

KLHL3 gene

kelch like family member 3

Normal Function

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.

Health Conditions Related to Genetic Changes

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.

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

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of KLHL3 ([https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=26249\[geneid\]](https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=26249[geneid]))

Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28%28KLHL3%5BTIAB%5D%29+OR+%28kelch+like+family+member+3%5BTIAB%5D%29%29+OR+%28kelch-like+family+member+3%5BTIAB%5D%29+OR+%28kelch-like+protein+3+isoform+1%5BTIAB%5D%29+OR+%28kelch-like+protein+3+isoform+2%5BTIAB%5D%29+OR+%28kelch-like+protein+3+isoform+3%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D%29%29>)

Catalog of Genes and Diseases from OMIM

- KELCH-LIKE 3; KLHL3 (<https://omim.org/entry/605775>)

Gene and Variant Databases

- NCBI Gene (<https://www.ncbi.nlm.nih.gov/gene/26249>)
- ClinVar ([https://www.ncbi.nlm.nih.gov/clinvar?term=KLHL3\[gene\]](https://www.ncbi.nlm.nih.gov/clinvar?term=KLHL3[gene]))

References

- Boyden LM, Choi M, Choate KA, Nelson-Williams CJ, Farhi A, Toka HR, Tikhonova IR, Bjornson R, Mane SM, Colussi G, Lebel M, Gordon RD, Semmekrot BA, Poujol A, Valimaki MJ, De Ferrari ME, Sanjad SA, Gutkin M, Karet FE, Tucci JR, Stockigt JR, Keppler-Noreuil KM, Porter CC, Anand SK, Whiteford ML, Davis ID, Dewar SB, Bettinelli A, Fadrowski JJ, Belsha CW, Hunley TE, Nelson RD, Trachtman

H, ColeTR, Pinsk M, Bockenhauer D, Shenoy M, Vaidyanathan P, Foreman JW, Rasoulpour M, Thameem F, Al-Shahrouri HZ, Radhakrishnan J, Gharavi AG, Goilav B, Lifton RP. Mutations in kelch-like 3 and cullin 3 cause hypertension and electrolyte abnormalities. *Nature*. 2012 Jan 22;482(7383):98-102. doi: 10.1038/nature10814. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/22266938>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278668/>)

- Louis-Dit-Picard H, Barc J, Trujillano D, Miserey-Lenkei S, Bouatia-Naji N, Pylypenko O, Beaurain G, Bonnefond A, Sand O, Simian C, Vidal-Petiot E, Soukaseum C, Mandet C, Broux F, Chabre O, Delahousse M, Esnault V, Fiquet B, Houillier P, Bagnis CI, Koenig J, Konrad M, Landais P, Mourani C, Niaudet P, Probst V, Thauvin C, Unwin RJ, Soroka SD, Ehret G, Ossowski S, Caulfield M; International Consortium for Blood Pressure (ICBP); Bruneval P, Estivill X, Froguel P, Hadchouel J, Schott JJ, Jeunemaitre X. KLHL3 mutations cause familial hyperkalemic hypertension by impairing ion transport in the distal nephron. *Nat Genet*. 2012 Mar 11;44(4):456-60, S1-3. doi: 10.1038/ng.2218. Erratum In: *Nat Genet*. 2012;44(5):609. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/22406640>)
- Mori Y, Wakabayashi M, Mori T, Araki Y, Sohara E, Rai T, Sasaki S, Uchida S. Decrease of WNK4 ubiquitination by disease-causing mutations of KLHL3 through different molecular mechanisms. *Biochem Biophys Res Commun*. 2013 Sep 13;439(1):30-4. doi: 10.1016/j.bbrc.2013.08.035. Epub 2013 Aug 17. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/23962426>)
- Ohta A, Schumacher FR, Mehellou Y, Johnson C, Knebel A, Macartney TJ, Wood NT, Alessi DR, Kurz T. The CUL3-KLHL3 E3 ligase complex mutated in Gordon & Shypertension syndrome interacts with and ubiquitylates WNK isoforms: disease-causing mutations in KLHL3 and WNK4 disrupt interaction. *Biochem J*. 2013 Apr 1;451(1):111-22. doi: 10.1042/BJ20121903. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/23387299>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3632089/>)
- Shibata S, Zhang J, Puthumana J, Stone KL, Lifton RP. Kelch-like 3 and Cullin3 regulate electrolyte homeostasis via ubiquitination and degradation of WNK4. *Proc Natl Acad Sci U S A*. 2013 May 7;110(19):7838-43. doi:10.1073/pnas.1304592110. Epub 2013 Apr 1. Citation on PubMed (<https://pubmed.ncbi.nlm.nih.gov/23576762>) or Free article on PubMed Central (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3651502/>)

Genomic Location

The *KLHL3* gene is found on chromosome 5 (<https://medlineplus.gov/genetics/chromosome/5/>).

Last updated March 1, 2016