A novel heterozygous mutation in the glucokinase gene is responsible for an early-onset mild form of maturity-onset diabetes of the young, type 2

Keywords: Anti-GAD antibodies; Glucokinase; Hyperglycaemia; Maturity-onset diabetes of the young; MODY

1. Introduction

Maturity-onset diabetes of the young (MODY) refers to a group of autosomal-dominant, clinically and genetically heterogeneous forms of monogenic diabetes (MD). All MODY subgroups present as mild asymptomatic hyperglycaemia in non-obese children, adolescents and young adults who often have a positive family history, indicating an autosomal-dominant trait. The most frequent disease genes are GCK encoding glucokinase, and HFN1A encoding hepatocyte nuclear factor-1 alpha. The GCK gene is located on chromosome 7 (7p15.3-15.1) and contains 12 exons that encode the 465 amino-acid protein glucokinase, one of the four members of the hexokinase family of enzymes. Glucokinase is mainly expressed in pancreatic β cells and hepatocytes, where it catalyzes the first and most important stage in glucose metabolism, the production of glucose 6-phosphate. It plays a major role in the regulation of insulin release and has been termed the glucose sensor of pancreatic β cells. GCK mutations leading to MODY are inactivating and heterozygous, whereas heterozygous activating mutations can lead to persistent hyperinsulinaemic hypoglycaemia of infancy (PHHI), while homozygous inactivating mutations can cause permanent neonatal DM (PNDM) [1]. Missense, nonsense, frame-shift and splice-site mutations have also been reported, spread over exons 1a and 2-10 [2].

On the other hand, autoantibodies against islet and β-cell antigens can appear early in life, although their pathogenic roles remain unclear [3].

This report is of a novel heterozygous inactivating GCK gene mutation in a boy with a strong family history of DM who was positive for anti-glutamic acid decarboxylase (anti-GAD) antibodies. The patient was case #11 in a prospective prevention trial of oral calcitriol published recently by our group [4].

2. Patient and methods

This 5-year-old boy, with a height of 108.9 cm (−0.55 SDS) and body mass index (BMI) of 15.2 kg/m² (−0.24 SDS), was referred for evaluation because of mild fasting hyperglycaemia (blood glucose values 100–120 mg/dL) and a slightly elevated haemoglobin A1c (HbA1c) levels of 6.5% (normal: 4.0–6.0%) since the age of two years. He was born appropriate for gestational age (AGA) at term, and his growth and neurological development were normal. The physical examination was unremarkable. A standard oral glucose tolerance test (OGTT) using the equivalent of 1.75 kg was performed, and showed fasting, 1-h and 2-h glucose levels of 115, 249 and 192 mg/dL, respectively, whereas insulin was 5, 23 and 20 IU/L, respectively, and C-peptide was 0.5, 3.1 and 2.5 ng/mL, respectively. The results were compatible with significantly impaired glucose tolerance (IGT) due to low insulin secretion and analogous C-peptide levels. Pancreatic islet-cell autoantibodies (ICAs), insulin autoantibodies (IAAs) and anti-islet antigen 2 (anti-IA2) antibodies were negative, whereas anti-GAD antibodies were positive at 1.6 IU/mL (normal: <1 IU/mL). Genetic analysis of the human leucocyte antigen (HLA) region revealed neither high-risk nor protective haplotypes for type 1 diabetes (T1D).

However, the patient’s family history was strongly positive for an inherited form of DM. The patient’s father (aged 42), the paternal aunt (aged 44) and her daughter (aged 17) all had a mild form of DM. The father reported fasting hyperglycaemia and elevated HbA1c since infancy, and was taking sulphonylurea treatment and considered to have type 2 diabetes (T2D). He was also negative for T1D autoantibodies, and latent autoimmune diabetes in adults (LADA) had been excluded. The paternal grandmother was diagnosed with gestational diabetes at the age of 28 years, which proved persistent, and was taking sulphonylurea treatment at the age of 72. The patient’s mother and sister both had normal glucose tolerance profiles.

Based on the boy’s clinical presentation and family history, MODY 2 was suspected [5]. A normocaloric low-glycaemic-index diet was introduced and regular physical activity was suggested. The boy is now 12 years old with a fasting plasma glucose ranging from 90 to 105 mg/dL and an HbA1c between 6.2 and 7.1%, suggesting satisfactory glycaemic control.

Genomic DNA was extracted from peripheral blood, using standard protocols, from both the patient and his father. Exons
3. Results and discussion

The boy’s mild fasting hyperglycaemia over a period of three years, HbA1c just above normal, OGTT showing with low insulin response, strong family history – all in the absence of obesity and insulin resistance – were highly suggestive of MODY [6], despite being positive for anti-GAD antibodies, which was corrected (0.9 IU/mL) after 1.7 years of taking 0.25 mcg/day of calcitriol [4]. The risk of T1D is strongly associated with the number of positive antibodies. Some, but not all, children positive for IAA, often the first anomaly to be detected in childhood, will also develop anti-GAD65 and anti-IA2. The age of appearance of ICAs and mean levels of IAAs, but not anti-GAD65 or anti-IA2, may be predictive of the onset of T1D [4].

DNA sequencing of GCK, one of the most common MODY genes, revealed a novel heterozygous mutation in exon 8: c.908G>T (ref seq NM_000162.3) in both the patient and his father. (The paternal aunt and her daughter received genetic counselling, but refused genetic testing.) This point mutation is a missense mutation at amino-acid position 303 replacing arginine with leucine (p.R303L) in a highly conserved hexokinase C-terminal domain of the enzyme, which is suggestive of a functional impact of the mutation [7] despite the lack of functional assessment of GCK activity. This novel mutation has so far not been reported in MODY patients or in controls, and is not found in the US National Heart, Lung, and Blood Institute (NHLBI) Exome Variant database. However, a different GCK mutation at the same codon has been reported and published [7]: c.907C>T; ref seq NM_000162.3 (p.R303W). Prediction programmes in silico were also not equivocal: SIFT, deleterious; MutationTaster, disease-causing; PolyPhen-2, benign). Over 600 different GCK mutations (many not proven as inactivating) have been described, including a wide heterogeneity in clinical phenotype [8]. Diagnosis, as in our case, is usually incidental and before the sustained mild hyperglycaemia from birth at non-diabetic levels, which seldom requires treatment apart from an appropriate diet, as only 2% require insulin and microvascular complications are rare [9,10].

Identification of the genetic aetiology in a young person with diabetes is important. While it is not possible to exclude autoimmunity in any paediatric patient with IGT, the clinical setting and suggestive family history may nevertheless lead to the correct diagnosis of MODY.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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References


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