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# Novel Mutation in the Hemojuvelin Gene (*HJV*) in a Patient with Juvenile Hemochromatosis Presenting with Insulin-dependent Diabetes Mellitus, Secondary Hypothyroidism and Hypogonadism

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
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**Conflict of interest:** None declared

**Patient:** Female, 26-year-old  
**Final Diagnosis:** Juvenile hemochromatosis type 2A  
**Symptoms:** Abdominal pain • adynamia • amenorrhea • arthralgia • dark skin • diabetic ketoacidosis • dyspnea • edema of lower limbs • hair loss  
**Medication:** —  
**Clinical Procedure:** Genetic analysis • hepatic biopsy • iron chelation • magnetic resonance imaging • phlebotomy  
**Specialty:** Endocrinology and metabolic • Hematology  
**Objective:** Rare disease

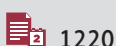
**Background:** Juvenile hemochromatosis is a rare genetic disease that leads to intense iron accumulation. The disease onset usually occurs before the third decade of life and causes severe dysfunction in various organs. The most classical clinical findings are hypogonadotropic hypogonadism, cardiomyopathy, liver fibrosis, glycemic changes, arthropathy and skin pigmentation. However, secondary hypothyroidism is not reported in these patients. Juvenile hemochromatosis has an autosomal recessive inheritance and might be type 2A or type 2B, due to mutation in either the hemojuvelin gene (*HJV*) or hepcidin antimicrobial peptide (*HAMP*) gene.

**Case Report:** A 26-year-old female patient was admitted with a recent history of diabetic ketoacidosis. Three months after that admission, she presented with arthralgia, diffuse abdominal pain, adynamia, hair loss, darkening of the skin and amenorrhea. Severe iron overload was found and findings in the hepatic biopsy were compatible with hemochromatosis. An upper abdominal magnetic resonance imaging (MRI) showed iron deposition in the liver and pancreas and pituitary MRI exhibited accumulation on the anterior pituitary. After 16 months the patient presented with dyspnea and lower limb edema, and cardiac MRI indicated iron deposition in the myocardium. The patient was diagnosed with juvenile hemochromatosis presenting with hypogonadotropic hypogonadism, cardiomyopathy, insulin-dependent diabetes mellitus, and secondary hypothyroidism. A novel homozygous mutation, c.697delC, in the *HJV* gene was detected.

**Conclusions:** We describe for the first time a severe and atypical case of juvenile hemochromatosis type 2A presenting classical clinical features, as well as secondary hypothyroidism resulting from a novel mutation in the *HJV* gene.

**MeSH Keywords:** Hemochromatosis • Hypothyroidism • Iron Overload • Pituitary Diseases

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/923108>



## Background

Juvenile hemochromatosis is a rare genetic disease that occurs with an intense accumulation of iron in the body [1]. This disease usually begins before the third decade of life [2] and causes serious lesions in various organs [1,2].

The most classical clinical findings are hypogonadotropic hypogonadism, cardiomyopathy, liver fibrosis [3,4], glycemic changes [2–4], arthropathy, and skin pigmentation [3,4]. However, secondary hypothyroidism has not been reported in these patients.

Juvenile hemochromatosis has an autosomal recessive inheritance and may be type 2A or type 2B, due to mutation in either the hemojuvelin gene (*HJV*) or hepcidin antimicrobial peptide (*HAMP*) gene [5]. In the Human Gene Mutation Database (HGMD) there are more than 50 mutations described in the *HJV* gene.

Here, we describe for the first time a severe and atypical case of juvenile hemochromatosis type 2A presenting classical clinical features, as well as secondary hypothyroidism resulting from a novel mutation in the *HJV* gene.

## Case Report

A 26-year-old female patient of African descent was admitted to the Endocrinology Unit, transferred from another hospital, with compensated diabetic ketoacidosis. Three months after that admission, she presented with arthralgia of the small and medium joints, diffuse abdominal pain, adynamia, hair loss, and darkening of the skin. The patient also reported a 7-month history of amenorrhea.

She reported normal pregnancy and childbirth without complications 7 years ago and denied alcohol intake, smoking, and use of illicit drugs. Her family history was positive for maternal dyslipidemia and she also had a sister with type 2 diabetes.

The patient had dry skin and areas of discrete hyperpigmentation on the face, limbs and abdomen. There were no signs of joint inflammation and the rest of the physical examination was otherwise normal.

Biochemical analysis was performed on a fasting blood sample and are reported in Table 1.

Since severe iron overload was found through blood testing, a hepatic biopsy was performed which showed marked deposition of iron. The deposition was more pronounced in hepatocytes than in the Kupffer cells; these findings were compatible

with hemochromatosis, and there were no signs of fibrosis (Figure 1A, 1B).

No mutations of the *HFE* and *HAMP* genes were found. However, a homozygous mutation, c.697delC, in the *HJV* gene was detected (Figure 2A). This single nucleotide deletion occurred at codon 233 (exon 4), resulting in a frameshift mutation leading to a premature stop codon at position 245 (Q233fsX245) (Figure 2B, 2C). *In silico* analysis for pathogenicity prediction using the program Mutation Taster classified this variant as “disease causing”. The patient’s parents, one sister and her daughter were genotyped as heterozygous carriers of the mutation (Figure 2D). The patient’s husband and her other sister were identified as homozygous for the wild type allele. According to a recent systematic literature review [5] and the HGMD database, the mutation c.697delC (Q233fsX245) has not been previously described.

An upper abdominal magnetic resonance imaging (MRI) showed a slightly enlarged liver and pancreas with a reduction in volume and T2-hypointense signals in the hepatic and pancreatic parenchyma; these findings were compatible with iron deposition (Figure 3). Furthermore, a pituitary MRI also showed a marked T2-hypointense signal and mild T1-hypointense signal in the anterior pituitary (Figure 4). The thyroid ultrasound, electrocardiogram, echocardiogram and articular x-ray of this patient were unremarkable.

After the diagnosis of juvenile hemochromatosis type 2A was confirmed, the patient was referred to the Hematology Department for frequent phlebotomies and iron chelation, and to the Endocrinology Department where she was treated with basal-bolus insulin and hormonal replacement with levothyroxine and estrogen/progesterone.

After 1 year, the patient presented with sudden malaise and palpitations, and a supraventricular tachycardia was diagnosed and successfully treated. After 4 months she returned to the clinic with dyspnea and lower limb edema, and echocardiographic examination showed moderate dilation of the cardiac chambers, significant left systolic and moderate right systolic dysfunction with pulmonary hypertension (PASP: 45 mmHg). A cardiac MRI showed significant iron deposition in the myocardium, chamber dilation, and global left ventricular dysfunction and a discrete enlargement of the left atrium (Figures 5A, 5B).

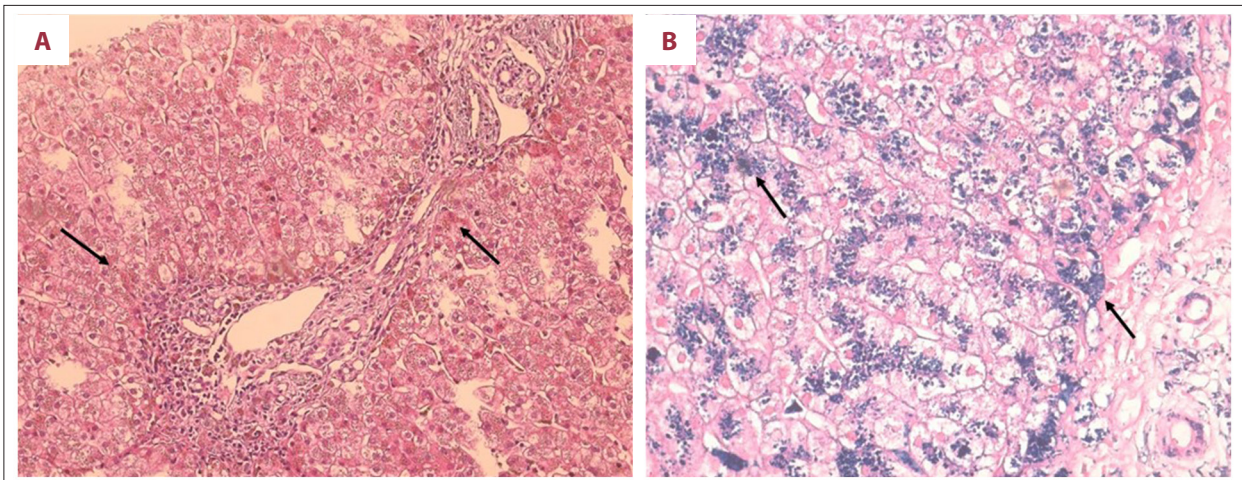
## Discussion

In this report, we demonstrated a novel mutation in the *HJV* gene in a patient with classical features of juvenile hemochromatosis. To the best of our knowledge, this is the first description of central hypothyroidism with pituitary imaging

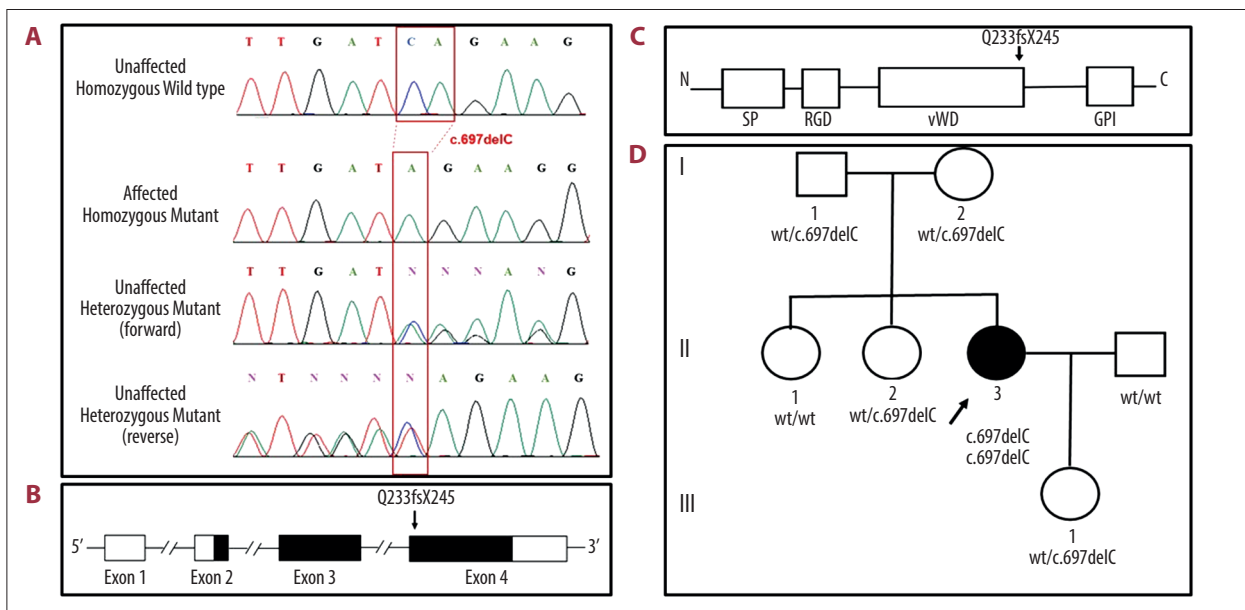
**Table 1.** Laboratory tests of the patient.

Laboratory tests	Result	Reference range	Method
<b>Serum ferritin</b>	<b>8377</b>	13–150 µg/L	Colorimetric
<b>Transferrin saturation</b>	<b>105</b>	20–50%	Calculated using iron and TIBC
<b>Serum iron</b>	<b>46.89</b>	6.62–25.95 µmol/L	Colorimetric
Hemoglobin	12.1	12–16 g/dL	Photometric
Hematocrit	35	35–47%	Electrical bioimpedance
Direct coombs	Negative	Negative	Column agglutination
Total/direct bilirubin	0.51/0.23	Up to 1.2/up to 0.4 mg/dL	Colorimetric
<b>Alkaline phosphatase</b>	<b>169</b>	35–80 U/L	Colorimetric
<b>GGT</b>	<b>202</b>	6–71 U/L	Colorimetric
<b>AST</b>	<b>217</b>	6–46 U/L	IFCC optimized
<b>ALT</b>	<b>61</b>	6–49 U/L	IFCC optimized
Creatinine	0.05	0.035–0.124 mmol/L	Colorimetric
Sodium	139	136–145 mmol/L	Selective electrode
Potassium	4.4	3.5–5.1 mmol/L	Selective electrode
<b>Fasting glycaemia</b>	<b>8.65</b>	3.33–5.49 mmol/L	Enzymatic
HbA1c	5.3	4–6%	HPLC
<b>C Peptide</b>	<b>0.56</b>	1.1–4.4 ng/mL	ECLIA
Anti-GAD	<10	<10 U/mL	RIA
Calcium	2.32	2.15–2.55 mmol/L	Colorimetric
Phosphorus	3.5	2.5–4.5 mg/dL	Molybdate
Magnesium	0.86	0.65–1.06 mmol/L	Colorimetric
Albumin	4.3	3.5–5.2 g/dL	Colorimetric
PTH	22	4–58 pg/mL	ECLIA
<b>Estradiol</b>	<b>&lt;5</b>	>55 pg/mL	ECLIA
<b>FSH</b>	<b>1.63</b>	25–134 UI/L	ECLIA
<b>LH</b>	<b>1.1</b>	7.7–58 UI/L	ECLIA
PRL	233.2	101.7–487.6 mUI/L	ECLIA
<b>TSH</b>	<b>2.0</b>	0.27–4.2 mUI/L	ECLIA
<b>Free T4</b>	<b>0.69</b>	0.93–1.7 ng/dL	ECLIA
AntiTPO	15	Up to 34 UI/mL	ECLIA
Antithyroglobulin	11.02	<115 UI/mL	ECLIA
Cortisol	12.5	5.0–25.0 µg/dL	ECLIA
ACTH	30	7–63 pg/mL	ECLIA
IGF-1	260	103–322 ng/mL	CLIA

GGT – gamma glutamyl transferase; AST – aspartate aminotransferase; ALT – alanine aminotransferase; FSH – follicle stimulating hormone; LH – luteinizing hormone; PRL – prolactin; TSH – thyroid stimulating hormone; ACTH – adrenocorticotrophic hormone; IGF-1 – insulin-like growth factor 1; TIBC – total iron-binding capacity; IFCC – International Federation of Clinical Chemistry; HPLC – high performance liquid chromatography; RIA – radioimmunoassay; ECLIA – electrochemiluminescence immunoassay; CLIA – chemiluminescence immunoassay.



**Figure 1.** Photomicrography of hepatic hemochromatosis. (A) Hepatic tissue with preserved lobular architecture and presence of golden brown granular deposits within hepatocytes (indicated by the black arrow) (hematoxylin and eosin 200×); (B) Perl's stain showing bluish iron deposits in hepatocyte cytoplasm (indicated by the black arrow) (400×).

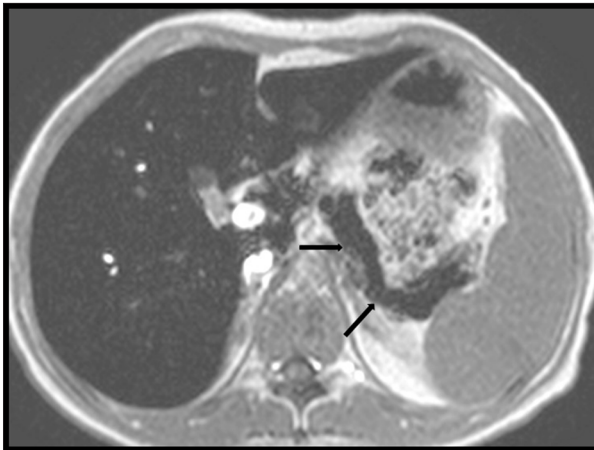


**Figure 2.** Genetic analysis of *HJV* gene in a Brazilian family with juvenile hemochromatosis. (A) Electropherograms showing homozygous wild type (wt), affected homozygous mutant and heterozygous carrier. The box indicates loss of the single nucleotide C in the codon 233 of the *HJV* gene (mutation c.697delC). Polymerase chain reaction (PCR) products were sequenced by Sanger method using the automatic sequencer AB 3500 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA). (B) Schematic representation of genomic organization of *HJV* gene. The novel mutation c.697delC identified in the index case was localized in the exon 4 resulting in premature stop codon at position 245 (Q233fsX245). (C) Schematic representation of hemojuvelin protein functional domains. The novel mutation Q233fsX245 (c.697delC) is indicated by the arrow. SP, signal peptide; RGD, tri-amino acid motif; vWD, von Willebrand-like domain. (D) Genealogy of the family in this study. The arrow indicates juvenile hemochromatosis index case. Open symbols represent unaffected, filled black symbols represents affected individuals. The genotypes are shown below each family member.

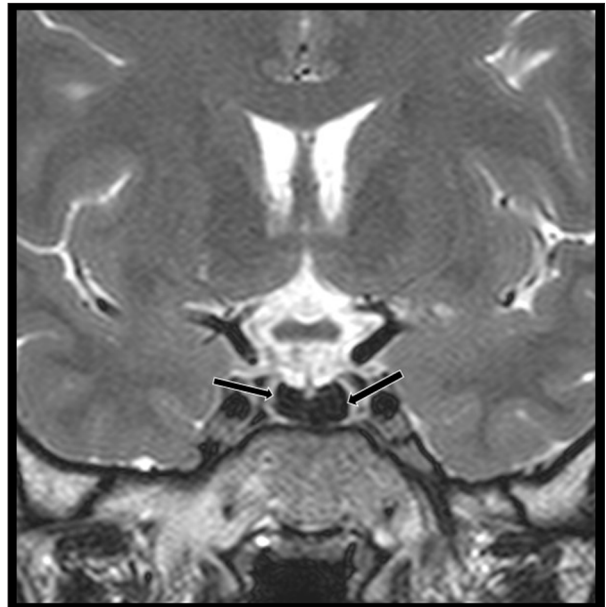
compatible with iron deposition in a patient with juvenile hemochromatosis.

The single nucleotide deletion in the c.697delC variant leads to a frameshift mutation and produces a short-truncated protein

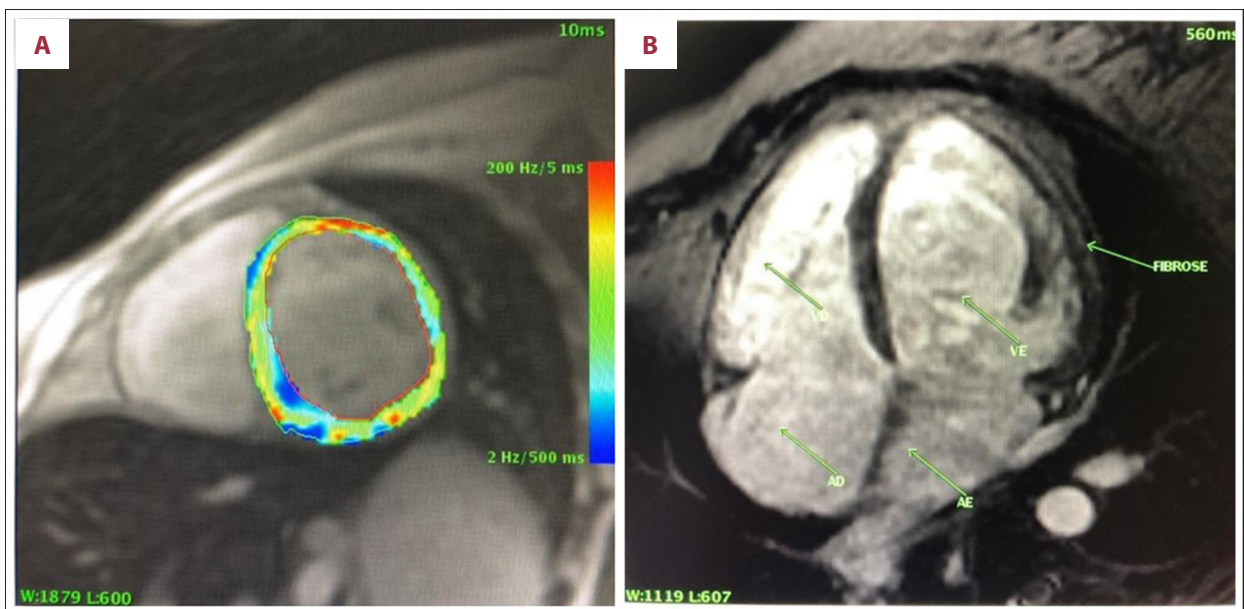
without the glycosylphosphatidylinositol (GPI) 6-linked axon leader molecule. The absence of GPI, a transmembrane domain, suggests that the mutant protein cannot be expressed on the surface of the hepatocyte. Thus, patients homozygous for this mutation are unable to induce hepcidin transcription [6].



**Figure 3.** Magnetic resonance imaging of the abdomen, compatible with iron deposition. Axial T1-weighted image demonstrates marked signal reduction in both the pancreas (indicated by the black arrow) and liver. Signal intensity of the spleen is normal.



**Figure 4.** Magnetic resonance imaging (MRI) of the pituitary gland, compatible with iron deposition MRI coronal T2-weighted image shows the anterior lobe of the pituitary gland with a significantly low signal (indicated by the black arrow).



**Figure 5.** Cardiac magnetic resonance imaging with significant iron deposition. (A) T2\* map shows the accumulation of iron, with an estimated value of 9.5 ms. (B) Late enhancement sequence showing mesocardial fibrosis in the lateral wall of the left ventricle.

Deficiency in the synthesis of hepcidin results in elevation of plasma iron and transferrin saturation resulting in consequent iron deposition in parenchymal cells, particularly those of the endocrine system and cardiomyocytes that are rich in mitochondria and poor in antioxidant factors; therefore, these cells

are more susceptible to the oxidative stress caused by excess iron [2,4,7]. The extent of lesions in the organs is variable and depends on the moment of onset and the magnitude of iron overload, which results from the extent of hepcidin deficiency and the type of mutation [4]. In a recent review evaluating

the phenotype of patients with juvenile hemochromatosis, the median serum ferritin concentration (FS) and transferrin saturation (TS) in the *HJV* group were 2925 µg/L and 96%, respectively [3]. Our patient had significantly higher indexes (FS=8377 ng/mL and TS=105%), which suggested intense concentration and deposition of iron in several tissues and the generation of serious lesions in the affected organs.

The more intense and early accumulation of iron in juvenile hemochromatosis seems to be responsible for the greater severity and diversification of affected organs, especially the heart and pituitary gland; other affected organs included the liver, pancreas, and skin and to a lesser extent, the joints [3]. Although iron deposition has been described in all pituitary cell lines, there is a pronounced predilection for gonadotropes, with rare descriptions of involvement of the other lineages [5,8–11]. In our report, the patient presented the full spectrum of juvenile hemochromatosis lesions, with the additional finding of secondary hypothyroidism, suggested by the low free T4 levels, on more than one occasion, and inappropriately normal thyroid stimulating hormone (TSH) under stable clinical condition, negative thyroid autoimmunity and pituitary siderosis in MRI. Secondary hypothyroidism was previously described in rare patients with type 1 hemochromatosis and none of these

patients presented evidence of pituitary iron deposition by imaging methods [8,9,12–14]. Dhillon et al. [15] recently also reported hypothyroidism in 4 patients with hereditary hemochromatosis. However, in this case series there was no detailed description of the type of hypothyroidism encountered, if primary or secondary [15].

## Conclusions

We conclude that in the present case, the novel mutation c.697delC (Q233fsX245) in the *HJV* gene might be related to the high iron overload seen in this patient, leading to classical features of juvenile hemochromatosis and unprecedented hypothyroidism secondary to thyrotrophic lesions. Juvenile hemochromatosis associated with *HJV* gene mutation should be also considered in the differential diagnosis of multiple endocrinopathies which are symptomatic in young adult patients.

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