KLHL3 Gene

Subjects: Genetics & Heredity
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Kelch like family member 3

Keywords: genes

1. Introduction

The *KLHL3* gene provides instructions for making a protein that plays a role in the cell machinery that breaks down (degrades) unwanted proteins, called the ubiquitin-proteasome system.

The KLHL3 protein is one piece of a complex known as an E3 ubiquitin ligase. E3 ubiquitin ligases function as part of the ubiquitin-proteasome system by tagging damaged and excess proteins with molecules called ubiquitin. Ubiquitin serves as a signal to specialized cell structures known as proteasomes, which attach (bind) to the tagged proteins and degrade them. The ubiquitin-proteasome system acts as the cell's quality control system by disposing of damaged, misshapen, and excess proteins. This system also regulates the level of proteins involved in several critical cell activities such as the timing of cell division and growth.

The KLHL3 protein identifies the target of the E3 ubiquitin ligase complex and attaches the complex to it. Complexes containing the KLHL3 protein tag proteins called WNK1 and WNK4 with ubiquitin. The WNK1 and WNK4 proteins are involved in controlling blood pressure in the body. By regulating the amount of these proteins available, KLHL3 plays a role in blood pressure control.

2. Health Conditions Related to Genetic Changes

2.1. Pseudohypoaldosteronism Type 2

At least 36 *KLHL3* gene mutations have been found to cause pseudohypoaldosteronism type 2 (PHA2), a condition characterized by high blood pressure (hypertension) and high levels of potassium in the blood (hyperkalemia). These mutations alter the KLHL3 protein, impairing its ability to attach to the E3 ubiquitin ligase complex or to WNK4. As a result, the complex is unable to tag WNK4 with ubiquitin, and degradation of the protein is impaired. An excess of WNK4 disrupts normal control of blood pressure, leading to hypertension and the other features of PHA2. It is unknown if WNK1 is affected by the abnormal E3 ubiquitin ligase complex or whether WNK1 plays a role in development of PHA2 caused by *KLHL3* gene mutations.

3. Other Names for This Gene

- kelch-like family member 3
- kelch-like protein 3 isoform 1
- kelch-like protein 3 isoform 2
- kelch-like protein 3 isoform 3
- KIAA1129
- PHA2D

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