Pseudohypoaldosteronism Type 2E (PHA2E): A Comprehensive Disease Characterization

Disease: Pseudohypoaldosteronism Type 2E (PHA2E) **MONDO ID:** MONDO:0013782 · **OMIM:** 614496 **Causal gene: CUL3** (cullin-3, HGNC:2553, NCBI Gene 8452, chromosome 2q36.2) **Category:** Mendelian, monogenic hypertension

Summary

Pseudohypoaldosteronism type 2E (PHA2E) is the CUL3 (cullin-3)-caused subtype of familial hyperkalemic hypertension (FHHt), also known as Gordon syndrome or pseudohypoaldosteronism type II (PHAII). It is a rare, autosomal-dominant, predominantly *de novo* Mendelian disorder in which mutations cause skipping of CUL3 exon 9, producing an in-frame deletion of 57 amino acids (CUL3Δ403-459, "CUL3-Δ9"). PHA2E is distinguished among the four FHHt genes (WNK1, WNK4, KLHL3, CUL3) as the **most severe subtype**, typically presenting in childhood with hypertension, hyperkalemia, hyperchloremic metabolic acidosis, hypercalciuria, suppressed renin, and normal or high aldosterone — all with a normal glomerular filtration rate (PMID: 22266938; PMID: 29361671).

Mechanistically, CUL3 is the scaffold of a cullin-RING E3 ubiquitin ligase that, together with the BTB-Kelch adaptor KLHL3, ubiquitinates WNK1/WNK4 kinases for proteasomal degradation. The PHA2E mutant ligase fails to degrade WNK kinases normally; the accumulated WNKs hyperactivate the downstream kinases SPAK (STE20/SPS1-related proline/alanine-rich kinase) and OSR1 (oxidative stress-responsive kinase 1), which phosphorylate and activate the thiazide-sensitive Na-Cl cotransporter (NCC) in the renal distal convoluted tubule (DCT). This drives excessive NaCl reabsorption (→ hypertension) and impaired potassium secretion (→ hyperkalemia) (PMID: 29361671; PMID: 39699086).

Beyond the renal lesion, a faithful knock-in mouse model (CUL3^WT/Δ403-459^) reveals a **vascular component** to the hypertension, consistent with the WNK-SPAK/OSR1 pathway's role in vascular smooth muscle arterial tone (PMID: 26286618; PMID: 26152401). The prognosis is

excellent with treatment: thiazide diuretics (which directly inhibit the hyperactivated NCC) plus dietary salt restriction produce dramatic normalization of blood pressure and electrolytes. Untreated or late-diagnosed disease carries morbidity including growth and developmental impairment in children and risk of life-threatening hyperkalemic arrhythmia.

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1. Disease Information

PHA2E is a rare inherited monogenic form of low-renin hypertension within the FHHt/Gordon syndrome/PHAII spectrum. It is defined molecularly by its causal gene, **CUL3 (cullin-3)**, which distinguishes it from the other PHAII subtypes caused by WNK1 (PHA2C), WNK4 (PHA2B), and KLHL3 (PHA2D).

Key identifiers:

Resource	Identifier
MONDO	MONDO:0013782
OMIM	614496 (PSEUDOHYPOALDOSTERONISM, TYPE IIE; PHA2E)
Causal gene	CUL3 (HGNC:2553; NCBI Gene 8452; chromosome 2q36.2)
Disease family	Familial hyperkalemic hypertension (FHHt) / Gordon syndrome / PHAII

Synonyms and alternative names: pseudohypoaldosteronism type 2 caused by mutation in CUL3; CUL3 pseudohypoaldosteronism type 2; PHA2E; Gordon syndrome (CUL3-related); familial hyperkalemic hypertension, CUL3 type.

Information source: The disease-level characterization here derives principally from aggregated disease-level resources (OMIM, published case series, and mechanistic studies) combined with individual patient case reports. PHA2E is sufficiently rare that no large patient-level EHR registries exist specifically for the CUL3 subtype; evidence comes from case reports, small pedigree studies, and mechanistic mouse/cell models.

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2. Etiology

Primary cause — genetic. PHA2E is caused by heterozygous, dominant, predominantly *de novo* mutations in **CUL3**. Boyden et al. (2012) used exome sequencing across 41 unrelated PHAII families to identify CUL3 (and KLHL3) as causal genes: *"KLHL3 mutations are either recessive or dominant, whereas CUL3 mutations are dominant and predominantly de novo"* (PMID: 22266938). A key convergent feature is that diverse CUL3 mutations — spanning splice-donor and splice-acceptor sites flanking exon 9 — all produce the same outcome: *"Diverse CUL3 mutations all result in skipping of exon 9, producing an in-frame deletion"* (PMID: 22266938).

Genetic risk factors. The causal variants are the CUL3 exon-9 splice-site mutations themselves. There are no known common susceptibility loci or modifier alleles established specifically for PHA2E; the disorder is monogenic with high penetrance.

Environmental risk factors. Dietary sodium (salt) load worsens the hypertensive phenotype because the underlying defect is excessive renal NaCl reabsorption; dietary potassium load exacerbates hyperkalemia. These are modifiers of expression rather than causes.

Protective factors. Dietary sodium restriction is a protective/ameliorating environmental factor, reducing the substrate for NCC-driven NaCl retention. No genetic protective variants are established.

Gene-environment interactions. The core interaction is between the CUL3 genotype (which fixes NCC in a hyperactive state) and dietary salt and potassium intake, which determine the magnitude of hypertension and hyperkalemia. Co-occurrence of a second channelopathy variant can modify phenotype — a notable case reported a girl carrying both SCNN1A (PHAI) and CUL3 (PHAII) mutations, producing a complex mixed salt-handling phenotype (PMID: 36303414).

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3. Phenotypes

The core phenotype is a biochemical and hemodynamic constellation. Bruel et al. (2016) summarize the typical picture: *"The typical clinical picture of Gordon syndrome includes, apart from arterial hypertension and dyskaliemia, hyperchloremia metabolic acidosis, hypercalciuria, a low rate of renin, and most frequently, a normal or high rate of aldosterone. Dental abnormalities and growth retardation can also be associated"* (PMID: 27369102).

Phenotype	Type	HPO term (suggested)	Characteristics
Arterial hypertension	Clinical sign	HP:0000822 (Hypertension)	Childhood-onset possible; severe in CUL3; the defining feature
Hyperkalemia	Laboratory abnormality	HP:0002153	Present despite normal GFR; can be life-threatening
Hyperchloremic metabolic acidosis	Laboratory abnormality	HP:0004879 / HP:0001947	Characteristic of PHAII
Hypercalciuria	Laboratory abnormality	HP:0002150	Associated finding
Suppressed plasma renin	Laboratory abnormality	— (low renin)	Low renin is diagnostic
Normal/high aldosterone	Laboratory abnormality	—	Distinguishes from true hypoaldosteronism
Growth retardation	Physical manifestation	HP:0001510 (Growth delay)	In pediatric cases, linked to persistent acidosis/ hypertension
Dental abnormalities	Physical manifestation	HP:0000164 (Abnormality of the teeth)	Reported association in Gordon syndrome
Short stature	Physical manifestation	HP:0004322	Reported in some cases

Age of onset: CUL3/PHA2E tends to present earlier and more severely than other FHHt subtypes — often in childhood. A representative CUL3 case was a 7-year-old girl with hypertension, growth retardation, hyperkalemia and metabolic acidosis carrying a *de novo* exon-9 splice mutation (PMID: 27369102).

Severity: CUL3 produces the most severe form of FHHt (PMID: 29361671).

Progression: Chronic and lifelong, but highly responsive to treatment. Untreated, persistent metabolic acidosis and hypertension may lead to significant growth and developmental impairments in pediatric patients (PMID: 41380172).

Frequency / quality of life: Hypertension and the biochemical triad are present in essentially all affected individuals; growth retardation and dental abnormalities are variable associations. With appropriate thiazide therapy, quality of life is largely preserved; untreated disease impairs growth/development and carries cardiac arrhythmia risk from hyperkalemia.

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4. Genetic / Molecular Information

Causal gene: CUL3 (cullin-3), HGNC:2553, NCBI Gene 8452, located at chromosome 2q36.2. OMIM gene entry 603136; disease entry 614496.

Pathogenic variants. The pathognomonic lesion is **skipping of exon 9**, caused by heterozygous mutations at the intron 8 / exon 9 splice-acceptor site and the exon 9 / intron 9 splice-donor site, as well as some exonic variants. All converge on an in-frame deletion of 57 amino acids (residues 403-459): **CUL3Δ403-459** (PMID: 22266938; PMID: 27378813).

- **Variant classification (ACMG/AMP):** Pathogenic (established, recurrent, functionally validated disease-causing variants).
- **Variant type/class:** Predominantly splice-site variants producing an in-frame exon-skip; functionally equivalent to an internal deletion.
- **Allele frequency:** Effectively absent from population databases (gnomAD) — these are private, predominantly *de novo* pathogenic variants, consistent with a severe, early-onset dominant disorder.
- **Somatic vs germline:** Germline; a large fraction arise *de novo* in the proband.
- **Functional consequence:** A combination of **loss of function** (impaired WNK ubiquitylation) and abnormal **gain/altered function** (auto-ubiquitylation, loss of regulatory interactions). Schumacher et al. (2015) showed: *"the PHA2E mutant, CUL3(Δ403-459), is severely compromised in its ability to ubiquitylate WNKs, possibly due to altered structural flexibility. Instead, CUL3(Δ403-459) auto-ubiquitylates and loses interaction with two important Cullin regulators: the COP9-signalosome and CAND1"* (PMID: 26286618). The dual gain/loss nature is emphasized in PMID: 29897280.

Why CUL3 is more severe. The same study notes: *"These findings may explain the severity of the FHHt phenotype caused by CUL3 mutations compared to those reported in KLHL3 or WNK kinases"* (PMID: 26286618). Loss of COP9-signalosome (CSN) binding is central — the catalytically active CSN subunit JAB1 fails to associate with the deleted CUL3 4-helix bundle

domain (PMID: 29897280), and disrupted CSN binding has been confirmed as a major contributor to the FHHt phenotype in a renal CSN-deficient mouse (PMID: 30301860; see also PMID: 31813255).

Modifier genes: Within the pathway, the levels/activity of WNK1, WNK4, KLHL3, SPAK, OSR1, and NCC (SLC12A3) modulate the net phenotype. No formal modifier loci are established for PHA2E.

Epigenetic information: No disease-specific DNA methylation or histone modification signatures have been established for PHA2E. (CUL3 itself regulates protein stability of many substrates via ubiquitination/neddylation — a post-translational rather than epigenetic mechanism.)

Chromosomal abnormalities: None characteristic; PHA2E is a single-gene splice-defect disorder, not a copy-number or structural disorder.

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5. Environmental Information

PHA2E is a genetic disorder; environmental factors modulate expression rather than cause disease.

- **Environmental factors:** No toxic, radiation, or occupational exposures are implicated as causes.
- **Lifestyle factors:** Dietary **sodium (salt)** intake worsens hypertension; dietary **potassium** intake worsens hyperkalemia. Salt restriction is beneficial.
- **Infectious agents:** None. PHA2E is not an infectious or post-infectious disease.

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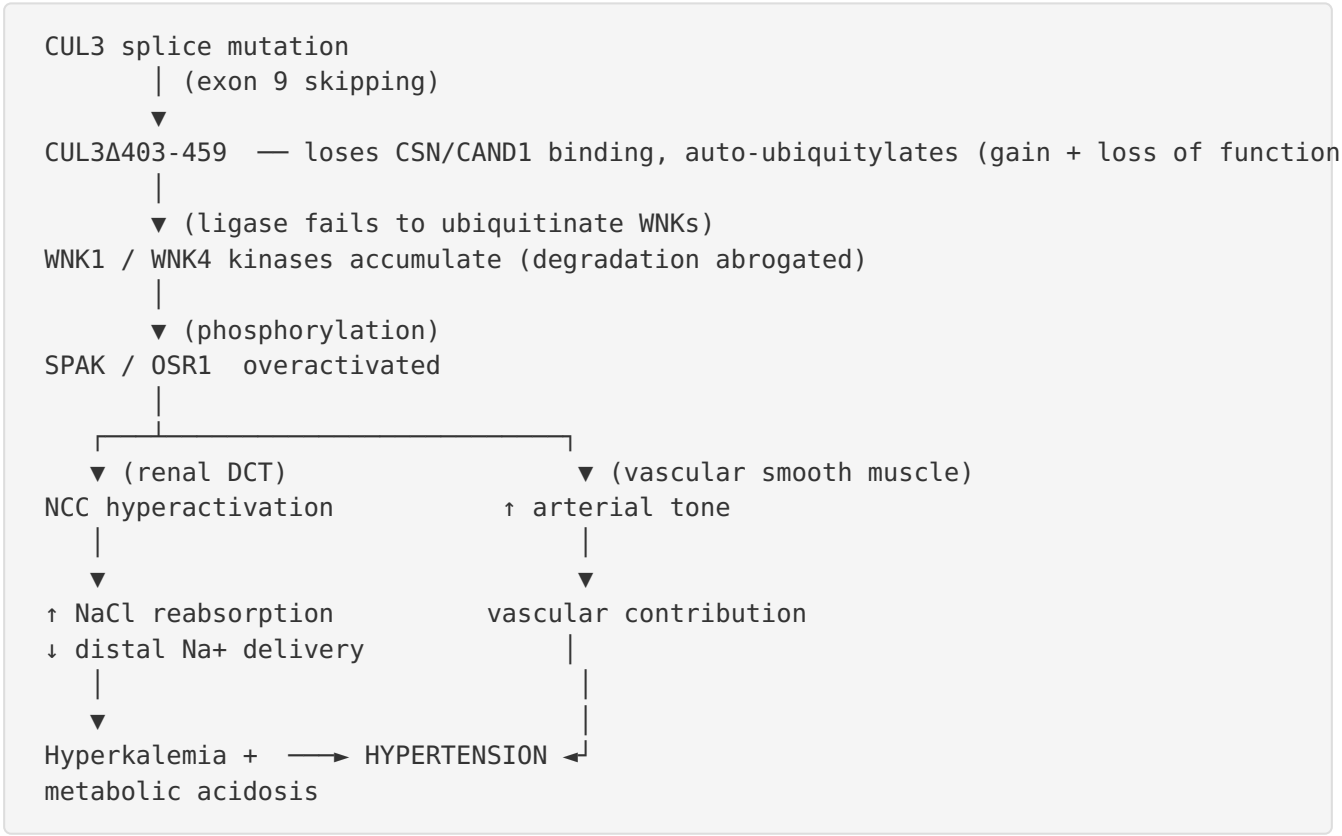
6. Mechanism / Pathophysiology

Ordered causal chain

1. A heterozygous *de novo* **CUL3 splice-site mutation** disrupts splicing → **leads to** skipping of exon 9 and an in-frame deletion (CUL3Δ403-459). (PMID: 22266938)

2. CUL3Δ403-459 protein **results in** a structurally altered cullin-RING E3 ligase that loses binding to the COP9 signalosome (CSN) and CAND1, and instead auto-ubiquitylates. (PMID: 26286618; PMID: 29897280)
3. The defective CUL3-KLHL3 ligase **fails to ubiquitinate WNK1/WNK4 kinases** → proteasomal degradation of WNKs is abrogated → **leads to** cytoplasmic accumulation of WNK kinases. (PMID: 29361671)
4. Accumulated WNK kinases **phosphorylate and activate SPAK and OSR1** (overactivation). (PMID: 29361671)
5. Active SPAK/OSR1 **phosphorylate and activate the thiazide-sensitive Na-Cl cotransporter (NCC)** in the distal convoluted tubule. (PMID: 29361671; PMID: 39699086) 6a. **Renal branch:** NCC hyperactivation → increased NaCl reabsorption → volume expansion → **hypertension**; reduced distal Na^+ delivery impairs K^+ and H^+ secretion → **hyperkalemia and hyperchloremic metabolic acidosis**. (PMID: 39699086) 6b. **Vascular branch (demonstrated in mouse, inferred in human):** The same WNK-OSR1/SPAK-SLC12a cascade is active in vascular smooth muscle, where it regulates arterial tone — contributing a vascular component to hypertension evidenced by altered arterial pulse waveform in the CUL3 knock-in mouse. (PMID: 26286618; PMID: 26152401)

ASCII mechanistic diagram



Detail by category

- **Molecular pathways:** The CUL3/KLHL3–WNK–SPAK/OSR1–NCC pathway. Ferdaus & McCormick frame it as a therapeutic target: *"The disease familial hyperkalemic hypertension is caused by mutations in with-no-lysine (WNK) kinases 1 and 4 and in cullin-3 and kelch-like 3, components of an E3 ubiquitin ligase complex that promotes WNK kinase degradation"* (PMID: 27076645).
- **Cellular processes:** Protein polyubiquitination (GO:0000209), protein targeting for proteasomal degradation, cullin-RING ligase activity (Cul3-RING ubiquitin ligase complex GO:0031463), protein neddylation (GO:0045116; CUL3 is NEDD8-modified), sodium ion transmembrane transport (GO:0035725), regulation of blood pressure (GO:0008217).
- **Protein dysfunction:** Altered structural flexibility of the mutant cullin scaffold; impaired substrate (WNK) ubiquitylation; aberrant auto-ubiquitylation; loss of CSN/CAND1 regulatory interactions (PMID: 26286618).
- **Biochemical abnormalities:** Transporter (NCC) hyperactivity; E3 ligase dysfunction; dysregulated NEDD8/CSN deneddylation cycle.

- **Tissue damage mechanisms:** Primarily functional (electrolyte/volume dysregulation) rather than destructive; chronic hypertension can cause downstream end-organ effects, and DCT-specific CSN disruption can cause tubular injury (PMID: 39205661).
- **Immune/metabolic/epigenetic:** No primary autoimmune, metabolic-enzyme, or epigenetic mechanism is implicated.

Upstream vs downstream: Upstream = CUL3 ligase defect → WNK accumulation. Downstream = SPAK/OSR1 → NCC → NaCl retention → clinical phenotype. **Cell types:** DCT epithelial cell (CL:1000768 kidney distal convoluted tubule epithelial cell), vascular smooth muscle cell (CL:0000359). **GO biological processes:** GO:0000209 (protein polyubiquitination), GO:0035725 (sodium ion transmembrane transport), GO:0008217 (regulation of blood pressure).

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7. Anatomical Structures Affected

- **Primary organ:** Kidney (UBERON:0002113), specifically the **renal distal convoluted tubule (DCT)** (UBERON:0001292). Cornelius et al.: *"In the kidney, these mutations ultimately cause hyperactivation of NCC along the renal distal convoluted tubule. Hypertension results from increased NaCl retention, and hyperkalemia by impaired K[+ secretion]"* (PMID: 39699086).
- **Secondary / body systems:** Cardiovascular system (hypertension, vascular smooth muscle involvement; UBERON:0004535), endocrine/renin-angiotensin-aldosterone axis (suppressed renin), skeletal/dental (growth retardation, dental abnormalities).
- **Tissue and cell level:** Renal tubular epithelium — DCT epithelial cells (CL:1000768) where KLHL3, CUL3, WNK kinases, and NCC are co-expressed (PMID: 22266938); vascular smooth muscle cells (CL:0000359) where the WNK-OSR1/SPAK-SLC12a cascade regulates arterial tone (PMID: 26152401). Downstream potassium handling involves the connecting tubule/collecting duct (ENaC/ROMK) secondarily — notably ROMK expression remained unaltered in the CUL3Δ403-459 mouse, indicating hyperkalemia arises chiefly from reduced distal Na^+ delivery rather than ROMK loss (PMID: 27378813).
- **Subcellular level:** Cytoplasm (WNK kinase accumulation), plasma/apical membrane (NCC), and the Cul3-RING ubiquitin ligase complex (GO:0031463). GO cellular components: GO:0005737 (cytoplasm), GO:0016020 (membrane), GO:0031463 (Cul3-RING ligase complex).
- **Localization / lateralization:** Bilateral renal involvement; systemic (not lateralized) hypertension.

8. Temporal Development

- **Onset:** Congenital genetic basis; clinical onset frequently in childhood for CUL3/PHA2E (the most severe subtype), though biochemical abnormalities may be detected at various ages. Onset pattern is insidious/chronic. Representative case: 7-year-old girl (PMID: 27369102); a 9-year follow-up of early-onset PHAII has been reported (PMID: 41380172).
- **Progression:** Chronic, lifelong, non-remitting without treatment, but not typically a destructive/degenerative course. Hypertension shows a positive relationship with age, as in the general population (PMID: 11903313).
- **Progression rate / course:** Stable-chronic; electrolyte abnormalities and hypertension persist until treated.
- **Patterns:** No spontaneous remission; treatment-induced normalization is rapid and dramatic with thiazides. **Critical period:** Childhood is a window where untreated acidosis and hypertension impair growth and development — early diagnosis and intervention are key (PMID: 41380172).

9. Inheritance and Population

- **Epidemiology:** FHHt/Gordon syndrome is a very rare cause of hypertension. Among 5,100 patients referred to a tertiary hypertension unit, 7.3% had hyperkalemia and FHHt was a rare diagnosis within that group (PMID: 39229746). More than 90 single cases/families of FHHt have been reported historically, with marked phenotypic heterogeneity (PMID: 11903313). CUL3 (PHA2E) is one of the rarer and most severe subtypes. Precise prevalence/incidence figures for the CUL3 subtype specifically are not established.
- **Inheritance pattern:** Autosomal dominant, **predominantly *de novo*** for CUL3 (PMID: 22266938). CUL3 and KLHL3 variants segregated in 63% of previously unexplained FHHt pedigrees (PMID: 24266877).
- **Penetrance:** High (effectively complete for the biochemical phenotype in reported pedigrees).
- **Expressivity:** Variable — severity of biochemical abnormalities varies among individuals and families (PMID: 11903313).
- **Genetic anticipation:** Not applicable (not a repeat-expansion disorder).

- **Germline mosaicism / founder effects / consanguinity / carrier frequency:** Given the predominantly *de novo* nature of CUL3 variants, founder effects and consanguinity are not typical features (unlike recessive KLHL3). No meaningful carrier frequency applies to a *de novo* dominant disorder.
- **Population demographics:** No ethnic or geographic predilection established for PHA2E. **Sex ratio:** Autosomal — expected ~1:1 male:female. **Age distribution:** Childhood onset is characteristic of the CUL3 subtype.

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10. Diagnostics

Biochemical diagnosis. PHA2E is suspected on the triad of **hyperkalemia, hyperchloremic metabolic acidosis, and hypertension with suppressed plasma renin and normal GFR**, with normal or high aldosterone and hypercalciuria (PMID: 27369102; PMID: 6384650).

Test	Finding in PHA2E	Notes
Serum potassium	Elevated (hyperkalemia)	HP:0002153
Serum chloride / bicarbonate	Hyperchloremia, low HCO_3 (metabolic acidosis)	HP:0004879
Plasma renin activity	Suppressed/low	diagnostic clue
Plasma aldosterone	Normal or high	distinguishes from hypoaldosteronism
Urinary calcium	Elevated (hypercalciuria)	HP:0002150
eGFR	Normal	rules out renal failure
Urinary exosomal NCC	Increased NCC abundance	supportive, research/translational (PMID: 28511177)

Genetic testing (confirmatory). Diagnosis is confirmed by molecular testing of the four FHHt genes — WNK1, WNK4, KLHL3, CUL3 — via next-generation sequencing (gene panel or exome), with attention to splice-site variants causing CUL3 exon-9 skipping. Network-medicine-informed diagnostic panels (e.g., PHA-X incorporating CNV detection and ACMG/AMP curation) have been proposed (PMID: 41569463). Genetic testing is indispensable for precise subtyping, which directs etiology-specific management and prognostication (PMID: 41982973).

Differential diagnosis. PHAII must be distinguished from conditions producing *hypotension*: PHA type I (salt-wasting, hypotension, elevated aldosterone), type 4 RTA/hypoaldosteronism (aldosterone deficiency, low BP), and other causes of hyperkalemia (renal failure, drugs). The discriminating feature is the direction of blood pressure: *"Hyperabsorption of chloride in the distal nephron leads to pseudohypoaldosteronism type II, which is linked with hypertension, whereas blood pressure in the other mentioned disorders is decreased"* (PMID: 6384650). A **spectacular therapeutic response to thiazide** also serves as a diagnostic pointer (PMID: 27369102).

Screening. No newborn or population screening program exists; cascade genetic testing of first-degree relatives is appropriate once a familial variant is identified, though *de novo* status is common in CUL3.

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11. Outcome / Prognosis

PHA2E is a **chronic, lifelong but highly treatable** condition with an **excellent prognosis when diagnosed and treated**. Thiazide diuretics produce dramatic ("spectacular") normalization of blood pressure and kalemia (PMID: 27369102).

- **Survival/mortality:** Not a directly lethal disorder when treated; life expectancy is expected to be near-normal with therapy. Severe untreated hyperkalemia can cause life-threatening cardiac arrhythmia.
- **Morbidity:** Untreated or late-diagnosed disease causes morbidity — *"persistent metabolic acidosis and hypertension may lead to significant growth and developmental impairments in pediatric patients"* (PMID: 41380172). Chronic hypertension carries the usual long-term cardiovascular/renal end-organ risks if uncontrolled.
- **Prognostic factors:** Timeliness of diagnosis and treatment adherence are the dominant determinants. *"A timely diagnosis of FHH is important for effective management of hypertension, electrolyte imbalance correction with tailored treatment, and genetic counseling"* (PMID: 39229746).
- **Recovery potential:** The biochemical and hemodynamic abnormalities are fully reversible with thiazide therapy; genotype-specific (NCC-targeted) treatment is highly effective.

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12. Treatment

First-line pharmacotherapy — thiazide diuretics. Thiazides directly inhibit the hyperactivated NCC, reversing hypertension, hyperkalemia, and acidosis — often with dramatic effect. Boyden et al.: *"Disease features are reversed by thiazide diuretics, which inhibit the Na-Cl cotransporter in the distal nephron of the kidney; KLHL3 and CUL3 are expressed in this location"* (PMID: 22266938). Glover et al. confirm FHHt *"is effectively treated by thiazide diuretics and/or dietary salt restriction"* (PMID: 24266877). NCIT: thiazide diuretic (e.g., hydrochlorothiazide, NCIT:C29181); chlorthalidone.

Dietary / supportive measures. Sodium (salt) restriction reduces substrate for NaCl retention; potassium restriction and, if needed, potassium-binding resins address hyperkalemia. Klaus: *"sodium restriction and chloruretic diuretics (thiazide) in type II of pseudohypoaldosteronism"* (PMID: 6384650).

Treatment strategy / personalized medicine. PHA2E is a model of genotype-guided therapy: identifying a CUL3/KLHL3-WNK pathway defect directs clinicians specifically to NCC-blocking thiazides rather than empirical antihypertensives. The CUL3/KLHL3–WNK–SPAK/OSR1 pathway is itself being pursued as a target for novel antihypertensive agents, with the appeal that *"its inhibition may not only reduce renal sodium reabsorption along multiple segments but may also reduce vascular tone"* (PMID: 27076645).

Advanced/experimental therapeutics: No gene therapy, cell therapy, or RNA-based therapy is clinically available or in trials specifically for PHA2E; the pathway (WNK/SPAK inhibitors) is at the preclinical/translational stage.

Treatment outcomes and adverse events: Response is typically excellent and rapid. Thiazide adverse effects to monitor include hypokalemia (useful here, as it counters the hyperkalemia), hyponatremia, hyperuricemia, and volume depletion; doses are titrated to normalize potassium and blood pressure.

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13. Prevention

- **Primary prevention:** Not applicable as a genetic *de novo* disorder — occurrence cannot be prevented. Risk-factor modification (salt restriction) prevents symptomatic worsening.
- **Secondary prevention (early detection):** Measuring blood pressure in children and recognizing the hyperkalemia/acidosis/hypertension triad enables early diagnosis; the title

of PMID: 27369102 itself stresses "the importance of measuring blood pressure in children." Early thiazide treatment prevents growth/developmental complications.

- **Tertiary prevention:** Ongoing thiazide therapy plus dietary salt/potassium management prevents hypertensive end-organ damage and hyperkalemic arrhythmia.
- **Genetic counseling:** Important for affected families — explaining autosomal-dominant transmission (50% risk to offspring of an affected individual) and the predominantly *de novo* origin in CUL3. Cascade genetic testing and counseling are recommended (PMID: 39229746).
- **Immunization / public health / environmental interventions:** Not applicable.

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14. Other Species / Natural Disease

- **Taxonomy / orthologs:** CUL3 is highly conserved. Mouse *Cul3* (NCBI Gene 26554; *Mus musculus*, NCBI Taxon 10090) is the principal experimental ortholog. The WNK-SPAK/OSR1-NCC signaling axis is conserved across mammals.
- **Natural disease in other species:** No well-documented naturally occurring CUL3-exon-9 Gordon syndrome equivalent is established in companion animals or wildlife (no specific OMIA entry identified for this exact condition in the reviewed literature).
- **Comparative biology:** The knock-in mouse (below) recapitulates the human disease closely, demonstrating strong evolutionary conservation of the disease mechanism.
- **Transmission / zoonosis:** Not applicable — PHA2E is a non-transmissible genetic disorder.

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15. Model Organisms

Primary model — CUL3Δ403-459 knock-in mouse. A knock-in mouse carrying the PHA2E deletion faithfully recapitulates the disease: *"Deletion of exon 9 from CUL3 (affecting residues 403-459, CUL3(Δ403-459)) causes a severe form of FHHt (PHA2E) that is recapitulated closely in a knock-in mouse model"* (PMID: 27378813).

Model	Type	Key findings	Reference
CUL3^WT/Δ403-459^ knock-in mouse	Mammalian, knock-in (heterozygous)	Recapitulates hyperkalemia/ hypertension; reveals arterial pulse-waveform changes = vascular component	PMID: 26286618
CUL3Δ403-459 mouse (ROMK study)	Mammalian, knock-in	NCC activation via WNK accumulation; ROMK expression unaltered → hyperkalemia from reduced distal Na^+ delivery	PMID: 27378813
Renal CSN (JAB1)-deficient mouse	Mammalian, conditional (Pax8/ LC1)	Deficient COP9-signalosome binding contributes importantly to the FHHt phenotype	PMID: 30301860
DCT-specific CSN disruption mouse	Mammalian, conditional	DCT-specific CSN disruption (not CUL3 itself) causes tubular injury	PMID: 39205661
Cultured kidney cells expressing Cul3Δ403-459	In vitro	Dissected dual gain/loss of function; JAB1 fails to bind deleted 4-helix bundle	PMID: 29897280

Phenotype recapitulation: Excellent — the knock-in mouse reproduces the renal electrolyte/ hypertension phenotype and additionally uncovered the vascular contribution not previously appreciated. **Limitations:** Mouse models of the mutant have been central to resolving the still-debated balance of gain-of-function vs loss-of-function mechanisms (PMID: 29361671); subtle human features (dental abnormalities, growth retardation) are less emphasized in models. **Applications:** Dissecting the CUL3-CSN-WNK-SPAK-NCC cascade, testing WNK/SPAK inhibitors, and probing renal vs vascular contributions to hypertension.

Key Findings (with evidence)

F1 — PHA2E is caused by dominant, predominantly *de novo* CUL3 mutations causing exon-9 skipping

Boyden et al. (2012) identified CUL3 and KLHL3 as PHAII genes across 41 families; CUL3 mutations are dominant and predominantly *de novo*, and diverse mutations converge on exon-9 skipping (CUL3Δ403-459). *"KLHL3 mutations are either recessive or dominant, whereas CUL3 mutations are dominant and predominantly de novo"* and *"Diverse CUL3 mutations all result in skipping of exon 9, producing an in-frame deletion"* (PMID: 22266938).

F2 — Mechanism: CUL3-Δ9 abrogates WNK degradation, hyperactivating SPAK/OSR1-NCC

"In CUL3-Δ9-mediated FHHt, proteasomal degradation of WNKs is abrogated, leading to overactivation of the WNK targets [SPAK] and oxidative stress-response kinase-1, which directly phosphorylate and activate the thiazide-sensitive Na[-Cl cotransporter]" (PMID: 29361671); NCC hyperactivation occurs along the DCT, producing hypertension and hyperkalemia (PMID: 39699086).

F3 — CUL3 causes the most severe FHHt; thiazides reverse it

"Autosomal dominant mutations in cullin-3 (Cul3) cause the most severe form of familial hyperkalemic hypertension (FHHt)" (PMID: 29361671); disease features reverse with thiazides (PMID: 22266938).

F4 — A CUL3Δ403-459 knock-in mouse recapitulates PHA2E

"Deletion of exon 9 from CUL3 ... causes a severe form of FHHt (PHA2E) that is recapitulated closely in a knock-in mouse model" (PMID: 27378813).

F5 — The mutant auto-ubiquitylates and loses CSN/CAND1 binding (explains severity)

"the PHA2E mutant, CUL3(Δ403-459), is severely compromised in its ability to ubiquitylate WNKs ... Instead, CUL3(Δ403-459) auto-ubiquitylates and loses interaction with two important Cullin regulators: the COP9-signalosome and CAND1"; *"These findings may explain the severity of*

the FHHt phenotype caused by CUL3 mutations compared to those reported in KLHL3 or WNK kinases" (PMID: 26286618); dual gain/loss of function and JAB1/CSN disruption (PMID: 29897280; PMID: 30301860).

F6 — PHA2E hypertension has a vascular component

"These mice also show changes in the arterial pulse waveform, suggesting a vascular contribution to their hypertension not reported in previous FHHt models" (PMID: 26286618); the WNK-OSR1/SPAK-SLC12a cascade is present in VSMCs and regulates arterial tone (PMID: 26152401).

F7 — Full clinical phenotype

"The typical clinical picture ... includes ... arterial hypertension and dyskaliemia, hyperchloremia metabolic acidosis, hypercalciuria, a low rate of renin, and most frequently, a normal or high rate of aldosterone. Dental abnormalities and growth retardation can also be associated" (PMID: 27369102); growth/developmental impairment from persistent acidosis/hypertension (PMID: 41380172).

Evidence Base

PMID	Title (abbrev.)	Role
22266938	*Mutations in KLHL3 and CUL3 cause hypertension and electrolyte abnormalities*	Landmark: identifies CUL3 cause, exon-9 skipping, *de novo* dominance, thiazide reversal
29361671	*Mechanisms and controversies in mutant Cul3-mediated FHHt*	Core mechanism; CUL3 = most severe FHHt
39699086	*Familial Hyperkalemic Hypertension*	NCC/DCT localization of lesion
26286618	*Characterisation of the Cullin-3 mutation...*	Protein dysfunction; CSN/CAND1 loss; vascular component
29897280	*Dual gain and loss of cullin 3 function...*	Mechanistic dissection; JAB1/CSN
30301860	*Renal COP9 Signalosome Deficiency...*	CSN binding deficiency drives FHHt
27378813	*ROMK expression unaltered in CUL3Δ403-459 mouse*	Knock-in model; hyperkalemia mechanism
26152401	*KLHL3/CUL3 ubiquitin ligase and WNK signaling...*	Vascular smooth muscle pathway
27076645	*The CUL3/KLHL3-WNK-SPAK/OSR1 pathway as antihypertensive target*	Pathway definition; drug target
27369102	*Gordon syndrome: BP measurement in children*	Clinical phenotype; CUL3 pediatric case; thiazide response
41380172	*Diagnostic pitfalls... 9-year follow-up of early-onset PHAII*	Morbidity; growth/developmental impairment
24266877	*Detection of mutations in KLHL3 and CUL3 in FHHt families*	Epidemiology; treatment
39229746	*Prevalence of Hyperkalemia and FHHt in 5100 patients*	Rarity; diagnosis importance
11903313	*Phenotypic/genetic heterogeneity of FHHt*	Historical epidemiology; AD inheritance; variable expressivity
6384650	*Primary hypoaldosteronism, pseudo-hypoaldosteronism...*	Differential diagnosis; thiazide treatment
41569463	*PHA demystification; diagnostic panels*	Diagnostic panel design

PMID	Title (abbrev.)	Role
41982973	*Chinese children with PHA case series*	Value of genetic subtyping

Limitations and Knowledge Gaps

1. **Precise epidemiology unknown:** No reliable prevalence/incidence estimate exists for the CUL3 subtype specifically; it is simply "very rare." Case counts are small.
2. **Mechanistic controversy:** The relative contributions of gain-of-function (auto-ubiquitylation, altered substrate repertoire, KLHL3 degradation) versus loss-of-function (impaired WNK ubiquitylation) remain debated (PMID: 29361671; PMID: 29897280).
3. **Vascular contribution not fully quantified in humans:** The vascular component is demonstrated in mice (PMID: 26286618); its magnitude in human PHA2E is inferred, not directly measured.
4. **Limited data on non-renal phenotypes:** Dental abnormalities and growth retardation are reported as associations, but their frequency, mechanism, and reversibility are not well quantified.
5. **No omics datasets** (transcriptomic/proteomic/metabolomic) specific to PHA2E patient tissue were available in this investigation; molecular profiling evidence is derived from mechanistic cell/mouse studies.
6. **No formal modifier genes or genotype-phenotype correlation** within CUL3 variants is established beyond the shared exon-9-skipping outcome.

Proposed Follow-up Experiments / Actions

1. **Human vascular phenotyping:** Measure arterial stiffness/pulse-wave velocity in genetically confirmed PHA2E patients to test whether the mouse-observed vascular component is clinically relevant and whether it responds to thiazides.
2. **Natural-history registry:** Establish a CUL3-specific FHHt registry to quantify age of onset, penetrance, growth/dental outcomes, and long-term cardiovascular/renal endpoints with and without early treatment.

3. **CSN/neddylation-targeted studies:** Given that loss of CSN/JAB1 binding is central to CUL3 severity, test whether modulating neddylation (e.g., NEDD8-pathway tools) in the knock-in mouse corrects NCC hyperactivation — a potential precision-therapy avenue.
4. **WNK/SPAK inhibitor translation:** Advance preclinical WNK-SPAK/OSR1 inhibitors in the CUL3Δ403-459 mouse, directly comparing renal and vascular blood-pressure effects against thiazide.
5. **Patient-derived omics:** Perform transcriptomic/proteomic profiling of patient-derived cells or urinary exosomes (NCC abundance) to develop non-invasive biomarkers of disease activity and treatment response (PMID: 28511177).
6. **Growth-impairment mechanism:** Investigate whether early acidosis correction fully rescues growth in pediatric PHA2E, clarifying the critical intervention window.

Ontology Term Appendix

- **MONDO:** MONDO:0013782 (PHA2E)
- **Gene (HGNC):** CUL3 (HGNC:2553)
- **HPO:** HP:0000822 (Hypertension), HP:0002153 (Hyperkalemia), HP:0004879/HP:0001947 (Hyperchloremic metabolic acidosis), HP:0002150 (Hypercalciuria), HP:0001510 (Growth delay), HP:0000164 (Dental abnormality)
- **GO (BP):** GO:0000209 (protein polyubiquitination), GO:0045116 (protein neddylation), GO:0035725 (sodium ion transmembrane transport), GO:0008217 (regulation of blood pressure)
- **GO (CC):** GO:0031463 (Cul3-RING ubiquitin ligase complex), GO:0005737 (cytoplasm), GO:0016020 (membrane)
- **CL:** CL:1000768 (kidney distal convoluted tubule epithelial cell), CL:0000359 (vascular associated smooth muscle cell)
- **UBERON:** UBERON:0002113 (kidney), UBERON:0001292 (distal convoluted tubule), UBERON:0004535 (cardiovascular system)
- **CHEBI:** thiazide diuretics (e.g., hydrochlorothiazide), sodium chloride, potassium
- **NCIT:** Thiazide diuretic / hydrochlorothiazide (antihypertensive intervention)

Report compiled from autonomous iterative investigation (5 iterations, 13 confirmed findings, 30 papers reviewed). Evidence source types span human clinical case reports/series, model-organism (mouse knock-in) studies, and in vitro mechanistic studies, as noted throughout.
