SPR Gene

Subjects: Genetics & Heredity
Contributor: Karina Chen

sepiapterin reductase

Keywords: genes

1. Normal Function

The *SPR* gene provides instructions for making the sepiapterin reductase enzyme. This enzyme is involved in the last of three steps in the production of a molecule called tetrahydrobiopterin (BH4). Other enzymes help carry out the first and second steps in this process. The sepiapterin reductase enzyme converts a molecule called 6-pyruvoyl-tetrahydropterin to tetrahydrobiopterin. Tetrahydrobiopterin helps process several building blocks of proteins (amino acids), and is involved in the production of chemicals called neurotransmitters, which transmit signals between nerve cells in the brain. Specifically, tetrahydrobiopterin is involved in the production of two neurotransmitters called dopamine and serotonin. Among their many functions, dopamine transmits signals within the brain to produce smooth physical movements, and serotonin regulates mood, emotion, sleep, and appetite.

2. Health Conditions Related to Genetic Changes

2.1. Dopa-responsive dystonia

At least four mutations in the *SPR* gene have been found to cause dopa-responsive dystonia. This condition is characterized by a pattern of involuntary muscle contractions (dystonia), tremors, and other uncontrolled movements and usually responds to treatment with a medication called L-Dopa. Dopa-responsive dystonia can be caused by mutations in one copy or both copies of the *SPR* gene in each cell. These mutations lead to the production of a sepiapterin reductase enzyme with reduced or absent function. In most parts of the body, there are alternate pathways that do not use sepiapterin reductase for the production of tetrahydrobiopterin, but these processes do not occur in the brain. Therefore, people with sepiapterin reductase deficiency have a lack of tetrahydrobiopterin in the brain, which affects the production of dopamine and serotonin. The lack of these two neurotransmitters causes the movement problems and other characteristic features of dopa-responsive dystonia.

2.2. Sepiapterin reductase deficiency

More than a dozen mutations in the *SPR* gene have been found to cause sepiapterin reductase deficiency, a condition characterized by progressive problems with movement. Sepiapterin reductase deficiency results when two copies of the *SPR* gene are mutated in each cell. These mutations include changes that replace amino acids; alter the way the gene's instructions are pieced together to produce the enzyme; or result in a shortened, nonfunctional enzyme. All these mutations lead to the production of enzymes with reduced or no function. A common mutation in affected individuals that replaces the amino acid arginine with the amino acid glycine at position 150 in the enzyme (written as Arg150Gly or R150G) prevents the production of any sepiapterin reductase.

SPR gene mutations disrupt the production of sepiapterin reductase. Most *SPR* gene mutations result in an enzyme with little or no function. A nonfunctional sepiapterin reductase leads to a lack of tetrahydrobiopterin and a decrease in the production of dopamine and serotonin in the brain. The shortage of these neurotransmitters causes the movement abnormalities and other features of sepiapterin reductase deficiency.

Sepiapterin reductase deficiency is more severe than dopa-responsive dystonia likely because both copies of the *SPR* gene are mutated, which leads to a more severe enzyme shortage than in dopa-responsive dystonia, in which only one copy of the gene has a mutation.

3. Other Names for This Gene

- SDR38C1
- sepiapterin reductase (7,8-dihydrobiopterin:NADP+ oxidoreductase)
- short chain dehydrogenase/reductase family 38C, member 1
- SPRE_HUMAN

References

1. Abeling NG, Duran M, Bakker HD, Stroomer L, Thöny B, Blau N, Booij J, Poll-TheBT. Sepiapterin reductase deficiency an autosomal recessive DOPA-responsivedystonia. Mol Genet Metab. 2006 Sep-Oct;89(1-2):116-20.
2. Arrabal L, Teresa L, Sánchez-Alcudia R, Castro M, Medrano C, Gutiérrez-Solana L, Roldán S, Ormazábal A, Pérez-Cerdá C, Merinero B, Pérez B, Artuch R, Ugarte M,Desviat LR. Genotype-phenotype correlations in sepiapterin reductase deficiency. A splicing defect accounts for a new phenotypic variant. Neurogenetics. 2011Aug;12(3):183-91. doi: 10.1007/s10048-011-0279-4.
3. Bonafé L, Thöny B, Penzien JM, Czarnecki B, Blau N. Mutations in thesepiapterin reductase gene cause a novel tetrahydrobiopterin-dependentmonoamine-neurotransmitter deficiency without hyperphenylalaninemia. Am J HumGenet. 2001 Aug;69(2):269-77.
4. Ikemoto K, Suzuki T, Ichinose H, Ohye T, Nishimura A, Nishi K, Nagatsu I,Nagatsu T. Localization of sepiapterin reductase in the human brain. Brain Res.2002 Nov 8;954(2):237-46.
5. Longo N. Disorders of biopterin metabolism. J Inherit Metab Dis. 2009Jun;32(3):333-42. doi: 10.1007/s10545-009-1067-2.Erratum in: J Inherit Metab Dis. 2009 Jun;32(3):457.
6. Steinberger D, Blau N, Goriuonov D, Bitsch J, Zuker M, Hummel S, Müller U.Heterozygous mutation in 5'-untranslated region of sepiapterin reductase gene(SPR) in a patient with dopa-responsive dystonia. Neurogenetics. 2004Sep;5(3):187-90.
7. Zorzi G, Redweik U, Trippe H, Penzien JM, Thöny B, Blau N. Detection ofsepiapterin in CSF of patients with sepiapterin reductase deficiency. Mol GenetMetab. 2002 Feb;75(2):174-7.