein		6396
AAAS	Aladin WD repeat nucleoporin	AAA, AAASb, ADRACALA, ADRACALIN, ALADIN, GL003	8086
AAMP	Angio associated migratory cell protein		14
AHI1	Abelson helper integration site 1	AHI-1, JBTS3, ORF1, dJ71N10.1	54806
AMBRA1	Autophagy and beclin 1 regulator 1	DCAF3, WDR94	55626
APAF1	Apoptotic peptidase activating factor 1	APAF-1, CED4	317
ARPC1A	Actin related protein 2/3 complex subunit 1A	Arc40, HEL-68, HEL-S-307, SOP2Hs, SOP2L	10552
ARPC1B	Actin related protein 2/3 complex subunit 1B	ARC41, PLTEID, p40-ARC, p41-ARC	10095
ATG16L1	Autophagy related 16 like 1	APG16L, ATG16A, ATG16L, IBD10, WDR30	55054
ATG16L2	Autophagy related 16 like 2	ATG16B, WDR80	89849
B3KMW5	Highly similar to WD repeat protein 3		
B3KP68	Highly similar to homo sapiens selective LIM binding factor		
B3KP80	Highly similar to BTB/POZ domain-containing protein KCTD3		
B3KRR8	Highly similar to WD repeat protein 6		11180
B3KUA2	Highly similar to transducin-like enhancer protein 3		7090
B3KVI6	Highly similar to lipopolysaccharide-responsive and beige-like anchor protein		
B3KXA3	Highly similar to homo sapiens echinoderm microtubule associated protein like 1 (EML1)		
B3KXN4	Highly similar to WD repeat protein 1		
B4DDD4	WD repeat-containing protein 27	WDR27	253769
B4DDU7	Highly similar to aladin		
B4DE62	Highly similar to transducin-like enhancer protein 2		
B4DEF9	Highly similar to transducin-like enhancer protein 1		7088
B4DGB7	Highly similar to homo sapiens WD repeat domain 10 (WDR10)		
B4DGE3	Highly similar to homo sapiens SEC31-like 2 (SEC31L2), transcript variant 1		
B4DK45	Highly similar to WD repeat protein 6		
B4DL97	Highly similar to homo sapiens echinoderm microtubule associated protein like 3		256364
B4DMH3	Coronin		
B4DN30	Highly similar to WD repeat protein 21A		26094
B4DNL1	Highly similar to periodic tryptophan protein 1 homolog		
B4DPZ3	Highly similar to cytoplasmic dynein 1 intermediate chain 2		1781
B4DT22	Highly similar to peptidylprolyl isomerase domain and WD repeat-containing protein 1		23398
B4DTI1	Moderately similar to glutamate-rich WD repeat-containing protein 1		
B4DVD2	Highly similar to guanine nucleotide-binding protein subunit beta 2-like 1		

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Supplemental Table S1. Continued

Gene name	Full name of the protein	Alternative name of the gene	Gene ID from NCBI RefSeq
B4DVM5	Highly similar to WD repeat protein 24		
B4DVQ7	Highly similar to WD repeat protein 13		
B4DVX0	Highly similar to neurobeachin-like 1		
B4DWC6	Highly similar to guanine nucleotide-binding protein subunitbeta 2-like 1		
B4DX09	Moderately similar to bromodomain and WD repeat domain-containing protein 2		
B4DX93	Highly similar to cytoplasmic dynein 1 intermediate chain 2		
B4DYK8	B4DYK8		
B4DZX5	Moderately similar to homo sapiens WD repeat domain 1 (WDR1), transcript variant 2		
B4E018	Highly similar to WD repeat protein 74		
B4E068	Moderately similar to WD repeat protein 79		
B4E074	Highly similar to Notchless homolog 1		
B4E0E6	Highly similar to homo sapiens denticleless homolog (DTL)		51514
B4E1H5	Highly similar to cell division cycle protein 20 homolog		
B4E286	Highly similar to WD repeat protein 19		
B4E2R3	Highly similar to homo sapiens G protein beta subunit-like (GBL)		
B4E303	Highly similar to Notchless homolog 1		
B4E345	Weakly similar to protein groucho		
B4E383	Highly similar to DNA excision repair protein ERCC-8		
B4E3M9	Highly similar to breast carcinoma amplified sequence 3		
B6EXY3	Tyrosine-protein kinase receptor		
B7Z2F5	Highly similar to echinoderm microtubule-associated protein-like 2		
B7Z2P6	Highly similar to homo sapiens WD repeat domain 42A (WDR42A)		
B7Z475	Highly similar to F-box-like/WD repeat protein TBL1XR1		
B7Z6H0	Highly similar to sterol regulatory element-binding protein cleavage-activating protein		22937
B7Z872	Highly similar to echinoderm microtubule-associated protein-like 2		
B7Z918	Highly similar to echinoderm microtubule-associated protein-like 2		
BCAS3	BCAS3 microtubule associated cell migration factor	MAAB, GAOB1	54828
BOP1	BOP1 ribosomal biogenesis factor		23246
BRWD1	Bromodomain and WD repeat domain containing 1	C21orf107, DCAF19, N143, WDR9, WRD9	54014
BRWD3	Bromodomain and WD repeat domain containing 3	BRODL, MRX93	254065
BTRC	Beta-transducin repeat containing E3 ubiquitin protein ligase	BETA-TRCP, FBW1A, FBXW1, FBXW1A, FWD1, bTrCP, bTrCP1, betaTrCP	8945
BUB3	BUB3 mitotic checkpoint protein	BUB3L, hBUB3	9184
C2ORF44	WD repeat and coiled coil containing	WDCP, MMAP, PP384	80304
CDC20	Cell division cycle 20	CDC20A, bA276H19.3, p55CDC	991
CDC20B	Cell division cycle 20B	G6VTS76519	166979
CDC40	Cell division cycle 40	EHB3, PRP17, PRPF17	51362
CDRT1	CMT1A duplicated region transcript 1	C170RF1, C17ORF1, C17ORF1A, FBXW10B, FBXW10P1, HREP, SM25H2	374286
CFAP43	Cilia and flagella associated protein 43	C10orf79, HYDNP1, SPGF19, WDR96, bA373N18.2	80217

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Supplemental Table S1. Continued

Gene name	Full name of the protein	Alternative name of the gene	Gene ID from NCBI RefSeq
CFAP44	Cilia and flagella associated protein 44	SPGF20, WDR52	55779
CFAP52	Cilia and flagella associated protein 52	WDR16, WDRPUH	146845
CFAP57	Cilia and flagella associated protein 57	VWS2, WDR65	149465
CHAF1B	Chromatin assembly factor 1 subunit B	CAF-1, CAF-IP60, CAF1, CAF1A, CAF1P60, MPHOSPH7, MPP7	8208
CIAO1	Cytosolic iron-sulfur assembly component 1	CIA1, WDR39	9391
CIRH1A	UTP4 small subunit processome component	UTP4, CIRHIN, NAIC, TEX292	84916
COPA	COPI coat complex subunit alpha	AILJK, HEP-COP, alpha-COP	1314
COPB2	COPI coat complex subunit beta 2	MCPH19, beta'-COP	9276
CORO1A	Coronin 1A	CLABP, CLIPINA, HCORO1, IMD8, TACO, p57	11151
CORO1B	Coronin 1B	CORONIN-2	57175
CORO1C	Coronin 1C	HCRNN4	23603
CORO2A	Coronin 2A	CLIPINB, IR10, WDR2	7464
CORO2B	Coronin 2B	CLIPINC	10391
CORO6	Coronin 6		84940
CORO7	Coronin 7	0610011B16Rik, CRN7, POD1	79585
CSTF1	Cleavage stimulation factor subunit 1	CstF-50, CstFp50	1477
DAW1	Dynein assembly factor with WD repeats 1	ODA16, WDR69	164781
DCAF10	DDB1 and CUL4 associated factor 10	WDR32	79269
DCAF11	DDB1 and CUL4 associated factor 11	GL014, PRO2389, WDR23	80344
DCAF12	DDB1 and CUL4 associated factor 12	CT102, TCC52, WDR40A, KIAA1892	25853
DCAF12L1	DDB1 and CUL4 associated factor 12 like 1	KIAA1892L, WDR40B	139170
DCAF12L2	DDB1 and CUL4 associated factor 12 like 2	WDR40C	340578
DCAF13	DDB1 and CUL4 associated factor 13	GM83, HSPC064, Sof1, WDSOF1	25879
DCAF4	DDB1 and CUL4 associated factor 4	WDR21, WDR21A	26094
DCAF4L1	DDB1 and CUL4 associated factor 4 like 1	WDR21B	285429
DCAF4L2	DDB1 and CUL4 associated factor 4 like 2	WDR21C	138009
DCAF5	DDB1 and CUL4 associated factor 5	BCRG2, BCRP2, D14S1461E, WDR22	8816
DCAF6	DDB1 and CUL4 associated factor 6	1200006M05Rik, ARCAP, IQWD1, MSTP055, NRIP, PC326	55827
DCAF7	DDB1 and CUL4 associated factor 7	AN11, HAN11, SWAN-1, WDR68	10238
DCAF8	DDB1 and CUL4 associated factor 8	GAN2, H326, WDR42A	50717
DCAF8L1	DDB1 and CUL4 associated factor 8 like 1	WDR42B	139425
DCAF8L2	DDB1 and CUL4 associated factor 8 like 2	WDR42C	347442
DDB2	Damage specific DNA binding protein 2	DDBB, UV-DDB2, XPE	1643
DENND3	DENN domain containing 3		22898
DKFZ-P434D199	U5 small nuclear ribonucleoprotein 40 kDa protein	SNRNP40	
DKFZ-P451A177	Uncharacterized protein DKFZp451A177	DKFZp451A177	
DKFZ-P779C159	Uncharacterized protein DKFZp779C159	DKFZp779C159	
DMWD	DM1 locus, WD repeat containing	D19S593E, DMR-N9, DMRN9, gene59	1762

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Supplemental Table S1. Continued

Gene name	Full name of the protein	Alternative name of the gene	Gene ID from NCBI RefSeq
DMXL1	Dmx like 1		1657
DMXL2	Dmx like 2	RC3, PEPNS, DFNA71, EIEE81	23312
DNAI1	Dynein axonemal intermediate chain 1	CILD1, DIC1, ICS1, PCD	27019
DNAI2	Dynein axonemal intermediate chain 2	CILD9, DIC2	64446
DPH7	Diphthamide biosynthesis 7	C9orf112, RRT2, WDR85	92715
DTL	Denticleless E3 ubiquitin protein ligase homolog	CDT2, RAMP, DCAF2, L2DTL	51514
DYNC1I1	Dynein cytoplasmic 1 intermediate chain 1	DNCI1, DNCIC1	1780
DYNC1I2	Dynein cytoplasmic 1 intermediate chain 2	DIC74, DNCI2, IC2, NEDMIBA	1781
EDC4	Enhancer of mRNA decapping 4	GE1, Ge-1, RCD8, HEDL5, HEDLS, RCD-8	23644
EED	Embryonic ectoderm development	EED, COGIS, WAIT1	8726
EIF2A	Eukaryotic translation initiation factor 2A	CDA02, EIF-2A, MST089, MSTP004, MSTP089	83939
EIF3B	Eukaryotic translation initiation factor 3 subunit B	EIF3-ETA, EIF3-P110, EIF3-P116, EIF3S9, PRT1	8662
EIF3I	Eukaryotic translation initiation factor 3 subunit I	EIF3S2, PRO2242, TRIP-1, TRIP1, eIF3-beta, eIF3-p36	8668
ELP2	Elongator acetyltransferase complex subunit 2	StIP, MRT58, SHINC-2, STATIP1	55250
EML1	EMAP like 1	BH, ELP79, EMAP, EMAP-1, EMAPL	2009
EML2	EMAP like 2	ELP70, EMAP-2, EMAP2	24139
EML3	EMAP like 3	ELP95, EMAP3, EMAP95	256364
EML4	EMAP like 4	C2orf2, ELP120, EMAP-4, EMAPL4, ROPP120	27436
EML4-ALK	Tyrosine-protein kinase receptor	EML4-ALK	
EML5	EMAP like 5	EMAP-2, EMAP-5, FAP16	161436
EML6	EMAP like 6		400954
ERCC8	ERCC excision repair 8, CSA ubiquitin ligase complex subunit	CSA, CKN1, UVSS2	1161
FBXW10	F-box and WD repeat domain containing 10	Fbw10, HREP, SM25H2, SM2SH2	10517
FBXW11	F-box and WD repeat domain containing 11	BTRC2, BTRCP2, FBW1B, FBXW1B, Fbw11, Hos	23291
FBXW12	F-box and WD repeat domain containing 12	FBW12, FBXO12, FBXO35	285231
FBXW2	F-box and WD repeat domain containing 2	Md6, FBW2, Fwd2	26190
FBXW4	F-box and WD repeat domain containing 4	DAC, FBW4, FBWD4, SHFM3, SHSF3	6468
FBXW5	F-box and WD repeat domain containing 5	Fbw5	54461
FBXW7	F-box and WD repeat domain containing 7	AGO, CDC4, FBW6, FBW7, FBX30, FBXO30, FBXW6, SEL-10, SEL10, hAgo, hCdc4	55294
FBXW8	F-box and WD repeat domain containing 8	FBW6, FBW8, FBX29, FBXO29, FBXW6	26259
FBXW9	F-box and WD repeat domain containing 9	Fbw9, MEC-15	84261
FLJ00012	FLJ00012 protein		89849
FLJ00025	FLJ00025 protein	FLJ00025	
FZR1	Fizzy and cell division cycle 20 related 1	CDC20C, CDH1, FZR, FZR2, HCDH, HCDH1	51343
GEMIN5	Gem nuclear organelle associated protein 5	GEMIN-5	25929
GNB1	G protein subunit beta 1	MRD42	2782

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Supplemental Table S1. Continued

Gene name	Full name of the protein	Alternative name of the gene	Gene ID from NCBI RefSeq
GNB1L	G protein subunit beta 1 like	DGCRK3, FKSG1, GY2, WDR14, WDVCF	54584
GNB2	G protein subunit beta 2		2783
GNB2L1	Receptor for activated C kinase 1	GNB2L1, Gnb2-rs1, H12.3, HLC-7, PIG21	10399
GNB3	G protein subunit beta 3	CSNB1H	2784
GNB4	G protein subunit beta 4	CMTD1F	59345
GNB5	G protein subunit beta 5	GB5, IDDCA, LADCI, gbeta5	10681
GRWD1	Glutamate rich WD repeat containing 1	CDW4, GRWD, RRB1, WDR28	83743
GTF3C2	General transcription factor IIIC subunit 2	TFIIIC-BETA, TFIIIC110	2976
H0YL77	Uncharacterized protein		
H3BRJ5	Uncharacterized protein		
HERC1	HECT and RLD domain containing E3 ubiquitin protein ligase family member 1	p532, p619, MDFPMR	8925
HIRA	Histone cell cycle regulator	DGCR1, TUP1, TUPLE1	7290
HPS5	HPS5 biogenesis of lysosomal organelles complex 2 subunit 2	AIBP63, BLOC2S2	11234
IFT122	Intraflagellar transport 122	CED, CED1, FAP80, SPG, WDR10, WDR10p, WDR140	55764
IFT140	Intraflagellar transport 140	MZSDS, RP80, SRTD9, WDTC2, c305C8.4, c380F5.1, gs114	9742
IFT172	Intraflagellar transport 172	BBS20, NPHP17, RP71, SLB, SRTD10, osm-1, wim	26160
IFT80	Intraflagellar transport 80	ATD2, FAP167, SRTD2, WDR56	57560
KATNB1	Katanin regulatory subunit B1	KAT, LIS6	10300
KCTD3	Potassium channel tetramerization domain containing 3	NY-REN-45	51133
KIF21A	Kinesin family member 21A	CFEOM1, FEOM1, FEOM3A	55605
KIF21B	Kinesin family member 21B		23046
LLGL1	LLGL scribble cell polarity complex component 1	DLG4, HUGL, LLGL, Lgl1, Mgl1, HUGL1, HUGL-1	3996
LLGL2	LLGL scribble cell polarity complex component 2	HGL, Hugl-2, LGL2	3993
LRBA	LPS responsive beige-like anchor protein	BGL, CDC4L, CVID8, LAB300, LBA	987
LRRK2	Leucine rich repeat kinase 2	PARK8, RIPK7, ROCO2, AURA17, DARDARIN	120892
LRWD1	Leucine rich repeats and WD repeat domain containing 1	CENP-33, ORCA	222229
LYST	Lysosomal trafficking regulator	CHS, CHS1	1130
MAPKBP1	Mitogen-activated protein kinase binding protein 1	JNKBP-1, JNKBP1, NPHP20	23005
MED16	Mediator complex subunit 16	DRIP92, THRAP5, TRAP95	10025
MIOS	Meiosis regulator for oocyte development	MIO, Sea4, Yulink	54468
MLST8	MTOR associated protein, LST8 homolog	GBL, GbetaL, LST8, POP3, WAT1	64223
NBAS	NBAS subunit of NRZ tethering complex	ILFS2, NAG, SOPH	51594
NBEA	Neurobeachin	BCL8B, LYST2	26960
NBEAL1	Neurobeachin like 1	A530083I02Rik, ALS2CR16, ALS2CR17	65065
NBEAL2	Neurobeachin like 2	BDPLT4, GPS	23218
NEDD1	NEDD1 gamma-tubulin ring complex targeting factor	GCP-WD, TUBGCP7	121441
NLE1	Notchless homolog 1	NLE	54475

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Supplemental Table S1. Continued

Gene name	Full name of the protein	Alternative name of the gene	Gene ID from NCBI RefSeq
NOL10	Nucleolar protein 10		79954
NSMAF	Neutral sphingomyelinase activation associated factor	FAN, GRAMD5	8439
NUP214	Nucleoporin 214	CAN, CAIN, IIAE9	8021
NUP37	Nucleoporin 37	MCPH24, p37	79023
NUP43	Nucleoporin 43	bA350J20.1, p42	348995
NWD1	NACHT and WD repeat domain containing 1		284434
NWD2	NACHT and WD repeat domain containing 2	KIAA1239	57495
PAAF1	Proteasomal ATPase associated factor 1	PAAF, Rpn14, WDR71	80227
PAFAH1B1	Platelet activating factor acetylhydrolase 1b regulatory subunit 1	LIS1, LIS2, MDCR, MDS, NudF, PAFAH	5048
PAK1IP1	PAK1 interacting protein 1	MAK11, PIP1, WDR84, bA421M1.5, hPIP1	55003
PALB2	Partner and localizer of BRCA2	FANCN, PNCA3	79728
PAN2	Poly(A) specific ribonuclease subunit PAN2	USP52	9924
PEX7	Peroxisomal biogenesis factor 7	PBD9B, PTS2R, RCDP1, RD	5191
PHIP	Pleckstrin homology domain interacting protein	ndrp, BRWD2, DIDOD, WDR11, DCAF14, CHUJANS	55023
PIK3R4	Phosphoinositide-3-kinase regulatory subunit 4	VPS15, p150	30849
PLAA	Phospholipase A2 activating protein	DOA1, NDMSBA, PLA2P, PLAP	9373
PLRG1	Pleiotropic regulator 1	Cwc1, PRL1, PRP46, PRPF46, TANGO4	5356
POC1A	POC1 centriolar protein A	PIX2, SOFT, WDR51A	25886
POC1B	POC1 centriolar protein B	PIX1, CORD20, TUWD12, WDR51B	282809
PPP2R2A	Protein phosphatase 2 regulatory subunit B alpha	B55A, PR52A, PR55A, B55ALPHA, PR55alpha	5520
PPP2R2B	Protein phosphatase 2 regulatory subunit B beta	B55BETA, PP2AB55BETA, PP2AB-BETA, PP2APR55B, PP2APR55BETA, PR2AB55BETA, PR2ABBETA, PR2A-PR55BETA, PR52B, PR55-BETA, PR-55BETA, SCA12	5521
PPP2R2C	Protein phosphatase 2 regulatory subunit B gamma	B55-GAMMA, B55gamma, IMYPNO, IMYPNO1, PR52, PR55G	5522
PPP2R2D	Protein phosphatase 2 regulatory subunit B delta	B55D, B55delta, MDS026	55844
PPWD1	Peptidylprolyl isomerase domain and WD repeat containing 1		23398
PREB	Prolactin regulatory element binding	SEC12	10113
PRPF19	Pre-mRNA processing factor 19	PSO4, SNEV, PRP19, UBOX4, hPSO4, NMP200	27339
PRPF4	Pre-mRNA processing factor 4	HPRP4, HPRP4P, PRP4, Prp4p, RP70, SNRNP60	9128
PWP1	PWP1 homolog, endonuclein	IEF-SSP-9502	11137
PWP2	PWP2 small subunit processome component	EHOC-17, PWP2H, UTP1	5822
Q2VIM1	RcCDC20	RcCDC20	
Q53F40	F-box protein FBW7 isoform 2 variant		
Q59EB2	Uncharacterized protein		374286
Q59EY9	Transducin-like enhancer of split 3 splice variant 1 variant		
Q59EZ2	Telomerase protein component 1 variant		
Q59F81	Coronin		

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Supplemental Table S1. Continued

Gene name	Full name of the protein	Alternative name of the gene	Gene ID from NCBI RefSeq
Q59FM2	PWP2 periodic tryptophan protein homolog		
Q59GC6	Serine/threonine-protein phosphatase 2A 55 kDa regulatory subunit B		
Q59GN6	WD repeat domain 23 isoform 1 variant		80344
Q6ZP32	Highly similar to Serine/threonine protein phosphatase 2A, 55 kDa regulatory subunit B		
Q6ZS54	FLJ45821 fis		
Q6ZW40	FLJ41631 fis		
Q6ZW98	Moderately similar to Human actin binding protein p57		
Q8N797	FLJ25882 fis		
Q8N7X6	FLJ40237 fis		
Q8TCI4	FLJ23854 fis		
Q9H8N9	Weakly similar to BETA-TRCP (BETA-TRANSDUCIN REPEAT-CONTAINING PROTEIN)		57590
Q9NWG8	FLJ10035 fis		
Q9Y6S1	R26610_1		
RAE1	Ribonucleic acid export 1	Gle2, MIG14, MRNP41, Mnrp41, dJ481F12.3, dJ800J21.1	8480
RBBP4	RB binding protein 4, chromatin remodeling factor	NURF55, RBAP48	5928
RBBP5	RB binding protein 5, histone lysine methyltransferase complex subunit	RBQ3, SWD1	5929
RBBP7	RB binding protein 7, chromatin remodeling factor	RbAp46	5931
RFWD2	COP1–COP1 E3 ubiquitin ligase	COP1, CFAP78, FAP78, RNF200	64326
RFWD3	Ring finger and WD repeat domain 3	FANCW, RNF201	55159
RIC1	RIC1 homolog, RAB6A GEF complex partner 1	CATIFA, CIP150, KIAA1432, bA207C16.1	57589
RPTOR	Regulatory associated protein of MTOR complex 1	KOG1, Mip1	57521
RRP9	Ribosomal RNA processing 9, U3 small nucleolar RNA binding protein	RNU3IP2, U3-55K	9136
SCAP	SREBF chaperone		22937
SEC13	SEC13 homolog, nuclear pore and COPII coat complex component	D3S1231E, SEC13L1, SEC13R, npp-20	6396
SEC31A	SEC31 homolog A, COPII coat complex component	ABP125, ABP130, HSPC275, HSPC334, NEDSOSB, SEC31L1	22872
SEC31B	SEC31 homolog B, COPII coat complex component	SEC31B-1, SEC31L2	25956
SEH1L	SEH1 like nucleoporin	Seh1, SEH1A, SEH1B, SEC13L	81929
SHKBP1	SH3KBP1 binding protein 1	PP203, Sb1	92799
SMU1	SMU1 DNA replication regulator and spliceosomal factor	BWD, SMU-1, fSAP57	55234
SNRNP40	Small nuclear ribonucleoprotein U5 subunit 40	40K, HPRP8BP, PRP8BP, PRPF8BP, SPF38, WDR57	9410
SPAG16	Sperm associated antigen 16	PF20, WDR29	79582
STRAP	Serine/threonine kinase receptor associated protein	MAWD, PT-WD, UNRIP	11171
STRN	STRN		6801
STRN3	Striatin 3	PPP2R6B, S/G2NA, SG2NA	29966
STRN4	Striatin 4	PPP2R6C, ZIN, zinedin	29888
STXBP5	Syntaxin binding protein 5	LGL3, LLGL3, Nbla04300	134957
STXBP5L	Syntaxin binding protein 5 like	LLGL4	9515
TAF5	TATA-box binding protein associated factor 5	TAF(II)100, TAF2D, TAFII-100, TAFII100	6877

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Supplemental Table S1. Continued

Gene name	Full name of the protein	Alternative name of the gene	Gene ID from NCBI RefSeq
TAF5L	TATA-box binding protein associated factor 5 like	PAF65B	27097
TBC1D31	TBC1 domain family member 31	Gm85, WDR67	93594
TBL1X	Transducin beta like 1 X-linked	CHNG8, EBI, SMAP55, TBL1	6907
TBL1XR1	TBL1X receptor 1	C21, DC42, IRA1, MRD41, TBLR1	79718
TBL1Y	Transducin beta like 1 Y-linked	DFNY2, TBL1	90665
TBL2	Transducin beta like 2	WBSCR13, WS-betaTRP	26608
TBL3	Transducin beta like 3	SAZD, UTP13	10607
TECPR2	Tectonin beta-propeller repeat containing 2	KIAA0329, SPG49	9895
TEP1	Telomerase associated protein 1	TLP1, TP1, TROVE1, VAULT2, p240	7011
THOC3	THO complex 3	THO3, hTREX45	84321
THOC6	THO complex 6	WDR58, fSAP35	79228
TLE1	TLE family member 1, transcriptional corepressor	ESG, ESG1, GRG1	7088
TLE2	TLE family member 2, transcriptional corepressor	ESG, ESG2, GRG2	7089
TLE3	TLE family member 3, transcriptional corepressor	ESG, ESG3, GRG3, HsT18976	7090
TLE4	TLE family member 4, transcriptional corepressor	BCE-1, BCE1, E(spI), E(spl), ESG, ESG4, GRG4, Grg-4	7091
TLE6	TLE family member 6, subcortical maternal complex member	GRG6, PREMBL	79816
TRAF7	TNF receptor associated factor 7	CAFDADD, RFWD1, RNF119	84231
TSSC1	EARP complex and GARP complex interacting protein 1	EIPR1, EIPR-1	7260
TULP4	TUB like protein 4	TUSP	56995
UTP15	UTP15 small subunit processome component	NET21	84135
UTP18	UTP18 small subunit processome component	CGI-48, WDR50	51096
UTP4	UTP4 small subunit processome component	CIRH1A, CIRHIN, NAIC, TEX292	84916
VPRBP	DCAF1–DDB1 and CUL4 associated factor 1	DCAF1, RIP	9730
WDF3	WD40-and FYVE-domain containing protein 3	WDF3	
WDFY1	WD repeat and FYVE domain containing 1	FENS-1, FENS1, WDF1, ZFYVE17	57590
WDFY2	WD repeat and FYVE domain containing 2	PROF, WDF2, ZFYVE22	115825
WDFY3	WD repeat and FYVE domain containing 3	ALFY, BCHS, MCPH18, ZFYVE25	23001
WDFY4	WDFY family member 4	C10orf64	57705
WDHD1	WD repeat and HMG-box DNA binding protein 1	AND-1, AND1, CHTF4, CTF4	11169
WDPCP	WD repeat containing planar cell polarity effector	BBS15, C2orf86, CHDTHP, CPLANE5, FRITZ, FRTZ	51057
WDR1	WD repeat domain 1	AIP1, HEL-S-52, NORI-1	9948
WDR11	WD repeat domain 11	BRWD2, DR11, HH14, SRI1, WDR15	55717
WDR12	WD repeat domain 12	YTM1	55759
WDR13	WD repeat domain 13	MG21	64743
WDR17	WD repeat domain 17		116966
WDR18	WD repeat domain 18	Ipi3, R32184_1	57418
WDR19	WD repeat domain 19	ATD5, CED4, DYF-2, FAP66, ORF26, Oseg6, PWDMP, SRTD5, IFT144, NPHP13	57728
WDR20	WD repeat domain 20	DMR	91833
WDR24	WD repeat domain 24	C16orf21, JFP7	84219
WDR25	WD repeat domain 25	C14orf67	79446

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Supplemental Table S1. Continued

Gene name	Full name of the protein	Alternative name of the gene	Gene ID from NCBI RefSeq
WDR26	WD repeat domain 26	CDW2, GID7, MIP2, SKDEAS	80232
WDR27	WD repeat domain 27		253769
WDR3	WD repeat domain 3	DIP2, UTP12	10885
WDR31	WD repeat domain 31		114987
WDR33	WD repeat domain 33	NET14, WDC146	55339
WDR34	Dynein 2 intermediate chain 2	CFAP133, DIC5, FAP133, SRTD11, WDR34, bA216B9.3	89891
WDR35	WD repeat domain 35	CED2, FAP118, IFT121, IFTA1, SRTD7	57539
WDR36	WD repeat domain 36	GLC1G, TA-WDRP, TAWDRP, UTP21	134430
WDR37	WD repeat domain 37	NOCGUS	22884
WDR38	WD repeat domain 38		401551
WDR4	WD repeat domain 4	GAMOS6, MIGSB, TRM82, TRMT82, hWH	10785
WDR41	WD repeat domain 41	MSTP048	55255
WDR43	WD repeat domain 43	NET12, UTP5	23160
WDR44	WD repeat domain 44	RAB11BP, RPH11, SYM-4	54521
WDR45	WD repeat domain 45	JM5, NBIA4, NBIA5, WDRX1, WIPI-4, WIPI4	11152
WDR45B	WD repeat domain 45B	NEDSBAS, WDR45L, WIPI-3, WIPI3	56270
WDR46	WD repeat domain 46	BING4, C6orf11, FP221, UTP7	9277
WDR47	WD repeat domain 47		22911
WDR48	WD repeat domain 48	P80, SPG60, UAF1	57599
WDR49	WD repeat domain 49		151790
WDR5	WD repeat domain 5	BIG-3, CFAP89, SWD3	11091
WDR53	WD repeat domain 53		348793
WDR54	WD repeat domain 54		84058
WDR55	WD repeat domain 55		54853
WDR59	WD repeat domain 59	CDW12, FP977, p90-120	79726
WDR5B	WD repeat domain 5B		54554
WDR6	WD repeat domain 6		11180
WDR60	Dynein 2 intermediate chain 1	DYNC2I1, FAP163, DIC6, FAP163, SRPS6, SRTD8	55112
WDR61	WD repeat domain 61	REC14, SKI8	80349
WDR62	WD repeat domain 62	C19orf14, MCPH2	284403
WDR63	Dynein axonemal intermediate chain 3	DNAI3, DIC3, NYD-SP29	126820
WDR64	WD repeat domain 64		128025
WDR66	Cilia and flagella associated protein 251	CFAP251, CaM-IP4, SPGF33	144406
WDR7	WD repeat domain 7	TRAG	23335
WDR70	WD repeat domain 70		55100
WDR72	WD repeat domain 72	AI2A3	256764
WDR73	WD repeat domain 73	GAMOS, GAMOS1, HSPC264	84942
WDR74	WD repeat domain 74	Nsa1	54663
WDR75	WD repeat domain 75	NET16, UTP17	84128
WDR76	WD repeat domain 76	CDW14	79968

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Supplemental Table S1. Continued

Gene name	Full name of the protein	Alternative name of the gene	Gene ID from NCBI RefSeq
WDR77	WD repeat domain 77	p44, MEP50, MEP-50, HKMT1069, Nbla10071, p44/Mep50	79084
WDR78	Dynein axonemal intermediate chain 4	DNAI4, DIC4	79819
WDR81	WD repeat domain 81	CAMRQ2, HYC3, PPP1R166, SORF-2	124997
WDR82	WD repeat domain 82	MST107, MSTP107, PRO2730, PRO34047, SWD2, TMEM113, WDR82A	80335
WDR83	WD repeat domain 83	MORG1	84292
WDR86	WD repeat domain 86		349136
WDR87	WD repeat domain 87	NYD-SP11	83889
WDR88	WD repeat domain 88	PQWD	126248
WDR89	WD repeat domain 89	C14orf150, MSTP050	112840
WDR90	WD repeat domain 90	C16orf15, C16orf16, C16orf17, C16orf18, C16orf19, POC16	197335
WDR91	WD repeat domain 91	HSPC049, SORF-1, SORF1	29062
WDR92	WD repeat domain 92		116143
WDR97	WD repeat domain 97	KIAA1875	340390
WDSUB1	WD repeat, sterile alpha motif and U-box domain containing 1	UBOX6, WDSAM1	151525
WDTC1	WD and tetratricopeptide repeats 1	ADP, DCAF9	23038
WIPI1	WD repeat domain, phosphoinositide interacting 1	ATG18, ATG18A, WIPI49	55062
WIPI2	WD repeat domain, phosphoinositide interacting 2	ATG18B, Atg21, CGI-50, IDDSSA, WIPI-2	26100
WRAP53	WD repeat containing antisense to TP53	DKCB3, TCAB1, WDR79	55135
WRAP73	WD repeat containing, antisense to TP73	WDR8	49856
WSB1	WD repeat and SOCS box containing 1	SWIP1, WSB-1	26118
WSB2	WD repeat and SOCS box containing 2	SBA2	55884
ZNF106	Zinc finger protein 106	SH3BP3, ZFP106, ZNF474	64397

WDR, WD40-repeat; NCBI, National Center for Biotechnology Information.

Supplemental Table S2. List of WDR Proteins Related to Other Disorders

WDR protein	Phenotype	MIM number	Mode of inheritance
Immune deficiency			
COPA	Autoimmune interstitial lung, joint, and kidney disease	616414	AD
CORO1A	Immunodeficiency	615401	AR
LYST	Chediak-Higashi syndrome	214500	AR
LRBA	Immunodeficiency	614700	AR
RFWD3	Fanconi anemia, complementation group W	617784	AR
NBEAL2	Gray platelet syndrome	139090	AR
DDB2	Xeroderma pigmentosum	278740	AR
Eye defect			
PRPF4	Retinitis pigmentosa	615922	AD
POC1B	Cone-rod dystrophy	615973	AR
HPS5	Hermansky-Pudlak syndrome	614074	AR
KIF21A	Fibrosis of extraocular muscles, congenital	135700	AD
WDR36	Glaucoma, open angle	609887	Multifactoral
GNB3	Hypertension	145500	Multifactoral
	Night blindness	617024	AR
Cancer predisposition			
NUP214	Encephalopathy, acute, infection-induced	618426	AR
	Leukemia, acute myeloid, somatic	601626	
	Leukemia, T-cell acute lymphoblastic, somatic	613065	
PALB2	Breast cancer, susceptibility to	114480	Multifactoral
	Pancreatic cancer, susceptibility to	613348	
	Fanconi anemia, complementation group N	610832	
GNB1	Leukemia, acute lymphoblastic, somatic	613065	
	Mental retardation	616973	AD
Skeletal defect			
EED	Cohen-Gibson syndrome	617561	AD
POC1A	Short stature, onychodysplasia, facial dysmorphism, and hypotrichosis	614813	AR
TECPR2	Spastic paraplegia 49, autosomal recessive	615031	AR
Inflammation			
ATG16L1	Inflammatory bowel disease (Crohn disease)	611081	Not determined
ARPC1B	Platelet abnormalities with eosinophilia and immune-mediated inflammatory disease	617718	AR
Others[a]			
WRAP53	Dyskeratosis congenita	613988	AR
NBAS	Infantile liver failure syndrome	616483	AR
	Short stature, optic nerve atrophy, and Pelger-Huet anomaly	614800	AR
TLE6	Preimplantation embryonic lethality	616814	AR
TRAF7	Cardiac, facial, and digital anomalies with developmental delay	618164	AD
TBL1Y	Deafness, Y-linked	400047	YL
WDR72	Amelogenesis imperfecta, type IIA3	613211	AR
PEX7	Peroxisome biogenesis disorder	614879	AR
	Rhizomelic chondrodysplasia punctata, type 1	215100	AR

WDR, WD40-repeat; MIM, Mendelian Inheritance in Man; AD, autosomal dominant; AR, autosomal recessive; YL, Y-linked.
[a]Including multi-organ defects, liver failure, cardiovascular defects, and embryonic lethality.