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Dopamine Beta-Hydroxylase Deficiency

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Summary

Clinical characteristics

Dopamine beta-hydroxylase (DBH) deficiency is characterized by lack of sympathetic noradrenergic function resulting in profound deficits in autonomic regulation of cardiovascular function (orthostatic hypotension) and other autonomic dysfunction (ptosis, nasal stuffiness, sleep difficulties, and impaired ejaculation in males). Although DBH deficiency is present from birth, the diagnosis is often not generally recognized until late childhood. In the perinatal period, DBH deficiency has been complicated by vomiting, dehydration, hypotension, hypothermia, and hypoglycemia requiring repeated hospitalization, and the diagnosis may be identified fortuitously in the neonatal period with investigation of hypoglycemia. Children may report reduced exercise capacity. By early adulthood, individuals have profound orthostatic hypotension, greatly reduced exercise tolerance, ptosis, and nasal stuffiness. Presyncopal symptoms include dizziness, blurred vision, dyspnea, nuchal discomfort, and chest pain; symptoms may worsen in hot environments or after heavy meals or alcohol ingestion. Some individuals have abnormal kidney function, joint laxity, hypotonia, high-arched palate, anemia, and/or hypoglycemia.

Diagnosis/testing

The diagnosis of DBH deficiency is established in a proband with profound neurogenic orthostatic hypotension, minimal or absent plasma concentrations of norepinephrine and epinephrine, a five- to tenfold elevation of plasma dopamine, and biallelic pathogenic variants in *DBH* identified by molecular genetic testing.

Management

Targeted therapy: Administration of L-threo-3,4-dihydroxyphenylserine (droxidopa) restores plasma norepinephrine concentration and alleviates orthostatic hypotension and other symptoms of abnormal cardiovascular regulation.

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Treatment of manifestations: Other treatment options for orthostatic hypotension (fludrocortisone, midodrine) are not as effective as droxidopa; surgical correction of ptosis as needed; standard treatment for nasal stuffiness and reduced kidney function.

Surveillance: Annual evaluation of efficacy of droxidopa and review of adverse events; referral to autonomic specialist prior to surgery or becoming pregnant; measurement of blood urea nitrogen and plasma creatinine to assess kidney function every two years or more often if loss of kidney function is evident; plasma magnesium and potassium every two years.

Agents/circumstances to avoid: Untreated individuals should avoid hot environments, strenuous exercise, standing motionless, and dehydration; nephrotoxic drugs should be avoided.

Pregnancy management: Routine blood pressure monitoring during pregnancy and delivery, with adjustment of droxidopa dosage as needed; extra doses of droxidopa may be required during delivery, and dose adjustment may be required post partum.

Genetic counseling

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

Diagnosis

No consensus clinical diagnostic criteria have been published for dopamine beta-hydroxylase (DBH) deficiency. A clinical assessment including orthostatic vital signs and an ophthalmic exam should be the initial step; if indicated, this should be followed by autonomic function testing and plasma catecholamine analysis.

Suggestive Findings

DBH deficiency **should be suspected** in individuals with the following clinical, physiologic, and laboratory findings [Vincent & Robertson 2002, Timmers et al 2004].

Clinical findings

- Presentation:
  - Typical presentation is in adolescence with lifelong difficulties with lightheadedness, fatigue, inability to tolerate standing, reduced exercise capacity, recurrent syncope, and recurrent squatting to compensate for poor cardiovascular regulation.
  - Infants may present with recurrent vomiting, dehydration, hypotension, hypothermia, and hypoglycemia requiring repeated hospitalization.
- Poor cardiovascular regulation evident from supine, seated, and standing vital signs:
  - A low-to-normal supine blood pressure and low or normal supine heart rate
  - Severely symptomatic orthostatic hypotension with systolic blood pressure falling below 80 mm Hg in the upright position, consistent with sympathetic noradrenergic failure
  - An intact compensatory rise in heart rate with standing, consistent with preserved parasympathetic function
  - Inability to stand motionless for more than a few minutes
- Other autonomic dysfunction evident from an ophthalmic examination:
  - Ptosis in some individuals

    - A marked decrease in intraocular pressure with standing [Phillips et al 2013]
    - Somewhat small pupils that respond to light and accommodation and dilate to noradrenergic agonists (phenylephrine) but not to indirect sympathomimetics (hydroxyamphetamine). Parasympatholytics dilate the pupils appropriately.
- A comprehensive history and physical examination (including neurologic exam) typically reveal the following:
    - High-arched palate
    - Hyperextensible joints
    - Hypotonia
    - Sluggish deep tendon reflexes
    - Mild facial muscle weakness
    - Intact sweating consistent with intact sympathetic cholinergic function

Laboratory findings. The following are likely pathognomonic to DBH deficiency:

- Minimal or absent plasma norepinephrine and epinephrine. Plasma norepinephrine concentration should be below the limits of detection (<25 pg/mL or 0.15 nmol/L).
- Five- to tenfold elevation of plasma dopamine. Plasma dopamine concentration is frequently higher than 100 pg/mL (0.65 nmol/L).

  Note: Very low (rather than undetectable) levels of norepinephrine can be reported in some assays due to interference substances.

Establishing the Diagnosis

The diagnosis of DBH deficiency **is established** in a proband with profound neurogenic orthostatic hypotension, minimal or absent plasma concentrations of norepinephrine and epinephrine, a five- to tenfold elevation of plasma dopamine, and biallelic pathogenic (likely pathogenic) variants in *DBH* identified by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and 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 *DBH* variants of uncertain significance (or of one known *DBH* pathogenic variant and one *DBH* variant of uncertain significance) does not establish or rule out 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). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *DBH* 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.

- **A multigene panel** that includes *DBH* and other genes of interest (see Differential Diagnosis) may be considered to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (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 DBH deficiency is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

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 Dopamine Beta-Hydroxylase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
DBH	Sequence analysis [3]	100% [4]
	Gene-targeted deletion/duplication analysis [5]	None reported [4]

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. Wassenberg et al [2021] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications. Exome and genome sequencing may be able to detect deletions/duplications using breakpoint detection or read depth; however, sensitivity can be lower than gene-targeted deletion/duplication analysis.

Clinical Characteristics

Clinical Description

Dopamine beta-hydroxylase (DBH) deficiency is characterized by a lack of sympathetic noradrenergic function resulting in profound deficits in autonomic regulation of cardiovascular function and other autonomic dysfunction. Most individuals have abnormal kidney function, and some have joint laxity, hypotonia, high-arched palate, anemia, and/or hypoglycemia (in childhood). To date, only about two dozen individuals have been reported with a pathogenic variant in *DBH*. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. Dopamine Beta-Hydroxylase Deficiency: Frequency of Select Features

Feature		Proportion of Persons w/Feature [1]
Abnormal cardiovascular regulation	Severe orthostatic hypotension	21/21
	Postprandial hypotension	3/7
	Epileptiform symptoms	4/12
	EKG abnormalities	2/12
Other autonomic dysfunction	Nasal stuffiness	10/10
	Ptosis	12/14
	Sleep irregularities	5/7
	Impaired ejaculation	4/4
Kidney manifestations	Increased BUN	6/9
	Increased plasma creatinine	6/11
	Polyuria/nocturia	3/9
Neuromuscular manifestations	Joint laxity	6/10
	Muscle hypotonia	3/9
	Sluggish deep tendon reflexes	3/9
Other	High-arched palate	9/10
	Anemia	9/15
	Hypoglycemia in infancy	4/12

BUN = blood urea nitrogen

1. Number of individuals with the finding / total number evaluated for the finding

Onset. Although DBH deficiency appears to be present from birth, the diagnosis is not generally recognized until late childhood, when orthostatic hypotension becomes more severe. Infants can present with ptosis, vomiting, dehydration, hypotension, hypothermia, and hypoglycemia requiring repeated hospitalization. Symptoms worsen in late adolescence with profound orthostatic hypotension, fatigue, greatly reduced exercise tolerance, ptosis, and nasal stuffiness.

Syncope and exercise intolerance. Presyncopal symptoms include dizziness, blurred vision, dyspnea, nuchal discomfort, and occasionally chest pain. These symptoms may worsen in hot environments or after heavy meals or alcohol ingestion.

Children with DBH deficiency have recurrent syncope and markedly reduced exercise capacity. Symptoms worsen in late adolescence with profound orthostatic hypotension, fatigue, and greatly reduced exercise tolerance.

Other autonomic dysfunction. Ptosis is common in individuals with DBH deficiency and can be noted at an early age. Delay in opening of the eyes has occurred in infancy, and ptosis is seen in most affected infants. Nasal stuffiness is prevalent. Males experience retrograde or prolonged ejaculation.

Kidney function. Most individuals have mildly elevated blood urea nitrogen and plasma creatinine by the time the diagnosis is made. It has been proposed that the cause of this mild but consistent kidney impairment is related to the repeated hypotension or the high renal levels of dopamine, but an underlying cause has not been determined. Kidney function does not seem to improve with droxidopa therapy [Wassenberg et al 2021] (see Management, Targeted Therapy).

High palate. Physicians who inspect the palate often report that individuals with DBH deficiency have a high-arched palate [Man in 't Veld et al 1988; Cheshire et al 2006; E Garland, unpublished data]. This, however, is generally a subjective determination; it is not known how frequently it is either not assessed or reported incorrectly.

Hypoglycemia. Because so few individuals have been diagnosed with DBH deficiency, there has not been a clear explanation for the occurrence of hypoglycemic episodes in some infants. It is not known if this is related to the absence of norepinephrine and epinephrine or the elevated levels of dopamine. Investigators have speculated that it may result from loss of the counterregulatory actions of epinephrine that protect against hypoglycemia [Man in 't Veld et al 1987]. In contrast to the reports of hypoglycemia during the perinatal period, a girl age 15 years studied with a hyperglycemic clamp had a normal fasting glucose level but insulin resistance [Arnold et al 2017]. Her hyperinsulinemia persisted after a year of droxidopa treatment, despite improved orthostatic tolerance and restoration of plasma norepinephrine [Arnold et al 2017].

Cognitive function. Despite the lack of norepinephrine, persons with DBH deficiency have relatively normal mental status.

- Five affected individuals and ten matched healthy unaffected participants underwent a comprehensive battery of neurocognitive testing in addition to brain MRI, pupillometry, and EEG. Performance of the affected individuals, whether on or off droxidopa treatment, was similar to that of the unaffected individuals in most respects, suggesting that other systems compensate for absent norepinephrine in affected individuals.
- Brain MRI studies revealed a smaller total brain volume in the affected individuals compared to unaffected individuals, although relative proportions of white and gray matter and cerebrospinal fluid were similar in the two groups.
- In addition, affected individuals had a temporal attention deficit when they were not on treatment. During an attentional blink task, participants were asked to identify two digits, separated by a variable number of letters. Attentional blink refers to the deficit in processing the second digit when it is presented within 200-400 msec of the first. Accuracy in identifying the second digit was impaired in affected individuals not on treatment, but performance improved with droxidopa treatment [Jepma et al 2011].

Prognosis. There are no systematic follow-up studies that can help define the prognosis of this disorder. Some individuals die in infancy, possibly related to hypoglycemia. A few anecdotal cases of premature death have been reported [Wassenberg et al 2021].

One individual was not diagnosed with DBH deficiency until age 73 years despite having long-lasting orthostatic hypotension [Despas et al 2010], suggesting that DBH deficiency may not necessarily shorten life span.

Genotype-Phenotype Correlations

There are no known genotype-phenotype correlations.

Prevalence

The prevalence of DBH deficiency is unknown. Only 25 affected individuals, all of western European descent, have been reported in the literature, suggesting that it is a rare disorder. It is likely that other individuals have been diagnosed but not reported in the literature.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

The combination of minimal or absent plasma norepinephrine and epinephrine and a five- to tenfold elevation of plasma dopamine is likely pathognomonic of dopamine beta-hydroxylase (DBH) deficiency and distinguishes DBH deficiency from other disorders. DBH enzymatic function depends on the availability of the cofactor ascorbic acid, which is generated by transmembrane ascorbate-dependent reductase CYB561, encoded by *CYB561*. Therefore, biallelic pathogenic variants in *CYB561* result in impaired DBH function with very low levels of norepinephrine but normal levels of dopamine [van den Berg et al 2018, Shibao et al 2020]. Other catecholamine disorders, such as aromatic L-amino acid decarboxylase deficiency, have clinical presentations distinct from that of DBH deficiency.

Acquired disorders / disorders of unknown cause

- **Pure autonomic failure / autonomic neuropathy** is a degenerative disorder of the autonomic nervous system presenting in middle to late life. Like DBH deficiency, it is characterized by severe orthostatic hypotension. It differs from DBH deficiency in that it affects both the sympathetic and parasympathetic nervous systems. Hypohidrosis is common. Individuals with pure autonomic failure have marked hypersensitivity to all pressor and depressor stimuli. Plasma and urinary norepinephrine concentrations are greatly reduced, sometimes to 10% of normal, but plasma dopamine concentrations are normal or low rather than elevated as in DBH deficiency.
- **Multiple system atrophy** (MSA; OMIM 146500) is an adult-onset neurodegenerative disorder characterized by ataxia, parkinsonism, & autonomic dysfunction and severe orthostatic hypotension (like DBH deficiency) but without compensatory tachycardia. MSA is further characterized by extrapyramidal or cerebellar findings, erectile dysfunction, constipation/diarrhea, urinary symptoms, and hypohidrosis. Onset is typically over age 50 years with rapid progression to death within approximately eight years of diagnosis. No genetic cause has been identified in the vast majority of affected individuals.
- **Systemic illness.** Some dysautonomias result from well-characterized autonomic neuropathies secondary to systemic illnesses such as diabetes mellitus.

Genetic disorders with orthostatic hypotension to consider in the differential diagnosis of DBH deficiency are summarized in Table 3.

Table 3. Genetic Disorders with Orthostatic Hypotension in the Differential Diagnosis of Dopamine Beta-Hydroxylase Deficiency

Gene	Disorder	MOI	Features of Disorder	
			Overlapping w/DBH deficiency	Distinguishing from DBH deficiency
ATP7A	Occipital horn syndrome (See *ATP7A*-Related Copper Transport Disorders.)	XL	• DBH activity is depressed in *ATP7A*-related copper transport disorders (DBH is a copper-dependent enzyme). • Plasma catechol concentrations are distinctively abnormal at all ages in affected males.	• In infants w/classic Menkes disease: loss of developmental milestones, hypotonia, seizures, poor growth at age 2-3 mos, & characteristic hair changes (short, sparse, coarse, twisted, often lightly pigmented); death usually by age 3 yrs • "Occipital horns," distinctive wedge-shaped calcifications at sites of attachment of trapezius muscle & sternocleidomastoid muscle to occipital bone; lax skin & joints; bladder diverticula; inguinal hernias; vascular tortuosity; low serum copper & serum ceruloplasmin concentrations

Table 3. continued from previous page.

Gene	Disorder	MOI	Features of Disorder	
			Overlapping w/DBH deficiency	Distinguishing from DBH deficiency
CYB561	Cytochrome b561 deficiency (OMIM 618182)	AR	• Sympathetic dysfunction evident by severe symptomatic orthostatic hypotension from infancy or early childhood • Undetectable or very low plasma & urinary norepinephrine & epinephrine • Impaired renal function, mild anemia, episodic hypoglycemia • Can be treated w/droxidopa [2]	• No ptosis • No orthostatic tachycardia in response to drop in blood pressure • No skeletal muscle hypotonia • Normal plasma dopamine
ELP1	Familial dysautonomia	AR	• Autonomic dysfunction (GI problems, orthostatic hypotension) & autonomic crises (hypertensive vomiting attacks) • Cardiovascular instability • Age-related decline in renal function	• Occurs almost exclusively in persons of Ashkenazi Jewish descent • Sensory neuropathy • Normal resting plasma norepinephrine, greatly ↑ during autonomic crisis
TTR	Hereditary transthyretin amyloidosis	AD	• Orthostatic hypotension • Attacks of nausea & vomiting • Mild-to-severe kidney disease can develop.	• Amyloidosis (can involve heart, CNS, eyes, & kidneys) • Sensorimotor neuropathy; constipation alternating w/diarrhea; anhidrosis; urinary retention or incontinence • Onset typically in 3rd-5th decade, but may be later

AD = autosomal dominant; AR = autosomal recessive; CNS = central nervous system; DBH = dopamine beta-hydroxylase; GI = gastrointestinal; MOI = mode of inheritance; XL = X-linked

1. Goldstein et al [2008]

2. van den Berg et al [2018], Shibao et al [2020]

Management

No clinical practice guidelines for dopamine beta-hydroxylase (DBH) deficiency have been published. In the absence of published guidelines, the following recommendations are based on the authors' personal experience managing individuals with this disorder.

Evaluations Following Initial Diagnosis

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

Table 4. Dopamine Beta-Hydroxylase Deficiency: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Abnormal cardiovascular regulation	Posture study w/measurements of orthostatic vitals (supine & standing blood pressure & heart rate)	Useful to gauge efficacy & dose titration of droxidopa
	Assessment of standing time (length of time that affected person is able to stand)	Can be used as a surrogate for orthostatic vitals in children
Kidney function	Plasma creatinine & BUN	

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Hypoglycemia	Blood glucose in those diagnosed in infancy	High index of suspicion & aggressive treatment is needed to avoid severe hypoglycemia in infants.
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of DBH deficiency to facilitate medical & personal decision making

BUN = blood urea nitrogen; DBH = dopamine beta-hydroxylase; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Targeted Therapy

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

Droxidopa. The treatment of choice is administration of L-threo-3,4-dihydroxyphenylserine (or droxidopa, marketed in the United States as Northera®). Droxidopa is converted directly to norepinephrine by L-aromatic amino acid decarboxylase, thereby bypassing DBH (see Figure 1).

- Administration of 100-600 mg droxidopa orally two or three times daily increases blood pressure and concomitantly restores plasma norepinephrine to the normal range, although plasma epinephrine concentration still remains below a detectable level.
- Droxidopa reduces, but does not completely normalize, plasma concentration of dopamine [Biaggioni & Robertson 1987].
- This favorable alteration in catecholamines alleviates the orthostatic hypotension and restores function to a near-normal level. Note: An affected female completed a marathon approximately five years after her diagnosis while taking 1,200 mg of droxidopa daily [Garland et al 2005].
- Droxidopa improves but does not normalize kidney function, anemia, or hypomagnesemia [Wassenberg et al 2021].

Supportive Care

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

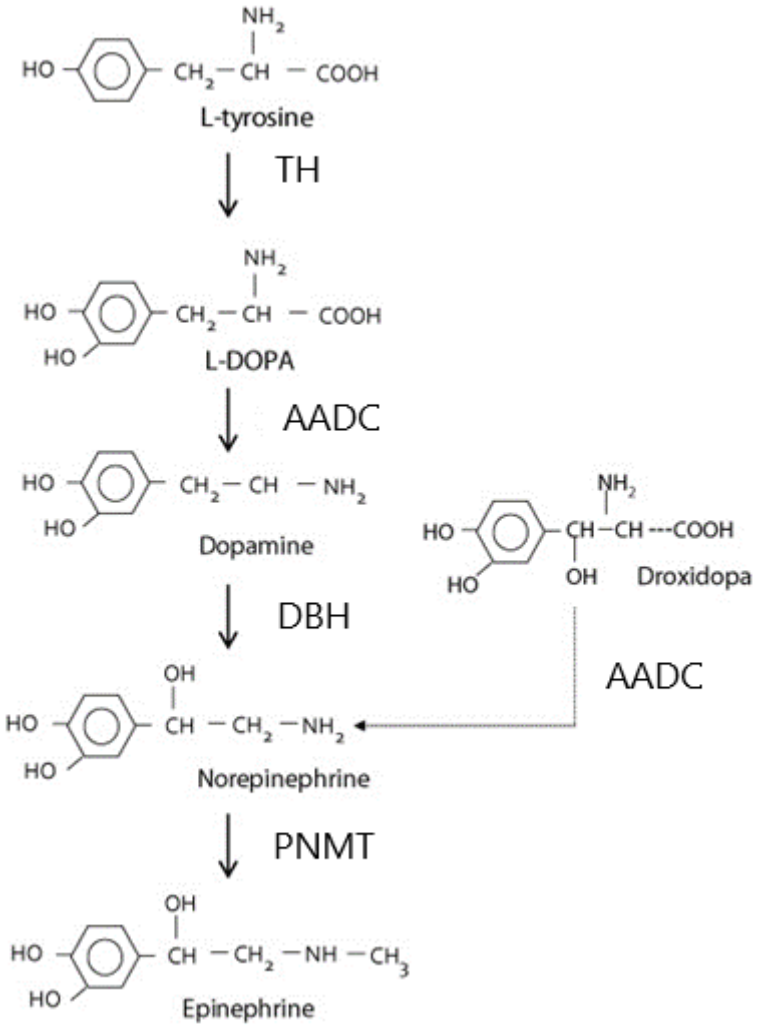

Figure 1. Synthesis of norepinephrine from dopamine or droxidopa

AADC = aromatic L-amino acid decarboxylase; DBH = dopamine beta-hydroxylase; PNMT = phenylethanolamine N-methyltransferase; TH = tyrosine hydroxylase

Table 5. Dopamine Beta-Hydroxylase Deficiency: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Orthostatic hypotension	Treatment options: • Droxidopa (See Targeted Therapy.) • Fludrocortisone (0.1-0.3 mg daily) provides some benefit, but marked orthostatic hypotension still occurs. • Midodrine (2.5-10 mg 3x/day)	Persons w/DBH deficiency respond somewhat to standard therapeutic approaches for autonomic failure but not nearly as well as they respond to droxidopa.
	Squatting or sitting / lying down can prevent falls.	By the time they are diagnosed, affected persons have generally developed ways of coping w/presyncopal symptoms.
Ptosis	Surgical correction as needed	
Nasal stuffiness	Standard treatment as needed	
Reduced kidney function	• Standard treatment as needed • Avoid nephrotoxic drugs.	

Surveillance

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

Table 6. Dopamine Beta-Hydroxylase Deficiency: Recommended Surveillance

System/Concern	Evaluation	Frequency
Abnormal cardiovascular regulation	Assess efficacy of droxidopa for orthostatic hypotension & symptoms of abnormal cardiovascular regulation w/adjustment of dosage as needed.	At least annually
	Persons on droxidopa should be encouraged to report any adverse events to their physician.	At each visit
	Referral to autonomic specialist; the type or dose of anesthesia may need to be modified & droxidopa doses regulated.	Prior to undergoing surgical procedures or becoming pregnant.
Kidney function	• BUN & plasma creatinine to assess kidney function • Plasma magnesium & potassium	At least every 2 yrs; more often in those w/↓ kidney function

BUN = blood urea nitrogen

Agents/Circumstances to Avoid

Untreated individuals with DBH deficiency should avoid hot environments, strenuous exercise, standing motionless, and dehydration.

Nephrotoxic drugs should be avoided.

Evaluation of Relatives at Risk

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

Pregnancy Management

The safety of using droxidopa during pregnancy has not been systematically evaluated, but its use appears justified considering that it is converted to norepinephrine, and that withholding treatment is likely to be riskier. At least three affected women have successfully given birth following uncomplicated deliveries while on droxidopa treatment [Scurrah et al 2002; I Biaggioni, personal observations].

Despite the limited data available, continuing droxidopa treatment during pregnancy has been recommended [Wassenberg et al 2021]. It is recommended that affected pregnant women have their blood pressure monitored regularly throughout the pregnancy and delivery so that the droxidopa dose can be modified as needed. One or two extra doses of droxidopa should be available as needed at the time of delivery. Dose adjustment may also be required post partum.

The effects of maternal droxidopa therapy on the developing fetus have not been studied in humans; however, studies on pregnant animals do not suggest an increased risk for malformations in offspring. See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Dopamine beta-hydroxylase (DBH) 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 *DBH* pathogenic variant.
- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *DBH* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) appear to be asymptomatic and are not at risk of developing the disorder. However, systematic evaluation of autonomic function in carriers has been insufficient to rule out any impairment.

Sibs of a proband

- If both parents are known to be heterozygous for a *DBH* 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) appear to be asymptomatic and are not at risk of developing the disorder. However, systematic evaluation of autonomic function in carriers has been insufficient to rule out any impairment.

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

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

Carrier Detection

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

Biochemical genetic testing. Biochemical testing is not recommended for determining carrier status. Many healthy individuals without a pathogenic variant in *DBH* have extremely low plasma DBH activity, so DBH activity measurement does not provide information on carrier status. A systematic study of heterozygotes (carriers) has not been performed, but those parents of individuals with DBH deficiency (i.e., carriers) who have been studied have had normal autonomic function and normal catecholamine levels.

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 affected, are carriers, or are at risk of being carriers.

Prenatal Testing and Preimplantation Genetic Testing

Once the *DBH* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

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

Resources

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

- **Autonomic Disorders Consortium**
  Autonomic Disorders Consortium

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. Dopamine Beta-Hydroxylase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
DBH	9q34.2	Dopamine beta-hydroxylase	DBH database	DBH	DBH

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 Dopamine Beta-Hydroxylase Deficiency (View All in OMIM)

223360	ORTHOSTATIC HYPOTENSION 1; ORTHYP1
609312	DOPAMINE BETA-HYDROXYLASE, PLASMA; DBH

Molecular Pathogenesis

DBH encodes dopamine beta-hydroxylase (3,4-dihydroxyphenylethylamine, ascorbate:oxygen oxidoreductase; DBH), a copper-requiring dimeric or tetrameric enzyme located in central and peripheral noradrenergic neurons and in the adrenal medulla. DBH also requires molecular oxygen and ascorbic acid or some other electron source for enzyme activity. DBH catalyzes the conversion of dopamine to norepinephrine, a critical neurotransmitter in the central nervous system and in sympathetic noradrenergic pathways essential for cardiovascular regulation. Absence of functional DBH prevents synthesis of norepinephrine.

Mechanism of disease causation. DBH deficiency occurs through a loss-of-function mechanism.

***DBH*-specific laboratory considerations.** DBH is localized within the soluble and membrane fractions of secretory vesicles of noradrenergic neurons. The soluble form of the enzyme is secreted into the circulation and is often measured in an enzymatic assay (plasma DBH activity). About 4% of the population has undetectable plasma DHB activity but normal plasma norepinephrine (and therefore normal vesicular DBH activity). A variant in the *DBH* promoter region, c.-979T>C, contributes to up to 52% of the variation in plasma DBH activity [Zabetian et al 2001], but *DBH* variants can cause low plasma DBH activity unrelated to norepinephrine deficiency [Deinum et al 2004].

Table 7. *DBH* Variants Referenced in This GeneReview

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000787.4	c.-979T>C	--	Benign variant that contributes to ≤52% of normal variation in DBH activity [Zabetian et al 2001]

DBH = dopamine-beta-hydroxylase
Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

Author Notes

Dr Biaggioni has 40 years' experience investigating the interaction between neural (autonomic), metabolic (renin-angiotensin, insulin, incretins), and local (adenosine, nitric oxide) mechanisms involved in cardiovascular regulation. In particular, he is interested in how these interactions participate in the pathophysiology of autonomic disorders. He directs the Vanderbilt Autonomic Dysfunction Center, a multidisciplinary program that includes neurologists, cardiologists, geriatricians, and clinical pharmacologists dedicated to the evaluation and treatment of individuals with autonomic disorders. He leads an active research program, with continued NIH funding for over 35 years that has resulted in over 360 peer-reviewed publications. The focus of this research program is to apply clinical research to the development of novel treatment strategies for autonomic disorders. His group has participated in the discovery of new autonomic diseases and in the development of novel devices, medications, and repurposing of approved drugs for the treatment of individuals with autonomic disorders.

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