Glucokinase mutations in young children with hyperglycemia

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Abstract

Background The etiology of mild hyperglycemia without ketoacidosis in young children is often unknown. Maturity onset diabetes of youth (MODY) is a form of diabetes mellitus (DM) characterized by fasting hyperglycemia without evidence for autoimmune destruction of β-cells.

Methods We genetically analyzed four families of young children with fasting hyperglycemia with family histories of diabetes for mutations in the genes for hepatocyte nuclear factor 4 alpha (*HNF4α*), glucokinase (*GCK*), and hepatocyte nuclear factor 1 alpha (*HNF1α*), the genes responsible for MODY1, MODY2, and MODY3, respectively.

Results We identified mutations in *GCK* (Gly258Asp, Arg303Trp, and Arg191Gln) in three of the four families. Molecular genetic characterization in these children clarified the etiology and prognosis of the hyperglycemia and allowed discontinuation of insulin therapy in one family.

Conclusions We conclude that molecular evaluation for MODY in children with mild fasting hyperglycemia without ketosis with family histories of diabetes can provide important prognostic information to guide therapy and exclude preclinical type 1 diabetes mellitus.

Keywords MODY; diabetes; incidental hyperglycemia; glucokinase

Introduction

Young children with acute illnesses frequently demonstrate physiologic hyperglycemia related to the stress of the intercurrent illness [1]. In contrast, hyperglycemia detected on routine laboratory evaluation of apparently healthy children is unusual, and suggests the possibilities of preclinical type 1 diabetes mellitus (T1DM) [2], type 2 diabetes (T2DM), and rare genetic forms of diabetes including maturity onset diabetes of the young (MODY). Rarely, in patients with other associated ophthalmologic or neurological involvement, the hyperglycemia may be due to Wolfram syndrome or diabetes and deafness associated with mitochondrial tRNA mutations.

MODY has rarely been studied as a cause of isolated hyperglycemia in young children, in part owing to the initial report of MODY by Tattersall describing MODY as non-insulin dependent diabetes in young adults [3]. Six different types of MODY have now been described, all autosomal, dominantly inherited, and some with specific clinical characteristics, such as renal cysts and internal genitourinary anomalies in MODY5 [4]. MODY2 and MODY3 are the two most common forms of MODY, accounting for

more than 80% of MODY in Caucasian patients [5–8]. MODY2 is caused by mutations in glucokinase (*GCK*), the enzyme that catalyzes the first step of the glycolytic pathway in the pancreatic β-cell, converting glucose to glucose-6-phosphate and acting as the glucose sensor of ambient glucose concentrations for the β-cell. Heterozygous loss of function mutations of this enzyme lead to mild fasting hyperglycemia from a young age [9,10].

Heterozygous mutations in *HNF1α* cause MODY3 through effects on transcription in the islets and liver. Despite similar mild elevations in fasting plasma glucose concentrations, mutations in *HNF4α* and *HNF1α* lead to significantly higher plasma glucose concentrations after glucose administration compared to *GCK* mutations. Furthermore, glucose homeostasis and insulin secretion tend to deteriorate over time in patients with *HNF4α* or *HNF1α* mutations, eventually requiring treatment with oral hypoglycemic drugs or insulin, while patients with *GCK* mutations tend to remain stable over time. With improved methods for molecular diagnosis, it has become increasingly feasible to characterize hyperglycemia in young children, and such stratification allows for increased accuracy in prognosis and more individualized monitoring and treatment.

We report the molecular characterization of four young, asymptomatic children with incidental hyperglycemia detected during routine laboratory examination. A mutation in *GCK* was identified in three children, providing important prognostic information, which was used to guide management and allowed discontinuation of insulin treatment in one subject.

Methods

Four families were referred from July 2003 to June 2004 to a pediatric endocrinologist (EC or RR) for evaluation of fasting non-progressive hyperglycemia and abnormal glucose levels in their first-degree relatives. Growth was evaluated using the NCHS criteria [11], which have been shown to be applicable to contemporary Chilean populations [12]. Birth weight was analyzed according to local normative data [13]. The study was approved by the Institutional Review Board at Columbia University. Parents signed an informed consent, and children gave verbal assent.

Plasma glucose concentrations were determined by glucose oxidase. Insulin concentration was determined by radioimmunoassay as previously described [14]. HbA_{1c} was determined by ion exchange chromatography (DCA 2000, Bayer Diagnostics, Tarrytown, NY). Oral glucose tolerance tests (OGTT) were performed with 1.75 g/kg of anhydrous glucose (maximum 75 g). Subjects were classified according to the American Diabetes Association classification [15] and diagnosed as having impaired fasting glucose, impaired glucose tolerance (IGT) or diabetes mellitus (DM). Autoantibodies were measured by enzyme-linked immunosorbent assay as previously described [16]. Screening for serological anti-GAD65, anti-IA2, and IAA autoantibodies was performed by radioimmunoassay (^{125}I-RIA kit from DRG diagnostic, Mountainside, NJ, USA). For IAA autoantibodies, we considered a sample 'positive' when the binding percentage between the autoantibody and the kit ^{125}I-tracer was greater than +3 standard deviations compared to controls (greater than 5.8%). For anti-GAD65 and anti-IA2, concentrations over 0.9 U/mL and 0.75 U/mL, respectively, were considered positive.

Genomic DNA was isolated from leukocytes in whole blood by cell lysis followed by DNA extraction and precipitation according to manufacturer's instructions (Promega). Each proband was bidirectionally sequenced for all the coding exons of *GCK*, HNF1α, and HNF4α. When a mutation was identified, all other family members were sequenced only for the exon containing the mutation. Polymerase chain reaction (PCR) for amplification of small fragments utilizing primers listed in Table 1 consisted of 20 μL reaction volumes composed of 100 ng genomic DNA, 1X reaction buffer supplied by Boehringer Mannheim in which the [$MgCl_2$] was 1.5 mM, 0.25 mM each dNTP, 100 ng of each PCR primer, and 1 U Taq polymerase. All thermocycling were performed with 35 cycles of denaturation at 94 °C for 30 s, annealing at 58 °C (unless otherwise specified) for 30 s and extension at 72 °C for 30 s.

PCR products were purified after electrophoresis through a 2% agarose gel using the Qiaquick DNA purification columns (Qiagen Inc., Valencia, CA). Fluorescent dideoxy termination sequencing of purified PCR products was performed using an ABI 377 sequencer using standard reagents and under conditions as recommended by the manufacturer. The sequence was analyzed using the Sequencher software to compare subjects' sequence to that of control Caucasians without diabetes and the published reference sequence. In addition, each electropherogram was visually reviewed to identify any heterozygous DNA variants not detected by the automated sequencing software.

Results

Three of the four families tested positive for *GCK* mutations are reported in detail. The fourth family demonstrated no mutation in the coding sequence for the genes for MODY 1, 2, or 3. Briefly, the proband of the last family was a healthy 7.5-year-old boy with a fasting blood glucose concentration of 131 mg/dL and negative autoantibodies. His weight and height were normal. Three generations on the maternal side of the family have DM. The father is glucose intolerant.

Family 1 (Figure 1)

The proband (subject IV.3) was a six-year-old boy, referred for evaluation of short stature. His weight was

Table 1. Primers, PCR fragment sizes, and annealing temperatures used to screen *GCK, HNF1α*, and *HNF4α* for mutations

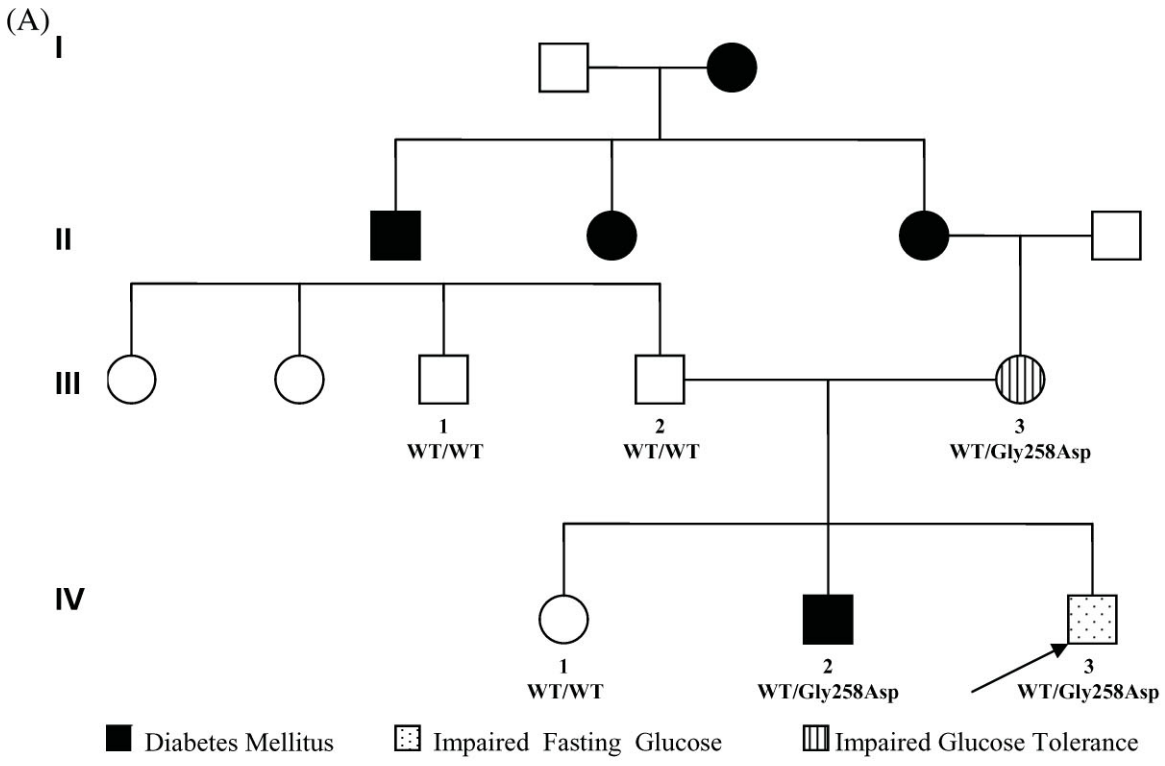
Fragment	Forward primer	Reverse primer	Fragment Size (bp)	Annealing Temp (°C)
GCK-a1	TCCACTTCAGAAGCCTACTG	TCAGATTCTGAGGCTCAAAC	195	58
GCK-b1	AGCAGGCAGGAGCATCTCTG	GCTGCTCTCCCAGTGCAAAG	147	58
GCK-c1	CCAGACTCTCCTCTGAACTC	GAAGAAGAGGTTCCATCTGA	145	58
GCK-3	TAATATCCGGCTCAGTCACC	CTGAGATCCTGCATGCCTTG	295	61
GCK-4	TAGCTTGGCTTGAGGCCGTG	TGAAGGCAGAGTTCCTCTGG	272	58
GCK-5	TAGCACCCTGCCTCCAGTAT	TCAAGTCCTGCCAAGAAGC	249	58
GCK-6	CCAGCACTGCAGCTTCTGTG	GAGCCTCGGCAGTCTGGAAG	176	58
GCK-7	AGTGCAGCTCTCGCTGACAG	CATCTGCCGCTGCACCAGAG	285	58
GCK-8	TGCCTGCTGATGTAATGGTC	TGAGACCAAGTCTGCAGTGC	263	61
GCK-9	ACTGTCGGAGCGACACTCAG	CTTGGAGCTTGGGAACCGCA	367	58
GCK-10	GTCGACTGCGTGCAGGGCGC	TGTGGCATCCTCCCTGCGCT	263	61
HNF-1α 1	GGCAGGCAAACGCAACCCACG	GAAGGGGGGCTCGTTAGGAGC	483	58
HNF-1α 2	ATCCCGTCCTTGCCCTCT	CCAGCCCCACCTATGAGT	389	58
HNF-1α 3	TCACGGCTTTCTGTGC	AATGGGCTTAGGTTCAA	263	58
HNF-1α 4	CAGAACCCTCCCCTTCATGCC	GGTGACTGCTGTCAATGGGAC	397	58
HNF-1α 5	GGCAGACAGGCAGATGGCCTA	GCCTCCCTAGGGACTGCTCCA	346	58
HNF-1α 6	TGGAGCAGTCCCTAGGGAGGC	GTTGCCCCATGAGCCTCCCAC	322	58
HNF-1α 7	GGTCTTGGGCAGGGGTGGGAT	CTGCAATGCCTGCCAGGCACC	347	58
HNF-1α 8	GAGGCCTGGGACTAGGGCTGT	CTCTGTCACAGGCCGAGGGAG	229	58
HNF-1α 9	CCTGTGACAGAGCCCCTCACC	CGGACAGCAACAGAAGGGGTG	287	58
HNF-1α 10	GTACCCCTAGGGACAGGCAGG	ACCCCCCAAGCAGGCAGTACA	251	58
HNF4α-1	AGGCCAAGACTCCCAGCAGA	CCCACCCCAAAGTTGAGTGC	357	61
HNF4α-2	TTCCTGAAGCCTCACTCCCTTC	GTGCCCATTTCCCAGCTGAA	248	61
HNF4α-3	GCCAGGGCCCTAGTTCTGTC	AATGACTGTCGGGGAGCTGTG	236	61
HNF4α-4	CACCCCCTACTCCATCCCTGT	CTGGGGAGAATGGAGGTGGA	242	61
HNF4α-5	CCCGGACATCTCCAGCATTT	GCCCACTACTGCCCACCATC	232	61
HNF4α-6	GCAGCCTTCCCAAGGGTACA	TGGGTGAGTGCCATGCTAGG	203	61
HNF4α-7	GGAGAGGGGTCAACCCAAGG	GGGATGGCTTAGGAGGTGTGC	240	61
HNF4α-8	CAGGGGACATCTGGGTCTTG	TGTGTGAGGCCTGTCTCCTG	383	61
HNF4α-9	TGCATCCCAGACTCTCCATCC	AGCCCCATCCTCACCCTTTG	244	61
HNF4α-10	TTTCCCGGGCCTCTTCATTT	TCGCCAACCTGGGTTTGTTT	985	61
HNF4α-11	GGCTGTGGTGAGGGAAGACG	CCCCTTGACTTGGGGAGTGA	1132	61

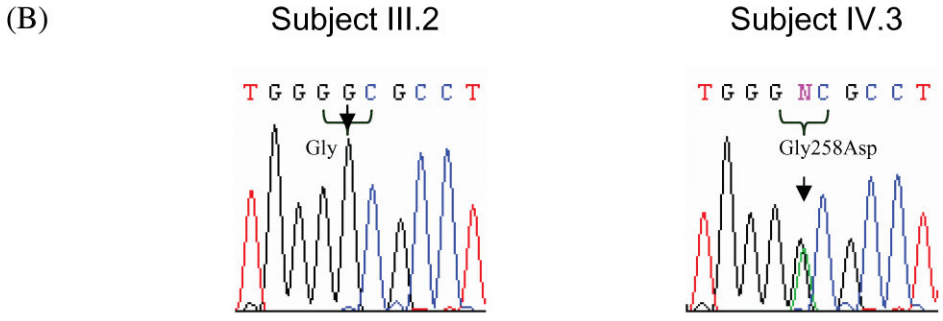
normal with a body mass index (BMI) in the 82nd percentile. Routine laboratory evaluation revealed fasting hyperglycemia of 126 and 131 mg/dL. OGTT showed a normal 2-h glucose concentration of 129 mg/dL, and the post-prandial glucose obtained throughout the day remained approximately 150 mg/dL. The HbA_{1c} was 6.8%. A diagnosis of preclinical T1DM was presumptively made, and he was treated with 1–2 units/day (<0.5 U/kg/day) of neutral protamine Hagedorn (NPH) insulin, given once daily. Despite the low dose of insulin, his HbA_{1c} remained elevated at 6.6% (normal range: <5.7%). The patient never showed any evidence of ketoacidosis.

The brother (subject IV.2) was a healthy asymptomatic 11.4-year-old boy, with an elevated glucose of 135 mg/dL on a routine preoperative laboratory examination for an elective tonsillectomy. His weight was normal with a BMI in the 68th percentile. He was diagnosed with presumptive early stage T1DM and started on 2 units of NPH insulin. Despite ongoing puberty, he remained in optimal metabolic control, with no increased requirement for insulin.

The mother (subject III.3), of Spanish and native descent, was a non-obese woman, diagnosed with gestational diabetes during the pregnancies of subjects IV.2 and IV.3. During the pregnancy of subject IV.2, she received insulin treatment, and the baby's birth weight was 2040 g (small for the gestational age). In the pregnancy with the proband, no insulin was administered, and his birth weight was 3320 g (40th percentile). No treatment was given to the mother after delivery. An OGTT was performed 7 years after her last pregnancy and demonstrated IGT (Figure 1(c)). Recently, at the age of 37, she had a normal ophthalmologic exam and no evidence of microalbuminuria. The maternal family history was significant for several maternal relatives with DM, without micro or macrovascular complications. The maternal grandmother is currently 57 years and has not developed any DM-related complications. The father (subject III.2) and a paternal uncle (subject III.1), of Spanish and native descent, had normal glucose and HbA_{1c} levels.

The three hyperglycemic subjects had normal basal and stimulated insulin levels (Figure 1(c)). C-peptide levels were 0.3, 0.3, and 0.5 ng/mL in subjects IV.2, IV.3, and III.3, respectively. Pancreatic autoantibodies were negative in all three hyperglycemic subjects. Sequence analysis in the proband demonstrated a heterozygous G to A transition at coding nucleotide 773, located in exon 7 of *GCK*, predicting a Gly258Asp substitution in the gene for MODY2. No other coding variants in *GCK, HNF1α*, and *HNF4α* were observed. The same mutation was then identified in IV.2 and III.3 but not in subjects IV.1, III.1, and III.2. Insulin was then discontinued in subjects IV.2 and IV.3. Subsequently, both children remained in optimal metabolic control, with fasting blood





(C)

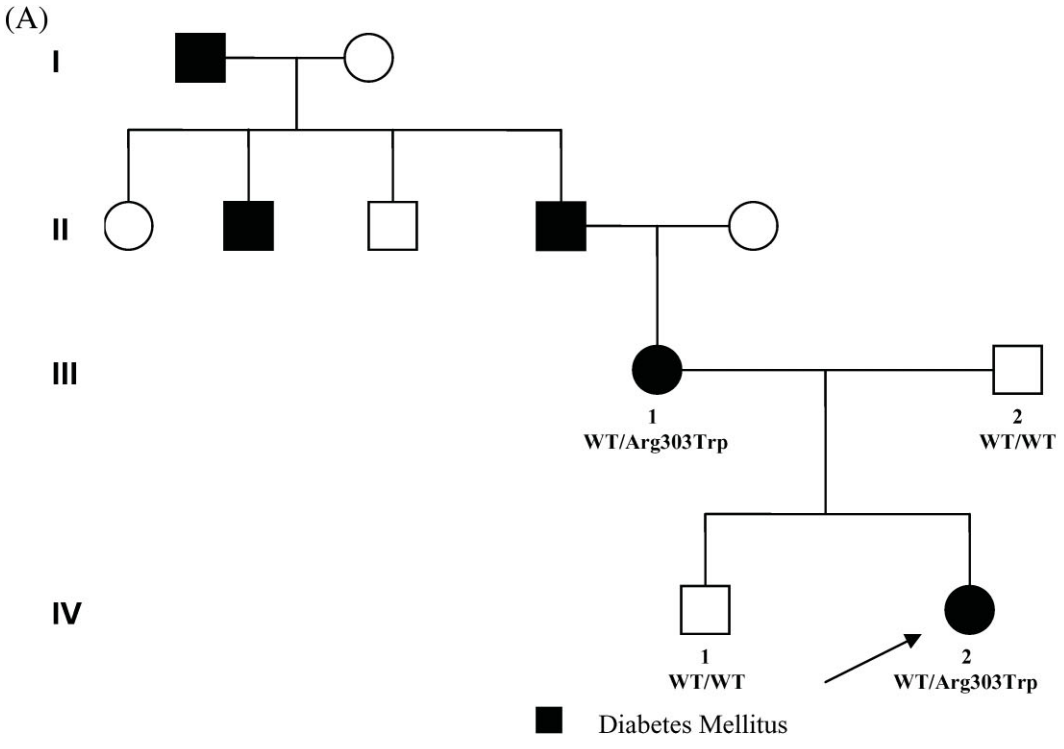
Subject	Genotype	Age (yr)	BMI (Kg/m^2)	Blood glucose (mg/dl)		Insulin (μU/ml)	
				Fasting	OGTT 2hr	Fasting	OGTT 2hr
IV. 1	WT/WT	16	23.6	96	98	10.6	80.4
IV. 2	WT/Gly258Asp	12	19.4	104	226	7.3	74.3
IV. 3	WT/Gly258Asp	6.4	17.2	138	129	6.1	19.4
III. 1	WT/WT	30	24.6	89	-----	-----	-----
III. 2	WT/WT	37	27.5	98	104	10.3	44.1
III. 3	WT/Gly258Asp	36	24.2	122	180	9.8	56.7

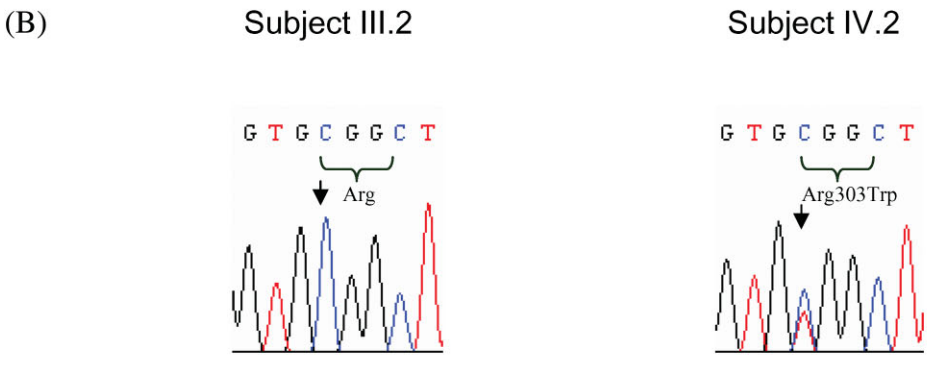
Figure 1. Family 1. (a) The proband, subject IV.3, is indicated by an arrow. WT denotes wild type allele. (b) *GCK* sequence in the proband and the healthy parent demonstrates a heterozygous G to A transition at coding nucleotide 773 in the proband (exon 7), predicting a Gly258Asp substitution. (c) Clinical characteristics of the subjects studied

glucose concentrations between 100 and 130 mg/dL and an HbA_{1c} of 6–6.3%.

Family 2 (Figure 2)

The proband (subject IV.2) was a 19-month-old girl whose mother was diagnosed with DM at the age of 17. The toddler was asymptomatic, but her mother performed repeated capillary blood glucose tests and demonstrated fasting blood glucose concentrations from 130 to 150 mg/dL. An OGTT demonstrated a 2-h glucose concentration of 155 mg/dL and fasting insulin of 4.8 µU/mL. Pancreatic autoantibodies were negative. Her mother's diabetes had been treated with insulin during her pregnancy. The proband's birth weight was 2750 g





(C)

Subject	Genotype	Age (yr)	BMI (Kg/m^2)	Blood glucose (mg/dl) Fasting	OGTT 2hr	Insulin (μU/ml)	HbA1c (%)
IV. 1	WT/WT	4	15.5	86	120	5.1	5.2
IV. 2	WT/Arg303Trp	1.5	15.7	130-150	155	4.8	6.6
III. 1	WT/Arg303Trp	38	20.3	128	230	-----	6.1
III. 2	WT/WT	33	30.1	84	-----	-----	-----

Figure 2. Family 2. (a) The proband, subject IV.2, is indicated by an arrow. WT denotes wild type allele. (b) Genetic analysis of *GCK* in the proband and in the unaffected father. DNA sequence analysis of codon 303 showed a heterozygous C to T transition at coding nucleotide 907 (exon 8) in subjects IV.2 and III.1, predicting an Arg303Trp substitution. (c) Clinical characteristics of the subjects

(10th percentile). Postnatal growth and development were normal, with a weight-to-height ratio in the 23rd percentile. Her fasting glucose remains between 100 and 135 mg/dL, without therapy.

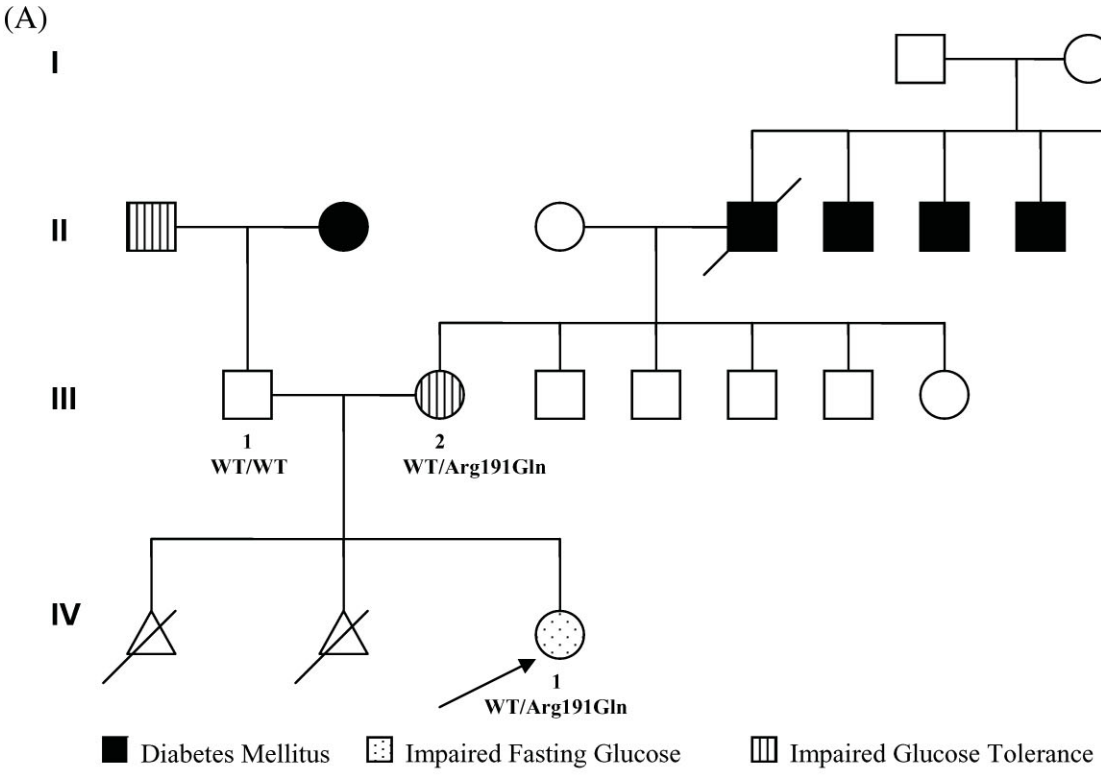
Her mother (III.1) is a non-obese woman diagnosed with T2DM at the age of 17. She was treated with different sulfonylureas from diagnosis, with frequent symptoms of hypoglycemia, and received insulin during the pregnancy of the proband. Upon receipt of the molecular diagnosis, glibeclamide was discontinued, with no deterioration of metabolic control. Her last screening for microvascular complications was performed at the age of 40 and demonstrated a normal fundoscopic exam and no microalbuminuria. The maternal family, of Spanish origin, has four consecutive generations with DM, without diabetic complications. The maternal great

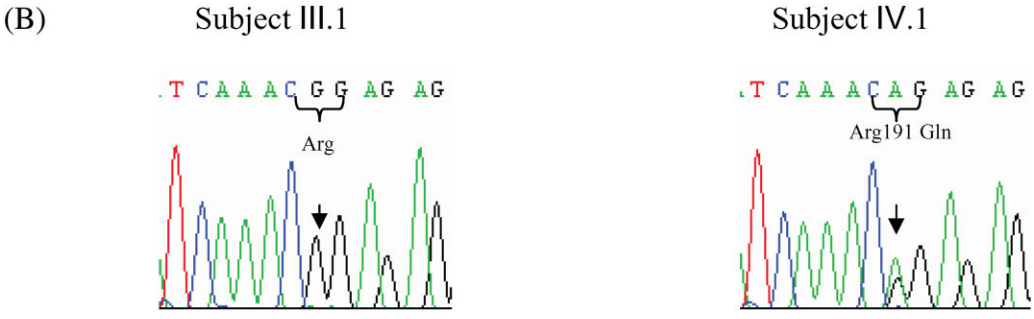
grandfather, was diagnosed with diabetes at an early age. Although he never received treatment for DM, he never developed any complications of DM and died at the age of 72 years of a cause unrelated to diabetes. The maternal grandfather, now 72 years, has not developed any diabetic complications. The father (III.2) has normal blood glucose levels and is of Spanish origin.

Genetic analysis of the proband demonstrated a heterozygous *GCK* C to T transition at coding nucleotide 907 (exon 8) in subjects IV.2 and III.1, predicting an Arg303Trp substitution in the gene for MODY2. No other coding variants in *GCK, HNF1α*, and *HNF4α* were observed in the proband. Subjects IV.1 and III.2 did not have the Arg303Trp mutation.

Family 3 (Figure 3)

The proband (subject IV.1), an asymptomatic 2.9-year-old toddler was diagnosed with hyperglycemia when fasting





(C)

Subject	Genotype	Age (yr)	BMI (Kg/m^2)	Blood glucose (mg/dl) Fasting	Blood glucose (mg/dl) OGTT 2hr	Insulin (μU/ml) Fasting	Insulin (μU/ml) OGTT 2hr
IV. 1	WT/Arg191Gln	2.9	16	101	138	3.0	14.5
III. 1	WT/WT	41	32	88	121	20	250
III. 2	WT/Arg191Gln	43	23	117	186	11.8	63.5

Figure 3. Family 3. (a) The proband, subject IV.1, is indicated by an arrow. WT denotes wild type allele. (b) Genetic analysis of *GCK* in the proband and the unaffected father. DNA sequence analysis showed a heterozygous G to A transition at nucleotide 572 (exon 5) producing an Arg191Gln in IV.1 and III.2. (c) Clinical characteristics of the subjects studied

glucose was measured because of a family history of DM. She had fasting hyperglycemia and normal stimulated values on OGGT, classifying her as impaired fasting glucose. She has been controlled with diet only and has maintained fasting blood glucose of 105–107 mg/dL and HbA_{1c} of 5.3 to 6.0%. Her height and weight are normal for her age (BMI in the 57th percentile).

Her mother (subject III.2) was diagnosed with gestational diabetes in two prior pregnancies that resulted in intrauterine fetal demise. During the pregnancy of the proband, she was treated with insulin from the tenth week of gestation. The proband was born at term, weighing 2455 g (second percentile). After delivery, mild fasting hyperglycemia persisted in the mother in the glucose-intolerant range. She has been treated with diet only and has remained in good metabolic control with fasting blood glucose from 101 to 111 mg/dL. A normal ophthalmologic exam and no microalbuminuria were recorded at the age of 41. Her father and three paternal uncles also have DM (Figure 3). The paternal and maternal families are of Spanish origin.

The father (subject III.1), an obese 41-year-old man, has a positive family history of T2DM, associated with elevated basal and stimulated insulin levels, suggesting the presence of insulin resistance in his family. The proband, IV.1, and her mother, III.2, both had a heterozygous MODY2 G to A transition at nucleotide 572 of *GCK* (exon 5) producing an Arg191Gln. No other coding variants in *GCK, HNF1α*, and *HNF4α* were detected in the proband. The proband's father, III.1, did not have the Arg191Gln mutation.

Discussion

We report three young children with asymptomatic hyperglycemia, family histories of diabetes, and mutations in *GCK* (MODY2). By establishing a molecular diagnosis a clear etiology for the hyperglycemia was provided with important prognostic information, which was used to guide therapy of the child and other family members. In one family it provided the reassurance that the hyperglycemia in two young children did not represent early T1DM, and allowed discontinuation of insulin therapy. The identification of a *GCK* mutation also provided assurance about the long-term prognosis and diabetic complications.

Each of the three families had characteristic clinical features of MODY2, such as onset before age 25, autosomal dominant transmission, nonketotic non-progressive mild hyperglycemia not associated with secondary diabetic complications, mildly elevated HbA_{1c}, and negative pancreatic autoantibodies [17]. During the OGTT, there was a mild increase in glucose concentrations, a characteristic that has been used to differentiate it from other types of MODY [18]. However, this has not been consistently observed in patients with MODY2 [6], and we observed heterogeneous responses to glucose administration in different subjects.

The American Diabetes Association consensus recommends screening for hyperglycemia in overweight children at high risk for diabetes or children with two of the following risk factors: a family history of type 2 diabetes in first- and second-degree relatives, high-risk ethnic groups (native Americans, African-Americans, Hispanic Americans, Asians/South Pacific Islanders), and signs of insulin resistance such as acanthosis nigricans, hypertension, dyslipidemia, and polycystic ovary syndrome [19] The children in this study met screening recommendations based on of the family history and ethnicity but were younger than the age of 10 and had a normal weight, which are usually recommended for screening. Our data suggest that in certain circumstances, a strong family history alone with autosomal dominantly inherited early onset diabetes may be sufficient to screen for fasting hyperglycemia.

The presence of incidental hyperglycemia in a healthy child, not associated with intercurrent illness, has been described as a risk factor for developing T1DM [20]. As demonstrated in this study, genetic evaluation for MODY mutations should be performed in young children with even mild fasting hyperglycemia not associated with physiological stress, especially if a mild increase of blood glucose levels during the OGTT and negative pancreatic autoantibodies are observed in a non-obese child with a family history of diabetes [21]. The family history should include gestational diabetes and fasting hyperglycemia. Our study suggests that if patients are properly selected and fulfill the clinical features of MODY, the molecular studies will have a high yield, 75% in this small case series.

Molecular definition of MODY2 allows individualized diabetes treatment that does not require intensive treatment. As shown for the extended family members in the three MODY2 families, this type of diabetes does not lead to chronic complications. Only follow-up every 6–12 months with measurement of HbA_{1c} is recommended [21], providing the family with relief from intensive glycemic monitoring.

Molecular diagnosis of a *GCK* mutation may also provide valuable information for the management of diabetes during pregnancy, and prenatal testing to manage the pregnancy is theoretically possible although not yet commonly employed. If the mother carries a MODY mutation, insulin treatment is indicated if the fetus exhibits macrosomia, suggesting that the fetus does not carry the *GCK* mutation and has hyperglycemia and hyperinsulinemia [22,23]. In contrast, when the fetus also carries the *GCK* mutation, the fetus requires higher glucose concentrations to stimulate insulin release and glucose uptake for normal fetal growth. When both the mother and the fetus carry *GCK* mutations, maternal insulin treatment may lead to decreased fetal growth as shown in three of the pregnancies described above, leading to increased risk of hypertension, dyslipidemia, and IGT, later in life [24]. Ellard *et al*. evaluated clinical parameters to differentiate gestational diabetes related to a *GCK* mutation and found that persistent postpartum

hyperglycemia, a small rise in glucose in the OGTT, and a positive family history of DM or IGT were distinguishing features of patients with a *GCK* mutation [25].

The mutations described in this article are the first *GCK* mutations to be published in the Chilean population. The Gly258Arg mutation has not been previously reported, although a Gly258Cys mutation has been reported in an Italian child with MODY [26]. Furthermore, glycine at amino acid 258 is highly conserved across multiple species, making the Gly258Arg substitution that segregates with diabetes in the family likely to be pathogenic. The remaining two mutations, Arg303Trp and Arg191Gln, have been previously reported in a Swedish and an Italian subject, respectively [6,27].

We conclude that the presence of isolated fasting hyperglycemia in young children should lead to the evaluation of the family history and measurement of fasting glucose in the parents. This will help in determining the likelihood of an inherited etiology that can be used to stratify patients into those warranting further molecular investigation. Identification of the molecular etiology can provide individualized prognostic information and guide medical management including the need for insulin therapy, management of diabetes during pregnancy, and determination of other family members at risk.

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