U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: Blau N, Pearson TS, Kurian MA, et al. Aromatic L-Amino Acid Decarboxylase Deficiency. 2023 Oct 12. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Aromatic L-Amino Acid Decarboxylase Deficiency

Synonym: AADC Deficiency

Nenad Blau, PhD,[1] Toni S Pearson, MD, MBBS,[2] Manju A Kurian, MRCP, PhD,[3] and Sarah H Elsea, PhD, FACMG[4]

Created: October 12, 2023.

Summary

Clinical characteristics

Individuals with aromatic L-amino acid decarboxylase (AADC) deficiency typically have complex symptoms, including motor, behavioral, cognitive, and autonomic findings. Symptom onset is in early infancy, typically within the first six months of life. The most common initial symptoms are often nonspecific, and include feeding difficulties, hypotonia, and developmental delay. More specific symptoms include oculogyric crises (which occur in the vast majority of affected individuals, typically starting in infancy), movement disorders (especially dystonia), and autonomic dysfunction (excessive sweating, temperature instability, ptosis, nasal congestion, hypoglycemic episodes). Sleep disturbance is present in a majority of affected individuals and can include insomnia, hypersomnia, or both. Mood disturbance, including irritability and anxiety, are also common. Brain MRI is typically either normal or may demonstrate nonspecific abnormalities, such as mild diffuse cerebral atrophy or delayed myelination. Seizures are an uncommon finding, occurring in fewer than 5% of affected individuals.

Diagnosis/testing

The diagnosis of AADC deficiency is established in a proband who has the following core diagnostic testing results: biallelic pathogenic variants in *DDC* identified by molecular genetic testing OR cerebrospinal fluid (CSF) or plasma neurotransmitter profile consistent with AADC deficiency AND significantly reduced AADC enzyme activity in plasma.

Author Affiliations: 1 Division of Metabolism, University Children's Hospital Zurich, Zurich, Switzerland; Email: nenad.blau@kispi.uzh.ch. 2 Departments of Pediatrics and Neurology, Nationwide Children's Hospital; Ohio State University College of Medicine, Columbus, Ohio; Email: toni.pearson@nationwidechildrens.org. 3 Developmental Neurosciences, Zayed Centre for Research into Rare Disease in Children, UCL GOS Institute of Child Health; Department of Neurology, Great Ormond Street Hospital, London, United Kingdom; Email: manju.kurian@ucl.ac.uk. 4 Department. of Molecular & Human Genetics Baylor College of Medicine, Houston, Texas; Email: sarah.elsea@bcm.edu.

Management

Targeted therapies: Treatments can include the use of dopamine agonists (pramipexole, ropinirole, rotigotine patch, or bromocriptine), MAO inhibitors (selegiline or tranylcypromine), vitamin B_6 (pyridoxine, pyridoxal phosphate), folinic acid, and (in rare cases) levodopa in a preparation without carbidopa. Putaminal delivery of eladocagene exuparvovec (Upstaza®) was approved in the European Union and United Kingdom for the treatment of individuals aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of AADC deficiency with a severe phenotype (i.e., individuals who cannot sit, stand, or walk); this treatment is not currently FDA approved for use in the United States.

Supportive care: Feeding therapy with consideration of gastrostomy tube placement or jejunal feeding; anticholinergic drugs and/or sleep induction for movement disorders / oculogyric crisis; xylometazoline or oxymetazoline nasal drops for autonomic dysfunction; melatonin or clonidine for sleep disturbance; and standard therapies for epilepsy, developmental delay / intellectual disability, musculoskeletal issues, bowel dysfunction (constipation, diarrhea, or gastroesophageal reflux disease), strabismus, visual impairment, obstructive sleep apnea, hypoglycemia, and hearing loss.

Surveillance: At each visit: measurement of growth parameters; evaluation of nutritional status and safety of oral intake; monitor frequency and severity of oculogyric crises and movement disorders; assess for new manifestations, such as seizures, changes in tone, and movement disorders; monitor developmental progress and educational needs; monitor for behavioral issues and symptoms of anxiety, ADHD, ASD, aggression, & self-injury; clinical assessment for kyphoscoliosis and hip dislocation; monitor for constipation, diarrhea, gastroesophageal reflux, and abdominal discomfort or pain; and monitor for evidence of aspiration, respiratory insufficiency, sleep disturbance, and frequency of respiratory infections. Annually: obtain hip and spinal radiographs (until skeletal maturity); consider cardiology evaluation; consider continuous glucose monitoring, especially in younger affected individuals. Per treating clinicians: ophthalmology evaluation; monitor for cardiac function and rhythm defects; monitor for symptoms of obstructive sleep apnea and nasal congestion. In those on levodopa treatment: monitor CSF neurotransmitters, including 5-methyltetrahydrofolate levels, as clinically indicated to assess for secondary folate deficiency, particularly if neurologic symptoms worsen. In those on bromocriptine therapy: echocardiogram and EKG every 6-12 months to monitor for vavlulopathy caused by valve fibrosis (the risk is lower than with other ergot-derived dopamine agonists such as pergolide, but not absent).

Agents/circumstances to avoid: Ergot-derived dopamine agonists with strong serotonergic (5-HT2B) agonist action (pergolide and cabergoline) due to risk of cardiac valvulopathy and other fibrotic complications; levodopa in most affected individuals who do not have ligand binding site pathogenic variants; dopamine receptor antagonists (e.g., metoclopramide, antipsychotic medications), which may worsen primary disease symptoms.

Evaluation of relatives at risk: Testing of all at-risk sibs of any age is warranted to allow for early diagnosis and treatment of AADC deficiency. Molecular genetic testing is recommended if the pathogenic variants in the family are known; measurement of CSF neurotransmitters (to evaluate for the characteristic profile) and plasma AADC enzyme activity is recommended if the pathogenic variants in the family are not known.

Pregnancy management: Successful pregnancy has been documented in an affected woman with a mild phenotype who took low-dose pramipexole and selegiline during pregnancy.

Genetic counseling

AADC deficiency is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *DDC* 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. If both *DDC* pathogenic variants have been identified in an affected

family member, molecular genetic carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible.

Diagnosis

Consensus clinical diagnostic criteria for aromatic L-amino acid decarboxylase (AADC) deficiency have been published [Wassenberg et al 2017].

Suggestive Findings

AADC deficiency **should be considered** in individuals with the following clinical and supportive laboratory findings and family history.

Clinical findings

- Infantile hypotonia
- Ptosis
- Oculogyric crises (an involuntary and prolonged upward deviation of the eyes, often precipitated by such factors as fatigue, diurnal variation, intercurrent illness, or metabolic stress)
- Dystonia and other hyperkinetic movement disorders
- Hypokinesia and other features of parkinsonism
- Excessive sweating
- Stridor and nasal congestion
- Sleep disorder (hypersomnolence or insomnia)
- Autonomic dysfunction
- Developmental delay / intellectual disability, most often in the severe to profound range

Supportive laboratory findings

- Cerebrospinal fluid (CSF) neurotransmitter profile typically demonstrates:
  - Low levels of 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG);
  - Normal concentrations of pterins (neopterin and biopterin);
  - High concentrations of levodopa, 3-O-methyldopa (3-methoxytyrosine; 3-OMD), and 5-hydroxytryptophan (5-HT).
- Plasma neurotransmitter (untargeted metabolomics) profile typically demonstrates:
  - High level of 3-OMD;
  - Low levels of 5-HIAA, vanillylmandelate (VMA), HVA, and dopamine-3-O-sulfate (D3OS);
  - Low to normal level of 3-methoxytyramine sulfate (3-MTS).
- Increased urinary concentration of vanillactic acid (VLA)
- Low whole-blood serotonin concentration
- Increased serum prolactin concentration, which is nonspecific

Note: Because elevations of these metabolites individually are not entirely specific to AADC deficiency, more specific testing is required to establish or rule out the diagnosis of AADC deficiency (see Establishing the Diagnosis).

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

Establishing the Diagnosis

The diagnosis of AADC deficiency **is established** in a proband who has the following core diagnostic testing results (see Figure 1):

- Biallelic pathogenic (or likely pathogenic) variants in *DDC* identified by molecular genetic testing (see Table 1)

OR

- CSF or plasma neurotransmitter profile consistent with AADC deficiency (see above) AND
- Significantly reduced activity of the enzyme AADC in plasma

Because of its relatively high sensitivity, *DDC* molecular genetic testing demonstrating biallelic pathogenic or likely pathogenic variants can obviate the need for enzymatic testing or even neurotransmitter profiling; therefore, *DDC* molecular genetic testing is increasingly the first-line diagnostic test for AADC deficiency.

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 *DDC* variants of uncertain significance (or of one known *DDC* pathogenic variant and one *DDC* variant of uncertain significance) does not establish or rule out the diagnosis (see Figure 1). (3) If genetic testing reveals a variant of unknown clinical significance (or biallelic variants of unknown clinical significance), a CSF neurotransmitter profile consistent with AADC deficiency can support the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, 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. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of AADC deficiency has not been considered are more likely to be diagnosed using genomic testing (see Option 2).

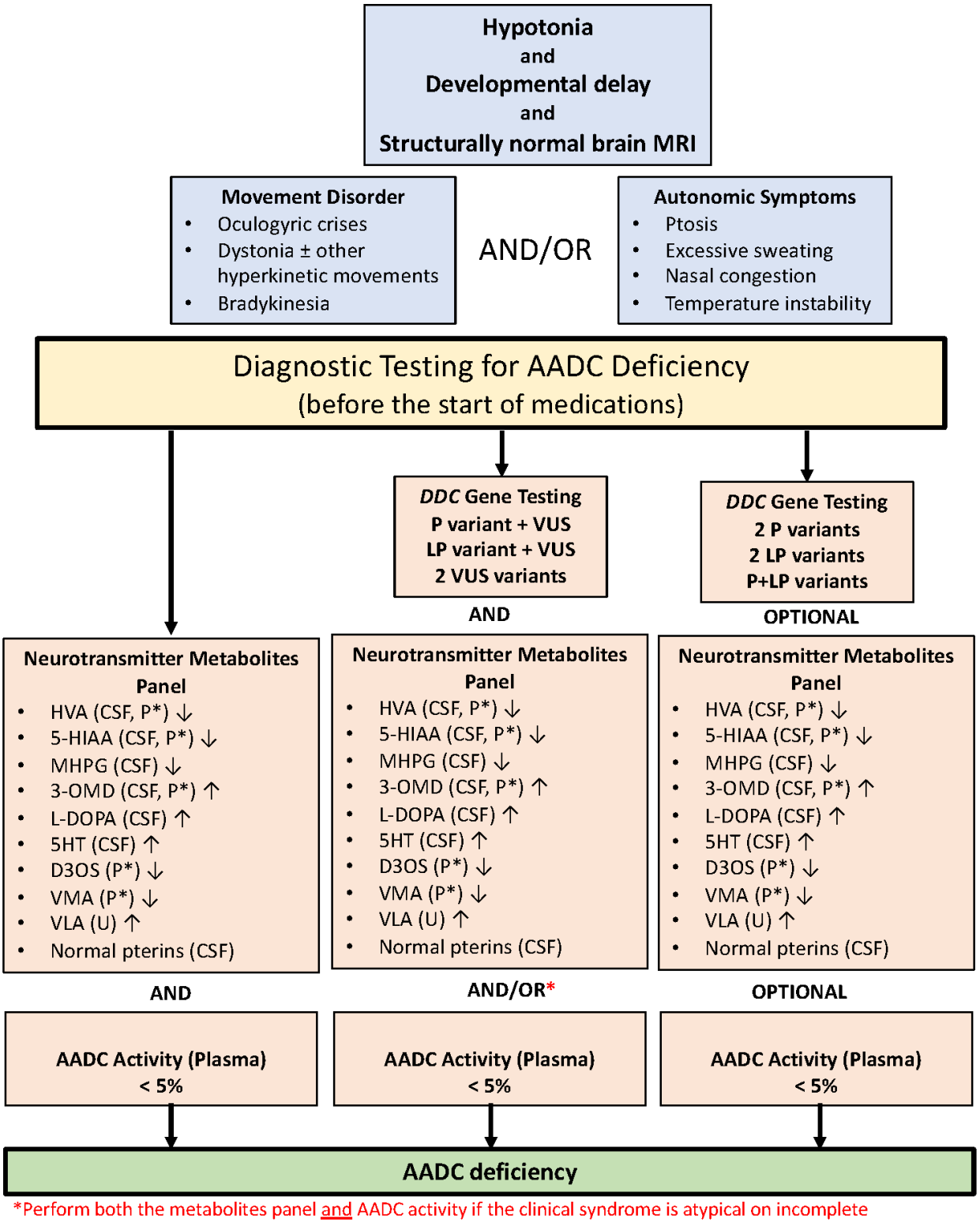
Option 1

When the clinical and preliminary laboratory findings suggest the diagnosis of AADC deficiency, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing**
  - Sequence analysis of *DDC* 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 only one or 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.

  Note: Targeted analysis for the c.714+4A>T pathogenic founder variant may be performed first in individuals of Asian (particularly Chinese, Taiwanese, or Japanese) ancestry (see Molecular Genetics).

- **A multigene panel** (e.g., a seizure/epilepsy panel, a dystonia / movement disorder / juvenile parkinsonism panel, a neuromuscular panel) that includes *DDC* 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



3-OMD: 3-O-methyldopa
5-HIAA: 5-hydroxyindoleacetic acid
5HT: 5-hydroxytryptophan
AADC: L-aromatic amino acid decarboxylase
D3OS: dopamine 3-O-sulfate
DDC: L-dopa decarboxylase gene
HVA: homovanillic acid
L-DOPA: L-3,4-dihydroxyphenylalanine
LP: likely pathogenic
MHPG: 3- methoxy-4-hydroxyphenolglycol
MRI: magnetic resonance imaging
P: pathogenic
VMA: vanillylmandelic acid
VUS: variant of unknown significance
P*: untargeted plasma metabolomics

Figure 1. Diagnostic flowchart to establish a diagnosis of AADC deficiency

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 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 AADC deficiency has not been considered, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is an option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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

Table 1. Molecular Genetic Testing Used in Aromatic L-Amino Acid Decarboxylase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
DDC	Sequence analysis [3]	>99% [4, 5, 6]
	Gene-targeted deletion/duplication analysis [7]	Rare [8]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include 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. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. The spectrum of variants identified in *DDC* and reported by Himmelreich et al [2022] include about 51% pathogenic missense variants, 15% pathogenic splice site variants, 3% pathogenic frameshift variants, 2% pathogenic nonsense variants, 1% pathogenic in-frame variants, and the remaining are classified as variants of unknown clinical significance.
6. A pathogenic founder variant, c.714+4A>T, has been observed in individuals of Asian (particularly Chinese, Taiwanese, or Japanese) ancestry [Hwu et al 2018, Dai et al 2020, Wen et al 2020].
7. 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.
8. One single large deletion has been reported [Himmelreich et al 2022].

Clinical Characteristics

Clinical Description

The aromatic L-amino acid decarboxylase (AADC) enzyme catalyzes the last step in the biosynthesis of the monoamine neurotransmitters dopamine and serotonin. Dopamine itself is a precursor for the synthesis of epinephrine and norepinephrine. Therefore, the clinical features of AADC deficiency are caused by a severe combined deficiency of dopamine, serotonin, epinephrine, and norepinephrine.

Individuals with AADC deficiency typically have complex symptoms, including motor, behavioral, cognitive, and autonomic findings. Symptom onset is in early infancy, typically within the first six months of life

[Wassenberg et al 2017, Pearson et al 2020, Rizzi et al 2022]. The most common initial symptoms are often nonspecific, and include feeding difficulties, hypotonia, and developmental delay. The key to clinical diagnosis lies in the subsequent recognition of a constellation of symptoms that suggest a monoamine neurotransmitter disorder: oculogyric crises (which occur in the vast majority of affected individuals, typically starting in infancy), movement disorders (especially dystonia), and autonomic dysfunction (excessive sweating, temperature instability, ptosis, nasal congestion, hypoglycemic episodes) [Wassenberg et al 2017, Pearson et al 2020, Rizzi et al 2022]. To date, about 350 individuals have been reported with AADC deficiency [Himmelreich et al 2022, Himmelreich et al 2023]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Select Features of Aromatic L-Amino Acid Decarboxylase Deficiency

Feature	% of Persons w/ Feature	Comment
Hypotonia	>90%	Most common initial symptom; onset in infancy
Oculogyric crises	>90	Onset in infancy
Developmental delay / intellectual disability	>90%	Often in severe-to-profound range, although some affected persons are only mildly affected
Movement disorders	>90%	Hypokinesia & dystonia are common. Dyskinesia (chorea, athetosis) may occur.
Feeding difficulties	70%-80%	May incl impaired oral feeding, gastroesophageal reflux, vomiting, &/or feeding intolerance
Dysautonomia	70%-80%	May incl excessive sweating, ptosis, &/or nasal congestion
Sleep disturbance	50%-75%	Insomnia & hypersomnia both occur.
Mood disturbance	50%-75%	May incl irritability, anxiety

Developmental delay (DD) and intellectual disability (ID). Delay in acquisition of motor milestones during infancy (e.g., head control, independent sitting) is a common early symptom. Motor and speech delay ranges from mild to severe. Affected individuals with severe disease (approximately 80% of reported affected individuals) typically have very limited development of motor skills; those with milder disease (approximately 5%-10% of reported affected individuals) may walk independently, typically by age eight years, in those who achieve ambulation. The degree of intellectual disability also tends to correlate with the severity of motor disability and the number and severity of other symptoms.

Neurologic features. AADC deficiency is a developmental rather than a neurodegenerative disorder, but neurologic symptoms commonly evolve over time. For example, oculogyric crises tend to peak in severity during infancy and early childhood and become less frequent during late adolescence, even in those with severe disease.

- **Hypotonia** is the most common initial symptom and is often noticed in early infancy. Low tone is prominent in the neck and trunk muscles; tone in the limbs may fluctuate from low to high due to the variable presence of dystonia (see below).
- **Oculogyric crises** are episodes characterized by intermittent or sustained eye deviation, usually upward or to the side, which may be accompanied by involuntary movements of the face, trunk, and/or limbs. Mild episodes may last for several minutes and involve the eyes only. Severe episodes last for many hours, and symptoms may include whole-body dystonic posturing, difficulty breathing, and sweating. Oculogyric crises occur in more than 90% of people with AADC deficiency and typically begin within the first six months of life. Episodes may initially be mistaken for seizures. Clinical features that distinguish an oculogyric crisis from a seizure are the long duration (an oculogyric crisis can last for many hours) and intact alertness (during an oculogyric crisis, a person remains awake and alert).

- **Movement disorders**
  - Hypokinesia is common. The combination of hypotonia, hypokinesia, and ptosis (see below) in infancy may be mistaken for a neuromuscular condition. Differentiating features of AADC deficiency on neurologic examination are the presence of normal or brisk deep tendon reflexes and recognition of dystonia in the limbs, if present.
  - Dystonia (involuntary movements or postures) is the most common hyperkinetic movement disorder experienced by affected individuals. Dystonia typically fluctuates with activity and state, worsening in the context of action, stress, discomfort, and fatigue. Older children may experience a pattern of diurnal variation, with worsening at the end of the day and improvement following sleep.
  - Other hyperkinetic movement disorders including chorea, athetosis, myoclonus, and tremor may occur, usually intermittently.
- **Dysautonomia.** Autonomic dysfunction may manifest with a variety of symptoms:
  - Excessive sweating
  - Temperature instability
  - Ptosis, miosis
  - Cardiovascular abnormalities, including hypotension, bradycardia, and other heart rhythm disturbances
  - Upper airway obstruction (see below)
  - Hypoglycemic episodes (see below)
  - Gastrointestinal symptoms (see below)
- **Epilepsy.** Seizures are uncommon (<5% of reported individuals) [Rizzi et al 2022]. Oculogyric crises can be mistaken for seizures (see above).

Behavioral problems. Mood symptoms, including irritability and anxiety, occur in 50%-60% of affected individuals [Pearson et al 2020]. Behavioral features consistent with autism spectrum disorder have been reported in some individuals.

Neuroimaging. Brain MRI is typically either normal or may demonstrate nonspecific abnormalities, such as mild diffuse cerebral atrophy or delayed myelination [Wassenberg et al 2017].

Growth. Many affected individuals experience growth impairment, including short stature and poor weight gain.

Other associated features

- **Respiratory abnormalities**
  - Upper airway obstruction. Nasal congestion and stridor are common (due to a combination of airway hypotonia and catecholamine deficiency). This symptom is most pronounced in infants and young children, who can have audible breathing.
  - Acute worsening of upper airway obstruction may occur during an oculogyric crisis, leading to a need for airway support in some affected individuals.
- **Sleep disorder.** Hypersomnia is common in infancy. Children and adolescents may experience a range of sleep difficulties, including problems with sleep induction and insomnia with frequent nocturnal waking. Sleep apnea is also reported, which can result in premature mortality [Wassenberg et al 2017]. Sleep difficulties may be treated with melatonin (to aid induction) and clonidine (see Management).
- **Gastrointestinal problems** may include gastrointestinal dysmotility leading to gastroesophageal reflux disease, feeding intolerance, vomiting, diarrhea, and/or constipation. More severely affected individuals may have issues with aspiration, which can lead to aspiration pneumonia. Many affected individuals benefit from placement of a gastrostomy tube (see Management).

- **Endocrinologic.** Episodic hypoglycemia occurs in about one third of affected individuals and presents with typical symptoms such as lethargy, unresponsiveness, pallor, and sweating. Common triggers are concurrent illness, stress, and prolonged fasting.
- **Other ophthalmologic involvement.** Many individuals with AADC deficiency have bilateral ptosis as an autonomic manifestation of catecholamine deficiency. Ptosis may be present in infancy and can persist into adulthood. In some it may fluctuate (e.g., it may be worse in the context of fatigue, illness, or metabolic stress). However, most affected individuals do not required treatment for ptosis. Some affected individuals experience strabismus, for which ophthalmology evaluation and consideration of treatment is recommended (see Management).

Prognosis. There is an increased risk of early death due to medical complications such as pneumonia and aspiration. Sudden unexplained death may occur at any age, presumed to be due to an acute cardiorespiratory event. Current survival data is derived from retrospective cohorts. Hwu et al [2012] described 20 living affected individuals and ten deceased affected individuals who died between the ages of one and seven years, all of whom had a severe phenotype, suggesting about a one third childhood mortality risk in a population from Taiwan. However, the risk of death also depends upon choices about supportive medical interventions, such as tracheostomy/gastrostomy tube placement. Survival into the third decade of life has been reported in several individuals with mild-to-moderate phenotypes, and at least one affected individual was known to be living at age 36.8 years [Pearson et al 2020]. Successful pregnancy has been documented in a female age 26 years with a mild phenotype [Mastrangelo et al 2018] (see Pregnancy Management).

Genotype-Phenotype Correlations

No genotype-phenotype correlations for *DDC* have been identified. However, one individual has been reported with a c.304G>A (p.Gly102Ser) pathogenic variant who was responsive to levodopa therapy (see Targeted Therapies) [Chang et al 2004]. This specific pathogenic variant is located very close to the levodopa substrate binding pocket between Ile101 and Phe103. It is possible that other pathogenic variants in and around the levodopa substrate binding pocket may affect access to the active site and may confer levodopa responsiveness, but this has not yet been proven.

Nomenclature

AADC deficiency has also been referred to as dopa decarboxylase deficiency.

Prevalence

The worldwide incidence of AADC deficiency is not known. The condition is thought to be more prevalent in certain populations that originate from Asia, particularly Taiwan, Japan, and China, due to a founder pathogenic variant (c.714+4A>T) [Lee et al 2009, Hwu et al 2018, Dai et al 2020, Wen et al 2020, Himmelreich et al 2022]. A recent gnomAD-based study estimated worldwide incidence of AADC deficiency to be about 1:1,300,000 [Park et al 2023].

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Monoamine neurotransmitter deficiencies associated with defects in the synthesis of dopamine (tyrosine hydroxylase deficiency) or dopamine and serotonin deficiency (sepiapterin reductase deficiency and other

tetrahydrobiopterin [BH4] deficiencies) may present with similar clinical features to aromatic L-amino acid decarboxylase (AADC) deficiency. These disorders can be biochemically distinguished from AADC deficiency by the absence of elevated 3-O-methyldopa (3-OMD) on a cerebrospinal fluid neurotransmitter profile.

Broad categories of disorders with clinical features that may resemble those of AADC deficiency are summarized in Table 3.

Table 3. Clinical Differential Diagnosis of Aromatic L-Amino Acid Decarboxylase Deficiency

Differential Diagnosis Category	Clinical Features of AADC Deficiency	
	That may resemble other disorders in this category	Distinguishing from other disorders in this category
Infantile-onset neuromuscular disorders	• Hypotonia • Hypokinesia • Ptosis	• Dystonia • Oculogyric crises • Autonomic features (ptosis, nasal congestion, excessive sweating) • Presence of normal or brisk deep tendon reflexes
Infantile-onset complex dystonia or parkinson-dystonia syndromes	• Hypotonia • Hypokinesia • Dystonia • Oculogyric crises	Autonomic features (ptosis, nasal congestion, excessive sweating)
Early-onset epilepsy	Symptoms of an oculogyric crisis, such as eye deviation & body stiffening, may be mistaken for focal seizures.	Oculogyric crises often last for hours & awareness is intact during episodes, unlike seizures.

AADC = aromatic L-amino acid decarboxylase

Pyridoxine-dependent epilepsy (PDE) syndromes associated with PLPBP deficiency (pyridoxal 5'-phosphate homeostasis protein deficiency), PNPO deficiency (pyridox[am]ine 5'-phosphate oxidase deficiency), and PDE – *ALDH7A1* may be associated with laboratory findings (elevated 3-OMD and low homovanillic acid) overlapping those of AADC deficiency, since pyridoxal phosphate is the cofactor of AADC. Although neonatal- or infantile-onset seizures are usually the predominant clinical feature in these treatable forms of vitamin B_6-dependent early-onset epileptic encephalopathy, movement disorder features (opisthotonus, oculogyric crisis) and a biochemical profile compatible with AADC deficiency were reported in a two-month-old child with PLPBP deficiency who did not have seizures [Johnstone et al 2019].

Management

Consensus clinical practice guidelines for aromatic L-amino acid decarboxylase (AADC) deficiency have been published [Wassenberg et al 2017].

Evaluations Following Initial Diagnosis

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

Table 4. Aromatic L-Amino Acid Decarboxylase Deficiency: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Constitutional	Measurement of growth parameters	To assess for poor weight gain & short stature

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Neurologic	Full neurologic exam to evaluate tone & presence of hypokinetic & hyperkinetic movement disorders	• Consider brain MRI scan. • Consider EEG if seizures are a concern. • Consider EMG/nerve conduction studies based on symptoms (e.g., reduced limb use, absent reflexes, concerns about pyridoxine-induced neuropathy).
	Assess for oculogyric crises.	Evaluate frequency & severity of oculogyric crises w/daily parental diary records.
	Assess for autonomic features.	• Evaluate clinical impact of any nasal congestion, sweating, & temperature instability. • See also **Cardiovascular** in this table.
Development	Developmental assessment	• To incl motor, adaptive, cognitive, & speech-language eval (incl assessment for communication aids) • Eval for early intervention / special education needs
Neurobehavioral/ Psychiatric	Neuropsychiatric eval	Consider assessment for behavioral concerns, irritability, anxiety, & findings suggestive of ASD.
Musculoskeletal	Orthopedics / physical medicine & rehab team / PT & OT eval	To incl assessment of: • Gross motor & fine motor skills • Contractures • Mobility, ADL, & need for adaptive devices • Need for PT (to improve gross motor skills) &/or OT (to improve fine motor skills)
Gastrointestinal/ Feeding	Gastroenterology / nutrition / feeding team eval	• To incl eval of aspiration risk • To evaluate nutritional status to meet caloric requirements • Consider eval for gastrostomy tube / jejunal feeding system / Nissen fundoplication in those w/dysphagia, severe GERD, &/or aspiration risk. • Evaluate for GI dysmotility: GERD, constipation, diarrhea, abdominal discomfort
Eyes	Ophthalmologic eval	To assess for ptosis, miosis, strabismus, & visual function
Cardiovascular	Consider echocardiogram / EKG / Holter monitor eval.	• To assess cardiac rhythm & function • Consider referral to cardiologist.
Respiratory/ Sleep	Respiratory eval	• To assess for respiratory risk & susceptibility to chest infections • Consider need for prophylactic antibiotics, winter viral vaccines, & chest PT.
	Detailed assessment of sleep pattern	Consider sleep study if concerns regarding breathing pattern / apnea / nocturnal waking.
Endocrine	Measurement of blood glucose	• To assess for hypoglycemia • Consider referral to endocrinologist for monitoring & treatment (see Management and Surveillance).
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of AADC deficiency 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	Assess need for: • Community or online resources such as Parent to Parent and the AADC Research Trust; • Social work involvement for parental support; • Home nursing referral; • Respite provision.

ADL = activities of daily living; ASD = autism spectrum disorder; EKG = electrocardiography; EMG = electromyography; GERD = gastroesophageal reflux disease; GI = gastrointestinal; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for AADC deficiency; however, gene therapy trials are currently under way (see Therapies Under Investigation).

Targeted Therapies

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

Table 5 lists current FDA-approved targeted therapies for AADC deficiency. Additionally, putamenal delivery of eladocagene exuparvovec (Upstaza®) was approved in the European Union and United Kingdom for the treatment of individuals aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of AADC deficiency with a severe phenotype (i.e., individuals who cannot sit, stand, or walk) (see Therapies Under Investigation). This treatment is not currently FDA approved for use in the United States.

Table 5. Aromatic L-Amino Acid Decarboxylase Deficiency: Targeted Therapies

Treatment Class	Mechanism of Action	Specific Drugs [1]	Dose	Comments
Dopamine agonists [2, 3]	Direct activation of postsynaptic dopamine receptors	Pramipexole	• Starting dose of 5 µg/kg/day of base in 1-3 divided doses • Increase dose every 3-7 days by 5 µg/kg/day • Max dose usually around 75 µg/kg/day, but higher doses have been anecdotally used (up to 100-110 µg/kg/day)	• Distinction in salt & base content (base dosages provided) • Non-ergot D2 agonist, w/ preference for D3 receptor • Drug-induced dyskinesias may be evident, so low starting dose & slow incremental dosage increases are recommended.

Table 5. continued from previous page.

Treatment Class	Mechanism of Action	Specific Drugs [1]	Dose	Comments
		Ropinirole	• Start 0.25 mg/day once daily, a few hours before bedtime. • Increase gradually every 3-7 days to 0.5-4.0 mg/day in 3 divided doses • Max dose 0.3 mg/kg/day or 24 mg/day	• Non-ergot D2 agonist w/ preference for D3 receptor • Avoid in severe kidney failure. • Risk of drug-induced dyskinesia • Very limited experience in AADC deficiency [4]
		Rotigotine patch	Usually in persons > age 12 yrs & >15 kg (but has been anecdotally used in younger persons): • Start 1-2 mg/day patch • Increase weekly by 1-2 mg • Max 8 mg/day patch	• Non-ergot D2 agonist w/ preference for D3 receptor; also has effect on other dopamine receptors (D1, D2, & D5; & α2B & 5-HT1A agonist) • Do not cut patches. • Risk of drug-induced dyskinesias; if evident, aim for lower daily dose &/or slower increase • Skin reactions occur sometimes (in around one third of persons). • Sulfite can lead to allergic reactions. • Remove patch during MRI/ electrocardioversion due to aluminum content.
		Bromocriptine	• Start 0.1 mg/kg/day (max 1.25 mg/day) • Increase weekly by 0.1 mg/kg/day (max 1.25 mg/day) up to target dose of 0.5 mg/kg/day (max 30 mg/day) in 2-3 divided doses	Cardiac screening is recommended prior to start & every 6-12 mos during treatment, to screen for vavlulopathy caused by valve fibrosis (see Table 7).
MAO inhibitors [3]	Prevent breakdown of serotonin & dopamine	Selegiline	• Start 0.1 mg/kg/day in 2-3 divided doses • Increase incrementally every 2 wks by 0.1 mg/kg/day up to 0.3 mg/kg/day or 10 mg/day	• Give final dose of the day no later than mid-afternoon, as it can affect sleeping pattern. • Most persons treated w/this drug also receive dopamine agonists &/or pyridoxine. [5]

Table 5. continued from previous page.

Treatment Class	Mechanism of Action	Specific Drugs [1]	Dose	Comments
		Tranylcypromine	• Start 0.1 mg/kg/day in 2 doses • Increase every 2 wks by 0.1 mg/kg/day up to 0.5 mg/kg/day • Max dose 30 mg/day	• Give final dose of the day no later than mid-afternoon, as it can affect sleeping pattern. • Occurrence of "cheese effect" (hypertensive crises when foods w/high content of tyramine are ingested) is very unlikely in persons w/AADC deficiency due to their low levels of dopamine, norepinephrine, & epinephrine. • Most persons treated w/this drug also receive dopamine agonists &/or pyridoxine. [5]
Vitamin B_6 [3]	Cofactor of AADC enzyme	Pyridoxine	• Start at 100 mg/day in 2 doses • Max dose 200 mg/day	• Pyridoxine may be drug of choice over PLP due to its lower cost & increased availability. • Chronic use in high doses can cause severe sensorimotor polyneuropathy.
		Pyridoxal phosphate (PLP)	• Start at 100 mg/day in 2 doses • Max dose 200 mg/day	• Consider if pyridoxine is not tolerated. • Dose limits should be followed due to concerns about side effects (e.g., chronic use in high doses can cause severe sensorimotor polyneuropathy).
Folinic acid	For prevention & treatment of cerebral folate deficiency	Calcium folinate	• 1-2 mg/kg/day • Usual dose 15 mg 1x/day, but can be titrated upward according to CSF 5-MTHF levels	• May be used if evidence of low 5-MTHF on CSF neurotransmitter analysis • Generally well tolerated • Anecdotally, some affected persons are given prophylactic calcium folinate, as it is postulated that the raised 3-OMD levels seen in AADC deficiency can deplete cerebral folate levels.

Table 5. continued from previous page.

Treatment Class	Mechanism of Action	Specific Drugs [1]	Dose	Comments
Levodopa [6]	Conversion to dopamine for direct activation of dopamine receptors	Levodopa in preparation w/o carbidopa	• Start 0.5-1 mg/kg/day in 3 divided doses • Increase fortnightly by 1 mg/kg to 5 mg/kg/day only if clinical effective. • Further increase to max 15 mg/kg/day may be considered.	• Substrate for AADC to form dopamine; effective in certain persons w/substrate binding site variants. • Start as first-line treatment only if known binding site variant. • Monitor CSF neurotransmitters, incl 5-MTHF levels, during treatment (see Table 7).

3-OMD = 3-O-methyldopa; AADC = aromatic L-amino acid decarboxylase; CSF = cerebrospinal fluid; MAO = monoamine oxidase; MTHF = methylenetetrahydrofolate

1. Note that medications often have limited benefit, especially in individuals who have severe symptoms.

2. Pergolide and cabergoline should be avoided because of the risk of fibrotic complications (see Agents/Circumstances to Avoid).

3. Considered a first-line treatment

4. Leuzzi et al [2015]

5. Wassenberg et al [2017]

6. Individuals who have a specific pathogenic variant affecting the levodopa binding site may be levodopa responsive. Most individuals with AADC deficiency do not respond to levodopa treatment. Levodopa in combination with carbidopa is avoided because carbidopa inhibits the AADC enzyme (see Agents/Circumstances to Avoid).

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 6).

Table 6. Aromatic L-Amino Acid Decarboxylase Deficiency: Supportive Care

Manifestation/Concern	Treatment	Considerations/Other
Poor weight gain / Failure to thrive	• Feeding therapy • Gastrostomy tube placement or jejunal feeding 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
Movement disorders / Oculogyric crises	• Anticholinergic drugs (benztropine, trihexyphenidyl, etc.) • Sleep induction	• Benzodiazepines can be considered in certain circumstances (i.e., as needed for dystonic or sustained oculogyric crises). • Other medications used for hyperkinetic movement disorders incl gabapentin, clonidine.
Autonomic dysfunction	Xylometazoline or oxymetazoline nasal drops	• Do not use for more than 5-7 days in a row to prevent habituation. • Hypertensive crises if used in tandem w/MAO inhibitors is unlikely in AADC deficiency given monoamine deficiency.
Epilepsy	Standardized treatment w/ASM by experienced neurologist	• Many ASMs may be effective; none has been demonstrated effective specifically for this disorder. • Education of parents/caregivers [1] w/emergency care plan & rescue medication for prolonged episodes
Developmental delay / Intellectual disability	See Developmental Delay / Intellectual Disability Management Issues.	

Table 6. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Musculoskeletal issues	Orthopedics / physical medicine & rehab / PT & OT incl stretching to prevent contractures, standing/weight-bearing to prevent hip dysplasia	Consider need for positioning & mobility devices, adaptive aids, accessible parking placard.
Bowel dysfunction	Standard treatment for constipation, diarrhea & GERD	• Stool softeners, prokinetics, osmotic agents, or laxatives for constipation, as needed • Anti-reflux medication may be indicated.
Strabismus / Visual impairment	Standard treatment per ophthalmologist	Ptosis generally does not require treatment.
Abnormal cardiac rhythm or function	Standard treatment per cardiologist	
Obstructive sleep apnea	Standard treatment per otolaryngologist	May incl CPAP &/or BiPAP
Sleep disturbance	Melatonin	Initial dose is typically 3 mg/day given 1-2 hrs before onset of sleep; maximum dose is 5-8 mg/day
	Clonidine	• Initial dose typically starts at 1 µg/kg at night (w/ blood pressure monitoring) before bed up to max of 0.3 mg/day • May have some benefit in also treating irritability
Hypoglycemia	Standard treatment per endocrinologist, which usually incl feeding plan to prevent low blood glucose levels	Emergency plan for mgmt of acute hypoglycemia, & feeding regimen for periods of intercurrent illness or metabolic stress
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.

AADC = aromatic L-amino acid decarboxylase; ASM = anti-seizure medication; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; GERD = gastroesophageal reflux disease; MAO = monoamine oxidase; 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 Considerations

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

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

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

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

- IEP services:
  - An IEP provides specially designed instruction and related services to children who qualify.
  - IEP services will be reviewed annually to determine whether any changes are needed.
  - Special education law requires that children participating in an IEP be in the least restrictive environment feasible at school and included in general education as much as possible, when and where appropriate.
  - Vision consultants should be a part of the child's IEP team to support access to academic material.
  - PT, OT, and speech services will be provided in the IEP to the extent that the need affects the child's access to academic material. Beyond that, private supportive therapies based on the affected individual's needs may be considered. Specific recommendations regarding type of therapy can be made by a developmental pediatrician.
  - As a child enters the teen years, a transition plan should be discussed and incorporated in the IEP. For those receiving IEP services, the public school district is required to provide services until age 21.
- A 504 plan (Section 504: a US federal statute that prohibits discrimination based on disability) can be considered for those who require accommodations or modifications such as front-of-class seating, assistive technology devices, classroom scribes, extra time between classes, modified assignments, and enlarged text.
- Developmental Disabilities Administration (DDA) enrollment is recommended. DDA is a US public agency that provides services and support to qualified individuals. Eligibility differs by state but is typically determined by diagnosis and/or associated cognitive/adaptive disabilities.
- Families with limited income and resources may also qualify for supplemental security income (SSI) for their child with a disability.

Motor Dysfunction

Gross motor dysfunction

- Physical therapy is recommended to maximize mobility and to reduce the risk for later-onset orthopedic 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 dystonia, consider involving appropriate specialists to aid in management of baclofen, 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 can safely to eat by mouth, feeding therapy (typically from an occupational or speech therapist) is recommended to help improve coordination or sensory-related feeding issues. Feeds can be thickened or chilled for safety. When feeding dysfunction is severe, an NG-tube or G-tube may be necessary.

Communication issues. Consider evaluation for alternative means of communication (e.g., augmentative and alternative communication [AAC]) for individuals who have expressive language difficulties. An AAC evaluation can be completed by a speech-language pathologist who has expertise in the area. The evaluation will consider

cognitive abilities and sensory impairments to determine the most appropriate form of communication. AAC devices can range from low-tech, such as picture exchange communication, to high-tech, such as voice-generating devices. Contrary to popular belief, AAC devices do not hinder verbal development of speech, but rather support optimal speech and language development.

Social/Behavioral Concerns

Children may qualify for and benefit from interventions used in treatment of autism spectrum disorder, including applied behavior analysis (ABA). ABA therapy is targeted to the individual child's behavioral, social, and adaptive strengths and weaknesses and typically performed one on one with a board-certified behavior analyst.

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

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

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended.

Table 7. Aromatic L-Amino Acid Decarboxylase Deficiency: Recommended Surveillance

System/Concern	Evaluation	Frequency
Feeding	• Measurement of growth parameters (height, weight, head circumference) • Eval of nutritional status & safety of oral intake	At each visit
Neurologic	Monitor frequency & severity of oculogyric crises.	
	Monitor severity & functional impact of movement disorder.	
	Monitor those w/seizures as clinically indicated.	
	Assess for new manifestations such as seizures, changes in tone, & movement disorders.	
	Monitor CSF neurotransmitters, incl 5-MTHF levels, to assess for secondary folate deficiency during treatment w/levodopa or if neurologic symptoms worsen.	As clinically indicated
Development	Monitor developmental progress & educational needs.	At each visit
Speech & communication	Monitor ability to communicate & speech development.	
Neurobehavioral/ Psychiatric	Monitor behavior & for symptoms of anxiety, ADHD, ASD, aggression, & self-injury.	
Musculoskeletal	Monitor clinically for kyphoscoliosis & hip dislocation.	
	Hip & spine radiographs	Annually until skeletal maturity
Gastrointestinal	Monitor for constipation, diarrhea, gastroesophageal reflux, & abdominal discomfort or pain.	At each visit
Eyes	Ophthalmology eval	Per treating clinicians
Cardiovascular	Monitor for cardiac function & rhythm defects.	Consider annual Cardiology visit
	Echocardiogram & EKG [1]	Every 6-12 mos if on bromocriptine

Table 7. continued from previous page.

System/Concern	Evaluation	Frequency
Respiratory/ Sleep	Monitor for evidence of aspiration, respiratory insufficiency, sleep disturbance, & frequency of respiratory infections (incl need for hospital admission / intensive care).	At each visit
	Monitor for symptoms of obstructive sleep apnea & nasal congestion.	Per treating clinicians
Endocrine	Monitor for hypoglycemia	Consider continuous glucose monitoring, esp in younger patients.
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; CSF = cerebrospinal fluid; EKG = electrocardiography; MTHF = methyltetrahydrofolate

1. To screen for cardiac valvulopathy caused by valve fibrosis (the risk is lower than with other ergot-derived dopamine agonists such as pergolide, but not absent).

Agents/Circumstances to Avoid

Avoid the following:

- Ergot-derived dopamine agonists with strong serotonergic (5-HT2B) agonist action (pergolide and cabergoline) due to risk of cardiac valvulopathy caused by valve fibrosis [Antonini & Poewe 2007, Wassenberg et al 2017]
- Levodopa in most affected individuals who do not have ligand binding site pathogenic variants
- Dopamine receptor antagonists (e.g., metoclopramide, antipsychotic medications), which may worsen primary disease symptoms

Evaluation of Relatives at Risk

Testing of all at-risk sibs of any age is warranted to allow for early diagnosis and treatment of AADC deficiency. For at-risk sibs when prenatal testing was not performed:

- Molecular genetic testing is recommended, if the pathogenic variants in the family are known; and/or
- Measure CSF neurotransmitters (to evaluate for the characteristic profile) and plasma AADC enzyme activity.

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

Pregnancy Management

Successful pregnancy has been documented in a 26-year-old female with a mild phenotype [Mastrangelo et al 2018]. This individual was being treated with escitalopram, pyridoxine, pramipexole (0.78 mg/day), and selegiline (up to 7.5 mg/day) around the time of conception. Both escitalopram and pyridoxine were discontinued and the doses of pramipexole and selegiline were decreased to 0.26 mg/day and 5 mg/day, respectively, without worsening of her neurologic symptoms. While this pregnant woman did develop preeclampsia at 31 weeks' gestation, she ultimately was able to deliver a small birth weight (small for gestational age) male infant at 38 weeks' gestation (term) who experienced transient hypoglycemia and tachypnea in the first few days of life. The infant was noted to be healthy with typical growth in the following months of life; long-term outcome information for the infant was not reported. The authors concluded that low dosages of

pramipexole and selegiline during pregnancy could have good efficacy for the affected pregnant woman and may have a good safety profile [Mastrangelo et al 2018].

In general, selegiline use during pregnancy is often avoided due to concerns about potential vasoconstrictive effects. One infant in a set of twins exposed to this medication and to levodopa/carbidopa and entacapone for the treatment of Parkinson disease during pregnancy was found to have a ventricular septal defect [Seier & Hiller 2017].

In general, pramipexole is not anticipated to increase the rate of malformations in exposed human pregnancies, and there have been limited reports of normal birth outcomes in exposed infants [Seier & Hiller 2017].

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Gene therapy using one-time targeted delivery of a gene vector (AAV2-AADC) directly to the brain has been developed. Two different brain target sites have been studied for AADC deficiency: the putamen and the midbrain [Hwu et al 2012, Chien et al 2017, Pearson et al 2021, Tai et al 2022]. Studies are ongoing to determine the optimal target site and dose.

- **Eladocagene exuparvovec (Upstaza®).** In 2022, putamenal delivery of eladocagene exuparvovec (Upstaza®) was approved in the European Union and United Kingdom for the treatment of patients age 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of AADC deficiency with a severe phenotype (i.e., patients who cannot sit, stand, or walk). Approval of the treatment followed reported improvements in symptoms and motor function in 26 affected individuals (ages 1.7-8.5 years) who were enrolled in three consecutive clinical trials (compassionate use, Phase I/II, Phase IIb) [Tai et al 2022]. Oculogyric crises were reported to decrease in severity after gene therapy, and three of the 24 individuals who had long-term follow up (2-10 years) gained the ability to walk independently.
- **Midbrain gene delivery** is being studied in an ongoing Phase I/II trial (NCT02852213). In an initial study of seven affected individuals (ages 4-9 years) with severe motor impairment, midbrain gene delivery resulted in complete resolution of oculogyric crises in 6/7 individuals, attainment of independent sitting within 12 months in 4/7, walking with two-hand support by 18 months in 2/7, and improved mood and sleep [Pearson et al 2021].

Both the putamenal and midbrain delivery approaches to gene therapy lead to detectable increases in the concentration of the dopamine metabolite homovanillic acid in cerebrospinal fluid. Greater increases are observed following midbrain gene delivery, which directly targets dopaminergic neurons. Neither approach addresses the serotonin deficiency that is also part of AADC deficiency.

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

Aromatic L-amino acid decarboxylase (AADC) deficiency 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 a *DDC* pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *DDC* 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, the following possibilities should be considered:
  - 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].
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant 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 a *DDC* 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.
- Affected sibs tend to have similar clinical disease severity, although some variability has been observed (e.g., mild and moderate phenotypes described in the same family) [Pearson et al 2020]. Differences in response and tolerance to medications may influence the clinical course.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with AADC deficiency are obligate heterozygotes (carriers) for a pathogenic variant in *DDC*.

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

Carrier Detection

Molecular genetic carrier testing for at-risk relatives requires prior identification of the *DDC* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives 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 be carriers of AADC deficiency, particularly if both partners are of the same ancestral background. A pathogenic founder variant has been observed in individuals of Asian (particularly Chinese, Taiwanese, or Japanese) ancestry (see Table 9).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. If both *DDC* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Biochemical genetic testing. Prenatal enzyme testing of amniocytes, amniotic fluid, or chorionic villi has not been reported to date.

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.

- **AADC Family Network**
  www.aadcfamilynetwork.org
- **AADC Research Trust**
  United Kingdom
  www.aadcresearch.org
- **MedlinePlus**
  Aromatic l-amino acid decarboxylase deficiency
- **National Organization for Rare Disorders (NORD)**
  Aromatic L-Amino Acid Decarboxylase Deficiency
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  metabolicsupportuk.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. Aromatic L-Amino Acid Decarboxylase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

DDC	7p12.2-p12.1	Aromatic-L-amino-acid decarboxylase	DDC @ LOVD BIOMDB: Database of Mutations Causing Tetrahyrdobiopterin Deficiencies (DDC)	DDC	DDC

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 Aromatic L-Amino Acid Decarboxylase Deficiency (View All in OMIM)

107930	DOPA DECARBOXYLASE; DDC
608643	AROMATIC L-AMINO ACID DECARBOXYLASE DEFICIENCY; AADCD

Table 8. Other Molecular Resources: IEMbase Entries for Aromatic L-Amino Acid Decarboxylase Deficiency (View All in IEMbase)

IEMbase Number	IEMbase Entry Name
IEM0077	Aromatic L-amino acid decarboxylase deficiency

Molecular Pathogenesis

DDC encodes aromatic L-amino acid decarboxylase (AADC), a homodimeric pyridoxal 5-prime phosphate (PLP)-dependent enzyme that catalyzes the decarboxylation of L-3,4-dihydroxyphenylalanine (DOPA) to dopamine, L-5-hydroxytryptophan to serotonin, and L-tryptophan to tryptamine [Bertoldi 2014]. This is the final step in the biosynthesis of the monoamine neurotransmitters serotonin and dopamine; dopamine is the precursor for norepinephrine and epinephrine. Most of the clinical manifestations of AADC deficiency can be explained by the deficiency of these four neurotransmitters. Dopamine deficiency affects cognitive function, emotion, and voluntary movement. Reduced expression of norepinephrine and epinephrine can impact attention, mood, sleep patterns, cognition, and stress hormone levels. Lastly, disturbance of serotonin can affect memory, learning, mood, sleep patterns, cardiovascular function, body temperature, and endocrine function [Brun et al 2010].

Mechanism of disease causation. Loss of function

Biochemical genetic testing. Dopamine-containing medications may falsely elevate the levels of 3-O-methyldopa (3-OMD), creating a false positive result. These same medications also may enhance in vitro enzyme activity, masking true enzyme deficiency.

Table 9. *DDC* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000790.4 NP_000781.2	c.304G>A	p.Gly102Ser	Levodopa-responsive pathogenic variant [Chang et al 2004]
NM_000790.4	c.714+4A>T	--	Founder variant in persons of Japanese, Taiwanese, & Chinese descent [Wassenberg et al 2017]; AF = 36% [Himmelreich et al 2022]

Table 9. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000790.4 NP_000781.2	c.1040G>A	p.Arg347Gln	AF = 7% [Himmelreich et al 2022]
	c.1234C>T	p.Arg412Trp	AF = 4% [Himmelreich et al 2022]

AF = allele frequency
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

Nenad Blau, PhD, and **Sarah Elsea, PhD, FACMG,** are chairs and **Toni Pearson, MD, MBBS,** is a member of the ClinGen Dopa Decarboxylase (Aromatic L-Amino Acid Decarboxylase) Variant Curation Expert Panel (VCEP), a panel of clinical, academic, and industry experts in the fields of genetics, pediatric neurology, functional genetics, and biochemistry assembled in pursuit of providing high-quality and systematic curation of *DDC* variants. With research progressing and gene therapy emerging, determining the pathogenicity of variants is critical to ongoing efforts toward diagnosis and patient care. Curation efforts will synergize with ongoing functional studies, analyses of function and genotype-phenotype correlations, and efforts to identify effective precision medications.

Sarah H Elsea is a clinical biochemical geneticist, Professor of Molecular & Human Genetics at Baylor College of Medicine, and Director of Clinical Genomics in the BCM-Human Genome Sequencing Center. Web page: www.bcm.edu/people-search/sarah-elsea-21035

Acknowledgments

This work was supported in part by Nenad Blau IEMbase Endowment Fund of the MCF, Marin County, CA, USA.

Sarah Elsea acknowledges research support for AADC deficiency research from PTC Therapeutics, support for metabolomics, genomics, and newborn screening research and development in neurotransmitter deficiencies from Speragen, Inc., and the SSADH Association.

Revision History

- 12 October 2023 (ma) Review posted live
- 9 January 2023 (nb) Original submission

References

Literature Cited

Antonini A, Poewe W. Fibrotic heart-valve reactions to dopamine-agonist treatment in Parkinson's disease. Lancet Neurol. 2007;6:826-9. PubMed PMID: 17706566.

Bertoldi M. Mammalian dopa decarboxylase: structure, catalytic activity and inhibition. Arch Biochem Biophys. 2014;546:1-7. PubMed PMID: 24407024.

Brun L, Ngu LH, Keng WT, Ch'ng GS, Choy YS, Hwu WL, Lee WT, Willemsen MA, Verbeek MM, Wassenberg T, Régal L, Orcesi S, Tonduti D, Accorsi P, Testard H, Abdenur JE, Tay S, Allen GF, Heales S, Kern I, Kato M, Burlina A, Manegold C, Hoffmann GF, Blau N. Clinical and biochemical features of aromatic L-amino acid decarboxylase deficiency. Neurology. 2010;75:64-71. PubMed PMID: 20505134.

Chang YT, Sharma R, Marsh JL, McPherson JD, Bedell JA, Knust A, Bräutigam C, Hoffmann GF, Hyland K. Levodopa-responsive aromatic L-amino acid decarboxylase deficiency. Ann Neurol. 2004;55:435-8. PubMed PMID: 14991824.

Chien YH, Lee NC, Tseng SH, Tai CH, Muramatsu S, Byrne BJ, Hwu WL. Efficacy and safety of AAV2 gene therapy in children with aromatic L-amino acid decarboxylase deficiency: an open-label, phase 1/2 trial. Lancet Child Adolesc Health. 2017;1:265-73. PubMed PMID: 30169182.

Dai W, Lu D, Gu X, Yu Y, et al. Aromatic L-amino acid decarboxylase deficiency in 17 mainland China patients: clinical phenotype, molecular spectrum, and therapy overview. Mol Genet Genomic Med. 2020;8:e1143. PubMed PMID: 31975548.

Himmelreich N, Bertoldi M, Alfadhel M, Alghamdi MA, Anikster Y, Bao X, Bashiri FA, Zeev BB, Bisello G, Ceylan AC, Chien YH, Choy YS, Elsea SH, Flint L, Garcia-Cazorla A, Gijavanekar C, Gumus EY, Hamad MH, Hismi B, Honzik T, Hubschmann OK, Hwu WL, Ibanez-Mico S, Jeltsch K, Julia-Palacios N, Kasapkara CS, Kurian MA, Kusmierska K, Liu N, Ngu LH, Odom JD, Ong WP, Opladen T, Oppeboen M, Pearl PL, Perez B, Pons R, Rygiel AM, Shien TE, Spaull R, Sykut-Cegielska J, Tabarki B, Tangeraas T, Thony B, Wassenberg T, Wen Y, Yakob Y, Yin JGC, Zeman J, Blau N. Prevalence of *DDC* genotypes in patients with aromatic L-amino acid decarboxylase (AADC) deficiency and in silico prediction of structural protein changes. Mol Genet Metab. 2023;139:107624. PubMed PMID: 37348148.

Himmelreich N, Montioli R, Garbade SF, Kopesky J, Elsea SH, Carducci C, Voltattorni CB, Blau N. Spectrum of DDC variants causing aromatic l-amino acid decarboxylase (AADC) deficiency and pathogenicity interpretation using ACMG-AMP/ACGS recommendations. Mol Genet Metab. 2022;137:359-81. PubMed PMID: 36427457.

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389-97. PubMed PMID: 35834113.

Hwu WL, Chien YH, Lee NC, Li MH. Natural history of aromatic L-amino acid decarboxylase deficiency in Taiwan. JIMD Rep. 2018;40:1-6. PubMed PMID: 28856607.

Hwu WL, Muramatsu S, Tseng SH, Tzen KY, Lee NC, Chien YH, Snyder RO, Byrne BJ, Tai CH, Wu RM. Gene therapy for aromatic L-amino acid decarboxylase deficiency. Sci Transl Med. 2012;4:134ra61. PubMed PMID: 22593174.

Johnstone DL, Al-Shekaili HH, Tarailo-Graovac M, Wolf NI, Ivy AS, Demarest S, Roussel Y, Ciapaite J, van Roermund CWT, Kernohan KD, Kosuta C, Ban K, Ito Y, McBride S, Al-Thihli K, Abdelrahim RA, Koul R, Al Futaisi A, Haaxma CA, Olson H, Sigurdardottir LY, Arnold GL, Gerkes EH, Boon M, Heiner-Fokkema MR, Noble S, Bosma M, Jans J, Koolen DA, Kamsteeg EJ, Drögemöller B, Ross CJ, Majewski J, Cho MT, Begtrup A, Wasserman WW, Bui T, Brimble E, Violante S, Houten SM, Wevers RA, van Faassen M, Kema IP, Lepage N. Care4Rare Canada Consortium, Lines MA, Dyment DA, Wanders RJA, Verhoeven-Duif N, Ekker M, Boycott KM, Friedman JM, Pena IA, van Karnebeek CDM. PLPHP deficiency: clinical, genetic, biochemical, and mechanistic insights. Brain. 2019;142:542-59. PubMed PMID: 30668673.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519-22. PubMed PMID: 28959963.

Lee HF, Tsai CR, Chi CS, Chang TM, Lee HJ. Aromatic L-amino acid decarboxylase deficiency in Taiwan. Eur J Paediatr Neurol. 2009;13:135-40. PubMed PMID: 18567514.

Leuzzi V, Mastrangelo M, Polizzi A, Artiola C, van Kuilenburg AB, Carducci C, Ruggieri M, Barone R, Tavazzi B, Abeling NG, Zoetekouw L, Sofia V, Zappia M, Carducci C. Report of two never treated adult sisters with aromatic L-amino acid decarboxylase deficiency: a portrait of the natural history of the disease or an expanding phenotype? JIMD Rep. 2015;15:39-45. PubMed PMID: 24788355.

Mastrangelo M, Manti F, Patanè L, Ferrari S, Carducci C, Carducci C, Mangili G, Leuzzi V. Successful pregnancy in a patient with L-amino acid decarboxylase deficiency: therapeutic management and clinical outcome. Mov Disord Clin Pract. 2018;5:446-7. PubMed PMID: 30838302.

Park JE, Lee T, Ha K, Cho EH, Ki CS. Carrier frequency and incidence of aromatic L-amino acid decarboxylase deficiency: a gnomAD-based study. Pediatr Res. 2023. Epub ahead of print. PubMed PMID: 37286773.

Pearson TS, Gilbert L, Opladen T, Garcia-Cazorla A, Mastrangelo M, Leuzzi V, Tay SKH, Sykut-Cegielska J, Pons R, Mercimek-Andrews S, Kato M, Lucke T, Oppeboen M, Kurian MA, Steel D, Manti F, Meeks KD, Jeltsch K, Flint L. AADC deficiency from infancy to adulthood: symptoms and developmental outcome in an international cohort of 63 patients. J Inherit Metab Dis. 2020;43:1121-30. PubMed PMID: 32369189.

Pearson TS, Gupta N, San Sebastian W, Imamura-Ching J, Viehoever A, Grijalvo-Perez A, Fay AJ, Seth N, Lundy SM, Seo Y, Pampaloni M, Hyland K, Smith E, de Oliveira Barbosa G, Heathcock JC, Minnema A, Lonser R, Elder JB, Leonard J, Larson P, Bankiewicz KS. Gene therapy for aromatic L-amino acid decarboxylase deficiency by MR-guided direct delivery of AAV2-AADC to midbrain dopaminergic neurons. Nat Commun. 2021;12:4251. PubMed PMID: 34253733.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Rizzi S, Spagnoli C, Frattini D, Pisani F, Fusco C. Clinical features in aromatic L-amino acid decarboxylase (AADC) deficiency: a systematic review. Behav Neurol. 2022;2022:2210555. PubMed PMID: 36268467.

Seier M, Hiller A. Parkinson's disease and pregnancy. an updated review. Parkinsonism Relat Disord. 2017;40:11-17. PubMed PMID: 28506531.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Tai CH, Lee NC, Chien YH, Byrne BJ, Muramatsu SI, Tseng SH, Hwu WL. Long-term efficacy and safety of eladocagene exuparvovec in patients with AADC deficiency. Mol Ther. 2022;30:509-18. PubMed PMID: 34763085.

Wassenberg T, Molero-Luis M, Jeltsch K, Hoffmann GF, Assmann B, Blau N, Garcia-Cazorla A, Artuch R, Pons R, Pearson TS, Leuzzi V, Mastrangelo M, Pearl PL, Lee WT, Kurian MA, Heales S, Flint L, Verbeek M, Willemsen M, Opladen T. Consensus guideline for the diagnosis and treatment of aromatic l-amino acid decarboxylase (AADC) deficiency. Orphanet J Rare Dis. 2017;12:12. PubMed PMID: 28100251.

Wen Y, Wang J, Zhang Q, Chen Y, Bao X. The genetic and clinical characteristics of aromatic L-amino acid decarboxylase deficiency in mainland China. J Hum Genet. 2020;65:759-69. PubMed PMID: 32409695.

License