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Okur-Chung Neurodevelopmental Syndrome

Synonym: *CSNK2A1*-Related Neurodevelopmental Syndrome

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Summary

Clinical characteristics

Individuals with Okur-Chung neurodevelopmental syndrome (OCNDS) frequently have nonspecific clinical features, delayed language development, motor delay, intellectual disability (typically in the mild-to-moderate range), generalized hypotonia starting in infancy, difficulty feeding, and nonspecific dysmorphic facial features. Developmental delay affects all areas of development, but language is more impaired than gross motor skills in most individuals. Intellectual disability has been reported in about three quarters of individuals. Less common findings may include kyphoscoliosis, postnatal short stature, disrupted circadian rhythm leading to sleep disturbance, seizures, and poor coordination.

Diagnosis/testing

The diagnosis of OCNDS is established in a proband with suggestive findings and a heterozygous pathogenic variant in *CSNK2A1* identified by molecular genetic testing.

Management

Treatment of manifestations: Feeding therapy and consideration of gastrostomy tube placement in those with persistent feeding issues; consideration of growth hormone therapy (as directed by an endocrinologist) in those with short stature and evidence of partial growth hormone deficiency; standard treatment of epilepsy (as directed by a neurologist) with anti-seizure medication; consideration of intravenous immune globulin treatment (as directed by an immunologist) for demonstrated hypogammaglobulinemia; physical therapy / occupational therapy / rehabilitation medicine for those with hypotonia and/or motor coordination issues; standard supportive developmental therapies; standard treatment of scoliosis, constipation, congenital heart defects, renal anomalies / pelviectasis, and sleep disorders.

Surveillance: At each visit: measure growth parameters, growth velocity, and nutritional status; monitor for signs of ongoing feeding issues / safety of oral intake and constipation; assess new neurologic manifestations (seizures, changes in tone, movement disorders, poor coordination); monitor developmental progress, behavior, and

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educational needs; monitor for evidence of frequent or unusual infections and for signs and symptoms of sleep disturbance. Every one to three years: ophthalmology evaluation.

Genetic counseling

OCNDS disorder is expressed in an autosomal dominant manner and typically caused by a *de novo CSNK2A1* pathogenic variant. Therefore, the risk to other family members is presumed to be low. Rarely, individuals diagnosed with OCNDS have the disorder as the result of a *CSNK2A1* pathogenic variant inherited from an affected parent or an unaffected parent with low-level mosaicism in the blood. Once a *CSNK2A1* pathogenic variant has been identified in an affected family member, prenatal testing and preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for Okur-Chung neurodevelopmental syndrome (OCNDS) have been published.

Suggestive Findings

OCNDS **should be considered** in individuals with the following clinical findings.

Clinical findings

- Mild-to-moderate developmental delay (DD) or intellectual disability (ID)
- Generalized hypotonia in infancy and/or childhood
- Speech delay

AND

- Any of the following features presenting in infancy or childhood:
  - Infant feeding difficulties
  - Seizures, ranging from a single seizure event to intractable epilepsy
  - Behavioral findings including stereotypic movements, autism spectrum disorder, aggressiveness and tantrums, and attention-deficit/hyperactivity disorder
  - Slow growth, failure to thrive, or difficulty gaining weight
  - Nonspecific dysmorphic features (See Clinical Characteristics.)

Family history. Because OCNDS is typically caused by a *de novo* pathogenic variant, most probands represent a simplex case (i.e., a single occurrence in a family).

Establishing the Diagnosis

The diagnosis of OCNDS **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in *CSNK2A1* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *CSNK2A1* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing in a child with DD or an older individual with ID may begin with chromosomal microarray analysis (CMA). Other options include use of a multigene panel or exome or genome sequencing.

Note: Single-gene testing (sequence analysis of *CSNK2A1*, followed by gene-targeted deletion/duplication analysis) is rarely useful and typically NOT recommended.

- **An ID multigene panel** that includes *CSNK2A1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition in a person with a nondiagnostic CMA while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. Of note, given the rarity of OCNDS, 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 ID multigene panel with the additional advantage that exome sequencing includes genes recently identified as causing ID, 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 Okur-Chung Neurodevelopmental Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
CSNK2A1	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [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. Okur et al [2016], Trinh et al [2017], Vissers et al [2017], Akahira-Azuma et al [2018], Chiu et al [2018], Colavito et al [2018], Owen et al [2018], Angione et al [2019], Duan et al [2019], Nakashima et al [2019], Martinez-Monseny et al [2020], Miller et al [2020], Quaio et al [2020], Seo et al [2020], van der Werf et al [2020], Wang et al [2020], Wu et al [2020], Stranneheim et al [2021], Wang et al [2021], Wu et al [2021]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Clinical Characteristics

Clinical Description

Individuals with Okur-Chung neurodevelopmental syndrome (OCNDS) frequently have nonspecific clinical features, delayed language development, motor delay, intellectual disability, generalized hypotonia starting in infancy, difficulty feeding, and nonspecific dysmorphic facial features.

To date, 51 individuals have been identified with a pathogenic variant in *CSNK2A1* [Okur et al 2016, Trinh et al 2017, Akahira-Azuma et al 2018, Chiu et al 2018, Colavito et al 2018, Owen et al 2018, Angione et al 2019, Duan et al 2019, Nakashima et al 2019, Martinez-Monseny et al 2020, Wu et al 2020, Seo et al 2020, Wu et al 2021]. The following description of the phenotypic features associated with this condition is based on 36 individuals with clinical data from these reports.

Table 2. Select Features of Okur-Chung Neurodevelopmental Syndrome

Feature	Proportion of Persons w/Feature	Comment
Developmental delay / intellectual disability	35/35 [1]	Generally mild-to-moderate, w/language development most affected domain
Dysmorphic facial features	29/36	Round face & short, broad nasal tip
Behavioral issues	27/36	
Hypotonia	22/36	Generally mild
Brain MRI abnormalities	11/20 [2]	Nonspecific
Musculoskeletal findings	15/36	Kyphoscoliosis, loose joints, hernia
Difficulty feeding	14/36	From infancy to childhood
Postnatal short stature	14/36	Generally 2-3 SD below mean
Difficulty gaining weight	13/36	
Sleep issues	13/36	Disrupted circadian rhythm
Microcephaly / smaller head (absolute or relative)	12/36	
Seizures	11/36	No specific type
Ataxia / gait difficulties / poor coordination	9/36	

SD = standard deviation(s)
1. One individual was too young for assessment [Colavito et al 2018].
2 The number of individuals reported to have had brain MRI performed

Developmental delay (DD) and intellectual disability (ID). The majority of affected individuals have DD affecting all areas of development. However, language development is more impaired than gross motor skills in most individuals. ID has also been reported in about three quarters of individuals. The average age of acquisition of selected early developmental milestones is as follows (Figure 1):

- Sitting: 11 months (n=20)
- Walking: 28.8 months (n=25)
- First meaningful words: 38.3 months (n=18)

Behavioral findings. Affected individuals have been reported to be affectionate and happy when they are able to communicate. The most common behavior issues reported:

- Stereotypic movements (~1/3 of affected individuals)
- Autism spectrum disorder (~1/4)
- Aggressiveness and tantrums in part related to inability to communicate needs (~1/4)
- Attention-deficit/hyperactivity disorder (~1/5)

Seizures/epilepsy. About one third of affected individuals have been reported to have had a seizure at least once. Some individuals with only a single seizure have not been treated with anti-seizure medication; those with multiple unprovoked seizures have been treated (see Management).

- Intractable seizures reported in some individuals
- Status epilepticus reported in one individual

Other neurologic features

- Mild hypotonia noted from infancy was reported in about two thirds of affected individuals.
- Gait abnormalities and poor motor coordination were reported in about one sixth of individuals. Ataxia has also been reported in a few individuals [Okur et al 2016, Colavito et al 2018].

Gastrointestinal

- Infant feeding difficulties are common and manifest as poor suck in early infancy or difficulty transitioning to solid foods later in infancy.
- Feeding and swallowing difficulties may require gastrostomy tube placement.
- Constipation is common.

Growth. Some affected individuals are smaller at birth, although true intrauterine growth restriction is rare. About one third of affected individuals have been reported to have short stature (14/36; 38%) or failure to thrive (13/36; 36%), with height and weight usually measuring between 2 and 3 SD below the mean for either growth domain in those individuals.

Only one reported individual had congenital microcephaly. Outside of the newborn period, most affected individuals have an occipitofrontal circumference that is below the mean but still within the normal range for age and sex.

Musculoskeletal features. The most common musculoskeletal issues are scoliosis/kyphosis and loose/hyperextensible joints associated with hypotonia. Umbilical and inguinal hernias have also been reported.

Sleep. Sleep issues mainly stemming from circadian rhythm disturbance in early childhood may pose challenges for families. Rarely, individuals may also experience sleep apnea [Chiu et al 2018, Nakashima et al 2019].

Neuroimaging. More than half of the individuals for whom brain MRI results were reported had nonspecific abnormalities. Abnormalities reported in more than one individual include delayed myelination (n=3), smaller anterior pituitary gland (n=2), and thin corpus callosum (n=2). Other reported abnormal brain findings are simple gyral pattern, cerebellar vermis hypoplasia, cerebral atrophy, mega cisterna magna, solid lesion of the pineal gland with minor cystic inclusions, duplication of the pituitary gland, Rathke cleft cysts, and absent olfactory bulbs.

Other associated features (rare)

- **Ophthalmologic involvement** is nonspecific (e.g., strabismus) and infrequent.
- **Endocrinologic.** Partial growth hormone deficiency has been reported in two individuals [Chiu et al 2018, Wu et al 2021].
- **Immunologic.** Individuals with OCNDS tend to have frequent minor infections, and a few individuals have documented IgG deficiency (hypogammaglobulinemia) and/or IgA deficiency.

- **Genitourinary abnormalities.** Pelvicaliectasia, duplicated renal collection system, ectopic kidney, and labial adhesions have rarely been reported.
- **Cardiovascular findings.** Atrial septal defect has been reported in three unrelated individuals; pulmonary valve abnormality and tetralogy of Fallot have each been reported in one individual.
- **Skin.** Dry skin, eczema, palmar erythema, and cutis marmorata have each been reported in one individual.
- **Facial features.** No specific dysmorphic features have been observed. If present, dysmorphic features include round facies and short, broad nasal tip.

Prognosis. OCNDS is typically not a progressive disease, and individuals achieve many developmental milestones; however, speech difficulties may persist long term. It is unknown whether life span in OCNDS is abnormal; based on current data, life span is not limited by this condition. Data on possible progression are still limited.

Genotype-Phenotype Correlations

The majority of *CSNK2A1* pathogenic variants are located in functional domains (Figure 2) of the protein; however, current data are insufficient to support genotype-phenotype correlations.

Prevalence

OCNDS is rare and the exact prevalence is unknown. Only 51 individuals have been reported in the literature; others have been diagnosed but are not yet included in publications.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *CSNK2A1*.

Differential Diagnosis

Because the phenotypic features associated with Okur-Chung neurodevelopmental syndrome (OCNDS) are not sufficient to diagnose this condition, 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 Okur-Chung neurodevelopmental syndrome (OCNDS) have been published.

Evaluations Following Initial Diagnosis

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

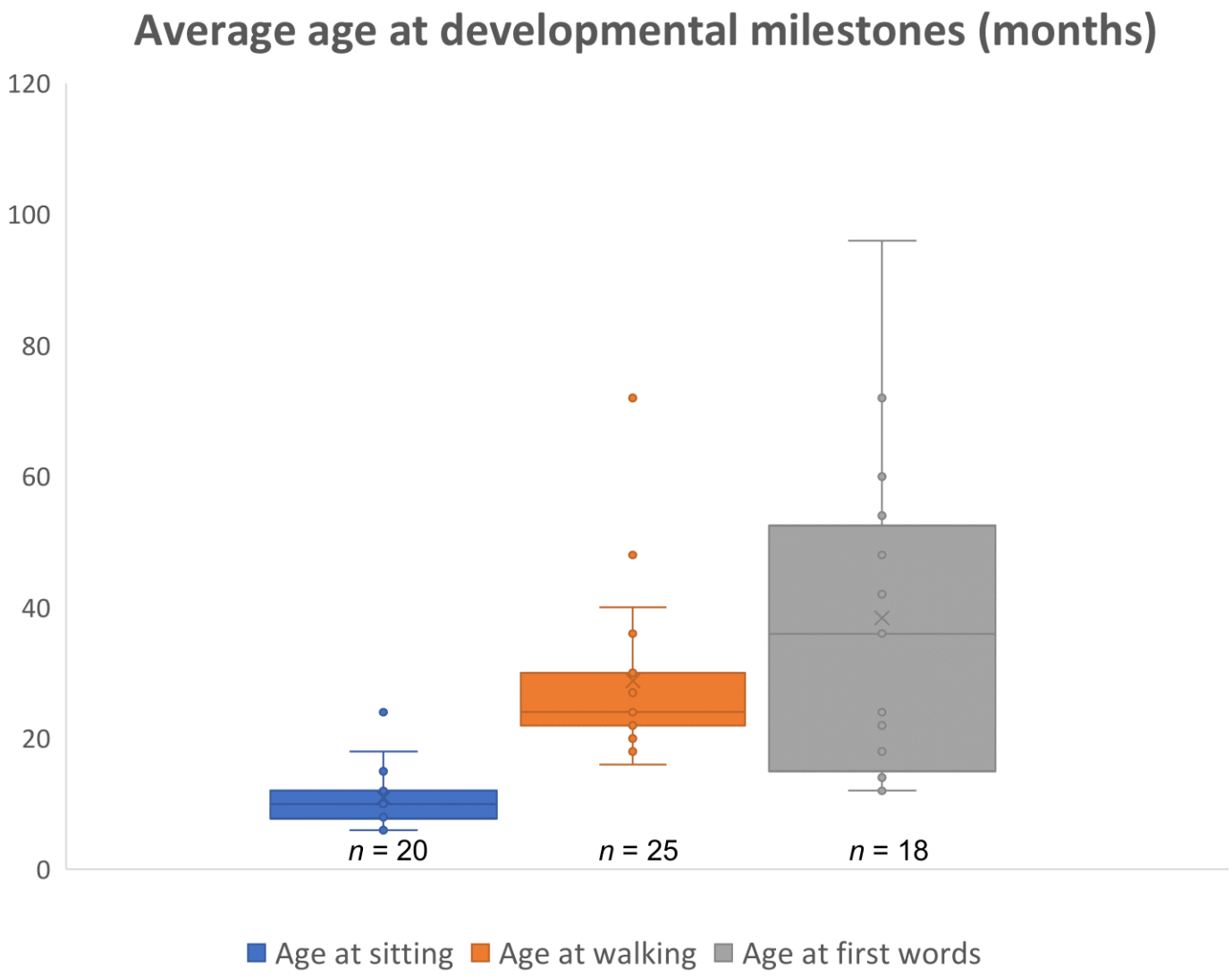

Figure 1. Average age at which affected individuals achieved three developmental milestones: unsupported sitting, walking, and first words. The *n* values below the bar plots indicate the number of individuals for whom data were available for a given milestone. Data derived from Okur et al [2016], Trinh et al [2017], Vissers et al [2017], Akahira-Azuma et al [2018], Chiu et al [2018], Colavito et al [2018], Owen et al [2018], Angione et al [2019], Duan et al [2019], Nakashima et al [2019], Martinez-Monseny et al [2020], Miller et al [2020], Quaio et al [2020], Seo et al [2020], van der Werf et al [2020], Wang et al [2020], Wu et al [2020], Stranneheim et al [2021], Wang et al [2021], Wu et al [2021].

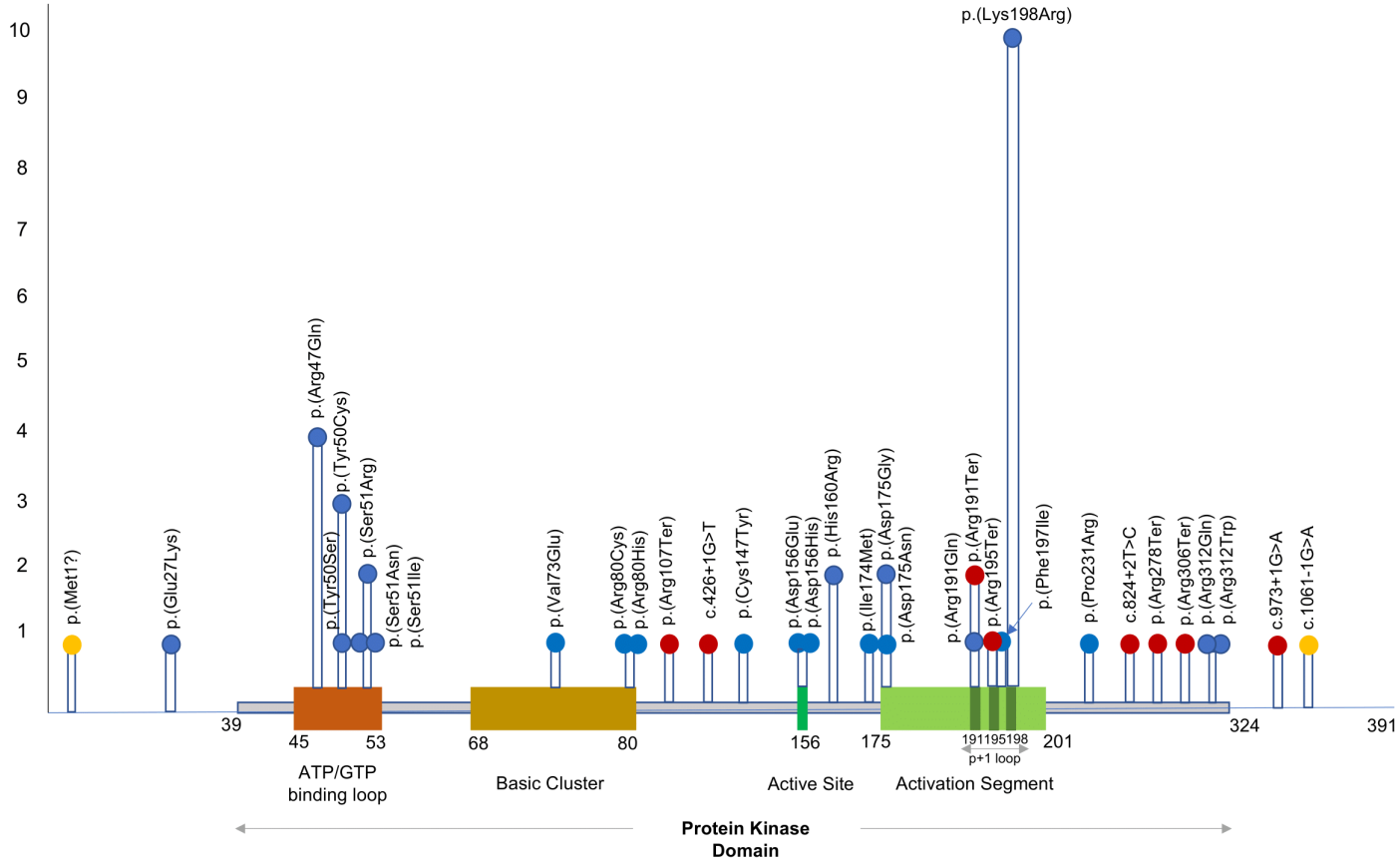

Figure 2. Lollipop plot of reported pathogenic *CSNK2A1* variants in the literature (n=51) and two-dimensional representation of their locations in the CSNK2A1 protein (x-axis). Blue-filled circles are missense pathogenic variants and red-filled circles are loss-of-function pathogenic variants. Gold-filled circles are predicted pathogenic splice variants. Variant numbering is according to NM_177559.3.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Okur-Chung Neurodevelopmental Syndrome

System/Concern	Evaluation	Comment
Constitutional	Measure weight, length/height, & head circumference.	To assess for poor weight gain / failure to thrive, short stature, & microcephaly
Neurologic	Neurologic eval	• Consider EEG & possible head MRI if seizures are a concern. • Assess gait & coordination.
Hypotonia / Poor coordination	Orthopedics / physical medicine & rehab / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
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 sleep disturbances, ADHD, anxiety, &/or findings suggestive of ASD
Musculoskeletal	Orthopedics	To incl assessment of scoliosis, esp in adolescents

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of oromotor function, aspiration risk, & nutritional status • Consider eval for gastrostomy tube placement in persons w/dysphagia &/or aspiration risk.
Eyes	Ophthalmologic eval	To assess for strabismus & refractive error
Cardiovascular	Echocardiography	To assess for presence of congenital heart defects
Genitourinary	Consider renal ultrasound.	To assess for presence of renal anomalies & pelviectasis
Immunologic	Consider baseline assessment of quantitative immunoglobulin levels.	In those w/recurrent &/or unusually severe infections
Respiratory/ Sleep	Assessment for signs & symptoms of poor sleep &/or sleep apnea	Consider referral to a sleep disorder clinic &/or sleep study.
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of OCNDS 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; OCNDS = Okur-Chung neurodevelopmental syndrome; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Okur-Chung Neurodevelopmental Syndrome

Manifestation/ Concern	Treatment	Considerations/Other
Poor weight gain / Failure to thrive	• 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
Short stature	Growth hormone therapy may be considered in those w/ evidence of partial growth hormone deficiency.	In consultation w/endocrinologist
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]
Hypotonia / Motor coordination problems	Orthopedics / physical medicine & rehab / PT & OT	Consider need for PT.
DD/ID/Behavior issues	See Developmental Delay / Intellectual Disability Management Issues.	
Scoliosis	Standard treatment by orthopedist	
Constipation	Stool softeners, prokinetics, osmotic agents, or laxatives as needed	

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Strabismus / Refractive errors	Standard treatment per ophthalmologist	Treatment of refractive errors &/or strabismus
Congenital heart defects	Standard treatment per cardiologist	
Renal anomalies / Pelviectasis	Standard treatment per urologist	
Hypogamma-globulinemia	Standard treatment per immunologist	Consider IVIG treatment for demonstrated immunoglobulin deficiencies.
Sleep disorders	Standard treatment per sleep medicine specialist	
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.	Consider involvement in adaptive sports or Special Olympics.

ASM = anti-seizure medication; DD = developmental delay; ID = intellectual disability; IVIG = Intravenous immune globulin; 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 for access to occupational, physical, speech, and feeding therapy as well as infant mental health services, special educators, and sensory impairment specialists. In the US, early intervention is a federally funded program available in all states 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 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 problems.
- Consider use of durable medical equipment and positioning devices as needed (e.g., wheelchairs, walkers, bath chairs, orthotics, adaptive strollers).

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

Oral motor dysfunction 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, when necessary.

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

Surveillance

Table 5. Recommended Surveillance for Individuals with Okur-Chung Neurodevelopmental Syndrome

System/Concern	Evaluation	Frequency
Feeding/Growth	• Measure growth parameters & growth velocity. [1] • Evaluate nutritional status & safety of oral intake.	At each visit
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures, changes in tone, mvmt disorders, & poor coordination.	
Development	Monitor developmental progress & educational needs.	
Psychiatric/ Behavioral	Behavioral assessment for anxiety, attention, & aggressive or self-injurious behavior	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Gastrointestinal	Monitor for ongoing feeding issues & signs/symptoms of constipation.	
Immunologic	Monitor for evidence of frequent or unusual infections. [2]	
Respiratory/Sleep	Monitor for signs/symptoms of sleep disturbance.	
Family/ Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	
Eyes	Ophthalmologic assessment	Every 1-3 yrs

OT = occupational therapy; PT = physical therapy
1. Low threshold for evaluation for growth hormone deficiency in those with a poor growth velocity
2. Consider assessment of quantitative immunoglobulins and referral to immunologist, if present.

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

Okur-Chung neurodevelopmental syndrome (OCNDS) 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 OCNDS whose parents have undergone molecular genetic testing have the disorder as a result of a *de novo CSNK2A1* pathogenic variant.
- Rarely, individuals diagnosed with OCNDS have the disorder as the result of a *CSNK2A1* pathogenic variant inherited from an affected parent or an unaffected parent with low-level mosaicism in the blood [Author, unpublished data].
- Molecular genetic testing is recommended for the parents of the proband to confirm their 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 [Author, unpublished data]. 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.

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

- If the *CSNK2A1* pathogenic variant found 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 parental germline mosaicism [Author, unpublished data].
- If a parent of the proband is known to have the *CSNK2A1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the variant is 50%.

Offspring of a proband. Each child of an individual with OCNDS has a 50% chance of inheriting the *CSNK2A1* pathogenic variant.

Other family members. Given that most probands with OCNDS reported to date have the disorder as a result of a *de novo CSNK2A1* 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 CSNK2A1* pathogenic variant. There is, however, a recurrence risk to sibs based on the possibility of parental germline mosaicism. Given this risk, prenatal and preimplantation genetic testing may be considered.

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

Resources

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

- **CSNK2A1 Foundation**
  Email: info@csnk2a1foundation.org
  www.csnk2a1foundation.org
- **Simons Searchlight**
  CSNK2A1

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. Okur-Chung Neurodevelopmental Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CSNK2A1	20p13	Casein kinase II subunit alpha	CSNK2A1 @ LOVD	CSNK2A1	CSNK2A1

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 Okur-Chung Neurodevelopmental Syndrome (View All in OMIM)

115440	CASEIN KINASE II, ALPHA-1; CSNK2A1
617062	OKUR-CHUNG NEURODEVELOPMENTAL SYNDROME; OCNDS

Molecular Pathogenesis

CSNK2A1 regulates the downstream expression of more than 500 genes as a member of the serine/threonine kinase family of proteins [Borgo et al 2021]. It is postulated that pathogenic variants in *CSNK2A1* disrupt the expression levels of genes that regulate neurologic development [Dominguez et al 2021].

Mechanism of disease causation. Loss of function that leads to reduced kinase activity or abnormal localization of the CK2α protein [Dominguez et al 2021]

Table 6. Notable *CSNK2A1* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment
NM_177559.3 NP_808227.1	c.593A>G	p.Lys198Arg	Mutational hot spot [1, 2]
	c.140G>A	p.Arg47Gln	Mutational hot spot [2, 3]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Okur et al [2016], Akahira-Azuma et al [2018], Chiu et al [2018], Owen et al [2018], Nakashima et al [2019], van der Werf et al [2020], Stranneheim et al [2021]
2. Author, unpublished data
3. Okur et al [2016], Chiu et al [2018], Owen et al [2018], Seo et al [2020]

Chapter Notes

Author Notes

Simons Searchlight: CSNK2A1

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