

## LETTER TO THE EDITOR

# A novel case of diabetes MODY1 and chronic hereditary pancreatitis: coexistence of two infrequent genetic mutations



## Un nuevo caso de diabetes MODY1 y pancreatitis crónica hereditaria: coexistencia de dos mutaciones genéticas poco frecuentes

Dear Editor:

Maturity-onset diabetes of the young (MODY), is group of an uncommon genetic disorders characterised by autosomal dominant inheritance of a single nucleotide mutation, absence of pancreatic autoimmunity biomarkers and of clinical signs of insulin resistance. It represents between 1 and 5% of cases of diabetes mellitus (DM) and includes up to 15 subtypes, that differ from each other according to the mutated gene. The MODY1 subtype is secondary to a mutation in the hepatocyte nuclear factor 4 alpha (HNF4A) gene (accounts for 5–10% of the MODY).<sup>1</sup> Chronic pancreatitis (CP) can be secondary to environmental factors (alcohol consumption, smoking or hypertriglyceridemia); and/or hereditary genetic alterations (genes PRSS1, CFTR, SPINK1, CTRC). Among the genetic causes of CP, mutations in the chymotrypsin gene C (CTRC) is the less frequent.<sup>2</sup> Furthermore, several mutations in HNF4A and CTRC genes with uncertain meaning were described separately.<sup>3</sup> Nevertheless little is known about the interactions between these mutations in the same individual. We report for the first time the clinical features of the coexistence of two mutations of uncertain meaning in the genes HNF4A and CTRC, respectively. Informed consent was obtained from the patient. All the data included in the report comes from the medical history. No data presented in the paper was previously shared or ceded.

A 62 years old male patient has been controlled for diabetes in our hospital since 2012. The patient, native of Morocco, has lived in Spain in the last 30 years. No relevant medical family history, except for his mother diagnosed with orally treated type 2 diabetes when 60 years old was referred. He was diagnosed with diabetes mellitus (DM) with 41 years and normoweighted, in form of simple hyperglycemia in a routine analysis. DM was initially classified as type 2, receiving oral treatment and maintaining HbA1c levels between 6.4 and 7.2% (DCCT 4.7–6.4%). Autoimmune

tests were negative (anti-GAD65 < 5 U/ml (0–5 U/ml) and anti-IA2 < 7.5 U/ml (0–7.5 U/ml)). The patient presented progressive deterioration of HbA1c requiring insulin treatment, but with detectable C peptide (0.93 ng/ml). He has not developed any microangiopathic or macroangiopathic complications. Patient suffered also of hypertriglyceridemia under treatment with fibrates. It should be noted that the cholesterol lipidic profile always showed levels of total cholesterol < 150 mg/dl, HDL-cholesterol > 50 mg/dl and LDL-cholesterol < 100 mg/dl. During clinical follow up, he presented an episode of abdominal pain. A CT scan was performed, showing gross calcifications and atrophy of the body and tail of the pancreas, suggestive of chronic pancreatitis. He had former alcohol consumption of 1–2 units/week, but he was abstinent in the last 10 years. At the last visit he was overweight (weight 83 kg, height 175 cm, BMI 27.1 kg/m<sup>2</sup>) and presented with no clinical signs of CP or steatorrhea. Laboratory tests: AST: 32 IU/L (12–50 IU/L), ALT: 26 IU/L (8–50 IU/L), Alkaline Phosphatase: 60 IU/L (30 – 120 IU/L), Gamma GT: 24 IU/L (9–55 IU/L), Amylase 21 U/L (8–53 U/L), Lipase 46 U/L (21–67 U/L), faecal elastase > 200 µg/g in 2 determinations (normal value > 200 µg/g). The genetic study of hereditary pancreatitis (HP) showed a mutation of CTRC gene on p.Glu225Ala at position 674 (c. 674A>C) of exon 7. The mutation 674A>6 (p.Glu225Ala) of CTRC is considered rare with an overall allele frequency of 0.04% on general population and has an uncertain meaning.<sup>3</sup>

In this context and with a clinical evolution not entirely compatible neither with Type 2 or Type 1 diabetes, a genetic study of MODY was performed showing mutation in heterozygosis c.1321A>G; p.(Ile441Val) in the HNF4A. The clinical phenotype was suggestive of MODY1 (progressive insulin deficiency, hypertriglyceridemia). Nevertheless, the significance of this mutation was catalogued as uncertain. Interestingly, the patient had hypertriglyceridemia, while mutations in HNF4A were associated with low levels.<sup>4</sup> Nevertheless, it seems that higher HDL-cholesterol is a more sensitive factor associated with MODY-1 than triglycerides and the case presented during whole follow-up HDL-cholesterol levels > 50 mg/dl, above the expected value for gender and type2 DM.<sup>4</sup> Mutations of CTRC alone are not likely to be a clinical cause of hereditary pancreatitis; however they do confer an increase of it through interaction with environmental factors or other genetic mutations, such as mutations in HNF4A, as in the case of our patient.

**Table 1** Genotype and phenotype characteristics of the family members.

| Family member | Age (years) | Gender | Gene HNF4A  | Gene CTRC                       | Gene CTRFA    | DM  | PC  |
|---------------|-------------|--------|---|---------------------------------|---------------|-----|-----|
| Mother        | 80          | F      | No alterations found  | Not available                   | Not available | Yes | No  |
| Father        | 85          | M      | Change on nucleotide c.1321A>G; p. (Ile441Val) in heterozygosis | Not available                   | Not available | No  | No  |
| Patient       | 62          | M      | Change on nucleotide c.1321A>G; p. (Ile441Val) in heterozygosis | c.674A>C, p.Glu225Ala of exon 7 | No            | Yes | Yes |
| Son           | 30          | M      | Change on nucleotide c.1321A>G; p. (Ile441Val) in heterozygosis | c.674A>C, p.Glu225Ala of exon 7 | No            | No  | No  |
| Son           | 33          | M      | Change on nucleotide c.1321A>G; p. (Ile441Val) in heterozygosis | No                              | No            | No  | No  |

CTRC mutations increase trypsin activity by losing the property of CTRC to reduce trypsinogen activation, impairing peptide degradation and carboxypeptidase activation necessary for insulin production, inducing a pathological folding in the endoplasmic reticulum. In consequence cell stress, increased nuclear factor kappa B (NF- $\kappa$ B) and apoptosis are seen. Mutations on HNF4A cause mitochondrial dysfunction by selectively inhibiting the generation of ATP, resulting in reducing the insulin mRNA levels, impaired hyperpolarisation of mitochondrial membrane, down-regulation of GLUT-2, aldolase B or L-PK.<sup>5</sup> Additionally, alcohol and fatty acids cause massive intracellular Ca<sup>2+</sup> release and intracellular trypsinogen to trypsin activation,<sup>6</sup> making though a pathological synergic effect. First degree relatives underwent genetic study – Table 1. Those that presented one mutation had no clinical expression. This finding supports the theory of complex interactions between the genetic predisposition and environmental factors in the development of CP and DM. In this case, two genetic mutations with uncertain clinical significance became significant when they coexisted and interacted with environmental factors (alcohol consumption, dyslipidemia). More studies of the clinical repercussion of these genetic mutations and the consequences of their interactions are needed and are an open field to explore.

## Conflict of interest

All the authors declare no conflict of interest.

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Efrain Cordero-Vázquez<sup>a</sup>, Francesca Filippi-Arriaga<sup>b</sup>, Irene Hernández Hernández<sup>a</sup>, Stephanie Solange Tasayco Haman<sup>c</sup>, Andreea Ciudin<sup>a,d,\*</sup>

<sup>a</sup> Endocrinology and Nutrition Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain

<sup>b</sup> Clinical Pharmacology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain

<sup>c</sup> Gastroenterology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain

<sup>d</sup> Universitat Autònoma de Barcelona, Spain

\* Corresponding author.

E-mail address: [aciudin@vhebron.net](mailto:aciudin@vhebron.net) (A. Ciudin).