



Pseudohypoaldosteronism Type II

Synonyms: Familial Hyperkalemic Hypertension, Gordon's Syndrome, PHAII

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Summary

Clinical characteristics

Pseudohypoaldosteronism type II (PHAII) is characterized by hyperkalemia despite normal glomerular filtration rate (GFR) and frequently by hypertension. Other associated findings in both children and adults include hyperchloremia, metabolic acidosis, and suppressed plasma renin levels. Aldosterone levels are variable, but are relatively low given the degree of hyperkalemia (elevated serum potassium is a potent stimulus for aldosterone secretion). Hypercalciuria is well described.

Diagnosis/testing

The diagnosis of PHAII is established in a proband:

- With hyperkalemia (in the setting of normal glomerular filtration), hypertension, metabolic acidosis, hyperchloremia, and suppressed plasma renin levels;
AND/OR
- By the identification of a heterozygous pathogenic variant in *CUL3*, *WNK1*, or *WNK4* or a heterozygous pathogenic variant or biallelic pathogenic variants in *KLHL3*.

Management

Treatment of manifestations: Electrolyte and blood pressure abnormalities of PHAII in children and adults are often corrected with thiazide diuretics.

Prevention of secondary complications: Control of blood pressure is important to reduce the risk of cardiovascular and renal disease and stroke.

Surveillance: Routine electrolyte and blood pressure measurements.

Agents/circumstances to avoid: Untreated individuals with PHAII should avoid excessive intake of foods high in salt and potassium as these may exacerbate hypertension and hyperkalemia.

Evaluation of relatives at risk: Measurement of serum potassium concentration and blood pressure or identification of the known familial *CUL3*, *KLHL3*, *WNK1*, and *WNK4* pathogenic variant(s) in first-degree relatives of individuals with PHAII allows for early diagnosis and treatment .

Pregnancy management: Affected pregnant women should undergo routine monitoring of electrolytes and blood pressure, with adjustments to antihypertensive medication dosage as needed. Some antihypertensive medications, including thiazide diuretics, have been associated with adverse fetal outcome, especially when taken during the first trimester of pregnancy; referral to an obstetrics group with expertise in high-risk pregnancies should be considered.

Genetic counseling

PHAII is frequently inherited in an autosomal dominant manner; PHAIID (caused by pathogenic variants in *KLHL3*) may also be inherited in an autosomal recessive manner. Many pathogenic variants in *CUL3* arise *de novo* and are not inherited from a parent. Each child of an individual with autosomal dominant PHAII has a 50% chance of inheriting the pathogenic variant. Prenatal testing for a pregnancy at increased risk is possible if the pathogenic variant(s) in the family are known.

Diagnosis

No formal diagnostic criteria for PHAII have been published.

Suggestive Findings

Pseudohypoaldosteronism type II (PHAII) **should be suspected** in individuals with the following clinical features, supportive laboratory findings, and family history.

Clinical features. Hypertension (blood pressure >140/90 mm Hg) generally manifesting in adolescence or adulthood but also reported in children. Note: The absence of frank hypertension does not preclude the diagnosis.

Supportive laboratory findings

- Hyperkalemia in the absence of impaired glomerular filtration
 - Serum concentration of potassium ranges from mildly (serum K ~5.0-6.0 mmol/L) to severely elevated (>8.0 mmol/L) (normal range: ~3.5-5.1 mmol/L).
 - This finding is nearly universal in affected individuals at all ages.
- Metabolic acidosis: serum concentration of bicarbonate ranging from 14 to 24 mmol/L (normal range: ~22-29 mmol/L)
- Hyperchloremia: serum concentration of chloride ranging from 105 to 117 mmol/L (normal range: ~99-108 mmol/L)
- Suppressed plasma renin levels
- Variable serum aldosterone levels that tend to be relatively suppressed in the context of hyperkalemia
- Serum calcium and parathyroid hormone levels that are normal. However, hypercalciuria is noted in at least a subset of individuals.

Family history. A first-degree relative with similar findings. Note: Absence of a family history of a first-degree relative with similar findings does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of PHAII is **established** in a proband with hyperkalemia (in the setting of normal glomerular filtration) often accompanied by hypertension, metabolic acidosis, hyperchloremia, and suppressed plasma renin

levels **and/or** by the identification of a heterozygous pathogenic variant in *CUL3*, *KLHL3*, *WNK1*, or *WNK4* or biallelic pathogenic variants in *KLHL3* (see Table 1). Note: PHAII is sometimes referred to by a subtype designation based on the associated gene; see Nomenclature.

Molecular genetic testing approaches can include **serial single-gene testing** and use of a **multigene panel**.

Serial single-gene testing

- It is reasonable to perform sequence analysis for pathogenic variants in *CUL3* and/or *KLHL3* first.
- If only one pathogenic variant in *KLHL3* is identified in an individual in whom autosomal recessive inheritance is suspected, gene-targeted deletion/duplication analysis of *KLHL3* should be considered.
- Sequence analysis of *WNK4* may be performed next.
- If no pathogenic variant is identified through sequencing of *WNK4*, gene-targeted deletion/duplication analysis of *WNK1* may be considered next.
- If no disease-causing deletion or duplication is found in *WNK1*, consider sequencing of *WNK1*.

A **multigene panel** that includes *CUL3*, *KLHL3*, *WNK1*, and *WNK4* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included and the sensitivity of multigene panels vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

Table 1. Molecular Genetic Testing Used in Pseudohypoaldosteronism Type II

Gene ¹	Proportion of PHAII Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants ² Detectable by Method	
		Sequence analysis ³	Gene-targeted deletion / duplication analysis ⁴
<i>CUL3</i>	25/86 families reported	All reported cases to date	None reported
<i>KLHL3</i>	41/86 families reported ⁵	AD: 29/86 AR: 12/86	Unknown ⁶
<i>WNK1</i>	8/86 families reported	See footnote 7.	2/2 ⁸
<i>WNK4</i>	8/86 families reported	All reported cases to date	None reported

Table 1. continued from previous page.

Gene ¹	Proportion of PHAII Attributed to Pathogenic Variants in Gene	Proportion of Pathogenic Variants ² Detectable by Method	
		Sequence analysis ³	Gene-targeted deletion / duplication analysis ⁴
Unknown ⁹	4/52 ¹⁰	NA	

AD = autosomal dominant; AR = autosomal recessive

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on allelic variants detected in this gene.

3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

4. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

5. Both heterozygous (autosomal dominant) and biallelic (autosomal recessive) pathogenic variants in *KLHL3* cause PHAII [Mayan et al 2004, Boyden et al 2012, Picard et al 2015a, Mitani et al 2016].

6. No data on detection rate of gene-targeted deletion/duplication analysis are available.

7. Recently, six kindreds (9 individuals) were reported in preliminary results to have pathogenic missense variants in *WNK1* (detailed in Molecular Genetics).

8. Two large deletions have been reported (see Molecular Genetics) [Wilson et al 2001].

9. An additional locus on 1q31-q42 has been identified as harboring a gene associated with PHAII [Mansfield et al 1997]. The identity of this gene is unknown. PHAII has been reported in at least ten families that lack identifiable pathogenic variants in *CUL3*, *KLHL3*, *WNK1*, and *WNK4* [Boyden et al 2012, Glover et al 2014].

10. Denominator is from the only report to document the number of PHAII individuals who did not have variants in *CUL3*, *KLHL3*, *WNK1*, or *WNK4* [Boyden et al 2012].

Clinical Characteristics

Clinical Description

Pseudohypoaldosteronism type II (PHAII) is characterized by hyperkalemia despite normal glomerular filtration rate (GFR) and frequently by hypertension. More than 180 individuals and families with PHAII have been reported.

The clinical presentation of PHAII is heterogeneous. The most consistent clinical feature in both children and young adults is hyperkalemia [Gordon 1986]. As with essential hypertension, blood pressure is usually normal in young persons, with hypertension developing later in life. Untreated individuals with elevated blood pressure are at risk of developing complications of hypertension including cardiac disease, renal impairment, and stroke.

Other associated findings in both children and adults include hyperchloremia, metabolic acidosis, and suppressed plasma renin levels. Aldosterone levels are variable, but are relatively low given the degree of hyperkalemia (elevated serum potassium is a potent stimulus for aldosterone secretion). Hypercalciuria is also well described in PHAII [Mayan et al 2004].

Other features reported in a subset of individuals with PHAII include short stature, myalgias, periodic paralysis, and dental abnormalities [Gordon 1986]. It has been suggested that these findings may be more prevalent in individuals with severe hyperkalemia and metabolic acidosis; however, exceptions have been reported [Gordon 1986, Farfel et al 2011].

Phenotype Correlations by Gene

Individuals with a heterozygous *CUL3* pathogenic variant tend to have more severe hyperkalemia and metabolic acidosis, earlier development of hypertension, and greater likelihood of growth impairment compared to those harboring *KLHL3*, *WNK1*, or *WNK4* alterations [Boyden et al 2012].

In general, clinical manifestations of PHAII appear to be milder in individuals with a heterozygous *WNK1* or *WNK4* pathogenic variant compared to those with a heterozygous *CUL3* or a heterozygous or biallelic *KLHL3* pathogenic variant(s) [Boyden et al 2012].

Individuals with biallelic *KLHL3* pathogenic variants may have a more severe phenotype than individuals with a heterozygous pathogenic variant in *KLHL3* [Boyden et al 2012, Louis-Dit-Picard et al 2012].

Nomenclature

The term "pseudohypoaldosteronism" has historically been used to describe the finding of persistent hyperkalemia despite the presence of normal or elevated serum levels of aldosterone [Schambelan et al 1981]. The term was initially used to describe persons with an inherited disorder characterized by hyperkalemia, elevated serum aldosterone, and volume depletion (now referred to as pseudohypoaldosteronism type I).

Therefore, the term "pseudohypoaldosteronism" is a misnomer in the context of PHAII, as affected individuals have hyperkalemia with hypertension (instead of volume depletion). Some authorities prefer the descriptive name familial hyperkalemic hypertension (FHHT) for this reason.

PHAII is sometimes referred to by a subtype designation based on the associated gene, as follows:

- PHA type IIA (PHA2A): Unknown genetic cause (see Table 1, footnotes 9 and 10)
- PHA type IIB (PHA2B): *WNK4*
- PHA type IIC (PHA2C): *WNK1*
- PHA type IIE (PHA2E): *CUL3*
- PHA type IID (PHA2D): *KLHL3*

Prevalence

The prevalence of the disorder is unknown. To date more than 180 individuals and families with PHAII have been reported.

Genetically Related (Allelic) Disorders

WNK1. Hereditary sensory and autonomic neuropathy type IIA (HSAN2A) is associated with apparent loss-of-function variants in specific exons of *WNK1*. Missense variants in *WNK1* have been reported in association with hypokalemic salt-losing tubulopathy in two unrelated individuals [Zhang et al 2013].

CUL3*, *KLHL3*, *WNK4. No phenotypes other than those discussed in this *GeneReview* are known to be associated with pathogenic variants in *CUL3*, *KLHL3*, or *WNK4*.

Differential Diagnosis

Other causes of hyperkalemia. Hyperkalemia resulting from the following can generally be distinguished from hyperkalemia caused by PHAII on the basis of plasma renin levels, which are increased in the following conditions and suppressed in PHAII:

- Chronic kidney disease, especially when secondary to diabetes, is the most commonly identified cause of hyperkalemia.

- When renal function is normal, consider the following:
 - Hypoaldosteronism or acquired renal tubular acidosis (type 4), particularly in the setting of marked volume depletion
 - Medication effects. Examples include potassium-sparing diuretics (e.g., spironolactone), nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin inhibitors, trimethoprim, and cyclosporine.
 - Primary adrenal insufficiency or deficiency of an adrenal synthetic enzyme

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with pseudohypoaldosteronism type II (PHAII), the following evaluations (if not performed as part of the diagnostic evaluation) are recommended:

- Serum electrolyte analysis
- Noninvasive blood pressure measurement
- Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Electrolyte and blood pressure abnormalities of PHAII are often corrected with thiazide diuretics. Metabolic abnormalities and hypertension generally improve within one week.

Different thiazide diuretics exist, with different dosing regimens. In general dosing is titrated to normalization of blood pressure. It is possible that dosing will need to be increased over time or that additional anti-hypertensives will be required to adequately control blood pressure.

There are no established guidelines regarding age at which treatment should begin for individuals with PHAII, but affected children who have hypertension are generally treated.

Prevention of Primary Manifestations

See Treatment of Manifestations.

Prevention of Secondary Complications

Control of blood pressure is important to reduce the risk for cardiovascular and renal disease and stroke.

Surveillance

Appropriate surveillance includes routine electrolyte and blood pressure measurements, monitored in the same manner as for any person treated with a thiazide diuretic.

Agents/Circumstances to Avoid

Untreated individuals with PHAII should avoid excessive intake of foods high in salt and potassium as these may exacerbate hypertension and hyperkalemia.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from prompt initiation of treatment. Evaluations can include:

- Measurement of serum potassium concentration and blood pressure;
- Molecular genetic testing if the pathogenic variant(s) in the family are known.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

During the pregnancy of a woman with PHAII, electrolytes and blood pressure should be monitored regularly and blood pressure medication adjusted as needed.

Some antihypertensive medications (including thiazide diuretics) have been associated with adverse fetal outcome, especially when taken during the first trimester of pregnancy. The best time to discuss the risk to the fetus associated with a maternal medication is prior to conception. Women with PHAII who become pregnant should be referred to an obstetrics group with expertise in high-risk pregnancies.

See [MotherToBaby](#) for further information on medication use during pregnancy.

Therapies Under Investigation

Search [ClinicalTrials.gov](#) in the US and [EU Clinical Trials Register](#) in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Pseudohypoaldosteronism type II (PHAII) is most commonly inherited in an autosomal dominant manner. PHAIID can also be inherited in an autosomal recessive manner.

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Many individuals diagnosed with PHAII have an affected parent.
- A proband with PHAII may have the disorder as the result of a *de novo* pathogenic variant [Gong et al 2008].

Fifteen of 182 reported cases have been *de novo*; 14/15 caused by a heterozygous pathogenic *CUL3* variant and 1/15 caused by a heterozygous *KLHL3* pathogenic variant [Boyden et al 2012, Tsuji et al 2013, Picard et al 2015a].

- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include clinical evaluation (electrolyte analysis and blood pressure measurement) and/or molecular genetic testing if a *CUL3*, *KLHL3*, *WNK1*, or *WNK4* pathogenic variant has been identified in the proband.

- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent (although no instances of germline mosaicism have been reported, it remains a possibility).
- Evaluation of parents may determine that one is affected but has escaped previous diagnosis because of failure to recognize the syndrome as a result of a milder phenotypic presentation, early death of the parent before the onset of symptoms, or late onset of the disease in the affected parent. Therefore, an apparently negative family history cannot be confirmed until appropriate evaluations have been performed.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents: if a parent of the proband is affected or has a pathogenic variant, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low. However, the sibs of a proband with clinically unaffected parents are still at increased risk for PHAII because of the possibility of reduced penetrance in a parent.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, the risk to sibs is slightly greater than that of the general population (though still <1%) because of the possibility of parental germline mosaicism.

Offspring of a proband. Each child of an individual with PHAII has a 50% chance of inheriting the *CUL3*, *KLHL3*, *WNK1*, or *WNK4* pathogenic variant.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent is affected or has a pathogenic variant, his or her family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *KLHL3* pathogenic variant).
- Carriers of a *KLHL3* pathogenic variant associated with autosomal recessive PHAIIID are typically asymptomatic and do not appear to be at risk of developing the disorder; however, thorough clinical analysis of such individuals over time has not been reported.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Carriers of a *KLHL3* pathogenic variant associated with autosomal recessive PHAIIID are typically asymptomatic and are not thought to be at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with autosomal recessive PHAIIID are obligate heterozygotes (carriers) for a pathogenic variant in *KLHL3*.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *KLHL3* pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *KLHL3* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Testing

Once the *CUL3*, *KLHL3*, *WNK1*, or *WNK4* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for PHAI are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While use of prenatal testing is a personal choice, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- **Genetic Disorders of Mucociliary Clearance Consortium**
gdmcc.rarediseasesnetwork.org
- **Metabolic Support UK**
United Kingdom
Phone: 0845 241 2173
metabolicsupportuk.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Pseudohypoaldosteronism Type II: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
CUL3	2q36.2	Cullin-3		CUL3	CUL3

Table A. continued from previous page.

KLHL3	5q31.2	Kelch-like protein 3	KLHL3 @ LOVD	KLHL3	KLHL3
WNK1	12p13.33	Serine/threonine-protein kinase WNK1	WNK1 @ LOVD WNK1 homepage - Leiden Muscular Dystrophy pages	WNK1	WNK1
WNK4	17q21.2	Serine/threonine-protein kinase WNK4	WNK4 database	WNK4	WNK4

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

Table B. OMIM Entries for Pseudohypoaldosteronism Type II (View All in OMIM)

145260	PSEUDOHYPOALDOSTERONISM, TYPE IIA; PHA2A
601844	PROTEIN KINASE, LYSINE-DEFICIENT 4; WNK4
603136	CULLIN 3; CUL3
605232	PROTEIN KINASE, LYSINE-DEFICIENT 1; WNK1
605775	KELCH-LIKE 3; KLHL3
614491	PSEUDOHYPOALDOSTERONISM, TYPE IIB; PHA2B
614492	PSEUDOHYPOALDOSTERONISM, TYPE IIC; PHA2C
614495	PSEUDOHYPOALDOSTERONISM, TYPE IID; PHA2D
614496	PSEUDOHYPOALDOSTERONISM, TYPE IIE; PHA2E

Molecular Pathogenesis

Pathogenic variants in the genes encoding two members of the WNK protein family of serine-threonine kinases, *WNK1* and *WNK4*, have been implicated in the pathogenesis of pseudohypoaldosteronism type II (PHAII) [Wilson et al 2001]. Members of this kinase family are named WNK (or with *no* lysine [*K*]) kinases because of their unique substitution of cysteine for lysine at a highly conserved residue within the catalytic kinase domain [Xu et al 2000]. Over the past decade, members of the WNK kinase family have been shown to regulate the coordinated transport of Na⁺, K⁺, and Cl⁻ ions across epithelia in a variety of tissues [Kahle et al 2008].

Alterations in *WNK1* and *WNK4* are present in only a minority of individuals with PHAII, motivating the search for additional genetic contributions to the disorder in other families. Recently, pathogenic variants in kelch-like 3 (*KLHL3*) and cullin 3 (*CUL3*) have been identified in the majority of families with PHAII [Boyden et al 2012, Louis-Dit-Picard et al 2012]. The protein products of *CUL3* and *KLHL3* function together as part of the cullin-RING E3 ubiquitin ligase complex, which has a role in ubiquitin-mediated protein degradation.

The electrolyte and blood pressure abnormalities in individuals with PHAII are readily corrected with thiazide diuretics, inhibitors of the Na-Cl cotransporter (NCC; encoded by *SLC12A3*) expressed in the renal distal convoluted and connecting tubules (see Management, Treatment of Manifestations). This clinical observation led to the initial hypothesis that increased activity of NCC could play a role in the pathogenesis of PHAII [Gordon 1986]. However, to date, no PHAII-causing variants in the gene encoding NCC have been demonstrated.

CUL3

Gene structure. *CUL3* is widely expressed and has several alternatively spliced isoforms. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. *CUL3* alterations causing PHAII occur within intron 8, exon 9, or intron 9 and disrupt splicing of exon 9. This results in a 57-amino acid in-frame deletion.

Normal gene product. *CUL3* is a component of the cullin-RING E3 ubiquitin ligase complex, which functions in ubiquitin-mediated proteolysis. Immunostaining of mouse kidney demonstrates that *CUL3* is present throughout the nephron [Boyden et al 2012].

Abnormal gene product. It has been suggested that *CUL3* pathogenic variants in PHAII may disrupt ubiquitination of at least a subset of KLHL3 targets [Boyden et al 2012]. The observation that all reported *CUL3* pathogenic variants impair splicing of exon 9 and result in an in-frame deletion of a segment of *CUL3* may hint at the functional specificity of these pathogenic variants [Boyden et al 2012].

KLHL3

Gene structure. *KLHL3* is widely expressed with at least three alternatively spliced isoforms reported. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Dominant *KLHL3* pathogenic variants that cause PHAII are missense alternations that cluster in segments connecting beta-strands of Kelch propeller blades within the C-terminal Kelch propeller domain and disrupt substrate binding.

Recessive *KLHL3* pathogenic variants occur throughout the gene and include frameshift and premature termination variants.

Normal gene product. *KLHL3* is a component of the cullin-RING E3 ubiquitin ligase complex, which functions in ubiquitin-mediated proteolysis. *KLHL3* contains an N-terminal bric-a-brac tramtrack broad complex (BTB) domain that has a role in binding to *CUL3* and a BTB and C-terminal Kelch (BACK) domain. *KLHL3* also contains a C-terminal six-bladed Kelch propeller domain that functions in substrate binding.

Wild type *KLHL3* has been shown to bind to *WNK4* and *WNK1* [Ohta et al 2013, Shibata et al 2013, Wakabayashi et al 2013]. Furthermore, binding of *KLHL3* to *WNK4* has been shown to result in ubiquitination and degradation of *WNK4* in vitro, suggesting that *KLHL3* normally regulates *WNK4* levels via ubiquitin-mediated proteolysis [Shibata et al 2013, Wakabayashi et al 2013, Wu & Peng 2013]. Expression of *KLHL3* together with binding of *KLHL3* to *WNK1* has also been shown to result in ubiquitination of *WNK1* [Ohta et al 2013].

Immunostaining of mouse kidney demonstrates that *KLHL3* is predominantly present in the distal convoluted tubule and collecting duct [Boyden et al 2012, Louis-Dit-Picard et al 2012].

Abnormal gene product. Missense variants in *KLHL3* that cause PHAII disrupt binding to *WNK4*, *WNK1*, or *CUL3* and lead to decreased ubiquitination and increased levels of *WNK4* [Mori et al 2013, Ohta et al 2013, Shibata et al 2013, Wakabayashi et al 2013]. Mutated *KLHL3* has also been shown to decrease *WNK4*-mediated clearance of ROMK from the cell membrane [Shibata et al 2013].

WNK1

Gene structure. *WNK1* transcript variant 1 (reference sequence [NM_018979.3](#)) has 30 exons and encodes the most common protein isoform. Alternatively spliced transcript variants have been described; the full-length nature of all of them has yet to be determined. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. Pathogenic variants in *WNK1* were initially reported in two families with PHAII [Wilson et al 2001]. Both are large deletions (41 kb and 21 kb) that occur within the 60-kb intron 1 of *WNK1*. The deletions do not affect the coding sequence of the flanking exons. Recently, 6 kindreds (9 individuals) were

reported to have pathogenic missense variants in *WNK1*, coupled with a phenotype that includes hyperkalemia and acidosis; the hypertension was minimal. The pathogenic missense variants clustered in the region homologous to the acidic domain mutated in *WNK4* [Picard et al 2015b].

Table 2. Selected *WNK1* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
g.18538_59810del ^{1, 2}	See footnote 3.	NG_007984.2
g.28500_50277del ²	See footnote 3.	

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

1. Deletion within intron 1 (also known as NG_007984.2:c.759+12272_760-5774del)

2. Wilson et al [2001]

3. No amino acid change is expected.

Normal gene product. *WNK1* encodes at least four different alternatively spliced *WNK1* transcripts (See see Table A, **Gene** further details). The interplay between these isoforms is complex. Two variants were initially identified: a longer isoform with ubiquitous tissue expression (L-*Wnk1*) and a smaller isoform that lacks the 5' kinase domain of the larger isoform and appears to be kidney-specific (KS-*Wnk1*) [Delaloy et al 2003, O'Reilly et al 2003]. A neuronal isoform of *WNK1* (termed *Wnk1/HSN2*) that is highly expressed in the cell body of sensory ganglia neurons and neuronal projections has been identified. Pathogenic variants in an alternatively spliced exon of the transcript that encodes this isoform cause autosomal recessive [hereditary sensory and autonomic neuropathy type 2](#), a disorder of progressive sensory deficit to touch, temperature, and pain [Shekarabi et al 2008].

The L-*Wnk1* isoform can activate the kinase SPAK (encoded by *STK39*), which in turn can phosphorylate and activate NCC (the Na-Cl cotransporter) encoded by *SLC12A3*. The KS-*Wnk1* isoform, expressed predominantly along the distal nephron, binds to and inhibits the activity of L-*Wnk1* in *Xenopus* [Subramanya et al 2006] and transgenic mice [Liu et al 2011]. *WNK1* can also interact, through a conserved "HQ" domain, with other *WNK* kinases, including *WNK4*. These interactions have complex functional effects [Yang et al 2003, Chávez-Canales et al 2014].

As a multifunctional regulator of ion channels and transporters, *WNK1* also inhibits the K⁺ channel ROMK1, encoded by *KCNJ1* [Liu et al 2009] and (probably via phosphorylation of downstream kinase SGK-1) activates the amiloride-sensitive Na⁺ channel ENaC encoded by *SCNN1A*, *SCNN1B*, and *SCNN1G* [Xu et al 2005, Hadchouel et al 2010].

Abnormal gene product. Both of the known *WNK1* deletions causing PHAII occur within the first intron of the gene and do not affect the amino acid structure of the gene product(s). It was initially shown that deletion within the first intron increases *WNK1* transcription in peripheral leukocytes [Wilson et al 2001]. Subsequent work demonstrated that the intron deletion leads to increased L-*Wnk1* expression in the distal convoluted tubule [Vidal-Petiot et al 2013]. These findings support the hypothesis that the deletion within the first intron leads to increased expression of L-*Wnk1*, which should phosphorylate and stimulate NCC.

A knockout mouse model of L-*Wnk1* has also been generated, and mice with a heterozygous targeted disruption of the L-*Wnk1* transcript have significantly decreased blood pressure compared to wild type [Zambrowicz et al 2003]. Mice with targeted disruption of KS-*Wnk1* exhibited increased activity of NCC, altered function of the ROMK (encoded by *KCNJ1*) and BKCa potassium channels, and decreased ENaC expression [Hadchouel et al 2010], confirming previous in vitro observations.

WNK4

Gene structure. *WNK4* has 19 exons. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. All reported pathogenic variants are missense alterations. All pathogenic variants reported to date have been identified in exons 7 and 17 [Wilson et al 2001, Golbang et al 2005, Brooks et al 2012].

Table 3. Selected *WNK4* Pathogenic Variants

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.1679A>G	p.Glu560Gly	NM_032387.4 NP_115763.2
c.1682C>T	p.Pro561Leu	
c.1684G>A	p.Glu562Lys	
c.1690G>C	p.Asp564His	
c.1691A>C	p.Asp564Ala	
c.1693C>G	p.Gln565Glu	
c.3505A>G	p.Lys1169Glu	
c.3553C>T	p.Arg1185Cys	

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See [Quick Reference](#) for an explanation of nomenclature.

Normal gene product. *WNK4* product is a 1,243-amino acid protein encoded by a 3,732-nucleotide open reading frame within a 4-kb cDNA transcript. Northern blot analysis showed expression primarily within the kidney, but immunofluorescence studies have shown the protein is present in the epithelial lining of a variety of tissues including the colon, liver, and pancreas [Kahle et al 2004a].

WNK4 has been shown to regulate the activity of a number of ion transporters through heterologous expression in *Xenopus* oocytes and in mammalian cell systems [Kahle et al 2008]. The major effect of *WNK4* in vivo appears to be stimulation of NCC; it may also inhibit ROMK [Kahle et al 2003, Wilson et al 2003]. *WNK4* has also been reported to increase paracellular chloride permeability in mammalian kidney cells via claudin phosphorylation [Kahle et al 2004b, Yamauchi et al 2004, Tatum et al 2007]. Like *WNK1*, *WNK4* also regulates other structurally diverse but functionally related ion channels including ENaC [Ring et al 2007a, Ring et al 2007b] and the cation nonselective TRP channels TRPV4 and TRPV5 [Fu et al 2006]. Deletion of *WNK4* results in a phenotype that resembles Gitelman syndrome, indicating that the predominant *WNK4* effect in vivo is stimulation of NCC [Castañeda-Bueno et al 2012, Takahashi et al 2014].

Abnormal gene product. The effects of PHAII-associated *WNK4* pathogenic variants on the above targets have been evaluated in vitro in oocytes and mammalian cells and in vivo in mouse models [reviewed in Chávez-Canales et al 2014].

Important information about the mechanisms underlying *WNK4*-related PHAII came from the development and characterization of mouse models of PHAII [Laloti et al 2006, Yang et al 2007]. Mice transgenic for a chromosomal segment encoding the murine *Wnk4* with a Gln562Glu pathogenic variant (orthologous to the human p.Gln565Glu pathogenic variant) had hyperkalemia, higher blood pressure, and hypercalciuria compared to mice transgenic for a chromosomal segment encoding wild type *Wnk4* [Laloti et al 2006]. In addition, marked hyperplasia of the distal convoluted tubule (DCT) and increased expression of NCC were noted in mutated *Wnk4* transgenic mice but not in wild type *Wnk4* transgenic mice. All abnormalities were entirely corrected when mutated *Wnk4* transgenic mice were crossed with mice harboring a targeted disruption of the

gene encoding NCC, indicating that the effect of mutated *Wnk4* on NCC activity alone is sufficient to cause the PHAI phenotype. Essentially similar findings were reported in a mouse *Wnk4* mutated knock-in model of PHAI [Yang et al 2007].

Most PHAI-causing variants in WNK4 cluster within a highly conserved noncatalytic domain just distal to the kinase domain. Recent in vitro studies have demonstrated that this segment is critical for binding to KLHL3, and PHAI-associated variants within this domain disrupt interactions between WNK4 and KLHL3 [Ohta et al 2013, Shibata et al 2013, Wakabayashi et al 2013]. Due to the role of KLHL3 in ubiquitin-mediated proteolysis (see *KLHL3*), this should lead to increased WNK4 levels. Indeed, increased WNK4 levels are reported in the WNK4 mouse models of PHAI discussed above [Shibata et al 2013, Wakabayashi et al 2013].

It has also been suggested that pathogenic variants within this segment disrupt a calcium-sensing mechanism important in the regulation of WNK4 kinase activity [Na et al 2012]. Similarly, the PHAI-associated p.Arg1185Cys pathogenic variant (located near the C-terminus of WNK4 and separate from this domain) has also been implicated in impaired calcium sensing and altered phosphorylation by SGK1 [Na et al 2013].

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Chapter Notes

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