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IDEDNIK Syndrome

Synonyms: Intellectual Disability, Enteropathy, Deafness, Peripheral Neuropathy, Ichthyosis, and Keratoderma Syndrome; Keratitis-Ichthyosis-Deafness, Autosomal Recessive (KIDAR) Syndrome; MEDNIK Syndrome; MEDNIK-like Syndrome

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Summary

Clinical characteristics

IDEDNIK syndrome is characterized by enteropathy, poor weight gain, growth deficiency, skin manifestations (ichthyosis, erythroderma, and keratoderma), sparse hair, global developmental delay, mild-to-severe intellectual disability, and deafness. Additional manifestations can include liver disease, recurrent infections, and hematologic and ocular manifestations (photophobia, corneal scarring, and keratitis). Reduced serum ceruloplasmin and total copper levels are common. Some individuals have findings on brain MRI (cerebral atrophy, basal ganglia abnormalities, and thin corpus callosum). Death prior to age two years occurs in some individuals due to severe enteropathy or sepsis; in others survival into adulthood is reported.

Diagnosis/testing

The diagnosis of IDEDNIK syndrome is established in a proband by identification of biallelic pathogenic variants in *AP1B1* or *AP1S1* by molecular genetic testing.

Management

Targeted therapy: Treatment with oral zinc acetate therapy to reduce liver copper overload has been reported to improve behavioral disturbances, skin manifestations, and cognitive function in some individuals. Zinc sulfate may be an alternative, less expensive treatment option. Experience is limited with this targeted therapy.

Supportive care: Dietary modification and potential parenteral supplementation for enteropathy; feeding therapy; gastrostomy tube placement as needed; treatment options for skin manifestations include low-dose oral acitretin, skin emollients and topical lactic acid, frequent emollient application and short courses of topical cortical steroids or pimecrolimus ointment, and 50% urea ointments; developmental and educational support; hearing aids as needed for sensorineural hearing loss; community hearing services; standard treatment of

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seizures and peripheral neuropathy by an experienced neurologist; supportive treatment as needed for liver disease; standard treatment for recurrent infections; supportive treatment as needed for hematologic manifestations, and occasionally transfusion may be necessary; standard treatment of cataracts and other ocular manifestations per ophthalmologist; treatment of cryptorchidism per urologist; treatment of hypothyroidism and growth hormone deficiency per perinatologist; social work and family support.

Surveillance: At each visit, assess growth parameters, nutritional status, safety of oral intake, diarrhea, skin and hair manifestations, developmental progress and educational needs, mobility and self-help needs, seizures and peripheral neuropathy, behavioral issues, liver function tests, complete blood count, evidence of aspiration and respiratory infections, and family needs. Audiology evaluation as recommended by audiologist; ophthalmology evaluation for keratitis, cataract, and accommodative esotropia as recommended by ophthalmologist; assess thyroid function and for growth hormone deficiency as recommended by endocrinologist.

Evaluation of relatives at risk: Clarify the genetic status of apparently asymptomatic older and younger at-risk sibs in order to identify as early as possible those who would benefit from prompt initiation of zinc acetate treatment.

Genetic counseling

IDEDNIK syndrome is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for an *AP1B1* or *AP1S1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. Once the *AP1B1* or *AP1S1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

No consensus clinical diagnostic criteria for IDEDNIK syndrome have been published.

Suggestive Findings

IDEDNIK syndrome **should be suspected** in probands with the following clinical, laboratory, histopathology, and imaging findings and family history.

Clinical findings

- Infantile-onset diarrhea
- Poor weight gain and growth deficiency
- Skin and hair manifestations: ichthyosis, erythroderma, hyperkeratosis, sparse hair, and alopecia
- Global developmental delay
- Hypotonia
- Sensorineural hearing loss
- Intellectual disability (mild to severe)
- Hepatomegaly
- Recurrent infections
- Ocular manifestations: photophobia, corneal scarring, and keratitis
- Characteristic facial features: high anterior hairline, frontal bossing, low-set ears, and depressed nasal bridge

Laboratory findings

- Reduced ceruloplasmin and total serum copper levels
- Increased serum free copper level

- Elevated transaminases
- Elevated plasma total bile acid levels
- Elevated very long-chain fatty acids
- Anemia and/or thrombocytopenia
- Increased urinary copper excretion (2 individuals)

Histopathology

- Duodenal biopsy: mild villous blunting
- Liver biopsy: increased copper content (1 individual), liver fibrosis (3 individuals), cirrhosis (2 individuals)

Imaging findings on brain MRI

- Cerebral atrophy (8 of 11 individuals)
- Basal ganglia abnormalities (3 of 9 individuals)
- Thin corpus callosum (3 of 5 individuals)

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history or consanguinity does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of IDEDNIK syndrome **is established** in a proband by identification of biallelic pathogenic (or likely pathogenic) variants in *AP1B1* or *AP1S1* 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 can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *AP1B1* or *AP1S1* variants of uncertain significance (or of one known pathogenic variant and one variant of uncertain significance in the same gene) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (concurrent gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Concurrent gene testing. Sequence analysis of *AP1B1* and *AP1S1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

A neurodevelopmental, gastrointestinal, or genodermatosis multigene panel that includes *AP1B1*, *AP1S1*, and other genes of interest (see Differential Diagnosis) may be considered 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 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 IDEDNIK syndrome, some panels for neurodevelopmental, gastrointestinal, or genodermatosis disorders may not include these genes. (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 IDEDNIK syndrome has not been considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible. To date, the majority of *AP1B1* and *AP1S1* pathogenic variants reported (e.g., missense, nonsense) are within the coding region and are likely to be identified on exome sequencing that includes copy number analysis.

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 IDEDNIK Syndrome

Gene [1]	Proportion of IDEDNIK Syndrome Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants [2] Identified by Method	
		Sequence analysis [3]	Gene-targeted deletion/duplication analysis [4]
AP1B1	42% [5]	82% [5]	18% [5, 6]
AP1S1	58% [5]	100% [5]	None reported [5, 7]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in these genes.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. 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. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. To date, two large *AP1B1* deletions have been reported in individuals with IDEDNIK syndrome.
7. To date, no large intragenic *AP1S1* deletions/duplications have been reported in individuals with IDEDNIK syndrome.

Clinical Characteristics

Clinical Description

IDEDNIK syndrome is characterized by enteropathy, growth deficiency, skin manifestations (ichthyosis, erythroderma, and keratoderma), sparse hair, global developmental delay, mild-to-severe intellectual disability, and deafness. Additional manifestations can include liver disease, recurrent infections, and hematologic and ocular manifestations. To date, 24 individuals have been diagnosed with IDEDNIK syndrome – ten individuals with *AP1B1*-related IDEDNIK syndrome [Alsaif et al 2019, Boyden et al 2019, Ito et al 2021, Meriç et al 2021, Vornweg et al 2021, Faghihi et al 2022, Vasconcelos et al 2023] and 14 individuals with *AP1S1*-related IDEDNIK syndrome [Saba et al 2005, Montpetit et al 2008, Martinelli et al 2013, Incecik et al 2018, Klee et al 2020, Lu et al 2023]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. IDEDNIK Syndrome: Frequency of Select Features

Feature		Proportion of Persons w/Feature [1]	
		AP1B1-related IDEDNIK syndrome (n=10)	*AP1S1*-related IDEDNIK syndrome (n=14)
GI manifestations / poor growth	Infantile-onset diarrhea	3/3	14/14
	Poor weight gain	8/8	5/5
	Growth deficiency	8/8	7/7
Skin & hair manifestations	Ichthyosis	10/10	8/8
	Erythroderma	9/10	6/7
	Hyperkeratosis	8/10	6/7
	Sparse hair	8/10	1/1
	Alopecia	4/7	NR
Development / neurologic manifestations	Global developmental delay	10/10	7/7
	Hypotonia	2/2	6/6
	Sensorineural hearing loss	10/10	8/8
	Intellectual disability	4/9	8/8
	Peripheral neuropathy	NR	3/6
	Seizures	1/1	2/2
	Cerebral atrophy	2/5	6/6
	Basal ganglia abnormalities	NR	3/6
	Thin corpus callosum	3/5	NR
Liver manifestations	Hepatopathy [2]	3/4	9/9
	Hepatomegaly	2/3	1/1
	Elevated transaminases	4/6	8/8
	Elevated total bile acid levels	1/2	4/4
Immune system / hematologic manifestations	Recurrent infections	6/6	3/3
	Anemia	2/4	1/1
	Thrombocytopenia	3/6	1/1
Ocular manifestations	Photophobia	6/7	NR
	Corneal scarring	3/5	NR
	Keratitis	2/4	NR
Laboratory findings	Reduced ceruloplasmin	6/8	6/6
	Reduced total serum copper	6/8	6/6

NR = not reported

1. Because limited clinical details are available for some reported individuals included in this table, the denominator represents the total number of individuals in whom the corresponding finding was reported.

2. Some reports describe liver disease as hepatopathy without providing additional information.

Enteropathy. Severe, persistent diarrhea typically begins in early infancy, resulting in significant nutritional deficiencies and poor weight gain. Diarrhea is often persistent. Individuals with *AP1S1*-related IDEDNIK

syndrome exhibit a more severe form of diarrhea that has resulted in death within the first few months of life in some infants.

Growth deficiency. Birth weight can vary from between two to three standard deviations (SD) below the mean to normal. Poor weight gain is common and weight in older children ranges from one to five SD below the mean. One infant with a birth weight of 2,660 grams had significant weight loss by age two months [Klee et al 2020]. Body mass index in some individuals is more than three SD below the mean [Alsaif et al 2019, Vasconcelos et al 2023].

Birth length can also vary from normal to three SD below the mean. Growth deficiency varies but can be progressive, with a height range of 2-3 SD below the mean to 4.7 SD below the mean (reported in 1 child, age 3 years) [Alsaif et al 2019]. In one child, growth delay was partially attributed to deficient pancreatic enzyme production, which spontaneously recovered in childhood [Boyden et al 2019]. Severe short stature with growth hormone deficiency and hypothyroidism was noted in one individual [Meriç et al 2021].

Head circumference is often normal at birth. Head circumference reported in children with IDEDNIK syndrome varies from one to two SD below the mean [Faghihi et al 2022], and progressive microcephaly (decreasing from normal to 2 SD below the mean) has been reported in one child, age seven years [Martinelli et al 2013, Alsaif et al 2019].

Skin manifestations include ichthyosis, erythroderma, and hyperkeratosis. Skin involvement becomes apparent at or shortly after birth. Ichthyosis, a defining feature of IDEDNIK syndrome, is characterized by dry, scaly skin. The severity of ichthyosis can vary widely among individuals. It can affect the entire body or be more pronounced in the extremities. Erythroderma and hyperkeratosis are present in infancy and early childhood. The severity ranges from mild, with diffuse thin, white scaling and pink erythroderma, to more severe forms, including exfoliative erythroderma that progressively worsens, often accompanied by severe pruritus. Ichthyosiform erythroderma, generalized scaling, erythematous plaques, and migrating patches have all been reported. Hyperkeratosis can also be moderate to pronounced, affecting specific areas (e.g., scalp, palmar and plantar surfaces), to nearly the entire body and sometimes accompanied by papules.

Hair manifestations. The majority of affected individuals exhibit sparse scalp hair, while four individuals presented with partial alopecia. Alopecia has been described as patchy with thick, yellow, plate-like scales on the scalp. Some affected individuals were described as having slow-growing scalp hair with normal texture, while others had wiry, woolly, or brittle hair. Some individuals had grayish hair color. One individual had trichorrhexis nodosa, confirmed with light microscopy [Martinelli et al 2013]. However, direct and polarizing light microscopy were normal in another affected individual.

Global developmental delay. Hypotonia causing motor delay is a frequently reported feature (8/8 reported individuals), and four individuals had more pronounced hypotonia in the lower limbs [Saba et al 2005]. In early childhood, affected individuals show mild-to-moderate global developmental delay, ranging from absent head control at age five months in one individual to delayed onset of sitting and walking. Most affected individuals respond well to physical therapy, and by late childhood these individuals have normal motor development.

Speech development is also frequently delayed. Of note, factors such as sensorineural hearing loss contribute to speech delay as well as specific delays in nonverbal communication [Faghihi et al 2022].

Sensorineural hearing loss. Eighteen of 18 reported individuals have sensorineural hearing loss, with variability in severity. While some affected individuals exhibit hearing impairment from infancy, others experience a gradual progression to profound hearing loss. One individual had mild unilateral hearing loss at age eight months [Lu et al 2023]. One individual was noted to have partial hearing loss as an infant and developed profound hearing loss after an episode of meningitis at age three years [Boyden et al 2019].

Intellectual disability. The severity of intellectual disability varies markedly, ranging from mild to severe. Individuals with *AP1B1*-related IDEDNIK syndrome typically exhibit normal cognitive function to moderate intellectual disability. Conversely, most affected individuals with *AP1S1*-related IDEDNIK syndrome tend to have severe intellectual disability.

Seizures. Three individuals were noted to exhibit seizures; one had febrile seizures with onset at age 2.5 years, controlled with an anti-seizure medication [Meriç et al 2021]. Another individual had an episode of myoclonic seizures on postnatal day eight that responded to phenobarbital [Klee et al 2020]. Phenobarbital was also effective in managing seizures in the third individual at 11 days of life [Lu et al 2023].

Peripheral neuropathy. All three reported adults (ages: 19 years, 27 years, and 28 years) with *AP1S1*-related IDEDNIK syndrome presented with peripheral neuropathy; the age of onset of neuropathy was not reported. To date, no affected individuals with *AP1B1*-related IDEDNIK syndrome have been reported to have peripheral neuropathy; this might be due to the young age of most reported individuals with *AP1B1*-related IDEDNIK syndrome, suggesting that the development of peripheral neuropathy could be age dependent [Martinelli et al 2013, Alsaif et al 2019]. Although peripheral neuropathy has not been identified in the only known adult with *AP1B1*-related IDEDNIK syndrome, last evaluated at age 33 years, nerve conduction studies have not been done [Boyden et al 2019].

Neurobehavioral/psychiatric manifestations. One individual with severe intellectual disability showed features of autism spectrum disorder at age seven years, including deficits in social interaction and communication, repetitive behaviors, and inflexible adherence to routines [Martinelli et al 2013].

Liver manifestations. Liver involvement in IDEDNIK syndrome manifests variably as hepatopathy, elevated transaminases, elevated plasma total bile acid levels, and/or hepatomegaly. Twelve individuals were reported to have hepatopathy, and elevated liver transaminases were reported in twelve individuals. Cholestasis and elevated plasma total bile acid levels were reported in five individuals, with two individuals reported to have icterus. Three individuals had hepatomegaly. Liver fibrosis was reported in three individuals, and cirrhosis in two individuals. Liver biopsy was obtained from two individuals, and only one of these showed liver copper accumulation.

Recurrent infections. Nine individuals with IDEDNIK syndrome experienced recurrent infections, typically respiratory in nature, and one individual died of septic shock [Klee et al 2020].

Hematologic manifestations. Mild-to-moderate anemia has been reported in three individuals. Low serum ferritin was also present in one individual with mild anemia [Vasconcelos et al 2023]. Anemia without acute bleeding in one individual required transfusion therapy [Klee et al 2020].

Thrombocytopenia was reported in four individuals. One individual had platelet counts with range 223-843 K/μL [Lu et al 2023]. One individual had mild episodic thrombocytopenia throughout her life; another individual with persistent moderate thrombocytopenia had dysmegakaryopoiesis identified on bone marrow biopsy [Boyden et al 2019]. There are no reports of individuals developing myelodysplastic syndrome or acute myelogenous leukemia.

Intermittent peripheral eosinophilia was reported in one individual (range 0.15-1.21 K/μL) [Lu et al 2023].

Ocular manifestations. While the ocular phenotype varies among individuals, photophobia is notably the most common feature, affecting six individuals. Additional ocular manifestations include bilateral ectropion (3 individuals), corneal scarring (3 individuals), keratitis (2 individuals), cataracts (2 individuals), high myopia (1 individual), and hyperopic astigmatism with accommodative esotropia (1 individual).

Characteristic facial features. High anterior hairline and low-set ears were described in seven individuals. Depressed nasal bridge was described in six individuals, and frontal bossing was described in two individuals.

Other

- Hypoplastic scrotum with cryptorchidism (1 individual)
- Testicular atrophy (1 individual)
- Primary hypothyroidism and growth hormone deficiency (1 individual)
- Dilated cardiomyopathy identified on echocardiogram resolved in the first year of life (1 individual)
- Recurrent venous thromboses (1 individual)
- Severe osteoporosis (1 individual)
- Prominent abdomen (2 individuals)

Prognosis. Death in early childhood (prior to age two years) has been reported in eight individuals with *AP1S1*-related IDEDNIK syndrome due to severe enteropathy or sepsis. Survival into adulthood is possible; one reported individual with *AP1S1*-related IDEDNIK syndrome is alive at age 28 years. Early demise in infancy is not common in those with *AP1B1*-related IDEDNIK syndrome.

Phenotype Correlations by Gene

Individuals with *AP1B1*-related IDEDNIK syndrome typically exhibit normal intellect to moderate intellectual disability. Conversely, most affected individuals with *AP1S1*-related IDEDNIK syndrome have severe intellectual disability.

Individuals with *AP1S1*-related IDEDNIK syndrome are more likely to have cerebral atrophy and hepatopathy; severe infantile-onset diarrhea is also more common, resulting in death within the first few months of life in some infants. Peripheral neuropathy has only been reported in individuals with *AP1S1*-related IDEDNIK syndrome.

Nomenclature

IDEDNIK syndrome was initially referred to as **erythrokeratodermia variabilis type 3** (EKV3) [Saba et al 2005]. The disorder was renamed **MEDNIK syndrome** (*m*ental retardation, *e*nteropathy, *d*eafness, peripheral *n*europathy, *i*chthyosis, and *k*eratoderma) [Montpetit et al 2008] and later IDEDNIK syndrome (reflecting an emphasis on *i*ntellectual *d*isability rather than *m*ental retardation) [Lu et al 2023].

The *AP1B1*-related phenotype was initially described as **MEDNIK-like syndrome** [Alsaif et al 2019, Ito et al 2021] and is categorized in OMIM (242150) as **KIDAR syndrome** (*k*eratitis-*i*chthyosis-*d*eafness, *a*utosomal *r*ecessive) [Vornweg et al 2021, Faghihi et al 2022, Vasconcelos et al 2023]. The authors observe that IDEDNIK syndrome is a more accurate and clinically useful categorization because (1) the *AP1B1*-related phenotype aligns most closely with the features encompassed by the IDEDNIK acronym and (2) keratitis may not be a defining feature of the syndrome (thus challenging the suitability of the KIDAR nomenclature).

Prevalence

IDEDNIK syndrome is rare, with only 24 affected individuals reported to date.

A founder variant (c.183-2A>G) has been described in the French Canadian population from Quebec [Saba et al 2005, Montpetit et al 2008]. To date, eight individuals from this population have been identified with IDEDNIK syndrome; carrier frequency in this population has not been reported.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *AP1B1* or *AP1S1*.

Differential Diagnosis

IDEDNIK syndrome presents a combination of clinical and biochemical signs overlapping several disorders, including Menkes disease and Wilson disease (see Table 3).

Table 3. Genes of Interest in the Differential Diagnosis of IDEDNIK Syndrome

Gene	Disorder	MOI	Features of Disorder	
			Overlapping w/IDEDNIK syndrome	Distinguishing from IDEDNIK syndrome
ATP7A	Menkes disease (See *ATP7A*-Related Copper Transport Disorders.)	XL	Low serum copper & ceruloplasmin concentrations; growth deficiency, sparse hair, hypotonia, ID, seizures	Kinky hair & connective tissue abnormalities (e.g., lax skin, vascular tortuosity)
ATP7B	Wilson disease	AR	Low serum ceruloplasmin concentration, high liver copper concentration; hepatomegaly, hepatic cirrhosis, anemia	Kayser-Fleischer rings, renal tubular dysfunction, osteoporosis, tremor, dementia, drooling
CP	Aceruloplasminemia	AR	↓ serum copper, ↓ serum ceruloplasmin	Iron deposition in liver, pancreas, basal ganglia, thalamus, & cerebellum; diabetes mellitus
SLC33A1	Huppke-Brendel syndrome	AR	↓ serum copper, ↓ serum ceruloplasmin; hearing loss, sparse hair, hypotonia, ID	Lack of GI manifestations assoc w/ IDEDNIK syndrome
SNAP29	CEDNIK (*ce*rebral *d*ysgenesis, *n*europathy, *i*chthyosis, & palmoplantar *k*eratoderma) syndrome (OMIM 609528)	AR	Ichthyosis, keratoderma, poor growth, sensorineural hearing loss, peripheral neuropathy, DD/ID	Constipation, scoliosis, brain MRI findings (thickened cortex, pachygyria, polymicrogyria, hypomyelination, leukodystrophy, white matter signal abnormalities)

AR = autosomal recessive; DD = developmental delay; ID = intellectual disability; GI = gastrointestinal; MOI = mode of inheritance; XL = X-linked

Management

No clinical practice guidelines for IDEDNIK syndrome have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with IDEDNIK syndrome, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. IDEDNIK Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
General	Consultation w/metabolic physician / biochemical geneticist	
GI / Feeding / Nutrition	• Consultation w/ gastroenterologist & dietitian • Assessment for aspiration risk	May require dietary modifications, supplementation, tube feeding, or parenteral nutrition
Integument	Dermatology consultation	

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval • Eval for early intervention / special education
Musculoskeletal	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)
Hearing	Audiologic eval for sensorineural hearing loss	
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern. • Assess for peripheral neuropathy esp in older persons.
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	For persons age >12 mos: screening for behavior concerns incl ASD
Liver manifestations	Assessment of liver function: ALT, AST, bilirubin, ALP, prothrombin time, INR, albumin, total protein, GGT, & serum ammonia	Note: Liver biopsy is not routinely recommended but may be indicated under certain clinical conditions.
Recurrent infections	• Assess for recurrent mastoiditis, sinusitis, & otitis media. • ENT consultation as needed • Immunology or infectious disease consultation as needed	
Hematologic	• CBC to assess for anemia, thrombocytopenia, neutropenia, & peripheral eosinophilia • Referral to hematology w/bone marrow biopsy if indicated	
Ocular manifestations	Ophthalmologic eval	To assess for reduced vision, abnormal ocular movement, best corrected visual acuity, refractive errors, strabismus, & more complex findings (e.g., cataract) that may require referral for subspecialty care &/or low vision services
Genitourinary	Assess for cryptorchidism.	
Endocrine	• If severe short stature: assess thyroid function (thyroxine, TSH). • Assess for growth hormone deficiency.	Note: Severe short stature w/growth hormone deficiency & hypothyroidism was noted in only 1 person [Meriç et al 2021].
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of IDEDNIK syndrome to facilitate medical & personal decision making

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Family support & resources	By clinicians, wider care team, & family support organizations	Assessment of family & social structure to determine need for: • Community or online resources such as Parent to Parent & Human Disease Genes website series (HDG) • Social work involvement for parental support • Home nursing referral

ADHD = attention-deficit/hyperactivity disorder; ADL = activities of daily living; ALP = alkaline phosphatase; ALT = alanine transaminase; ASD = autism spectrum disorder; AST = aspartate transaminase; CBC = complete blood count; GGT = gamma-glutamyl transferase; GI = gastrointestinal; INR = international normalized ratio; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy; TSH = thyroid-stimulating hormone

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

IDEDNIK syndrome presents a unique combination of clinical and biochemical signs that overlap Menkes disease and Wilson disease. Treatment with zinc acetate, a drug shown to reduce intestinal copper absorption in Wilson disease, has been found to significantly improve clinical manifestations in individuals with IDEDNIK syndrome, including reducing liver copper and plasma total bile acid levels and improving behavioral disturbances, cognitive function, and itching. This finding suggests a new approach to treating individuals with IDEDNIK syndrome as a copper metabolism defect [Bruha et al 2011, Martinelli et al 2013].

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

Treatment with oral zinc acetate therapy (50 mg/day) to reduce liver copper overload results in marked improvement of behavioral disturbances and clear relief from itching Martinelli et al [2013]. Cognitive function also improved; after one year of treatment, intellectual abilities advanced from severe to moderate intellectual disability. Serum transaminases, plasma ceruloplasmin (2.0 µmol/l), serum free copper level (<1.6 µmol/l), and urinary copper excretion (0.06 µmol/l/24 h) normalized, along with a striking reduction of plasma total bile acid levels (10.2 µmol/l) and liver copper overload (0.42 µg/mg); blood and urine lactate were constantly normal.

Note: Zinc sulfate has also been used as an alternative, less expensive treatment option [Incecik et al 2018]. Dose and results of zinc sulfate treatment are not published to date. Zinc acetate or zinc sulfate treatment cannot yet be recommended as standard of care given the limited experience and data supporting their use. However, these therapies may be considered after a thorough discussion with the treatment team.

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5).

Table 5. IDEDNIK Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Enteropathy	Dietary modification & potential parenteral supplementation (e.g., thickened 3232A formula [Mead Johnson] or RCF formula [Abbott Nutrition])	
Poor weight gain	• Feeding therapy • Gastrostomy tube placement may be required for persistent feeding issues.	Low threshold for clinical feeding eval &/or radiographic swallowing study when showing clinical signs or symptoms of dysphagia
Skin manifestations	Treatment options: • Low-dose oral acitretin • Skin emollients & topical lactic acid (2%) • Frequent emollient applications & short courses of topical corticosteroids or pimecrolimus ointment • 50% urea ointments on palmoplantar skin can result in modest benefit.	These treatments may lead to some improvement of skin manifestations.
Developmental delay / Intellectual disability / Neurobehavioral issues	See Developmental Delay / Intellectual Disability Management Issues.	
Sensorineural hearing loss	Hearing aids may be helpful, per otolaryngologist.	Community hearing services through early intervention or school district
Seizures	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; phenobarbital has been demonstrated effective in 2 persons w/this disorder. • Education of parents/caregivers [1]
Peripheral neuropathy	Supportive treatments as indicated	
Liver disease	Supportive treatment as needed	
Recurrent infections	Standard treatment per ENT, immunologist, &/or infectious disease specialist	
Hematologic	• Supportive treatment as indicated • Occasionally, transfusion may be necessary.	
Eyes	Standard treatment of cataracts & other ocular manifestations per ophthalmologist	
Genitourinary	Treatment of cryptorchidism per urologist	
Endocrine	Treatment of hypothyroidism & growth hormone deficiency per endocrinologist	
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; RCF = Ross carbohydrate free

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 US; 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 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.

Neurobehavioral/Psychiatric 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

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. IDEDNIK Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Gastrointestinal/Feeding	• Measurement of growth parameters • Eval of nutritional status & safety of oral intake • Assessment of diarrhea	At each visit
Dermatology	Assessment of skin & hair manifestations	
Development	Monitor developmental progress & educational needs.	
Musculoskeletal	Physical medicine, OT/PT assessment of mobility, self-help skills	
Audiology	Audiologic eval for sensorineural hearing loss	Frequency per audiologist

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Neurologic	• Monitor those w/seizures as clinically indicated. • Assess for new manifestations such as seizures & peripheral neuropathy.	At each visit
Neurobehavioral/ Psychiatric	Behavioral assessment for ASD	
Liver manifestations	Liver function tests (ALT, AST, bilirubin, ALP, prothrombin time, INR, albumin, total protein, GGT, & serum ammonia) to assess liver health	
	Note: Liver biopsy is not routinely recommended but may be indicated under certain clinical conditions.	Only as needed
Recurrent infections / Respiratory	Monitor for evidence of aspiration, respiratory infections.	At each visit
Hematologic	CBC	
Ophthalmologic involvement	Assess for keratitis, cataract, & accommodative esotropia.	Frequency per ophthalmologist
Endocrine	• Assess thyroid function (thyroxine, TSH). • Assess for growth hormone deficiency.	Frequency per endocrinologist
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

ALP = alkaline phosphatase; ALT = alanine transaminase; ASD = autism spectrum disorder; AST = aspartate transaminase; CBC = complete blood count; GGT = gamma-glutamyl transferase; INR = international normalized ratio; OT = occupational therapy; PT = physical therapy; TSH = thyroid-stimulating hormone

Evaluation of Relatives at Risk

Although it is expected that sibs of a proband who have inherited biallelic *AP1B1* or *AP1S1* pathogenic variants would have signs of IDEDNIK syndrome in infancy, it is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk sibs in order to identify as early as possible those who would benefit from prompt initiation of zinc acetate treatment.

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

IDEDNIK syndrome is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an *AP1B1* or *AP1S1* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for an *AP1B1* or *AP1S1* pathogenic variant and to allow reliable recurrence risk assessment. If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an *AP1B1* or *AP1S1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. To date, individuals with IDEDNIK syndrome are not known to reproduce.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of an *AP1B1* or *AP1S1* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *AP1B1* or *AP1S1* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk sibs for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are carriers or are at risk of being carriers.

- Carrier testing should be considered for the reproductive partners of individuals known to have an *AP1B1* or *AP1S1* pathogenic variant, particularly if consanguinity is likely. An *AP1S1* founder variant has been identified in French Canadian families in Quebec (see Table 7).

Prenatal Testing and Preimplantation Genetic Testing

Once the *AP1B1* or *AP1S1* pathogenic variants have 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 and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic 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.

- **Alexander Graham Bell Association for the Deaf and Hard of Hearing**
  Phone: 866-337-5220 (toll-free); 202-337-5221 (TTY)
  Fax: 202-337-8314
  Email: info@agbell.org
  Listening and Spoken Language Knowledge Center
- **American Society for Deaf Children**
  Phone: 800-942-2732 (ASDC)
  Email: info@deafchildren.org
  deafchildren.org
- **Foundation for Ichthyosis and Related Skin Types, Inc. (FIRST)**
  Phone: 215-997-9400; 800-545-3286
  Email: info@firstskinfoundation.org
  firstskinfoundation.org
- **National Association of the Deaf**
  Phone: 301-587-1788 (Purple/ZVRS); 301-328-1443 (Sorenson); 301-338-6380 (Convo)
  Fax: 301-587-1791
  Email: nad.info@nad.org
  nad.org

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. IDEDNIK Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	HGMD	ClinVar
AP1B1	22q12.2	AP-1 complex subunit beta-1	AP1B1	AP1B1

Table A. continued from previous page.

AP1S1	7q22.1	AP-1 complex subunit sigma-1A	AP1S1	AP1S1

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 IDEDNIK Syndrome (View All in OMIM)

242150	KERATITIS-ICHTHYOSIS-DEAFNESS SYNDROME, AUTOSOMAL RECESSIVE; KIDAR
600157	ADAPTOR-RELATED PROTEIN COMPLEX 1, BETA-1 SUBUNIT; AP1B1
603531	ADAPTOR-RELATED PROTEIN COMPLEX 1, SIGMA-1 SUBUNIT; AP1S1
609313	MEDNIK SYNDROME; MEDNIK

Molecular Pathogenesis

AP1B1 and *AP1S1* encode the large beta subunit and small sigma subunit, respectively, of the adaptor protein complex 1 (AP-1). This complex mediates trafficking between the trans-Golgi network, endosomes, and the plasma membrane. Pathogenic variants in *AP1B1* or *AP1S1* result in the defective functioning of the AP-1 complex, crucial for proper intracellular trafficking of copper transporters (encoded by *ATP7A* and *ATP7B*), leading to abnormal copper metabolism and a unique clinical and biochemical phenotype combining features of Menkes disease and Wilson disease [Martinelli et al 2013, Alsaif et al 2019].

Mechanism of disease causation. Loss of function

***AP1B1*-specific laboratory technical considerations.** *AP1B1* has homologous upstream and downstream regions that can complicate PCR amplification and sequence analysis. Specific primers and in silico PCR may be required [Alsaif et al 2019].

Table 7. Pathogenic Variants Referenced in This *GeneReview* by Gene

Gene	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
AP1S1	NM_001283	c.183-2A>G	--	Founder variant in persons of French Canadian descent from Quebec [Saba et al 2005, Montpetit et al 2008]

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.

Chapter Notes

Author Notes

Dr Fowzan Alkuraya (falkuraya@kfshrc.edu.sa) is actively involved in clinical research regarding individuals with IDEDNIK syndrome. Dr Alkuraya would be happy to communicate with persons who have any questions regarding diagnosis of IDEDNIK syndrome or other considerations. Dr Alkuraya is also interested in hearing from clinicians treating families affected by IDEDNIK syndrome in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

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