

# FOXL2 Gene

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Contributor: Vivi Li

Forkhead box L2

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## 1. Normal Function

The *FOXL2* gene provides instructions for making a protein that attaches (binds) to specific regions of DNA and helps control the activity of particular genes. On the basis of this role, the FOXL2 protein is called a transcription factor. The protein contains one area where a protein building block (amino acid) called alanine is repeated multiple times. This stretch of alanines is known as a polyalanine tract or poly(A) tract. The function of this poly(A) tract is unknown.

The FOXL2 protein is active in multiple tissues, including the eyelids, the ovaries, and a hormone-producing gland at the base of the brain called the pituitary. It is likely involved in the development of muscles in the eyelids. Before birth and in adulthood, the FOXL2 protein regulates the growth and division (proliferation) of hormone-producing ovarian cells called granulosa cells. This protein is also involved in the breakdown of fats, steroid hormones, and potentially harmful molecules called reactive oxygen species in the ovaries. The FOXL2 protein also plays a role in controlled cell death (apoptosis) in the ovaries.

## 2. Health Conditions Related to Genetic Changes

### 2.1 Blepharophimosis, Ptosis, and Epicanthus Inversus Syndrome

More than 260 mutations in the *FOXL2* gene have been found to cause blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES). There are two types of BPES; both types I and II involve abnormalities of the eyelids that prevent them from fully opening. Type I also includes an early loss of ovarian function (primary ovarian insufficiency) in women, which can lead to difficulty conceiving a child.

It is difficult to predict the type of BPES that will result from the many *FOXL2* gene mutations. However, mutations that result in a partial loss of FOXL2 protein function generally cause BPES type II. These mutations probably impair regulation of the normal development of muscles in the eyelids, resulting in malformed eyelids that cannot open fully. A common mutation in people with BPES type II adds extra alanines to the poly(A) tract in the FOXL2 protein.

Mutations that lead to a complete loss of FOXL2 protein function often cause BPES type I. These mutations impair both the regulation of normal eyelid development and various activities in the ovaries. These changes result in eyelid malformations and abnormally accelerated maturation of granulosa cells in the ovaries and the premature death of egg cells.

Five percent of mutations that cause BPES occur outside the *FOXL2* gene in a neighboring region of DNA that normally controls the activity of the gene, known as a regulatory region. Approximately 12 percent of mutations causing BPES are deletions involving the *FOXL2* gene. The deletions vary in size from a single DNA building block (base pair) to the entire gene. Some people with BPES have large DNA deletions that remove not only the *FOXL2* gene but one or more neighboring genes. Individuals with these large DNA deletions have the signs and symptoms of BPES, but they can also have other features. The combination of additional features depends on which genes are included in the deletion, but can include an unusually small head (microcephaly), intellectual disability, heart defects, and growth delay.

## 2.2 Coloboma

## 2.3 Other Disorders

At least three mutations in the *FOXL2* gene are thought to cause primary ovarian insufficiency without any other features of BPES. Primary ovarian insufficiency causes a woman's menstrual periods to become less frequent and eventually stop before age 40. Women with this condition can have difficulty conceiving a child (subfertility) or have a complete inability to conceive (infertility).

The *FOXL2* gene mutations that cause primary ovarian insufficiency lead to a reduction in protein function, preventing the FOXL2 protein from controlling genes that regulate various activities in the ovaries. The resulting abnormal gene activity accelerates the maturation of granulosa cells and causes the premature death of egg cells. This altered function seems to affect the protein's regulation of activities in the ovaries but not in the eyelids.

## 2.4 Cancers

Some gene mutations are acquired during a person's lifetime and are present only in certain cells. These changes, which are called somatic mutations, are not inherited. A specific somatic mutation in the *FOXL2* gene has been found in a type of ovarian cancer that occurs in adulthood called adult granulosa cell tumor. This mutation replaces the amino acid cysteine with the amino acid tryptophan at position 134 in the FOXL2 protein (written as Cys134Trp or C134W). This mutation is thought to interfere with regulation of granulosa cell proliferation and alter the protein's role in apoptosis. As a result granulosa cells grow and divide unregulated, leading to tumor formation.

## 3. Other Names for This Gene

- BPES
- BPES1
- forkhead transcription factor FOXL2
- FOXL2\_HUMAN
- PFRK

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