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Dopamine Beta-Hydroxylase Deficiency

[*Norepinephrine Deficiency*]

David Robertson, MD
Professor; Departments of Medicine, Pharmacology, and Neurology
Vanderbilt University
david.robertson@mcmail.vanderbilt.edu

Emily M Garland, PhD
Instructor, Department of Medicine
Vanderbilt University
emily.garland@vanderbilt.edu

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Summary

Disease characteristics. Dopamine beta-hydroxylase (DBH) deficiency is characterized by normal parasympathetic and sympathetic cholinergic function but with a lack of sympathetic noradrenergic 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 adulthood. In the perinatal period, DBH deficiency has been complicated by vomiting, dehydration, hypotension, hypothermia, and profound 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. Life expectancy is unknown.

Diagnosis/testing. The diagnosis of DBH deficiency is based on clinical findings, including poor cardiovascular regulation, other autonomic dysfunction, and intact sweating. Physiologic findings of autonomic function indicate that complete DBH deficiency encompasses sympathetic noradrenergic failure and adrenomedullary failure but intact vagal and sympathetic cholinergic function. Biochemical features unique to DBH deficiency include minimal or undetectable plasma norepinephrine and epinephrine AND a five- to tenfold elevation of plasma dopamine, a finding probably pathognomonic of DBH deficiency. The *DBH* gene is the only gene known to be associated with DBH deficiency; *DBH* molecular genetic testing is available on a research basis only.

Management. Treatment for DBH deficiency is supportive and directed at relieving orthostatic symptoms. Administration of DL or L-threo-3,4-dihydroxyphenylserine (DOPS) alleviates the orthostatic hypotension and other symptoms. Individuals do not respond well to standard therapeutic approaches for autonomic failure. Surgery can correct ptosis. Renal function is assessed every five years, or more often if loss of function is evident.

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. Prenatal testing may be available through a laboratory offering custom prenatal testing to

families in which the disease-causing mutations have been identified in an affected family member in a research laboratory.

Diagnosis

Clinical Diagnosis

Physical examination of individuals with dopamine beta-hydroxylase (DBH) deficiency reveals [Timmers et al 2004] the following:

- Poor cardiovascular regulation
  - A low normal supine blood pressure and low supine heart rate
  - Systolic blood pressure below 80 mm Hg in the upright position
  - A compensatory but attenuated rise in heart rate with standing
  - Inability to stand motionless for more than a minute
- Other autonomic dysfunction
  - Ptosis in some individuals
  - Somewhat small pupils that respond to light and accommodation but not to hydroxyamphetamine. Parasympatholytics dilate the pupils appropriately.
- Intact sweating
- Joint and muscle findings
  - Hyperextensible joints
  - Sluggish deep-tendon reflexes
  - Mild facial-muscle weakness
  - Hypotonic skeletal muscles
  - Arched palate

[Robertson et al 1991, Vincent & Robertson 2002]

Physiologic tests of autonomic function. Physiologic tests of autonomic function may provide diagnostic information of great specificity [Robertson 1997]. Autonomic function testing results 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].

- Cold pressor testing causes either a fall or no change in blood pressure.
- Isometric handgrip exercise fails to significantly increase blood pressure.
- 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.
- Muscle sympathetic nerve activity measured by microneurography is normal.

Pharmacologic tests of autonomic function. There is a several-fold hypersensitivity to α1-adrenoceptor agonists and β-adrenoceptor agonists.

- Propranolol, a β-adrenergic antagonist, does not lower heart rate.

- Intravenous atropine raises heart rate by 40-60 beats per minute.
- Pindolol, a β-adrenergic antagonist with some sympathomimetic activity, raises heart rate.
- Clonidine, a partial agonist of α2-adrenoceptors that acts centrally to reduce sympathetic outflow and lower blood pressure in normal individuals, can also exert peripheral pressor effects by stimulation of vascular α2-adrenoceptors [Robertson et al 1983, Onrot et al 1987]. Individuals with DBH deficiency have no fall in seated mean arterial pressure following the administration of clonidine. On the contrary, significant increases in blood pressure are seen with higher doses of this agent.

Testing

Dopamine beta-hydroxylase (EC 1.14.17.1) catalyzes the hydroxylation of dopamine (DA) to norepinephrine (NE). Although individuals with DBH deficiency lack plasma DBH activity and DBH immunoreactivity [Robertson et al 1986, Man in't Veld et al 1987, O'Connor et al 1994], the most helpful diagnostic test is measurement of the concentration of the plasma catecholamines dopamine and norepinephrine [Robertson 1997].

Plasma catecholamines. Biochemical features unique to DBH deficiency:

- Minimal or undetectable plasma NE and epinephrine AND a five- to tenfold elevation of plasma DA. This combination is probably pathognomonic of DBH deficiency [Robertson et al 1991]. Although baroreflex afferent as well as catecholamine release mechanisms are intact, DA is apparently released in place of NE.
- Metabolites of NE are low or absent in plasma, urine, and CSF.
- Metabolites of DA such as homovanillic acid (HVA) and 3-methoxytyramine are elevated [Robertson et al 1986, Man in't Veld et al 1987, Biaggioni et al 1990].

Note: (1) It is essential to assay both NE and DA with their metabolites 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, Robertson et al 1991].

The plasma DA concentration responds to various physiologic and pharmacologic stimuli as does NE in normal subjects.

- Tyramine, for example, which normally is taken up by the norepinephrine transporter and stimulates NE release into the synapse, has no such effect in persons with DBH deficiency. NE remains undetectable after administration of high doses of tyramine, while DA increases [Robertson et al 1986]. This increase in plasma DA concentration probably reflects release of neuronal DA stores, but in some individuals, it may be the result of tyramine conversion to DA [Jacob et al 2003].
- 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.

Plasma DBH enzymatic assay. DBH is released into the synaptic cleft during vesicular exocytosis. A fraction of the DBH released into the synaptic cleft spills over into the blood, where it can be detected. Plasma levels of DBH enzyme activity vary over a wide range in different individuals, and most individuals with low levels of plasma DBH enzyme activity do not have DBH deficiency. DBH enzyme activity is undetectable in the blood of individuals with DBH deficiency [Robertson et al 1986, Man in't Veld et al 1987]. In addition to DA, DBH catalyzes the hydroxylation of tyramine and other b-phenylethylamine derivatives.

Assays for DBH enzymatic assay:

- A spectrophotometric procedure based on the enzymatic conversion of the substrate tyramine into the product octopamine in the presence of excess ascorbate, sodium fumarate, catalase, N-ethylmaleimide, and pargyline. The octopamine is then oxidized to *p*-hydroxybenzaldehyde [Nagatsu & Udenfriend 1972, Kato et al 1974, Kato et al 1978].
- A two-step enzyme radioassay that incorporates conversion of phenylethylamine to phenylethanolamine by DBH, then metabolism of phenylethanolamine to N-methylphenylethanolamine by phenylethanolamine N-methyltransferase (PNMT) and radioactive S-adenosylmethionine [Goldstein et al 1971, Molinoff et al 1971, Weinshilboum & Axelrod 1971]
- High performance liquid chromatographic (HPLC) procedures [Matsui et al 1981]

Plasma DBH immunoassay. This assay measures the total protein antigenically related to DBH, including inactive forms of the enzyme. Lack of DBH immunoreactivity in cerebrospinal fluid or plasma suggests absent enzyme, rather than inactive enzyme, as the cause of DBH deficiency [O'Connor et al 1994].

Immunocytochemical examination. DBH is located almost exclusively in the chromaffin granules of the adrenal medulla and in the large dense-core synaptic vesicles of both central and peripheral adrenergic and noradrenergic neurons [Axelrod 1972]. Immunocytochemical examination of sympathetic fibers reveals undetectable DBH protein [Mathias et al 1990].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *DBH,* mapped to chromosome 9q34 [Craig et al 1988] is the only gene known to be associated with DBH deficiency.

Molecular genetic testing: Research

- **Direct DNA analysis.** Mutations in the *DBH* gene have been identified in individuals with DBH deficiency. *DBH* molecular genetic testing is available on a research basis only.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Dopamine Beta-Hydroxylase Deficiency

Test Method	Mutations Detected	Mutation Detection Rate	Test Availability
Direct DNA analysis [1]	*DBH*	50-100% [2]	Research only

1. Direct DNA methods may include mutation analysis, mutation scanning, sequence analysis, or other means of molecular genetic testing to detect a genetic alteration associated with dopamine beta-hydroxylase deficiency.
2. Cho et al 2003

Testing Strategy for a Proband

The most helpful diagnostic test is measurement of the concentration of the plasma catecholamines dopamine and norepinephrine.

Genetically Related Disorders

The four putative disease mutations for DBH deficiency identified by Kim et al (2002) have not been reported in other autonomic disorders [Cho et al 2003]. Three additional mutations have been associated with DBH deficiency in the Netherlands [Deinum et al 2004]. The mutant alleles were also present in unaffected family members but were not present in 100 control individuals.

Several polymorphisms in the *DBH* gene have been identified. Linkage and association studies have been conducted with these polymorphisms in individuals with schizophrenia, migraine, attention deficit/hyperactivity disorder, Parkinson disease, and alcoholism, with mixed results [Meszaros et al 1996, Wei et al 1996, Wei et al 1998, Williams et al 1999, Lea et al 2000, Zabetian et al 2001, Kohnke et al 2002, Roman et al 2002, Mochi et al 2003, Yamamoto et al 2003, Healy et al 2004, Johnstone et al 2004, Bhaduri et al 2005].

Clinical Description

Natural History

Dopamine beta-hydroxylase deficiency is characterized by normal parasympathetic and sympathetic cholinergic function but with a lack of sympathetic noradrenergic 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].

Although DBH deficiency appears to be present from birth, the diagnosis is not generally recognized until adulthood.

The full clinical spectrum of DBH deficiency is not known because of the limited number of cases reported. Clinical features reported in 14 affected individuals (ten female, four male) are included in Table 2.

In the perinatal period, DBH deficiency has been complicated by vomiting, dehydration, hypotension, hypothermia, and profound hypoglycemia requiring repeated hospitalization. Delay in opening of the eyes has occurred and ptosis of the eyelids is seen in most affected infants.

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.

Symptoms generally worsen in late adolescence. By early adulthood, affected individuals have profound orthostatic hypotension, greatly reduced exercise tolerance, ptosis of the eyelids, and nasal stuffiness. Males experience retrograde or prolonged ejaculation.

Clinical features of DBH deficiency are included in Table 2.

Table 2. Clinical Features of DBH Deficiency

Feature	# of Individuals Studied	# of Individuals (%)
Severe orthostatic hypotension	14	14 (100)
Anemia	10	8 (80)
Impaired ejaculation (n=2 males)	3	6 (100%)

Ptosis of eyelids	8	7 (88)
Abnormal sexual maturation	8	0 (0)
Hyperflexible or hypermobile joints	8	6 (75)
ECG abnormalities [1]	7	2 (29)
Epileptiform symptoms	7	3 (43)
Nasal stuffiness	6	6 (100)
Hypoglycemia	6	2 (33)
Sluggish deep-tendon reflexes	6	3 (50)
Increased plasma creatinine	6	2 (33)
Polyuria/nocturia	5	3 (60)
High palate	5	5 (100)
Increased BUN	5	3 (60)
Muscle hypotonia	4	2 (50)
Postprandial hypotension	4	3 (75))
Sleep irregularities	3	3 (100)
Impaired ejaculation	3	3 (100)
T-wave abnormalities (ECG)	3	0 (0)

Data are taken from the first six published cases.

1. ECG=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.

An age-related elevation in blood urea nitrogen has been noted in four affected individuals in the United States [Garland et al 2005]. This may be evidence of a loss of renal function, and one of these individuals may require dialysis. The three oldest individuals with DBH deficiency also have hypomagnesemia, the relevance of which is unknown.

Atrial fibrillation developed in one individual [Biaggioni et al 1990]. Another individual had a T wave with reduced amplitude, which may reflect an electrolyte abnormality [Man in't Veld et al 1987].

The life expectancy of affected individuals is unknown. At least two individuals are now in their fifties, and none of those diagnosed with DBH deficiency has died.

Since so few individuals have been diagnosed with DBH deficiency, it is not known what relationship the less common findings have to the absence of DBH or elevated levels of dopamine; they may be fortuitous findings. However, the investigators [Man in't Veld et al 1987] speculated that hypoglycemia may result from adrenomedullary failure and the T-wave abnormalities from failure of noradrenergic control. Since dopamine inhibits both the synthesis and secretion of prolactin, some degree of hypoprolactemia is not surprising in these individuals.

Genotype-Phenotype Correlations

Because of the small number of individuals diagnosed with DBH deficiency, it is not possible to determine correlations between specific phenotypes and mutations in the *DBH* gene.

Prevalence

The prevalence of DBH deficiency is unknown. Only 14 affected individuals, all of Western European descent, have been reported in the literature, suggesting that it is a rare disorder.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

The striking catecholamine abnormalities distinguish DBH deficiency from other disorders. Other catecholamine disorders, such as aromatic 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 the sympathetic and parasympathetic nervous systems but spares the adrenal medulla. Hypohidrosis is common. Individuals with pure autonomic failure have marked hypersensitivity to all pressor and depressor stimuli. Plasma and urinary NE concentrations are greatly reduced, sometimes to 10% of normal; plasma DA concentrations are normal or low. In contrast to DBH deficiency, urinary DA concentrations are about 50% of normal.

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

Familial dysautonomia. Familial dysautonomia (FD) affects the development and survival of sensory, sympathetic, and parasympathetic neurons. It is a debilitating disease present from birth. Progressive neuronal degeneration continues throughout life. Affected individuals have gastrointestinal dysfunction, vomiting crises, recurrent pneumonia, altered sensitivity to pain and temperature, and cardiovascular instability. About 40% of individuals have autonomic crises. Clinically, DBH deficiency is distinguished from familial dysautonomia by normal tearing, intact corneal and deep tendon reflexes, normal sensory function, normal senses of taste and smell, and lack of abnormal cholinergic sensitivity and intradermal histamine response. Familial dysautonomia is seen almost exclusively in individuals of Ashkenazi heritage, whereas individuals with DBH deficiency have not to date been of Ashkenazi Jewish descent. Individuals with familial dysautonomia have high rates of excretion of HVA and low rates of excretion of the NE metabolite 3-methoxy-4-hydroxymandelic acid (VMA); plasma DA and 3,4-dihydroxyphenylacetic acid (DOPAC) levels are relatively normal [Goldstein et al 1996]. Inheritance is autosomal recessive. The diagnosis of familial dysautonomia is established by molecular genetic testing of the *IKBKAP* gene. Two mutations account for more than 99% of mutant alleles in individuals of Ashkenazi Jewish descent.

ATP7A-related copper transport disorders. Menkes disease and occipital horn syndrome (OHS) are disorders of copper transport caused by mutations in the copper-transporting ATPase gene, *ATP7A*. Inheritance is X-linked. DBH is a copper-dependent enzyme, and thus DBH activity is depressed in affected individuals, leading to high plasma and CSF concentrations of DOPA, DOPAC, and DA; low concentrations of dihydroxyphenylglycol (DHPG); and approximately normal concentrations of NE [Kaler et al 1993]. Severe orthostatic hypotension has been reported [Christodoulou et al 1998]. However, individuals with Menkes disease and occipital horn syndrome can be differentiated from those with DBH deficiency by clinical findings. Infants with classic Menkes disease have loss of developmental milestones, hypotonia, seizures, failure to thrive at two to three months of age, and characteristic changes of the hair (short, sparse, coarse, twisted, often lightly pigmented). Death occurs between seven

months and 3.5 years of age. Occipital horn syndrome is characterized by "occipital horns," distinctive wedge-shaped calcifications at the sites of attachment of the trapezius muscle and the sternocleidomastoid muscle to the occipital bone. Affected individuals also have lax skin and joints, bladder diverticula, inguinal hernias, and vascular tortuosity. Intellect is normal or slightly reduced. Serum copper concentration and serum ceruloplasmin concentration are low. Molecular genetic testing of *ATP7A* detects mutations in more than 95% of affected individuals.

Transthyretin amyloidosis. Transthyretin amyloidosis is characterized by the neuropathic changes of peripheral neuropathy and autonomic neuropathy as well as non-neuropathic changes of nephropathy, cardiomyopathy, vitreous opacities, and CNS amyloidosis. The disease usually begins in the third or fourth decade, but the onset of symptoms may be later. The cardinal feature of transthyretin amyloid polyneuropathy is slowly progressive sensorimotor and autonomic neuropathy. Autonomic neuropathy may occur as the first clinical symptom of the disease; symptoms include orthostatic hypotension, constipation alternating with diarrhea, attacks of nausea and vomiting, delayed gastric emptying, sexual impotence, anhidrosis, and urinary retention or incontinence. Molecular genetic testing of the *TTR* gene detects more than 99% of disease-causing (amyloidogenic) mutations.

Shy-Drager syndrome (SDS) (central autonomic failure). Shy-Drager syndrome also includes extrapyramidal or cerebellar findings. A familial disorder with symptoms resembling those of Shy-Drager syndrome has been reported [Lewis 1964, Ilson et al 1982]. Little is known about the autonomic problems in these individuals. The age of onset in these individuals and in those with typical Shy-Drager is well into adulthood, in contrast to that observed in DBH deficiency.

Management

Evaluations at Initial Diagnosis to Establish the Extent of Disease

The extent of functional disturbance can be assessed by determining the length of time that the affected individual is able to stand (standing time) and by the medical history.

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 DL or L-threo-3,4-dihydroxyphenylserine (DOPS). DOPS is converted directly to NE by L-aromatic amino acid decarboxylase, thereby bypassing DBH (Figure 1). Administration of 100 to 500 mg DOPS 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 [Robertson et al 1991,van den Meiraker et al 1996]. DOPS administration restores DOPA to within the normal range and reduces DA somewhat, but plasma concentration of DA and its metabolites remains somewhat elevated [Biaggioni & Robertson 1987,Robertson et al 1990,Thompson et al 1995]. This favorable alteration in catecholamines alleviates the orthostatic hypotension and restores function to a near-normal level [Robertson 1997].

Individuals with DBH deficiency do not respond well to standard therapeutic approaches for autonomic failure.

- Fludrocortisone, at dosages of 0.1-0.4 mg daily, has been used with some benefit, but marked orthostatic hypotension still occurs.
- Indomethacin (50 mg 3x daily) has been of limited benefit in raising blood pressure.

- Some pressor response to phenylpropanolamine (25 mg) is observed, presumably owing to the denervation hypersensitivity of vascular α-adrenoceptors [Robertson et al 1990].
- Metyrosine, a tyrosine hydroxylase inhibitor, raises blood pressure and reduces urinary DA concentration in individuals with DBH deficiency. However, the dose normally used for pheochromocytoma has too much of a pressor effect and has some side effects, including sedation [Robertson et al 1990].

Ptosis can be corrected by surgery.

Sinus problems should be treated as needed.

Prevention of Primary Manifestations

DOPS can improve the orthostatic hypotension and symptoms, but these recur if treatment is stopped.

Prevention of Secondary Complications

The effect of DOPS on renal function is unknown.

Surveillance

Renal function should be assessed every five years and more often if a loss of function is evident.

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

Agents/Circumstances to Avoid

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

Testing of Relatives at Risk

Siblings should be tested only if symptomatic.

Therapies Under Investigation

Search Clinical Trials.gov 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, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Dopamine beta-hydroxylase deficiency is inherited in an autosomal recessive manner [Kim et al 2002].

Risk to Family Members

This section is written from the perspective that molecular genetic testing for this disorder is available on a research basis only and results should not be used for clinical purposes. This perspective may not apply to families using custom mutation analysis. —ED.

Parents of a proband

- The parents of an affected child are obligate heterozygotes and therefore carry one mutant allele.
- Heterozygotes (carriers) are asymptomatic.

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.
- Once an at-risk sib is known to be unaffected, the risk of his/her being a carrier is 2/3.
- Heterozygotes (carriers) are asymptomatic.

Offspring of a proband. The offspring of an individual with DBH deficiency are obligate heterozygotes (carriers) for a disease-causing mutation in the *DBH* gene.

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

Carrier Detection

- Carrier testing using molecular genetic techniques is not offered because it is not clinically available.
- Biochemical testing is not recommended for determining carrier status. There are many individuals without DBH deficiency who have extremely low plasma DBH activity. Parents of some of the individuals with DBH deficiency have normal autonomic function and normal catecholamine levels.

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk is before pregnancy.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant in situations in which molecular genetic testing is available on a research basis only. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

No laboratories offering molecular genetic testing for prenatal diagnosis of DBH deficiency are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the disease-causing mutations have been identified in an affected family member in a research or clinical laboratory. For laboratories offering custom prenatal testing, see 

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Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified in an affected family member in a research laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

TableA. Molecular Genetics of Dopamine Beta-Hydroxylase Deficiency

Gene Symbol	Chromosomal Locus	Protein Name
DBH	9q34	Dopamine beta-hydroxylase

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for Dopamine Beta-Hydroxylase Deficiency

223360	DOPAMINE BETA-HYDROXYLASE DEFICIENCY, CONGENITAL
609312	DOPAMINE BETA-HYDROXYLASE, PLASMA; DBH

Table C. Genomic Databases for Dopamine Beta-Hydroxylase Deficiency

Gene Symbol	Entrez Gene	HGMD
DBH	1621 (MIM No. 223360)	DBH

For a description of the genomic databases listed, click here.

Normal allelic variants: The *DBH* gene is approximately 23 kb and is composed of 12 exons [Kobayashi et al 1989]. Linkage of *DBH* to the ABO blood group locus on chromosome 9 has been demonstrated [Perry et al 1991]. Two kinds of cDNA (types A and B) encoding DBH have been isolated from a pheochromocytoma cDNA library [Kobayashi et al 1989]. The two types differ from each other by 300 bp in the 3' untranslated region.

Pathologic allelic variants: Molecular genetic analysis of the *DBH* gene of two unrelated individuals with DBH deficiency and their families shows that both individuals are heterozygotes for variants affecting expression of DBH protein. Both individuals are heterozygous for IVS1 + 2T↓C. Patient 1 also has a missense mutation in exon 2 (D100E), whereas Patient 2 carries two missense mutations, V87M in exon 1 and D331N in exon 6, all in *trans* to the IVS1 + 2T↓C. Transfection of plasmids containing *DBH* gene fragment from either the normal or mutant IVS1 + 2T↓C allele into COS-7 cells revealed that the mutant construct generated an abnormal transcript consistent with the use of a cryptic donor splice site (GT) starting at IVS1 + 506 [Kim et al 2002]. The aberrantly spliced product contains coding sequence for an altered amino acid sequence followed by a premature stop codon. However, there is evidence, at least in vitro, that the mutation allows some residual expression of properly spliced DBH message. It is possible that a specific haplotype in these individuals, rather than a single variant, may be necessary to produce the DBH deficiency phenotype. Both individuals have copies of three other variants residing on noncoding sequences (-1021 C↓T, IVS3 + 8C↓T, and IVS10 + 415G↓A) in the same haplotype containing IVS1 + 2T↓C. Since homozygosity at the T allele of -1021 C↓T strongly associates with very low plasma DBH activity [Zabetian et al 2001, 2003], this is an attractive candidate.

Among the missense mutations, D100E and D331N are more likely to be pathogenic because they occur at highly conserved positions [Kim et al 2002]. It is not known how these mutations affect splicing or the activity or stability of the DBH protein.

The IVS1 + 2T↓C mutation and three additional mutations in exons 3, 4 and 11 have been identified in four families with DBH deficiency in the Netherlands [Deinum et al 2004]. The affected individuals were a IVS1 + 2T↓C homozygote, a IVS1 + 2T↓C/c.575delA compound heterozygote, a G764T homozygote, and a IVS1 + 2T↓C/A1625G compound heterozygote.

Table 3. Mutations observed in DBH

Nucleotide Change	Location	Amino Acid Change	Mutation Type
C-1021T	5' flanking		Noncoding
G259A	Exon 1	V87M	Missense
IVS1+2T↓C	Intron 1		Noncoding
C300A	Exon 2	D100E	Missense
c.575delA	Exon 3		Frameshift
IVS3+8C↓T	Intron 3		Noncoding
G764T	Exon 4	C255F	Missence
G991A	Exon 6	D331N	Missense
IVS10+415A0↓G	Intron 10		Noncoding
A1625G	Exon 11	Y542C	Missence

Normal gene product: 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 exists in membrane (of neuronal vesicles) and soluble (intravesicular) forms [Dhawan et al 1987], depending on the presence or absence, respectively, of a signal peptide [Lewis & Asnani 1992]. The tetrameric glycoprotein has a molecular weight of approximately 290,000 daltons. The four subunits are linked by disulfide bridges into two dimers, which are joined to each other by non-covalent bonds. There are two to seven moles of copper per mole of DBH, and the copper is essential for enzyme activity [Robertson et al 1990]. DBH also requires molecular oxygen and ascorbic acid or some other electron source for enzyme activity.

Linkage and association studies have established the *DBH* locus as the major gene controlling DBH levels in body fluids [Wilson et al 1988, Zabetian et al 2001].

Tenfold differences in serum DBH concentrations are commonly reported, with the *DBH* gene being the major contributor to the variability in activity levels [Weinshilboum & Axelrod 1971]. Heritability of serum DBH concentration is estimated to be 0.98. Oligogenic inheritance accounts for almost all of the large individual variation in serum DBH concentration found in the human population [Weinshilboum 1978, Elston et al 1979, Goldin et al 1982, Vuchetich et al 1991]. Several polymorphisms in the *DBH* gene that correlate with the level of DBH activity have been identified. The most compelling evidence relates a -1021C↓T polymorphism in the 5' flanking region of the gene to low DBH activity [Zabetian et al 2001]. An *Msp*I polymorphic site in intron 9 [Wei et al 1996], a 19-bp insertion/deletion polymorphism in the promoter region [Cubells et al 1998, Robinson et al 2001], a 444 g/a polymorphism in the 3' end of exon 2 [Cubells et al 1998], and a GT microsatellite repeat in the 5' promoter region [Wei et al 1997, Cubells et al 1998] have also been associated with DBH activity.

Some apparently normal individuals have consistent levels of very low DBH activity [Weinshilboum et al 1975, Zabetian et al 2001]. In European Americans, homozygosity at the T allele of -1021C↓T predicted the very low DBH activity trait, and activity values in heterozygotes formed an intermediate distribution, indicating codominant inheritance. It is

noteworthy that while a handful of these individuals with low plasma DBH have the syndrome of complete DBH deficiency, most do not. Although their detailed phenotype remains unexplored, they do have nearly normal plasma concentrations of norepinephrine and epinephrine [Weinshilboum et al 1975] and do not have orthostatic symptoms.

Abnormal gene product: The IVS1+2T↓C variant results in an aberrantly spliced product containing a premature stop codon. The mechanism by which the missense mutations in exons 1, 2, and 6 produce a loss of DBH function is unknown.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

SDS/MSA Support Group
PO Box 279
Coupland, TX 78615

National Dysautonomia Research Foundation
PO Box 301
Red Wing, MN 55066-2108
Phone: 651-267-0525
Fax: 651-267-0524
Email: webmaster@ndrf.org
www.ndrf.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Chapter Notes

Revision History

- 16 December 2005 (me) Comprehensive update posted to live Web site
- 4 September 2003 (me) Review posted to live Web site
- 27 June 2003 (dr) Original submission

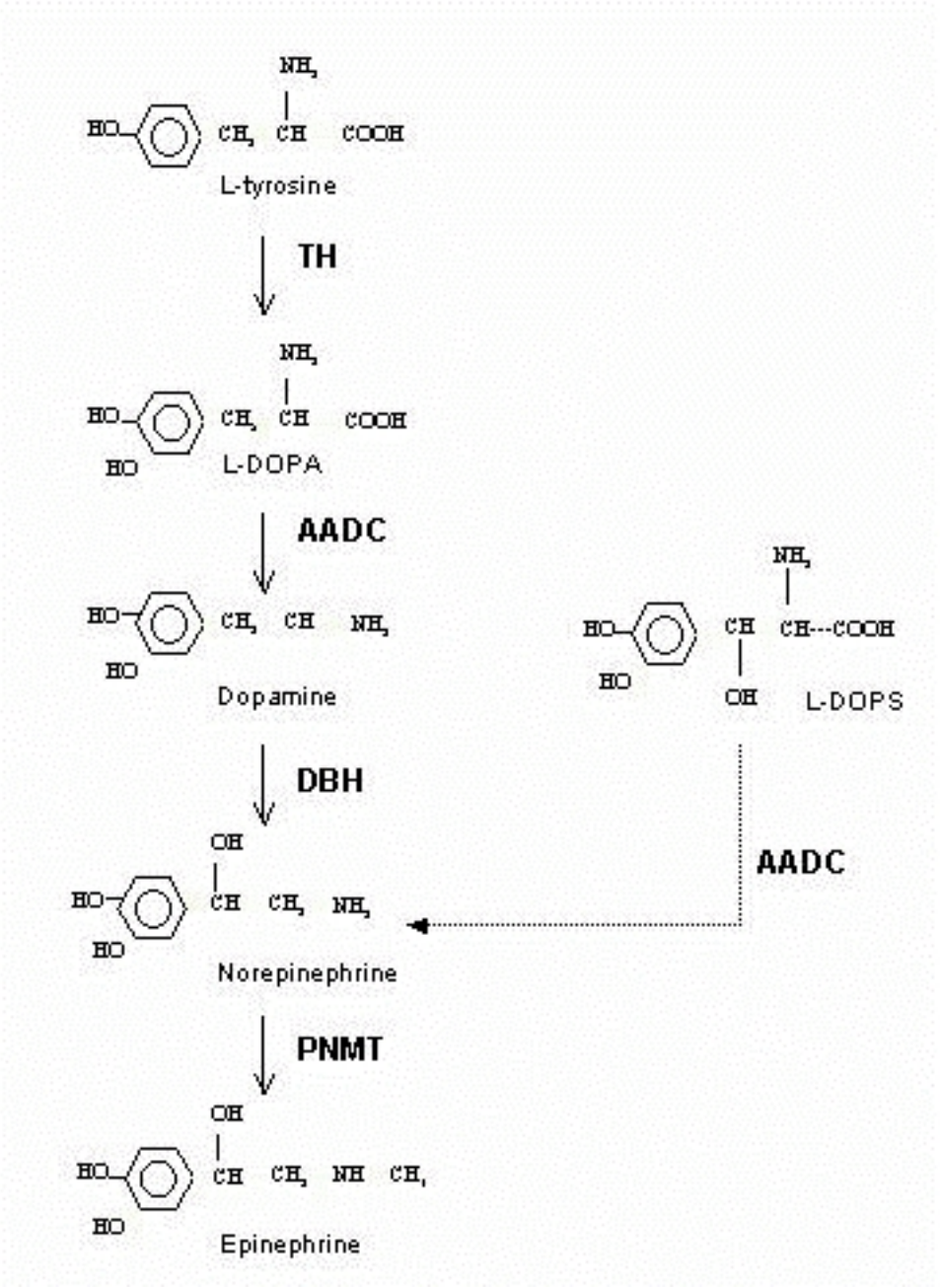

Figure 1. Synthesis of norepinephrine from dopamine or L-DOPS