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Allan-Herndon-Dudley Syndrome

Synonyms: MCT8 Deficiency, MCT8-Specific Thyroid Hormone Cell-Membrane Transporter Deficiency

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Summary

Clinical characteristics

Allan-Herndon-Dudley syndrome (AHDS), an X-linked disorder, is characterized in males by neurologic findings (hypotonia and feeding difficulties in infancy, developmental delay / intellectual disability ranging from mild to profound) and later-onset pyramidal signs, extrapyramidal findings (dystonia, choreoathetosis, paroxysmal movement disorder, hypokinesia, masked facies), and seizures, often with drug resistance. Additional findings can include dysthyroidism (manifest as poor weight gain, reduced muscle mass, and variable cold intolerance, sweating, elevated heart rate, and irritability) and pathognomonic thyroid test results. Most heterozygous females are not clinically affected but may have minor thyroid test abnormalities.

Diagnosis/testing

The diagnosis of AHDS is established in a male proband with suggestive findings and a hemizygous *SLC16A2* pathogenic variant identified by molecular genetic testing, and in a female proband by identification of a heterozygous pathogenic variant in *SLC16A2*.

Management

Treatment of manifestations: Multidisciplinary team to provide standard care for hypotonia, poor feeding, DD/ID, spasticity, and extrapyramidal movement disorders. Standard treatment with anti-seizure medication by an experienced neurologist. Thyroid hormone replacement therapy during childhood has no beneficial effect and could be dangerous by worsening dysthyroidism.

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Surveillance: In children, assess the following every six months until age four years, then once a year: developmental progress & educational needs; neurologic examination for new manifestations (e.g., seizures, changes in tone, movement disorders); spine for scoliosis and hips for dislocation; mobility and self-help skills.

Agents/circumstances to avoid: Administration of L-T_4 or L-T_3 alone can exacerbate the high serum T_3 levels and the resulting hypermetabolism.

Therapies under investigation: A T_3 analog TRIAC (acide 3,3',5-triiodothyroacetique) has been tested for a maximum of one year in an international multicentric study of 46 individuals with AHDS. The main objective, normalization of the free T_3 blood level, was achieved. Other favorable findings were increased body weight; decreased heart rate, systolic blood pressure, and hypertension; and improved development in seven children, two of whom had started TRIAC treatment before age four years and achieved independent sitting and full head control after 12 months of treatment.

Genetic counseling

AHDS is inherited in an X-linked manner. If the mother of a proband has an *SLC16A2* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the variant will be heterozygotes (carriers) and usually will not be clinically affected but may have minor thyroid test abnormalities. Once the *SLC16A2* pathogenic variant has been identified in an affected family member, carrier testing of at-risk female relatives, prenatal testing for a pregnancy at increased risk, and preimplantation genetic testing are possible.

Diagnosis

Formal diagnostic criteria for Allan-Herndon-Dudley syndrome have not been established.

Suggestive Findings

Allan-Herndon-Dudley syndrome (AHDS) **should be considered** in males with the following clinical findings, brain imaging, and thyroid hormone profiles.

Clinical Findings

Neurologic

- Onset before age two years often with hypotonia and feeding difficulties
- Developmental delay / intellectual disability ranging from mild to profound intellectual disability
- Extrapyramidal findings: dystonia, choreoathetosis, paroxysmal movement disorder, hypokinesia, hypomimia (masked facies)
- Pyramidal signs
- Late-onset seizures, often with drug resistance

Dysthyroidism

- Poor weight gain
- Reduced muscle mass
- Variably present: cold intolerance, sweating, elevated heart rate, irritability

Craniofacial. Common facial findings that may be attributed to prenatal and infantile hypotonia include ptosis, open mouth, and a tented upper lip. Ear length is above the 97th centile in about half of adults. Cup-shaped ears, thickening of the nose and ears, upturned earlobes, and a decrease in facial creases and a long face are also reported.

Laboratory Findings

Males with AHDS have pathognomonic thyroid test results (Figure 1) including the following:

- High serum 3,3',5-triiodothyronine (usually free T_3) concentration and low serum 3,3',5'-triiodothyronine (reverse T_3, or rT_3) concentration

  Note: All males with *SLC16A2* pathogenic variants had high serum T_3 concentration and, when obtained, low serum rT_3 concentration. This holds true for both total and free hormone concentrations in serum.

- Serum tetraiodothyronines (total T_4 and free T_4) concentration are often reduced, but may be within the low normal range

- Free T_3/T_4 ratio >0.75 (expressed as mmol/mmol) [Remerand et al 2019]

- Serum TSH concentrations that are normal or slightly elevated (Figure 1) [Refetoff & Dumitrescu 2007, Dumitrescu & Refetoff 2009, Remerand et al 2019]

Imaging

Brain MRI in children under age five years usually shows severely delayed myelination mimicking hypomyelination, which subsequently improves over time (Figure 2) [Holden et al 2005, Kakinuma et al 2005, Sijens et al 2008, Vaurs-Barrière et al 2009, Gika et al 2010, Tsurusaki et al 2011, Tonduti et al 2013, Remerand et al 2019].

Note: Early reports of normal brain MRI findings in this disorder were from older individuals. Cerebral atrophy is also a frequent sign associated with hypomyelination.

Establishing the Diagnosis

Male proband. The diagnosis of AHDS **is established** in a male proband with suggestive findings and a hemizygous *SLC16A2* pathogenic (or likely pathogenic) variant identified by molecular genetic testing (see Table 1).

Female proband. The diagnosis of AHDS **is usually established** in a female proband by identification of a heterozygous pathogenic (or likely pathogenic) variant in *SLC16A2* 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 hemizygous or heterozygous *SLC16A2* variant of uncertain significance does not establish or rule out a diagnosis.

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of AHDS is broad, individuals with the distinctive clinical and laboratory findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of AHDS has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

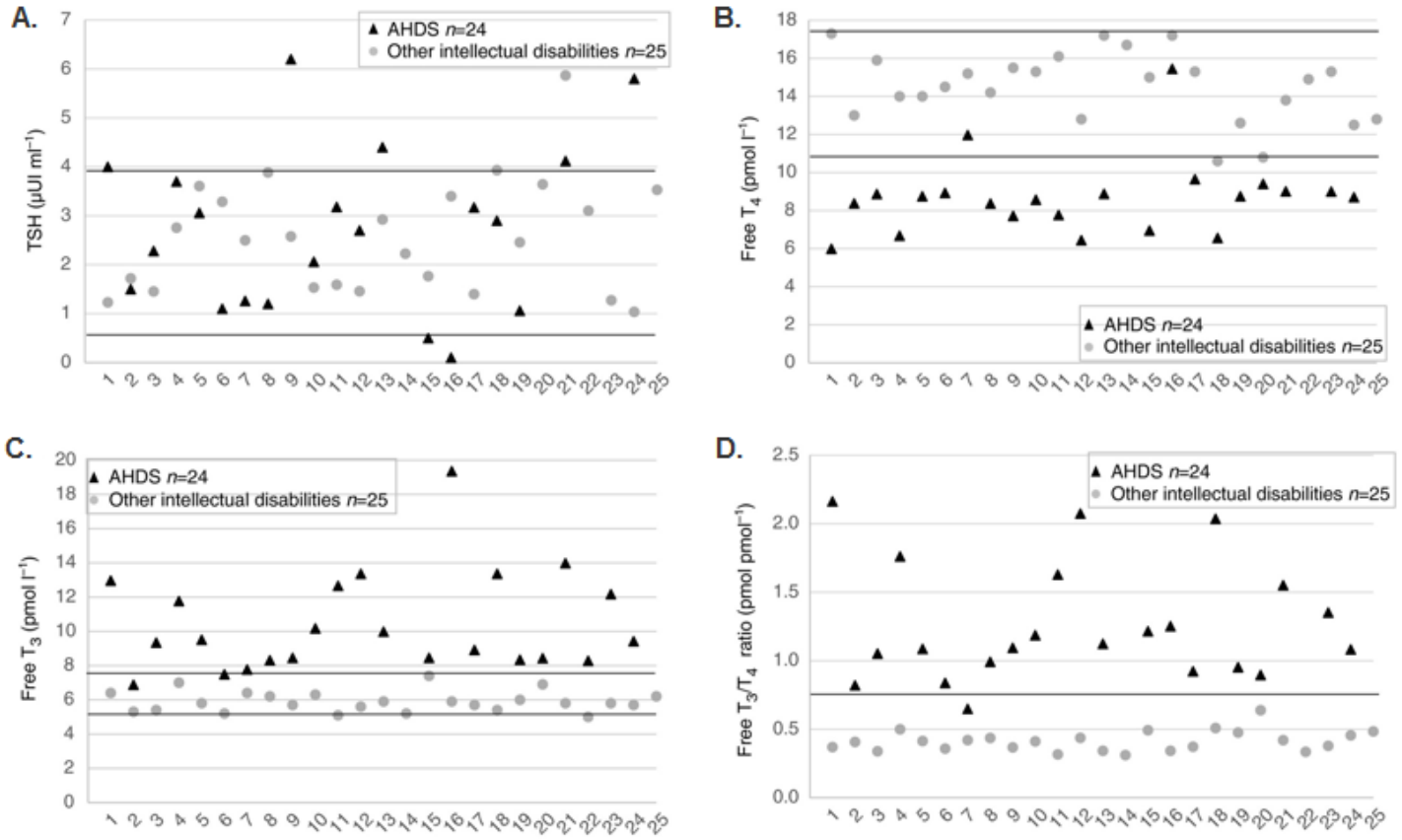

Figure 1. Thyroid profiles of 24 patients with AHDS (black triangles) compared to 25 male patients with other genetically defined intellectual disability (gray circles). Serum levels of:

A. TSH *

B. Free T_4

C. Free T_3

D. Free T_3/T_4

* Note that low TSH level in AHDS patients 15 and 16 were due to L-thyroxine supplementation.

From Remerand et al [2019]. Republished with permission of John Wiley and Sons.

Option 1

Single-gene testing. Sequence analysis of *SLC16A2* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants. If no pathogenic variant is found, gene-targeted deletion/duplication analysis is usually performed next to detect intragenic deletions or duplications.

An intellectual disability, leukodystrophy, or abnormal movement disorder multigene panel that includes *SLC16A2* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the 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*. (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

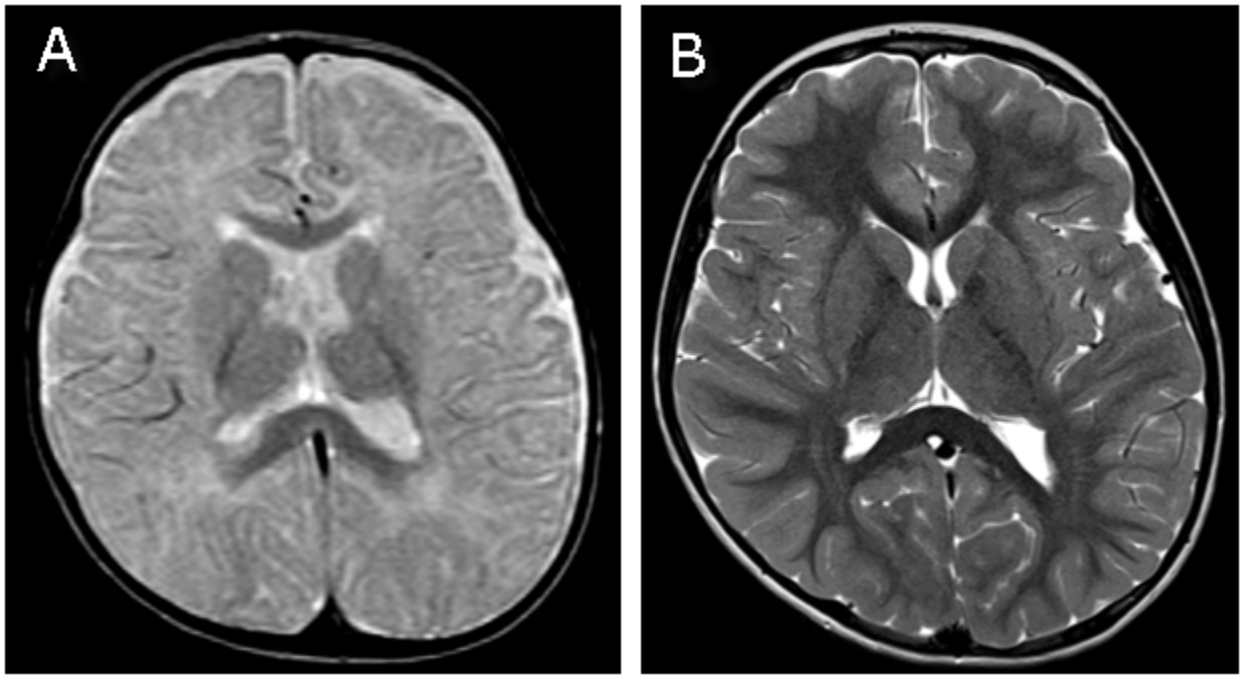

Figure 2. (A) T_2-weighted sequences of the brain MRI of a child age 12 months with AHDS showing diffusely abnormal white matter; (B) same child at age 7 years showing improved myelination with time

analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder, a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

Comprehensive genomic testing does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

If exome sequencing is not diagnostic, **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

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

Table 1. Molecular Genetic Testing Used in Allan-Herndon-Dudley Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
SLC16A2	Sequence analysis [3]	~85 [4]
	Gene-targeted deletion/duplication analysis [5]	~15% [4, 6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. García-de Teresa et al [2015], Remerand et al [2019]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. Due to the presence of repetitive elements, deletions of exon 1 with varying breakpoints are frequently observed [García-de Teresa et al 2015].

Clinical Characteristics

Clinical Description

Allan-Herndon-Dudley syndrome (AHDS), an X-linked disorder, is characterized in males by neurologic findings (hypotonia and feeding difficulties in infancy, developmental delay [DD] / intellectual disability [ID]) and later-onset pyramidal signs, extrapyramidal findings, and seizures, often with drug resistance. Dysthyroidism can manifest as poor weight gain, reduced muscle mass and variable cold intolerance, sweating, elevated heart rate, irritability, and pathognomonic thyroid test results. Most heterozygous females are not clinically affected but may have minor thyroid test abnormalities.

Affected Males

To date, information on about 200 individuals with a pathogenic variant in *SLC16A2* has been published [Groeneweg et al 2019, Remerand et al 2019]. The following description of the phenotypic features associated with this condition is based on the report by Remerand et al [2019].

Table 2. Select Features of Allan-Herndon-Dudley Syndrome in Affected Males

Feature [1]		% of Persons w/Feature
Prenatal/ neonatal findings	Weak fetal movements	1.4%-16.6%
	Fetal arrhythmia	0%-1.4%
	Neonatal hypotonia	4.4%-9.4%
	Premature birth	0%-0.7%
	Neonatal hypotrophy	0%-4.2%
	Congenital microcephaly	0%-0.7%
	Congenital macrocephaly	0%-0.7%
	Hydramnios	0%-1.4%
	Neonatal jaundice	0%-20.8%

Table 2. continued from previous page.

Feature [1]		% of Persons w/Feature
Growth	Weight gain deficiency	33.3%
	Low weight	37%-66.6%
	Short stature	12.6%-29.1%
	Microcephaly	10%-33.3%
DD/ID	ID	100% [2]
	Severe-to-profound ID	37.5%-83.3% [2]
	Mild-to-moderate ID	16.6%-62.5% [2]
	Oral language	19.9%-69%
	Walking	19.9%-62%
Neuromuscular	Axial hypotonia	74%-100%
	Amyotrophy	34.5%-88%
	Spasticity/hyperreflexia	70.8%-94%
	Dystonia	0%-75%
	Choreoathetosis	0%-50%
	Paroxysms or kinesigenic dyskinesias	0%-9%
	Ataxia	0%-60%
	Seizures	14.8%-29.1%
	Nystagmus	0%-16.6%
Skeletal	Pectus excavatum	9.1%-58%
	Kyphoscoliosis	21.1%-53.0%
	Flat feet with valgus	4.3%-77%
Other	Narrow/elongated myopathic face	31%-75%
	Cryptorchidism	2.8%-33.3%
	Peripheral dysthyroidism	27.9%-66.6%
Brain MRI	Severely delayed myelination	33.1%-79.1%
	Myelination improvement	8.4%-62.4%
	Brain atrophy	17%-41.6%

DD = developmental delay; ID = intellectual disability

1. Features and percentages of persons with feature were evaluated from the cohorts of Schwartz et al [2005], Remerand et al [2019], and the entire literature reporting persons with AHDS. Variation in percentages can be attributed to either the non-evaluation or lack of systematic evaluation of features in different reports.

2. Expressed as % of all males with AHDS. All affected persons had ID ranging from mild to profound.

Prenatal/neonatal findings. Infants with AHDS have normal length, weight, and head circumference at birth. Hypotonia, feeding difficulties and early weight gain deficiency can appear in the first weeks or months of life. Prolonged neonatal jaundice has recently been reported.

Growth. Weight gain lags behind linear growth; low weight is a frequent feature Linear growth is frequently normal initially, but between 10 and 30% of males with time have short stature; microcephaly becomes apparent with age.

Developmental delay / intellectual disability. Most affected males have profound-to-severe intellectual disability with no acquisition of walking; most affected males never speak or may develop only garbled sounds secondary to severely dysarthric speech.

Less frequently, affected males have mild-to-moderate intellectual disability, and develop the ability to walk (with or without aid) and use of language allowing academic learning with aid.

Neuromuscular. Truncal hypotonia, a main feature of AHDS, persists into adulthood. Adults are described with "limber neck" or poor head control.

Progressive hypertonicity of the limbs with brisk reflexes, ankle clonus, and extensor plantar responses (Babinski sign) leads to spastic quadriplegia and joint contractures.

Overall muscle mass (particularly proximally) is reduced and associated with generalized muscle weakness.

It is common for affected males to experience purposeless movements described as dystonic and/or athetoid and characteristic paroxysms or kinesigenic dyskinesias [Brockmann et al 2005, Fuchs et al 2009]. These can be triggered by somatosensory stimuli, including changing clothes or diaper, or lifting the affected child. During attacks, the body extends and the mouth opens; stretching or flexing of the limbs lasts as long as one to two minutes.

Some authors also reported abnormal movements as ataxia [Schwartz et al 2005].

Seizures typically begin during infancy or early childhood. Drug resistance is common [Schwartz & Stevenson 2007, Remerand et al 2019].

Rotary nystagmus and disconjugate eye movements have been reported but are not common [Dumitrescu et al 2004, Remerand et al 2019].

Skeletal. Pectus excavatum and kyphoscoliosis are most likely the result of hypotonia and reduced muscle mass.

Behavior. Generally, affected individuals are attentive, friendly, and docile. They are not aggressive or destructive.

Other. Peripheral dysthyroidism can be expressed as cold intolerance, sweating, intestinal transit disorders, tachycardia, high blood pressure, and sleep disorders.

Life span. Early death has occurred in some individuals, usually caused by recurrent infections and/or aspiration pneumonia. In a few instances survival beyond age 70 years has been reported.

Affected Heterozygous Females

Heterozygous females are generally asymptomatic and have no specific phenotypic findings. About 25% of heterozygous female have an abnormal thyroid profile with elevated T_3 levels without any neurologic manifestations [Ramos et al 2011, García-de Teresa et al 2015].

Developmental delay and intellectual disability have been reported in heterozygous females in rare instances, perhaps due to skewed X-chromosome inactivation [Dumitrescu et al 2004, Schwartz et al 2005, Herzovich et al 2007, García-de Teresa et al 2015]. One female had typical features of AHDS with a *de novo* translocation disrupting *SLC16A2* and unfavorable nonrandom X-chromosome inactivation [Frints et al 2008]. One exception of note was the finding in one female of a whole or partial deletion of one X chromosome and a *SLC16A2* pathogenic variant on the other X chromosome. However, whether a causative relationship exists between *SLC16A2* pathogenic variants and cognitive impairments in heterozygous females has yet to be proven [Schwartz et al 2005].

Genotype-Phenotype Correlations

It has been repeatedly reported that the severity of the clinical phenotype is related to the residual transport capacity of the mutated MCT8 protein. Large deletions in *SLC16A2* are assumed to result in complete inactivation of MCT8 and a consequently severe phenotype. While the most frequent large *SLC16A2* deletions are of exon 1, deletions of exons 2-4, exons 2-6, exon 3, exons 3-4, and exon 6 have also been reported [Friesema et al 2004, Jansen et al 2007, Vaurs-Barrière et al 2009, Visser et al 2009, Friesema et al 2010, Gika et al 2010, Zung et al 2011, Yamamoto et al 2013, Anık et al 2014, García-de Teresa et al 2015, Remerand et al 2019].

Several *SLC16A2* pathogenic missense variants and an in-frame single amino-acid deletion (Table 7) have been associated with considerable residual MCT8 thyroid hormone transport capacity and a milder clinical phenotype, including some speech development, some reading/writing ability, and/or the ability to walk with or without support [Schwartz et al 2005, Jansen et al 2008, Vaurs-Barrière et al 2009, Visser et al 2009, Visser et al 2013, Philips et al 2014, Novara et al 2017, Masnada et al 2019, Remerand et al 2019]. Independent walking and speech development are unusual in affected males with other pathogenic variants.

Nomenclature

This condition was named MCT8-specific thyroid hormone cell-membrane transporter deficiency following identification of the causative gene, *SLC16A2*, and the defect in thyroid hormone metabolism.

Because of the overlap of clinical findings in individuals with an *SLC16A2* pathogenic variant and Allan-Herndon-Dudley syndrome (AHDS), Schwartz et al [2005] analyzed *SLC16A2* and identified variants in six families with MCT8-specific thyroid hormone cell-membrane transporter deficiency. Thus, AHDS and MCT8-specific thyroid hormone cell-membrane transporter deficiency are synonyms.

Prevalence

Prevalence of Allan-Herndon-Dudley syndrome (AHDS) is unknown; however, the identification of more than 160 affected individuals in approximately 15 years suggests that the syndrome is more common than previously thought.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *SLC16A2*.

Differential Diagnosis

Many disorders demonstrate hypotonia and severe intellectual disability in an X-linked or autosomal recessive inheritance pattern. The main differential diagnoses, described in Table 3, also demonstrate dystonia, spasticity, seizures, or other features that overlap with the neurologic phenotype of Allan-Herndon-Dudley syndrome. More widely, all diseases leading to X-linked intellectual disability, hypomyelinating leukodystrophies or precocious dystonia should be considered as differential diagnoses.

Table 3. Genes of Interest in the Differential Diagnosis of Allan-Herndon-Dudley Syndrome (AHDS)

Gene [1]	DiffDx Disorder	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/AHDS	Distinguishing from AHDS
GJC2	Pelizaeus-Merzbacher-like disease [2]	AR	PMD-like	Normal free T_3/T_4 ratio
MECP2	*MECP2* duplication syndrome	XL	In males: infantile hypotonia, severe ID, absent speech, progressive spasticity, & seizures	
PLP1	Pelizaeus-Merzbacher disease (See *PLP1* Disorders.)	XL	• Males may present in infancy or early childhood w/nystagmus, hypotonia, & severe DD/ID. • Progresses to severe spasticity & ataxia • MRI shows persistant diffuse hypomyelination.	
THRA	Nongoitrous congenital hypothyroidism 6 (OMIM 614450)	AD	• Mild-to-moderate ID • Motor delay, dystonia • Short stature w/delayed bone age • ↑ free T_3/T_4 ratio	• Consider in differential diagnosis of mild forms of AHDS. • Improvement w/L-thyroxine therapy • Normal MRI

AD = autosomal dominant; AR = autosomal recessive; DD = developmental delay; DiffDx = differential diagnosis; ID = intellectual disability; MOI = mode of inheritance; PMD-like = Pelizaeus-Merzbacher–like disease; XL = X-linked

1. Genes are in alphabetic order

2. Of note, in one study *SLC16A2* pathogenic variants were reported in 11% of 53 families with a severe form of Pelizaeus-Merzbacher-like disease with an unusual improvement in myelination with age [Vaurs-Barrière et al 2009].

Management

No current published guidelines exist to establish the extent of disease or proper management in an individual diagnosed with Allan-Herndon-Dudley syndrome (AHDS). The following recommendations are based on current literature and the authors' experience.

Evaluations Following Initial Diagnosis

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

Table 4. Recommended Evaluations Following Initial Diagnosis in Individuals with Allan-Herndon-Dudley Syndrome

System/Concern	Evaluation	Comment
Constitutional	Measure height, weight, BMI, head circumference	To be regularly followed
Neurologic	Neurologic eval	• To incl brain MRI • Consider EEG if seizures are a concern.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech/language eval • Eval for early intervention / special education

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	Orthopedic, physical medicine & rehab, PT, & OT eval	To include assessment of: • Gross motor & fine motor skills • Contractures & kyphoscoliosis • Mobility, activities of daily living, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
	Osteoporosis evaluation in non-ambulatory patients	• Osteodensitometry (DXA) • Phospho-calcic equilibrium
Gastrointestinal/ Feeding	Gastroenterology, nutrition, & feeding team eval	• To incl eval of aspiration risk & nutritional status • Consider eval for gastric tube placement in patients w/dysphagia &/or aspiration risk.
Gastrointestinal	Assess for constipation	May be assoc w/weight loss & exacerbation of abnormal movements (dystonia, choreoathetosis)
Pulmonary	Respiratory function	• To incl lung function & respiratory status • Consider eval of noninvasive ventilation or antibiotic therapy in patients w/recurrent respiratory infections & hypoventilation.
Thyroid	Free T_3, free T_4, total T_4, TSH, T_3	Only if treatment w/T_3 analogs
	Signs of dysthyroidism	Signs of dysthyroidism can incl tachycardia, high blood pressure, intestinal troubles, osteoporosis, weight loss.
Miscellaneous/ Other	Consultation w/clinical geneticist &/or genetic counselor	To incl genetic counseling
	Family support/resources	Assess: • Use of community or online resources such as Parent to Parent; • Need for social work involvement for parental support; • Need for home nursing referral.

BMI = body mass index; DXA = dual-energy x-ray absorptiometry; OT = occupational therapy; PT = physical therapy

Treatment of Manifestations

Table 5. Treatment of Manifestations in Individuals with Allan-Herndon-Dudley Syndrome (AHDS)

Manifestation/ Concern	Treatment	Considerations/Other
DD/ID	See DD/ID Management Issues.	
Poor weight gain / Failure to thrive	• Feeding therapy • Nissen fundoplication & 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
Gastrointestinal	• Constipation: laxatives, enemas, transanal irrigation • Feeding difficulties: See DD/ID Management Issues. • Symptomatic GERD: antireflux therapy	Management may improve weight gain & ↓ abnormal movement
Drooling	Glycopyrolate or scopolamine	Consider the ↑ risk for hyposalivation assoc w/↑ risk for dental caries

Table 5. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Spasticity	Orthopedics / physical medicine & rehab / PT & OT incl stretching to help avoid contractures & falls	• To prevent contractures • Consider need for positioning & mobility devices, disability parking placard.
Dystonia	Medications such as anticholinergics, L-DOPA, carbamazepine, or lioresal	These therapies have shown no or mild efficacy. DBS has not been evaluated.
Choreoathetosis	No specific medication	DBS has not been evaluated in AHDS.
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many different ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1]
Musculoskeletal	• Hip dislocation &/or kyphoscoliosis: orthopedic surgery • Osteoporosis: calcium & vitamin D supplementation; bisphosphonate therapy as needed	
Thyroid test abnormalities	None	• Thyroid hormone replacement therapy during childhood has no beneficial effect & could worsen dysthyroidism. • See Therapies Under Investigation.
Dysthyroidism	Treatment of tachycardia &/or high blood pressure, when evident	
Sleep disorder	First consider sleep education; then melatonin or hydroxyzine dichlorhydrate as first medications	
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; DBS = deep brain stimulation; DD = developmental delay; GERD = gastroesophageal reflux disease; ID = intellectual disability; 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 (DD/ID) 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 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 by 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.

Surveillance

Table 6. Recommended Surveillance for Individuals with Allan-Herndon-Dudley Syndrome

System/Concern	Evaluation	Frequency
DD/ID	Monitor developmental progress & educational needs.	Every 6 mos until age 4 yrs, then 1x/yr
Neurologic	Monitor those w/seizures as clinically indicated.	Every 6 mos in those w/epileptic seizures
	Assess for new manifestations (e.g., seizures, changes in tone, movement disorders).	Every 6 mos until age 4 yrs, then 1x/yr
Poor weight gain / Failure to thrive	Measurement of growth parameters; eval of nutritional status & safety of oral intake	Every 3 mos in case of poor weight gain, otherwise every 6 mos until age 4 yrs, then 1x/yr
Musculoskeletal	Orthopedics: monitor for scoliosis, joint problems	Every 6 mos until age 4 yrs, then 1x/yr or as needed
	Physical medicine, OT/PT assessment of mobility, self-help skills	
	Osteodensitometry (DXA); phospho-calcic equilibrium	1x/yr in nonambulatory patients
Thyroid test abnormalities	No specific follow up	None if not being treated w/thyroid analogs
Signs of dysthyroidism 1	History & physical exam for tachycardia, high blood pressure, intestinal problems	Every 6 mos until age 4 yrs, then 1x/yr or as needed
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources) & care coordination.	As requested/needed

DD/ID = developmental delay / intellectual disability; DXA = dual-energy x-ray absorptiometry; OT = occupational therapy; PT = physical therapy

Agents/Circumstances to Avoid

Administration of L-T_4 or L-T_3 alone can exacerbate the high serum T_3 levels and the resulting hypermetabolism.

Evaluation of Relatives at Risk

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

Pregnancy Management

Two unaffected heterozygous pregnant women with unaffected fetuses were treated with L-T_4 in the second half of pregnancy [Ramos et al 2011]. It is unclear if this had any effect, either beneficial or detrimental, on the fetus.

Of note, many unaffected heterozygous mothers have given birth to normal unaffected children without any prenatal treatment.

Therapies Under Investigation

Recently, an T_3 analog TRIAC (acide 3,3',5-triiodothyroacetique) has been tested in an international multicentric study, coordinated by the Erasmus University (Rotterdam, Netherlands) [Groeneweg et al 2019]; 46 persons with AHDS were included and treated with a maximum of one year of TRIAC.

The main objective was the normalization of the free T_3 blood level; T_3 concentration declined significantly (reduction of 61% of baseline). Other findings: a mean increase of body weight of 2.7 kg, a mean decrease of heart rate over 24 hours of five beats per minute, a mean decrease of systolic blood pressure from the 78th centile to the 61st centile, and a mean decrease of hypertension from 34% to 9%.

On neurologic examination, of the seven individuals with a completely inactivating *SLC16A2* variant who had started TRIAC treatment before age four years, two reached independent sitting and achieved full head control after 12 months of treatment.

Seven mild and transient adverse effects related to TRIAC occurred in six individuals: three had increased perspiration and three reported irritability.

Beginning in 2017 the European Medicines Agency (EMA) granted TRIAC orphan designation for the treatment of AHDS (EMA/695502/2017).

To follow this first clinical study, an international Phase II trial (NCT02396459) to investigate the effects of TRIAC on neurodevelopmental outcomes in children younger than 30 months with AHDS will begin recruiting in early 2020.

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.

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

Allan-Herndon-Dudley syndrome (AHDS) is inherited in an X-linked manner.

Risk to Family Members

Parents of a male proband

- The father of an affected male will not have the disorder nor will he be hemizygous for the *SLC16A2* pathogenic variant; therefore, he does not require further evaluation/testing.
- In a study of 24 affected individuals, 17 males had inherited the *SLC16A2* pathogenic variant from their mother [Remerand et al 2019].
- In a family with more than one affected individual, the mother of an affected male is an obligate heterozygote (carrier). Note: If a woman has more than one affected child and no other affected relatives

and if the *SLC16A2* pathogenic variant cannot be detected in her leukocyte DNA, she most likely has germline mosaicism.

- If a male is the only affected family member (i.e., a simplex case), the mother may be a heterozygote (carrier) or the affected male may have a *de novo SLC16A2* pathogenic variant, in which case the mother is not a carrier. *De novo* variants have been reported in AHDS [Dumitrescu et al 2004; Author, personal communication]. In a study of 24 affected individuals, seven had a *de novo SLC16A2* pathogenic variant [Remerand et al 2019].

Sibs of a male proband. The risk to the sibs depends on the genetic status of the mother:

- If the mother of the proband has an *SLC16A2* pathogenic variant, the chance of transmitting it in each pregnancy is 50%. Males who inherit the pathogenic variant will be affected; females who inherit the variant will be carriers and will usually not be clinically affected but may have minor thyroid test abnormalities (see Clinical Description).
- If the proband represents a simplex case (i.e., a single occurrence in a family) and if the *SLC16A2* pathogenic variant cannot be detected in the leukocyte DNA of the mother, the risk to the sibs of a proband is much reduced, but greater than that of the general population because of the possibility of maternal germline mosaicism. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a male proband. Affected males are not known to reproduce.

Other family members. The proband's maternal aunts may be at risk of being carriers (typically asymptomatic, although they may have minor thyroid test abnormalities) for the pathogenic variant and the aunts' offspring, depending on their sex, may be at risk of being carriers for the pathogenic variant or of being affected.

Note: Molecular genetic testing may be able to identify the family member in whom a *de novo* pathogenic variant arose – information that could help determine genetic risk status of the extended family.

Heterozygote Detection

Molecular genetic testing of at-risk female relatives to determine their genetic status is most informative if the *SLC16A2* pathogenic variant has been identified in the proband.

Note: (1) Females who are heterozygous (carriers) for this X-linked disorder will typically be asymptomatic, although they may have minor thyroid test abnormalities (see Clinical Description). (2) Identification of female heterozygotes requires either (a) prior identification of the *SLC16A2* pathogenic variant in the family or, (b) if an affected male is not available for testing, molecular genetic testing first by sequence analysis, and if no pathogenic variant is identified, by gene-targeted deletion/duplication analysis.

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 young adults who are carriers or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SLC16A2* 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.

- **MCT8-AHDS Foundation**
  Canada
  Email: contact@mct8.info
  www.mct8.info
- **Una Vita Rara AHDS-MCT8 ONLUS (Italian AHDS-MCT8 Family Association)**
  Via Foina, 34
  25040 Monticelli Brusati (BS)
  Italy
  Phone: 39 329 0648896
  Email: unavitarara@gmail.com
  www.unavitarara.it
- **American Association on Intellectual and Developmental Disabilities (AAIDD)**
  Phone: 202-387-1968
  Fax: 202-387-2193
  www.aaidd.org
- **Association Française Xtraordinaire**
  France
  Phone: 09 70 40 61 40
  Email: contact@xtraordinaire.org
  www.xtraordinaire.org
- **CDC - Developmental Disabilities**
  Phone: 800-CDC-INFO
  Email: cdcinfo@cdc.gov
  Intellectual Disability
- **EURORDIS-Rare Diseases Europe**
  Email: eurordis@eurordis.org
  Find a patient organization
- **MedlinePlus**
  Intellectual Disability

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Allan-Herndon-Dudley Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SLC16A2	Xq13.2	Monocarboxylate transporter 8	SLC16A2 @ LOVD	SLC16A2	SLC16A2

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 Allan-Herndon-Dudley Syndrome (View All in OMIM)

300095	SOLUTE CARRIER FAMILY 16 (MONOCARBOXYLIC ACID TRANSPORTER), MEMBER 2; SLC16A2
300523	ALLAN-HERNDON-DUDLEY SYNDROME; AHDS

Molecular Pathogenesis

Monocarboxylate transporter 8 (MCT8), the protein product of *SLC16A2*, is thought to play a crucial role in neuronal T_3 uptake and in endothelial cells allowing partial entry of thyroid hormone through the blood-brain barrier. MCT8 deficiency results in an insufficient supply of T_3 to nuclear T_3 receptors. Thyroid hormone plays a crucial role in brain development. Thus, it is presumed that the decreased access of T_3 to brain cells can lead to the severe defects in neurologic development seen in males with AHDS [Friesema et al 2006, Roberts et al 2008, Ceballos et al 2009] and in the control of blood thyroid hormone.

Mechanism of disease causation. AHDS results from a loss of function of the MCT8 protein. Most pathogenic variants are loss-of-function variants that cause decreased activity or complete inactivation of the MCT8 thyroid hormone cell-membrane transporter [Friesema et al 2006]. Variants leading to incomplete inactivation of the protein can lead to milder phenotypes (see Table 7).

***SLC16A2*-specific laboratory technical considerations.** *SLC16A2* has two translation start sites, which generate proteins of either 613 amino acids or 539 (NP_006508.2) amino acids. The transcript encoding the 539-amino-acid protein is the one currently recognized by NCBI (Table 7).

Table 7. Notable *SLC16A2* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_006517.4 NP_006508.2	c.359C>T (c.581C>T)	p.Ser120Phe (p.Ser194Phe)	Assoc w/milder psychomotor delays [Schwartz et al 2005, Jansen et al 2008, Vaurs-Barrière et al 2009, Visser et al 2009, Visser et al 2013, Philips et al 2014, Novara et al 2017, Masnada et al 2019, Remerand et al 2019]
	c.980G>A (c.1202G>A)	p.Gly327Glu (p.Gly401Glu)	
	c.1079T>G (c.1301T>G)	p.Leu360Trp (p.Leu434Trp)	
	c.1111C>T (c.1333C>T)	p.Arg371Cys (p.Arg445Cys)	
	c.1253T>C (c.1475T>C)	p.Leu418Pro (p.Leu492Pro)	
	c.1279_1281del (c.1501_1503del, 1497_1499delCTT)	p.Phe427del (p.Phe501del)	

Table 7. continued from previous page.

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change (Alias [1])	Comment [Reference]
	c.1403T>C (c.1625T>C)	p.Leu469Pro (p.Leu543Pro)	
	c.1469G>A (c.1691G>A)	p.Gly490Glu (p.Gly564Glu)	
	c.1481T>C (c.1703T>C)	p.Leu494Pro (p.Leu568Pro)	
	c.1604delC (c.1826delC)	p.Pro535LeufsTer71 (p.Pro609Leufs)	

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. Variant designation on previously used transcript NM_006517.3.

Chapter Notes

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