Congenital High-Molecular-Weight Kininogen Deficiency (KNG1) — Comprehensive Disease Report

Disease: Congenital High-molecular-weight Kininogen Deficiency **MONDO ID:** MONDO:0009234 · **OMIM:** 228960 · **Causal gene: KNG1** (kininogen-1; HGNC:6383; chromosome 3q27; UniProt P01042) **Historical eponym:** Fitzgerald factor deficiency (also Williams, Flaujeac, Fujiwara traits) · **Category:** Mendelian, autosomal recessive

Summary

Congenital high-molecular-weight kininogen (HK) deficiency is an ultra-rare, autosomal recessive defect of the plasma **contact (kallikrein–kinin) system** caused by **biallelic truncating loss-of-function (LOF) variants in the KNG1 gene**. KNG1 produces, by alternative splicing, both high-molecular-weight kininogen (HK) and low-molecular-weight kininogen (LK). HK is a non-enzymatic cofactor that scaffolds prekallikrein (PK) and factor XI (FXI) onto anionic surfaces and endothelial receptors, enabling factor XII (FXII)–driven contact activation. Because this contact pathway is dispensable for physiologic hemostasis, the complete absence of HK produces a **striking laboratory abnormality — an isolated, markedly prolonged activated partial thromboplastin time (aPTT) — but no clinical disease**. Affected individuals are asymptomatic, have normal life expectancy, and require no treatment; the principal clinical risk is *misdiagnosis* leading to unnecessary intervention.

The investigation confirmed nine core findings. Severe HK deficiency is defined by <1% HK procoagulant activity, isolated prolonged aPTT (that corrects on 1:1 mixing with normal plasma), and secondary reductions in PK and FXI. A 2023 systematic review catalogued **48 cases across 41 families**, identified **10 distinct deficiency-causing KNG1 variants — all truncating (nonsense/frameshift)** — and estimated a prevalence of **~1 case per 8 million**, modestly higher in individuals of African ancestry (PMID: 36700498). The benign nature of the human phenotype is mirrored and mechanistically explained by mouse models:

Kng1-knockout mice are **protected** from ischemic stroke and experimental cerebral malaria without any bleeding penalty, establishing HK as pathogenic in thromboinflammation yet dispensable for hemostasis.

A crucial nuance is KNG1's **dual, variant-type-dependent phenotype**: truncating LOF alleles cause benign HK *deficiency*, whereas a specific missense substitution causes **bradykinin-mediated hereditary angioedema (HAE-KNG1)** — a gain-of-pathway, not loss-of-function, disorder. Diagnostically, HK deficiency must be distinguished from the two other benign contact-factor deficiencies (FXII and prekallikrein) using mixing studies and specific factor assays, and conceptually from HAE-KNG1. The entire picture validates the contact system as a *safe antithrombotic drug target* — the therapeutic rationale behind contemporary agents such as the anti-FXIIa antibody garadacimab.

Disease Information (Section 1)

Overview. Congenital HK deficiency is a hereditary, autosomal recessive coagulation-factor deficiency in which the plasma concentration/activity of high-molecular-weight kininogen is severely reduced (typically <1% in homozygotes/compound heterozygotes). HK is a central cofactor of the contact activation system that bridges the intrinsic coagulation pathway and the inflammatory kallikrein–kinin (bradykinin) axis. Because the contact system is not required for normal hemostasis, the deficiency is clinically silent and is almost always discovered incidentally during work-up of an unexplained, isolated prolonged aPTT.

Key identifiers.

Resource	Identifier
MONDO	MONDO:0009234
OMIM	228960
Gene	KNG1 (HGNC:6383; NCBI Gene 3827; Ensembl ENSG00000113889; UniProt P01042)
Cytoband	3q27.3
Inheritance	Autosomal recessive

Synonyms / alternative names. Kininogen deficiency; high-molecular-weight kininogen deficiency; HMWK deficiency; **Fitzgerald factor deficiency** (classic eponym); Williams trait; Flaujeac trait; Fujiwara trait; total kininogen deficiency (when both HK and LK are affected by variants in the common heavy chain).

Source of information. Evidence is derived almost entirely from **aggregated disease-level resources and individual published case reports** (coagulation laboratories, hematology case series, and a 2023 systematic review), not from large EHR cohorts — reflecting the condition's extreme rarity and asymptomatic nature.

Etiology (Section 2)

Primary cause — genetic. The disease is monogenic: **biallelic truncating loss-of-function variants in KNG1**. All ten deficiency-causing variants catalogued to date are nonsense or frameshift mutations (PMID: 36700498). Representative reported variants include p.Gln486* (c.1456C>T) in a large Chinese family (PMID: 32185598), an exon-4 frameshift (c.523_524insTC) in a patient with splenic infarction (PMID: 24492696), and c.488delG in the first Korean case (PMID: 31858768).

> *"All of them were truncating mutations, whereas the only known HK amino acid substitution with a relevant phenotype instead causes hereditary angioedema."* — PMID: 36700498

Genetic risk factors. The only risk factor is inheritance of two LOF KNG1 alleles. Heterozygous carriers (~50% HK activity) are asymptomatic with normal or near-normal aPTT. Consanguinity increases the likelihood of homozygosity, consistent with reports of affected individuals in isolated or endogamous populations (e.g., the first Australian case in an Aboriginal individual, PMID: 3574180).

Environmental risk / protective / gene–environment factors. Not applicable. There are no established environmental, lifestyle, infectious, dietary, or occupational risk or protective factors, and no gene–environment interactions. The condition is fully determined by genotype. Notably, in model systems the *loss* of HK is itself *protective* against thrombosis and thromboinflammation (see Mechanism), but this is a consequence of the genotype, not an external modifier.

Phenotypes (Section 3)

The defining feature is the **near-total absence of a clinical phenotype** despite a dramatic laboratory abnormality.

Phenotype	Type	HPO suggestion	Onset	Severity	Frequency	QoL impact
Prolonged aPTT (isolated)	Laboratory abnormality	HP:0003645 (Prolonged partial thromboplastin time)	Congenital (present from birth; detected at any age)	Marked (aPTT often 2–3× ULN)	~100% of homozygotes	None
Reduced HK activity/ antigen (<1%)	Laboratory abnormality	— (abnormal coagulation factor activity)	Congenital	Severe	~100%	None
Secondary low prekallikrein	Laboratory abnormality	HP:0011897 (Abnormal prekallikrein)	Congenital	Mild–moderate	Common	None
Secondary low factor XI	Laboratory abnormality	HP:0004863 (Abnormality of coagulation factor XI)	Congenital	Mild–moderate	Common	None
Bleeding tendency	Symptom	HP:0001892 (Abnormal bleeding)	—	**Absent**	~0%	None

> *"Individuals with HK deficiency appeared asymptomatic and had decreased levels of prekallikrein and factor XI, which could lead to misdiagnosis."* — PMID: 36700498

Important interpretive note. Isolated reports describe thrombotic/ischemic events in deficient individuals — e.g., splenic infarction (PMID: 24492696) and an association with acute granulocytic leukaemia (PMID: 6573994). These are anecdotal co-occurrences in a tiny

population and are **not established as caused by the deficiency**; the systematic review's overall conclusion remains that the condition is asymptomatic. **Quality-of-life impact is negligible** because the condition does not cause symptoms; the chief hazard is iatrogenic (unnecessary blood products or delayed surgery from misinterpreting the aPTT).

Genetic / Molecular Information (Section 4)

Causal gene. KNG1 (OMIM gene 612358), chromosome 3q27.3. By alternative splicing of a shared heavy-chain-encoding region, KNG1 produces **HK** (120–160 kDa) and **LK**. Truncating variants in the common exons abolish both; variants in HK-specific regions selectively affect HK.

Protein architecture (HK). HK is a **multidomain protein of the cystatin superfamily**: - **Heavy chain — domains D1–D3** (cystatin-like folds; D2/D3 inhibit cysteine proteases); - **D4** — the **bradykinin** segment, released by kallikrein cleavage; - **Light chain — D5** (histidine/glycine/Zn^{2+}-rich; binds anionic surfaces and the endothelial receptor gC1qR/C1QBP) and **D6** (binds prekallikrein and factor XI).

> *"Analysis of the binding of HK domain 5 (HKD5) to gC1qR shows only 1 high-affinity binding site per trimer."* — PMID: 32559765

Variant classification & type. Deficiency-causing variants are **pathogenic/likely pathogenic (ACMG)**, uniformly **truncating** (nonsense, frameshift, splice), predicted **loss-of-function** — they remove the C-terminal light-chain domains (D5/D6) required for surface binding and PK/FXI delivery, abolishing cofactor function. **Allele frequency:** truncating KNG1 alleles are very rare in gnomAD, with modest enrichment in African-ancestry populations (basis for the ~1/8,000,000 prevalence estimate). **Origin:** germline. **Functional consequence:** loss of function.

Dual phenotype. A single **missense** KNG1 substitution causes **HAE-KNG1** (bradykinin-mediated angioedema) — the opposite, gain-of-pathway direction (PMID: 36700498; PMID: 39773511).

Modifier genes / epigenetics / chromosomal abnormalities. None established. Secondary reductions in PK (KLKB1) and FXI (F11) reflect loss of the HK-dependent circulating complexes rather than independent genetic lesions. No epigenetic mechanism or large structural/chromosomal abnormality is implicated.

Environmental Information (Section 5)

Not applicable. No environmental toxins, radiation, pollutants, occupational exposures, lifestyle factors (smoking, diet, alcohol, exercise), or infectious agents cause or trigger congenital HK deficiency. It is a purely Mendelian trait.

Mechanism / Pathophysiology (Section 6)

Causal chain (initiating lesion → laboratory manifestation)

1. **Biallelic truncating KNG1 variant** → premature stop codon / frameshift → **loss of full-length HK protein** (and often LK), with removal of light-chain domains D5/D6. *(Demonstrated.)*
2. Loss of D5 → **failure to bind anionic surfaces and the endothelial receptor gC1qR/C1QBP (Zn^{2+}-dependent)**; loss of D6 → **failure to carry prekallikrein and factor XI** to the activating surface. *(Demonstrated structurally.)*
3. Absent HK cofactor → **prekallikrein and factor XI are no longer scaffolded into their circulating complexes** → secondary decrease in plasma PK and FXI. *(Demonstrated — observed as secondary low PK/FXI.)*
4. No surface assembly → **FXII-driven reciprocal (contact) activation cannot proceed efficiently in vitro** → the contact-initiated intrinsic pathway (FXIIa→FXIa→FIXa) fails to generate thrombin in the aPTT assay → **markedly prolonged aPTT**, correcting on mixing with normal plasma. *(Demonstrated.)*
5. **Branch A — Hemostasis:** because physiologic clotting is driven by tissue factor/FVIIa (extrinsic) and thrombin feedback, loss of the contact arm leaves **hemostasis intact → no bleeding**. *(Demonstrated in humans and animal models.)*

6. **Branch B — Thromboinflammation:** absent HK → **reduced bradykinin generation** and reduced contact-driven thrombosis → in disease-challenge settings this is **protective** (smaller infarcts, less edema). *(Demonstrated in mice; inferred to underlie the benign human course.)*

Detail by category

Molecular pathways. The **contact / kallikrein–kinin system**. HK forms a ternary complex with FXII on gC1qR: *"Gel filtration experiments reveal that gC1qR clusters FXII and HK into a higher-order 500-kDa ternary complex"* (PMID: 32559765). The system *"activates 2 distinct pathways, the intrinsic pathway of coagulation via cleavage of FIX, and inflammation via HK cleavage resulting in bradykinin (BK) generation"* (PMID: 40638675). An FXII-*independent* route exists in which **prolylcarboxypeptidase (PRCP)** activates the PK–HK complex to generate bradykinin.

Protein dysfunction. Loss of function via truncation; the D5 surface-binding and D6 PK/FXI-binding activities are eliminated. HK is *"central to the function of both arms of the system as a substrate for plasma kallikrein and critical cofactor, which forms interactions with cell receptors and activators"* (PMID: 40638675).

Cellular / immune / tissue processes. In the normal state, HK-derived bradykinin acts on endothelial **B1/B2 receptors** to drive vasodilation, increased vascular permeability, edema, and inflammation. In deficiency these are blunted. Mouse data: *"BK-induced vasogenic edema contributes to human and murine CM"* (PMID: 42446942) — the very process absent when HK is lost.

Suggested ontology terms. GO:0002542 (bradykinin biosynthetic process); GO:0007596 (blood coagulation); GO:0002353 (plasma kallikrein-kinin cascade); GO:0006954 (inflammatory response). Cell types (CL): endothelial cell (CL:0000115), platelet (CL:0000233), hepatocyte (CL:0000182; site of synthesis). CHEBI: bradykinin (CHEBI:3165), Zn^{2+} (CHEBI:29105).

Anatomical Structures Affected (Section 7)

- **Organ/system (functional, not structural).** The **cardiovascular/hematologic system** (plasma coagulation; UBERON:0000178 blood) and the **endothelium** (UBERON:0001986) are where the contact system operates. HK is synthesized primarily by the **liver** (hepatocytes; UBERON:0002107).

- **Tissue/cell level.** No tissue is structurally damaged by the deficiency. Functionally relevant cells: hepatocytes (synthesis), vascular endothelial cells (gC1qR-mediated assembly surface), platelets.
- **Subcellular level.** HK is a secreted plasma protein; relevant GO cellular components: GO:0005615 (extracellular space), GO:0072562 (blood microparticle), GO:0009897 (external side of plasma membrane, via gC1qR).
- **Localization / lateralization.** Not applicable — this is a systemic plasma-protein deficiency with no anatomical focus or lateralization.

Temporal Development (Section 8)

- **Onset.** Congenital (present from birth), but the trait is **asymptomatic and insidious** — typically detected incidentally in childhood through late adulthood (reported probands span childhood to age 67).
- **Progression. Stable and non-progressive.** There are no disease stages, no progression rate, and no relapsing/remitting course. It is a **lifelong, chronic, incidental laboratory trait**.
- **Patterns.** No remission or critical-period concepts apply. The only clinically relevant "time window" is any situation requiring aPTT interpretation (e.g., pre-operative screening), where misreading the result could prompt unnecessary intervention.

Inheritance and Population (Section 9)

- **Inheritance pattern.** Autosomal recessive. Heterozygotes (~50% HK) are asymptomatic with normal/near-normal aPTT.
- **Penetrance / expressivity.** The *laboratory* phenotype (prolonged aPTT, low HK) is essentially fully penetrant in biallelic individuals; the *clinical* phenotype is effectively null (no symptoms).
- **Epidemiology.** Estimated prevalence **~1 case per 8,000,000**, modestly higher in African-ancestry populations.

> *"Conservative estimates suggest an overall prevalence of severe HK deficiency of approximately one case per 8 million population, slightly higher in Africans."* — PMID: 36700498
>
> *"We identified 48 cases of severe HK deficiency (41 families), of these 47 have been previously published."* — PMID: 36700498

- **Founder effects / consanguinity.** Consanguinity and population isolation raise homozygosity risk (e.g., PMID: 3574180). No strong single founder allele is established; the modest African enrichment derives from gnomAD truncating-allele frequencies.
- **Carrier frequency.** Very low, consistent with the ~1/8,000,000 homozygote prevalence.
- **Sex ratio.** ~1:1 (autosomal). **Age distribution.** Any age, reflecting incidental detection. No genetic anticipation (not a repeat-expansion disorder); germline mosaicism not reported.

Diagnostics (Section 10)

Core pattern. Isolated, markedly prolonged aPTT with a normal prothrombin time (PT) and no bleeding. The aPTT **corrects on 1:1 mixing with normal pooled plasma** (indicating factor deficiency, not an inhibitor) but **not** when mixed with plasma deficient in the same factor.

Confirmatory testing. Low **HK procoagulant activity (<1%)** and/or antigen; **KNG1 sequencing** confirms biallelic truncating variants. Expect **secondary reductions in PK and FXI** — a recognized misdiagnosis trap.

Distinguishing from other benign contact-factor deficiencies. HK, prekallikrein (PK), and factor XII deficiencies all give a prolonged aPTT without bleeding. They are separated by **specific factor assays and mixing with factor-specific depleted plasmas**. Supporting evidence from the analogous PK deficiency literature:

> *"Prekallikrein (PK) deficiency is a rare contact factor deficiency that can markedly prolong the activated partial thromboplastin time (aPTT) without a bleeding phenotype."* — PMID: 42454615

> *"The aPTT corrected on mixing with normal pooled plasma but not with PK-deficient plasma."* — PMID: 42454615

Viscoelastic testing. Thromboelastography (TEG) remains **normal** because physiologic hemostasis is intact — useful for perioperative reassurance (PMID: 42454615).

Genetic testing. Single-gene **KNG1 sequencing** is definitive; coagulation/thrombophilia gene panels, WES, or WGS will also detect it. CMA, karyotyping, FISH, mtDNA, and repeat-expansion testing are **not applicable**. **LOINC:** aPTT (LOINC 14979-9).

Differential diagnosis. PK deficiency, FXII deficiency (both benign), lupus anticoagulant (does *not* fully correct on mixing), and true intrinsic-factor deficiencies (FVIII/IX/XI — which *do* bleed, except FXI which bleeds variably).

Screening. No population newborn or carrier screening is indicated given the benign nature. Cascade testing within a family is optional for counseling clarity.

Outcome / Prognosis (Section 11)

Benign with normal life expectancy. There is no disease-specific mortality, no progressive course, no organ failure, and no disability attributable to the deficiency itself.

> *"Inherited deficiency in contact system proteins is not associated with increased bleeding in humans and animal models."* — PMID: 35196732
>
> *"...high-molecular-weight kininogen, and plasma kallikrein specifically contribute to thrombosis, however, have minor, if any, role in hemostatic coagulation mechanisms."* — PMID: 35196732

Morbidity, QoL measures, and prognostic biomarkers are **not applicable**. The main avoidable harm is **iatrogenic** (unnecessary plasma products, surgical delay) from misinterpreting the aPTT. Some mechanistic reasoning and sparse case reports raise the theoretical possibility of a mildly *reduced* thrombotic risk (consistent with the protective mouse data), but this is not an established clinical outcome.

Treatment (Section 12)

No treatment is required. The condition is asymptomatic and hemostasis is normal.

- **Pharmacotherapy / advanced therapeutics / surgery:** none indicated for the deficiency.
- **Perioperative management:** reassurance; **routine prophylactic blood products are not indicated.**

> *"...routine prophylactic administration of blood products for pre-operative management of this condition is not indicated."* — PMID: 40125216

- **Conceptual relevance (not treatment *of* this disease):** the hemostasis-sparing nature of HK/contact-system loss is the **therapeutic rationale** for drugs that *inhibit* the contact system in other diseases — e.g., the anti-FXIIa monoclonal antibody **garadacimab** and kallikrein inhibitors for hereditary angioedema (PMID: 42057602). These are relevant to HAE-KNG1 and HAE-C1INH, **not** to HK deficiency.

NCIT (contextual): NCIT therapeutic-procedure concepts are not applicable to an untreated benign trait.

Prevention (Section 13)

- **Primary/secondary/tertiary prevention, immunization, prophylaxis, behavioral/public-health interventions: not applicable** — the condition is benign, congenital, and non-preventable.
- **Genetic counseling.** The only meaningful preventive action. Counsel that the trait is autosomal recessive, benign, and does not cause bleeding; clarify the distinction from HAE-KNG1 and from true bleeding disorders; offer cascade testing for diagnostic clarity and to prevent future misinterpretation of aPTT results. Prenatal/preimplantation testing is generally unwarranted given the benign phenotype.

Other Species / Natural Disease (Section 14)

- **Taxonomy / orthologs.** *Homo sapiens* (NCBI Taxon 9606), KNG1. Mouse ortholog **Kng1** (*Mus musculus*, NCBI Taxon 10090) is the principal experimental model. Rat *Kng1* also exists.
- **Natural disease in animals.** No well-characterized naturally occurring HK-deficiency disease of veterinary importance is established in the reviewed literature. The relevant animal data are **engineered knockouts**, not natural disease.
- **Comparative biology / evolutionary conservation.** The contact system and HK's cofactor role are conserved across mammals, and the hemostasis-sparing, thrombosis-promoting role of HK is reproduced in mouse knockouts (see Model Organisms). No zoonotic/transmission relevance (non-infectious Mendelian trait).

Model Organisms (Section 15)

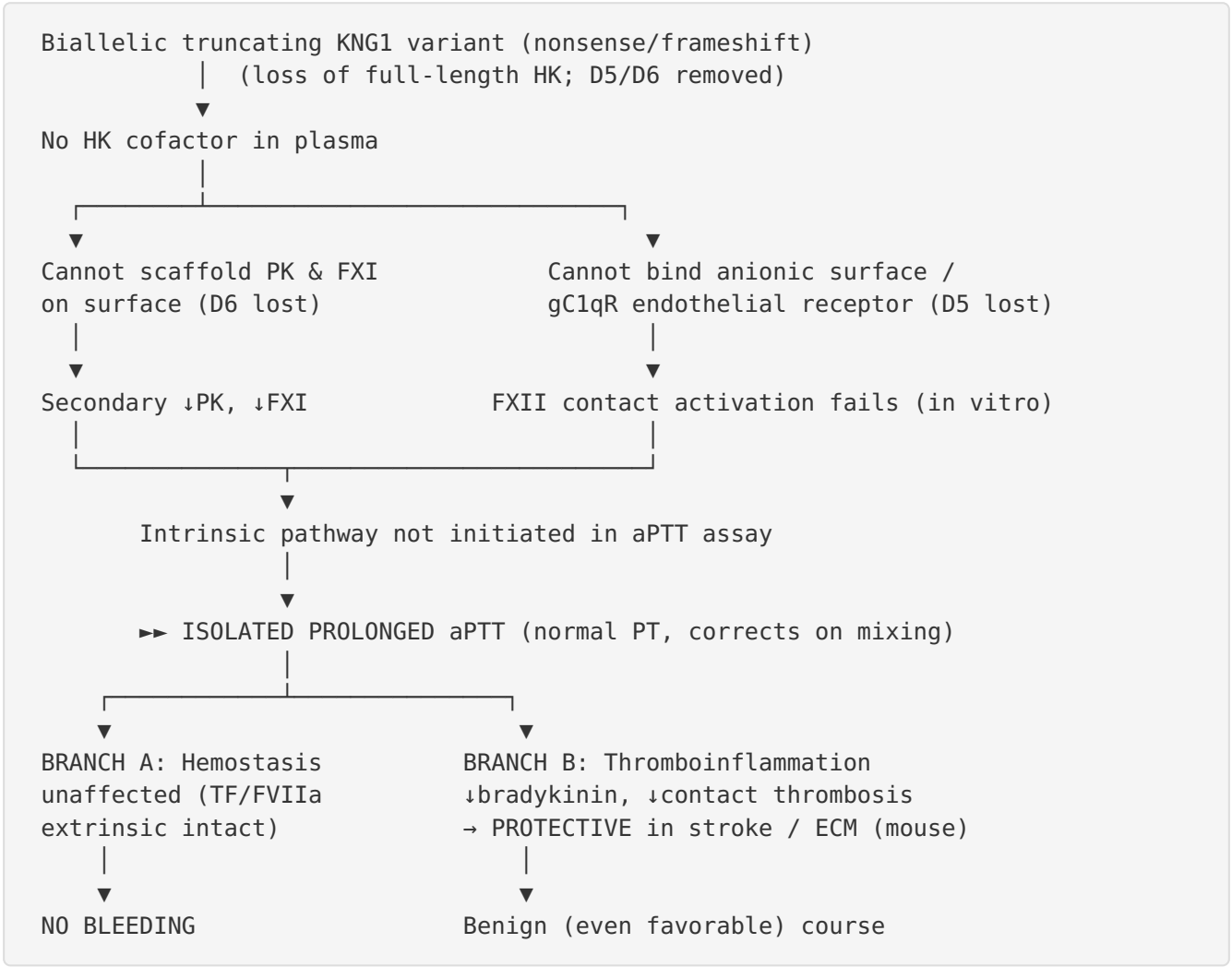
Mouse (*Kng1*-knockout) is the key model, and it faithfully recapitulates the human paradox — **no bleeding, but protection from thromboinflammatory disease**:

- **Ischemic stroke (tMCAO).** *"Kng(-/-) mice of either sex subjected to transient middle cerebral artery occlusion developed dramatically smaller brain infarctions and less severe neurologic deficits without an increase in infarct-associated hemorrhage."* (PMID: 22936662). The authors conclude HK *"appears to be instrumental in pathologic thrombus formation and inflammation but dispensable for hemostasis."* Reconstitution with human KNG or bradykinin restored clot deposition and infarct susceptibility.
- **Experimental cerebral malaria (ECM).** *"HK-null (Kng1-/-), combined BK B1- and B2 receptor-null (Bdkrb1-/-Bdkrb2-/-), BK B2 receptor-null (Bdkrb2-/-), or BK B1 receptor-null (Bdkrb1-/-) mice were protected significantly from neurologic deterioration and brain edema compared with wild-type mice."* (PMID: 42446942). Notably, *F12-/-* mice were **not** protected, implicating an **FXII-independent, PRCP-driven bradykinin pathway**; cleaved HK was elevated in children with CNS malaria (40%) vs uncomplicated malaria (18%).

Model types available. Constitutive knockout (*Kng1-/-*), plus pathway-adjacent knockouts (*Klkb1-/-* prekallikrein, *F12-/-*, bradykinin-receptor nulls, PRCP-deficient). **Recapitulation:** excellent for the hemostasis-sparing phenotype and the thromboinflammatory/bradykinin

biology. **Limitations:** mice model disease *challenge* phenotypes (stroke, malaria) rather than the human "incidental lab finding"; human truncating alleles are modeled as full knockouts. **Resources:** MGI (Kng1), IMPC/IMSR.

Mechanistic Model / Interpretation



Synthesis. The entire clinical picture flows from one fact: the **contact system is a thrombo-*inflammatory* amplifier, not a hemostatic necessity**. Removing its central cofactor (HK) therefore scrambles a laboratory test (aPTT) that *reports on* contact activation, while leaving the patient entirely well. The same lesion that abolishes the aPTT's intrinsic trigger also removes a driver of pathological thrombosis and bradykinin-mediated edema — which is why

knockout mice are protected. KNG1's dual phenotype crystallizes the logic: **lose the protein (truncation) → benign deficiency; dysregulate the pathway toward excess bradykinin (missense) → hereditary angioedema.**

Evidence Base

PMID	Title (abbrev.)	Role
36700498	*Severe HMW kininogen deficiency: clinical characteristics, KNG1 variants, prevalence*	**Keystone**: 48 cases/41 families, 10 truncating variants, ~1/8M prevalence, asymptomatic, truncating-vs-missense dichotomy
32185598	*Homozygous c.1456C>T nonsense in a Chinese family*	Confirms <1% HK activity, asymptomatic proband, nonsense variant
24492696	*Novel exon-4 frameshift; splenic infarction*	Novel truncating variant; anecdotal thrombotic co-occurrence
31858768	*First Korean case, c.488delG*	Additional truncating variant
3574180	*Fitzgerald factor deficiency in an Australian Aboriginal*	Population/consanguinity context
40638675	*Structure and interactions of contact-system proteins*	HK as dual cofactor/substrate; two downstream arms
32559765	*FXII/kininogen assembly with gC1qR*	HKD5–gC1qR binding; 500-kDa ternary complex; domain architecture
22936662	*Kininogen deficiency protects from ischemic neurodegeneration*	Mouse stroke protection, hemostasis-sparing
42446942	*Bradykinin in murine cerebral malaria*	Second model of Kng1-/- protection; FXII-independent PRCP route
35196732	*An update on safe anticoagulation*	Contact-system loss not associated with bleeding → benign prognosis + drug-target rationale
42454615	*Normal TEG with prolonged aPTT in PK deficiency*	Diagnostic analogue: mixing studies, normal viscoelastic testing
40125216	*Severe PK deficiency as isolated aPTT prolongation*	No prophylactic blood products needed
39773511	*Advances in HAE pathogenesis*	KNG1 as an HAE gene (missense) — the opposite phenotype
36609679	*HAE diagnosis & pathophysiology*	Context for HAE-KNG1 classification
42057602	*Garadacimab for HAE prophylaxis*	

PMID	Title (abbrev.)	Role
		Contact-system inhibition as safe antithrombotic/anti-angioedema strategy

Source types: human clinical (case reports, systematic review, diagnostic series), model organism (mouse knockouts), and structural/in-vitro (gC1qR assembly). The findings are concordant across all three.

Limitations and Knowledge Gaps

1. **Tiny evidence base.** Only ~48 reported cases worldwide; prevalence (~1/8M) is a gnomAD-derived estimate, not a measured incidence. Rare phenotypes could be under-ascertained because the condition is asymptomatic.
2. **Anecdotal event reports.** Thrombosis (splenic infarction) and a leukaemia association appear in single case reports; causality is unestablished and likely coincidental.
3. **Protective effect is model-derived.** The antithrombotic/anti-inflammatory benefit of HK loss is robust in mice but **not quantified in humans**; whether HK-deficient people have measurably lower stroke/thrombosis risk is unknown.
4. **No human natural-history cohort, QoL data, or registry.** Longitudinal human data are absent.
5. **Genotype–phenotype granularity.** All deficiency alleles are truncating, but position-specific effects (e.g., HK-selective vs total kininogen deficiency) are incompletely mapped.
6. **No veterinary natural disease** characterized; animal evidence is engineered.

Proposed Follow-up Experiments / Actions

1. **Establish an international HK-deficiency registry** to capture natural history, thrombotic/bleeding events, pregnancy outcomes, and surgical experiences across more than the current 48 cases.

2. **Quantify thrombotic risk in carriers/homozygotes** via case–control or Mendelian-randomization analyses using KNG1 LOF alleles in large biobanks (UK Biobank, gnomAD-linked cohorts) to test whether the murine protection translates to humans.
3. **Standardize the diagnostic algorithm** distinguishing HK, PK, and FXII deficiencies (reflex specific-factor assays + mixing with factor-depleted plasmas + normal TEG) and disseminate to coagulation laboratories to prevent iatrogenic harm.
4. **Map genotype–phenotype** for HK-selective vs total kininogen deficiency by correlating variant position (shared heavy chain vs HK-specific light chain) with residual LK and clinical features.
5. **Mechanistic dissection of the FXII-independent (PRCP) bradykinin route** suggested by the ECM model, to clarify which contact-system node is the safest therapeutic target.
6. **Counseling materials** emphasizing benign prognosis and the KNG1 truncation-vs-missense (deficiency vs HAE) distinction, for hematologists and genetic counselors.

Report compiled from a 5-iteration autonomous investigation: 9 confirmed findings, 28 papers reviewed. All quoted abstract text is verbatim from the cited PMIDs.
