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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 but normal parasympathetic and sympathetic cholinergic function. Affected individuals exhibit profound deficits in autonomic regulation of cardiovascular function that predispose to orthostatic hypotension. Although DBH deficiency appears to be present from birth, the diagnosis is not generally recognized until late childhood. The combination of ptosis of the eyelids in infants and children, together with hypotension, is suggestive of the disease. In the perinatal period, DBH deficiency has been complicated by vomiting, dehydration, hypotension, hypothermia, and hypoglycemia requiring repeated hospitalization; children have reduced exercise capacity. By early adulthood, individuals have profound orthostatic hypotension, greatly reduced exercise tolerance, ptosis of the eyelids, 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. Life expectancy is unknown, but some affected individuals have lived beyond age 60 years.

Diagnosis/testing

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

Management

Treatment of manifestations: Administration of L-threo-3,4-dihydroxyphenylserine (droxidopa) restores norepinephrine and alleviates the orthostatic hypotension and other symptoms. Affected individuals do not respond as well to standard therapeutic approaches for autonomic failure. Surgery can correct ptosis.

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Surveillance: Renal function (measurement of plasma creatinine and BUN concentrations) is assessed every two years or more often if loss of renal function is evident; plasma magnesium and potassium should also be assessed. Yearly evaluation of efficacy of droxidopa against orthostatic hypotension as dosage adjustment may be required. Consultation with autonomic specialist prior to surgery or becoming pregnant.

Agents/circumstances to avoid: Untreated individuals should avoid hot environments, strenuous exercise, standing motionless, and dehydration.

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. At conception, each sib of an affected individual has 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. Carrier testing for at-risk relatives is possible if both pathogenic variants in the family are known. Once the *DBH* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Diagnosis

Individuals with dopamine beta-hydroxylase (DBH) deficiency are often first encountered during adolescence, complaining of lifelong difficulties with lightheadedness and fatigue and an inability to tolerate standing or exercise. Affected individuals and their parents will report behaviors (e.g., squatting) used to compensate for the problems with standing.

Suggestive Findings

No formal testing strategy has been presented for DBH deficiency; a clinical assessment including orthostatic vital signs and an ophthalmic exam should be the initial step and, if indicated, this should be followed by autonomic function testing and plasma catecholamine analysis.

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

Clinical Findings

- 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
  - A compensatory rise in heart rate with standing
  - Inability to stand motionless for more than a few minutes
  - Cardiovascular findings consistent with sympathetic failure but preserved parasympathetic function
- 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 but not to hydroxyamphetamine. Parasympatholytics dilate the pupils appropriately.
- A comprehensive history and physical examination (including neurologic exam) that typically reveal the following:

- Intact sweating consistent with intact sympathetic cholinergic function
- Skeletal and muscle findings in some affected individuals:
  - Arched palate
  - Hyperextensible joints
  - Sluggish deep-tendon reflexes
  - Mild facial-muscle weakness
  - Hypotonic skeletal muscles

Findings on Physiologic Testing

Physiologic tests of autonomic function, when available, may provide diagnostic information of great specificity. Autonomic function test results (Table 1) indicate that complete DBH deficiency encompasses sympathetic noradrenergic failure and adrenomedullary failure but intact vagal and sympathetic cholinergic function [Biaggioni & Robertson 1987, van den Meiracker et al 1996, Bartoletti-Stella et al 2015].

- The Valsalva maneuver results in a profound fall in blood pressure together with an increase in heart rate reflecting parasympathetic withdrawal. The phase IV overshoot of the Valsalva maneuver does not occur.
- Hyperventilation causes a fall in blood pressure.
- Cold pressor testing causes either a fall or no change in blood pressure.
- Isometric handgrip exercise fails to significantly increase blood pressure.

Note: Click here for results of further physiologic tests of autonomic function.

Table 1. Results of Autonomic Function Testing in Individuals with Dopamine Beta-Hydroxylase Deficiency (DBHD)

		DBHD [1]	Control [1]	Number: DBHD/Control	P Value
Age (years)		26±14	34±10		0.033
Sinus arrhythmia ratio		1.3±0.21	1.4±0.21	8/86	0.266
Valsalva phase II	Delta SBP (mm Hg)	-41±25	-7±22	7/55	<0.001
	Delta HR (bpm)	29±11	30±16	7/53	0.828
Valsalva phase IV	Delta SBP (mm Hg)	-22±18	23±16	8/84	<0.001
	Delta HR (bpm)	5±9	-8±11	8/82	0.001
	Valsalva ratio	1.3±0.20	1.7±0.39	8/79	<0.001
Hyper-ventilation	Delta SBP (mm Hg)	-14±12	-7±12	9/86	454
	Delta HR (bpm)	14±19	11±11	8/86	0.308
Cold pressor	Delta SBP (mm Hg)	4±10	21±14	8/83	0.001
	Delta HR (bpm)	16±11	10±11	7/83	0.183
Handgrip	Delta SBP (mm Hg)	2±6	17±13	7/83	0.003
	Delta HR (bpm)	15±11	10±10	7/83	0.230

EM Garland, unpublished data from Vanderbilt Autonomic Dysfunction Center
HR = heart rate; SBP = systolic blood pressure
1. Mean ± SD

Specialized testing, such as a cardiac ^{123} I-metaiodobenzylguanidine scan, microneurography, and skin biopsies stained by the PGP pan neuronal marker and the DβH-specific adrenergic marker, can be used to confirm the selective loss of peripheral sympathetic noradrenergic function [Donadio et al 2016].

Laboratory Findings

Plasma catecholamines. Biochemical features unique to DBH deficiency:

- Minimal or absent plasma norepinephrine (NE) and epinephrine AND a five- to tenfold elevation of plasma dopamine (DA). This combination is probably pathognomonic of DBH deficiency.
  - Plasma NE concentration should be below the limits of detection (<25 pg/mL or 0.15 nmol/L).
  - Plasma DA concentration is frequently higher than 100 pg/mL (0.65 nmol/L). One atypical individual who was not diagnosed until age 73 years was reported to have a plasma DA concentration of 10,000 pg/mL (67 nmol/L) [Despas et al 2010].
- Although both baroreflex afferent and catecholamine release mechanisms are intact, DA is released in place of NE.

Note: (1) It is essential to assay both NE and DA and to use a procedure with high specificity for these catechols. (2) With some radioenzymatic methods for catecholamine determinations, a proportion of the DA may be erroneously measured as epinephrine [Robertson et al 1986]. (3) Very low (rather than undetectable) levels of NE can be reported in some assays and are also likely due to interference substances.

The plasma DA concentrations respond to various physiologic and pharmacologic stimuli in a way that mimics that of NE in normal individuals:

- A change from supine to upright posture doubles or triples the plasma DA concentration. This observation suggests that sympathetic nerves and reflex arcs are intact, but DA (rather than NE) is stored and released at the sympathetic synapse.
- Central sympatholytics lower plasma dopamine [Biaggioni & Robertson 1987].

Click here for information pertaining to pharmacologic findings that can be seen in individuals with DBH.

Establishing the Diagnosis

The diagnosis of DBH **is established** in a proband with profound neurogenic orthostatic hypotension, minimal or absent plasma concentrations of norepinephrine and epinephrine, and a five- to tenfold elevation of plasma dopamine; the diagnosis is confirmed with identification of biallelic pathogenic variants in *DBH* by molecular genetic testing (see Table 2).

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

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of dopamine beta-hydroxylase deficiency is broad, 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 dopamine beta-hydroxylase deficiency has not been considered are more likely to be diagnosed using genomic testing (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* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

- **A multigene panel** that includes *DBH* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 2).

  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 is not considered because an individual has atypical phenotypic features, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is the most commonly used genomic testing method; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if exome sequencing is not diagnostic.

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

Table 2. Molecular Genetic Testing Used in Dopamine Beta-Hydroxylase Deficiency

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
DBH	Sequence analysis [3]	17/17 [4]
	Gene-targeted deletion/duplication analysis [5]	Unknown [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. All variants reported to date
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

Click here for information on the plasma DBH enzymatic assay.

Clinical Characteristics

Clinical Description

Dopamine beta-hydroxylase (DBH) deficiency is characterized by a lack of sympathetic noradrenergic function but normal parasympathetic and sympathetic cholinergic function. Affected individuals exhibit profound

deficits in autonomic regulation of cardiovascular function, but apparently only subtle signs of central nervous system dysfunction [Robertson et al 1986, Man in 't Veld et al 1987, Timmers et al 2004, Jepma et al 2011].

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.

Features by age. The full clinical spectrum of DBH deficiency is not known because of the limited number of cases reported. Clinical features reported in 21 affected individuals (13 female, 8 male) are included in Table 3.

- Infancy:
  - In the perinatal period, DBH deficiency has been complicated by vomiting, dehydration, hypotension, hypothermia, and hypoglycemia requiring repeated hospitalization.
  - Delay in opening of the eyes has occurred and ptosis of the eyelids is seen in most affected infants.
- Childhood:
  - Children with DBH deficiency have markedly reduced exercise capacity, perhaps because of hypotension engendered by physical exertion.
  - The syncope associated with postural hypotension often suggests seizures and prompts trials of anticonvulsive medication despite lack of abnormalities on the electroencephalogram.
  - Mental and physical development are normal.
- Adolescence and early adulthood:
  - Symptoms generally worsen in late adolescence.
  - By early adulthood, affected individuals demonstrate profound orthostatic hypotension, fatigue, greatly reduced exercise tolerance, ptosis of the eyelids, and nasal stuffiness. Insulin resistance has been reported in an affected female age 15 years [Arnold et al 2017].
  - Males experience retrograde or prolonged ejaculation.

Clinical features of DBH deficiency are included in Table 3.

Table 3. Clinical Features of DBH Deficiency

Feature	# of Individuals [1]
Severe orthostatic hypotension	21/21 (100%)
Anemia	9/15 (60%)
Ptosis of eyelids	12/14 (86%)
Hyperflexible or hypermobile joints	6/10 (60%)
EKG abnormalities [2]	2/12 (17%)
Epileptiform symptoms	4/12 (33%)
Nasal stuffiness	10/10 (100%)
Hypoglycemia	4/12 (33%)
Sluggish deep-tendon reflexes	3/9 (33%)
Increased plasma creatinine	6/11 (54%)
Polyuria/nocturia	3/9 (33%)
High palate	9/10 (90%)
Increased BUN	6/9 (67%)
Muscle hypotonia	3/9 (33%)
Postprandial hypotension	3/7 (43%)
Sleep irregularities	5/7 (71%)

Table 3. continued from previous page.

Feature	# of Individuals [1]
Impaired ejaculation	4/4 (100%)

1. Number of individuals with the finding/total number evaluated for the finding
2. EKG = electrocardiogram

Presyncopal symptoms include dizziness, blurred vision, dyspnea, nuchal discomfort, and occasionally chest pain. Symptoms may worsen in hot environments or after heavy meals or alcohol ingestion. Occasional bouts of unexplained diarrhea occur.

Renal function. Elevated blood urea nitrogen has been noted in six affected individuals in the USA [Garland et al 2005a, Garland et al 2009]. This may be evidence of a loss of renal function. A nephrologist who evaluated an individual age 16 years with a disproportionately high BUN (32 mg/dL) and slightly elevated creatinine (1.09 mg/dL) proposed that renal perfusion was reduced and that a BUN/Cr ratio <25 should be targeted. Although droxidopa acutely improved the ratio, the BUN/Cr ratio was further increased after a year of droxidopa treatment. The estimated GFR of an affected female age 57 years was reduced to 18 mL/min/1.73 m^2 [Emily Garland, personal observation]. Another patient with unexpectedly low eGFR and elevated creatinine was found, by electron microscopy, to have abnormal, fused mitochondria in the proximal, but not the distal, tubules. Associated problems with the glomerular-tubular balance can be at least partially reversed by treatment with droxidopa [Wassenberg et al 2017].

Cognitive function. Despite the lack of norepinephrine, persons with DBH deficiency apparently 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].

Ptosis. Ptosis of the eyelids, defined as a reduction in the margin reflex distance, is common in individuals with DBH deficiency and can be noted at an early age. It was reported in the first descriptions of individuals with this disorder in the late 1980s and in more than 85% of all cases in the published literature. Levator function is intact. Some individuals undergo levator advancement surgery [Phillips et al 2013], which may mask this aspect of the phenotype.

Olfactory function is relatively unaffected in individuals with DBH deficiency, who have intact noradrenergic neurons, in contrast to the marked deficit in individuals with pure autonomic failure, who have peripheral neuronal degeneration [Garland et al 2011].

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 of the individuals. 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 report 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].

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

Life span. Four persons with DBH deficiency are known to have died. A woman age 57 years had chronic kidney disease and was undergoing treatment for breast cancer. Her listed cause of death at an assisted living facility was cardiac arrhythmia. Autopsy of a male age 28 years reported "scattered pyknotic cerebral neurons, isolated microfoci of cortical gliosis, cardiac arteriolar smooth muscle hypertrophy, scattered fibrosis in the cardiac conduction system, and sclerotic renal glomeruli." Cardiac dysrhythmia, possibly related to fibrosis in the cardiac conduction system, may have contributed to the patient's sudden demise [Cheshire et al 2006]. One individual died at age 20 years, possibly by suicide. A person age 63 died of unknown causes. Other affected individuals are likely to be deceased, but there are no published reports of causes of death or of effects of the disorder on life span.

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 the life span.

Genotype-Phenotype Correlations

There are no known genotype-phenotype correlations.

Prevalence

The prevalence of DBH deficiency is unknown. Only 23 affected individuals, all of western European descent, have been reported in the literature, suggesting that it is a rare disorder.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

The striking catecholamine abnormalities distinguish DBH deficiency from other disorders. Other catecholamine disorders described in the past, such as aromatic L-amino acid decarboxylase deficiency, have clinical presentations distinct from that of DBH deficiency [Swoboda et al 2003].

Pure autonomic failure / autonomic neuropathy. Pure autonomic failure or Bradbury-Eggleston syndrome 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; plasma dopamine concentrations are normal or low, rather than elevated as in DBH deficiency.

Systemic illness. Some dysautonomias result from well-characterized autonomic neuropathies secondary to systemic illnesses such as diabetes mellitus.

Other disorders with orthostatic hypotension to consider in the differential diagnosis of DBH deficiency are summarized in Table 4.

Table 4. Disorders with Orthostatic Hypotension to Consider in the Differential Diagnosis of Dopamine Beta-Hydroxylase (DBH) Deficiency

Disorder	Gene(s)	MOI	Clinical Description / Comments	Distinguishing Clinical Features
Familial dysautonomia (FD)	*ELP1* [1]	AR	• Affects development & survival of sensory, sympathetic, & parasympathetic neurons • Debilitating disease present from birth; progressive neuronal degeneration continues throughout life • Gastrointestinal dysfunction; vomiting crises • Recurrent pneumonia • Altered sensitivity to pain & temperature • Cardiovascular instability • ~40% of individuals have autonomic crises • Age-related decline in renal function noted [2]	In DBH deficiency: • Normal tearing; intact corneal & deep tendon reflexes; normal sensory function; normal senses of taste & smell • Lack of abnormal cholinergic sensitivity & intradermal histamine response In FD: • Occurs almost exclusively in persons of Ashkenazi heritage • High rates of excretion of HVA & low rates of excretion of VMA; plasma DHPG concentration is low; plasma DOPA & DA concentrations are ↑ [3]
ATP7A-related copper transport disorders (Menkes disease & occipital horn syndrome)	*ATP7A* [4]	XL	DBH is a copper-dependent enzyme & thus DBH activity is depressed in individuals w/*ATP7A*-related copper transport disorders, leading to: • High plasma & CSF concentrations of DOPA, DOPAC, & DA • Low concentrations of DHPG • Approximately normal concentrations of NE	• In infants w/classic Menkes disease: loss of developmental milestones, hypotonia, seizures, failure to thrive at age 2-3 mos, & characteristic hair changes (short, sparse, coarse, twisted, often lightly pigmented); death usually by age 3 yrs • In OHS: "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; intellect normal or slightly ↓; serum copper & serum ceruloplasmin concentrations are low.
Familial transthyretin amyloidosis	*TTR*	AD	• Slowly progressive peripheral sensorimotor neuropathy & autonomic neuropathy as well as non-neuropathic changes of nephropathy, cardiomyopathy, vitreous opacities, & CNS amyloidosis • Cardinal feature: slowly progressive sensorimotor & autonomic neuropathy • Autonomic neuropathy may be 1st clinical symptom.	In familial transthyretin amyloidosis: • Constipation alternating w/diarrhea; attacks of nausea & vomiting; delayed gastric emptying; sexual impotence; anhidrosis; urinary retention or incontinence • Onset typically in 3rd-5th decade, but may be later

Table 4. continued from previous page.

Disorder	Gene(s)	MOI	Clinical Description / Comments	Distinguishing Clinical Features
Multiple system atrophy (Shy-Drager syndrome) (OMIM 146500)	*COQ2* [5]	AR AD	• Adult-onset neurodegenerative disorder causing combination of ataxia, parkinsonism, & autonomic dysfunction • Poor response to levodopa • Severe orthostatic hypotension w/out compensatory tachycardia	In multiple system atrophy: • Extrapyramidal or cerebellar findings • Erectile dysfunction, constipation/ diarrhea, urinary symptoms, decreased sweating are prevalent. • Onset age >30 yrs; rapidly progressive to death w/in ~3 yrs of diagnosis
Cytochrome b561 deficiency (OMIM 618182)	*CYB561* [6]	AR	• Sympathetic dysfunction evident by severe symptomatic orthostatic hypotension from infancy or early childhood w/out compensatory tachycardia • Undetectable or very low plasma & urinary norepinephrine & epinephrine, w/normal dopamine • Impaired renal function, mild anemia, episodic hypoglycemia • Shortened life span • Can be treated w/droxidopa	In CYB561 deficiency: • No ptosis • No orthostatic tachycardia in response to drop in blood pressure • No skeletal muscle hypotonia

AD = autosomal dominant; AR = autosomal recessive; DA = dopamine; DHPG = dihydroxyphenylglycol; DOPA = 3,4-dihydroxyphenylalanine; DOPAC = 3,4-dihydroxyphenylacetic acid; HVA = homovanillic acid; MOI = mode of inheritance; NE = norepinephrine; OHS = occipital horn syndrome; VMA = 3-methoxy-4-hydroxymandelic acid; XL = X-linked

1. Two pathogenic variants account for more than 99% of pathogenic alleles in individuals of Ashkenazi Jewish descent.

2. Elkayam et al [2006]

3. Goldstein et al [2008]

4. Molecular genetic testing of *ATP7A* detects pathogenic variants in more than 95% of affected individuals.

5. No genetic cause has been identified for the vast majority of affected individuals.

6. van den Berg et al [2018]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with dopamine beta-hydroxylase (DBH) deficiency, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Review of medical history to understand medical issues in context of the diagnosis of DBH deficiency. It can be helpful to recognize that some findings from a previous medical history or exam may be associated with the diagnosis of DBH deficiency and thus amenable to treatment with droxidopa.
- Assessment of standing time (length of time that the affected individual is able to stand)
- Assessment of renal function with, at a minimum, plasma and urinary electrolytes, creatinine, and BUN
- Ophthalmic examination with measurement of margin reflex distance to establish presence or absence of ptosis, followed by consideration of possible benefit of surgery
- Measurement of palate for an objective diagnosis of high-arched palate, which can cause feeding difficulties in infancy and breathing or sleeping difficulties. In the absence of these symptoms, no further evaluation or treatments are required.
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

For the most part, treatment for DBH deficiency is supportive and directed at relieving orthostatic symptoms.

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

- Administration of 100-600 mg droxidopa orally twice or three times daily increases blood pressure and concomitantly restores plasma NE to the normal range; however, urinary NE excretion exceeds normal levels.
- Although NE becomes detectable, plasma epinephrine concentration still remains below a detectable level.
- Droxidopa administration restores the dopamine precursor, L-3,4-dihydroxyphenylalanine (DOPA), to within the normal range and reduces dopamine (DA) somewhat, but plasma concentration of DA and its metabolites remains somewhat elevated [Biaggioni & Robertson 1987].
- This favorable alteration in catecholamines alleviates the orthostatic hypotension and restores function to a near-normal level. An affected female completed a marathon approximately five years after her diagnosis, while taking 1,200 mg of droxidopa daily [Garland et al 2005b].

Individuals with DBH deficiency respond somewhat to standard therapeutic approaches for autonomic failure but not nearly as well as they respond to droxidopa.

- Fludrocortisone, at dosages of 0.1-0.3 mg daily, has been used with some benefit, but marked orthostatic hypotension still occurs.
- Midodrine 2.5-10 mg three times/day can be used to treat orthostatic hypotension.

By the time they are diagnosed, affected individuals have generally developed ways of coping with their presyncopal symptoms. Squatting or sitting/lying down can prevent falls.

Ptosis can be corrected by surgery.

Nasal stuffiness should be treated as needed.

Surveillance

Renal function should be assessed by BUN and plasma creatinine at a minimum of every two years and more often if a loss of function is evident. Plasma magnesium and potassium should also be assessed.

Affected individuals should be queried at least yearly about continued efficacy of droxidopa against orthostatic hypotension and symptoms. Adjustment of dosage may be required.

Individuals on droxidopa should be encouraged to report any adverse events to their physician.

Affected persons or their physicians should consult with an autonomic specialist prior to undergoing surgical procedures or becoming pregnant. The type or dose of anesthesia may need to be modified, and droxidopa doses regulated.

Agents/Circumstances to Avoid

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

Evaluation of Relatives at Risk

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

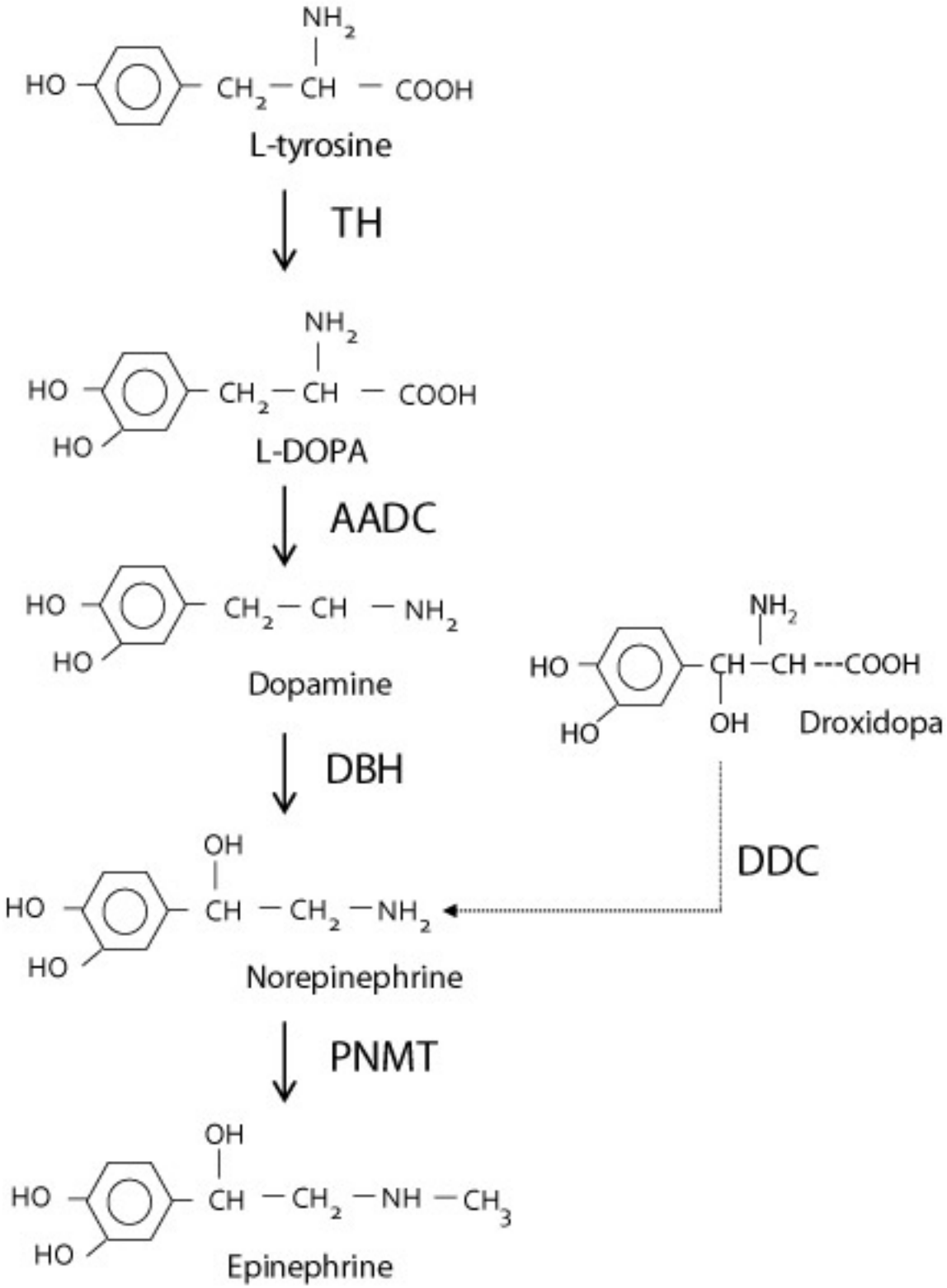

Figure 1. Synthesis of norepinephrine from dopamine or droxidopa

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 [Scurrah et al 2002; Author, personal observation] following uncomplicated deliveries while on droxidopa treatment.

Based on these experiences, 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 to be taken 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 deficiency is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *DBH* pathogenic variant).
- Heterozygotes (carriers) appear to be asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has 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, clarification of carrier status, 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.

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).

Prenatal Testing and Preimplantation Genetic Testing

Once the *DBH* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

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

Resources

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

- **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

Introduction. Dopamine-beta-hydroxylase (3,4-dihydroxyphenylethylamine, ascorbate:oxygen oxidoreductase; DBH) is 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 protein prevents synthesis of norepinephrine (noradrenaline).

Mechanism of disease causation. DBH deficiency occurs through a loss-of-function mechanism. Ten *DBH* pathogenic variants have been reported in individuals with DBH deficiency [Kim et al 2002, Deinum et al 2004, Kim et al 2011, Bartoletti-Stella et al 2015, Donadio et al 2016]. The majority are missense variants, with one splice variant, one frameshift, and one deletion.

***DBH*-specific laboratory considerations.** Some apparently unaffected individuals consistently have very low DBH activity [Zabetian et al 2001]. Although a few individuals with low plasma DBH concentrations have clinical features of DBH deficiency, the vast majority with low plasma DBH concentrations are unaffected.

Several *DBH* variants that correlate with variation in the level of DBH activity have been identified in individuals neither affected by nor carriers of DBH deficiency. A variant in the promoter region, c.-979T>C, contributes up to 52% of the variation [Zabetian et al 2001].

Table 5. Notable *DBH* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000787 NP_000778	c.-979T>C		Variant that contributes up to 52% of normal variation in DBH activity [Zabetian et al 2001]
	c.339+2T>C		Common pathogenic variant that causes abnormal splicing [Kim et al 2002, Deinum et al 2004, Kim et al 2011, Phillips et al 2013, Arnold et al 2017]
	c.342C>A	p.Asp114Glu	Abnormal protein retained in cell, suggesting abnormal trafficking & secretion [Kim et al 2011]
	c.1085C>A	p.Ala362Glu	
	c.1033G>A	p.Asp345Asn	Identified in USA [Kim et al 2002, Erez et al 2010, Phillips et al 2013]. Abnormal protein retained in cell, suggesting abnormal trafficking & secretion [Kim et al 2011]
	c.301G>A	p.Val101Met	Identified in USA [Kim et al 2002, Erez et al 2010, Phillips et al 2013]
	c.806G>T	p.Cys269Phe	Identified in the Netherlands [Deinum et al 2004]
	c.1667A>G	p.Tyr556Cys	
	c.617delA	p.Glu206GlyfsTer82	

Table 5. continued from previous page.

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
	c.1374+24T>G		Identified in Italy [Bartoletti-Stella et al 2015, Donadio et al 2016]
	c.1409C>T	p.Thr470Met	

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.

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Chapter Notes

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