A Novel Mutation in ATP7B Gene, A Rare Manifestation of Wilson's Disease with Liver Failure

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Introduction

Wilson's disease (WD) is a rare genetic condition characterized by excess copper build up. Due to the presence of several genotypic and phenotypic variances; diagnosis can be challenging. We report a case of acute liver failure due to a novel ATP7B gene mutation, which has never been reported before.

Case Description

A 16-year-old previously healthy male presented to the hospital with abdominal pain, nausea and vomiting for 3 days. Family history was significant for a sister who passed away due to "hepatitis", he denied using alcohol or Tylenol; of note, parents immigrated from Honduras. On examination he was hemodynamically stable, jaundiced with marked scleral icterus, furthermore he was also lethargic and somnolent. His labs showed acute liver failure and acute kidney injury. Further workup included genetic testing with, alpha 1-antitrypsin, copper, ceruloplasmin and iron studies. Serum toxicology was negative. Infectious and autoimmune work-up was performed including ANA, anti-smooth muscle antibody; EBV, HSV, CMV, Hepatitis panel, VZV serologies; total IgG and subclasses, IgA, IgM, soluble IL-2, and *Treponema Cruzi*, which all came back negative other than low ceruloplasmin 6.0 mg/dL, and high 24hr urine copper excretion. Patient was diagnosed with decompensated liver failure due to Wilson's disease and thus was listed for liver transplant at MELD-Na of 41. He later underwent orthotopic liver transplant. Of note, his detailed genetic studies with whole exome sequencing (WES) identified, two likely pathogenic ATP7B variants (c.3446G >C & c.2355G >A) (see Table-1). Postoperatively, he improved considerably. Moreover, patient and his entire family were also seen by genetic counselor once he was discharged home.

Discussion

Wilson's disease is an autosomal recessive disease involving ATP7B gene, responsible for copper metabolism. Around 1019 mutations for ATP7B gene have been reported in literature. In our patient, p.(G1149A) variant was inherited from his father and has been reported before, however p.(K785=) variant has been unreported. This mutation alters the last nucleotide of the exon and causes aberrant splicing (see Figure-1). The fact that our patient exclusively had liver failure without any other organ system involvement in the setting of a novel mutation makes it a unique case for gastroenterologists for timely diagnosis and management of WD. Early treatment with copper chelators and zinc salts can not only halt the disease progression but may also prevent end organ damage.

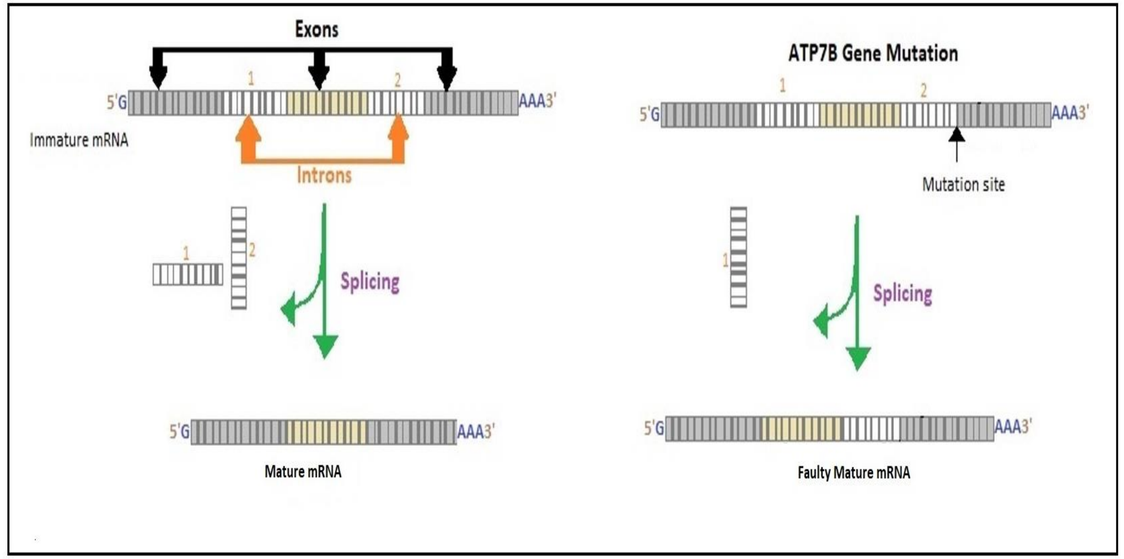

Figure-1: A diagrammatic representation of mutated splicing site. Splicing is a process whereby introns (non-coding part) of mRNA are removed allowing for joining of exons (coding part of mRNA) resulting in mature mRNA which is then used for protein synthesis. The p.(K785=) mutation in ATP7B gene destroys the splicing donor site affecting downstream protein production leading to a dysfunctional copper metabolism.

Table-1: Causative Variant(s) in Disease Genes Associated with Reported Phenotype.

Gene	Disease	Mode of Inheritance	Variant	Zygosity	Inherited Form	Classification
ATP7B	ATP7B-related Wilson disease	Autosomal Recessive	c.3446 G>C p.(G1149A)	Heterozygous	Father	Likely Pathogenic Variant
ATP7B	ATP7B-related Wilson disease	Autosomal Recessive	c.2355 G>A p.(K785=)	Heterozygous	Unknown	Likely Pathogenic Variant

References

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