

## HSD17B10 gene

hydroxysteroid 17-beta dehydrogenase 10

### Normal Function

The *HSD17B10* gene provides instructions for making a protein called HSD10. This protein is located within mitochondria, the energy-producing centers inside cells, where it has several different functions.

The HSD10 protein is important for the production (synthesis) of proteins in mitochondria. (While most protein synthesis occurs in the fluid surrounding the nucleus, called the cytoplasm, a few proteins are synthesized in the mitochondria.) During protein synthesis, whether in the cytoplasm or in mitochondria, molecules called transfer RNAs (tRNAs) help assemble protein building blocks (amino acids) into the chains that form proteins. The HSD10 protein is involved in making functional mitochondrial tRNA. It forms a complex with an enzyme called TRMT10C to modify tRNAs so that they are more stable and can function properly. In addition, the complex interacts with another enzyme called PRORP to perform an enzymatic function called mitochondrial RNase P (mtRNase P) that cuts precursor RNA molecules, which is an essential step to generating tRNA molecules. Normal mitochondrial protein production, which requires tRNAs, is essential for the formation of the protein complexes that convert the energy from food into a form cells can use.

The HSD10 protein also plays an important role in processing several substances in the body. It helps break down the amino acid isoleucine. Specifically, it is responsible for the fifth step in this process, in which 2-methyl-3-hydroxybutyryl-CoA is converted into 2-methylacetoacetyl-CoA. Through a similar mechanism, the HSD10 protein also processes a group of fats called branched-chain fatty acids.

The HSD10 protein is also thought to be involved in chemical reactions involving female sex hormones (estrogens) and male sex hormones (androgens). HSD10 turns off (inactivates) a potent form of estrogen called 17 $\beta$ -estradiol by converting it to a weaker form called estrone. HSD10 also generates a potent androgen called dihydrotestosterone from a weak androgen called 3 $\alpha$ -androstenediol. These reactions are critical for maintaining appropriate levels of male and female sex hormones.

The HSD10 protein also plays a role in certain chemical reactions involving neurosteroids, which are substances that regulate the activity of the nervous system. This protein inactivates two neurosteroids called allopregnanolone and allotetrahydrodeoxycorticosterone. These neurosteroids interact with receptors that

prevent the brain from being overloaded with too many signals. By regulating the activity of these neurosteroids, the HSD10 protein may help maintain normal brain function. However, other proteins in the body can also carry out these reactions, and the importance of HSD10 in these functions is unclear.

## Health Conditions Related to Genetic Changes

### HSD10 disease

More than 10 *HSD17B10* gene mutations have been found to cause HSD10 disease, a disorder characterized by intellectual disability, impaired speech and movement, and a weakened heart muscle (cardiomyopathy). This disorder affects males more frequently and severely than females; many affected males do not survive beyond early childhood.

Almost all of the mutations change single amino acids in the HSD10 protein. One mutation, which has been found in multiple unrelated individuals, replaces the amino acid arginine with the amino acid cysteine at position 130 in the protein (written as Arg130Cys or R130C). This mutation results in a nonfunctional protein that is quickly broken down by the cell. Other mutations do not reduce the amount of HSD10 protein in cells, but impair its function in other ways.

A shortage or impaired function of HSD10 disrupts mtRNase P function, which impairs the processing of mitochondrial precursor RNA and the generation of tRNA molecules. A shortage of functional HSD10 also impairs the modification of tRNAs to make them more stable, further reducing the amount of functional tRNA molecules. This reduction in functional tRNAs decreases mitochondrial protein synthesis and the production of energy in the cell. The reduction of energy particularly affects the brain, eyes, and heart, leading to the characteristic features of HSD10 disease.

While the shortage of functional HSD10 protein caused by *HSD17B10* gene mutations also reduces the processing of isoleucine and other substances in the body, this mechanism does not appear to be primarily involved in the development of HSD10 disease.

Some individuals have *HSD17B10* gene mutations that affect only the breakdown of 2-methyl-3-hydroxybutyryl-CoA, which can be detected with laboratory tests, but do not have the signs and symptoms of HSD10 disease.

### Other disorders

One specific mutation in the *HSD17B10* gene causes a form of X-linked intellectual disability called MRXS10. This disorder is characterized by intellectual disability, uncontrollable movements of the limbs (choreoathetosis), and abnormal behavior. The mutation replaces the DNA building block (nucleotide) cysteine with the nucleotide adenine at position 605 in the *HSD17B10* gene (written as 605C>A). Although this mutation does not change the sequence of amino acids that makes up the HSD10 protein, it can disrupt how information in the gene is spliced together to make a blueprint for producing the protein. As a result, there is reduced production of the HSD10 protein.

It is unclear how the shortage of HSD10 results in the signs and symptoms of MRXS10.

At least 22 individuals who have intellectual disability without other signs and symptoms have been found to have small duplications of genetic material that include *HSD17B10* and nearby genes on the X chromosome. The extra copy of the *HSD17B10* gene leads to increased production of the HSD10 protein, which may affect neurosteroid regulation. Extra copies of other genes in this region of the X chromosome may also play a role in causing intellectual disability.

### Other Names for This Gene

- 17-beta-hydroxysteroid dehydrogenase type 10
- 17 $\beta$ -HSD10
- 2-methyl-3-hydroxybutyryl-CoA dehydrogenase
- 3-hydroxy-2-methylbutyryl-CoA dehydrogenase
- 3-hydroxyacyl-CoA dehydrogenase II
- ABAD
- amyloid-beta peptide binding alcohol dehydrogenase
- CAMR
- ERAB
- HADH2
- HCD2
- HSD10
- hydroxysteroid (17-beta) dehydrogenase 10
- MHBD
- MRPP2
- SCHAD
- SDR5C1
- short chain 3-hydroxyacyl-CoA dehydrogenase
- short chain dehydrogenase/reductase family 5C, member 1
- short chain type dehydrogenase/reductase XH98G2
- type 10 17b-HSD
- type 10 17beta-hydroxysteroid dehydrogenase

### Additional Information & Resources

#### Tests Listed in the Genetic Testing Registry

- Tests of HSD17B10 ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=3028\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=3028[geneid]))

### Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28HSD17B10%5BALL%5D%29+OR+%28%282-methyl-3-hydroxybutyryl-CoA+dehydrogenase%5BTIAB%5D%29+OR+%283-hydroxy-2-methylbutyryl-CoA+dehydrogenase%5BTIAB%5D%29+OR+%28ABAD%5BTIAB%5D%29+OR+%28ERAB%5BTIAB%5D%29+OR+%28HADH2%5BTIAB%5D%29+OR+%28MHBD%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5BIa%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D%29>)

### Catalog of Genes and Diseases from OMIM

- HSD10 MITOCHONDRIAL DISEASE; HSD10MD (<https://omim.org/entry/300438>)
- 17-BETA-HYDROXYSTEROID DEHYDROGENASE X; HSD17B10 (<https://omim.org/entry/300256>)

### Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/3028>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=HSD17B10\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=HSD17B10[gene]))

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## Genomic Location

The *HSD17B10* gene is found on the X chromosome (<https://medlineplus.gov/genetics/chromosome/x/>).

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