

# SERPINA6 Gene

Subjects: Genetics & Heredity

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serpin family A member 6

Keywords: genes

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## 1. Normal Function

The *SERPINA6* gene provides instructions for making a protein called corticosteroid-binding globulin (CBG), which is primarily produced in the liver. The CBG protein attaches (binds) to a hormone called cortisol, which has numerous functions, such as maintaining blood sugar levels, protecting the body from stress, and suppressing inflammation. When cortisol is bound to CBG, the hormone is turned off (inactive). Normally, around 80 to 90 percent of the body's cortisol is bound to CBG, 5 to 10 percent is unbound and active, and the remaining cortisol is bound to another protein called albumin. When cortisol is needed in the body, CBG delivers the cortisol to the appropriate tissues and releases it, causing cortisol to become active. In this manner, CBG regulates the amount of cortisol that is available for use in the body. The amount of total cortisol in the body consists of both bound (inactive) and unbound (active) cortisol.

## 2. Health Conditions Related to Genetic Changes

### 2.1. Corticosteroid-binding globulin deficiency

More than 10 mutations in the *SERPINA6* gene have been found to cause corticosteroid-binding globulin deficiency. This condition can cause extreme tiredness (fatigue), low blood pressure (hypotension), or chronic pain. However, some people with this condition do not experience any symptoms.

The mutations that cause corticosteroid-binding globulin deficiency often decrease the CBG protein's ability to bind to cortisol; some severe mutations prevent the production of any CBG protein. With less functional CBG to bind cortisol, people with corticosteroid-binding globulin deficiency usually have increased unbound cortisol levels. Typically, the body decreases cortisol production to compensate, resulting in a reduction in total cortisol.

It is unclear how a decrease in CBG protein and total cortisol leads to the signs and symptoms of corticosteroid-binding globulin deficiency. Since the CBG protein is needed to transport cortisol to specific tissues at certain times, it may be that while cortisol is available in the body, the cortisol is not getting to the tissues that require it. A decrease in cortisol may influence widening or narrowing of the blood vessels, contributing to abnormal blood pressure. Some researchers think the features may influence each other and that fatigue could be a result of chronic pain rather than a symptom of the disorder itself. There may also be other genetic or environmental factors that influence whether an affected individual is more likely to develop pain or fatigue.

### 2.2. Other disorders

A normal variation (polymorphism) in the *SERPINA6* gene has been associated with an increased risk of developing chronic fatigue syndrome. This condition involves prolonged episodes of extreme tiredness (fatigue) that can last for months and interfere with daily activities, as well as general symptoms, such as sore throat or headaches. The *SERPINA6* gene polymorphism associated with chronic fatigue syndrome replaces the protein building block (amino acid) alanine with the amino acid serine at position 224 in the CBG protein (written as Ala224Ser or A224S). This change likely increases the amount of CBG protein that is available. It is unknown how increasing CBG protein levels contributes to the risk of developing chronic fatigue syndrome, but it is likely that many other factors, both genetic and environmental, contribute to the development of this complex disorder.

### 3. Other Names for This Gene

- CBG
- CBG\_HUMAN
- corticosteroid binding globulin
- corticosteroid-binding globulin
- serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 6
- serpin A6
- serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 6
- transcortin

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