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WDR62 Primary Microcephaly

Synonyms: Autosomal Recessive Primary Microcephaly 2 With or Without Cortical Malformations, MCPH2

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Summary

Clinical characteristics

In *WDR62* primary microcephaly (*WDR62*-MCPH), microcephaly (occipitofrontal circumference [OFC] ≥2 standard deviations below the mean) is usually present at birth, but in some instances becomes evident later in the first year of life. Growth is otherwise normal. Except for brain malformations in most affected individuals, no other congenital malformations are observed. Central nervous system involvement can include delayed motor development, mild-to-severe intellectual disability (ID), behavior problems, epilepsy, spasticity, and ataxia.

Diagnosis/testing

The diagnosis of *WDR62*-MCPH is established in a proband with suggestive clinical findings and biallelic pathogenic variants in *WDR62* identified by molecular genetic testing.

Management

Treatment of manifestations: Treatment is symptomatic. Care by a multidisciplinary team (often including a pediatric neurologist, developmental pediatrician, speech-language pathologist, occupational and physical therapist, medical geneticist, and social worker) is recommended.

Surveillance: Follow up at each visit to assess: neurologic manifestations and response to medications for those with seizures; developmental progress and educational needs; speech-language development; behavior; physical therapy / occupational therapy needs; and social support.

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Genetic counseling

WDR62-MCPH is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *WDR62* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *WDR62* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives, prenatal testing, and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for *WDR62* primary microcephaly (*WDR62*-MCPH) have been established.

Suggestive Findings

WDR62 primary microcephaly (*WDR62*-MCPH) **should be suspected** in individuals with the following clinical and neuroimaging findings and family history [Ruaud et al 2022].

Clinical findings

- Microcephaly, usually congenital (identified before birth by ultrasound examination) with an occipitofrontal circumference ≥2 standard deviations (SD) below the mean at birth. In some instances, microcephaly may occur after birth, but within the first year of life.
- Normal or delayed motor development
- Mild-to-severe intellectual disability
- Epilepsy
- Behavior disorders
- Pyramidal signs (from hemiplegia or quadriplegia to spasticity or brisk deep-tendon reflexes)
- Ataxia
- Absence of intrauterine growth restriction and other congenital anomalies

Imaging findings. See Table 1.

Table 1. *WDR62* Primary Microcephaly: Frequency of MRI Findings by Cohort

MRI Finding	Cohort 1 [Ruaud et al 2022] [1]	Cohort 2 Literature review [2]
All types of malformations of cortical development [3]	13/15 (87%)	41/51 (80%)
• Pachygyria	10/15 (67%)	12/51 (24%)
• Simplified gyral pattern	8/15 (53%)	15/51 (29%)
• Severe malformations of cortical development [4]	5/15 (33%)	18/52 (35%)
○ Polymicrogyria	3/15 (20%)	9/51 (18%)
○ Schizencephaly	1/15 (7%)	5/51 (10%)
○ Lissencephaly	1/15 (7%)	3/51 (6%)
○ Neuronal heterotopia	1/15 (7%)	6/51 (12%)
Hypoplastic/dysgenetic corpus callosum	3/15 (20%)	22/51 (43%)

Table 1. continued from previous page.

MRI Finding	Cohort 1 [Ruaud et al 2022] [1]	Cohort 2 Literature review [2]
Unilateral/bilateral ventricular enlargement	3/15 (20%)	9/51 (18%)

1. Ruaud et al [2022] described 17 individuals from 14 families newly diagnosed with *WDR62* primary microcephaly. The table provides information on the 15 individuals for whom data are available.
2. Ruaud et al [2022] performed a comprehensive literature review of 137 individuals from 59 families previously diagnosed with *WDR62* primary microcephaly [Bilgüvar et al 2010, Nicholas et al 2010, Yu et al 2010, Bhat et al 2011, Kousar et al 2011, Murdock et al 2011, Bacino et al 2012, Farag et al 2013, Memon et al 2013, Sajid Hussain et al 2013, McDonell et al 2014, Poulton et al 2014, Rupp et al 2014, Banerjee et al 2016, Bastaki et al 2016, Wang et al 2018, Miyamoto et al 2017, Naseer et al 2017, Sgourdou et al 2017, Cherkaoui Jaouad et al 2018, Kvarnung et al 2018, McSherry et al 2018, Nardello et al 2018, Naseer et al 2019, Yi et al 2019, Zombor et al 2019, Rasool et al 2020]. The table provides information on the 51 individuals for whom data are available.
3. Including pachygyria, simplified gyral pattern, and severe malformations of cortical development
4. Including polymicrogyria, schizencephaly, lissencephaly, and neuronal heterotopia

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *WDR62* primary microcephaly (*WDR62*-MCPH) **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *WDR62* identified by molecular genetic testing (see Table 2).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of biallelic *WDR62* variants of uncertain significance (or of one known *WDR62* pathogenic variant and one *WDR62* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel) (see Option 1) and **comprehensive genomic testing** (exome sequencing, genome sequencing) (see Option 2). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not.

Note: Single-gene testing (sequence analysis of *WDR62* followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

Option 1

A multigene panel that includes *WDR62* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 2. Molecular Genetic Testing Used in *WDR62* Primary Microcephaly

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
WDR62	Sequence analysis [3]	~99% [4]
	Gene-targeted deletion/duplication analysis [5]	<1% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Ruaud et al [2022]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. One intragenic deletion has been reported to date [Ruaud et al 2022].

Clinical Characteristics

Clinical Description

To date, 153 individuals have been reported with *WDR62* primary microcephaly (*WDR62*-MCPH). The findings in these 153 individuals are summarized in Table 3 as Cohort 1 – 17 affected individuals reported by Ruaud et al [2022] (including 1 previously reported by Nicholas et al [2010]); and Cohort 2 – literature review of findings in 137 affected individuals compiled by Ruaud et al [2022].

Table 3. *WDR62* Primary Microcephaly: Frequency of Select Features by Cohort

Feature		Cohort 1 [Ruaud et al 2022] [1]	Cohort 2 Literature review [2]
OFC		17/17 [3]	72/137 [4]
Motor development		• Normal: 6/17 w/independent walking < age 18 mos • Delayed: 9/17 w/independent walking < age 3.5 yrs • Nonambulatory: 2/17 at age 16 yrs	44/60 walk independently (age: 2-29 yrs)
Language development		• Normal: 4/17 • Delayed language w/speech disorders:11/17 • No language: 2/17	44/59 able to talk (words to short sentences, age: 2-29 yrs)
ID	Mild	3/11	NA
	Moderate	4/11	2 individuals [5]
	Severe	4/11	NA
Epilepsy		12/17	41/109

Table 3. continued from previous page.

Feature	Cohort 1 [Ruaud et al 2022] [1]	Cohort 2 Literature review [2]
Behavior	Behavior disorders: 10/16 [6]	Behavior disorders: 21/24 • Hyperkinesia: 4/21 • Self-injury: 5/21 • Aggressiveness: 15/21 • Confusion: 2/21
Spasticity	6/17	15/29
Ataxia	7/17 (congenital: 6/7, progressive: 1/7)	1/29

ID = intellectual disability; NA = not available; OFC = occipitofrontal circumference
1. Ruaud et al [2022] described 17 individuals from 14 families newly diagnosed with *WDR62* primary microcephaly. The Cohort 1 column reports the number of affected individuals for each feature over the number of individuals for whom data for that feature are available.
2. Ruaud et al [2022] compiled a comprehensive literature review [Bilgüvar et al 2010, Nicholas et al 2010, Yu et al 2010, Bhat et al 2011, Kousar et al 2011, Murdock et al 2011, Bacino et al 2012, Farag et al 2013, Memon et al 2013, Sajid Hussain et al 2013, McDonell et al 2014, Poulton et al 2014, Rupp et al 2014, Banerjee et al 2016, Bastaki et al 2016, Wang et al 2018, Miyamoto et al 2017, Naseer et al 2017, Sgourdou et al 2017, Cherkaoui Jaouad et al 2018, Kvarnung et al 2018, McSherry et al 2018, Nardello et al 2018, Naseer et al 2019, Yi et al 2019, Zombor et al 2019, Rasool et al 2020] consisting of 137 individuals from 59 families previously diagnosed with *WDR62* primary microcephaly. The Cohort 2 column reports the number of affected individuals with each feature over the number of individuals for whom data for that feature are available.
3. Defined as 4 standard deviations (SD) (±1.5 SD) below the mean at last examination (mean age: 12 years, 4 months)
4. Defined as 6.3 SD (±2.4 SD) below the mean at last examination (mean age: 12 years, 10 months)
5. Poulton et al [2014], Yi et al [2019]
6. Including hyperkinesia, aggressiveness, hypersociability, poor concentration, and disinhibition

Occipitofrontal circumference (OFC). In *WDR62*-MCPH, unlike other primary microcephalies, OFC may be within the normal range prenatally and at birth (mean: 2.4 SD [±1.046 SD] below the mean, range: 0.5 to 5 SD below the mean). The trajectory for growth of the OFC usually declines with age to reach a mean of 6.4 SD (±2.7 SD) below the mean in adulthood (range: 2 to 14 SD below the mean in Cohorts 1 and 2).

Growth. Intrauterine growth restriction is rare. Weight and length are usually normal at birth.

Neurologic findings. The ataxia reported in early childhood in six children spontaneously improved with age. Lower-extremity spasticity was present in two individuals.

In two other individuals, progressive cerebellar involvement was noted. In one individual, progressive motor decline associated with tremor and ataxia appeared in the second decade without cerebellar atrophy on brain MRI. In the other individual, ataxia manifesting as truncal hypotonia and inability to sit without support at age 20 years was associated with cerebellar atrophy on MRI.

Epilepsy. In Cohort 1:

- Of the five individuals who had severe malformations of cortical development (i.e., polymicrogyria, schizencephaly, lissencephaly, and neuronal heterotopia), all five had epilepsy (see Table 1).
- Of 11 individuals who had a normal MRI or pachygyria and/or simplified gyral pattern, six had epilepsy.

Comparable information on epilepsy is not available for Cohort 2; however, it is notable that the proportion of individuals with severe cortical malformations in the two cohorts is similar (see Table 1).

Infantile spasms and focal and generalized seizures occurred mostly within the first two years. All types of generalized seizures were reported (tonic, clonic, atonic, myoclonic, and absences).

Developmental skills. Despite the high proportion of malformations of cortical development in this disorder, 15 of 17 individuals in Cohort 1 were able to walk, and 11 of 17 were able to speak at least a few words. Similar developmental skills were reported in Cohort 2.

Intellectual disability (ID). An assessment of 11 of 17 individuals in Cohort 1 using Wechsler scales determined that three had mild ID, four had moderate ID, and four had severe ID. Severe or moderate ID was observed in three of four individuals with severe cortical malformation and three of seven individuals without severe cortical malformation.

Individuals with mild-to-moderate ID had significant autonomy in daily life and good social interactions (based on Vineland Adaptive Behavior Scales). Regardless of the degree of ID, autonomy in daily life scores were higher than communication scores in affected individuals.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified [Ruaud et al 2022].

Nomenclature

WDR62-MCPH is also designated as MCPH2 (i.e., the second *m*icro*c*ephaly *p*rimary *h*ereditary locus identified by linkage analysis).

Prevalence

A review of the literature in 2021 identified 153 individuals with *WDR62*-MCPH from 73 families [Ruaud et al 2022].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *WDR62*.

Differential Diagnosis

The primary microcephalies are a group of rare, phenotypically and etiologically heterogeneous disorders of brain growth characterized by (1) a head circumference close to or greater than 2 SD below the mean at birth and greater than 3 SD below the mean by age one year, and (2) mild-to-severe intellectual disability. Additional clinical or neuroimaging features can be associated. Most primary microcephalies are inherited in an autosomal recessive manner. To date, pathogenic variants in more than 100 genes are known to cause primary microcephaly (for review, see Jayaraman et al [2018]).

Primary microcephaly may be clinically subdivided into two broad phenotypic categories (while valuable for clinical management and for differential diagnosis, it should be noted that this simple classification does not reflect underlying pathophysiologic mechanisms):

- **Isolated primary microcephaly** in which the primary microcephaly is not associated with extracerebral malformations (e.g., *ASPM*-MCPH, most tubulinopathies). Many isolated primary microcephalies are also known as *m*icro*c*ephaly, *p*rimary *h*ereditary (or MCPH), * although some may have different names for historical reasons.
- **Primary microcephaly with short stature** (microcephalic primary dwarfism), which includes Seckel syndrome, * osteodysplastic primordial dwarfism type 2, Meier-Gorlin syndrome, and others

* MCPH and Seckel syndrome may be further subdivided by the presence of cortical malformations and/or chorioretinopathy.

Syndromic primary microcephaly is a heterogeneous group in which primary microcephaly is associated with non-neurodevelopmental manifestations and growth impairment.

Selected genes associated with isolated primary microcephaly, primary microcephaly with short stature, and syndromic primary microcephaly (excluding those with a true clinically recognizable "syndromic gestalt," such as Rubinstein-Taybi syndrome, Cohen syndrome, Cornelia de Lange syndrome, and DiGeorge syndrome) are listed in Table 4.

OMIM phenotypic series referenced in Table 4 (see OMIM entries designated with the prefix "PS") are based on the presence of microcephaly and an associated feature. Due to the intrinsic phenotypic variability associated with pathogenic variants in each gene, there is considerable clinical overlap across all of these phenotypic series. Nevertheless, microcephaly, present at birth and usually severe by age one year, is the usual anchoring feature of the differential diagnosis for most clinicians.

Table 4. Disorders with Congenital Microcephaly to Consider in the Differential Diagnosis of *WDR62* Primary Microcephaly

Disorder / Phenotype	Gene(s) / Genetic Mechanism	MOI	Clinical Features of Disorder Distinguishing from *WDR62*-MCPH [1]	OMIM
MCPH	*ANKLE2* *ASPM* *CDK5RAP2* *CDK6* *CENPE* *CENPJ* *CEP135* *CEP152* *CIT* *COPB2* *KIF14* *KNL1* *MAP11* *MCPH1* *MFSD2A* *NCAPD2* *NCAPD3* *NCAPH* *NUP37* *PHC1* *SASS6* *STIL* *WDFY3* *ZNF335*	AR (AD) [2]	• *ANKLE2*-, *CENPJ*-, *CEP152*-, *KIF14*-, *NCAPD2*-, *PHC*-, & *ZNF335*-MCPH: May present w/IUGR (Seckel-like) • *MFSD2A*-MCPH: May have hydrocephalus • *STIL*-MCPH: May have holoprosencephaly • *ZNF335*-MCPH: Early lethality	PS251200
Periventricular heterotopia w/ microcephaly	*ARFGEF2*	AR	PVNH	608097
Microcephaly, short stature, & polymicrogyria ± seizure	*RTTN*	AR	Short stature, polymicrogyria, severe ID	614833

Table 4. continued from previous page.

Disorder / Phenotype	Gene(s) / Genetic Mechanism	MOI	Clinical Features of Disorder Distinguishing from *WDR62*-MCPH [1]	OMIM
Malformations of cortical development (See Congenital Fibrosis of the Extraocular Muscles & Tubulinopathies Overview.)	*CTNNA2* *KIF2A* *KIF5C* *TUBA1A* *TUBA8* *TUBB* *TUBB2A* *TUBB2B* *TUBB3* *TUBG1*	AD (AR) [3]	Lissencephaly & polymicrogyria; fusion between caudate & putamen nuclei w/indistinct anterior arm of internal capsule; neonatal seizures	PS614039
Baraitser-Winter cerebrofrontofacial syndrome	*ACTB* *ACTG1*	AD	Pachygyria; lissencephaly; hypertelorism, broad nose w/large tip & prominent root, coloboma; normocephaly	243310 614583
Microcephaly & polymicrogyria	*EOMES*	AR	Microcephaly & polymicrogyria	604615
RAB18 deficiency (Warburg micro syndrome, Martsolf syndrome)	*RAB3GAP1* *RAB3GAP2* *RAB18* *TBC1D20*	AR	Microphthalmia, microcornea, congenital cataracts, optic atrophy; polymicrogyria; spastic diplegia; hypogonadism; severe ID	600118 614222 614225
Microcephaly & chorioretinopathy (MCCRP)	*PLK4* *TUBGCP4* *TUBGCP6*	AR	• Chorioretinopathy (inconstant) • *PLK4*-MCCRP: IUGR (Seckel-like)	PS251270
Microcephaly ± chorioretinopathy, lymphedema, or ID	*KIF11*	AD	Chorioretinopathy & lymphoedema (inconstant); ID uncommon	152950
Polymicrogyria bilateral frontoparietal (See Polymicrogyria Overview.)	*ADGRG1* (*GPR56*)	AR	Bilateral frontal or perisylvian polymicrogyrie; cobblestone-like lissencephaly; normocephaly	606854
Lissencephaly 6 w/microcephaly	*KATNB1*	AR	Microlissencephaly & pachygyria	616212
Asparagine synthetase deficiency	*ASNS*	AR		615574
Serine biosynthesis defects	*PHGDH* *PSAT1* *PSPH*	AR	Neonatal seizures	601815 610992 614023

AD = autosomal dominant; AR = autosomal recessive; ID = intellectual disability; IUGR = intrauterine growth restriction; MCPH = microcephaly, primary hereditary; MOI = mode of inheritance; PS = phenotypic series; PVNH = periventricular nodular heterotopia

1. Disorders are associated with intellectual disability unless otherwise noted.

2. MCPH associated with the listed genes is inherited in an autosomal recessive manner with the exception of *WDFY3*-MCPH, which is inherited in an autosomal dominant manner.

3. Cortical dysplasia, complex, with other brain malformations (CDCBM) associated with the listed genes is inherited in an autosomal dominant manner with the exception of *CTNNA2*- and *TUBA8*-related CDCBM, which are inherited in an autosomal recessive manner.

Management

No clinical practice guidelines for *WDR62* primary microcephaly (*WDR62*-MCPH) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *WDR62*-MCPH, the evaluations summarized in Table 5 are recommended.

Table 5. Recommended Evaluations Following Initial Diagnosis in Individuals with *WDR62* Primary Microcephaly

System/Concern	Evaluation	Comment
Constitutional	Measure height, weight, OFC.	
Neurologic	Neurologic eval	Evaluate for spasticity & cerebellar findings. If seizures are a concern: • Consider EEG; • Evaluate for malformations of cortical development (e.g., polymicrogyria, lissencephaly, schizencephaly, neuronal heterotopia), which are known to be assoc w/epilepsy.
Development	Developmental assessment	• Incl motor, adaptive, cognitive & speech-language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Eval by primary care provider &/or mental health specialist	Incl screening for presence of behavior issues, incl sleep disturbances, ADHD, & anxiety
Spasticity/ Ataxia	Orthopedics / physical medicine & rehab / PT & OT eval	Assess: • Gross motor & fine motor skills; • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills); • Possible progression of ataxia.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *WDR62*-MCPH to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support.	

ADHD = attention-deficit/hyperactivity disorder; MOI = mode of inheritance; OFC = occipitofrontal circumference; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Treatment is symptomatic. Care by a multidisciplinary team, often including a pediatric neurologist, developmental pediatrician, speech-language pathologist, occupational and physical therapist, medical geneticist, and social work team, is recommended to address individual needs.

Table 6. Treatment of Manifestations in Individuals with *WDR62* Primary Microcephaly

Manifestation/Concern	Treatment	Considerations/Other
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Speech delay	By speech-language pathologist	AAC in case of severe oral communication disorder
Behavior issues	Behavioral cognitive therapy [1]	Methylphenidate is seldom effective in ADHD. [2]

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Epilepsy	Treatment by experienced neurologist w/ASM according to type of seizures	• Lamotrigine, levetiracetam, sodium valproate, vigabatrin, oxcarbazepine, & sulthiame have been mostly effective as monotherapy. • Multitherapy may be required; some seizures may resist treatment w/2 or 3 ASMs. • Education of parents/caregivers is helpful. [3]
Spasticity/Ataxia	Physical medicine & rehab / PT & OT	• Spasticity: stretching to ↑ mobility; antispastic treatment (baclofen) &/or botulinum toxin treatment may be required. • Ataxia: no medications improve ataxia. • Mobility: use of a walker &/or wheelchair may eventually be required.
Family/Community	Ensure appropriate social work involvement to connect families w/local resources, respite care, & support.	Consider involvement in adaptive sports or Special Olympics.

AAC = augmentative and alternative communication; ADHD = attention-deficit/hyperactivity disorder; ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability; OT = occupational therapy; PT = physical therapy

1. Applied behavior analysis (ABA) therapy is therapy targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses; it is typically performed one on one with a board-certified behavior analyst.

2. Authors, personal observation

3. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

The following information represents typical management recommendations for individuals with developmental delay / intellectual disability in the United States (US); standard recommendations may vary from country to country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states that provides in-home services to target individual therapy needs.

Ages 3-5 years. In the US, developmental preschool through the local public school district is recommended. Before placement, an evaluation is made to determine needed services and therapies, and an individualized education plan (IEP) is developed for those who qualify based on established motor, language, social or cognitive delay. The early intervention program typically assists with this transition. Developmental preschool is center based; for children too medically unstable to attend, home-based services are provided.

All ages. Consultation with a developmental pediatrician is recommended to ensure the involvement of appropriate community, state, and educational agencies (US) and to support parents in maximizing quality of life. Some issues to consider:

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine if any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.

    - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
    - As a child enters teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Communication Issues

Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Consultation with a developmental pediatrician may be helpful in guiding parents through appropriate behavior management strategies or providing prescription medications, such as medication used to treat attention-deficit/hyperactivity disorder, when necessary.

Concerns about serious aggressive or destructive behavior can be addressed by a pediatric psychiatrist.

Surveillance

Table 7. Recommended Surveillance for Individuals with *WDR62* Primary Microcephaly

System/Concern	Evaluation	Frequency
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as new-onset seizures, spasticity, contractures, & ataxia.	At each visit
Development	Monitor developmental progress & educational needs.	
Speech delay	Speech-language pathologist: Monitor speech development.	
Psychiatric/ Behavioral	• Ancillary behavior assessment for anxiety, attention, & aggressive or self-injurious behavior • Refer for formal eval if concern exists.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Family/ Community	Assess family need for social work support (e.g., respite care, other local resources) or follow-up genetic counseling if new questions arise (e.g., family planning).	

OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

The authors' research project on *WDR62* primary microcephaly, approved by the National Ethics Committee, is registered at ClinicalTrials.gov (NCT01565005). This project aims to correlate genotype, findings on brain imaging, and intellectual abilities of individuals with primary microcephaly (MCPH).

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

WDR62 primary microcephaly (*WDR62*-MCPH) is inherited in an autosomal recessive manner.

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *WDR62* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *WDR62* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - One of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant resulted in homozygosity for the pathogenic variant in the proband.

Sibs of a proband. If both parents are known to be heterozygous for a *WDR62* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

Offspring of a proband. To date, individuals with *WDR62*-MCPH are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *WDR62* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *WDR62* pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *WDR62* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  Autosomal recessive primary microcephaly

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. WDR62 Primary Microcephaly: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
WDR62	19q13.12	WD repeat-containing protein 62	WDR62	WDR62

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for WDR62 Primary Microcephaly (View All in OMIM)

604317	MICROCEPHALY 2, PRIMARY, AUTOSOMAL RECESSIVE, WITH OR WITHOUT CORTICAL MALFORMATIONS; MCPH2
613583	WD REPEAT-CONTAINING PROTEIN 62; WDR62

Molecular Pathogenesis

WDR62 is a microtubule minus-end mitotic spindle pole protein, located in dividing neural progenitors in humans. WDR62 is highly expressed in rodent and human forebrain during neurogenesis, especially in the ventricular and sub-ventricular zones. It plays a crucial role in spindle pole organization and orientation, and is involved in brain development during embryonic neurogenesis. In rodent models and human brain organoids, WDR62 depletion leads to fewer neural progenitors [Zhang et al 2019]. Whether this is due to premature differentiation or to mitotic delay and consequent death of these neural progenitors remains controversial.

Mechanism of disease causation. The majority of *WDR62* pathogenic variants are predicted to result in a loss of function.

Chapter Notes

Author Notes

Our research group in the child neurology and genetic departments at APHP-Robert Debré University Hospital is interested in understanding the natural history of primary microcephalies including *WDR62* primary microcephaly. In particular, our objective is to investigate the neurodevelopmental trajectory of affected individuals, as well as the effects of brain structure and organization on intellectual abilities.

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