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WDR26-Related Intellectual Disability

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Summary

Clinical characteristics

WDR26-related intellectual disability (ID) is characterized by developmental delay / intellectual disability, characteristic facial features, hypotonia, epilepsy, and infant feeding difficulties. To date 15 individuals, ages 24 months to 34 years, have been reported. Developmental delay is present in all individuals and ranges from mild to severe. All individuals have delayed speech. Although some begin to develop speech in the second year, others have remained nonverbal. Seizures, present in all affected individuals reported to date, can be febrile or non-febrile (tonic-clonic, absence, rolandic seizures); most seizures are self limited or respond well to standard treatment. Affected individuals are generally described as happy and socially engaging; several have stereotypies / autistic features (repetitive or rocking behavior, abnormal hand movements or posturing, and at times self-stimulation).

Diagnosis/testing

The diagnosis of *WDR26*-related ID is established in a proband with suggestive clinical features and a heterozygous pathogenic variant in *WDR26* identified by molecular genetic testing.

Management

Treatment of manifestations: Standard treatment of developmental delay / intellectual disability, seizures, infant feeding problems, and behavioral issues.

Surveillance: In infancy: regular assessment of swallowing, feeding, and nutritional status to determine safety of oral vs gastrostomy feeding. For all age groups: routine monitoring of developmental progress, educational needs, and behavioral issues.

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Genetic counseling

WDR26-related ID is inherited in an autosomal dominant manner. All individuals reported to date have the disorder as the result of a *de novo* pathogenic variant. If the *WDR26* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for *WDR26*-related intellectual disability have not been established.

Suggestive Findings

WDR26-related intellectual disability **should be considered** in individuals with the following findings [Skraban et al 2017]:

- Developmental delay or intellectual disability of variable degree
- Characteristic facial features including coarse features, prominent eyes with large-appearing irises, prominent maxilla, broad nasal tip, protruding upper lip, prominent upper gingiva, and widely spaced teeth (Figure 1)
- Central hypotonia
- Autistic features
- Seizures: both febrile and non-febrile
- Abnormal wide-based, ataxic, and/or stiff-legged gait

Establishing the Diagnosis

The diagnosis of *WDR26*-related ID **is established** in a proband with suggestive clinical features and identification of a heterozygous pathogenic (or likely pathogenic) variant in *WDR26* by molecular genetic testing (see Table 1).

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 a heterozygous *WDR26* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability typically begins with chromosomal microarray analysis (CMA). If CMA is not diagnostic, the next step is typically either a multigene panel or comprehensive genomic testing (exome sequencing, genome sequencing). Note: Single-gene testing (sequence analysis of *WDR26*, followed by gene-targeted deletion/duplication analysis) is of unproven utility, and unless *WDR26*-related ID is strongly suspected, it is typically NOT recommended.

- **Chromosomal microarray analysis (CMA)** using oligonucleotide or SNP arrays can identify chromosome 1q42 microdeletions that can include *WDR26*, causing *WDR26*-related ID (see Table 1).
- **An intellectual disability (ID) multigene panel** that includes *WDR26* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA 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

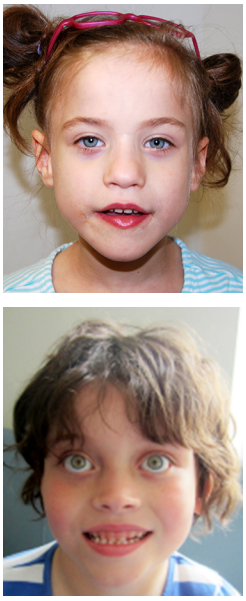

Figure 1. Four individuals with loss-of-function *WDR26* variants. Characteristic facial features include coarse appearance, prominent eyes, prominent maxilla, broad nasal tip, protruding upper lip, prominent upper gingiva, and widely spaced teeth.

Images published with permission of families

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 this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

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

- **Comprehensive genomic testing,** which does not require the clinician to determine which gene(s) are likely involved, is another option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis. Note: To date such variants have not been reported as a cause of *WDR26*-related ID.

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

Table 1. Molecular Genetic Testing Used in *WDR26*-Related Intellectual Disability

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
WDR26	Sequence analysis [3]	15/15 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown; see footnote 6.
	Chromosomal microarray [7]	Unknown; see footnote 8.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic 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. Skraban et al [2017]
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. No data on detection rate of gene-targeted deletion/duplication analysis are available.
7. Chromosomal microarray analysis (CMA) using oligonucleotide arrays or SNP arrays. CMA designs in current clinical use include the 1q42region.
8. To date, no individuals with isolated deletions of *WDR26* identified by CMA have been reported.

Clinical Characteristics

Clinical Description

WDR26-related intellectual disability is characterized by developmental delay / intellectual disability, epilepsy, and infant feeding difficulties. To date 15 individuals (10 female, 5 male) with intragenic pathogenic variants in *WDR26* have been reported; they range in age from 24 months to 34 years [Skraban et al 2017].

Developmental delay (DD) and intellectual disability (ID) are present in all individuals. Developmental delay ranges from mild in many to severe in approximately 30%. Sitting is delayed with an average of 11 months. Walking is delayed, with reported onset averaging 24 months but ranging from age 17 months to three years.

Speech development is a relative weakness. All individuals have delayed speech. Although some begin to develop speech in the second year, others remain nonverbal through childhood.

Seizures, described in all affected individuals reported to date, range in onset from the newborn period to age seven years.

Seizure types are generally mild and include febrile and non-febrile (tonic-clonic, absence, rolandic). Most are self limited or respond well to standard treatments.

Other neurodevelopmental features

- Hypotonia, present in nine of 12 reported individuals; typically mild
- Failure to thrive and infant feeding difficulties; reported in six of 15 individuals, with three requiring a gastrostomy tube at least temporarily
- An abnormal gait, described as wide-based, ataxic, and/or stiff-legged
- Structural brain anomalies, nearly all minor, noted in ten of 14 individuals; including the nonspecific findings (enlarged ventricles, thin corpus callosum, white matter volume loss, mild cerebellar hypoplasia, and pineal cyst) as well as a markedly abnormal left supratentorial hemisphere structure with pachygyria that required hemispherectomy (in 1 individual)
- Microcephaly; noted in three of 14 individuals

Behavior. Affected individuals are generally described as happy and socially engaging. Several have stereotypies / autistic features including repetitive or rocking behavior, abnormal hand movements or posturing, and at times self-stimulation. Most prefer to engage with other children and adults rather than pursue solitary activities. While active, most children are directable and can concentrate on tasks and are not typically reported to be hyperactive.

Other features

- **Ophthalmologic**
  - Strabismus and/or amblyopia (in 9/14)
  - Congenital abducens paresis (in 1)
  - Marcus Gunn jaw winking (in 1)
  - Refractive errors, including myopia and hyperopia
- **ENT**
  - Recurrent otitis media / eustachian tube dysfunction (5/15)
  - Cleft palate (1)
- **Respiratory abnormalities.** Mild tracheomalacia (1)
- **Gastrointestinal problems.** Constipation (4/12) and gastroesophageal reflux (3/13)
- **Musculoskeletal**
  - Mild contractures of the lower extremities (2)
  - *Pes cavus* (2)
  - Forefoot varus (1)
  - Hip dysplasia (1)
  - Osteopathia striata of the distal femurs (1)
- **Cardiac**
  - Ventricular septal defect (1)
  - Right-sided aortic arch (1)

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been established.

Nomenclature

WDR26-related intellectual disability has also been referred to as Skraban-Deardorff syndrome.

Prevalence

WDR26-related intellectual disability is rare. Only 15 individuals with intragenic pathogenic *WDR26* variants have been reported to date. These 15 were identified among some 21,400 individuals with intellectual disability who had exome sequencing, giving an estimated frequency of 1:1,500 for individuals with unknown causes of intellectual disability [Skraban et al 2017].

Genetically Related (Allelic) Disorders

Chromosome 1q41q42 deletions. More than 20 individuals have been reported with deletions of the chromosome 1q41q42 region ranging in size from 300 Kb to 10 Mb and including *WDR26* and varied subsets of other genes [Shaffer et al 2007]. Consistently, many individuals with 1q42 deletions demonstrate features that overlap those of individuals with intragenic pathogenic variants in *WDR26*, including facial dysmorphia, developmental delay, and a predisposition to seizures. Other clinical features seen in some individuals include cataracts, short stature, microcephaly, and multiple structural anomalies including nail hypoplasia, cleft palate, clubfoot, congenital heart disease, and congenital diaphragmatic hernia [Rice et al 2006, Mazzeu et al 2007,

Shaffer et al 2007, Slavotinek et al 2009, Filges et al 2010, Kantarci et al 2010, Rosenfeld et al 2011, Wat et al 2011, Au et al 2014, Cassina et al 2015, Yanagishita et al 2019].

Of relevance, *FBXO28*, which lies adjacent to *WDR26*, is often included in 1q41q42 chromosomal deletions. Recently, a *de novo FBXO28* frameshift variant was reported in an individual with developmental delay and seizures but absence of maxillary or gingival findings associated with mutation of *WDR26* [Balak et al 2018]; this individual also had central sleep apnea and nail anomalies not noted associated with *WDR26*. These observations suggest that effects of haploinsufficiency of both *WDR26* and *FBXO28* may influence the phenotype of 1q41q42 chromosomal deletions.

Differential Diagnosis

Developmental delay with delayed speech and febrile and/or non-febrile seizures, the most frequent features of *WDR26*-related ID, are relatively common and have an extensive differential diagnosis.

The following syndromes with significant phenotypic overlap with *WDR26*-related ID have been considered in some affected individuals before the diagnosis of *WDR26*-related ID was established (Table 2).

Table 2. Disorders with Developmental Delay / Intellectual Disability to Consider in the Differential Diagnosis of *WDR26*-Related Intellectual Disability

Differential Diagnosis Disorder	Gene / Genetic Mechanism	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping w/ *WDR26*-related ID	Distinguishing from *WDR26*-related ID
Angelman syndrome	Deficient expression/ function of maternally inherited *UBE3A* allele	See footnote 1.	• Happy demeanor • Seizures • Abnormal gait • Widely spaced teeth	• Inappropriate laughter/ excitability • Microcephaly common
Pitt-Hopkins syndrome	*TCF4* or deletion of the chromosome region in which *TCF4* is located	See footnote 2.	• Seizures • Widely spaced teeth • Full lips	• Episodic hyperventilation &/or breath-holding spells • Severe myopia
Alpha-thalassemia X-linked intellectual disability syndrome	*ATRX*	XL	• Hypotonia • Coarse facial features	• Alpha-thalassemia & HbH inclusion bodies • Genital anomalies • Microcephaly common • Postnatal growth deficiency
Kleefstra syndrome	*EHMT1* or deletion at 9q34.3	AD	• Seizures • Hypotonia • Autistic features	• Congenital malformations more common • Severe infections

AD = autosomal dominant; ID = intellectual disability; MOI = mode of inheritance; XL = X-linked

1. The risk to sibs of a proband depends on the genetic mechanism leading to the loss of *UBE3A* function: typically less than 1% risk for probands with a deletion or uniparental disomy, and as high as 50% for probands with an imprinting defect or a pathogenic variant of *UBE3A*.

2. Pitt-Hopkins syndrome is caused by haploinsufficiency of *TCF4*. Most individuals reported to date have represented simplex cases (i.e., a single occurrence in a family) resulting from a *de novo* pathogenic variant or deletion.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *WDR26*-related intellectual disability (ID), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with *WDR26*-Related ID

System/Concern	Evaluation	Comment
Constitutional	Assessment of height, weight, head circumference	Evaluation of growth parameters to identify those w/FTT
Neurologic	Neurologic evaluation	Incl EEG & brain MRI if seizures
Development	Developmental assessment	Incl assessment of age-appropriate motor, speech/language, cognitive skills.
Eyes	Ophthalmologic evaluation	For evidence of refractive error, strabismus ± amblyopia, cataracts, abnormal extraocular movement
ENT/Mouth	Consultation w/ENT	For those w/: • Recurrent otitis media • Cleft palate
Cardiovascular	Consultation w/cardiologist	If evidence of congenital heart defect
Respiratory	Consultation w/pulmonologist	If evidence of tracheomalacia
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team evaluation	For those w/: • Feeding difficulties, GERD, &/or FTT: assess swallowing, feeding, & nutritional status to determine safety of oral vs gastrostomy feeding • Constipation
Musculoskeletal	Consultation w/physiatrist	For those w/gait abnormalities
Psychiatric/ Behavioral	Neuropsychiatric evaluation	Screen individuals age >12 mos for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; ENT = ear, nose, and throat; FTT = failure to thrive; GERD = gastroesophageal reflux disease

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with *WDR26*-Related Intellectual Disability

Manifestation/ Concern	Treatment	Considerations/Other
Feeding difficulties &/or FTT	Standard care w/gastroenterologist & nutritionist &/or speech therapist	Gastrostomy tube placement may be required for persistent feeding issues.
Strabismus/ Amblyopia	Standard care as per treating ophthalmologist	

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Cardiac defects	Standard care as per treating cardiologist	
Seizures	Standard ASMs as recommended by an experienced neurologist. Consideration of brain MRI.	Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. [1]

ASMs= anti-seizure medications; FTT = failure to thrive

1. Education of parents regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for parents or caregivers of 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; 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 and 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; however, 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 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.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - 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.
- In the US:

- 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.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

Fine motor dysfunction. Occupational therapy is recommended for difficulty with fine motor skills that affect adaptive function such as feeding, grooming, dressing, and writing.

Oral motor dysfunction. Assuming that the individual is safe to eat by mouth, feeding therapy – typically from an occupational or speech therapist – is recommended for affected individuals who have difficulty feeding as a result of poor oral motor control.

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 Difficulties

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and is typically performed one on one with a board-certified behavior analyst.

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 (ADHD), when necessary.

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

Surveillance

Table 5. Recommended Surveillance for Individuals with *WDR26*-Related Intellectual Disability

System/Concern	Evaluation	Frequency
Constitutional	Eval of growth	Annually or more frequently if FTT
Eyes	Ophthalmologic eval	Annually or more frequently as needed

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
ENT/Mouth	ENT eval	As needed
Gastrointestinal/ Feeding	Assessment for constipation, gastroesophageal reflux, nutritional status, & feeding w/attention to poor weight gain, choking/gagging during feeds, & feeding refusal not otherwise explained	
Musculoskeletal	Physical therapy follow up for gait abnormality	
Neurologic	Follow up of seizure management	
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavorial	Developmental psychologist eval	
Miscellaneous/ Other	Assess family need for social work support, other local resources.	

FTT = failure to thrive

Evaluation of Relatives at Risk

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

Therapies Under Investigation

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. Note: There may not be clinical trials for this disorder.

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

WDR26-related intellectual disability (ID) is inherited in an autosomal dominant manner and is typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- All probands reported to date with *WDR26*-related ID whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo WDR26* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *WDR26* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the pathogenic variant most likely occurred *de novo* in the proband. Another possible explanation is that the proband inherited a pathogenic variant from a parent with germline mosaicism. Although theoretically possible, no instances of germline mosaicism have been reported to date.

- Theoretically, if the parent is the individual in whom the *WDR26* pathogenic variant first occurred, the parent may have somatic mosaicism for the variant and may be mildly/minimally affected.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents: if the *WDR26* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].

Offspring of a proband. Individuals with *WDR26*-related ID have not been known to reproduce; however, many are still children.

Other family members. Given that all probands with *WDR26*-related ID reported to date have the disorder as a result of a *de novo WDR26* pathogenic variant, the risk to other family members is presumed to be low.

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 parents of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Risk to future pregnancies is presumed to be low as the proband most likely has a *de novo WDR26* pathogenic variant. There is, however, a recurrence risk (~1%) to sibs based on the theoretic possibility of parental germline mosaicism [Rahbari et al 2016]. Given this risk, prenatal and preimplantation genetic testing may be considered.

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.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  aaidd.org
- **CDC - Child Development**
  Phone: 800-232-4636
  Developmental Disability Basics
- **MedlinePlus**
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  vor.net

- **The WDR26 Registry at the Children's Hospital of Philadelphia**
  Email: WDR26@email.chop.edu

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. WDR26-Related Intellectual Disability: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
WDR26	1q42.11-q42.12	WD repeat-containing protein 26	WDR26	WDR26

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 WDR26-Related Intellectual Disability (View All in OMIM)

617424	WD REPEAT-CONTAINING PROTEIN 26; WDR26
617616	SKRABAN-DEARDORFF SYNDROME; SKDEAS

Molecular Pathogenesis

WDR26-related intellectual disability (ID) results from haploinsufficiency of WDR26 function [Skraban et al 2017]. However, little is known regarding how haploinsufficiency leads to specific cellular or developmental pathobiology that results in the human phenotype.

Gene structure. The *WDR26* transcript NM_025160.6 has 14 exons, all of which contain coding sequence.

See Table A, **Gene** for a detailed summary of gene and protein information.

Pathogenic variants. The majority of *WDR26* pathogenic variants have been *de novo* frameshift or nonsense variants. However, several missense variants have been noted in exons 4 and 5. All reported pathogenic variants to date are private to individual families.

The observation that core features of the 1q41q42 deletion syndrome consistently overlap those of *WDR26*-related ID strongly supports *WDR26* haploinsufficiency as the basis of this deletion syndrome.

Normal gene product. The WDR26 protein includes 661 amino acids, and modeling suggests that it contains 14 variably perfect WD40 repeats. Together the 14 WD40 repeats compose two seven-bladed β propeller structures [Skraban et al 2017]:

- Domains WD1-WD7 (amino acids 1-353) comprise an N-terminal β propeller.
- Domains WD8-WD14 (amino acids 354-645) comprise a C-terminal β propeller, which includes the conserved LisH (LIS1 homology) and CTLH (C-terminal LIS homology) domains.

Although specific cellular functions for WDR26 are unclear, many WD40 repeat proteins play key roles in cellular scaffolding [Zhu et al 2004, Stirnimann et al 2010, Sun et al 2013].

Abnormal gene product. Most pathogenic *WDR26* variants result in haploinsufficiency caused by either loss-of-function variants or deletion of part or all of the gene. However, several *de novo* missense pathogenic variants have been identified in the CTLH (aa 156-231) and WD6 (aa 254-304) domains that disrupt WDR26 protein [Skraban et al 2017].

Chapter Notes

Author Notes

Dr Skraban is a member of the faculty at the University of Pennsylvania Perelman School of Medicine and the Children's Hospital of Philadelphia. Dr Deardorff is a member of the faculty at the University of Southern California Keck School of Medicine and the Children's Hospital Los Angeles. They are working to further understand the clinical features and molecular pathogenesis associated with *WDR26*-related disorders with a goal to improve the lives of patients. They welcome both clinical and scientific inquiries, as well as individuals interested in their ongoing research registry (wdr26@email.chop.edu).

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