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NOVEL PHENOTYPE DUE TO *KCNJ11* PATHOGENIC VARIANT ASSOCIATED WITH MATURITY-ONSET DIABETES OF THE YOUNG-KCNJ-11

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ABSTRACT

Introduction: Maturity-onset diabetes of the young (MODY) *KCNJ11* is caused by pathogenic variants in the KATP channel of the pancreatic β-cell leading to altered insulin secretion. Bi-allelic loss-of-function variants lead to neonatal diabetes mellitus (DM) whereas heterozygous gain-of-function variants lead to congenital hyperinsulinism. Heterozygous loss-of-function variants, however, are suggested to cause a bimodal pattern with hyperinsulinaemic hypoglycaemia in early life (with an often-mild presentation) and progressing to glucose intolerance in early adulthood.

Case description: We describe three family members with early-onset DM (or glucose intolerance) without clear features of type 1 or type 2 DM. A heterozygous likely pathogenic missense variant c.119G>A (p.(Gly40Asp)) was found in an autosomal dominant pattern. This variant was previously only linked to cases of congenital hyperinsulinism and had been described as likely pathogenic or pathogenic in patients with type 2 DM.

Conclusion: To our knowledge, this is the first report linking the c.119G>A KCNJ11 variant to a clinical context of MODY. We have no evidence in our patients of clinically significant hypoglycaemia at young age. However, we still hypothesise – congruent with the latest evidence – that there might be a bimodal pattern in individuals with this variant. This report adds to the clinical and genetic heterogenicity of MODY and illustrates the complexity of early diagnosis of MODY.

KEYWORDS

MODY-KCNJ11, diabetes, genetics, pathogenic variant

LEARNING POINTS

- We describe another clinical phenotype, namely diabetes mellitus, associated with a pathogenic variant in the *KCNJ11* gene that was previously only linked to congenital hyperinsulinism.
- An initial non-specific genetic variant for MODY always warrants an extensive clinical work-up, a thorough family history and segregation of the variant in family members.
- This case highlights the heterogeneous presentation of pathogenic variants in MODY genes.

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INTRODUCTION

Maturity-onset diabetes of the young (MODY), a subtype of diabetes mellitus (DM), is caused by impaired insulin secretion of the pancreatic beta (β)-cells and follows an autosomal dominant inheritance pattern. MODY-KCNJ11 is a less common variant, accounting for less than 1% of the MODY cases. The clinical phenotype of KCNJ11-MODY resembles that of HNF1A-MODY or HNF4A-MODY manifesting as a progressively deteriorating glucose tolerance[1]. *KCNJ11* encodes the protein Kir6.2, a subunit of the KATP channel of the β-cell and is responsible for the glucose-stimulated depolarisation. This causes a calcium influx which subsequently triggers insulin secretion.

Pathogenic gain-of-function (GOF) variants cause sustained opening of the KATP channel and make depolarisation and calcium influx less likely and thus impair insulin secretion, leading to neonatal diabetes mellitus (NDM)[2-4]. In contrast, loss-of-function (LOF) variants cause sustained closure of this channel and lead to an excessive insulin response and consequently hyperinsulinaemic hypoglycaemia in congenital hyperinsulinism (CHI). CHI most often results from a complete LOF due to bi-allelic LOF variants[2,3]. Heterozygous LOF variants, however, may lead to a milder CHI with an eventual progression to glucose intolerance or DM. To differentiate between these phenotypes, KATP GOF mutation variants are labelled KCNJ11-NDM/MODY, whereas KATP LOF hyperinsulinism is labelled KCNJ11-HI/MODY. Sulfonylureas have proved to be effective in the former and are suspected to be detrimental in the latter[5].

Diagnosing MODY remains challenging because of its low prevalence in comparison with type 1 diabetes mellitus (T1DM) or type 2 (T2DM), its atypical presentation, insufficient awareness from healthcare providers and the limited availability of genetic testing in some countries. We identified a family in which three affected members were diagnosed with impaired glucose tolerance or DM in early adulthood due to a pathogenic KCNJ11 variant.

CASE DESCRIPTION

The proband, an asymptomatic 20-year-old male with autism, iatrogenic sensorineural hearing loss and diabetic embryopathy at birth was found to have an elevated HbA1c of 6.6% (49 mmol/mol) on routine laboratory testing *(Table 1)*. No history of neonatal hypoglycaemia was reported. There was a strong family predisposition of early-onset DM spanning across two generations *(Fig. 1)*. His mother, her monozygotic twin and, more recently, his maternal cousin were all diagnosed with early-onset DM in the absence of obesity. A history of DM in the maternal grandparents of the proband could not be recalled.

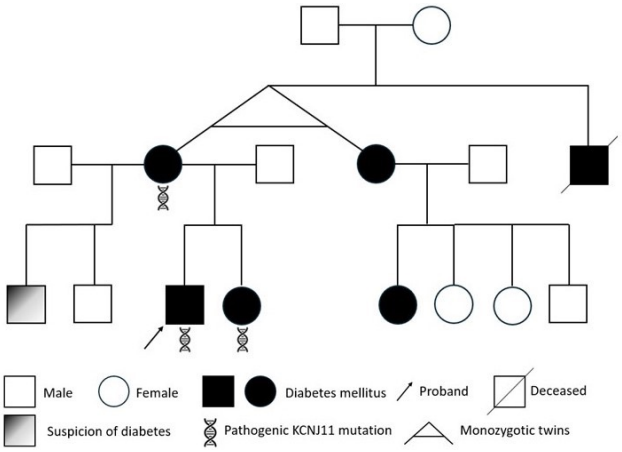


Figure 1. Family tree: visualisation of family history of DM.

The high family burden of DM, early onset and the absence of obesity and pancreatic autoimmunity warranted further genetic testing. A MODY gene panel identified a heterozygous variant c.119G>A (p.(Gly40Asp)) in the KCNJ11 gene, classified as likely pathogenic (class 4) according to the guidelines of the American College of Medical Genetics and Genomics (ACMG)[6]. This missense variant is rare in large population databases with an allele frequency of 0.00001859 (allele count 30/1613474, no homozygotes) in gnomAD v4.1.0. ClinVar contains an entry for this variant (RCV002227198.1) in an individual with MODY, but detailed phenotypic information is missing. The submitter last accessed ClinVar in May 2022, and at the time the variant was classified as a variant of uncertain significance (ACMG class 3). The clinical course of the proband is compatible with an insulin secretion defect, as is shown in an oral glucose tolerance test *(Table 2)*. This showed only a mild increase in both insulin and C-peptide levels. Lifestyle interventions were started and until now (two years after the diagnosis), no medical therapy has been required with consistently excellent glycaemic control

	Proband	Reference range
BMI (kg/m^2)	25.1	<25
Blood pressure (mmHg)	148/92	<130/90
HbA1c (%; mmol/mol)	6.6; 49	<6.5; < 48
LDL-cholesterol (mg/dl; mmol/l)	59; 1.53	<100; < 2.59
HDL-cholesterol (mg/dl; mmol/l)	45; 1.16	40–60; 1.03–1.55
Triglycerides (mg/dl; mmol/l)	179; 2.02	<150; < 1.69

Table 1. Baseline characteristics of the proband.

	Glucose (mg/dl)	C-peptide (µg/l)	Insulin (mU/l)
Baseline*	117	1.59	6.1
30 min	220	3.65	28
1h	226	5.23	36
2h**	169	7.28	44

Table 2. Oral glucose tolerance test with glucose, C-peptide and insulin levels.
**Impaired fasting glucose ≥100 mg/dl, DM if glucose ≥126 mg/dl*
***Impaired glucose tolerance if glucose ≥140 mg/dl, DM if glucose ≥200 mg/dl*

(HbA1c 6.3%; 45 mmol/mol).

Segregation analysis demonstrated that the variant was present in all affected family members (the proband's mother and sister); other family members were unavailable for genetic testing.

The proband's mother was diagnosed with T2DM at the age of 25 with a BMI of 29 kg/m^2 and in the absence of pancreatic autoimmunity. Initially, she was treated with metformin and sulfonylurea (gliclazide 60 mg); however, due to insufficient glycaemic control, the treatment was intensified to a four-times-daily insulin regimen. Over time, she experienced significant weight gain, requiring the addition of a GLP1 receptor agonist (dulaglutide 1.5 mg) without any beneficial effect on weight or glycaemic control and, ultimately, she even underwent bariatric surgery. Despite substantial weight loss (−39%), no remission of her DM was noted.

Recent evaluation demonstrated that after 24 years of poor glycaemic control, her C-peptide level remains detectable (3.3µg/l at a glucose level of 199 mg/dl; 10.6 mmol/l). She is now well controlled (HbA1c 6.9%, 49 mmol/mol) with metformin and a SGLT-2 inhibitor. As a consequence of her poor glycaemic control in the past, she developed multiple micro- and macrovascular complications.

The proband's sister was screened at the age of 19 after predictive genetic testing showed the presence of the KCNJ11 variant. She was found to have prediabetes (HbA1C of 6.3%; 45 mmol/mol), with a BMI of 37.1kg/m^2.

DISCUSSION

MODY is a heterogeneous, autosomal dominant disease, often misdiagnosed as T1DM or T2DM[1]. We describe three affected family members with an early adulthood onset (pre)diabetes. Genetic testing revealed a heterogeneous likely pathogenic variant in the KCNJ11 gene (c.119G>A, p.(Gly40Asp)) that showed an autosomal dominant inheritance pattern. An oral glucose tolerance test was suggestive for insufficient insulin secretion, consistent with our hypothesis that this type of DM is due to a genetic variant of the KCNJ11 gene with dysfunction of the pancreatic β-cell. Certain KCNJ11 variants, including this specific variant, have previously been described in patients with congenital hyperinsulinism[3]. Moreover, some KCNJ11 variants might lead to a bimodal pattern with congenital hyperinsulinism with an evolution to DM in early adulthood. Lastly, this specific variant is one of several MODY gene variants that are enriched in 25,699 cases with type 2 DM compared to 48,930 controls[3,7]. Collectively, these findings support our hypothesis that this KCNJ11 variant may account for the DM observed in this family and provided the rationale for segregation analysis and extensive phenotypic characterisation. Combining the following search terms: "c.119G>A (p.(Gly40Asp))", *KCNJ11*, MODY, neonatal DM, we found no cases in Pubmed, Medline or ClinVar databases linking this variant to a phenotype of DM in a young adult of a family with an autosomal dominant pattern. Previous reports have already illustrated that some pathogenic variants in KCNJ11 may cause both MODY (mono-allelic/heterozygous) and CHI (bi-allelic and mono-allelic), but the exact mechanisms are still poorly understood. Proposed mechanisms include downregulation of the calcium-dependent influx and a decrease of β-cell mass due to apoptosis, possibly secondary to chronically increased intracellular calcium levels[5].

Heterozygous LOF variants are generally associated with CHI rather than DM. The penetrance of these variants is incomplete, and individuals may experience asymptomatic episodes of hyperinsulinism in early childhood, followed by remission later in life. Vedovato et al. reported on a young woman in whom a dominantly inherited LOF *KCNJ11* variant leads to MODY[2]. Other reports describe heterozygous *KCNJ11* variants that cause both CHI at young age and MODY in early adulthood[8]. Similarly, in (partial) LOF ABCC8 variants, some patients progressed from hyperinsulinism to glucose intolerance, gestational diabetes or MODY[5,8-10]. Consistent with these autosomal dominantly inherited variants, we hypothesise that individuals with the c.119G>A (p.(Gly40Asp)) *KCNJ11* variant may exhibit a bimodal presentation with mild or asymptomatic hyperinsulinism at an early age and potential progression to glucose intolerance and in some cases DM in later life. Congruent with the latest evidence, we expect an incomplete LOF in our three patients leading to hyperinsulinism at an early age (although this was not clinically observed) with an evolution to glucose intolerance (prediabetes/DM). The insufficient treatment effect of SUs in the mother of the proband further contributes to this hypothesis. Scala et al. suggest SU therapy for GOF variants, but alternative glucose lowering therapies for LOF variants[5]. In retrospect, the diagnosis of T2DM in the proband's mother was probably inaccurate. Her clinical course demonstrates the necessity of an accurate and timely diagnosis of MODY. Unfortunately, limited cooperation of a significant part of the family of the

proband prevented us from performing extensive clinical, biochemical or genetic examination of all the possibly affected family members.

CONCLUSION

We report on a family exhibiting a MODY phenotype associated with a novel *KCNJ11* variant, previously only causally linked to cases of congenital hyperinsulinism. There is increasing evidence that certain heterozygous variants in the *KCNJ11* genes express themselves through a bimodal pattern with (often mild) congenital hyperinsulinism in childhood with spontaneous remission and evolution to glucose intolerance, gestational diabetes and MODY in adulthood. This has been previously established in both MODY-HNF4A and MODY-ABCC8 and, less common, in MODY-KCNJ11. This report adds to the clinical and genetic heterogenicity of MODY and illustrates the complexity of early diagnosis of MODY.

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