

Essential Fructosuria (MONDO:0009252): A Comprehensive Disease Characteristics Report

Summary

Essential fructosuria (EF) is a benign, lifelong, autosomal-recessive inborn error of carbohydrate metabolism caused by biallelic loss-of-function variants in **KHK**, the gene encoding **ketohehexokinase (fructokinase, EC 2.7.1.3)** on chromosome 2p23.3. KHK catalyzes the first, hepatic-predominant committed step of dietary fructose catabolism — the ATP-dependent phosphorylation of fructose to fructose-1-phosphate (F1-P). When this step is lost, ingested fructose is not metabolized at its normal rate and simply spills into the blood and urine, producing transient hyperfructosemia and fructosuria after fructose or sucrose ingestion. Because the metabolic block lies **upstream** of the point where toxic F1-P would accumulate, EF causes **no tissue injury, no hypoglycemia, and no clinical symptoms**. It requires no treatment and is most often discovered incidentally when reducing substances are detected in the urine. Its chief clinical importance is that it must not be mistaken for diabetes mellitus or for the far more dangerous **hereditary fructose intolerance (HFI)**.

The condition is one of the oldest known inborn errors of metabolism. The molecular basis was established by Bonthron and colleagues in 1994, who cloned human KHK and identified compound-heterozygous missense mutations (**p.Gly40Arg** and **p.Ala43Thr**) in a well-characterized affected family. Structural studies later modeled these substitutions in the KHK active site, and a Khk-knockout mouse recapitulated the fructosuric phenotype while additionally proving protected from diet-induced metabolic disease — directly linking the benign human condition to a tractable animal model and to the broader therapeutic interest in KHK inhibition for metabolic syndrome.

This report synthesizes the published literature with original population-genetic analyses of gnomAD v4 performed during this investigation. The genomic data reinforce the clinical picture: KHK is strongly **loss-of-function tolerant** ($LOEUF \approx 1.35$, $pLI \approx 0$), showing no signature of purifying selection against gene loss; the canonical disease allele p.Gly40Arg is European-predominant and is even found in a homozygous individual in general-population

data; and the aggregate pathogenic-allele burden implies EF is substantially rarer (~1 in 1–2 million) than the historically quoted ~1:130,000 figure, with a carrier frequency near 1 in 700. Together, these lines of evidence — classical biochemistry, modern genomics, and a knockout mouse — form a coherent and mutually reinforcing portrait of a genuinely harmless Mendelian trait.

1. Disease Information

Overview. Essential fructosuria is an asymptomatic metabolic trait in which dietary fructose appears in the blood and urine because the hepatic enzyme that normally initiates its breakdown — ketohexokinase/fructokinase — is deficient. It is a classical "non-disease": a biochemical abnormality with no pathological consequence.

"Essential fructosuria is one of the oldest known inborn errors of metabolism. It is a benign condition which is believed to result from deficiency of hepatic fructokinase (ketohexokinase, KHK, E.C.2.7.1.3)." — [PMID: 7833921](#)

Key identifiers.

Resource	Identifier
OMIM	229800
MONDO	MONDO:0009252
Orphanet	ORPHA:2056 (Essential fructosuria)
ICD-10	E74.1 (Disorders of fructose metabolism)
ICD-11	5C51.1 (Disorders of fructose metabolism)
MeSH	Fructose metabolism, inborn errors / "Fructosuria"
Gene	KHK (HGNC:6315), OMIM *614058, chromosome 2p23.3
Enzyme	Ketohexokinase / fructokinase, EC 2.7.1.3

Synonyms / alternative names. Fructokinase deficiency; ketohexokinase deficiency; hepatic fructokinase deficiency; benign fructosuria; "essential benign fructosuria." (Note: EF must be distinguished terminologically and clinically from "fructose intolerance," which denotes a different disease — see Section 10.)

Nature of the information source. The knowledge base here is derived almost entirely from **aggregated disease-level resources** (OMIM, Orphanet) and from a small number of **individual patient reports and family studies** (notably the compound-heterozygous family in Bonthron et al. 1994), supplemented in this report by **population-level genomic aggregation** (gnomAD v4). There is no large EHR cohort; the condition's rarity and benignity mean most knowledge comes from case reports and functional/genetic studies.

2. Etiology

Primary cause — genetic. EF is a monogenic, autosomal-recessive disorder caused by biallelic (homozygous or compound-heterozygous) loss-of-function variants in **KHK**. There is no environmental, infectious, or multifactorial contribution to disease causation; the only "environmental" element is dietary — fructose/sucrose/sorbitol intake is required to **reveal** the biochemical phenotype (fructosuria), but it does not cause disease.

"In a well-characterized family, in which three of eight siblings have fructosuria, all affected individuals are compound heterozygotes for two mutations Gly40Arg and Ala43Thr." — [PMID: 7833921](#)

Genetic risk factors. The causal variants are the KHK pathogenic alleles themselves — canonically **p.Gly40Arg (c.118G>A)** and **p.Ala43Thr** — plus the broader spectrum of KHK loss-of-function variants (108 high-confidence pLoF variants catalogued in gnomAD v4; see Section 4). No susceptibility loci or modifier genes have been established; none are expected given the simple, fully-penetrant recessive mechanism and benign outcome.

Environmental risk factors. None for disease causation. Age, sex, occupational, and toxic exposures are not relevant. Family history (consanguinity) increases the chance of homozygosity, as for any recessive trait.

Protective factors. Not applicable in the usual sense — there is no disease state to protect against. Of note, the KHK loss-of-function state is itself metabolically **protective** against fructose-driven harm: in mice, KHK deficiency prevents fructose-induced hyperglycemia, visceral obesity, and insulin resistance (see Sections 6 and 15). This is the basis for pharmacological KHK inhibition as a therapy for metabolic disease.

Gene–environment interaction. The only GxE relationship is that **dietary fructose intake determines the magnitude of fructosuria/hyperfructosemia** in genetically affected individuals. Without fructose exposure, affected individuals are biochemically silent. This interaction is physiological, not pathological.

3. Phenotypes

Essential fructosuria is remarkable for the **near-complete absence of a clinical phenotype**. The only reproducible manifestation is a laboratory abnormality.

"The only reported symptom of EF is the appearance of fructose in the urine following either oral or intravenous fructose administration." — [PMID: 29664676](#)

"Hereditary deficiency of ketohexokinase (KHK)... leads to essential fructosuria in humans, characterized by elevated levels of blood and urinary fructose following fructose ingestion but is otherwise clinically benign." — [PMID: 29870677](#)

Phenotype	Type	Onset	Severity	Progression	Frequency	HPO suggestion
Fructosuria (fructose in urine)	Laboratory abnormality	Present from birth; detectable whenever fructose is ingested	Benign	Stable, lifelong, episodic (tied to intake)	~100% of affected after fructose load	HP:0032262 (Fructosuria); HP:0003076 (Glycosuria — related urinary reducing substances)
Hyperfructosemia (elevated blood fructose)	Laboratory abnormality	Congenital trait; appears post-ingestion	Benign	Transient, intake-dependent	~100% after fructose load	No specific HPO; "Abnormal circulating fructose concentration" concept
Positive urine reducing substances	Laboratory abnormality	Any age	Benign (diagnostic pitfall)	Episodic	Frequent, intake-dependent	HP:0003076 (Glycosuria, broad)

Quality-of-life impact. None. EF does not affect daily functioning, growth, development, cognition, or well-being. No EQ-5D, SF-36, or PROMIS data exist because there is no morbidity to measure. The only practical "impact" is the risk of an unnecessary diagnostic workup or misdiagnosis (e.g., as diabetes mellitus) if the urinary reducing substance is wrongly attributed to glucose.

4. Genetic / Molecular Information

Causal gene. *KHK* (ketohexokinase; HGNC:6315; OMIM 614058), *chromosome 2p23.3 (2p23.2–23.3)*. *KHK* lies within ~500 kb of the glucokinase regulator gene *GCKR**, with which it is metabolically connected (GCKR inhibition of glucokinase is relieved by F1-P, the product of KHK).

"KHK maps to Chromosome (Chr) 2p23.2-23.3... The proximity of GCKR and KHK was further demonstrated... the two genes lie within 500 kb of each other." — [PMID: 8662230](#)

Pathogenic variants.

Variant	cDNA	Type	Classification	gnomAD v4 allele frequency	Notes
p.Gly40Arg	c.118G>A	Missense	Pathogenic	$\sim 2.1 \times 10^{-4}$ (1 homozygote observed)	Canonical EF allele; European-predominant
p.Ala43Thr	c.127G>A	Missense	Pathogenic	$\sim 7.3 \times 10^{-5}$	Second canonical allele; same conserved region
108 high-confidence pLoF variants	various	nonsense/frameshift/splice	Predicted pathogenic	$\Sigma AF \approx 4.2 \times 10^{-4}$	Aggregate loss-of-function burden
p.Val49Ile	—	Missense	Benign polymorphism	~ 0.37	Common; NOT pathogenic

Both canonical mutations arise from **G→A transitions** and alter the **same conserved region** of the protein; neither was present in 52 controls in the original study.

"Both mutations result from G→A transitions, and each alters the same conserved region of the KHK protein. Neither mutation was seen in a sample of 52 unrelated control individuals." — [PMID: 7833921](#)

Functional consequence. Loss of function (enzyme deficiency). Structural modeling of p.Gly40Arg and p.Ala43Thr in the KHK crystal structure places both substitutions in the context of the active site, explaining reduced/abolished fructose phosphorylation.

"Hepatic KHK deficiency causes the benign disorder essential fructosuria. The effects of the disease-causing mutations (Gly40Arg and Ala43Thr) have been modelled in the context of the KHK structure." — [PMID: 19237742](#)

Allele-frequency / ancestry stratification (gnomAD v4, this analysis). p.Gly40Arg overall AF $\approx 2.1 \times 10^{-4}$ with **1 homozygote** observed in the general population — direct evidence that the homozygous genotype is viable and benign. Ancestry-stratified:

Population	p.Gly40Arg AF
Non-Finnish European	2.6×10^{-4} (287/1,111,956; highest)
Middle Eastern	1.7×10^{-4}
Admixed American	8.9×10^{-5}
South Asian	5.8×10^{-5}
East Asian	5.0×10^{-5}
African / African-American	0
Ashkenazi Jewish	0
Finnish	0

A rarer alternate nucleotide change (G→C) also encoding p.Gly40Arg exists at AF $\approx 4.8 \times 10^{-6}$.

Constraint. KHK shows **no purifying selection against loss of function**: observed/expected LoF = 37 observed vs 36.0 expected (oe_lof ≈ 1.03 ; 90% CI 0.79–1.35), **LOEUF ≈ 1.35 , pLI $\approx 1.7 \times 10^{-13} \approx 0$** , lof_z ≈ -0.14 , mis_z ≈ -0.07 . LoF and missense variants occur at essentially the frequency expected by chance — population-genetic confirmation that losing fructokinase is fitness-neutral.

Somatic vs germline. All EF variants are **germline**. No somatic relevance.

Modifier genes / epigenetics / chromosomal abnormalities. None established. EF is not associated with aneuploidy, translocations, methylation changes, or chromatin disorders. GCKR colocalization raises the theoretical possibility of shared cis-regulation but has no demonstrated role in EF pathology.

Ontology / chemical terms. CHEBI:28757 (fructose); CHEBI:18105 (fructose-1-phosphate); CHEBI:15422 (ATP).

5. Environmental Information

- **Environmental factors (toxins, radiation, pollution):** None contribute to EF.
 - **Lifestyle / dietary factors:** Dietary **fructose, sucrose (a fructose–glucose disaccharide), and sorbitol** are the substrates that reveal the biochemical phenotype. Higher intake produces more pronounced hyperfructosemia/fructosuria but no symptoms. Diet is a *modulator of the biomarker*, not a cause of disease.
 - **Infectious agents:** Not applicable — EF is a monogenic metabolic trait with no infectious component.
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6. Mechanism / Pathophysiology

Causal chain (initiating lesion → clinical manifestation)

1. **Biallelic loss-of-function KHK variants** (e.g., p.Gly40Arg + p.Ala43Thr) → **lead to** a deficient/absent ketohexokinase enzyme in hepatocytes (and kidney/intestine). (*Demonstrated — Bonthron 1994; structural modeling.*)
2. Deficient KHK → **results in** failure to phosphorylate dietary fructose to fructose-1-phosphate (the first committed step of fructolysis). (*Demonstrated biochemically.*)
3. Unphosphorylated fructose is not trapped or committed to hepatic metabolism → **leads to** reduced hepatic fructose clearance and **accumulation of free fructose** in portal and systemic blood (hyperfructosemia). (*Demonstrated in KHK^{-/-} mice; inferred in humans.*)
4. Elevated plasma fructose exceeds the renal threshold / escapes tubular reabsorption → **results in** urinary excretion of fructose (**fructosuria**). (*Demonstrated — the defining clinical sign.*)
5. **Branch point — why no toxicity:** Because the block is **upstream** of F1-P formation, there is **no accumulation of fructose-1-phosphate** and hence **no phosphate/ATP trapping, no inhibition of gluconeogenesis/glycogenolysis, and no hypoglycemia or hepatotoxicity**

→ **results in** a clinically silent, benign course. (*This is the key contrast with HFI, where the block is one step downstream at aldolase B and F1-P accumulates toxically.*)

6. **Compensatory branch (inferred/modelled):** altered portal fructose absorption, slowed peripheral metabolism, near-absent renal fructose reabsorption, and upregulated alternate hepatic fructose pathways buffer the system. (*Predicted by mathematical modeling — Allen & Musante 2018.*)

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Dietary fructose
|
v
[KHK/fructokinase] <-- DEFICIENT in EF (block here, UPSTREAM)
|   X
v
Fructose-1-phosphate <-- does NOT accumulate in EF (benign)
|
v
[Aldolase B / ALDOB] <-- block here = HFI (F1-P accumulates, TOXIC)
|
v
Glyceraldehyde + DHAP --> glycolysis / gluconeogenesis

EF: fructose spills to blood & urine -> hyperfructosemia + fructosuria, NO toxicity
HFI: F1-P trapped -> Pi depletion, ATP loss -> hypoglycemia, liver & kidney injury

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Supporting detail

Molecular pathway. Fructolysis (KEGG hsa00051, fructose and mannose metabolism). KHK performs: fructose + ATP → fructose-1-phosphate + ADP.

"Fructose catabolism is initiated by its phosphorylation to fructose 1-phosphate, which is performed by ketohexokinase (KHK)." — [PMID: 19237742](#)

Protein dysfunction. KHK is a homodimeric α/β -fold enzyme with two isoforms (KHK-A, ubiquitous and low-level; KHK-C, high-level in liver/kidney/intestine) arising from alternative splicing of exon 3. EF results from loss of hepatic KHK-C activity. The disease missense substitutions sit in a conserved active-site region; catalysis involves a conformational change in which a β -sheet domain rotates to cap the active site.

Metabolic changes. The central change is diversion/non-clearance of fructose rather than toxic metabolite buildup. In KHK^{-/-} mice, deletion of KHK prevents fructose-induced hyperglycemia but causes dramatic hyperfructosemia (>1 mM) with reversed portal-to-systemic fructose gradients.

"Deletion of KHK prevented fructose-induced hyperglycemia, but caused dramatic hyperfructosemia (>1 mM) with reversed portal to systemic gradients." — [PMID: 26316589](#)

Protective downstream consequence. By preventing F1-P generation, KHK loss blocks fructose-driven de novo lipogenesis, visceral adipose inflammation, adiponectin resistance, and insulin resistance — which is why KHK inhibition is an active therapeutic target for MASLD/metabolic syndrome.

"KHK-KO mice consuming the same high-fructose diet remained lean, with normal insulin sensitivity and healthy visceral adipose tissue... This study demonstrates that blocking KHK and redirecting fructose metabolism to alternative pathways is an effective way to prevent visceral obesity and insulin resistance induced by high fructose." — [PMID: 25187370](#)

Immune involvement / tissue damage / oxidative stress. None in EF — there is no inflammation, fibrosis, necrosis, or oxidative injury, precisely because the toxic intermediate does not form.

Ontology suggestions. GO:0006000 (fructose metabolic process); GO:0019320 (hexose catabolic process); GO:0004454 (ketoheokinase activity); CL:0000182 (hepatocyte); CL:1000452 (kidney proximal tubule epithelial cell); CL:0002253 (intestinal epithelial cell). UBERON:0002107 (liver).

7. Anatomical Structures Affected

- **Primary organ: Liver (UBERON:0002107)** — the site of highest KHK-C expression and the principal location of dietary fructose metabolism. The enzymatic lesion is functional, not structural: there is **no hepatic damage** in EF.

- **Secondary organs: Kidney (UBERON:0002113) and small intestine (UBERON:0002108)** also express KHK-C and participate in fructose handling; the kidney is the route of fructose excretion (fructosuria). No organ sustains injury.
 - **Body systems:** Digestive/hepatobiliary and renal/urinary systems (functionally, not pathologically). No cardiovascular, nervous, respiratory, or endocrine involvement.
 - **Tissue/cell level:** Hepatocytes (CL:0000182) are the key cell type; also renal proximal tubule epithelium and intestinal epithelium. No cell population is destroyed or dysfunctional beyond the single enzyme deficiency.
 - **Subcellular level:** KHK is a **cytosolic (GO:0005829)** enzyme; fructolysis occurs in the cytoplasm. No organelle pathology (no mitochondrial, ER, lysosomal, or nuclear involvement).
 - **Localization / lateralization:** Systemic metabolic trait; not applicable as a focal or lateralized lesion. Fructosuria is a whole-organism biochemical state.
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8. Temporal Development

- **Onset: Congenital** — the genotype is present from conception and the biochemical trait is detectable from birth whenever fructose is ingested (e.g., upon introduction of fruit, sucrose, or sorbitol into the diet). Onset pattern is best described as present-from-birth and **asymptomatic**.
 - **Progression: Stable and non-progressive.** There are no disease stages, no end-stage, and no deterioration. The trait is **lifelong** and unchanging.
 - **Course pattern:** The *biomarker* is **episodic/fluctuating** (rises after fructose-containing meals, falls between them), but the *condition* is static. Disease duration is chronic-lifelong but entirely benign.
 - **Remission / critical periods:** Not applicable — there is no disease activity to remit and no window of vulnerability or intervention. "Remission" of fructosuria occurs trivially whenever fructose intake is withheld.
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9. Inheritance and Population

Inheritance pattern. Autosomal recessive. Affected individuals are homozygous or compound heterozygous for KHK loss-of-function alleles; heterozygous carriers are asymptomatic and biochemically normal.

Penetrance / expressivity. The biochemical phenotype (fructosuria after fructose load) is **fully penetrant** in biallelic individuals. Expressivity is essentially uniform (benign), modulated only by dietary fructose intake. No genetic anticipation (not a repeat-expansion disorder); germline mosaicism not relevant.

Epidemiology. The historical textbook estimate is **~1 in 130,000**. Original gnomAD v4 analysis in this report refines this downward:

- Aggregating 108 high-confidence pLoF variants ($\Sigma AF \approx 4.2 \times 10^{-4}$) with the two canonical missense alleles (p.Gly40Arg $AF \approx 2.1 \times 10^{-4}$; p.Ala43Thr $AF \approx 7.3 \times 10^{-5}$) gives a total pathogenic allele frequency $q \approx 7.1 \times 10^{-4}$.
- Predicted recessive disease frequency $q^2 \approx 5 \times 10^{-7}$ (**~1 in 2.0 million**).
- Predicted carrier frequency $2q \approx 1.4 \times 10^{-3}$ (**~1 in 700**).
- A conservative pLoF-only floor gives **~1 in 5.6 million** (carrier ~1 in 1,180).

The discrepancy with the historical figure likely reflects ascertainment: EF is asymptomatic, so many cases are never detected, and older prevalence estimates rested on incidental urinalysis findings in small, non-representative samples. The true frequency depends on whether all pLoF and both canonical missense alleles are fully penetrant for the trait.

Founder effects / population demographics. The canonical p.Gly40Arg allele is **European-predominant** (highest in Non-Finnish Europeans, 2.6×10^{-4}), absent in African/African-American, Ashkenazi Jewish, and Finnish gnomAD samples. This skew, together with a **homozygous p.Gly40Arg individual observed in the general population**, is consistent with a benign, viable, European-enriched allele rather than a deleterious one under selection.

"Both mutations result from G-->A transitions, and each alters the same conserved region of the KHK protein." — [PMID: 7833921](#)

Consanguinity. As with any rare recessive trait, consanguinity increases homozygosity risk, but given benignity this has no clinical import.

Sex ratio / age distribution. No sex predilection (autosomal). Present at all ages; detectable from infancy onward.

10. Diagnostics

How EF is found. Typically an **incidental finding** of positive urinary reducing substances (e.g., Benedict's/Clinitest positive) with a **negative glucose-specific test** (glucose oxidase dipstick negative). This classic discordance — "reducing substance positive, glucose negative" — is the diagnostic clue.

Laboratory tests. - **Urine reducing substances** positive; **urine glucose (glucose oxidase)** negative. - **Urine/serum fructose** elevated after fructose ingestion (identify the sugar by chromatography — TLC, GC, or HPLC — or enzymatic assay). LOINC: urine fructose measurement. - **Fructose tolerance test** (oral fructose load) shows prolonged hyperfructosemia and fructosuria **without hypoglycemia** (distinguishing EF from HFI, where fructose provokes hypoglycemia). - Liver function tests, renal function, phosphate, and uric acid are **normal** (abnormal in HFI).

Biomarkers. Blood and urinary fructose (metabolite biomarkers). No protein or genetic circulating biomarker beyond the sugar itself.

Imaging / electrophysiology / biopsy. Not indicated — there is no structural pathology. Liver histology is normal.

Genetic testing. Confirmatory **KHK sequencing** (single-gene test or inclusion in a carbohydrate-metabolism / inborn-errors gene panel) can identify biallelic pathogenic variants (e.g., p.Gly40Arg, p.Ala43Thr, or pLoF alleles). WES/WGS would detect KHK variants but is rarely warranted given benignity. Chromosomal microarray, karyotyping, FISH, mtDNA, and repeat-expansion testing are **not applicable**.

Clinical criteria / differential diagnosis. The essential differential is the **fructose metabolism disorders**:

Feature	Essential fructosuria (EF)	Hereditary fructose intolerance (HFI)
Deficient enzyme	Ketohexokinase (KHK/fructokinase)	Aldolase B (ALDOB)
Metabolic block	Upstream (fructose → F1-P)	Downstream (F1-P → triose)
Toxic intermediate	None	F1-P accumulates
Symptoms	None (benign)	Vomiting, abdominal pain, hypoglycemia; liver disease, renal tubular dysfunction, failure to thrive if undiagnosed
Dietary treatment	Not needed	Strict fructose/sucrose/sorbitol avoidance
Inheritance	AR	AR

"essential fructosuria caused by a deficiency of fructokinase, which has no clinical consequence and requires no dietary treatment" — [PMID: 18035330](#)

"In HFI, fructose ingestion generally induces gastro-intestinal (nausea and vomiting, abdominal pain, meteorism) and hypoglycemic symptoms." — [PMID: 18035330](#)

Other differentials for a urinary reducing substance: diabetes mellitus/glycosuria, galactosuria, pentosuria, lactosuria. EF's chief diagnostic hazard is **misclassification as diabetes**.

Screening. EF is **not** included in newborn screening panels (no clinical benefit, no actionable disease). Carrier/cascade screening is not indicated given benignity.

11. Outcome / Prognosis

- **Survival / mortality: Normal life expectancy.** EF carries **no excess mortality** and no disease-specific deaths.

- **Morbidity / disability: None.** No disability, no functional impairment, no complications. There are no organ failures, infections, or secondary problems attributable to EF.
- **Quality of life:** Unaffected. No validated QoL decrement.
- **Disease course / recovery:** The condition is a stable, benign, lifelong trait; "recovery" is not a relevant concept because there is no illness.
- **Prognostic factors / biomarkers:** None needed. The only "prognostic" caveat is iatrogenic: avoiding misdiagnosis (e.g., as diabetes) and avoiding unnecessary investigations or treatment.

"Essential fructosuria is one of the oldest known inborn errors of metabolism. It is a benign condition..." — [PMID: 7833921](#)

12. Treatment

No treatment is required or recommended. EF is benign and asymptomatic; dietary restriction is unnecessary (in contrast to HFI, which demands strict fructose avoidance).

"essential fructosuria caused by a deficiency of fructokinase, which has no clinical consequence and requires no dietary treatment" — [PMID: 18035330](#)

- **Pharmacotherapy / advanced therapeutics (gene, cell, RNA, targeted, immuno):** None indicated. There is nothing to correct.
- **Surgical / interventional / rehabilitative / supportive:** Not applicable.
- **Pharmacogenomics:** No KHK-genotype-guided drug considerations are established for EF itself. (Note the inverse scientific interest: KHK is a *drug target* in metabolic disease — pharmacological KHK inhibitors are in clinical development for MASLD, effectively inducing an EF-like state therapeutically. NCIT: "Ketohehexokinase Inhibitor" class of agents.)
- **Management principle:** Correct diagnosis, reassurance, and avoidance of unnecessary testing or treatment. Patient/clinician education to prevent confusion with diabetes or HFI. NCIT suggestions: C15245 (Patient Education/Counseling); observation/watchful waiting.

13. Prevention

Because EF is benign, **no prevention is warranted**.

- **Primary prevention:** Not applicable — there is no harm to prevent. (Dietary fructose avoidance would eliminate the biomarker but confers no health benefit.)
 - **Secondary prevention / screening:** Not applicable; EF is intentionally **not** screened for.
 - **Tertiary prevention:** Not applicable (no complications to prevent).
 - **Immunization / public health / prophylaxis / environmental interventions:** Not applicable.
 - **Genetic counseling:** Minimal. If identified, counseling simply reassures that the condition is harmless and clarifies autosomal-recessive recurrence risk (25% in sib pairs of two carriers), emphasizing that affected offspring would be healthy. The most valuable counseling point is distinguishing EF from HFI for the family.
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14. Other Species / Natural Disease

- **Taxonomy / orthologs:** KHK is conserved across mammals. Mouse **Khk** (NCBI Gene ID 16548) is orthologous to human **KHK** (NCBI Gene ID 3795). Structural studies confirm conformational changes in KHK are **conserved across isozymes and species** ([PMID: 41070915](#)), and mouse and human KHK-C share ~90% sequence identity with similar kinetic parameters.

"Similar kinetic parameters were calculated for the mouse and human enzymes and indicate that mice may be a suitable animal model for the study of fructose-related diseases." — [PMID: 38805243](#)

- **Natural disease in other species:** No naturally occurring essential-fructosuria phenotype of veterinary importance has been characterized (no significant OMIA entry describing a benign companion-animal fructokinase deficiency). The relevant models are **engineered**, not natural (Section 15).
- **Comparative biology / evolutionary conservation:** The fructolysis pathway and KHK's catalytic mechanism are evolutionarily conserved; the human and mouse enzymes are functionally interchangeable for study purposes. The lack of purifying selection on human

KHK (LOEUF ≈ 1.35) suggests the enzyme is dispensable for fitness, consistent with the benign natural history.

- **Transmission / zoonosis:** Not applicable (non-infectious genetic trait).

15. Model Organisms

Primary model — Khk-knockout mouse. A **Khk-knockout (KO) mouse** faithfully models essential fructosuria, exhibiting elevated blood and urinary fructose (hyperfructosemia/fructosuria) that mirror the human trait, while remaining otherwise healthy.

"a Khk knockout (KO) mouse line was generated and characterized" — [PMID: 29870677](#)

Phenotype recapitulation. Excellent for the core biochemical phenotype: - Reproduces hyperfructosemia and fructosuria (the defining features of EF). - Reproduces benignity (no toxicity). - **Additionally** demonstrates protection from diet-induced metabolic defects — KO mice on high-fructose diets stay lean, insulin-sensitive, and free of visceral adipose inflammation ([PMID: 29870677](#); [PMID: 25187370](#); [PMID: 26316589](#)).

Model limitations. The mouse captures the metabolic trait well but, because EF is asymptomatic in humans, there is no human "disease" phenotype to validate beyond the biochemistry. Species differences in fructose intake, endogenous fructose synthesis, and intestinal vs hepatic fructolysis mean the KO is used more as a tool for studying fructose biology and KHK-inhibition pharmacology than as a model of patient pathology.

Complementary models / tools. - **GLUT5 (Slc2a5) knockout mice** for fructose transport ([PMID: 26316589](#)). - **KHK crystal structures** (human KHK-A/KHK-C; mouse KHK-C Michaelis-like complex) enabling structure-based interpretation of disease variants and inhibitor design ([PMID: 19237742](#); [PMID: 38805243](#); [PMID: 41070915](#)). - **Mathematical/systems models** predicting the compensatory adaptations of EF ([PMID: 29664676](#)). - **In vitro** hepatocyte overexpression of wild-type vs kinase-dead KHK dissecting kinase-dependent and -independent effects ([PMID: 39418102](#)).

Resources: MGI (mouse Khk), IMPC/IMSR for availability of knockout lines.

Mechanistic Model / Interpretation

The entire biology of essential fructosuria follows from the **position of the lesion in the fructolysis pathway**. KHK sits at the very first committed step; aldolase B (ALDOB) sits at the second. A block at KHK (EF) prevents the formation of fructose-1-phosphate altogether, so the pathway simply stalls before any toxic intermediate can form — fructose harmlessly overflows into blood and urine. A block one step later at ALDOB (HFI) lets F1-P accumulate, sequestering inorganic phosphate, depleting ATP, and inhibiting gluconeogenesis and glycogenolysis, producing hypoglycemia and progressive liver and kidney injury. **Same pathway, adjacent enzymes, opposite clinical consequences** — EF is the textbook illustration that *where* a metabolic block occurs determines whether a mutation is benign or dangerous.

Three independent evidence streams converge on benignity:

Evidence stream	Finding	Implication
Classical biochemistry/genetics	Compound-het KHK missense variants cause fructosuria with no symptoms (Bonthron 1994)	Defines the molecular lesion and benign phenotype
Knockout mouse	Khk-KO reproduces fructosuria and is <i>protected</i> from metabolic disease	Confirms causality; shows loss is non-harmful, even advantageous under high fructose
Human population genetics (gnomAD v4)	KHK is LoF-tolerant (LOEUF ≈ 1.35 , pLI ≈ 0); homozygous p.Gly40Arg individual exists	No selection against gene loss $\rightarrow$ fitness-neutral $\rightarrow$ benign

This triangulation — demonstrated, modeled, and population-scale — makes EF one of the most securely characterized benign Mendelian traits.

Evidence Base

PMID	Title (abbrev.)	Evidence type	Role in this report
7833921	Molecular basis of essential fructosuria; cloning & mutation analysis of human KHK	Human genetic	Establishes causal gene, canonical variants (p.Gly40Arg, p.Ala43Thr), benign nature, AR inheritance
29870677	Khk-KO mice, a model for EF	Model organism	Confirms enzyme, phenotype, benignity; KO mouse model; metabolic protection
19237742	Structures of human KHK isoforms	Structural/in vitro	Structural modeling of disease variants in active site; KHK enzymatic role
18035330	HFI case / review	Human clinical	EF vs HFI differential; EF needs no treatment
29664676	Mathematical analysis of EF adaptations	Computational	Single clinical manifestation; predicted compensatory adaptations
26316589	Dietary fructose in KHK ^{-/-} & GLUT5 ^{-/-} mice	Model organism	KHK deletion → hyperfructosemia, no hyperglycemia; explains human fructosuria
25187370	KHK-dependent adipose changes	Model organism	KHK loss protects from fructose-induced insulin resistance/obesity
8662230	Colocalization of KHK & GCKR at 2p23	Human genetic	Chromosomal localization of KHK (2p23.2–23.3)
38805243	Michaelis-like complex of mouse KHK-C	Structural	Mouse–human KHK similarity; conformational catalysis; model validity
41070915	Conformational changes conserved across KHK isozymes/species	Structural	Evolutionary conservation of KHK mechanism
39418102	KHK knockdown vs inhibition	Model/in vitro	Kinase-dependent/-independent KHK effects; therapeutic distinction

PMID	Title (abbrev.)	Evidence type	Role in this report
35838297	Intestinal & hepatic fructose metabolism	Review	Context: fructolysis, F1-P signaling, KHK as drug target
30798914	Fructose hepatotoxicity & LDH-5	Human	Context: downstream fructose toxicity pathway (relevant to HFI contrast)
41781320	Hyperpolarized fructose MR	Methodological	Context: imaging fructose flux via KHK

Original analyses (this investigation): gnomAD v4 KHK variant and constraint analysis yielding carrier/disease frequency estimates, ancestry stratification of p.Gly40Arg, and the LoF-tolerance conclusion ($LOEUF \approx 1.35$, $pLI \approx 0$). These are computational/population-genetic findings derived from aggregated allele-frequency data.

Limitations and Knowledge Gaps

- 1. Small human evidence base.** The definitive genotype–phenotype link rests largely on a single well-characterized family (Bonthron 1994). The full allelic spectrum and penetrance of each KHK variant for the fructosuria trait are incompletely defined.
- 2. Penetrance assumption in prevalence modeling.** The gnomAD-based disease-frequency estimates assume that all high-confidence pLoF variants and both canonical missense alleles are fully penetrant for EF. If some pLoF variants escape nonsense-mediated decay or retain residual activity, the true frequency would differ. The estimate (~1 in 1–2 million) is a model, not a measured prevalence.
- 3. Ascertainment bias.** Because EF is asymptomatic, real-world prevalence is essentially unknowable from clinical ascertainment; published figures vary widely (historical ~1:130,000 vs genomic ~1:2,000,000).
- 4. No omics datasets on EF patients.** There are no transcriptomic, proteomic, or metabolomic profiles of EF individuals (beyond fructose measurement); molecular profiling is inferred from KHK biology and mouse models.
- 5. Functional validation of individual variants.** Most catalogued KHK pLoF/missense variants have not been functionally tested for enzyme activity; pathogenicity is predicted.

6. **No natural animal disease.** Comparative/veterinary data are limited to engineered mouse models; no spontaneous animal EF has been characterized.

Proposed Follow-up Experiments / Actions

1. **Functionally validate KHK variants.** Express the panel of gnomAD pLoF and missense alleles (including p.Gly40Arg, p.Ala43Thr, and the common benign p.Val49Ile) in a hepatocyte system and measure fructokinase activity to confirm which are truly loss-of-function — refining penetrance assumptions in the prevalence model.
 2. **Biobank-scale genotype–phenotype check.** Query large linked genomic–EHR cohorts (e.g., UK Biobank, All of Us) for biallelic KHK carriers and test the prediction that they are clinically indistinguishable from controls except for incidental fructosuria — directly measuring penetrance and any subtle protective metabolic associations (lower hepatic fat, improved insulin sensitivity).
 3. **Metabolic protection study.** Given the mouse data, test whether human biallelic KHK carriers show reduced rates of MASLD/metabolic syndrome — bridging EF biology to KHK-inhibitor drug development.
 4. **Structural confirmation.** Use the available KHK crystal structures (and AlphaFold) to quantitatively model the enzymatic impact of each disease variant (active-site perturbation, stability), complementing wet-lab assays.
 5. **Harmonize nomenclature and knowledge-base entries.** Ensure MONDO/OMIM/Orphanet entries clearly flag EF's benignity and its critical distinction from HFI to prevent clinical misclassification (diabetes, HFI).
 6. **Curate ancestry-aware carrier frequencies.** Publish population-stratified KHK pathogenic-allele frequencies (European-predominant p.Gly40Arg) to support any future carrier-screening interpretation, while noting that routine screening is not clinically indicated.
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Report compiled from a 5-iteration autonomous investigation integrating primary literature (14 papers reviewed) with original gnomAD v4 population-genetic analyses. Evidence types are labeled throughout as human clinical, model organism, in vitro/structural, or computational.

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