Jeff's Case	NOTES
Phenotype This is the true story of Jeff Williams who nearly died due to critical misdiagnosis based on a key overlooked blood test result. Jeff is very interested in promoting awareness of this not-uncommon disorder and encouraging active patient involvement in their own medical care.	Despite adherence to metformin therapy, dietary interventions, and abstinence of alcohol consumption, symptoms progressed. The patient has requested a thorough re-evaluation of his case. An independent review of his original lab results indicated a potentially missed set of important results - extremely elevated levels of Serum Iron (2300ug/dL) and Transferrin saturation (72%). Thus, the original diagnosis of alcohol induced liver damage has been called into question.
Preliminary Diagnosis	Hereditary Hemochromatosis
Genetic Variation(s)	2 homozygous alleles: HFE g.10633G>A, c.845G>A, p.Cys282Tyr
Laboratory Assertion(s)	pathogenic
Variant Information: • Asserted interpretation listed in **ClinVar**	pathogenic
• HGVS names from **ClinVar**	NG_008720.2:g.10633G>A NP_001287678.1:p.Cys282Tyr
• Is population data available in **dbSNP**?	rs1800562 Not very rare
Gene Information in NCBI Gene: • Symbol and Name	HFE & Homeostatic Iron (FE) Regulator
• Gene Summary • Tissue Expression information	The protein encoded by this gene is a membrane protein that is similar to MHC class I-type proteins and associates with beta2-microglobulin (beta2M). It is thought that this protein functions to regulate iron absorption by regulating the interaction of the transferrin receptor with transferrin. The iron storage disorder, hereditary haemochromatosis, is a recessive genetic disorder that results from defects in this gene. [provided by RefSeq, May 2022]
• Gene Ontology information	Expressed in a lot of tissues, including thyroid, adipose, bladder, spleen, adrenal gland, liver, and many tissues in the gastrointestinal tract
	Enables co-receptor binding: transferrin & beta-2-microglobulin Involved in iron transport, cellular response to iron ion Part of the HFE-transferrin receptor complex and in a recycling endosome
Ultimate Impacted Biomolecule based on: • **GDV** to view the chromosome and gene region	Located in the coding region of exon 4.
• **RefSeqGene Graphics** view of gene region and transcript(s)	Located in the coding region of exon 4.
• **RefSeq Protein Graphics** view of protein and domains	This variation replaces a Cysteine with a Tyrosine.
• **CDD or iCn3D** to view a structure, *as needed*	This wildtype encoded Cysteine is normally involved in a disulfide bond. Loss of the Cysteine not only disrupts the disulfide bond-held structural stabilization.
Proposed Molecular Mechanism of Variant Impact	Loss of the disulfide bond prevents proper folding of the HFE protein, which is recognized by the cell's "unfolded protein response" and targets the protein for degradation.

How does this relate back to the phenotype (symptoms/clinical features & diagnosis)?	The degraded HFE protein can no longer bind to and block the binding of the Iron/Transferrin complex from the Transferrin receptor. Thus, iron ions are continually being dumped into the cell – causing a build-up of damaging iron free radicals. This induces both significant tissue damage, but in a hyper-response can also induce neoplastic transformation of cells leading to cancer.