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ANKRD17-Related Neurodevelopmental Syndrome

Synonym: Chopra-Amiel-Gordon Syndrome (CAGS)

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Summary

Clinical characteristics

ANKRD17-related neurodevelopmental syndrome is characterized by developmental delay – particularly affecting speech – and variable intellectual disability. Additional features include autism spectrum disorder, attention-deficit/hyperactivity disorder, ophthalmologic abnormalities (strabismus and refractive errors), growth deficiency, feeding difficulties, recurrent infections, gait and/or balance disturbances, and epilepsy. Characteristic craniofacial features include triangular face shape, high anterior hairline, deep-set and/or almond-shaped eyes with periorbital fullness, low-set ears, thick nasal alae and flared nostrils, full cheeks, and thin vermilion of the upper lip. Less common but distinctive features include cleft palate with Pierre Robin sequence, renal agenesis, and scoliosis.

Diagnosis/testing

The diagnosis of *ANKRD17*-related neurodevelopmental syndrome is established in a proband with a heterozygous pathogenic variant in *ANKRD17* identified by molecular genetic testing.

Management

Treatment of manifestations: Developmental and educational support; standard treatments for seizures, behavioral findings, ophthalmologic involvement, genitourinary anomalies, and spasticity; feeding therapy with gastrostomy tube placement as needed for persistent feeding issues; routine immunizations; referral to immunologist for those with recurrent infections; family support and care coordination as needed.

Surveillance: Assess developmental progress, educational needs, seizures, changes in tone, movement disorders, growth, nutrition, feeding, and family needs at each visit; assess behavioral and musculoskeletal manifestations annually or as needed.

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Pregnancy management: The teratogenic risk to the fetus associated with the use of anti-seizure medication during pregnancy depends on the type of anti-seizure medication used, the dose, and the gestational age of the fetus.

Genetic counseling

ANKRD17-related neurodevelopmental syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant. If the *ANKRD17* pathogenic variant identified in the proband is not identified in either parent, the risk to sibs is low but greater than that of the general population because of the possibility of parental germline mosaicism. Once the *ANKRD17* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

ANKRD17-related neurodevelopmental syndrome **should be considered** in individuals with the following clinical findings.

Clinical findings

- Developmental delay particularly affecting speech
- Intellectual disability of variable severity
- Neurodevelopmental and behavioral disorders including autism spectrum disorder and attention-deficit/hyperactivity disorder
- Ophthalmologic abnormalities (refractive errors and strabismus)
- Growth deficiency (postnatal short stature and poor weight gain) accompanied by feeding difficulties
- Recurrent infections without identified immune deficiency
- Gait and/or balance disturbances
- Epilepsy, most commonly focal seizures with secondary generalization
- Dysmorphic craniofacial features (triangular face shape, high anterior hairline, deep-set and/or almond-shaped eyes with periorbital fullness, low-set ears, thick nasal alae and flared nostrils, full cheeks, thin vermilion of the upper lip, Pierre Robin sequence)
- Genitourinary anomalies including unilateral renal agenesis

Establishing the Diagnosis

The diagnosis of *ANKRD17*-related neurodevelopmental syndrome **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *ANKRD17* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic, and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variant" in this section is understood to include any likely pathogenic variant. (2) Identification of a heterozygous *ANKRD17* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing in a child with developmental delay or an older individual with intellectual disability may begin with **comprehensive genomic testing** (exome sequencing, genome sequencing) and/or **chromosomal microarray analysis** (CMA). Other options include use of a **multigene panel**. Note: Because many of the features of this disorder are nonspecific and overlap with a range of neurodevelopmental disorders,

single-gene testing (sequence analysis of *ANKRD17*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

An intellectual disability or autism spectrum disorder multigene panel that includes *ANKRD17* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition in a person with a nondiagnostic CMA while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given that *ANKRD17*-related neurodevelopmental syndrome is rare and relatively recently described, 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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used and yields results similar to an intellectual disability multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing intellectual disability whereas some multigene panels may not. **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 *ANKRD17*-Related Neurodevelopmental Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
ANKRD17	Sequence analysis [3]	95% [4]
	Gene-targeted deletion/duplication analysis [5]	2 persons [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Chopra et al [2021] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
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. Author, personal communications [2022]

Clinical Characteristics

Clinical Description

The most common clinical manifestations of *ANKRD17*-related neurodevelopmental syndrome are developmental delay – particularly affecting speech – and variable intellectual disability. Characteristic facial features have been described but may be subtle. Additional features include ophthalmologic abnormalities,

growth deficiency, feeding difficulties, gait and/or balance disturbances, epilepsy, and behavioral findings. Recurrent infections, particularly bacterial and involving the respiratory tract, have been reported. Nonspecific brain MRI findings have been reported in half of individuals. Less common but distinctive features include cleft palate with Pierre Robin sequence, renal agenesis, and scoliosis.

To date, 33 individuals with a pathogenic variant in *ANKRD17* have been reported [Chopra et al 2021]. The following description of the phenotypic features associated with this condition is based on this report.

Table 2. Select Features of *ANKRD17*-Related Neurodevelopmental Syndrome

Feature	Proportion of Persons w/ Feature [1]	Comment
Developmental delay (DD) / intellectual disability (ID)	30/33	ID may range from borderline to severe.
Speech delay	28/31	Speech delay, incl absence of speech, has been observed w/ varying degrees of ID/DD.
Ophthalmologic abnormalities	13/22	Typically strabismus & refractive errors
Growth deficiency	13/31	Postnatal height &/or weight ≥2 SD below mean
Feeding difficulties	11/26	↓ intake, which may require enteral feeding
Recurrent infections	11/32	Usually bacterial, but may also be viral
Gait/balance disturbances	8/24	
Epilepsy	9/32	

1. Chopra et al [2021]

Developmental delay (DD) and intellectual disability (ID). Most individuals with *ANKRD17*-related neurodevelopmental syndrome present with DD and/or ID. Development and cognitive abilities are variable, with disability ranging from borderline to severe. Normal cognition has been reported in two individuals, one of whom had a history of speech delay that improved with therapy and another with autism spectrum disorder.

The domain of speech is particularly affected in this disorder. Speech delay has been reported in nearly all individuals with *ANKRD17*-related neurodevelopmental syndrome, including those with intellectual abilities in the normal range. Most individuals eventually acquire words or short sentences with speech therapy, but a significant proportion remain nonverbal and rely on other means of communication.

Motor delay is also common, with an average age of walking of two years (range: 9 months to 4 years).

The trajectory of fine motor and social development is not completely understood at this time.

Developmental regression has been reported in one individual; however, this was thought to be secondary to poorly controlled epilepsy.

Other neurodevelopmental features

- Gait and balance abnormalities have been described in some individuals, in particular a wide-based or ataxic gait. No correlation between gait and neuroimaging abnormalities has been found.
- A subset of individuals manifest abnormalities in tone, including both hypotonia (typically truncal) and hypertonia with or without spasticity (typically distal).

Epilepsy has been reported in approximately one third of individuals with *ANKRD17*-related neurodevelopmental syndrome. Age of onset ranges from infancy to early adolescence. Individuals with

infantile-onset epilepsy tend to have more frequent seizures than those with childhood- or adolescent-onset epilepsy. Abnormal EEG in the absence of epilepsy has also been described.

The most common seizure type is focal seizures with secondary generalization. Other seizure types include Lennox-Gastaut epilepsy, tonic seizures with head deviation, myoclonic epilepsy, tonic-clonic epilepsy, and absence seizures. Efficacy of anti-seizure medications is variable, with refractory epilepsy in a minority of individuals.

Neurobehavioral/psychiatric manifestations. Autism spectrum disorder is present in some affected individuals. Stereotypic movements, particularly of the hands, have also been reported. Four individuals have been reported to have attention-deficit/hyperactivity disorder. Anxiety and depression have been reported in a single affected adult.

Ophthalmologic abnormalities were reported in more than half of affected individuals. Abnormalities were generally minor and included refractive errors and strabismus. Bilateral optic nerve hypoplasia was also reported in one individual.

Growth and feeding. Neonatal growth parameters are normal in most individuals. Postnatal growth deficiency (defined as height and/or weight equal to or greater than two standard deviations below the mean for age and sex) and/or failure to thrive have been reported in almost half of individuals. This is often accompanied by feeding difficulties, which may necessitate enteral tube feeding. The basis of these difficulties may be poor progression to solids, reduced appetite, and/or food aversions.

Microcephaly and, less commonly, macrocephaly have also been observed in affected individuals.

Recurrent infections have been reported in approximately one third of affected individuals. Infections are usually bacterial, but recurrent viral infections have also been reported. The most common sites of infection are the lower respiratory system and middle ear. One individual had a history of *Pseudomonas* and methicillin-resistant *Staphylococcal aureus* (MRSA) infection on his toes. Immunology assessments have not identified immunodeficiencies in any affected individuals.

Craniofacial features. Individuals with *ANKRD17*-related neurodevelopmental syndrome present with characteristic facial features, which may be subtle and only evident to a trained dysmorphologist. These include a triangular face shape, high anterior hairline, deep-set and/or almond-shaped eyes with periorbital fullness, low-set ears, thick nasal alae and flared nostrils, full cheeks, and a thin vermilion of the upper lip (Figure 1). Microcephaly (7/31 individuals), macrocephaly (4/31 individuals), and normal head size have all been reported. Cleft palate with Pierre Robin sequence was reported in two individuals, and unilateral cleft lip and palate was reported in one individual.

Musculoskeletal features

- Joint hypermobility has been reported in one third of affected individuals. In most individuals, hypermobility was generalized.
- Minor digital anomalies have been described, including brachydactyly, fifth digit clinodactyly, and prominent fingertip pads.
- Scoliosis has been reported in three individuals.

Genitourinary anomalies have been described in 15% of individuals. Unilateral renal agenesis has been described in three individuals. More minor genitourinary anomalies include crossed fused renal ectopia, urethral stricture, and cryptorchidism.

Pigmentary anomalies, including hypopigmented skin and hair, progressive vitiligo, hyperpigmented patches with overlying freckles, and café au lait macules have been described in a minority of individuals.

Brain MRI abnormalities were reported in almost half of individuals who had imaging records. Findings were generally nonspecific and included decreased white matter volume, thinning of the corpus callosum, optic nerve hypoplasia, focal hyperintensities, right temporal sclerosis, and dilated Virchow-Robin spaces. Periventricular nodular heterotopia was reported in a single affected individual. Thus far, no correlation between MRI abnormalities and abnormal neurologic examination or epilepsy has been demonstrated.

Other associated features

- **Cardiovascular features.** Two individuals were reported to have prominent venous patterns on the forehead and torso, one of whom was reported to be hypermobile. Congenital heart defects including patent foramen ovale, dysplastic aortic valve, and ventricular septal defect have been reported.
- **Endocrine features.** Hypoglycemia and hypothyroidism have each been reported in a single individual. Spontaneous vertebral fractures with hypercalciuria have been reported.
- **Hearing loss.** One individual with bilateral sensorineural hearing loss and another with conductive hearing loss have been reported.

Prognosis. Based on current data, there is no evidence that life span is limited by this condition, as several adults have been reported. Data on possible progression of behavior abnormalities or neurologic findings are still limited. Since many adults with disabilities have not undergone advanced genomic evaluation, it is likely that adults with this condition are underrecognized and underreported.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been identified. Individuals with pathogenic missense variants are clinically indistinguishable from those with truncating variants.

Penetrance

Based on current literature, penetrance is believed to be complete with variable expressivity.

Nomenclature

The title of this *GeneReview*, *ANKRD17*-related neurodevelopmental syndrome, is based on the dyadic naming approach proposed by Biesecker et al [2021] to delineate mendelian genetic disorders.

Prevalence

The prevalence of this rare genetic disorder is unknown. To date, 33 individuals with *ANRKD17*-related neurodevelopmental syndrome have been reported and well characterized [Chopra et al 2021], and the authors are aware of a further 14 individuals who are affected.

Genetically Related (Allelic) Disorders

4q13.3 contiguous microdeletions encompassing *ANKRD17* have been reported in several individuals, including three affected family members with a 1.56-Mb deletion and one individual with a 1.16-Mb microdeletion [Maldžienė et al 2020, Chopra et al 2021]. All reported individuals had intellectual disability, growth deficiency, and microcephaly. Additional reported features of *ANKRD17*-related neurodevelopmental syndrome included autism spectrum disorder, abnormal EEG, dilated Virchow-Robin spaces on brain MRI, congenital heart defects, and scoliosis. To date, no other genes implicated in neurodevelopment and no other genes intolerant to loss of function have been identified within the deleted regions.

Figure 1. Dysmorphic facial features of *ANKRD17*-related neurodevelopmental syndrome. Physical characteristics include a triangular face (I1, 4, 5, 6, 9, 15, 22, 30, 31, and 33), high anterior hairline (I1-10, 12, 15, 18, 25, 29, 30, 31, 32, and 33), deep-set (I2, 3, 6, 7, 30) or almond-shaped (I1, 4, 5, 12, 15, 22, 29, and 33) eyes with periorbital fullness (I1, 3, 4, 5, 8, 12), full cheeks (I2, 6, 7, 12, 18, 26, and 29), thick alae nasi with flared nostrils (I2, 3, 5, 6, 8, 9, 12, 25, 31), and a thin vermilion of the upper lip (I1, 3, 4, 5, 9, 10, 11, 15, 22, 26, 30, and 31).

Reproduced with permission from Chopra et al [2021]

Differential Diagnosis

Many of the features of *ANKRD17*-related neurodevelopmental syndrome are nonspecific, variable, and overlap with other genetic conditions. The more distinctive features of recurrent infections, scoliosis, Pierre Robin sequence, and renal agenesis only occur in a minority of individuals. All disorders with intellectual disability without other distinctive findings should be considered in the differential diagnosis. See OMIM Autosomal Dominant, Autosomal Recessive, Nonsyndromic X-Linked, and Syndromic X-Linked Intellectual Developmental Disorder Phenotypic Series.

Management

No clinical practice guidelines for *ANKRD17*-related neurodevelopmental syndrome have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *ANKRD17*-related neurodevelopmental 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 *ANKRD17*-Related Neurodevelopmental Syndrome

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Neurologic	Neurologic eval	• Consider brain MRI. • EEG
Psychiatric/ Behavioral	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl findings suggestive of ASD, ADHD, anxiety, &/or depression
Eyes	Ophthalmologic eval	To assess for ↓ vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus, & more complex findings that may require subspecialty referral
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of nutritional status • Consider eval for gastrostomy tube placement in persons w/inadequate caloric intake.
Immunologic	• Assess for recurrent infections. • Low threshold for immunologist referral	
Musculoskeletal	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Gait & balance • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills) • Scoliosis
Genitourinary	Kidney & urinary tract ultrasound	
Integument	Examine for pigmentary abnormalities.	

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Endocrine	• Assess for growth deficiency. • Consider measurement of thyroid function, serum & urine calcium; monitor for history of suggestive hypoglycemia symptoms.	
Hearing	Audiologic eval	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of *ANKRD17*-related neurodevelopmental syndrome to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent; • Social work involvement for parental support; • Home nursing referral.	

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ASD = autism spectrum disorder; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *ANKRD17*-related neurodevelopmental syndrome. Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This can include multidisciplinary care by specialists in neurology, speech therapy, physical therapy, occupational therapy, ophthalmology, mental health, and clinical genetics (see Table 4).

Table 4. Treatment of Manifestations in Individuals with *ANKRD17*-Related Neurodevelopmental Syndrome

Manifestation/Concern	Treatment	Considerations/Other
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Psychiatric/behavioral manifestations	Standard treatment per behavioral therapist &/or psychiatrist	
Ophthalmologic involvement	By ophthalmologist	Treatment of refractive errors &/or strabismus
Poor weight gain	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues, particularly low caloric intake.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs/symptoms of dysphagia
Recurrent infections	• Routine immunizations • Referral to immunologist	
Genitourinary anomalies	By nephrologist &/or urologist	

Table 4. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	Consider need for positioning & mobility devices, disability parking placard.
Family/Community	• Ensure appropriate social work involvement to connect families w/local resources, respite, & support. • Coordinate care to manage multiple subspecialty appointments, equipment, medications, & supplies.	• Ongoing assessment of need for palliative care involvement &/or home nursing • Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; OT = occupational therapy; PT = physical therapy
1. Education of parents/caregivers regarding common seizure presentations is appropriate. For information on non-medical interventions and coping strategies for children diagnosed with epilepsy, see Epilepsy Foundation Toolbox.

Developmental Delay / Intellectual Disability Management Issues

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

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

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

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

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision and hearing consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating,

assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic complications (e.g., contractures, scoliosis, hip dislocation).
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).
- For muscle tone abnormalities including hypertonia or dystonia, consider involving appropriate specialists to aid in management of baclofen, tizanidine, Botox®, anti-parkinsonian medications, or orthopedic procedures.

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 should be assessed at each visit and clinical feeding evaluations and/or radiographic swallowing studies should be obtained for choking/gagging during feeds, poor weight gain, frequent respiratory illnesses, or feeding refusal that is not otherwise explained. Assuming that the child is safe to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

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

Social/Behavioral Concerns

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 typically performed one on one with a board-certified behavior analyst.

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

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

Surveillance

Table 5. Recommended Surveillance for Individuals with *ANKRD17*-Related Neurodevelopmental Syndrome

System/Concern	Evaluation	Frequency
Development	Monitor developmental progress & educational needs.	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, & movement disorders.	
Psychiatric/ Behavioral	Behavioral assessment for ASD, ADHD, anxiety, aggression, or self-injury	Annually or as needed
Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake	At each visit
Musculoskeletal	• Physical medicine, OT/PT assessment of mobility, self-help skills • Clinical eval for scoliosis	Annually or as needed
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; OT = occupational therapy; PT = physical therapy

Evaluation of Relatives at Risk

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

Pregnancy Management

To date, there has been one affected individual in the literature who had a pregnancy [Chopra et al 2021]. In general, women with epilepsy or a seizure disorder of any cause are at greater risk for mortality during pregnancy than pregnant women without a seizure disorder; use of anti-seizure medication during pregnancy reduces this risk. However, exposure to anti-seizure medication may increase the risk for adverse fetal outcome (depending on the drug used, the dose, and the stage of pregnancy at which medication is taken). Nevertheless, the risk of an adverse outcome to the fetus from anti-seizure medication exposure is often less than that associated with exposure to an untreated maternal seizure disorder. Therefore, use of anti-seizure medication to treat a maternal seizure disorder during pregnancy is typically recommended. Discussion of the risks and benefits of using a given anti-seizure medication during pregnancy should ideally take place prior to conception. Transitioning to a lower-risk medication prior to pregnancy may be possible [Sarma et al 2016].

See MotherToBaby for further information on medication use during pregnancy.

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

ANKRD17-related neurodevelopmental syndrome is an autosomal dominant disorder typically caused by a *de novo* pathogenic variant.

Risk to Family Members

Parents of a proband

- Most probands reported to date with *ANKRD17*-related neurodevelopmental syndrome whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo ANKRD17* pathogenic variant.
- Rarely, individuals diagnosed with *ANKRD17*-related neurodevelopmental syndrome inherited an *ANKRD17* pathogenic variant from a parent.
  - In one family, a heterozygous mother with borderline intellectual disability, anxiety, depression, and short stature transmitted an *ANKRD17* pathogenic variant to an affected child [Chopra et al 2021].
  - Transmission of an *ANKRD17* pathogenic variant from an unaffected father with somatic and germline mosaicism to an affected child has also been reported [Chopra et al 2021].
- Molecular genetic testing is recommended for the parents of the proband regardless of family history to confirm parental genetic status and to allow reliable recurrence risk counseling.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism.* Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.

    * A parent with somatic and germline mosaicism for an *ANKRD17* pathogenic variant may have very subtle clinical features.
- The family history of some individuals diagnosed with *ANKRD17*-related neurodevelopmental syndrome may appear to be negative because of failure to recognize the disorder in heterozygous family members with subtle clinical features. Therefore, parental molecular genetic testing is recommended to demonstrate that neither parent is heterozygous for the *ANKRD17* pathogenic variant identified in 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 is known to have the *ANKRD17* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.
- If the *ANKRD17* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of germline mosaicism in a parent.
- If the parents have not been tested for the *ANKRD17* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low but still increased over that of the general population because of the possibility of variable expressivity resulting in a mild, unrecognized phenotype in a heterozygous parent and the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with *ANKRD17*-related neurodevelopmental syndrome has a 50% chance of inheriting the 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 *ANKRD17* pathogenic variant, the parent's family members may be at risk.

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

Once the *ANKRD17* pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

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

- **American Association on Intellectual and Developmental Disabilities (AAIDD)**

  Phone: 202-387-1968

  Fax: 202-387-2193

  www.aaidd.org

- **Global Genes**

  Phone: 949-248-RARE (7273)

  Email: careaboutrare@globalgenes.org

  www.globalgenes.org

- **Chopra-Amiel-Gordon Syndrome Registry**

  The investigators of this study aim to better understand the ANKRD17-related neurodevelopmental syndrome by gathering information about genetic variants, clinical features, and family history.

  Principal Investigator: Maya Chopra MBBS FRACP

  Email: Abigail.sveden@childrens.harvard.edu

  Delineating the Molecular Spectrum and the Clinical, Imaging and Neuronal Phenotype of Chopra-Amiel-Gordon Syndrome

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. ANKRD17-Related Neurodevelopmental Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
ANKRD17	4q13.3	Ankyrin repeat domain-containing protein 17	ANKRD17	ANKRD17

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 ANKRD17-Related Neurodevelopmental Syndrome (View All in OMIM)

615929	ANKYRIN REPEAT DOMAIN-CONTAINING PROTEIN 17; ANKRD17
619504	CHOPRA-AMIEL-GORDON SYNDROME; CAGS

Molecular Pathogenesis

Ankyrin repeat domain-containing protein 17 (ANKRD17) belongs to a group of proteins characterized by the presence of the ankyrin repeat motif [Li et al 2006]. These repeats are typically organized into linear arrays and serve as protein-protein interaction surfaces. A range of functions for this gene have been proposed:

- There is in vitro evidence for the role of ANKRD17 in cell cycle progression through cyclin E/CDK2 [Deng et al 2009].
- A role for ANKRD17 in antibacterial and antiviral immunity has also been proposed, via the NOD1/NOD2 [Menning & Kufer 2013] and RIG-I-like receptor-mediated pathway [Wang et al 2012].

The precise mechanism by which *ANKRD17* loss of function leads to the neurodevelopmental phenotype is unknown.

Mechanism of disease causation. The mutational spectrum of *ANKRD17*-related neurodevelopmental syndrome and the intolerance of this gene to loss of function in the general population (gnomAD pLI score = 1) is highly suggestive of haploinsufficiency as the underlying disease mechanism. Most missense variants in *ANKRD17* are believed to disrupt the stability of ankyrin repeats.

***ANKRD17*-specific laboratory technical considerations.** The *ANKRD17* gene contains two clusters of ankyrin repeats. Most pathogenic missense variants identified thus far are located in these clusters. Missense variants outside of the ankyrin repeat domain require careful interpretation.

Chapter Notes

Author Notes

Maya Chopra web page

Rosamund Stone Zander Translational Neuroscience Center web page

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