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# A Novel Mutation in the Hepatocyte Nuclear Factor 1-Alpha Detected in a Portuguese Family

## *Uma Nova Mutação no Fator Nuclear 1-Alfa do Hepatócito Detectada numa Família Portuguesa*

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**Abstract**

**Background:** We describe a maturity-onset diabetes of the young (MODY) family with a novel variant in the hepatocyte nuclear factor 1-alpha (*HNF1A*).
**Case Presentation:** A female non obese patient was diagnosed with diabetes at age 13, without insulinopenia evidence. She has been treated with non-insulin antidiabetic drugs since the diagnosis and has good glycemic control.
Her mother and maternal relatives had diabetes diagnosed at a young age.
The genetic screening identified the novel variant c.335C>G (p.Pro112Arg) in heterozygosity in the exon 2 of the *HNF1A* gene in both mother and daughter.
**Conclusion:** *In silico* prediction indicated that the variant identified is probably pathogenic. Furthermore the family clinical features are in accordance with the MODY 3 phenotype associated to *HNF1A* mutations.

**Keywords:** MODY; mutation screening; *HNF1A*; chronic diabetic complications

***Resumo***

**Introdução:** Descreve-se uma família com diabetes tipo *maturity-onset diabetes of the young* (MODY), com uma nova variante no fator nuclear 1-alfa do hepatócito (HNF1A).
**Caso Clínico:** Mulher, não obesa, com diagnóstico de diabetes aos 13 anos sem evidência de insulinopenia e medicada com anti-diabéticos não insulínicos desde o diagnóstico, com bom controlo glicémico.
A sua mãe e familiares maternos haviam sido diagnosticados com diabetes em idade jovem.
O teste genético identificou a nova variante c.335C>G (p.Pro112Arg) em heterozigotia no exão 2 do gene HNF1A em mãe e filha.
**Conclusão:** A predição *in silico* indica que a variante identificada é provavelmente patogénica. A apresentação clínica desta família está de acordo com o fenótipo de MODY3 associado a mutações no gene HNF1A.

**Palavras-chave:** MODY; teste genético; HNF1A; complicações crónicas da diabetes

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## > BACKGROUND

Maturity-Onset Diabetes of the Young (MODY) (MIM #606391) is a genetically and clinically heterogeneous group of disorders characterized by early onset of non-insulin-dependent diabetes (childhood, adolescence or young adulthood under 25 years) and autosomal dominant inheritance with high penetrance. [1,2,3,4,5] To date, there are mutations in at least thirteen different genes that result in the MODY phenotype. [6]

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MODY type 3 (MODY3) is characterized by a severe insulin secretion defect, a retained sensitivity to sulfonylureas, a decreased renal threshold for glucose reabsorption, and, in rare families, by liver adenomatosis. It is caused by a mutation in the hepatocyte nuclear factor-1-alpha (*HNF1A*) gene, which maps to chromosome 12q24.2. [1,2,3,5,7] More than 200 mutations in this gene have been identified in persons of all racial ethnic backgrounds and are the most common causes of MODY in northern Europe and a frequent cause of MODY in many other populations. [4,5,8] The penetrance of diabetes in patients with *HNF1A* mutations is 63% by age 25, 93.6% by age 50 and 98.7% by age 75. [9]
We describe a novel mutation in the *HNF1A* gene detected in a Portuguese family.

## > CASE PRESENTATION

### The Proband

39-year-old woman, referred to the Endocrinology outpatient department due to diabetes *mellitus* diagnosed at age 13. The previous medical history was negative.
The diagnosis of diabetes *mellitus* was made in laboratory tests of a "routine" checkup. At diagnosis, there was no diabetes ketoacidosis and the patient did not complain of polydipsia and polyuria. On physical examination she was not overweight (weight 55 Kg, height 1.56m, body mass index – BMI – 22.6 Kg/m$^2$) and the blood pressure was normal (123/56 mmHg). The fasting blood glucose (FBG) was 142 mg/dL, microalbuminuria was negative (1.9 mg/dL) and the lipid profile (total cholesterol 149 mg/dL, high density lipoprotein – HDL – 56 mg/dL, low density lipoprotein – LDL – 84 mg/dL, triglycerides 28 mg/dL), renal function (creatinine 0.6mg/dL), sodium (136 mmol/L) and potassium (4.7 mmol/L) were within the laboratory reference ranges.
During the first four years of disease, pharmacotherapy was not needed and since then the patient has been treated with non-insulin antidiabetic drugs (metformin and/or sulphonylureas), with good glycemic control (HbA1C between 5 and 7.2% – 31 and 5 mmol/mol). The only exceptions were the two pregnancies and breastfeeding periods, during which the patient was treated with NPH insulin. None of the newborns was macrosomic (3.155 kg and 3.665 kg, at week 40 and 39, respectively).
Nowadays, the patient is treated with metformin 850 mg three times a day, with good glycemic control – HbA1C 6.5% (48 mmol/mol) – and she has no microvascular or macrovascular complications of diabetes.

### The Relatives

The patient's mother of 65 years-old was diagnosed with diabetes at age 16 and was treated with non-insulin antidiabetic drugs until she was 53 years-old, when she started insulin. She was pregnant twice at age 21 and 26 and even during pregnancies and the breastfeeding periods insulin was not prescribed. After the second pregnancy she left the consultation during 14 years. At the time of diagnosis, the mother was not overweight (weight 52.6 Kg, height 1.55m, BMI 21.9 Kg/m$^2$). At age 54, she was submitted to laser photocoagulation for proliferative retinopathy. She has diabetic nephropathy with macroscopic proteinuria (the creatinine clearance is still within the normal values), arterial peripheral disease and cerebrovascular disease. Nowadays she is treated with an insulin analogue containing both a rapid-acting and an intermediate-acting insulin in the ratio of 30/70 (insulin aspart + insulin NPH) three times a day and has an HbA1C of 7.7% (61 mmol/mol). The abdominal ultrasound did not reveal liver adenomas.
The patient's maternal grandparents, uncles and cousins have also been diagnosed with diabetes at an early age. The two sons of the patient (13 and 7 years-old respectively), the patient's sister (44 years-old) and her sister's son are all healthy.
Considering the whole family phenotype, with diabetes *mellitus* that follows an autosomal dominant inheritance pattern, diagnosed at an early age, without risk factors and without insulin need over a long period of time, we investigated the family for the presence of monogenic diabetes.

### Investigation

The molecular analysis of the glucokinase (GCK) gene/MODY2 in the daughter by denaturing high-performance liquid chromatography did not identify any mutation.
The molecular analysis of the *HNF1A*/MODY3 gene by denaturing high-performance liquid chromatography and sequencing of exons 1–10 and flanking regions identified a novel variant c.335C>G (p.Pro112Arg) in heterozygosity in the exon 2 of the *HNF1A* gene in the daughter. Segregation analysis confirmed the presence of the variant in the proband's mother.
The novel c.335C>G caused a replacement of an amino acid conserved across mammalian species. Using PolyPhen-2, SNPs&GO, SNPeffect, SIFTBlink, MutationTaster and UMD-Predictor software for predicting the potential pathogenic effect, the variant was likely to be the disease-causing mutation.

**Outcome and Follow-Up**

The daughter and the mother have already been observed in genetic consultation, where the genetic counseling has been done. Segregation analysis of other family members is ongoing.

## > DISCUSSION

We describe a family with clinical diagnosis of MODY3 and a novel variant in the *HNF1A*/MODY3 gene: c.335C>G (p.Pro112Arg) in exon 2 of the gene. It is a missense variant in the DNA-binding-domain and it is located in an exon transcribed in the three *HNF1A* isoforms. This is highly likely to be a disease-causing mutation: in silico prediction indicated that the variant identified is probably pathogenic, and a previously established pathogenic variant at the same codon has been reported, suggesting that the amino-acid residue involved is functionally relevant. Moreover, assuming that this mutation is the etiology of MODY3 in this Portuguese family, it is in accordance to their disease phenotype, with an early age of diagnosis of diabetes in both the mother and the daughter (16 and 13 years-old respectively). It is known that the clinical expression of MODY3 is highly variable from one family to another or even within the same family, that the severity and the course of insulin secretion defect also varies and that molecular characteristics of the *HNF1A* mutation may play a role in the severity of the disease. [4] *HNF1A* is composed of three functional domains (dimerization domain, DNA-binding domain and transactivation domain), and three isoforms are generated by alternative splicing, with different transcriptional properties and tissue expression patterns. [4,9,10] Diabetes is diagnosed earlier (in a study with 356 patients it was revealed 10 years earlier) in patients carrying missense mutations located in the dimerization/DNA-binding domains than in those with a missense mutation in the transactivation domain, [8] as it was the case of the mutation identified in our family.

The case report also reassures the importance of genetic testing in patients with diabetes phenotype suggestive of MODY, as identification of gene mutation may lead to early diagnosis, treatment, regular surveillance and better prognosis. [1,2,3] Specifically in MODY3, patients may have the full spectrum of complications of diabetes and microvascular complications. Particularly those involving the retina or kidneys, are as common in patients with type 1 or type 2 diabetes, probably determined by the degree of glycemic control. (1,3) The patient's mother left the consultation during 14 years, what can explain the multiple complications of diabetes she has.

Our patient has already been referred for a Genetic consultation, so that all the relatives at risk can be screened and properly followed when indicated. <

***Patient consent:***

Written informed consent has been obtained from the patients for publication of the submitted article.

***Conflicts of interest:***

No potential conflicts of interest relevant to this article were reported from any author.

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**REFERENCES**

1. Fajans SS, Bell GI, Polonsky KS. Molecular Mechanisms and Clinical Pathophysiology of Maturity-Onset Diabetes of the Young. N Engl J Med. 2001; 345(13): 971-980.
2. Gardner DSL, Tai ES. Clinical Features and Treatment of Maturity Onset Diabetes of the Young (MODY). Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2012; 5: 101-108.
3. Aguilar-Salinas CA, Reyes-Rodríguez E, Ordóñez-Sánchez ML, Torres MA, Ramírez-Jiménez S, Domínguez-López A, et al. Early-Onset Type 2 Diabetes: Metabolic and Genetic Characterization in the Mexican Population. J Clin Endocrinol Metab. 2001; 86: 220-226.
4. Lehto M, Tuomi T, Mahtani MM, Widén E, Forsblom C, Sarelin L, et al. Characterization of the MODY3 Phenotype – Early--Onset Diabetes Caused by an Insulin Secretion Defect. J. Clin. Invest. 1997; 99(4): 582-591.
5. Forlani G, Zucchini S, Rocco A, Luzio R, Scipione M, Marasco E, et al. Double Heterozygous Mutations Involving Both HNF1A/MODY3 and HNF4A/MODY1 Genes. Diabetes Care. 2010; 33: 2336-2338.
6. Fajans SS, Bell GI. MODY: History, genetics, pathophysiology, and clinical decision making. Diabetes Care. 2011; 34:1878-1884.
7. Alemany MCM, Macian FM, Carinema SL, Miquel BP, Rojas JP, Perez JAC, Koninckx CR. Liver Adenomatosis and Maturity--Onset Diabetes of the Young (MODY) Type 3 Due to HNF1A Mutation Not Previously Described. J Endocrinol Metab. 2014; 4(3): 81-85.
8. Bellanné-Chantelot C, Carette C, Riveline JP, Valéro R, Gautier JF, Larger E, et al. The Type and the Position of HNF1A Mutation Modulate Age at Diagnosis of Diabetes in Patients with Maturity-Onset Diabetes of the Young (MODY)-3. Diabetes. 2008; 57: 503-508.

9. Ellard S. Hepatocyte Nuclear Factor 1 Alpha (HNF-1a) Mutations in Maturity-Onset Diabetes of the Young. Human Mutation. 2000; 16: 377-385.

10. Bach I, Mattei MG, Cereghini S, Yaniv M. Two Members of an HNF1 Homeoprotein Family are Expressed in Human Liver. Nucleic Acid Res. 1991; 19: 3553-3559.