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Clinical heterogeneity of hyperinsulinism due to *HNF1A* and *HNF4A* mutations

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Abstract

Background—Dominant inactivating mutations in *HNF1A* and *HNF4A* have been described to cause hyperinsulinism (HI) before evolving to diabetes. However, information available in the literature regarding the clinical phenotype is limited.

Objective—To report the prevalence of *HNF1A* and *HNF4A* mutations in a large cohort of children with HI, and to describe their genotypes and phenotypes.

Design—Retrospective descriptive study.

Methods—Medical records were reviewed to extract clinical information. Mutation analysis was carried out for 8 genes associated with HI (*ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HADH*, *HNF4A*, *HNF1A*, and *UCP2*).

Results—*HNF1A* and *HNF4A* mutations were identified in 5.9% (12 out of 204; *HNF1A* = 7, *HNF4A* = 5) of diazoxide-responsive HI probands. The clinical phenotypes were extremely variable. Two children showed evidence of ketone production during hypoglycemia, a biochemical profile atypical for hyperinsulinism. At the time of analysis, diazoxide was discontinued in 5 children at a median age of 6.8 years. None had developed diabetes mellitus at a median age of 7.0 years.

Conclusions—Given the heterogeneous clinical phenotypes of *HNF1A*- and *HNF4A*-HI, all children with transient, diazoxide-responsive HI without clear history of perinatal stress, should be screened for *HNF1A* and *HNF4A* mutations as it predicts the clinical course and affects the subsequent management plan.

Keywords

beta-cell; *HNF1A*; *HNF4A*; hypoglycemia; insulin; MODY

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1 | INTRODUCTION

Congenital hyperinsulinism (HI) is the most frequent and severe cause of persistent hypoglycemia in infants and children. HI is a heterogeneous condition in terms of molecular genetics, clinical presentation, responsiveness to medical treatment, requirement for surgery, and histopathology.

Dominant inactivating mutations in *HNF1A* and *HNF4A* have long been associated with maturity-onset diabetes of the young (MODY3 and MODY1).¹ Recently, it has been shown that the phenotype in individuals with these mutations is characterized by HI early in life before evolving to diabetes in later life.^{2–4} The pathophysiology for hyperinsulinism in early life followed by subsequent development of β -cell failure is still unclear.⁵ Information available in the literature regarding the clinical characteristics in *HNF1A*- and *HNF4A*-HI is limited to case reports or small case series with a short duration of follow-up and the prevalence is not known. The reported cases of HI associated with mutations in *HNF1A* and *HNF4A* have been diazoxide responsive with resolution of the HI during infancy, but lasting until childhood in some cases.

We hypothesized that mutations in *HNF1A* and *HNF4A* are a more common cause of diazoxide-responsive HI than previously appreciated. The objective of this study is to examine the prevalence of *HNF1A* and *HNF4A* mutations in a large cohort of children with HI, and to describe their genotype and phenotypes.

2 | METHODS

2.1 | Study design

This is a retrospective descriptive study. Clinical information was obtained by retrospective chart review.

2.2 | Subjects

Children with HI who were managed at The Children's Hospital of Philadelphia (CHOP) Hyperinsulinism Center between 1997 and June 2016 were included in the study. This study was approved by the institutional review board. Written informed consent was obtained from parents of probands included in the study.

The diagnosis of HI was based on evidence of increased insulin secretion/actions, including detectable plasma insulin or C-peptide, and/or inappropriately low plasma β -hydroxybutyrate (BOHB) (<1.8 mmol/L) and free fatty acids (FFA) concentrations (<1.7 mmol/L), and/or an inappropriate glycemic response to glucagon (increase of >30 mg/dL with blood samplings every 10 minutes for 40 minutes after intravenous or intramuscular injection of glucagon 1 mg, regardless of body weight) at the time of hypoglycemia.^{6,7} Children were defined as being diazoxide-responsive if during a 12 to 18 hours fasting test plasma glucose concentration was maintained >70 mg/dL or BOHB increased to >2.0 mmol/L. Resolution of HI was defined as having a normal fasting tolerance, as demonstrated by fulfilling the above criteria with 18 to 48 hours of fasting (depending on age) after

stopping diazoxide for at least 5 days. Children with perinatal stress-induced HI were excluded.

2.3 | Mutational analysis

Genomic DNA was obtained from peripheral blood (5 PRIME, Gaithersburg, Maryland) or saliva (Oragene DNA self-collection kit; DNA Genotek, Kanata, Ontario, Canada). Coding sequences and intron/exon splice junctions were amplified and directly sequenced on an ABI 3730 capillary DNA analyzer (Applied Bio-systems, Carlsbad, California). Mutation analysis was performed for all known HI loci either as a research test or in a commercial laboratory (*ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HNF4A*, *HNF1A*, *UCP2*, *HADH*). Mutation analysis for *HNF1A* and *HNF4A* was performed retrospectively as a research test in cases prior to 2012 and in commercial laboratories as part of a complete panel of hyperinsulinism genes for recent cases. Sequences were analyzed and compared with the published sequences for *HNF1A* (NM_000545) and *HNF4A* (NM_000457: exons 1a, 2–10; AY680697: exon 1d only; and U72959: exons 1b and 1c). Nucleotide and amino acid numbering for *HNF4A* is based on Chartier et al⁸ Novel genetic variants were searched against the Genome Aggregation Database (gnomeAD) that includes 141 352 unrelated individuals in order to determine population frequency.⁹ The functional consequences of novel, missense mutations were predicted with bioinformatics software, SIFT¹⁰ and PolyPhen2.¹¹ Human Splicing Finder was used to predict splicing alterations resulting from intronic mutations.¹²

2.4 | Statistical analysis

Descriptive statistics including mean, median, SE and interquartile range (IQR) were used according to the normality of the data. Wilcoxon rank sum tests, Pearson's χ^2 test were used to examine statistical significance since data was not normally distributed. Statistical analyses were performed using Stata (StataCorp. 2015, Stata Statistical Software: Release 14.1; StataCorp, College Station, TX).

3 | RESULTS

A total of 204 children with diazoxide-responsive HI were seen at CHOP between 1997 and June 2016 and were screened for mutations in the known HI loci (*ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HADH*, *HNF4A*, *HNF1A*, *UCP2*); mutations were identified in 99 of these children (49%). Of the 99 children with identified mutation, 7 had a mutation in *HNF1A*, and 5 had a mutation in *HNF4A*. Together, mutations in *HNF1A* and *HNF4A* accounted for 5.9% of all diazoxide-responsive cases (12/204) and 12.1% of diazoxide-responsive cases with an identified mutation (12/99).

Because 91% of children with diazoxide-unresponsive HI have an identified mutation in *ABCC8*, *KCNJ11*, or *GCK*, genetic testing for additional genes is not routinely performed either in the research lab, or in commercial laboratories using current testing strategies. However, we have completed additional genetic analysis of *HNF1A* and *HNF4A* in 13 out of 43 diazoxide-unresponsive cases without an identified mutation and did not find any pathogenic mutations in either *HNF4A* or *HNF1A*.

3.1 | Spectrum of mutations detected in *HNF1A* and *HNF4A*

As shown in Table 1 and Figure 1, a total of 10 unique mutations in *HNF1A* and *HNF4A* were identified in 12 children. Of these 10 mutations, 7 have been previously reported in the literature: 3 associated with diabetes, 2 associated with HI, and 2 associated with both diabetes and HI. The remaining 3 mutations are novel: 1 nonsense and 2 frameshift changes. Six children inherited the mutation from their fathers (*HNF1A* = 5, *HNF4A* = 1), while 4 cases inherited the mutation from their mothers (*HNF1A* = 2, *HNF4A* = 2). There was one *de novo* variant and parent-of-origin could not be confirmed in one child as parental samples were not available.

3.2 | Clinical and biochemical phenotype

The clinical characteristics are summarized in Table 2. There were no statistically significant differences between children with *HNF1A*-HI and *HNF4A*-HI, however, children who carried a mutation in *HNF4A* were more likely to be born large for gestational age (LGA: birth weight > 90th centile for gestational age) than were children with an *HNF1A* mutation. Six had family history of diabetes mellitus and among the 10 parents who carried a mutation, 5 were previously known to have either diabetes mellitus or gestational diabetes. None of the children had any history of significant perinatal stress.

The age of presentation ranged from day 1 of life to 2.3 years with no significant difference between the 2 groups. Some children presented with seizures, while others were discovered to be hypoglycemic during routine monitoring because of large birth weight or history of gestational diabetes. Their clinical severity varied from requiring a high intravenous glucose infusion rate (GIR) of up to 18 mg/kg/min to requiring frequent feedings but no intravenous dextrose.

Most children had typical HI biochemical profile characterized by hypoketotic hypoglycemia. However, 2 children (subject 1 and 8; *HNF1A* = 1; *HNF4A* = 1) had evidence of ketonemia with BOHB 1.8 mmol/L but inappropriate glycemic response to glucagon at time of hypoglycemia. Because of the atypical biochemical picture, additional testing with oral protein tolerance test (OPTT) was performed in one of the *HNF1A*-HI patients (subject 1) prior to obtaining the genetic results and it showed no evidence of protein-induced hypoglycemia. The detailed clinical characteristics of all the 12 children are summarized in Table 3.

3.3 | Pharmacological treatment with diazoxide

All children were treated with diazoxide. One *HNF1A*-HI child (subject 1) was only partially responsive as previously reported.⁴ This child was a full term, large for gestational age (4167 g) female. She had transient neonatal hypoglycemia that appeared to resolve after day 3 of life. She presented at 2 years of age with a hypoglycemic seizure. A diagnostic fasting study showed an abbreviated fasting tolerance of 10 hours and the diagnosis of HI was made based on an inappropriate glycemic response to glucagon (increase of 56 mg/dL). Her BOHB was elevated at 3.56 mmol/L during hypoglycemia. She was started on diazoxide 15 mg/kg/day but a repeat fasting study showed similar impaired fasting tolerance of 12 hours. She remained well with avoidance of prolonged fasting and diazoxide was stopped at

6.8 years of age. Resolution of HI was documented based on a normal fasting tolerance and a negative glycemic response to glucagon.

3.4 | Resolution of HI and development of diabetes mellitus

At the time of analysis, the median age of the children in this cohort was 7.0 years (IQR = 2.3–13.5 years). Diazoxide was discontinued in 5 children at a median age of 6.8 years (IQR = 4.0–6.9 years). Six were still on diazoxide at a median age of 2.3 years (IQR = 1.6–2.5 years). One was lost to follow-up soon after initiation of diazoxide.

Three children, now aged 14.9, 19.6 and 24.9 years, were lost to follow-up. For the rest of the children, only 2 reached the age of 10 years or older. Either hemoglobin A1c (HbA1c) or random glucose was used as screening tests for diabetes after age 10 and none of them had developed diabetes mellitus at the time of analysis.

3.5 | Development of extra-pancreatic features

In addition to HI, one child in our series with an *HNF4A* mutation (c.226c > t/p.Arg76Trp) developed extra-pancreatic features including hepatomegaly with elevated transaminase at 3 months of age with abundant glycogen on liver biopsy and renal Fanconi syndrome at 1 year as reported previously.⁴ A follow-up series identified this particular mutation to be associated with liver and renal manifestation similar to Fanconi-Bickel syndrome.^{13,14} In this patient, hepatomegaly resolved by the age of 1 year, liver dysfunction gradually improved and normalized by 8 years of age. Currently, at the age of 12 years, she continues to require supplementation with potassium and sodium phosphate, sodium bicarbonate and calcitriol. She has also developed nephrocalcinosis and mild chronic kidney disease with estimated glomerular filtration rate (eGFR) 66 mL/min/1.73 m.² No other children in the series developed other extra-pancreatic features.

4 | DISCUSSION

HNF1A and *HNF4A* mutations are well-accepted causes of MODY but whether the phenotype of individuals with *HNF1A* mutations, as those with *HNF4A* mutations, involves hyperinsulinism early in life has been controversial. However, multiple reports have now been published supporting this association.¹⁵ Moreover, in one of the published reports the evolution from hyperinsulinism to diabetes was documented in the same individual who was heterozygous for an *HNF1A* mutation (p.Arg272His) and presented with fetal macrosomia, hypoglycemia in childhood, followed by diabetes at the age of 19 years.¹⁶

Currently, most published data, especially on *HNF1A*-HI, are limited to case reports or small case series, and the exact prevalence of *HNF1A*- and *HNF4A*-HI is unknown. In a recent cohort of HI patients from Czech, *HNF1A*-HI was found to be the second commonest cause for HI.¹⁷ We herein report our series of *HNF1A*- and *HNF4A*-HI, which accounted for 5.9% of all diazoxide-responsive cases and 12.1% of diazoxide-responsive cases with an identified mutation in our cohort. The prevalence is likely to be under-reported. Some of these individuals might present with transient neonatal hypoglycemia, which may be attributed to maternal gestational diabetes (in which maternal diabetes could be caused by *HNF4A* or *HNF1A* mutations), without further workup/molecular diagnosis. Some might

present with some evidence of ketone production during hypoglycemia in their resolution phase, and therefore labeled as “ketotic hypoglycemia.”

We observed a very heterogeneous clinical course with variable presentation and severity. The severity of the HI ranged from mild transient hypoglycemia not requiring pharmacological treatment, to persistent HI requiring diazoxide for up to 7.3 years. Resolution of HI usually occurs in early childhood but could extend to mid childhood. This is consistent with previously reported cases.^{3,18,19} One of our patients was only partially responsive to diazoxide.

It was previously reported that birth weights in patients with *HNF1A* mutations are usually not affected while *HNF4A* mutations are associated with macrosomia² and most published cases of *HNF4A*-HI were born large LGA.^{18,19} In our series, 60% of our *HNF4A* patients were not LGA while *HNF1A* patients had variable birth weights. This probably reflects the fact that birth weight is determined by a complex interplay of multiple genetic and environmental factors. Therefore, a normal birth weight does not exclude the diagnosis and consideration for *HNF1A* and *HNF4A* genetic analysis should not be based on birth weight alone.

The diabetic phenotypes in *HNF1A* and *HNF4A* MODY have also been reported to be highly heterogeneous, with variable age of onset and symptoms at diagnosis.²⁰ This has been shown to be partly related to the type and position of the mutations, which determine the affected number and derivation of isoforms with differential expression in different tissues at different developmental stages, and ultimately the clinical phenotype.^{21,22} For example, in *HNF1A* MODY, missense mutations in the first 6 exons (predicted to affect all 3 isoforms) are associated with younger onset of diabetes.²³ Similarly, *HNF4A* mutations affecting exons 9 and 10 (absent from HNF4A3, HNF4A6, and HNF4A9 isoforms) are associated with later onset of diabetes compared to those with mutations in exons 2–8, where all isoforms were affected.²² Although we were unable to demonstrate a genotype/phenotype correlation for these cases as it relates to the type and position of the mutation, as in MODY, likely due to the relatively small sample size, genotypes could still be one of the factors contributing to the clinical heterogeneity in *HNF1A*- and *HNF4A*-HI and should be further evaluated in future studies.

Interestingly, 2 of the children in our series had some evidence of ketones production at times of hypoglycemia, which is atypical in HI. These 2 children presented relatively older at around 2 years of age. The diagnosis of HI was made based on suppressed FFA (<1.7 mmol/L) and inappropriate response to glucagon, which is highly specific for HI⁷ (however, specificity may be lower in the neonatal period). This prompted subsequent treatment with diazoxide and molecular analysis. This highlighted the importance of proper fasting study and critical sample in times of hypoglycemia even for children presenting with “ketotic hypoglycemia” at the “typical age.” These 2 patients have null mutations in *HNF1A* (nonsense mutation) and *4A* (frameshift mutation). One of them actually had history of neonatal hypoglycemia, which apparently resolved in few days with no further workup and all of them only presented for further investigations after the neonatal period. Therefore, we postulate that these patients had mild HI since birth that was not recognized until the fasting

interval between feedings increased with age. The mechanism underlying the elevation in betahydroxybutyrate in the setting of hyperinsulinism in these children is not known. It is possible that at the stage when these children were evaluated, the hyperinsulinism was resolving, rather than representing a different biochemical phenotype. This gives hint on the evolution of beta-cell abnormality over time on the spectrum from HI to MODY, which might be similar to the observation of age-dependent evolution in HI caused by dominant potassium channel defect, in which patients present with severe HI in the neonatal period, evolving into milder HI, and subsequently insulin deficiency or even diabetes mellitus in early adulthood.²⁴ In fact, it has been suggested that the phenotypes in *HNF4A*-HI can be explained partly by a partial reduction in potassium channel subunit Kir6.2 expression, and that it was demonstrated in mice model that Kir6.2 gene is a transcriptional target for *HNF4A*.²⁵ Therefore, it is possible that the difference in phenotype in neonates vs adults reflects an age-dependent difference in the mechanisms regulating insulin secretion. However, this should be interpreted with caution, especially in patient 1, in whom other markers for HI were absent. An alternative explanation for this case would be that he had resolved transient neonatal hypoglycemia, followed by ketotic hypoglycemia at the age of 2 years.

The median age at which diazoxide was discontinued in our series was 6.8 years, which is similar to most reported age of transition into a stable normoglycemic phase.^{18,26} None of the children in our series developed diabetes mellitus at the time of analysis. However, this is a young cohort with a median age of 7 years and some of the older patients, unfortunately, were lost to follow-up. Thus, we were unable to demonstrate the dual phenotype of *HNF1A* and *HNF4A* from HI to MODY in this cohort. This is not surprising since the reported mean age of diagnosing diabetes is 20 and 25 years in *HNF1A* and *HNF4A*, respectively.²

In addition to the effect on glucose homeostasis, extra-pancreatic features with transient liver dysfunction and renal Fanconi syndrome was observed in one of our patients. These specific extra-pancreatic features were reported to be mutation-specific to the *HNF4A*: c.226c > t/p.Arg76Trp mutation and are not observed in other *HNF4A* mutation carriers. While renal Fanconi's syndrome was reported to be the consistent feature, liver dysfunction was only observed in some cases.^{4,13,27} The underlying mechanism is still unclear. The fact that this is only observed with this specific mutation suggests this particular residue must be crucial for the hepatic and renal tubular function.^{4,13} Regardless, this well illustrates the wide regulatory network of *HNF4A*, not limiting to pancreatic β -cells but also liver and kidney.⁴

In addition to the relatively small number of cases in this cohort, one of the limitations of this study is the fact that it was retrospective, and hence, some of the clinical information was incomplete and there were some inconsistencies in characterizing the patients. However, inconsistencies in testing were minimal because all the fasting studies and glucagon stimulation test were standardized in our institution during the study period.

Identifying the molecular etiology in patients who might have mutations in *HNF1A* or *HNF4A* is beneficial to both the patient and their family. Because mutations in *HNF1A* and *HNF4A* are associated with the development of diabetes later in life, molecular diagnosis of *HNF1A* or *HNF4A* is important in order to guide appropriate follow-up and surveillance

after the HI has resolved. In addition, identifying asymptomatic parents or other family members who carry mutations enable early diagnosis of diabetes and initiation of treatment with sulfonylureas to avoid complications later in life. *HNF1A* and *HNF4A* mutations are inherited in an autosomal dominant fashion, so each child born to a mutation carrier will have a 50% risk of inheriting the mutation and will be at risk for macrosomia and neonatal hypoglycemia, which requires close monitoring and appropriate intervention. Thus, when evaluating cases of hyperinsulinism that are transient and diazoxide responsive, including those with evidence of some ketone production in the critical sample but inappropriate glycemic response to glucagon, clinicians should have a high index of suspicion for this form of hyperinsulinism and carry out mutation analysis for *HNF1A* and *HNF4A* when possible.

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(A) *HNF1A* Mutations (B) *HNF4A* Mutations **FIGURE 1.**

Mutations of the *HNF1A* and *HNF4A* genes. A total of 10 unique mutations in *HNF1A* (panel A) and *HNF4A* (panel B) were identified in 12 children with HI. Novel mutations not reported previously are **bolded**

TABLE 1

Mutations in *HNF1A* and *HNF4A* identified in 12 children with HI

Patient number	Gene	Exon	Nucleotide	Residue	Reference	Parent of origin ^a	Phenotype of parent of origin	Published phenotype
1	<i>HNF1A</i>	Exon 1	c.94 g > t	p.Glu32 ^a	Stancu, 2012	Paternal	Diabetes	HI
4, 5	<i>HNF1A</i>	Exon 3	c.654 t > a	p.Tyr218 ^a	Novel	Paternal (for both cases)	Nil	—
2	<i>HNF1A</i>	Exon 4	c.871 c > t	p.Pro291Ser	Bazalova, 2010	Paternal	Nil	MODY
3, 6	<i>HNF1A</i>	Exon 4	c.872dupC	p.Pro291fs	Yamagata, 1996	Maternal (for both cases)	Diabetes before pregnancy (3) GDM (6)	MODY
7	<i>HNF1A</i>	Exon 4	c.872delC	p.Pro291fs	Vaxillaire, 1997; Klupa, 2002	Paternal	Nil	MODY
11	<i>HNF4A</i>	Exons 2–6	c.89-?_c.709 +?	p.Asp30_Leu245del	Novel	Maternal	GDM	—
9	<i>HNF4A</i>	Exon 2	c.226 c > t	p.Arg76Trp	Flanagan, 2010	De novo	Nil	MODY, HI
10	<i>HNF4A</i>	Exon 2	c.239 g > a	p.Arg80Gln	Forlani, 2010	Paternal	Nil	MODY, HI
12	<i>HNF4A</i>	Exon 7	c.802delC	p.Gln268fs	Novel	Unknown	Father had diabetes at 38y	—
8	<i>HNF4A</i>	Exon 8	c.1004delT	p.Leu335fs	Snider, 2013	Maternal	GDM	HI

Abbreviations: GDM, gestational diabetes; HI, hyperinsulinism; MODY, maturity onset diabetes of the young; Nil, no history of hypoglycemia or diabetes mellitus. Patients 4 and 5 are siblings. Patient 1 had siblings with neonatal hypoglycemia.

^aBoth parents were tested by direct Sanger sequencing after the identification of the mutation in the proband (except for patient 12, in whom both parental samples were not available).

TABLE 2Clinical characteristics of *HNFI1A*- and *HNFI4A*-HI

Clinical parameters	HNFI1A (<i>n</i> = 7)	HNFI4A (<i>n</i> = 5)
Gestational age (wk)	40.0 (IQR = 39.0–40.0)	40.0 (IQR = 38.7–40.0)
Birth weight (g)	3815 (IQR = 3317–4167)	3845 (IQR = 3750–4010)
Birth weight (centiles)	77.5 (IQR = 44.0–92.0)	87.0 (IQR = 81–97)
LGA	28.6%	40.0%
SGA	14.3%	0
Age of presentation (d)	1.8 (IQR = 1.2–120.5)	1.1 (IQR = 1.1–1.1)
Maximum diazoxide maintenance dose (mg/kg/d)	14.0 (IQR = 10.0–15.0)	9.6 (IQR = 6.0–15.0)

Data presented as median (IQR). IQR, interquartile range; LGA, large for gestational age (birth weight > 90th centile for gestational age); SGA, small for gestational age (birth weight < 10th centile for gestational age).

Clinical and biochemical features of the 12 children with HNFs HI

TABLE 3

Subject no.	Mutations	Gestations (w)	Birth weight (centile)	Age of presentation	Clinical presentation	IV, GIR before diazoxide (mg/kg/min)	Plasma glucose (mg/dL)	BOHB (mmol/L)	Insulin (uU/mL)	C-peptide (ng/mL)	FFA (mmol/L)	IGFBP-1 (ng/mL)	Inappropriate glycemic Response to glucagon	Age of starting diazoxide	Age of stopping diazoxide
1	<i>HNF1A</i> c.94g>tp C3u32 ^d (paternal)	40	92	2 y (history of neonatal hypoglycemia)	Seizure	No IVF; frequent feed	47	3.56	<1.5	0.21	1.6	442	Yes	2 y	6.8 y
2	<i>HNF1A</i> c.871 c>A (paternal)	39	7	4 mo	Seizure	1.5	20	Hypo-ketotic ^d	Detectable insulin ^d	ND	ND	ND	Yes	4 mo	3.5 y
3	<i>HNF1A</i> c.872dupC (maternal)	38	71	Day 1	Routine check (GDM)	High GIR ^d	40	Urine ketone negative ^d	3.7	ND	ND	ND	No	2 wk	Still on diazoxide
4	<i>HNF1A</i> c.654 T>G (paternal)	40	Missing data	Day 2	Seizure	Missing data	44	Urine ketone negative ^d	2.3	ND	ND	ND	No	Day 7	7.3 y
5	<i>HNF1A</i> c.654 T>G (paternal)	40	44	4 mo	Fatiness	3.4	41	<0.3	<2	0.193	0.91	194	Yes	4 mo	Still on diazoxide
6	<i>HNF1A</i> c.872dupC (maternal)	41	84	Day 1	Routine check (GDM)	No IVF; frequent feed	45	0.84	<2	0.345	1.32	354	Yes	2 mo	Still on diazoxide
7	<i>HNF1A</i> c.872deC (paternal)	39.3	97	Day 1	Routine check (LGA)	1.7	44	<0.3	<2	0.772	0.43	169	Yes	Day 23	Still on diazoxide
8	<i>HNF2A</i> c.1004delTtp.Lue335fs (maternal)	40	26	2.3 y	Seizure, lethargy	No IVF; frequent feed	46	1.88	1.3	ND	0.96	374	Yes	2.3 y	6.9 y
9	<i>HNF4A</i> c.226 c>1 (de novo)	40	87	Day 1	Routine check ("borderline" LGA)	Missing data	36	0.1	7.5	ND	1.6	ND	Yes	4 wk	4 years
10	<i>HNF4A</i> c.239 G>A (paternal)	40	97	Day 1	Lethargy	High IV GIR ^d	42	Urine ketone negative ^d	High insulin ^d	Missing data	Missing data	Missing data	ND	2 wk	Lost to follow-up
11	<i>HNF4A</i> c.89 T>C709p>? (maternal)	36.8	98	Day 1	Routine check (GDM)	6	45	<0.3	<2	0.756	0.16	154	Yes	Day 11	Still on diazoxide
12	<i>HNF4A</i> c.802deC (unknown)	38.7	81	Day 1	Seizure	18	⁵⁷ <i>b</i>	Urine ketone negative ^d	5.5	ND	ND	ND	ND	Day 12	Still on diazoxide

Abbreviations: IVF, intravenous fluids; GDM, gestational diabetes; GIR, glucose infusion rate; LGA = large for gestational age; ND, not done.

^aNo actual figures available in patients' chart.

^bPlasma glucose documented in the critical sample = 57 mg/dL^a; glucose <50 mg/dL documented in other occasions.