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WAC-Related Intellectual Disability

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Summary

Clinical characteristics

WAC-related intellectual disability (ID) is typically characterized by variable degrees of developmental delay and/or intellectual disability. Behavioral abnormalities including anxiety, attention-deficit/hyperactivity disorder, and/or autism spectrum disorder are observed in the majority of older children and adults. Most affected infants have significant but nonspecific features at birth such as neonatal hypotonia and feeding problems. Some affected individuals come to medical attention with respiratory or vision problems. Facial features may be mildly dysmorphic, but are nonspecific. To date, 18 individuals have been identified with *WAC*-related ID.

Diagnosis/testing

The diagnosis of *WAC*-related ID is established in a proband by identification of a heterozygous pathogenic variant in *WAC* on molecular genetic testing.

Management

Treatment of manifestations: Standard treatment of developmental delay / intellectual disability, behavioral abnormalities, neonatal hypotonia, and feeding problems.

Surveillance: Regular dietary evaluation in infancy to ensure optimal nutritional status; routine monitoring of developmental progress and educational needs; assessment for anxiety, attention, and aggressive or self-injurious behavior.

Genetic counseling

WAC-related ID is inherited in an autosomal dominant manner. With the exception of one family with presumed parental germline mosaicism, all individuals diagnosed to date have the disorder as the result of a *de*

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novo pathogenic variant. Once the *WAC* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

No formal clinical diagnostic criteria exist for *WAC*-related intellectual disability.

Suggestive Findings

WAC-related intellectual disability (ID) **should be considered** in individuals with SOME OR ALL of the following suggestive findings:

- Developmental delay or variable degrees of intellectual disability
- One or more of the following:
  - Generalized hypotonia in infancy with or without associated oral hypotonia
  - Neonatal feeding difficulties, gastroesophageal reflux, and/or constipation
  - Behavioral abnormalities including anxiety, attention-deficit/hyperactivity disorder (ADHD), aggression, sleep disturbances, and autism spectrum disorder (ASD)
  - Respiratory problems: recurrent infections, asthma, and/or abnormal breathing pattern
  - Abnormal vision including cortical visual impairment, strabismus, and refractive errors

Other less specific features that may prompt further consideration of this diagnosis include:

- Seizures
- Abnormalities of the extremities including brachydactyly, presence of fetal finger pads, and planovalgus deformity of the feet
- Inverted nipples

Establishing the Diagnosis

The diagnosis of *WAC*-related ID **is established** in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *WAC* on molecular genetic testing (see Table 1).

Note: Per ACMG 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. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants.

Molecular genetic testing approaches can include a combination of **genomic testing** (comprehensive genomic sequencing) and **gene-targeted testing** (multigene panel or single-gene testing).

Gene-targeted testing requires the clinician to determine which gene(s) are likely involved, whereas genomic testing may not. Because the phenotypes of inherited intellectual disability overlap, most individuals with *WAC*-related ID are diagnosed by the following recommended testing or testing to be considered.

Recommended testing options to consider

- **A multigene panel** that includes *WAC* and other genes of interest (see Differential Diagnosis). 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*; thus, clinicians need to determine which multigene panel 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. Of

note, given the rarity of *WAC*-related intellectual disability, panels for intellectual disability may not include this gene. (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.

- **Comprehensive genomic testing** (when clinically available), including exome sequencing and genome sequencing.

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

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

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

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
WAC	Sequence analysis [3]	17/18 [4]
	Gene-targeted deletion/duplication analysis [5, 6]	1/18 [7]

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. Hamdan et al [2014], DeSanto et al [2015], Tammimies et al [2015], Lugtenberg et al [2016]. See Molecular Genetics, **Pathogenic variants**.
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. Individuals reported to have larger deletions that include more genes in the 10p12.1 region have phenotypic features that overlap those of *WAC*-related intellectual disability described in this *GeneReview* [Shahdadpuri et al 2008, Wentzel et al 2011, Okamoto et al 2012, Mroczkowski et al 2014, Sosoi et al 2015, Abdelhedi et al 2016]. Larger deletions may, however, be associated with more severe degrees of intellectual disability or additional features (such as cardiac anomalies) due to haploinsufficiency of other genes.
7. To date, one individual has been reported with an intragenic deletion encompassing exons 5 to 14 (originally detected by CMA) [Lugtenberg et al 2016].

Clinical Characteristics

Clinical Description

WAC-related intellectual disability is typically characterized by variable degrees of developmental delay and/or intellectual disability. Behavioral abnormalities including anxiety, attention-deficit/hyperactivity disorder, and/or autism spectrum disorder are observed in the majority of older children and adults. Most affected infants have significant but nonspecific features at birth such as neonatal hypotonia and feeding problems. Some affected individuals come to medical attention because of respiratory or vision problems; constipation is common. Although facial features may be mildly dysmorphic, they may not be observed universally and/or are often not specific enough to allow diagnosis.

To date, 18 individuals have been identified with a pathogenic variant in *WAC* [Hamdan et al 2014, DeSanto et al 2015, Tammimies et al 2015, Lugtenberg et al 2016].

Most Commonly Seen Features

Hypotonia. More than 75% of the infants (14 of 17 for whom this information was available) have significant hypotonia at birth and during infancy which may be the clinical finding for which they are initially evaluated. Oral hypotonia may contribute to the feeding difficulties as well as to speech delay.

Neonatal feeding difficulties have been reported in approximately 45% (7/16) of individuals with *WAC*-related ID. In addition to the hypotonia, gastroesophageal reflux was reported in two children and swallowing difficulties in one. The feeding difficulties are typically managed with oral feedings; only one child was dependent on a G-tube.

Developmental delay and intellectual disability. Delay in attainment of speech and/or motor milestones is a universal feature.

While the preliminary information available does not allow firm conclusions, approximately two thirds of the individuals reported to date are nonverbal at age 18 months. Although severe speech delay does not seem to be the rule, a few children remained nonverbal at age four years (and in some cases beyond). Dysarthria secondary to oral hypotonia was reported in some [Lugtenberg et al 2016].

Variable degrees of both fine motor and gross motor delay have been observed in almost all individuals for whom this information is available. Walking was achieved after age 21 months in the majority. Fine motor development may be equally affected as some individuals have been reported to have poor hand dexterity or clumsiness and difficulty in global coordination.

Intellectual disability, which appears to be present in the majority of affected individuals, is typically in the mild end of the spectrum and was only observed in the moderate-to-severe range in fewer than 20% (3/18). Of note, on formal IQ testing two individuals had results within the normal range (full-scale IQ scores 98 [DeSanto et al 2015] and 89 [Lugtenberg et al 2016]); both had had abnormal prior development, and the latter had a formal diagnosis of autism spectrum disorder. Two additional individuals had borderline intellectual functioning.

Behavioral problems of any type are present in more than 80% (15/16) of affected individuals. Sleep disturbances, reported in approximately two thirds of individuals, are among the most common. Although poorly characterized, frequent night awakenings appeared to be a problem in at least two individuals.

Attention-deficit/hyperactivity disorder and anxiety have been observed in 30%-40% of individuals.

Approximately 20% of reported individuals had a formal diagnosis of autism spectrum disorder (ASD). Autistic traits were reported in one individual.

Aggressive and self-injurious behavior was reported in a few individuals.

Abnormal vision. More than half of affected individuals had vision problems. Refractive errors as well as strabismus have been reported on several occasions, the latter in approximately one third of affected individuals. In a few individuals with poor vision of unknown cause, the cause was attributed to cortical visual impairment.

Gastrointestinal problems. Bowel dysmotility mainly manifest as constipation was observed in approximately one third (5/16) of individuals. Gastroesophageal reflux disease has been observed on occasion. Because the presence of gastrointestinal problems has not been systematically evaluated in all affected individuals, the actual prevalence may be higher.

Respiratory abnormalities, a feature in approximately 40% of reported individuals, included recurrent infections (5 individuals), asthma (2 occasions), and an abnormal breathing pattern (2 individuals) [Lugtenberg

et al 2016]. Because the presence of respiratory abnormalities has not been evaluated consistently in the available reports, the actual prevalence may be higher.

Facial gestalt. The most frequent features are a square-shaped face with a broad or prominent forehead, deeply set eyes with long palpebral fissures, broad or depressed nasal bridge, and wide mouth with a broad chin. Other features that may be observed include synophrys, hypertelorism, epicanthus, and bulbous nose or broad nasal tip. See Figure 1. Although DeSanto et al [2015] argue that loss-of-function pathogenic variants in *WAC* are associated with a recognizable phenotype, the facial features may not be observed universally and/or are often not specific enough to allow diagnosis.

Minor ear anomalies have been described in 50% of affected individuals (8/16), including posteriorly rotated ears and prominence of the antihelix (most commonly of the stem, although the superior and inferior crus can also be prominent).

Neuroimaging. While abnormal MRI findings have been observed in seven individuals with *WAC*-related ID, no consistent abnormality has been observed. Ventriculomegaly and prominence/enlargement of subarachnoid spaces have each been reported on two occasions. Other findings (each reported in 1 individual) include asymmetry of the hemispheres and a retrocerebellar arachnoid cyst.

Features Reported in 10%-30% of Affected Individuals

Seizures were observed in four of 17 reported individuals. The following were each reported in one individual:

- Tonic-clonic seizures
- Absence episodes
- Seizure-like activity
- Febrile convulsions

Obesity, reported in three of 18 individuals, was reported to be truncal in one individual; no details were provided on the other two.

Hearing loss, reported in two of 18, was inconsistent (1 had sensorineural hearing loss and 1 had conductive hearing loss) [DeSanto et al 2015].

Nonspecific kidney problems included:

- Mild unilateral renal caliectasis in one individual and right pelvic kidney in another [DeSanto et al 2015];
- A girl age nine years with unspecified kidney problems [Lugtenberg et al 2016].

Other

- **Foot abnormalities.** Usually plano-valgus deformity
- **Hand abnormalities.** Brachydactyly, presence of fetal finger pads, short hands, unilateral single tranverse palmar crease
- **Inverted nipples**

Genotype-Phenotype Correlations

To date only loss-of-function *WAC* variants have been reported in individuals with *WAC*-related intellectual disability. The small number of reported individuals is not sufficient to draw conclusions about genotype-phenotype correlations.

Variability in intellectual function has been observed in individuals with the same *WAC* variant:

Figure 1. Three individuals with *WAC*-related intellectual disability

Female age 19 years (1)

Male age 12 years (2a, 2b, 2c)

Female at age three years (3a) and at age 20 years (3b, 3c). Note the deeply set eyes, long palpebral fissures, wide mouth, and broad chin.

Note the broad/prominent forehead (in 2a, 3a) and depressed nasal bridge (3a).

- In two unrelated individuals with the variant c.1648C>T intellectual disability was mild in one and moderate in the other [Lugtenberg et al 2016].
- In two sibs with the same variant, intellectual functioning was borderline in one and normal in the other, who (despite a full-scale IQ score of 98) was reported to perform below average in some verbal and nonverbal skills (e.g., confrontation naming or spatial orientation) and to score low in evaluation of motor function [DeSanto et al 2015].

Nomenclature

WAC-related intellectual disability is also referred to as DeSanto-Shinawi syndrome (DESSH).

Penetrance

To date all individuals with *WAC*-related intellectual disability have the disorder as the result of a *de novo* pathogenic variant or germline mosaicism. Based on the published cases, the penetrance is complete (100%). Reliable estimates on the penetrance of the disorder are however difficult to establish given that most affected individuals have been identified through the discovery of a *de novo* and/or loss-of-function variant in *WAC*.

Prevalence

To date, 18 individuals with *WAC*-related intellectual disability (ID) have been reported in the literature.

In each of the following cohorts of children with ID and/or autism spectrum disorder (ASD), one child was found to have a *de novo WAC* pathogenic variant:

- One of 1,133 children with severe, undiagnosed, developmental disorders [Fitzgerald et al 2015]. Of note, children with easily recognized syndromes or large pathogenic copy number variants identified in prior genetic testing were excluded from this study.
- One of 258 unrelated children with ASD, all of whom were initially tested by chromosomal microarray analysis and 95 of whom were further investigated by trio exome sequencing (i.e., exome sequencing of the proband and both parents) [Tammimies et al 2015]

The prevalence of *WAC*-related ID may, however, be difficult to establish given the under-ascertainment of less severely affected individuals, the ascertainment bias for individuals with *de novo* or loss-of-function variants, and the genetic testing modalities implemented for prior exclusion of affected individuals in the evaluation of cohorts with ID/ASD.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Developmental delay, neonatal feeding difficulties, and hypotonia, the most frequent features in *WAC*-related intellectual disability, are relatively common and have an extensive differential diagnosis.

The syndromes in Table 2 show significant phenotypic overlap with *WAC*-related ID and have been considered in affected individuals before the diagnosis of *WAC*-related ID was established.

Table 2. Disorders to Consider in the Differential Diagnosis of *WAC*-Related Intellectual Disability

Disorder	Gene/Genetic Mechanism	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping w/*WAC*-Related ID	Distinguishing from *WAC*-Related ID
Prader-Willi syndrome [1]	Abnormal parent-specific imprinting w/in the Prader-Willi critical region	See footnote 2.	• Hypotonia, feeding difficulties in early infancy • Delayed motor milestones & language development	Obesity & food-seeking behaviors typically not a feature of *WAC*-related ID
Smith-Magenis syndrome [3]	Deletion or mutation of *RAI1* on chromosome 17p11.2 [4]	Virtually all *de novo*	Neonatal hypotonia w/feeding difficulties, DD & ID, & some behavioral disturbances (incl abnormal sleep patterns) [5]	Some characteristic behaviors (e.g., self-hugging, polyembolokoilamania)

Table 2. continued from previous page.

Disorder	Gene/Genetic Mechanism	MOI	Clinical Features of the Differential Diagnosis Disorder	
			Overlapping w/*WAC*-Related ID	Distinguishing from *WAC*-Related ID
Pitt-Hopkins syndrome	Haploinsufficiency of *TCF4*	Most *de novo*	• DD, ID, sleep disturbances, seizures, constipation • Facial features incl deep-set eyes & wide mouth w/prominent lower face • Abnormal breathing pattern (seen in 2 persons w/*WAC*-related ID) [6]	ID usually more severe
Angelman syndrome [5]	Disruption of maternally imprinted *UBE3A*	See footnote 7.	• DD, ID, sleep disorders • Seizures variably present in both (rare in *WAC*-related ID)	Usually nonverbal, w/more severe ID
KANSL1-related intellectual disability syndrome (Koolen-deVries syndrome)	500- to 650-kb heterozygous deletion at chromosome 17q21.31 incl *KANSL1* or a heterozygous *KANSL1* intragenic pathogenic variant [8]	Almost all *de novo*	• Neonatal/childhood hypotonia & DD w/ associated ID • Abnormal vision, epilepsy, & renal anomalies variably seen in both disorders (rare in *WAC*-related ID; in ~50% w/*KANSL1*-related ID	Characteristic facial gestalt (incl upslanting palpebral fissures, tubular/pear shaped nose w/ bulbous nasal tip & prominent ears)

DD = developmental delay; ID = intellectual disability; MOI = mode of inheritance

1. One individual reported by DeSanto et al [2015] reportedly had PWS testing.

2. The risk to the sibs of an affected child of having PWS depends on the genetic mechanism that resulted in the absence of expression of the paternally contributed 15q11.2-q13 region.

3. Among the ten individuals with *WAC*-related ID reported by Lugtenberg et al [2016], three had had normal *RAI1* testing prior to establishing the correct diagnosis.

4. Approximately 95% of individuals with Smith-Magenis syndrome have the disorder as a result of an interstitial 17p11.2 deletion, which may have been previously excluded by chromosomal microarray testing.

5. Two individuals reported by Lugtenberg et al [2016] had been previously tested for Angelman syndrome.

6. One individual reported by Lugtenberg et al [2016] had previously undergone *TCF4* testing.

7. The risk to sibs of a proband depends on the genetic mechanism leading to the loss of *UBE3A* function.

8. *KANSL1*-related ID syndrome is, on most occasions, readily diagnosed by detection of the typical 17q21.31 microdeletion on chromosomal microarray. Note: The 17q21.31 microdeletion cannot be identified by routine analysis of G-banded chromosomes or other conventional cytogenetic banding techniques.

Management

Evaluations and Referrals Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *WAC*-related intellectual disability, the evaluations and referrals outlined in Table 3 are recommended.

Note: Some evaluations are age dependent and may not be relevant at the time of initial diagnosis (e.g., recommendation for traits suggestive of autism spectrum disorder [ASD] in an infant).

Table 3. Recommended Evaluations and Referrals Following Initial Diagnosis of *WAC*-Related Intellectual Disability

System/Concern	Evaluation	Comment
Growth	Assessment of growth parameters to identify those w/failure to thrive	
Ophthalmology	Ophthalmology eval	
ENT	Audiology eval when clinical history is suggestive of a hearing problem	If abnormal, refer to otolaryngologist.
Gastroenterology/ Feeding	Baseline eval for presence of reflux &/or constipation; assessment for feeding problems	If needed, refer to gastroenterologist &/or feeding therapist for treatment.
Respiratory	Respiratory assessment when clinical history indicates presence of recurrent infections &/or asthma	If abnormal, refer to pulmonologist.
Genitourinary	Renal ultrasound exam when clinical history is suggestive of a renal problem	If abnormal, refer to nephrologist.
Psychiatric/ Behavioral	For persons age >12 mos: clinical screening for behavior problems incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD	Consider referral for formal testing, incl Autism Diagnostic Interview™ & Autism Diagnostic Observation Schedule.™
Neurologic	Assess for possible seizure activity.	If present, consider EEG &/or referral to neurologist.
Miscellaneous/ Other	Multidisciplinary developmental eval incl motor, speech/language eval, general cognitive, & vocational skills	Referral to developmental pediatrician &/or developmental psychologist
	Consultation w/clinical geneticist &/or genetic counselor	

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder

Treatment of Manifestations

Treatment can include the following.

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

Manifestation/Concern	Treatment
Recurrent infections &/or asthma	Standard treatment(s) per pulmonologist
Poor weight gain / Failure to thrive	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues. [1]
Gastroesophageal reflux disease &/or constipation	Standard treatment(s)
Seizures	Standard treatment(s) per neurologist
Abnormal vision &/or strabismus	Standard treatment(s) per ophthalmologist
Renal abnormalities	Standard treatment(s) per nephrologist

1. Diet diary and calorie counts may be requested.

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 by country.

Ages 0-3 years. Referral to an early intervention program is recommended for access to occupational, physical, speech, and feeding therapy. In the US, early intervention is a nationwide federally funded program available in all states.

Ages 3-5 years. In the US, developmental preschool through the local public school district may be considered. An evaluation will occur before placement to determine needed services and therapies and will be subsequently written into an individualized education plan (IEP).

Ages 5-21 years

- In the US, an IEP can be developed by the local public school district based on each individual's level of function. Severely affected children are permitted to remain in the public school district until age 21.
- Discussion about transition plans including financial, vocation/employment, and medical arrangements should begin at age 12 years. Developmental pediatricians can provide assistance with transition to adulthood.

All ages. Consultation with a developmental pediatrician is recommended to ensure appropriate community, state, and educational agencies are involved and to support parents.

Consideration of private supportive therapies based on the affected individual's needs is recommended. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.

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.
- Consider use of durable medical equipment as needed (e.g., 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. 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, assuming the individual is safe to eat by mouth.

Communication issues. Consider alternative means of communication for individuals who have expressive language difficulties, such as an augmentative and alternative communication (AAC) evaluation.

Social/Behavioral Concerns

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, when necessary.

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

Surveillance

The following are appropriate.

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

System/Concern	Evaluation [1]
Eyes	Ophthalmologic eval
ENT/Mouth	Audiologic eval
Gastrointestinal	Regular dietary eval in infancy to ensure optimal nutritional status
Genitourinary	Monitor those w/renal abnormalities as clinically indicated.
Neurologic	Monitor those w/seizures as clinically indicated.
Psychiatric	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior
Miscellaneous/Other	Monitor developmental progress & educational needs.

1. The frequency with which each evaluation or reassessment occurs should be tailored to the needs of the affected individual.

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

WAC-related intellectual disability (ID) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- To date, vertical transmission of *WAC*-related ID from an affected parent to a proband has not been reported.
- With the exception of one family with presumed parental germline mosaicism [DeSanto et al 2015], all individuals diagnosed to date with *WAC*-related ID have the disorder as the result of a *de novo* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.

- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the most likely explanation is a *de novo* variant in the proband. Parental germline mosaicism, presumed to have occurred in one reported family, is another possible explanation [DeSanto et al 2015].
- The family history of some individuals diagnosed with *WAC*-related ID may appear to be negative because of failure to recognize the disorder in family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.
- Note: If the parent is the individual in whom the 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 *WAC* pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism. One such case of recurrence as a result of presumed parental germline mosaicism has been reported [DeSanto et al 2015].
- If the parents have not been tested for the *WAC* pathogenic variant but are thought to be clinically unaffected, risk to sibs appears to be low but is still increased over that of the general population because of the possibility of a less severe, undiagnosed presentation in a parent or germline mosaicism in a parent.

Offspring of a proband

- Each child of an individual with *WAC*-related ID has a 50% chance of inheriting the *WAC* pathogenic variant.
- The degree of severity in offspring who inherit a *WAC* pathogenic variant cannot be predicted as clinical variability has been observed in affected sibs and in unrelated individuals with the same *WAC* pathogenic variant (see Genotype-Phenotype Correlations).

Other family members. The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *WAC* pathogenic variant, the parent's family members may be at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

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 affected or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the *WAC* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk 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.

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **MedlinePlus**
  Intellectual Disability
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  www.vor.net

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. WAC-Related Intellectual Disability: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
WAC	10p12.1	WW domain-containing adapter protein with coiled-coil	WAC	WAC

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 WAC-Related Intellectual Disability (View All in OMIM)

615049	WW DOMAIN-CONTAINING ADAPTOR WITH COILED-COIL REGION; WAC
616708	DESANTO-SHINAWI SYNDROME; DESSH

Gene structure. The longest *WAC* transcript variant NM_016628.4 consists of 14 exons encoding for 647 amino acids. Alternative splicing events yield at least two additional transcript variants of *WAC*: NM_100264.2 and NM_100486.3. See Table A, **Gene** for details.

Benign variants. Three presumably loss-of-function variants have been reported in the Exome Aggregation Consortium (ExAC) dataset [Lek et al 2016]. Each has been found in one individual among the specific population cohorts. Lugtenberg et al [2016] commented that these variants (all of which represent insertion/deletion events) may represent sequencing artifacts not validated by Sanger sequencing or could represent the mild end of the intellectual disability (ID) spectrum in the general population.

As also explicitly stated for at least some of these databases, attempts have been made to exclude individuals with severe pediatric diseases – which may not be the case for less severe phenotypes [Lek et al 2016].

Pathogenic variants. *WAC* pathogenic variants reported include 15 variants that predict loss of function (nonsense variants or small deletions or insertions) and one intragenic multiexon deletion [Lugtenberg et al 2016] (see Table 1). To date no missense variants have been reported in individuals with *WAC*-related ID.

The smallest region of overlap among 11 deletions of 10p12.1 is an 80-kb region containing only *WAC*, supporting a haploinsufficiency mechanism for *WAC*-related ID [Shahdadpuri et al 2008, Wentzel et al 2011, Okamoto et al 2012, Mroczkowski et al 2014, Sosoi et al 2015, Abdelhedi et al 2016]. Larger deletions may, however, be associated with more severe degrees of ID or additional features (e.g., cardiac anomalies) due to haploinsufficiency of other genes.

One frameshift variant (c.1885_1886delTT) reported by Lugtenberg et al [2016] in an individual with *WAC*-related ID is presumed to escape nonsense-mediated decay.

One variant (c.1648C>T) was found in two unrelated individuals with mild and moderate ID [Lugtenberg et al 2016].

Table 6. *WAC* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1648C>T [1]	p.Arg550Ter	NM_016628.4 NP_057712.2
c.1885_1886delTT	p.Leu629GlufsTer5	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. See Genotype/Phenotype Correlations.

Normal gene product. The protein encoded by *WAC* contains a WW domain and a coiled-coiled region. The WW domain, a protein module mediating protein-protein interactions, is found in a wide range of signaling proteins. Although the exact function of WAC is unknown, it has been suggested that it acts as a functional partner of RNF20/40, which has been shown to regulate histone H2B ubiquitination, a process regulating chromatin organization during transcription [Zhang & Yu 2011]. WAC also co-localizes with splicing factor SC35, a finding that could suggest a role in RNA processing [Xu & Arnaout 2002]. See Lugtenberg et al [2016] on the presumed role of WAC.

Abnormal gene product. Haploinsufficiency resulting from inactivation of one *WAC* allele is the cause of *WAC*-related ID.

Chapter Notes

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