



## Pseudohypoaldosteronism type 2

Pseudohypoaldosteronism type 2 (PHA2) is caused by problems that affect regulation of the amount of sodium and potassium in the body. Sodium and potassium are important in the control of blood pressure, and their regulation occurs primarily in the kidneys.

People with PHA2 have high blood pressure (hypertension) and high levels of potassium in their blood (hyperkalemia) despite having normal kidney function. The age of onset of PHA2 is variable and difficult to pinpoint; some affected individuals are diagnosed in infancy or childhood, and others are diagnosed in adulthood. Hyperkalemia usually occurs first, and hypertension develops later in life. Affected individuals also have high levels of chloride (hyperchloremia) and acid (metabolic acidosis) in their blood (together, referred to as hyperchloremic metabolic acidosis). People with hyperkalemia, hyperchloremia, and metabolic acidosis can have nonspecific symptoms like nausea, vomiting, extreme tiredness (fatigue), and muscle weakness. People with PHA2 may also have high levels of calcium in their urine (hypercalciuria).

### Frequency

PHA2 is a rare condition; however, the prevalence is unknown.

### Causes

PHA2 can be caused by mutations in the *WNK1*, *WNK4*, *CUL3*, or *KLHL3* gene. These genes play a role in the regulation of blood pressure.

The proteins produced from the *WNK1* and *WNK4* genes help control the amount of sodium and potassium in the body by regulating channels in the cell membrane that control the transport of sodium or potassium into and out of cells. This process primarily occurs in the kidneys. Mutations in either of these genes disrupt control of these channels, leading to abnormal levels of sodium and potassium in the body. As a result, affected individuals develop hypertension and hyperkalemia.

The proteins produced from the *CUL3* gene (called cullin-3) and the *KLHL3* gene help control the amount of *WNK1* and *WNK4* protein available. Cullin-3 and *KLHL3* are two pieces of a complex, called an E3 ubiquitin ligase, that tags certain other proteins with molecules called ubiquitin. This molecule acts as a signal for the tagged protein to be broken down when it is no longer needed. E3 ubiquitin ligases containing cullin-3 and *KLHL3* are able to tag the *WNK1* and *WNK4* proteins with ubiquitin, leading to their breakdown. Mutations in either the *CUL3* or *KLHL3* gene impair breakdown of the *WNK4* protein. (The effect of these mutations on the *WNK1* protein is unclear.) An

excess of WNK4 likely disrupts control of sodium and potassium levels, resulting in hypertension and hyperkalemia.

### **Inheritance Pattern**

This condition is usually inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In most cases caused by mutations in the *WNK1*, *WNK4*, or *KLHL3* gene, an affected person inherits the mutation from one affected parent. While some cases caused by *CUL3* gene mutations can be inherited from an affected parent, many result from new mutations in the gene and occur in people with no history of the disorder in their family.

Some cases caused by mutations in the *KLHL3* gene are inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

### **Other Names for This Condition**

- familial hyperkalemic hypertension
- familial hyperpotassemia and hypertension
- familial hypertensive hyperkalemia
- FHht
- Gordon hyperkalemia-hypertension syndrome
- Gordon's syndrome
- PHAI
- pseudohypoaldosteronism type II

### **Diagnosis & Management**

#### Genetic Testing Information

- What is genetic testing?  
[/primer/testing/genetic-testing](#)
- Genetic Testing Registry: Pseudohypoaldosteronism, type 2  
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1840389/>

#### Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov  
<https://clinicaltrials.gov/ct2/results?cond=%22pseudohypoaldosteronism+type+2%22+OR+%22Pseudohypoaldosteronism%22>

### Other Diagnosis and Management Resources

- GeneReview: Pseudohypoaldosteronism Type II  
<https://www.ncbi.nlm.nih.gov/books/NBK65707>

### **Additional Information & Resources**

#### Health Information from MedlinePlus

- Encyclopedia: Hyperkalemia  
<https://medlineplus.gov/ency/article/001179.htm>
- Encyclopedia: Metabolic Acidosis  
<https://medlineplus.gov/ency/article/000335.htm>
- Health Topic: High Blood Pressure  
<https://medlineplus.gov/highbloodpressure.html>

#### Genetic and Rare Diseases Information Center

- Pseudohypoaldosteronism type 2  
<https://rarediseases.info.nih.gov/diseases/4553/pseudohypoaldosteronism-type-2>

#### Additional NIH Resources

- National Heart Lung and Blood Institute: What is High Blood Pressure?  
<https://www.nhlbi.nih.gov/health-topics/high-blood-pressure>
- National Institute of Diabetes and Digestive and Kidney Diseases: The Kidneys and How They Work  
<https://www.niddk.nih.gov/health-information/kidney-disease/kidneys-how-they-work>

#### Educational Resources

- American Heart Association: What is High Blood Pressure?  
<https://www.heart.org/en/health-topics/high-blood-pressure/the-facts-about-high-blood-pressure/what-is-high-blood-pressure>
- JAMA Patient Page: Hypertension  
<https://jamanetwork.com/journals/jama/fullarticle/185954>
- KidsHealth from Nemours: High Blood Pressure (Hypertension)  
<https://kidshealth.org/en/parents/hypertension.html>
- Merck Manual Consumer Version: Sodium  
<https://www.merckmanuals.com/home/hormonal-and-metabolic-disorders/electrolyte-balance/overview-of-sodium-s-role-in-the-body>
- Orphanet: Pseudohypoaldosteronism type 2  
[https://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?Lng=EN&Expert=757](https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=757)

### Patient Support and Advocacy Resources

- National Kidney Foundation  
<https://www.kidney.org/>

### Clinical Information from GeneReviews

- Pseudohypoaldosteronism Type II  
<https://www.ncbi.nlm.nih.gov/books/NBK65707>

### Scientific Articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28pseudohypoaldosteronism+type+2%5BTIAB%5D%29+OR+%28PHAI%5BTIAB%5D%29+OR+%28PHA2%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

### Catalog of Genes and Diseases from OMIM

- PSEUDOHYPOALDOSTERONISM, TYPE IIA  
<http://omim.org/entry/145260>
- PSEUDOHYPOALDOSTERONISM, TYPE IIB  
<http://omim.org/entry/614491>
- PSEUDOHYPOALDOSTERONISM, TYPE IIC  
<http://omim.org/entry/614492>
- PSEUDOHYPOALDOSTERONISM, TYPE IID  
<http://omim.org/entry/614495>
- PSEUDOHYPOALDOSTERONISM, TYPE IIE  
<http://omim.org/entry/614496>

### **Sources for This Summary**

- 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, Välimäki 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, Cole TR, 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://www.ncbi.nlm.nih.gov/pubmed/22266938>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278668/>
- Chávez-Canales M, Zhang C, Soukaseum C, Moreno E, Pacheco-Alvarez D, Vidal-Petiot E, Castañeda-Bueno M, Vázquez N, Rojas-Vega L, Meermeier NP, Rogers S, Jeunemaitre X, Yang CL, Ellison DH, Gamba G, Hadchouel J. WNK-SPAK-NCC cascade revisited: WNK1 stimulates the activity of the Na-Cl cotransporter via SPAK, an effect antagonized by WNK4. *Hypertension*. 2014 Nov;64(5):1047-53. doi: 10.1161/HYPERTENSIONAHA.114.04036. Epub 2014 Aug 11.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/25113964>

- 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://www.ncbi.nlm.nih.gov/pubmed/22406640>
- McCormick JA, Ellison DH. The WNKs: atypical protein kinases with pleiotropic actions. *Physiol Rev.* 2011 Jan;91(1):177-219. doi: 10.1152/physrev.00017.2010. Review.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/21248166>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3035565/>
- 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's hypertension 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://www.ncbi.nlm.nih.gov/pubmed/23387299>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3632089/>
- Vidal-Petiot E, Elvira-Matelot E, Mutig K, Soukaseum C, Baudrie V, Wu S, Cheval L, Huc E, Cambillau M, Bachmann S, Doucet A, Jeunemaitre X, Hadchouel J. WNK1-related Familial Hyperkalemic Hypertension results from an increased expression of L-WNK1 specifically in the distal nephron. *Proc Natl Acad Sci U S A.* 2013 Aug 27;110(35):14366-71. doi: 10.1073/pnas.1304230110. Epub 2013 Aug 12.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/23940364>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3761585/>
- Wilson FH, Disse-Nicodème S, Choate KA, Ishikawa K, Nelson-Williams C, Desitter I, Gunel M, Milford DV, Lipkin GW, Achard JM, Feely MP, Dussol B, Berland Y, Unwin RJ, Mayan H, Simon DB, Farfel Z, Jeunemaitre X, Lifton RP. Human hypertension caused by mutations in WNK kinases. *Science.* 2001 Aug 10;293(5532):1107-12.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/11498583>
- Wilson FH, Kahle KT, Sabath E, Lalioti MD, Rapson AK, Hoover RS, Hebert SC, Gamba G, Lifton RP. Molecular pathogenesis of inherited hypertension with hyperkalemia: the Na-Cl cotransporter is inhibited by wild-type but not mutant WNK4. *Proc Natl Acad Sci U S A.* 2003 Jan 21;100(2):680-4. Epub 2003 Jan 6.  
*Citation on PubMed:* <https://www.ncbi.nlm.nih.gov/pubmed/12515852>  
*Free article on PubMed Central:* <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC141056/>

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