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CDK13-Related Disorder

Synonyms: *CDK13*-Related Congenital Heart Defects, Dysmorphic Facial Features, and Intellectual Developmental Disorder; *CDK13*-Related CHDFIDD

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Summary

Clinical characteristics

CDK13-related disorder, reported in 43 individuals to date, is characterized in all individuals by developmental delay / intellectual disability (DD/ID); nearly all individuals older than age one year display impaired verbal language skills (either absent or restricted speech). Other common findings are recognizable facial features in some individuals, behavioral problems (autism spectrum disorder or autistic traits/stereotypies, attention-deficit/hyperactivity disorder), feeding difficulties in infancy, structural cardiac defects, and seizures.

Diagnosis/testing

The diagnosis of *CDK13* disorder is established in a proband by identification of a heterozygous pathogenic variant in *CDK13* by molecular genetic testing.

Management

Treatment of manifestations: Management of DD/ID is per usual practice with attention to gross and fine motor skills, language and communication skills, and behavioral issues. Some children with feeding difficulties require tube feeding. Structural heart defects are treated in the usual manner by a cardiologist. Seizures are treated in the usual manner with anti-seizure medication.

Surveillance: For infants with feeding difficulties: Assess swallowing, feeding, nutritional status, and weight gain monthly during the first few months of life and then at least annually during childhood. Routine monitoring of developmental progress and educational needs. Annual assessment of behavior to identify new or evolving issues. As indicated by specialists: follow up of structural cardiac defects, seizures, scoliosis, constipation, and renal structural abnormalities.

Genetic counseling

CDK13 disorder is inherited in an autosomal dominant manner. To date all probands whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo CDK13* pathogenic variant.

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Individuals with *CDK13* disorder are not known to reproduce, and fertility has not been assessed. Given the estimated recurrence risk to sibs of 1% based on the theoretic possibility of parental germline mosaicism, prenatal testing and preimplantation genetic testing are options for parents of a child with *CDK13* disorder.

Diagnosis

No formal clinical diagnostic criteria for *CDK13* disorder have been published.

Suggestive Findings

CDK13 disorder **should be considered** in individuals with the following clinical and brain MRI findings.

Clinical findings

- Developmental delay / intellectual disability
- Structural cardiac defects
  - Atrial septal defects
  - Ventricular septal defects
  - Pulmonary valve abnormalities
  - Hypoplastic pulmonary artery
- Suggestive facial dysmorphisms (See Figure 1.)

Brain MRI. Nonspecific findings in 15 individuals included the following:

- Agenesis/hypogenesis of the corpus callosum (5 individuals)
- Aplasia of the cerebellar vermis
- Periventricular leukomalacia or periventricular gliosis (3)
- Spinal cord syrinx (2)
- Cerebellar tonsillar abnormalities (2)
- Diminished white matter volume (1)

Establishing the Diagnosis

The diagnosis of *CDK13* disorder **is established** in a proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *CDK13* by 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 **gene-targeted testing** (multigene panel) and **comprehensive genomic testing** (typically exome sequencing).

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *CDK13* disorder is nonspecific and indistinguishable from many other inherited disorders, it is most likely to be diagnosed by either a multigene panel (see Option 1) or genomic testing (see Option 2).

Option 1

A multigene panel that includes *CDK13* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the

Figure 1. Characteristic facial dysmorphisms in *CDK13* disorder include hypertelorism or telecanthus; upslanting palpebral fissures; epicanthal folds; highly arched eyebrows; wide nasal bridge; short, broad columella; small mouth with thin upper lip; and abnormal ear morphology.

Figure modified from Sifrim et al [2016], Bostwick et al [2017], Hamilton et al [2018], and Uehara et al [2018]

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 *CDK13* disorder, some panels for congenital heart disease and/or ID 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.

Option 2

When the diagnosis of *CDK13* disorder has not been considered, **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.

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 *CDK13*-Related Disorder

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
CDK13	Sequence analysis [3]	43/43 [4]
	Gene-targeted deletion/duplication analysis [5]	0/43

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. Sifrim et al [2016], Bostwick et al [2017], McRae et al [2017], Hamilton et al [2018], Uehara et al [2018], van den Akker et al [2018]
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.

Clinical Characteristics

Clinical Description

To date 43 individuals with *CDK13* disorder have been reported [Sifrim et al 2016, Bostwick et al 2017, McRae et al 2017, Hamilton et al 2018, Uehara et al 2018, van den Akker et al 2018]. The features that occur commonly within the phenotypic spectrum of *CDK13* disorder are discussed below; it is likely that our understanding of the phenotypic spectrum will evolve as additional affected individuals are identified.

The following are the most common clinical features of *CDK13* disorder.

Psychosocial and Cognitive Development

All individuals reported to date have had developmental delay (DD) or intellectual disability (ID), with four reported in the mild range. Forty-one of 42 individuals on whom data were available had a degree of learning disability or DD. One individual was reported with formal IQ testing in the low-normal range.

Nearly all individuals reported older than age one year have impaired verbal language skills with either absent or restricted speech. Some discrepancy in language developmental is evident: some children have better receptive than expressive language skills.

Autism spectrum disorder has been reported in 11 individuals; two additional individuals displayed autistic traits or stereotypies. ADHD or hyperactivity alone has been reported in seven individuals. Pica has been reported in two.

Seizures

Seizures have been reported in eight individuals with seizure types that include myoclonic, generalized tonic-clonic, and absence seizures. No correlation between the presence of structural brain abnormalities and seizure activity is apparent.

Gastrointestinal

The majority of infants with *CDK13* disorder have a history of feeding difficulties including slow feeding and gastroesophageal reflux; seven eventually required gastrostomy tube feeding. Five infants had severe constipation, and one had anal stenosis.

Cardiac

The overall prevalence of structural cardiac defects is approximately 46% (17 of 37 evaluated for cardiac abnormality). Although structural heart defects were present in all seven of the initially reported individuals with *CDK13* disorder, ascertainment was biased since these individuals were identified in a cohort with congenital heart disease. In contrast, four subsequent studies identified individuals with *CDK13* disorder without structural cardiac defects [Bostwick et al 2017, Hamilton et al 2018, Uehara et al 2018, van den Akker et al 2018].

A variety of cardiac defects have been reported in the 17 with known cardiac defects; the most common, seen alone or in combination, are atrial septal defect (in 10 individuals) and ventricular septal defect (in 5).

Hypoplastic pulmonary arteries, dilated pulmonary arteries, and/or pulmonary valve abnormalities were reported in six individuals. Ebstein's anomaly and tetralogy of Fallot have also been reported.

One of the oldest individuals reported to date had bicuspid aortic valve, aortic stenosis, and aortic insufficiency diagnosed in childhood; when last evaluated at age 38 years cardiac findings included left ventricular non-compaction and sick sinus syndrome requiring pacemaker implantation [Bostwick et al 2017]. While the cardiomyopathy and electrical disturbance in this individual could indicate age-related penetrance of additional cardiac sequelae, to date long-term follow-up information of heart defects is limited to this one individual. The cardiac status of the male age 54 years reported by van den Akker et al [2018] is unknown.

Other

Growth. Birth weight, length, and head circumference appear to be within the normal range.

Short stature in childhood is present in about half of affected individuals. Endocrinologic evaluations of short stature have not been performed.

Microcephaly is more common in older individuals and, thus, may be acquired. Macrocephaly has been reported in three individuals to date [van den Akker et al 2018].

Eyes. Strabismus was reported in more than half of individuals evaluated (17/31). Other eye anomalies appear rare.

Renal anomalies reported to date include duplicated collecting systems, dilated collecting systems, and fused renal ectopia. The prevalence of renal abnormalities is unknown given the limited reports of renal imaging in published cases.

Spinal abnormalities included the following:

- Scoliosis in the absence of known vertebral abnormalities, hyperlordosis
- Vertebral hemangiomas
- Cervical spinal fusions

- Sacral clefting
- Spina bifida
- Sacral bony prominence

Musculoskeletal joint contractures, present in 2/16, are presumed secondary to spasticity. Contractures of the neck extensors and spinal extensors that limit flexion of the neck and spine were most prominent and contributed to atypical hyperextended posturing that appeared during the first year of life coinciding with the onset of spasticity.

Contractures at the Achilles tendons and knees were less severe.

Abnormalities of tone ranged from diffuse hypotonia to axial spasticity resulting in hyperextended posturing. In one series hypotonia was present in 11/16 and spasticity in 2/16 [Bostwick et al 2017]. Both children with spasticity had severe hypotonia at birth that evolved during the first year of life into spasticity (axial > appendicular).

Dental abnormalities. Wide-spaced peg-shaped teeth were reported in four individuals.

Hair. One third of individuals have curly hair.

Craniosynostosis has been reported to date in three individuals, at least one of whom required surgery for lambdoid and bicoronal synostosis.

Genotype-Phenotype Correlations

The small number of published cases to date limits the statistical power for evaluating genotype-phenotype correlations.

A possible genotype-phenotype correlation is the observation that the greater the decrease in total kinase activity the more severe the phenotype [Hamilton et al 2018].

- Variants affecting the lysine residue at position 734 (p.Lys734Arg and p.Lys734Glu) are predicted to exhibit a total loss of kinase activity by analogy with other kinases, but are also thought to have little or no effect on global protein stability or the ability to bind cyclin K [Hamilton et al 2018]. Thus, this variant is thought to exhibit a stronger dominant-negative effect. Indeed, the phenotypes of two individuals reported to date with this variant are on the more severe end of the spectrum and both also share growth restriction, microcephaly, and moderate-to-severe DD or ID [Bostwick et al 2017, Hamilton et al 2018].
- Variants affecting the asparagine residue at position 842 (p.Asn842Ser, p.Asn842Asp) are expected to cause total loss of kinase activity due to loss of ATP binding. In one series, individuals with these variants also showed a more severe phenotype than those with other pathogenic variants [Hamilton et al 2018], a finding not observed in another study [Bostwick et al 2017].

Two individuals harboring a stop codon at the end of the kinase domain may have shown a milder phenotype [van den Akker et al 2018]. It was also noted that the three unrelated individuals with frameshift variants and the two individuals with nonsense variants located at the C-terminal end of the kinase domain were clinically indistinguishable from those with missense variants, suggesting both haploinsufficiency and dominant-negative effect as mechanisms and limiting genotype-phenotype correlations.

Penetrance

Penetrance based on 43 individuals reported to date appears to be complete: all reported variants have been *de novo* and no unaffected individuals with a *CDK13* pathogenic variant have been reported.

Prevalence

Forty-three individuals with *CDK13* disorder have been reported to date. The prevalence in the general population is unknown.

A *de novo CDK13* variant was detected in ~1.8% (7/398) of individuals in a cohort of individuals with syndromic congenital heart disease of unknown cause [Sifrim et al 2016].

In another cohort (which included some individuals from the Sifrim et al [2016] study) with developmental delay of unknown cause, a *de novo CDK13* variant was detected in ~0.3% (11/3158) [McRae et al 2017].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CDK13*.

Differential Diagnosis

Table 2. Disorders with Developmental Delay / Intellectual Disability and other Anomalies to Consider in the Differential Diagnosis of *CDK13*-Related Disorder

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
KAT6B-related disorders	*KAT6B*	AD	• Congenital heart defects • Agenesis of corpus callosum • Dental anomalies (hypoplastic teeth &/or delayed eruption of teeth) • Hypotonia	In *KAT6B*-disorders: • Syndrome-specific facial features • Patellar hypoplasia/agenesis • Flexion contractures at hips/knees • Long thumbs / great toes • Immobile mask-like face In *CDK13* disorder: • Sacral & vertebral abnormalities • Pulmonary artery hypoplasia • Pulmonary valve abnormalities
Kabuki syndrome	*KDM6A* *KMT2D*	XL AD	• Congenital heart defects • Dental anomalies, widely spaced teeth • Sagittal cleft vertebrae • Scoliosis	In Kabuki syndrome: • Syndrome-specific facial features • Brachydactyly • Ear pits • Coarctation of the aorta In *CDK13* disorder: • Pulmonary artery hypoplasia • Pulmonary valve abnormalities

Table 2. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Features	
			Overlapping	Distinguishing
Mowat-Wilson syndrome	*ZEB2*	AD	• Congenital heart defects incl pulmonary artery involvement • Agenesis or hypogenesis of corpus callosum • Constipation, anal stenosis	In Mowat-Wilson syndrome: • Syndrome-specific facial features • Hirschsprung disease • Axenfeld eye anomaly • Uplifted earlobes • Broad medial eyebrows In *CDK13* disorder: • Sacral & vertebral abnormalities

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

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *CDK13* disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to diagnosis) are recommended.

Table 3. Recommended Evaluations for *CDK13* Disorder Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Assessment of height & weight for failure to thrive	
Eyes	Ophthalmologic eval for strabismus, nystagmus, &/or refractive error	
ENT/Mouth	Baseline dental eval for wide-spaced peg-shaped teeth	Referral to orthodontist if significant dental abnormalities
Cardiovascular	Baseline echocardiogram for structural cardiac anomalies	
Gastrointestinal/ Feeding	• Assess swallowing, feeding, nutritional status, weight gain. • Assess for severe constipation / anal stenosis.	• Assess for need for tube feeding. • Determine if constipation requires specialized care.
Genitourinary	Renal ultrasound	To assess for renal structural abnormalities
Musculoskeletal	Spinal imaging to evaluate for scoliosis, lordosis, cervical vertebral fusions, & sacral abnormalities	
	Physical exam to evaluate for joint contractures	
	Eval for abnormal head shape	If present, consider imaging studies to evaluate for craniosynostosis.
Neurologic	Neurologic eval	• Brain MRI • EEG if seizure activity is suspected
Psychiatric/ Behavioral	Neuropsychiatric eval	Screen persons age >12 mos for behavior concerns incl sleep disturbances, ADHD, anxiety, &/or traits suggestive of ASD.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Miscellaneous/ Other	Developmental assessment	To incl motor, speech/language eval, general cognitive, & vocational skills
	Consultation w/clinical geneticist &/or genetic counselor	

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

Treatment of Manifestations

Dental. Refer to an orthodontist for wide-spaced or peg-shaped teeth beginning at age two years.

Cardiovascular. Refer to a cardiologist or cardiothoracic surgeon for treatment of structural heart defects.

Gastrointestinal. Refer to a gastroenterologist for evaluation and treatment when chronic constipation is present.

Musculoskeletal

- **Spinal abnormalities.** Refer to an orthopedist for consideration of surgical treatment or bracing of scoliosis, and further evaluation of vertebral hemangiomas or spinal fusions.
- **Contractures.** Physical therapy, including stretching of the limbs and spine, can prevent contracture development. Splints, braces, or surgical release can help treat spinal or limb contractures.
- **Craniosynostosis.** Refer to a multidisciplinary craniofacial clinic (preferably one affiliated with a pediatric academic medical center) where staged surgical procedures can be tailored to individual needs as indicated. Initial surgeries can occur as early as age three to six months.

Neurologic

- Standardized treatment with anti-seizure medication (ASM) by an experienced neurologist is indicated. No particular ASMs have shown increased efficacy in *CDK13* disorder [Author, personal observation].
- 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. 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 if feasible, 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 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.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of ASD, 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 ADHD, when necessary.

Surveillance

Table 4. Recommended Surveillance for Individuals with *CDK13*-Related Disorder

System/Concern	Evaluation	Frequency
Eyes	Ophthalmologic eval	Annually during childhood to monitor for strabismus or refractive errors
ENT/Mouth	Routine dental/orthodontics	As indicated if dental anomalies are present
Cardiovascular	• EKG to detect electrical disturbances • Echocardiogram to evaluate structural defects	As indicated if structural cardiac disease is present

Table 4. continued from previous page.

System/Concern	Evaluation	Frequency
Gastrointestinal/ Feeding	For those w/feeding difficulties: assessment of swallowing, feeding, nutritional status, weight gain	Monthly in 1st few mos of life, then at least yearly during childhood
	Constipation	As indicated if chronic constipation is present
Renal	For those w/renal structural abnormalities	Annual laboratory eval for renal function as indicated
Musculoskeletal	For those w/spinal abnormalities	Annual monitoring for scoliosis progression
	For those w/joint contractures	Annual monitoring of joints for restriction in range of motion
Neurologic	Monitor treatment effectiveness in those w/seizures.	As indicated if clinical seizure activity is suspected
Psychiatric/ Behavioral	Behavioral assessment	Annual assessment
Miscellaneous/ Other	Monitor developmental progress & educational needs.	Annual assessment
	Clinical genetics eval	Annually to update family of any new medical recommendations or changes to recommended mgmt

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

CDK13-related disorder is inherited in an autosomal dominant manner and is caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- All probands reported to date with *CDK13* disorder whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo CDK13* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
- If the *CDK13* 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.

Sibs of a proband. The risk to the sibs of the proband depends on the genetic status of the proband's parents: if the *CDK13* 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. To date, individuals with *CDK13* disorder are not known to reproduce and fertility has not been assessed.

Other family members. Given that all probands with *CDK13* disorder reported to date have the disorder as a result of a *de novo CDK13* 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 CDK13* 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 testing 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.

- **MedlinePlus**
  Intellectual Disability

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. CDK13-Related Disorder: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar

Table A. continued from previous page.

CDK13	7p14.1	Cyclin-dependent kinase 13	CDK13	CDK13

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 CDK13-Related Disorder (View All in OMIM)

603309	CYCLIN-DEPENDENT KINASE 13; CDK13
617360	CONGENITAL HEART DEFECTS, DYSMORPHIC FACIAL FEATURES, AND INTELLECTUAL DEVELOPMENTAL DISORDER; CHDFIDD

Molecular Pathogenesis

CDK13 encodes a member of the cyclin-dependent serine/threonine protein kinase family. Members of this family serve an essential cellular role as master switches in cell cycle control. The exact function of cyclin-dependent kinase 13 (CDK13) has not yet been determined, but it may play a role in mRNA processing and may be involved in regulation of hematopoiesis [Chen et al 2007, Blazek et al 2011, Kohoutek & Blazek 2012, Chen et al 2014, Liang et al 2015, Zhang et al 2016].

Gene structure. The canonic *CDK13* transcript variant (NM_003718.4) consists of 14 exons.

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

Pathogenic variants. All known pathogenic variants to date have occurred within the region encoding the protein kinase domain (spanning amino acids 697-998 of NP_003709.3). Within that domain there is additional clustering of variants within the ATP binding domain (amino acids 711-855) and the magnesium-binding site (at amino acid 842). In fact, approximately half of the pathogenic variants reported to date perturb the wild type asparagine residue at amino acid position 842 in the magnesium-binding site.

Pathogenic variants reported to date have included missense substitutions and splice site, frameshift, and nonsense variants [Bostwick et al 2017, Hamilton et al 2018, van den Akker et al 2018]. All reported variants to date are either proven or suspected to be *de novo*.

Table 5. *CDK13* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.2200A>G	p.Lys734Glu	NM_003718.4 NP_003709.3
c.2201A>G	p.Lys734Arg	
c.2524A>G	p.Asn842Asp	
c.2525A>G	p.Asn842Ser	
c.2898-1G>A	--	NM_003718.4

Variants listed in the table have been provided by the author. *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. Variant designation that does not conform to current naming conventions

Normal gene product. The canonic transcript (NM_003718.4) encodes a 1,512-amino acid protein, containing a proline-rich domain, alanine-rich domain, arginine-serine-rich domain, and serine-rich domains.

Abnormal gene product. A variety of mechanisms have been proposed to date; additional functional studies are needed to further understand the pathogenic mechanism. Initially it was proposed that the absence of loss-of-function variants in the first 29 known individuals and the clustering of reported missense variants within a single protein domain make haploinsufficiency an unlikely mechanism [Bostwick et al 2017]. It was later suggested that *CDK13* pathogenic variants act by a novel dominant-negative mechanism by potentially sequestering cyclin K into inactive complexes, thereby perturbing the function of the wild type protein [Hamilton et al 2018]. With the reporting of the first individuals with frameshift and nonsense variants, it was noted that the phenotypes were clinically indistinguishable from those with missense variants, favoring haploinsufficiency rather than a dominant-negative mechanism [van den Akker et al 2018].

Chapter Notes

Author Notes

Bret L Bostwick, MD is an assistant professor in the Department of Molecular and Human Genetics at Baylor College of Medicine in Houston, Texas. As a clinician and clinical researcher he has special interest in *CDK13*-related disorder and other neurodevelopmental disorders resulting from *de novo* pathogenic variants.

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