U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Kruszka P. Weiss-Kruszka Syndrome. 2019 Oct 31. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Weiss-Kruszka Syndrome

Synonym: *ZNF462* Disorder

Paul Kruszka, MD, MPH[1]

Created: October 31, 2019.

Summary

Clinical characteristics

Weiss-Kruszka syndrome is characterized by metopic ridging or synostosis, ptosis, nonspecific dysmorphic features, developmental delay, and autistic features. Brain imaging may identify abnormalities of the corpus callosum. Developmental delay can present as global delay, motor delay, or speech delay. Affected individuals may also have ear anomalies, feeding difficulties (sometimes requiring placement of a gastrostomy tube), and congenital heart defects. There is significant variability in the clinical features, even between affected members of the same family.

Diagnosis/testing

The diagnosis of Weiss-Kruszka syndrome is established in a proband with suggestive features and by identification of a heterozygous pathogenic variant in *ZNF462* or deletion of 9p31.2 involving *ZNF462*; rarely chromosome rearrangements that disrupt *ZNF462* have been reported.

Management

Treatment of manifestations: Referral to a craniofacial team and/or neurosurgeon for those with craniosynostosis; feeding therapy for those with feeding difficulties; gastrostomy tube placement for those with persistent feeding issues and/or dysphagia. Standard treatment for ptosis, developmental delay, autism, hearing loss, and congenital heart defects.

Surveillance: Assessment of head circumference and shape at each evaluation in infancy and early childhood. Measurement of growth parameters, evaluation of nutrition status and safety of oral intake, and assessment of developmental progress and educational needs at each visit. Ophthalmology and audiology evaluations based on degree of clinical suspicion.

Author Affiliation: 1 National Human Genome Research Institute National Institutes of Health Bethesda, Maryland; Email: paul.kruszka@nih.gov.

Genetic counseling

Weiss-Kruszka syndrome is inherited in an autosomal dominant manner. Approximately 95% of affected individuals have Weiss-Kruszka syndrome as the result of an apparently *de novo* pathogenic variant. Each child of an individual with Weiss-Kruszka syndrome has a 50% chance of inheriting the *ZNF462* pathogenic variant. Children who inherit a *ZNF462* pathogenic variant may be more or less severely affected than the affected parent because of intrafamilial clinical variability. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible if the *ZNF462* pathogenic variant in the family has been identified.

Diagnosis

Formal diagnostic criteria for Weiss-Kruszka syndrome have not been established.

Suggestive Findings

Weiss-Kruszka syndrome **should be suspected** in individuals presenting with the following clinical and brain MRI findings.

Clinical findings

- Metopic ridging or synostosis
- Ptosis
- Nonspecific dysmorphic features (see Clinical Description, **Craniofacial features**)
- Developmental delay and/or autistic features

Brain MRI findings. Corpus callosum abnormalities

Establishing the Diagnosis

The diagnosis of Weiss-Kruszka syndrome **is established** in a proband with suggestive features and by the identification of one of the following on molecular genetic testing [Weiss et al 2017] (see Table 1):

- A heterozygous pathogenic variant involving *ZNF462*
- A heterozygous deletion of 9q31.2 involving *ZNF462*

Note: Chromosome rearrangements that disrupt *ZNF462* have been rarely reported [Ramocki et al 2003, Talisetti et al 2003, Cosemans et al 2018].

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing and multigene panel) and **comprehensive genomic testing** (chromosomal microarray analysis, exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of Weiss-Kruszka syndrome is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited disorders with intellectual disability and/or nonspecific dysmorphic features are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic findings suggest the diagnosis of Weiss-Kruszka syndrome, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

Single-gene testing. Sequence analysis of *ZNF462* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *ZNF462*) that cannot be detected by sequence analysis.

An intellectual disability multigene panel that includes *ZNF462* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a non-diagnostic 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 over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of Weiss-Kruszka syndrome some 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 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.

Option 2

When the phenotype is indistinguishable from many other inherited disorders characterized by intellectual disability and nonspecific dysmorphic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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

Karyotype. Conventional cytogenetic analysis can be considered to exclude other large cytogenetic abnormalities or rare chromosome rearrangements that involve *ZNF462* if the phenotype is consistent with Weiss-Kruszka syndrome but the above-mentioned studies do not detect a pathogenic variant involving *ZNF462* [Ramocki et al 2003, Talisetti et al 2003, Cosemans et al 2018].

Table 1. Molecular Genetic Testing Used in Weiss-Kruszka Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ZNF462	Sequence analysis [3]	17/21 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]
	CMA [7]	2/8 [8]
	Karyotype	2/8 [9]

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. Kruszka et al [2019]
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. Gene-targeted deletion/duplication testing will detect deletions ranging from a single exon to the whole gene; however, breakpoints of large deletions and/or deletion of adjacent genes may not be detected by these methods.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.
7. Chromosomal microarray analysis (CMA) uses oligonucleotide or SNP arrays to detect genome-wide large deletions/duplications (including *ZNF462*) that cannot be detected by sequence analysis. The ability to determine the size of the deletion/duplication depends on the type of microarray used and the density of probes in the 9q31.2 region. CMA designs in current clinical use target the 9q31.2 region.
8. Weiss et al [2017]
9. Ramocki et al [2003], Talisetti et al [2003], Cosemans et al [2018]

Clinical Characteristics

Clinical Description

To date, 24 individuals from 21 families are have been identified with a pathogenic variant in *ZNF462* [Ramocki et al 2003, Talisetti et al 2003, Weiss et al 2017, Cosemans et al 2018, Kruszka et al 2019]. The following description of the phenotypic features associated with this condition is based on these reported cases.

Note: The reports by Ramocki et al [2003] and Talisetti et al [2003] describe the same individual; the authors speculated that this individual's features may have resulted from a fusion protein created by a balanced translocation that disrupted *ZNF462*.

Craniofacial features. The most common facial features (Figure 1):

- Ptosis (20/24; 83%)
- Downslanted palpebral fissures (13/24; 54%)
- Exaggerated Cupid's Bow (13/24; 54%)
- Arched eyebrows (12/24; 50%)
- Epicanthal folds (11/24; 46%)
- Short upturned nose with bulbous tip (11/24; 46%)

Fewer than half of affected individuals have metopic ridging or craniosynostosis involving the metopic or lambdoid suture (9/24; 38%).

Developmental delay. A vast majority (>75% of the known 24 affected individuals) have some type of developmental delay including global delay, motor delay, speech delay, or a combination of these.

- Speech delay is the most common finding, occurring in 42%.
- Motor delay is the second most common, occurring in 38%.

  Hypotonia is a contributor to motor delay, with 50% of individuals having decreased muscle tone.

A third (8 of the known 24 affected individuals) have an autism spectrum disorder.

Ears/hearing. 45% of probands had hearing loss or anomalies affecting the external ear configuration:

- Low-set ears in six (25%) of the 24 affected individuals
- Ear malformations in 12/24 affected individuals, including horizontal crux helix, prominent ears, ear pits, cupped ears, and overfolded ears
- Hearing loss of varying severity in three of the 24 affected individuals

Gastrointestinal. Feeding issues are prevalent, with half (12/24) of all affected individuals reporting difficulties and some requiring G-tube placement. Causes of feeding issues include the following:

- Gastroesophageal reflux requiring Nissen fundoplication
- Laryngomalacia leading to respiratory difficulty during oral feeding attempts
- Dysphagia
- Eosinophilic esophagitis
- Problems chewing

Heart malformations. A minority of affected individuals (5/24; 21%) have congenital heart malformations including ventricular septal defects, bicuspid aortic valve, transposition of the great arteries, and patent ductus arteriosus.

Limb anomalies. Roughly 25% of affected individuals have minor limb anomalies.

- Three have single palmar creases (13%)
- Three have fifth-finger clinodactyly (13%)
- One individual was reported to have proximally implanted thumbs, although this individual has a balanced translocation involving *ZNF462* and *KLF12* [Cosemans et al 2018].

Corpus callosum dysgenesis was initially thought to be a major characteristic of those with loss of function in *ZNF462* [Weiss et al 2017]; however, as more cases are ascertained, the fraction of affected individuals with corpus callosum dysgenesis may be closer to 25% (6/24). Seizures have not been described in any affected individuals to date.

Prognosis. It is unknown if life span in Weiss-Kruszka syndrome is reduced. One reported individual is alive at age 67 years [Weiss et al 2017]. Since many adults with disabilities have not undergone advanced genetic testing, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified.

Prevalence

This disorder is rare and the prevalence is unknown. Only 24 affected individuals from 21 families are known [Ramocki et al 2003, Talisetti et al 2003, Weiss et al 2017, Cosemans et al 2018, Kruszka et al 2019].

Figure 1. These four individuals demonstrate the most common facial characteristics of Weiss-Kruszka syndrome including ptosis, downslanted palpebral fissures, exaggerated Cupid's bow, and arched eyebrows.

Images published with permission

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *ZNF462*.

Differential Diagnosis

Table 2. Disorders with Intellectual Disability to Consider in the Differential Diagnosis of Weiss-Kruszka Syndrome

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/Weiss-Kruszka syndrome	Distinguishing from Weiss-Kruszka Syndrome
Blepharophimosis, ptosis, and epicanthus inversus	*FOXL2*	AD	• Ptosis • Ear anomalies • Arched eyebrows	• Blepharophimosis • Epicanthus inversus • Microphthalmia • Strabismus
Noonan syndrome	*BRAF* *KRAS* *LZTR1* [1] *MAP2K1* *NRAS* *PTPN11* *RIT1* *SOS1*	AD (AR) [1]	• Ptosis • Low set ears • Congenital heart disease	• Widely spaced eyes • DD is less common than in Weiss-Kruszka syndrome • Short stature • Webbed neck
Hereditary congenital ptosis 1 (OMIM 178300)	Unknown	AD	Ptosis	Brain, craniofacial, & heart malformations absent
Hereditary congenital ptosis 2 (OMIM 300245)	Unknown	XL	Ptosis	• XL inheritance • Brain, craniofacial, & heart malformations absent
Trigonocephaly I (OMIM 190440)	*FGFR1*	AD	Trigonocephaly	Mild synophrys

Table 2. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/Weiss-Kruszka syndrome	Distinguishing from Weiss-Kruszka Syndrome
Trigonocephaly 2 (OMIM 614485)	*FREM1*	AD	Trigonocephaly	Microcephaly in some individuals

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnosis; MOI = mode of inheritance; XL = X-linked

1. Autosomal recessive inheritance of *LZTR1*-related Noonan syndrome has been reported [Johnston et al 2018].

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Weiss-Kruszka syndrome, 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 Weiss-Kruszka Syndrome

System/Concern	Evaluation	Comment
Craniofacial	Physical exam to identify face shape & suture ridging	
Eyes	Ophthalmologic eval	To address ptosis
Development	Developmental assessment	To incl: • Motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Psychiatric/ Behavioral	Neuropsychiatric eval	Persons age >12 mos: screen for behavior concerns incl traits suggestive of ASD.
Ears/hearing	Audiology eval	To assess for hearing loss
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastrostomy tube placement in those w/ dysphagia &/or aspiration risk.
Cardiovascular	Cardiology consultation	Baseline echocardiogram recommended
Neurologic	Neurologic eval	
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	
	Family supports/resources	Assess need for: • Community or online resources, e.g., Parent To Parent; • Social work involvement for parental support.

ASD = autism spectrum disorder

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Weiss-Kruszka Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Craniosynostosis	Referral to a craniofacial team &/or neurosurgeon	For discussion of surgical correction
Ptosis	Standard treatment per ophthalmologist	
DD/ID	See Developmental Delay / Intellectual Disability Management Issues.	
Hearing loss	Hearing aids may be helpful; as per otolaryngologist.	Community hearing services through early intervention or school district
Feeding difficulties / dysphagia / poor weight gain	Feeding therapy; gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study if clinical signs or symptoms of dysphagia
Congenital heart defects	Standard treatment per cardiologist	
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Care coordination to manage multiple sub-specialty appointments, equipment, medications, & supplies	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

DD = delvelopmental delay; ID = intellectual disability

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.

Developmental Delay / Intellectual Disability Management Issues

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 federally funded program available in all states.

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.

Ages 5-21 years

- In the US, an IEP based on the individual's level of function should be developed by the local public school district. 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 the involvement of appropriate community, state, and educational agencies and to support parents in maximizing quality of life.

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., 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 due to 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.

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.

Surveillance

Table 5. Recommended Surveillance for Individuals with Weiss-Kruszka Syndrome

System/Concern	Evaluation	Frequency
Head	Assessment of head circumference & head shape	At each eval in infancy & early childhood
Eyes	Ophthalmology eval	Frequency to be determined by the degree of ptosis
Development	Monitor developmental progress & educational needs	At each visit
Ears	Audiology eval	Based on clinical suspicion
Feeding	Measurement of growth parameters	At each visit
	Eval of nutritional status & safety of oral intake	
Miscellaneous/ Other	Assess family need for social work support (e.g., respite care, other local resources) & care coordination.	

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

Weiss-Kruszka syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- 95% of individuals diagnosed with Weiss-Kruszka syndrome have the disorder as the result of a *de novo* *ZNF462* pathogenic variant.
- 5% of individuals diagnosed with Weiss-Kruszka syndrome have an affected parent. Clinical variability is reported in families; the phenotype in affected family members can range from isolated ptosis to agenesis of the corpus callosum and metopic craniosynostosis [Weiss et al 2017, Kruszka et al 2019].
- 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, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent. Parental germline mosaicism has been reported in one family [Kruszka et al 2019].
- The family history of some individuals diagnosed with Weiss-Kruszka syndrome may appear to be negative because of failure to recognize the disorder in more mildly affected family members. Therefore, an apparently negative family history cannot be confirmed unless molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents:

- If a parent of the proband has the *ZNF462* pathogenic variant, the risk to the sibs of inheriting the variant is 50%. Sibs who inherit a *ZNF462* pathogenic variant may be more or less severely affected than the proband because of intrafamilial clinical variability.
- If the *ZNF462* pathogenic variant cannot be detected in the leukocyte DNA of either parent and/or the parents are clinically unaffected, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental germline mosaicism [Kruszka et al 2019].

Offspring of a proband. Each child of an individual with Weiss-Kruszka syndrome has a 50% chance of inheriting the *ZNF462* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the *ZNF462* 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 mildly affected.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *ZNF462* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. However, because of the intrafamilial clinical variability observed in Weiss-Kruszka syndrome, molecular genetic test results cannot predict clinical findings.

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
- **VOR: Speaking out for people with intellectual and developmental disabilities**
  Phone: 877-399-4867
  Email: info@vor.net
  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. Weiss-Kruszka Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar

Table A. continued from previous page.

ZNF462	9q31.2	Zinc finger protein 462	ZNF462	ZNF462

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 Weiss-Kruszka Syndrome (View All in OMIM)

617371	ZINC FINGER PROTEIN 462; ZNF462
618619	WEISS-KRUSZKA SYNDROME; WSKA

Introduction. ZNF462 belongs to a zinc finger family of proteins with 23 zinc finger domains, making DNA binding a likely function [Chang et al 2007]. ZNF462 binds HeK9me3, identifying Znf462 as a chromatin reader involved in chromatin remodeling [Eberl et al 2013]. ZNF462 is also necessary for cell division during the cleavage stage [Laurent et al 2009], and is instrumental in maintaining chromatin structure in pluripotent cells [Massé et al 2010].

Mechanism of disease causation. Weiss-Kruszka syndrome occurs through a presumed loss-of-function mechanism. The molecular mechanism for the associated phenotype is unknown. The majority of reported pathogenic variants are in exon 3 [Kruszka et al 2019].

***ZNF462*-specific laboratory considerations.** *ZNF462* has 12 transcripts. There are two RefSeq isoforms for *ZNF462*: zinc finger protein 462 isoform 1 (NM_021224.6) is the longest transcript; isoform 2 (NM_001347997.1) uses an alternate in-frame splice site in the 5' coding region.

References

Literature Cited

Chang YS, Stoykova A, Chowdhury K, Gruss P. Graded expression of Zfp462 in the embryonic mouse cerebral cortex. Gene Expr Patterns. 2007;7:405–12. PubMed PMID: 17207666.

Cosemans N, Vandenhove L, Maljaars J, Van Esch H, Devriendt K, Baldwin A, Fryns JP, Noens I, Peeters H. ZNF462 and KLF12 are disrupted by a de novo translocation in a patient with syndromic intellectual disability and autism spectrum disorder. Eur J Med Genet. 2018;61:376–83. PubMed PMID: 29427787.

Eberl HC, Spruijt CG, Kelstrup CD, Vermeulen M, Mann M. A map of general and specialized chromatin readers in mouse tissues generated by label-free interaction proteomics. Mol Cell. 2013;49:368–78. PubMed PMID: 23201125.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Johnston JJ, van der Smagt JJ, Rosenfeld JA, Pagnamenta AT, Alswaid A, Baker EH, Blair E, Borck G, Brinkmann J, Craigen W, Dung VC, Emrick L, Everman DB, van Gassen KL, Gulsuner S, Harr MH, Jain M, Kuechler A, Leppig KA, McDonald-McGinn DM, Can NTB, Peleg A, Roeder ER, Rogers RC, Sagi-Dain L, Sapp JC, Schäffer AA, Schanze D, Stewart H, Taylor JC, Verbeek NE, Walkiewicz MA, Zackai EH, Zweier C, Zenker M, Lee B, Biesecker LG, et al. Autosomal recessive Noonan syndrome associated with biallelic LZTR1 variants. Genet Med. 2018;20:1175–85. PubMed PMID: 29469822.

Kruszka P, Hu T, Hong S, Signer R, Cogné B, Isidor B, Mazzola SE, Giltay JC, Van Gassen KLI, England EM, Pais L, Ockeloen CW, Sanchez-Lara PA, Kinning E, Adams DJ, Treat K, Torres-Martinez W, Bedeschi MF, Iascone M, Blaney S, Bell O, Tan TY, Delrue MA, Jurgens J, Barry BJ, Engle EC, Savage SK, Fleischer N, Martinez-Agosto JA, Boycott K, Zackai EH, Muenke M. Phenotype delineation of ZNF462 related syndrome. Am J Med Genet A. 2019;179:2075–82. PubMed PMID: 31361404.

Laurent A, Massé J, Omilli F, Deschamps S, Richard-Parpaillon L, Chartrain I, Pellerin I. ZFPIP/Zfp462 is maternally required for proper early Xenopus laevis development. Dev Biol. 2009;327:169–76. PubMed PMID: 19111535.

Massé J, Laurent A, Nicol B, Guerrier D, Pellerin I, Deschamps S. Involvement of ZFPIP/Zfp462 in chromatin integrity and survival of P19 pluripotent cells. Exp Cell Res. 2010;316:1190–201. PubMed PMID: 20219459.

Ramocki MB, Dowling J, Grinberg I, Kimonis VE, Cardoso C, Gross A, Chung J, Martin CL, Ledbetter DH, Dobyns WB, Millen KJ. Reciprocal fusion transcripts of two novel Zn-finger genes in a female with absence of the corpus callosum, ocular colobomas and a balanced translocation between chromosomes 2p24 and 9q32. Eur J Hum Genet. 2003;11:527–34. PubMed PMID: 12825074.

Talisetti A, Forrester SR, Gregory D, Johnson L, Schneider MC, Kimonis VE. Temtamy-like syndrome associated with translocation of 2p24 and 9q32. Clin Dysmorphol. 2003;12:175–7. PubMed PMID: 14564155.

Weiss K, Wigby K, Fannemel M, Henderson LB, Beck N, Ghali N, Anderlid BM, Lundin J, Hamosh A, Jones MC, Ghedia S, Muenke M, Kruszka P, et al. Haploinsufficiency of ZNF462 is associated with craniofacial anomalies, corpus callosum dysgenesis, ptosis, and developmental delay. Eur J Hum Genet. 2017;25:946–51. PubMed PMID: 28513610.

Chapter Notes

Revision History

- 31 October 2019 (ma) Review posted live
- 27 February 2019 (pk) Original submission

Note: Pursuant to 17 USC Section 105 of the United States Copyright Act, the *GeneReview* "Weiss-Kruszka Syndrome" is in the public domain in the United States of America.

License