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
and 212 in *Drosophila melanogaster*. WDR proteins are rarely present in prokaryotes [2]. Each WDR protein can have 4 to 16 copies of WD40s 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 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].

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].

**WDR PROTEINS IN HUMAN DISEASE**

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 is 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, tetraoctapeptide repeats and coiled coils motifs [22], facilitating the interaction and transport of multiple cargos such as tubulin and dynein components [22,36,37]. Primary cilia 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). PFAH1B1 (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]. PFAH1B1 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 PFAH1B1 [50]. PFAH1B1 is a microtubule-associated phosphoprotein and its direct interaction with cytoplasmic dynein heavy chain is important for neuronal migration, disruptions of which result in lissencephaly [52,53].

Mutations in KATNB1 (LIS6) are associated with complex cerebro 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/index.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 Tmm82p and forms a complex...
| WDR protein | Associated diseases | MIM number | Mode of inheritance |
|-------------|---------------------|------------|---------------------|
| LRRK2       | Parkinson disease   | 607060     | AD                  |
| PPP2R2B     | Spinocerebellar ataxia | 604326     | AD                  |
| TBL1XR1     | Mental retardation, Pierpont syndrome | 619644, 602342 | AD, AD |
| ERCC8       | Cockayne syndrome, type A, UV-sensitive syndrome | 216400, 614621 | AR, AR |
| PAFAH1B1 (LIS1) | Lissencephaly, Subcortical laminar heterotopia | 607432, 607432 | AD, 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                  |
| DYN1C12     | Neurodevelopmental disorder with microcephaly and structural brain anomalies | 618492 | AR |
| ELP2        | Mental disability   | 617270     | AR                  |
| GNB4        | Charcot-Marie-Tooth disease | 615185     | AR                  |
| SEC31A      | Neurodevelopmental disorder with spastic quadriplegia, optic atrophy, seizures, and structural brain anomalies | 616851 | 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 |
| WDF3Y       | Primary microcephaly | 617520     | AD                  |
| WDR62       | Primary microcephaly, with or without cortical malformations | 604317 | AR |
| AAS         | Achalasia-addisonian-alacrimia syndrome | 231550 | AR |
| BRWD3       | X-linked mental disability | 300659 | XLR |
| GNB5        | Intellectual developmental disorder with cardiac arrhythmia, Language delay and ADHD/cognitive impairment with or without cardiac arrhythmia | 617173, 617182 | AR, 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, Microcephaly, growth deficiency, seizures, and brain malformations | 618347, 618346 | AR, 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 MET-TL1, 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],

| 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 | AR |
| 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 with 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), IGF51 (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 adrenocorticotropic 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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### 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 |                      |                          |
| AAAS      | Aladin WD repeat nucleoporin | AAA, AASb, ADRA, ADRA- CALIN, ALADIN, GL003 | 8086                    |
| AAMP      | Angio associated migratory cell protein |                    |                          |
| 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                     |
| B3KV6     | 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                    |
| B4DT11    | Moderately similar to glutamate-rich WD repeat-containing protein 1 |                    |                          |
| B4DVS2    | Highly similar to guanine nucleotide-binding protein subunit beta 2-like |                    |                          |

*(Continued to the next page)*
### 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 |                             |                          |
| B4DX5     | 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 | C17ORF1, C17ORF1, C17ORF1A, FBXW10B, FBXW10P1, HREP, SM2H2 | 374286        |
| CFAP43    | Cilia and flagella associated protein 43 | C10orf79, HYDNP1, SPGF19, WDR96, BA373N18.2 | 80217          |

(Continued to the next page)
| 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        | MCH19, 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                            | 061001116Rik, 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     | CTI02, 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              | 26904                    |
| 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      | 1200000605Rik, ARCAP, IQW1, MTP05S, NRP, 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                    |
| DMWD       | DM1 locus, WD repeat containing        | D19S593E, DMR-N9, DMRN9, gene59 | 1762 |

(Continued to the next page)
| 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                    |
| DYNCl1    | Dynein cytoplasmic 1 intermediate chain 1 | DNIC1, DNIC1 | 1780                     |
| DYNCl2    | Dynein cytoplasmic 1 intermediate chain 2 | DNIC74, DNIC2, 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, etIF3-beta, etIF3-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, EMAP4, ROPP120 | 27436                    |
| EML4-ALK  | Tyrosine-protein kinase receptor | EML4-ALK | 161436                   |
| EML5      | EMAP like 5              | EMAP-2, EMAP-5, FAP16       | 400954                   |
| EML6      | EMAP like 6              |                             | 1161                     |
| ERCC8     | ERCC excision repair 8, CSA ubiquitin ligase complex subunit | CSA, CKN1, UVSS2 | 10517                    |
| FBXW10    | F-box and WD repeat domain containing 10 | Fbw10, HREP, SM25H2, SM2SH2 | 23291                    |
| 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, FBXO30, FBXO30, FBXO6, SEL-10, SEL-10, 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                    | 51343                    |
| FZR1      | Fizzy and cell division cycle 20 related 1 | CDC20C, CDH1, FZR, FZR2, HCDH, HCDH1 | 25929                    |
| GEMIN5    | Gem nuclear organelle associated protein 5 | GEMIN-5 | 2782                     |
| GN1B      | G protein subunit beta 1 | MRD42 | (Continued to the next page) |
| 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, WDVC | 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 | TFIIC-BETA, TFIIC110 | 2976 |
| H0YL77    | Uncharacterized protein |                               |               |
| H5BR5     | 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, WDR14p | 55764 |
| IFT140    | Intraflagellar transport 140 | MZSDS, RP80, SRTD9, WDC2, 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, LJS6 | 10300 |
| KCTD3     | Potassium channel tetramerization domain containing 3 | NY-REN-45 | 51133 |
| KIF21A    | Kinesin family member 21A | CFEOM1, FEO1, FEO3A | 55605 |
| KIF21B    | Kinesin family member 21B |                               | 23046 |
| LLGL1     | LLGL scribble cell polarity complex component 1 | DLG4, HULG, 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, RIP7K, 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 | JNKBP1, 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 | A530083102Rik, 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, CAI, IIAE9             | 8021                    |
| NUP37     | Nucleoporin 37           | MCPPH24, 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 |
| PAK1P1    | PAK1 interacting protein 1 | MAK11, PIPI, 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, t150 | 30849 |
| PLAA      | Phospholipase A2 activating protein | DOA1, NDMSBA, PLA2P, PLAP | 9373 |
| PLRG1     | Pleiotropic regulator 1  | Cwc1, PRL1, PRP46, PRP64, TANGO4 | 5336 |
| 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,PR2APR55BETA,PR52B,PR55-BETA,PR55BETA,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, endonuclease | IEF-SSP-9502 | 11137 |
| PWP2      | PWP2 small subunit processome component | EHO17, PWP2H, UTP1 | 5822 |
| Q2VM1     | RecCDC20 |                             |                         |
| Q53F40    | F-box protein FBW7 isoform 2 variant |                             |                         |
| Q59EB2    | Uncharacterized protein |                             | 374286 |
| Q59EY9    | Transducin-like enhancer of split 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                                                     |                                                    |                          |
| 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                                                                             |                                                    |                          |
| Q8TC14    | FLJ23854 fis                                                                             |                                                    |                          |
| Q9H8N9    | Weakly similar to BETA-TRCP (BETA-TRANSDUCIN REPEAT-CONTAINING PROTEIN)                   |                                                    |                          |
| Q9NWG8    | FLJ10035 fis                                                                             |                                                    |                          |
| Q9Y6S1    | R26610_1                                                                                 |                                                    |                          |
| RAE1      | Ribonucleic acid export 1                                                                | Gle2, MIG14, MRNP41, Mnp41, dJ481F12.3, dJ80021.1 | 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                                                  | 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                                                                          |                                                    |                          |
| SEC13     | SEC13 homolog, nuclear pore and COPII coat complex component                             | DJ3S1231E, 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                                                                    | Sch1, SEH1A, SEH1B, SEC13L                        | 81929                    |
| SHKB1P1   | SHKBP1 binding protein 1                                                                  | PP203, Sb1                                        | 92799                    |
| SMU1      | SMU1 DNA replication regulator and spliceosomal factor                                     | BWD, SMU-1, fISAP5                                 | 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                                                                                     |                                                    |                          |
| STRN3     | Striatin 3                                                                               | PPP2R6B, S-G2NA, SG2NA                             | 29966                    |
| STRN4     | Striatin 4                                                                               | PPP2R6C, ZIN, zinedin                              | 29888                    |
| STXB5P5   | Syntaxin binding protein 5                                                                | LGL3, LLGL3, Nbhu04300                             | 134957                   |
| STXB5P5L  | Syntaxin binding protein 5 like                                                           | LLGL4                                             | 9515                     |
| TAF5      | TATA-box binding protein associated factor 5                                              | TAF(I)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                   |
| TBL1 Y    | 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, ISAP35                | 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(spl), 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                    |
| WDH1D     | 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, SR11, 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                                           | Ip13, R32J84_1              | 57418                    |
| WDR19     | WD repeat domain 19                                           | ATD5, CED4, DYF-2, FAP66, ORF26, Oseg6, PWDMP, SRID5, 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, DRC5, 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, lWH | 10785                    |
| WDR41     | WD repeat domain 41      | MSTP048                      | 55555                    |
| 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, MCHP2              | 284403                   |
| WDR63     | Dynein axonemal intermediate chain 3 | DNA13, DIC3, NYD-SP29    | 126820                   |
| WDR64     | WD repeat domain 64      |                              | 128025                   |
| WDR66     | Cilia and flagella associated protein 251 | CFAP251, CaM-IP4, SPG33 | 144406                   |
| WDR7      | WD repeat domain 7       | TRAG                         | 23335                    |
| WDR70     | WD repeat domain 70      |                              | 55100                    |
| WDR72     | WD repeat domain 72      | A12A3                        | 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                                                     | DNA14, 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                                                                      | NYD-SP11                                                                                  | 349136                   |
| WDR87       | WD repeat domain 87                                                                      | NYD-SP11                                                                                  | 83889                    |
| WDR88       | WD repeat domain 88                                                                      | POWD                                                                                      | 126248                   |
| WDR89       | WD repeat domain 89                                                                      | C1orf150, MSTP050                                                                         | 112840                   |
| WDR90       | WD repeat domain 90                                                                      | C16orf15, C16orf16, C16orf17, C16orf18, C16orf19, POC16                                   | 197355                   |
| WDR91       | WD repeat domain 91                                                                      | HSPC049, SORF-1, SORF1                                                                   | 29062                    |
| WDR92       | WD repeat domain 92                                                                      | KIAA1875                                                                                   | 116143                   |
| WDR97       | WD repeat domain 97                                                                      | KIAA1875                                                                                   | 340390                   |
| WDSUB1      | WD repeat, sterile alpha motif and U-box domain containing 1                           | UBOX6, WDSAM1                                                                             | 151525                   |
| WDTCL1      | WD and tetratricopeptide repeats 1                                                       | ADP, DCAF9                                                                                | 23038                    |
| WIP11       | WD repeat domain, phosphoinositide interacting 1                                        | ATG18, ATG18A, WIP14                                                                      | 55062                    |
| WIP12       | WD repeat domain, phosphoinositide interacting 2                                        | ATG18B, Atg21, CGI-50, IDSSSA, WIP1-2                                                     | 26100                    |
| WRAP53      | WD repeat containing antisense to TP53                                                    | DKCB3, TCABI, 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.
| 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                                   |            |                     |
| GNB3       | Hypertension                                           | 609887     | Multifactoral       |
|            | Night blindness                                        | 145500     | Multifactoral       |
| **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**                                    |                                                        |            |                     |
| 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.

*Including multi-organ defects, liver failure, cardiovascular defects, and embryonic lethality.