

CISD2-Wolfram Syndrome

Clinical evidence summary | Fumihiko URANO, MD, PhD. Director of Wolfram Syndrome and Related Disorders Clinic. Samuel E. Schechter Professor of Medicine, Washington University School of Medicine, St. Louis, USA.

Overview and genetics

CISD2-Wolfram syndrome (historically termed Wolfram syndrome type 2) is an ultra-rare autosomal recessive multisystem disorder caused by biallelic CISD2 variants. CISD2 encodes ERIS/NAF-1 (miner1), an endoplasmic-reticulum-associated protein involved in iron–sulfur cluster transfer and mitochondrial function. The 2026 international consensus guidelines classify it as subtype D, distinct from WFS1-Wolfram syndrome.

Clinical manifestations

Characteristic manifestations include childhood-onset insulin-deficient diabetes mellitus and optic atrophy, with gastrointestinal ulceration and platelet abnormalities as distinguishing features. Severe upper-gastrointestinal bleeding, anemia, and esophageal or intestinal disease may precede the classic findings. Sensorineural hearing loss and arginine vasopressin deficiency can occur; the phenotype is variable.

Key human evidence

A 2023 series reported 13 individuals from nine families with the homozygous CISD2 p.Glu37Gln variant: 13/13 had gastrointestinal abnormalities, 6/13 diabetes, 5/13 optic atrophy, 5/13 arginine vasopressin deficiency, and 2/13 hearing loss. These small numbers and the predominance of one variant limit generalization across all CISD2 genotypes.

Diagnosis and initial evaluation

Consensus subtype D diagnosis incorporates childhood-onset (age <18 years) diabetes mellitus, optic atrophy, gastrointestinal ulceration, a platelet disorder, and biallelic pathogenic/likely pathogenic CISD2 variants. Assess the clinical pattern and interpret genetic findings with a medical geneticist/genetic counselor; pursue appropriate CISD2 sequencing and deletion/duplication testing. Evaluate glycemia, eyes/OCT, hearing, CBC/iron studies, bleeding/platelet function, GI symptoms, urinary function, and neurological status as indicated.

Management and counseling

There is no proven disease-modifying therapy specifically for CISD2-Wolfram syndrome. Provide coordinated multidisciplinary care, including endocrinology, neuro-ophthalmology, gastroenterology, hematology when indicated, audiology, neurology, and urology. Address diabetes, gastrointestinal ulceration/bleeding and iron deficiency promptly. Consensus recommendations support annual multidisciplinary assessment in children and every 1–2 years in clinically stable adults, with earlier assessment for deterioration. Counsel families regarding autosomal recessive inheritance (25% recurrence risk for two carrier parents).

Clinical takeaway

Consider CISD2 analysis in children with autoantibody-negative diabetes and optic atrophy, especially with peptic ulceration, GI bleeding, anemia, or platelet abnormalities. GI disease may precede diabetes or visual changes. Avoid excluding CISD2-Wolfram syndrome solely because the complete phenotype has not yet emerged.

Selected references

- [1] Josephine Elliott, Saumel Ahmadi, Patrick Yu-Wai-Man, Sarah Gladstone, Stephanie Gebel, Tracy Lynch, Timothy Barrett, Fumihiko Urano, International Wolfram Syndrome Clinical Guidelines Consortium. International Consensus Recommendations for the Clinical Management of Wolfram Syndrome: A Modified Delphi Study. Guidelines manuscript, version 55, Sept 25, 2026 (Statement 1, subtype D).
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- [3] Ateya R, et al. Wolfram Syndrome-2, a Cause of Severe Gastrointestinal Bleeding: A Case Series and a Literature Review. *JPGN Rep.* 2023;4:e339.
- [4] Wolfram Syndrome Type 2: A Systematic Review. *Int J Environ Res Public Health.* 2022;19:835.