Mild fasting hyperglycemia in children: high rate of glucokinase mutations and some risk of developing type 1 diabetes mellitus

Codner E, Rocha A, Deng L, Martínez-Aguayo A, Godoy C, Mericq V, Chung WK. Mild fasting hyperglycemia in children: high rate of glucokinase mutations and some risk of developing type 1 diabetes mellitus. Pediatric Diabetes 2009: 10: 382–388.

Background: Incidental hyperglycemia in children generates concern about the presence of preclinical type 1 diabetes mellitus (T1DM).
Objective: To genetically evaluate two common forms of maturity-onset diabetes of youth (MODY), the short-term prognosis in children with mild hyperglycemia, and a positive family history of diabetes mellitus.
Subjects: Asymptomatic children and adolescents (n = 14), younger than 15 yr, with fasting hyperglycemia, a positive family history of mild non-progressive hyperglycemia, and negative pancreatic autoantibodies were studied.
Patients and methods: Glucokinase gene (*GCK*) and hepatocyte nuclear factor 1 alpha gene (*HNF1A*) causing two common forms of MODY were sequenced. The clinical outcome was evaluated after a follow-up period of 2.8 ± 1.3 yr.
Results: *GCK* mutations were present in seven children. The confirmation of this diagnosis allowed discontinuation of insulin in two families and oral medications in three families. Mutations of *HNF1A* were not detected in any of the families. During the follow-up period, all the *GCK* mutation carrier children remained asymptomatic without medication and the last hemoglobin A1c levels were 6.4 ± 0.7%. In the *GCK*-negative children (n = 7), one developed T1DM, corresponding to 7.2% of the total group. Mild fasting hyperglycemia persisted during follow-up in four *GCK*-negative children and normalized in the remaining two.
Conclusions: The presence of mild persistent hyperglycemia in any patient without autoantibodies should lead to genetic analysis of *GCK*, particularly if there is a positive family history. Furthermore, those without *GCK* mutations should be followed with repeat autoantibody testing, and other genetic types of diabetes should be considered if hyperglycemia worsens.

Ethel Codner[a], Ana Rocha[a], Liyong Deng[b], Alejandro Martínez-Aguayo[c], Claudia Godoy[d], Verónica Mericq[a] and Wendy K Chung[b]

[a]Institute of Maternal and Child Research (I.D.I.M.I.), School of Medicine, University of Chile, Santiago, Chile; [b]Division of Molecular Genetics, Department of Pediatrics, Columbia University Medical Center, New York, NY, USA; [c]Department of Pediatrics, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile; and [d]Department of Pediatrics, Hospital Sótero del Río, Santiago, Chile

Key words: DM – genetics – glucokinase – hyperglycemia – incidental hyperglycemia – MODY – prognosis

Corresponding author:
Ethel Codner, MD
Institute of Maternal and Child Research (I.D.I.M.I.)
School of Medicine
University of Chile
Casilla 226-3
Santiago
Chile.
Tel: 562-424-8280;
fax: 562-424-7240;
e-mail: ecodner@med.uchile.cl

The presence of asymptomatic hyperglycemia in an apparently healthy child generates anxiety about the possibility of onset of type 1 diabetes mellitus (T1DM). Mild hyperglycemia in children is an infrequent finding (1) and is observed in only 0.013% of the children attending a pediatric office (2). Recently, the cutoff level of normal fasting blood glucose (BG) has been decreased to 100 mg/dL (3), which may be a reason for an increase in the referral of asymptomatic children with mildly elevated BG.

Several studies have evaluated the risk of progression to T1DM in children with mild hyperglycemia (4, 5), but these studies did not consider the study of monogenic forms of diabetes. In addition, they did not measure BG in the parents, who may have mild asymptomatic hyperglycemia too. Children with mild asymptomatic

hyperglycemia with a positive family history of mild hyperglycemia or gestational diabetes may have maturity-onset diabetes of youth (MODY), caused by a heterozygous inactivating mutation in the glucokinase gene (*GCK*), which is not associated with progression to severe insulinopenia. Patients with this type of diabetes show mild fasting hyperglycemia with normal or near normal BG levels during the postprandial state (6). First-degree relatives carrying the familial *GCK* mutation show a similar abnormality, often with a history of lifelong hyperglycemia, without complications or requirement of insulin or oral medications (7).

We report the clinical and molecular outcome of 14 children with mild fasting hyperglycemia, without signs of autoimmunity, and their follow-up for 2.8 yr.

Methods

Subjects

Fourteen children with persistent mild hyperglycemia were studied. The families were referred from July 2003 to June 2007 to a group of pediatric endocrinologists working in hospitals or private clinics in Santiago, Chile, for evaluation of fasting, non-progressive hyperglycemia. All the probands had at least three fasting BG levels above 100 mg/dL, a parent and grandparent with a similarly elevated BG, and negative islet autoantibodies. All the relatives had mild hyperglycemia, which did not require insulin treatment and lacked a history of microvascular complications. All the families that fulfilled the inclusion criteria during this 4-yr period are included in this study except one family that did not sign the inform consent and a second case who had multiple positive islet autoantibodies. The molecular genetics of three of these families was previously reported (8). The study was approved by the Institutional Review Board at Columbia University. Parents signed an inform consent written in Spanish, and children gave verbal assent.

We performed a complete physical examination and pubertal development assessment according to Marshall and Tanner. Weight was measured using a conventional Seca scale with a precision of 100 g, and height was measured with a Harpenden Stadiometer. Standard deviation (SD) scores were calculated for height, weight, and body mass index (BMI) using current National Center for Health Statistics (NCHS) standard curves (9). In addition, birth weight SD was also calculated employing Chilean standards (10).

Laboratory evaluation

Plasma glucose concentrations were determined by glucose oxidase after a minimum of 8 h of fasting. Insulin concentration was determined by radioimmunoassay as previously described (11). Hemoglobin A1c (HbA1c) was determined by ionic exchange chromatography (DCA 2000; Bayer Diagnostics, Tarrytown, NY, USA). 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 and diagnosed as having impaired fasting glucose, impaired glucose tolerance, or diabetes mellitus (DM) (3). Screening for serological anti-glutamic acid decarboxylase (GAD) 65, anti-islet antigen-2 (IA-2), and insulin autoantibodies was performed by immunoassay as previously described (8).

Molecular study of *GCK* was performed in all the patients because the phenotype of mild persistent familial hyperglycemia is highly suggestive of *GCK* mutations. Hepatocyte nuclear factor 1 alpha gene (*HNF1A*) was then sequenced in those without a *GCK* mutation because it is the second most common cause of MODY (12, 13). Hepatocyte nuclear factor 4 alpha gene (*HNF4A*) was not studied because of the low frequency of mutations (13). Analysis of hepatocyte nuclear factor 1 beta gene (*HNF1B*) was not considered in any of the families studied because *HNF1B* mutation carriers have renal abnormalities that were not present in any of the patients in the study.

Genomic DNA was isolated from leukocytes in whole blood by cell lysis followed by DNA extraction and precipitation according to manufacturer's instructions (Promega, Madison, WI, USA). Each proband was amplified by polymerase chain reaction (PCR) and purified as previously described (8) Amplicons were bidirectionally sequenced for all the coding exons and splice sites of *GCK* and *HNF1A* with the BigDye Terminator kit using an ABI 377 sequencer (Applied Biosystems, Foster City, CA, USA). When a mutation was identified, all other family members were sequenced only for the exon containing the mutation. Sequence was analyzed using SEQUENCHER software. In addition, each electropherogram was visually reviewed to identify any heterozygous DNA variants not detected by the automated sequencing software.

Statistical analysis

Comparisons of means between the group of patients with and without a *GCK* mutation were made using the Mann–Whitney *U* test. Differences in proportions between the two groups were evaluated using Fisher's exact test. Results are expressed as mean age $\pm$ SD. All statistical calculations were run on SPSS for Windows, version 10.0. A p value less than 0.05 was considered statistically significant.

Results

Clinical characteristics of the patients and type of abnormality of the glucose metabolism

The clinical characteristics of the probands are shown in Table 1. Eleven patients had normal weight, 2 were

overweight, and 1 was obese. Using a fasting BG cutoff level of 100 mg/dL, impaired fasting glucose and DM were diagnosed in 57.1 and 42.9% of the patients, respectively. However, in those patients with fasting hyperglycemia, only one patient had a fasting BG level higher than 140 mg/dL. She was a 1.6-yr-old girl who had a normal stimulated BG on the OGTT and an HbA1c of 6.6%.

Based on the stimulated glucose level on the OGTT, 50% of the patients were normal, 42.9% glucose intolerant, and 7.1% diabetic. The patient who was classified as diabetic based on the 2-h BG level on the OGGT was a 2.7-yr-old boy, who had a fasting BG level of 105 mg/dL and an HbA1c level of 5.7%. Mild hyperglycemia persisted for 6 months and normalized afterward.

Molecular study and treatment modifications after confirmation of *GCK* mutation

A *GCK* mutation was identified in 50% of the patients. Five different mutations were observed in these families (Gly258Asp, Arg303Trp, Thr209Met, Gly44Ser, and Arg191Gln). All these mutations have been previously reported, and Arg191Gln and Gly258Asp have previously been identified in children with MODY (14–16). Three unrelated families carried the same Arg191Gln mutation (Fig. 1). The remaining seven probands had normal *GCK* and *HNF1A* sequence, excluding the diagnosis of the most common forms of MODY in these kindreds.

The metabolic characteristics of the seven families with and without a *GCK* mutations are shown in Table 2. No statistical differences were observed between the groups regarding their anthropometry, BG, or insulin levels. However, many of the *GCK* probands were diabetic based on the fasting BG compared with the idiopathic group (71.4 vs. 14.3%, respectively, $p = 0.05$, chi-squared test).

Table 1. Clinical and anthropometric characteristics of children with mild asymptomatic hyperglycemia*

	Mean ± SD	Range
Number of children studied	14	
Male/female	8/6	
Age (yr)	8.4 ± 3.9	1.6–15.6
Body mass index (SD)	0.4 ± 0.9	−0.7 to 1.9
Height (SD)	−0.5 ± 1.0	−3.1 to 1.1
Birth weight (SD)	−0.3 ± 1.0	−2.3 to 1.6
Hemoglobin A1c (%)	6.2 ± 0.6	5.4 to 7.5
Fasting glucose (mg/dL)	121.4 ± 15.9	101–155
Stimulated glucose level, 2-h OGGT (mg/dL)	143.1 ± 29.7	105–201
Fasting insulin (μUI/mL)	5.2 ± 2.5	2–10.3
Stimulated insulin level, 2-h OGTT (μUI/mL)	26.2 ± 21.7	3.8–84.7
Fasting glucose level (n)		
Impaired fasting glucose	8/14	
Diabetes mellitus	6/14	
Stimulated glucose level on 2-h OGTT (n)		
Normal	7/14	
Glucose intolerance	6/14	
Diabetes mellitus	1/14	

OGTT, oral glucose tolerance test.
*Values listed are means ± SD.

In five families, corresponding to six subjects, medications were discontinued after identification of a *GCK* mutation. Insulin was discontinued in three children from two families after the molecular etiology was identified. HbA1c did not change after discontinuing the medications, remaining at the previous level of 6.5% before and after the intervention.

One of the families that could stop medications is shown in Fig. 1A. The proband (subject III.2), a 9-yr-old boy, had impaired fasting glucose and glucose intolerance and was treated with glargin insulin 1–2 units/d (<0.5 U/kg/d). Upon identification of an Arg191Gln *GCK* mutation, insulin treatment was discontinued and the HbA1c levels remained stable. The second family in which insulin treatment was discontinued has been reported previously (8) (Fig. 1B). Briefly, children IV.2 and IV.3 were initially treated with insulin until a Gly258Asp *GCK* mutation was identified. Insulin treatment was discontinued, and BG levels and HbA1c remained unchanged.

Other patients were able to discontinue taking oral medications. Illustrated in Fig. 1C, the mother (II.1) of the asymptomatic 8.9-yr-old proband (III.2) was initially treated with metformin and glybenclamide. Both drugs were successfully discontinued, and BG and HbA1c levels remained unchanged afterward.

In Fig. 1D, the proband (subject III.1) was a 15.6-yr-old girl who was evaluated for hirsutism at which time impaired fasting glucose was diagnosed. She had a normal BMI of 19 kg/m^2 (−0.4 SD). Her diabetic mother (subject II.1) had been treated with metformin and discontinued her medication after a Gly44Ser *GCK* mutation was identified. Her metabolic control remained unchanged after discontinuing metformin.

The mother (III.I) in Fig. 1E was diagnosed with DM at the age of 17 yr and was treated with sulfonylureas, which was associated with frequent hypoglycemic episodes, despite the use of 2.5–5 mg glyburide. Her medication was then changed to metformin, which was discontinued after an Arg303Trp mutation in *GCK* was identified. After discontinuation of oral medications, her BG remained unchanged, with fasting glucose of 100–140 mg/d.

Clinical outcome in children with a *GCK* mutation and those with idiopathic hyperglycemia

The clinical outcomes of the 14 children are shown in Fig. 2. The median time of observation was 2.8 ± 1.3 yr (range 1–4.8 yr). The seven children with

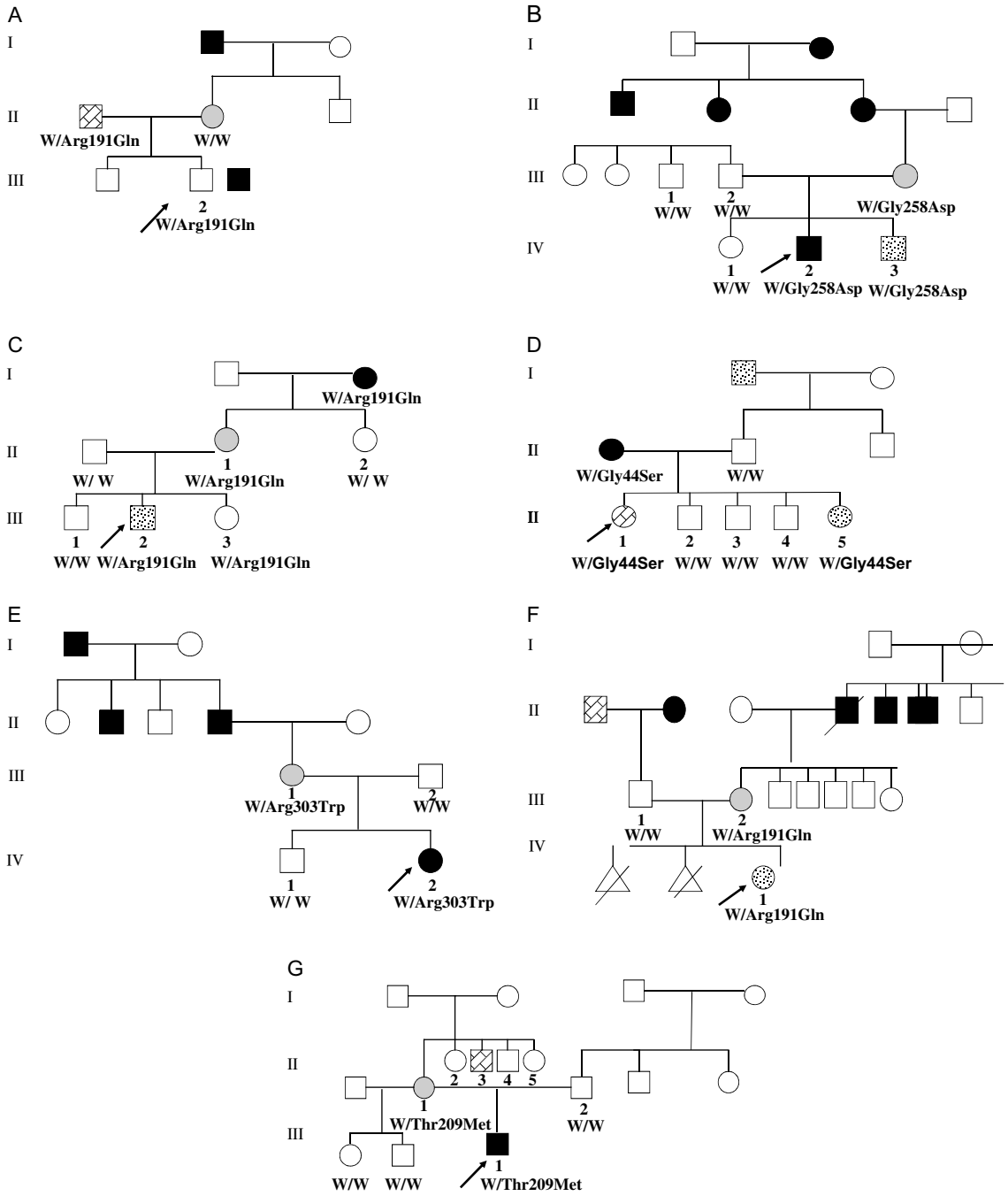

Fig. 1. Pedigree and molecular analysis of the seven families that harbor a *GCK* mutation. 'W' denotes wild-type allele. The proband are indicated by an arrow. Black squares/circles: diabetes mellitus. Light gray circles: gestational diabetes. Stippled squares/circles: impaired glucose tolerance. (A) Affected subjects had an Arg191Gln mutation. (B) Affected subjects had a Gly258Asp mutation. (C) Affected subjects had an Arg191Gln mutation. (D) Affected subjects had a Gly44Ser mutation. (E) Affected subjects had a Arg303Trp mutation. (F) Affected subjects had a Arg191Gln mutation. (G) Affected subjects had a Thr209Met mutation.

GCK mutations have remained under observation with surveillance of BG and HbA1c levels. This group of patients has been followed for 3.2 ± 1.5 yr, and the last fasting BG and HbA1c levels were 114 ± 13 mg/dL and 6.4 ± 0.7%, respectively. None of them is currently receiving medication. Counseling on healthy lifestyle and diet was provided.

One of the children with a negative sequence analysis for *GCK*, *HNF1A*, and *HNF4A* developed positive islet autoantibodies and progressive hyperglycemia 1 yr later leading to the diagnosis of T1DM. Initially, the boy was referred to a pediatric endocrinologist at the age of 11.1 yr for evaluation of short stature. The laboratory evaluation showed impaired fasting glucose

Table 2. Clinical and metabolic characteristics of probands with and without a *GCK* mutation*

	GCK	Idiopathic mild fasting hyperglycemia
Number of children studied	7	7
Age (yr)	8.1 ± 4.5	8.7 ± 3.5
Body mass index (SD)	0.4 ± 0.9	0.4 ± 0.8
Height (SD)	−0.7 ± 1.1	−0.2 ± 0.9
Birth weight (SD)	−0.4 ± 1.2	−0.1 ± 0.7
Hemoglobin A1c (%)	6.4 ± 0.7	6.2 ± 0.7
Fasting glucose (mg/dL)	128.1 ± 17.2	114.7 ± 12.2
Stimulated glucose level, 2-h	141.9 ± 27.4	144.4 ± 34.1
Fasting insulin (μUI/mL)	4.8 ± 1.6	5.5 ± 3.3
Stimulated insulin level, 2-h OGTT (μUI/mL)	18.1 ± 14.7	34.3 ± 25.4
Fasting glucose level (n)		
Impaired fasting glucose	2	6
Diabetes mellitus	5†	1
Stimulated glucose level on 2-h OGTT (n)		
Normal	3	3
Glucose intolerance	4	3
Diabetes mellitus	0	1

OGTT, Oral glucose tolerance test.
*Values listed are means ± SD.
†Proportion of patients with fasting glucose in the diabetic range $p = 0.051$.

(103–115 mg/dL), glucose intolerance on the OGTT, and negative islet autoantibodies. The father and paternal grandfather had a long-standing history of impaired fasting glucose. The child had stable BG for a year but then had progressive hyperglycemia subsequently. At the age of 12.9 yr, positive anti-GAD and anti-IA-2 autoantibodies were detected and fasting and postprandial BG increased to the 200 and 400 mg/dL, respectively. Treatment with glargine and multiple daily doses of aspart insulin was initiated. Currently, he is 13.4-yr-old and has been treated with multiple daily insulin injections for 6 months, with HbA1c of 7.2–8%.

Four children with idiopathic fasting hyperglycemia have had stable BG and two children normalized their BG. One of these two children has a fasting BG of 95 mg/dL with HbA1c level of 5.4% at the age of 16 yr. The second child who normalized his fasting BG had an HbA1c of 6.2% and fasting BG of 95 mg/dL at the age of 10 yr.

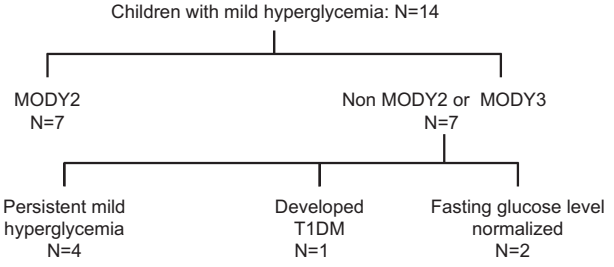

Fig. 2. Outcome of the children with mild hyperglycemia 2.8 ± 1.3 yr after initial diagnosis. T1DM, type 1 diabetes mellitus.

Discussion

We report on the genetic evaluation of *GCK* and *HNF1A* in a series of 14 young children and adolescents referred for asymptomatic hyperglycemia with a positive family history of mild hyperglycemia. We observed that half of these children carried a *GCK* mutation explaining their disturbed carbohydrate metabolism and accurately predicting a benign clinical course without pharmacological treatment. In the children without *GCK* or *HNF1A* mutations, 1 child of the 14 (7.2%) developed T1DM, despite negative islet autoantibodies at initial evaluation, suggesting the need for continued careful observation in these patients.

Development of T1DM has been reported in 2.1–32% of children with incidental hyperglycemia (4, 5, 17), which is similar to the findings in our report. Herskowitz-Dumont et al. prospectively followed children with incidental hyperglycemia for 18 months and observed a 32% incidence of T1DM. The risk of developing T1DM was associated with the presence of islet cell antibodies and a low stimulated insulin release during intravenous glucose tolerance test (17). Similar risk factors were also described by Schatz et al. in 1989 (5). More recently, Lorini et al. showed that children with incidental hyperglycemia exhibit a higher prevalence of the high-risk haplotypes and positive islet autoantibodies than the general population (4).

To characterize the etiology of mild hyperglycemia in children, the International Society of Pediatric and Adolescent Diabetes recommends molecular analysis of *GCK* in children who meet the following criteria: fasting BG of 100–150 mg/dL, hyperglycemia that is persistent and stable over a period of months or year, HbA1c just below or just above the upper normal limit, small increase of BG in the OGTT ($\Delta < 60$ mg/dL), and a parent with a similar abnormality (18). The fact that half of the children in our series who all met these criteria had identifiable mutations in *GCK* confirms the clinical applicability of these criteria.

Four children had persistent hyperglycemia without identifiable *GCK* or *HNF1A* mutations and may be explained by several hypotheses. One possibility is that a mutation such as a large deletion or regulatory mutation in *GCK* may not have been identified by the assay based on PCR amplification of coding exons, as recently reported by Ellard et al. (19). It is possible that

these patients have genetic variants in other genes for glycemic control besides *GCK* or *HNF1A*. It is also possible that some of these patients will develop T1DM, and the follow-up period is insufficient. Finally, it has been suggested by some authors that some people with a BG in the 100–110 mg/dL range do not have any disease and should be considered as part of the normal variation (20).

All the mutations we identified have been previously observed in many children (14, 15). Gly44Ser, Arg191Gln, Gly258Asp, and Thr209Met have previously observed in Italian subjects (14–16). Our results showed that three unrelated families share the same Arg191Gln *GCK* mutation. Several unrelated Italian families have also been identified with either the Arg191Gln or Arg191Trp *GCK* mutations, some of which are *de novo* (14). The increased frequency of mutations at this site is likely because of deamination of the cytosine leading to a C→T transversion, a common mutation mechanism. Mutations such as Arg191Gln cluster within the small domain of *GCK*, which is thought to be a mutational hot spot (21).

Most series evaluating the prevalence of *GCK* mutations have studied adult subjects. Recently, Sagen et al. studied adult subjects from a Norwegian registry of MODY subjects and determined that *GCK* mutations were less frequent than *HNF1A* mutations (12). However, these authors report adults with an average proband age of 32 yr. The high prevalence of *GCK* mutations in young children has also been observed in two Italian series (14, 21). These series suggest that the natural history of *GCK* and *HNF1A* is different, with decreased penetrance of the latter at young ages and suggest that *GCK* should be studied first in children with hyperglycemia.

There is significant clinical utility in making a genetic diagnosis of a *GCK* mutation in hyperglycemic children, providing reassurance of a good long-term prognosis and allowing successful discontinuation of medication highlighted by the two families able to discontinue insulin therapy in their children and three parents able to discontinue oral medications, without any detrimental effect on their metabolic control. Overtreatment of with oral hypoglycemic agents or insulin therapy has been previously reported (12) and may be especially risky for patients with *GCK* mutations because they have an altered counterregulatory response to hypoglycemia (22). The patients in our series did not benefit from drugs or insulin treatment, as has been previously suggested (12, 18, 23), and have remained stable off their medication.

The patients studied in our series with mild, non-progressive hyperglycemia, represent a group likely to have *GCK* mutations. The high prevalence of *GCK* mutations observed in our series emphasizes the concept that the presence of mild fasting non-progressive hyperglycemia should lead to the evaluation of fasting BG levels in other members of their family. In cases of mild familial hyperglycemia, without evidence of autoantibodies, *GCK* should be the first gene studied (24). If there is a family history of isolated, severe progressive hyperglycemia in the relatives, *HNF1A* should be also studied with consideration of reflexive testing of *HNF4A* if there is a strong family history consistent with autosomal dominant inheritance The study of other MODY genes was not recommended by a recent consensus for molecular genetic diagnosis for isolated hyperglycemia (24).

We conclude that the diagnosis of mild persistent hyperglycemia in children or adolescents should lead to the evaluation of fasting BG levels in the other members of their family. If the condition is familial, and no autoimmunity is present, genetic testing of *GCK* has a high yield for clarifying the diagnosis and avoiding unnecessary and potentially harmful treatment. Those patients without identified *GCK* mutations should be followed with repeat autoantibody testing, and other types of diabetes should be considered if hyperglycemia worsens.

Acknowledgements

We are grateful to all the families that were willing to participate in this study, to Patricia Lanzano for study coordination, to Dr Rossana Román, Hospital Clínico San Borja-Arriarán, Santiago, Chile, for referring patients, and to Dr Francisco Pérez-Bravo, INTA, University of Chile, for measuring autoantibodies. Sources of support: NIDDK 52431, DK63608 and DK26687.

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