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Sepiapterin Reductase Deficiency

Synonyms: Dopa-Responsive Hypersomnia, DYT-SPR, SPR Deficiency

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Summary

Clinical characteristics

The phenotypic spectrum of sepiapterin reductase deficiency (SRD), which ranges from significant motor and cognitive deficits to only minimal findings, has not been completely elucidated. Clinical features in the majority of affected individuals include motor and speech delay, axial hypotonia, dystonia, weakness, and oculogyric crises; symptoms show diurnal fluctuation and sleep benefit. Other common features include parkinsonian signs (tremor, bradykinesia, masked facies, rigidity), limb hypertonia, hyperreflexia, intellectual disability, psychiatric and/or behavioral abnormalities, autonomic dysfunction, and sleep disturbances (hypersomnolence, difficulty initiating or maintaining sleep, and drowsiness). Most affected individuals have nonspecific features in infancy including developmental delays and axial hypotonia; other features develop over time.

Diagnosis/testing

The diagnosis of sepiapterin reductase deficiency is established in a proband by detection of biallelic pathogenic variants in *SPR* on molecular genetic testing or characteristic abnormalities of CSF neurotransmitters and pterins.

Management

Treatment of manifestations: L-dopa in combination with carbidopa (or another peripheral decarboxylase inhibitor) is the main therapy used to correct CNS dopamine deficiency; 5-hydroxytryptophan (5-HTP), also in combination with carbidopa, has shown additional clinical benefit in some. When L-dopa/5HTP/carbidopa are not tolerated or sufficiently effective some individuals may benefit from use of other agents such as monoamine oxidase inhibitors, serotonin reuptake inhibitors, melatonin, dopamine agonists, anticholinergics, and methylphenidate. These medications most consistently correct motor abnormalities; however, in some individuals cognitive manifestations remain more refractory.

Prevention of secondary complications: Physical, occupational, and speech therapy may improve or maintain motor function.

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Surveillance: Data are insufficient to determine how frequently CSF levels of dopamine and serotonin metabolites should be evaluated and whether these levels should be used to adjust medication doses.

Agents/circumstances to avoid: Although adverse events with specific agents have not been reported in persons with SRD, the following should be avoided on a theoretic basis: sulfa drugs, methotrexate, nitrous oxide, neuroleptics, and other dopamine antagonists (e.g., metoclopramide).

Evaluation of relatives at risk: Although no data on outcomes are available, it is appropriate to use molecular genetic testing for the *SPR* pathogenic variants identified in the proband and/or analysis of CSF neurotransmitter metabolites and pterins to clarify the genetic status of apparently asymptomatic older and younger sibs of an affected individual in order to identify as soon as possible those who would benefit from early initiation of treatment to correct CNS dopamine and serotonin deficiency.

Genetic counseling

SRD 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 and prenatal testing for pregnancies at increased risk are possible if the *SPR* pathogenic variants in the family are known.

Diagnosis

No formal diagnostic criteria for sepiapterin reductase deficiency (SRD) have been published. A diagnostic algorithm is presented in a recent review [Friedman et al 2012].

Suggestive Findings

Sepiapterin reductase deficiency (SRD) should be suspected in individuals with characteristic clinical findings. The phenotypic spectrum is broad and suggestive signs are often nonspecific.

Core clinical features present in more than 65% of affected individuals:

- Motor and speech delay
- Axial hypotonia
- Dystonia
- Weakness
- Oculogyric crises
- Diurnal fluctuation and symptom improvement with sleep

Other common features:

- Intellectual disability
- Limb hypertonia and hyperreflexia
- Parkinsonian signs (tremor, bradykinesia, masked facies, rigidity)
- Psychiatric and/or behavioral abnormalities
- Sleep disturbances (hypersomnolence, difficulty initiating or maintaining sleep, drowsiness)
- Autonomic dysfunction (excessive sweating, ptosis, nasal congestion, temperature instability)

Individuals with any of the following three broad sets of findings should be considered to possibly have SRD [Friedman et al 2012]:

- Developmental delays with axial hypotonia
- Unexplained "cerebral palsy," especially if dystonia is present

- An L-dopa-responsive motor disorder that may include dystonia. L-dopa responsiveness is evaluated in the following manner: L-dopa (in combination with 10%-25% carbidopa) may be introduced at 1 mg/kg/day and advanced slowly by 1 mg/kg/day over days/weeks monitoring for symptomatic improvement and side effects as the dose is raised. Although data are insufficient to provide precise dosing guidelines, benefit is most often achieved at low dose and is dramatic and rapid (hours to days). Because the response may be delayed or require a high dose (≥10 mg/kg/d) (as has been observed in cyclohydrolase 1-deficient dopa-responsive dystonia [DYT-GCH1]), the dose should be increased and maintained for two to four weeks – barring side effects – to fully assess efficacy of L-dopa [Author, personal observation].

Note: Given the broad range of neurologic manifestations (from asymptomatic to severe global developmental delay) and dramatic response to L-dopa, clinicians should maintain a high index of suspicion for SRD or other monoamine neurotransmitter disorders (see Differential Diagnosis) in individuals with unexplained neurologic dysfunction.

Establishing the Diagnosis

The diagnosis of sepiapterin reductase deficiency is established in a proband by detection of biallelic pathogenic variants in *SPR* on molecular genetic testing (see Table 1) or characteristic abnormalities of CSF neurotransmitters and pterins.

Note: (1) While analysis of either sepiapterin reductase enzyme activity in fibroblasts or pterin levels in cytokine stimulated fibroblasts could be considered [Bonafé et al 2001a], neither test is widely available or commonly used. (2) A phenylalanine load test [Hyland et al 1997], which is not commonly used, could be considered when molecular testing and analysis of CSF neurotransmitters are not available. While an abnormal phenylalanine load is suggestive, it is not diagnostic of SRD, as abnormal results are observed in other BH_4 deficiencies (including DYT-GCH1).

Molecular genetic testing approaches may include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis is performed first, followed by consideration of gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found in an individual with characteristic clinical findings and/or abnormalities of CSF metabolites. Note: To date no *SPR* deletions or duplications requiring gene-targeted deletion/duplication analysis have been reported.
- **A multigene panel** that includes *SPR* and other genes of interest (see Differential Diagnosis) may also be considered. 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*; thus, clinicians need to determine which multigene panel 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. (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.

Table 1. Molecular Genetic Testing Used in Sepiapterin Reductase Deficiency

Gene [1]	Method	Proportion of Probands with Pathogenic Variants [2] Detectable by Method
SPR	Sequence analysis [3]	All sequence variants reported to date [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. A total of approximately 50 probands have been reported to date [Bonafé et al 2001a, Bonafé et al 2001b, Steinberger et al 2004, Neville et al 2005, Abeling et al 2006, Echenne et al 2006, Friedman et al 2006, Verbeek et al 2008, Clot et al 2009, Kusmierska et al 2009, Leu-Semenescu et al 2010, Mazzuca et al 2010, Wali et al 2010, Arrabal et al 2011, Bainbridge et al 2011, Dill et al 2012, Friedman et al 2012, Lohmann et al 2012, Thibert et al 2012, Leuzzi et al 2013, Koht et al 2014].
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques including quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and gene-targeted microarray designed to detect single-exon deletions or duplications.
6. A single report of deletion involving *SPR* is listed in ClinVar. In addition to *SPR*, this deletion involves *EMX1* and *SXN5*. No clinical details are provided and thus no conclusions can be drawn regarding the impact of deletion of *SPR*.

Characteristic CSF abnormalities of neurotransmitters and pterins include:

- Decreased levels of homovanillic acid (HVA) and 5-hyroxyindolacetic acid (5-HIAA);
- Normal to slightly increased levels of neopterin;
- Increased levels of total biopterin, dihydrobiopterin (BH2), and sepiapterin [Bonafé et al 2001b, Friedman et al 2012, Bonafé 2006].

  Note: (1) CSF should be collected using standardized protocols and analyzed by a laboratory with appropriate age-related reference ranges [Hyland et al 1993, Bräutigam et al 2002]. (2) Normal values vary by lab and by age.

Clinical Characteristics

Clinical Description

The phenotypic spectrum of sepiapterin reductase deficiency (SRD) has not been completely elucidated due to the small number of affected individuals reported to date, lack of systematic diagnostic evaluation and long-term follow up, and the absence of data on the prevalence and natural history of findings in untreated individuals. Of particular note, severity varies: some individuals manifest significant motor and cognitive deficits and others only minimal findings. Those with minimal findings may present at an older age or be identified because of the diagnosis of SRD in a sib [Arrabal et al 2011, Friedman et al 2012].

Clinical features in 38 individuals with SRD are summarized by Friedman et al [2012]. A few affected individuals not included in this review and described elsewhere have additional features [Steinberger et al 2004, Clot et al 2009, Lohmann et al 2012, Leuzzi et al 2013, Koht et al 2014].

Clinical features present in more than 65% of affected individuals include motor and speech delay, axial hypotonia, dystonia, weakness, oculogyric crises, and diurnal fluctuation of symptoms with sleep benefit. Other common features include parkinsonian signs (tremor, bradykinesia, masked facies, rigidity), limb hypertonia, hyperreflexia, intellectual disability, psychiatric and/or behavioral abnormalities, autonomic dysfunction, and

sleep disturbances (hypersomnolence, drowsiness, difficulty initiating or maintaining sleep related to alteration of the sleep-wake circadian rhythm).

Most affected individuals have nonspecific features in infancy including developmental delays and axial hypotonia. In the next few years other features that may develop include limb hypertonia, hyperreflexia, dystonia, and more apparent diurnal fluctuation and sleep disturbance.

In some instances, dystonia may present as paroxysmal stiffening of limbs and/or trunk with gaze deviation and tremor of the tongue, limbs, and/ or head [Dill et al 2012, Leuzzi et al 2013].

Numerous rarely reported findings overlap with those typical of other disorders of monoamine neurotransmitter biosynthesis (see Differential Diagnosis).

Seizures (mostly febrile) occasionally occur, though frequency may be over-reported as oculogyric crises and paroxysmal stiffening episodes may be confused with seizures.

A few reports note low birth weight [Bonafé et al 2001b, Leuzzi et al 2013], poor somatic growth [Lohmann et al 2012, Leuzzi et al 2013], and/or microcephaly [Blau et al 1998, Bonafé et al 2001b, Leuzzi et al 2013].

During later childhood, abnormalities in behavior and cognition become more apparent. These may be under-reported due to the prominence of the motor features.

While many affected individuals have intellectual disability, others with mild learning disabilities or normal cognition have been reported.

Psychiatric and/or behavioral findings most commonly include inattention, irritability, and anxiety; however, a wide range of symptoms may occur. It is hypothesized (though not yet proven) that early treatment may mitigate cognitive or psychiatric/behavioral abnormalities.

Genotype-Phenotype Correlations

Although several possible genotype-phenotype correlations have been suggested in individuals with biallelic *SPR* pathogenic variants, due to the small number of affected individuals these conclusions remain uncertain [Arrabal et al 2011, Friedman et al 2012]. Phenotypic variability is broad even among family members with identical pathogenic variants.

One individual heterozygous for a *SPR* pathogenic variant in the 5' untranslated region with a mild form of L-dopa-responsive dystonia and reduced SR activity in fibroblasts has been reported [Steinberger et al 2004].

Nomenclature

Two individuals originally reported as having "central" dihydropteridine reductase (DHPR) deficiency [Blau et al 1998, Blau et al 1999] were later diagnosed with SRD [Bonafé et al 2001b].

Prevalence

No data are available on the prevalence of SRD.

A total of approximately 50 probands have been reported to date [Bonafé et al 2001a, Bonafé et al 2001b, Steinberger et al 2004, Neville et al 2005, Abeling et al 2006, Echenne et al 2006, Friedman et al 2006, Verbeek et al 2008, Clot et al 2009, Kusmierska et al 2009, Leu-Semenescu et al 2010, Mazzuca et al 2010, Wali et al 2010, Arrabal et al 2011, Bainbridge et al 2011, Dill et al 2012, Friedman et al 2012, Lohmann et al 2012, Thibert et al 2012, Leuzzi et al 2013, Koht et al 2014].

SRD may be under-recognized due to lack of awareness.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *SPR*.

Differential Diagnosis

L-dopa-responsive motor disorders

- **Monoamine neurotransmitter disorders.** Defects in the synthesis of the monoamine neurotransmitters dopamine, serotonin, epinephrine, and norepinephrine result in a heterogeneous group of disorders. Neurologic manifestations of several of these disorders may respond to treatment with L-dopa [Nygaard et al 1991, Furukawa & Kish 1999] including SRD and the following:
  - **DYT-GCH1/GTP cyclohydrolase 1-deficient dopa-responsive dystonia** is characterized by childhood-onset dystonia and a dramatic and sustained response to low doses of oral levodopa. The average age of onset is approximately six years. This disorder typically presents with gait disturbance caused by foot dystonia, later development of parkinsonism, and diurnal fluctuation of symptoms. Initial symptoms are often gait difficulties attributable to flexion-inversion (equinovarus posture) of the foot. Occasionally, initial symptoms are arm dystonia, postural tremor of the hand, or slowness of movements. Brisk deep-tendon reflexes in the legs, ankle clonus, and/or the striatal toe (dystonic extension of the big toe) are present in many affected individuals. In general, gradual progression to generalized dystonia is observed. Intellectual, cerebellar, sensory, and autonomic disturbances do not occur. Manifestations of sepiapterin reductase deficiency typically begin earlier than those in DYT-GCH1/GTP cyclohydrolase 1-deficient dopa-responsive dystonia, although individuals with mild findings of SRD may mimic this condition.
  - **DYT-TH/tyrosine hydroxylase deficiency** is associated with a broad phenotypic spectrum that mirrors that observed in SRD. Based on severity of symptoms/signs as well as responsiveness to levodopa therapy, clinical phenotypes caused by *TH* pathogenic variants are divided into (1) TH-deficient dopa-responsive dystonia (DRD: the mild form of TH deficiency [DYT5b]), (2) TH-deficient infantile parkinsonism with motor delay (the severe form), and (3) TH-deficient progressive infantile encephalopathy (the very severe form). In contrast to SRD, individuals with DYT-TH do not have abnormalities of pterin or serotonin metabolism, though clinically these distinctions are not always apparent.
  - **Aromatic L-amino acid decarboxylase (AADC) deficiency** is a disorder of biogenic amine metabolism that leads to combined deficiency of serotonin and all catecholamines. Similar to SRD, symptoms begin in infancy and are characterized by developmental delay, axial hypotonia with limb hypertonia, dystonia and parkinsonian features including bradykinesia and rigidity. Chorea and oculogyric crises may be present. Autonomic and endocrinologic abnormalities also occur. Diurnal fluctuation may be present though is generally less pronounced than in SRD. A rare subset of patients show therapeutic benefit with L-dopa [Chang et al, 2004] or with other dopaminergic agents (dopamine agonists, methylphenydate, MAO inhibitors) that do not require AADC to be active.
- **Other.** Improvement with L-dopa may also occur in juvenile Parkinson disease (see below) or may be a nonspecific feature of several motor disorders.

Dystonia may be a prominent, though often late and not universal feature of SRD [Friedman et al 2012]. For a detailed differential for dystonia, see Dystonia Overview.

Cerebral palsy. Sepiapterin reductase deficiency (SRD) often presents with nonspecific symptoms including global delay with hypotonia or a nonspecific gait disorder, often with cognitive impairment. Hyperreflexia and/or striatal toe (simulating a Babinski reflex but without fanning of the toes) may be present. Oculogyric

crises, if recognized, are a frequent clue to dopamine deficiency syndrome; however, as other neurologic manifestations are nonspecific, affected individuals may be misdiagnosed with cerebral palsy or an undefined L-dopa-responsive motor disorder [Friedman et al 2012]. These features as well as the varied and nonspecific presentation may lead to a misdiagnosis of cerebral palsy [Friedman et al 2012]. The differential for global delay and cerebral palsy are broad and beyond the scope of this review.

A suggested algorithm for evaluation of patients with global delay with hypotonia, dystonia, or L-dopa-responsive motor disorder may be found in Friedman et al [2012].

Juvenile Parkinson disease. Parkinsonian signs are frequent and may suggest juvenile Parkinson disease, most commonly caused by mutation of *PRKN*, *PINK1*, *DJ1*, or *ATP13A2*. Typically manifestations in SRD begin at an earlier age than juvenile Parkinson disease. Differentiation between SRD and juvenile Parkinson disease is critical for prognostication and therapeutic management: Individuals with SRD may derive sustained benefit from L-dopa whereas those with juvenile Parkinson disease will develop complications with L-dopa therapy (and although it is controversial, dopamine agonists should be considered instead).

Disorders of biopterin metabolism. Tetrahydrobiopterin (BH_4) deficiencies are caused by biallelic pathogenic variants in one of the genes involving biosynthesis or recycling of BH_4, a cofactor in the phenylalanine, tyrosine, and tryptophan hydroxylation reaction. These genes and disorders are summarized in Table 2.

Table 2. Tetrahydrobiopterin (BH_4) Deficiencies

Gene	Disorder	OMIM
GCH1	GTP cyclohydrolase I deficiency	233910
PTS	6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency	261640
PCBD1	Pterin-4a-alpha-carbinolamine dehydratase deficiency	264070
QDPR	Dihydropteridine reductase (DHPR) deficiency	261630

Other. Symptoms, which result from impaired phenylalanine homeostasis and serotonin and catecholamine biosynthesis, overlap significantly with SRD. Unlike SRD, these conditions typically (though not always) present with hyperphenylalaninemia detected on newborn screening. More information on the BH_4 deficiencies can be found at www.biopku.org.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with sepiapterin reductase deficiency (SRD), the following evaluations are recommended:

- Consultation with a neurologist
- Physical therapy, occupational therapy, and speech therapy evaluations depending on severity of manifestations
- Neuropsychological evaluation depending on the severity of manifestations
- Social services consultation depending on the severity of manifestations
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Therapy is aimed at correcting central nervous system (CNS) neurotransmitter deficits.

Recommended treatments are based on the few reported cases in the literature and extrapolation from strategies employed in treatment of other neurotransmitter disorders.

While the medications discussed below reduce manifestations of SRD, response can range from complete resolution to partial improvement. These medications most consistently correct motor abnormalities while in some cognitive manifestations remain more refractory.

Often, medications must be prescribed "off-label" without established pediatric dose ranges [Friedman et al 2012]:

- **L-dopa** (0.1-16 mg/kg/day) in combination with 10%-25% carbidopa (or another peripheral decarboxylase inhibitor) is the main therapy to correct CNS dopamine deficiency. Optimal therapeutic level is determined by clinical response.

  Note: (1) Dose-related dyskinesias may occur [Abeling et al 2006, Neville 2007, Arrabal et al 2011, Friedman et al 2012]; they can be eliminated in most instances with reduced dosage or addition of a dopamine agonist to reduce fluctuations in dopaminergic stimulation [Lohmann et al 2012]. (2) Gastrointestinal side effects such as nausea may be reduced by increasing the proportion of administered carbidopa. (3) Although not reported, it is theoretically possible that individuals with SRD receiving high-dose L-dopa could develop cerebral folate deficiency and require supplementation with folinic acid (as has been observed in aromatic L-amino acid decarboxylase deficiency [Brun et al 2010]).

- **5-hydroxytryptophan** (5-HTP) (1-6 mg/kg/day) also in combination with **carbidopa** to correct CNS serotonin deficiency has shown additional clinical benefit in some.

- **Tetrahydrobiopterin** (BH_4; sapropterin dihydrocloride) may in theory be of benefit, although none was reported in four patients treated for only a short time [Friedman et al 2006, Friedman et al 2012]. Note that it is difficult to achieve adequate CNS levels of BH_4 due to limited transport across the blood brain barrier.

- **Other agents** used when L-dopa/5HTP/carbidopa are not tolerated or sufficiently effective which have shown benefit in single or small numbers of patients include:
  - Monoamine oxidase inhibitors (selegeline)
  - Serotonin reuptake inhibitors (sertraline)
  - Melatonin
  - Dopamine agonists (bromocriptine, pramipexole)
  - Anticholinergics
  - Methylphenidate

Prevention of Secondary Complications

Physical, occupational, and speech therapy may improve or maintain function.

Surveillance

Data are insufficient to determine how frequently CSF levels of dopamine and serotonin metabolites should be evaluated and whether these levels should be used to adjust medication doses. Practices range from at least annual assessment of CNS neurotransmitter metabolites to adjustment of neurotransmitter precursor therapy based solely on clinical manifestations.

Because clinical manifestations are more difficult to assess in children, it would seem prudent to evaluate CSF neurotransmitter metabolites two to four times yearly in children younger than age two years and at least yearly in children younger than age ten years.

Note: Plasma prolactin levels may inversely correlate with CNS dopamine levels but are neither a sensitive nor specific marker [Leuzzi et al 2002, Furukawa et al 2003, Concolino et al 2008].

Agents/Circumstances to Avoid

Although adverse events with specific agents have not been reported in persons with SRD, several should be avoided on a theoretic basis including:

- Sulfa drugs, which impair BH_4 biosynthesis by inhibiting sepiapterin reductase [Haruki et al 2013]
- Methotrexate, which inhibits dihydropteridine reductase, an enzyme involved in BH_4 regeneration [Woody & Brewster 1990]
- Nitrous oxide, which may impair folate metabolism [Wyatt & Gill 1999]
- Neuroleptics and other dopamine antagonists (e.g., metoclopramide)

Evaluation of Relatives at Risk

While no data on outcomes are available, it is appropriate to use molecular genetic testing for the *SPR* pathogenic variants identified in the proband and/or analysis of CSF neurotransmitter metabolites and pterins to clarify the genetic status of apparently asymptomatic older and younger sibs of an affected individual in order to identify as soon as possible those who would benefit from early initiation of treatment to correct CNS dopamine and serotonin deficiency.

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

Pregnancy Management

No pregnancies have been reported to date in women with SRD.

Based on reports that suggest that L-dopa may be advantageous during pregnancy in women with GTP cyclohydrolase 1-deficient dopa-responsive dystonia (DYT-GCH1), it would seem prudent for women with SRD to continue L-dopa therapy during pregnancy [Trender-Gerhard et al 2009, Watanabe & Matsubara 2012].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. 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

Sepiapterin reductase 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 *SPR* pathogenic variant).
- Heterozygotes are generally asymptomatic and are not at risk of developing the disorder. Current data are insufficient to associate clinical manifestations with heterozygosity for an *SPR* pathogenic variant; however, several anecdotal reports have raised this possibility, including the following:
  - An individual with a heterozygous *SPR* pathogenic variant in the 5' untranslated region and a mild L-dopa-responsive dystonia phenotype [Steinberger et al 2004]
  - Fibromyalgia which segregated with carrier status in one small pedigree [Bainbridge et al 2011]
  - The presence of other manifestations including dystonia and parkinsonism in relatives (who had not undergone molecular genetic testing) of individuals with SRD [Friedman et al 2006, Lohmann et al 2012]

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 the sib being a carrier of a *SPR* pathogenic variant is 2/3.
- Heterozygotes (carriers) are asymptomatic and are usually not at risk of developing the disorder (see **Parents of a proband**).

Offspring of a proband. Individuals with sepiapterin reductase deficiency have not been reported to reproduce; however, only a few identified individuals are of childbearing age.

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

Carrier (Heterozygote) Detection

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

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, 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 have or are at risk of having one or more *SPR* pathogenic variants.

Prenatal Testing and Preimplantation Genetic Testing

Once the *SPR* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible. Because individuals with biallelic *SPR* pathogenic variants may be asymptomatic, predicting the phenotype based on results of prenatal testing may not be reliable.

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.

- **Dystonia Society**
  89 Albert Embankment
  3rd Floor
  London SE1 7TP
  United Kingdom
  Phone: 0845 458 6211; 0845 458 6322 (Helpline)
  Fax: 0845 458 6311
  Email: support@dystonia.org.uk
  www.dystonia.org.uk
- **Dystonia Medical Research Foundation**
  Phone: 312-755-0198; 800-377-DYST (3978)
  Fax: 312-803-0138
  Email: dystonia@dystonia-foundation.org
  dystonia-foundation.org
- **Metabolic Support UK**
  United Kingdom
  Phone: 0845 241 2173
  www.metabolicsupportuk.org
- **Global Dystonia Registry**
  www.globaldystoniaregistry.org
- **International Working Group on Neurotransmitter Related Disorders (iNTD) Patient Registry**
  About iNTD

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. Sepiapterin Reductase Deficiency: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
SPR	2p13.2	Sepiapterin reductase	BIOMDBdb : Database of Mutations Causing BH4 Deficiencies and other PND (SPR) SPR database	SPR	SPR

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 Sepiapterin Reductase Deficiency (View All in OMIM)

182125	SEPIAPTERIN REDUCTASE; SPR
612716	DYSTONIA, DOPA-RESPONSIVE, DUE TO SEPIAPTERIN REDUCTASE DEFICIENCY

Gene structure. *SPR* spans 4.8 kb and comprises three exons. There is no evidence for alternative splicing variants [Bonafé 2006]. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Seventeen pathogenic variants have been reported in *SPR* [Friedman et al 2012, Koht et al 2014]. Pathogenic variants are homozygous or compound heterozygous except for a single individual heterozygous for a *SPR* pathogenic variant in the 5' untranslated region with a mild form of L-dopa-responsive dystonia and reduced sepiapterin reductase activity in fibroblasts [Steinberger et al 2004]. The authors did not report whether gene-targeted deletion/duplication analysis was performed to evaluate for deletion on the other allele.

Known pathogenic variants are missense, nonsense, and frameshift. Pathogenic variants have been found in all three exons, the 5' untranslated region, and the intronic region in the splicing acceptor consensus sequence preceding exon 3 [Bonafé 2006, Friedman et al 2012, Koht et al 2014].

Homozygosity for the intronic variant c.596-2A>G was the most common genotype found in a cohort of affected individuals from Malta, suggesting a possible founder effect [Neville et al 2005, Bonafé 2006, Friedman et al 2012].

Table 3. *SPR* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.596-2A>G	Abnormal splicing	NM_003124.4 NP_003115.1

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.

Normal gene product. *SPR* cDNA encodes a monomer of 261 amino acids. Sepiapterin reductase is a homodimer with a predicted molecular mass of 56 kd [Bonafé 2006].

Abnormal gene product. Biallelic pathogenic variants in *SPR* result in dysfunctional SR protein, decreased synthesis of BH_4, and accumulation of BH_2 and sepiapterin in the central nervous system. Alternative pathways in the liver and other tissues compensate for lack of sepiapterin reductase and account for normal phenylalanine levels and lack of neurotransmitter or pterin abnormalities in the periphery [Bonafé 2006].

Symptoms arise primarily from impaired central nervous system serotonin and catecholamine production. Reduced neurotransmitter production is the result of both reduced activity of tyrosine and tryptophan hydroxylases due to reduced levels of BH_4 cofactor as well as direct inhibition of these hydroxylases by accumulated BH_2 [Bonafé 2006]. In addition, altered BH_4:BH_2 ratios may uncouple nitric oxide synthase (an enzyme dependent on the BH_4 cofactor), and increase free radical production [Blau et al 2001, Bonafé et al 2001b]. The effect of these perturbations on the clinical picture is unclear.

Neurotransmitter deficiency is primarily responsible for clinical manifestations; however, several lines of evidence suggest that sepiapterin reductase deficiency may also affect maturation of the dopaminergic system as well as stabilization of the protein tyrosine hydroxylase [Okuno & Fujisawa1985, Takazawa et al 2008, Homma et al 2011, Homma et al 2013].

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Chapter Notes

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