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Case Report

Report of Prolonged Neonatal Hypoglycemia in Three Infants of Mothers With Variants in *HNF1A*

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ABSTRACT

Background/Objective: Genetic variants in hepatic nuclear factor 1α (*HNF1A*) cause maturity-onset diabetes of the young (MODY). We sought to examine whether *HNF1A* MODY variants also cause neonatal hypoglycemia.

Case Report: We present 3 infants with variants in *HNF1A* shared with their mothers. The infants experienced neonatal hypoglycemia, 2 extending beyond 1 year and the third resolving by 28 days, and all were large for gestational age (birth weights of >99th percentile). In 2 cases, genetic testing for neonatal hypoglycemia revealed pathogenic variants in *HNF1A*; 1 mother was previously diagnosed with *HNF1A* MODY, and the other's genetic testing and ultimate MODY diagnosis were prompted by her child's hypoglycemia workup. In the third case, the infant's persistent hypoglycemia prompted genetic testing, revealing an *HNF1A* variant of uncertain significance, which was then identified in the mother.

Discussion: Genetic variants causing *HNF1A* MODY have not been definitively linked to neonatal hypoglycemia or fetal overgrowth in utero. MODY caused by *HNF1A* is clinically similar to that caused by *HNF4A*, for which a causal relationship with neonatal hypoglycemia is more certain. Case reports have previously implicated variants in *HNF1A* in congenital hyperinsulinism; however, these cases have generally not been in families with MODY. The cases presented here suggest that *HNF1A* variants causing MODY may also cause neonatal hypoglycemia.

Conclusion: Although confounding factors make the assessment of neonatal hypoglycemia challenging, these cases offer potential support for single genetic variants in *HNF1A* causing both MODY and neonatal hypoglycemia, with associated fetal overgrowth in utero.

Introduction

Mutations in hepatic nuclear factor-1α (*HNF1A*) are among the most common causes of maturity-onset diabetes of the young (MODY). Also known as "MODY 3," *HNF1A* MODY is marked by glycosuria, progressive β-cell dysfunction, and sensitivity to sulfonylureas causing hypoglycemia.[1] *HNF1A* MODY is clinically similar to

Abbreviations: CGM, continuous glucose monitoring; CHI, congenital hyperinsulinism; EFW, estimated fetal weight; HbA1C, hemoglobin A1C; *HNF1A*, hepatic nuclear factor-1α; *HNF4A*, hepatocyte nuclear factor-4α; MODY, maturity-onset diabetes of the young; NICU, neonatal intensive care unit; T1D, type 1 diabetes; T2D, type 2 diabetes; VUS, variant of uncertain significance.

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hepatocyte nuclear factor-4α (*HNF4A*) MODY; however, only variants causing *HNF4A* MODY, but not *HNF1A* MODY, have been definitively linked to neonatal hypoglycemia and hyperinsulinism.[2] Studies focusing on infants with congenital hyperinsulinism (CHI) (vs focusing on families with MODY) have identified variants in *HNF1A*[2-10]; however, the evidence supporting a relationship between *HNF1A* and neonatal hypoglycemia remains on the level of case reports, and further reporting is needed to solidify this association. Additionally, to date, there is limited evidence of single mutations in *HNF1A* causing both neonatal hypoglycemia and MODY.[3,7]

Here, we present 3 cases of infants and mothers sharing variants in *HNF1A*, which demonstrate potential support for single genetic variants in *HNF1A* causing both neonatal hypoglycemia with associated fetal overgrowth in utero (suspected to be due to neonatal hyperinsulinism) and MODY.

Highlights

- Variants in hepatic nuclear factor-1α (HNF1A) cause a specific form of MODY.
- It is unclear if HNF1A variants causing MODY also cause neonatal hypoglycemia.
- We report on three infants with prolonged neonatal hypoglycemia and HNF1A mutations.
- Their mothers had pregestational diabetes and the same HNF1A mutations.
- Single mutations in HNF1A may cause both MODY and prolonged neonatal hypoglycemia

Clinical Relevance

These cases suggest that certain mutations in hepatic nuclear factor 1α are associated with hypoglycemia due to congenital hyperinsulinism and large-for-gestational-age birth weight. Additionally, it may be possible for a single variant to be associated with phenotypes of both hyperinsulinism and maturity-onset diabetes of the young within 1 family or even a single individual.

Case Report

Case 1

Maternal History

A 22-year-old woman presented for diabetes care during pregnancy. She was diagnosed with *HNF1A* MODY based on genetic testing (report unavailable) when she was approximately 15 years old. She was initially diagnosed with type 1 diabetes (T1D) at the age of 8 years and started on basal-bolus insulin therapy. Owing to excellent glycemic control and minimal insulin requirements, her diagnosis was changed to type 2 diabetes (T2D) at approximately 9 years of age, and she transitioned to metformin monotherapy. Her strong family history of diabetes mellitus in her brother, mother, and maternal aunt prompted genetic testing at the age of approximately 15 years, leading to a clinical diagnosis of *HNF1A* MODY. She subsequently transitioned to sulfonylurea monotherapy, which she continued initially during the pregnancy, prior to transitioning to a basal-bolus insulin regimen at 5 weeks of gestation because of frequent hypoglycemia. Glycemic control during pregnancy remained within to slightly above the goal range (fasting glucose level, 60-110 mg/dL; 2-hour postprandial glucose level, 100-184 mg/dL; hemoglobin A1C [HbA1C] level, 27-33 mmol/mol [4.6%-5.2%]; postpartum HbA1C level, 29 mmol/mol [4.8%]), with a reported maximum glucose level of 189 mg/dL on continuous glucose monitoring (CGM) throughout the entire pregnancy. Nevertheless, ultrasonography demonstrated fetal overgrowth (estimated fetal weight [EFW] of >90th percentile at 29 weeks).

Child History

She delivered a girl via cesarean delivery at 38 weeks and 2 days of gestation with a birth weight of 4.38 kg (>99th percentile) and Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. The infant's initial point-of-care glucose level was 30 mg/dL at 1 hour of life, with a confirmatory serum glucose level of 34 mg/dL. She received a 10% dextrose bolus, followed by continuous infusion for 7 days (maximum glucose infusion rate of 8.7 mg/kg/min) and fortification of feeds (24 kcal/oz); critical hypoglycemia laboratory samples were not collected. Feeds were not defortified until day 25 of life, and the infant remained admitted for approximately 1 month because of concerns regarding hypoglycemia and feeding difficulties. Prior to discharge, a 6-hour safety fast resulted in glucose values ranging between 57 and 68 mg/dL.

At her first endocrine evaluation at the age of 6 weeks, the infant was formula feeding every 1 to 2 hours. Home blood glucose monitoring, including with CGM, revealed blood glucose values routinely of 50 to 60 mg/dL despite frequent feeding. Diazoxide and hydrochlorothiazide were initiated for presumptive hyperinsulinism with rapid stabilization of glucose values. Subsequent genetic testing (University of Chicago 15-gene MODY panel, 2020) revealed a pathogenic variant in *HNF1A* (c.811C>T, p.Arg271Trp), previously described to cause MODY.[11] The child's father does not have diabetes, supporting that the high likelihood that the same variant is carried by the mother causing her MODY, despite her prior genetic testing results being unavailable. At approximately 1 year of age, the infant remains diazoxide-dependent.

Case 2

Maternal History

A 32-year-old woman presented for diabetes care at 11 weeks and 6 days of gestation. She was not diagnosed with MODY. She reported a history of hyperglycemia from the ages of 6 to 7 years followed by development of unprovoked hypoglycemia requiring frequent snacking throughout the day when she was in middle and high school. She was diagnosed with T2D at the age of 22 years, when she developed recurrent yeast infections. She was treated initially with metformin but reported having hypoglycemia and stopped medications for several years before starting saxagliptin. At the age of 27 years, she was told that she had T1D based on a C-peptide level of 1.02 ng/mL (with unknown concomitant glucose; reference range, 1.1-4.4 ng/mL), although the glutamic acid decarboxylase 65 antibody test result was negative. She was treated with basal-bolus insulin and later transitioned to an insulin pump with excellent glycemic control (HbA1C level of 31 mmol/mol (5.0%) upon presentation). She had a strong family history of young-onset diabetes, including her father, who was diagnosed with prediabetes at the age of 18 years and initiated insulin in his 30s, and her paternal half-sister, who was diagnosed with T1D at the age of 13 years. Outside of pregnancy, her body mass index ranged from 22.8 to 24.0 kg/m^2.

Throughout pregnancy, her basal insulin requirements remained very low (eg, total daily dose of basal insulin of 2.35 units in the third trimester), and she often had to suspend her basal insulin overnight to prevent hypoglycemia; her prandial requirements were higher and increased during pregnancy (eg,

insulin-to-carbohydrate ratio of 1:8 and insulin sensitivity factor of 1:60 in the third trimester). Despite tight glycemic control (eg, mean ± standard deviation, glucose level of 102 ± 29 mg/dL on CGM in a 14-day period during the second trimester and 87-97 ± 22 mg/dL over a 28-day period during the third trimester; time above range <5% throughout the pregnancy), fetal monitoring revealed fetal overgrowth first noted at 30 weeks of gestation (EFW, 85th-90th percentile), with fetal abdominal circumference measurements in the 97th to 100th percentiles.

Child History

Labor was induced at 38 weeks of gestation and complicated by chorioamnionitis. She delivered a girl via cesarean delivery (for failure to progress) with a birth weight of 3.90 kg (>99th percentile) and Apgar scores of 8 and 9 at 1 and 5 minutes, respectively. The initial glucose level within the first hour of life was <20 mg/dL, improving to 34 mg/dL after administration of dextrose gel and formula and then to 49 mg/dL after repeat administration of dextrose gel. Critical hypoglycemia laboratory samples were not collected. Hypoglycemia recurred within several hours, and she required admission to the neonatal intensive care unit (NICU) for intravenous dextrose infusion (weaned on day of life 4) and fortified feeds (continued during NICU course given ongoing intermittent hypoglycemia). She passed a 6-hour safety fast prior to discharge on day of life 28. Her NICU course was also complicated by transient hypoxia attributed to respiratory distress syndrome. Her subsequent medical history is notable for gastric reflux and feeding difficulties, which resolved in the second year of life.

Shortly after delivery, the mother and child underwent genetic testing (Baylor Genetics 25-gene MODY panel, 2016) given suspicion for MODY in the mother coupled with hypoglycemia in the infant. Testing revealed a pathogenic variant in the canonical splice site of intron 1 of *HNF1A* (c.326+1G>T) in both the mother and child. The mother alone was also found to have a variant of uncertain significance (VUS) in the *SLC2A2* gene (c.1068+5G>A).

Case 3

Maternal History

A 25-year-old woman with a history of class III obesity and hypothyroidism presented for diabetes care at 15 weeks of gestation. She was first diagnosed with gestational diabetes at the age of 23 years, treated with metformin during that pregnancy, and then diagnosed with T2D by a postpartum oral glucose tolerance test. She was treated with metformin with an HbA1C level of 60 mmol/mol (7.6%) 1 month prior to conception of the index child. All 4 of her grandparents were diagnosed with T2D; however, neither her parents nor her siblings were known to have diabetes. Her pregnancy was complicated by hyperglycemia requiring initiation of multiple daily injections of insulin, with inadequate control including both fasting and postprandial hyperglycemia (fasting glucose level, 90-125 mg/dL; 2-hour postprandial glucose level, 85-200 mg/dL in the second trimester) and an HbA1C level of 44 to 46 mmol/mol (6.2%-6.4%), as well as hypoglycemia late in the third trimester. Ultrasonography revealed fetal overgrowth (EFW, >90th percentile at 29 weeks and >97th percentile at 32 weeks) and polyhydramnios.

Child History

She delivered a boy via repeat cesarean delivery at 3 weeks and 0 days of gestation with a birth weight of 5.81 kg (>99th percentile) and Apgar scores of 9 and 9 at 1 and 5 minutes, respectively. The mother's blood glucose level immediately prior to cesarean delivery was 82 mg/dL. However, the child's glucose level shortly after delivery was 10 mg/dL, improving to only 17 mg/dL after oral administration of dextrose gel. The infant was transferred to the NICU where he was treated with 10% dextrose infusion and later continuous nasogastric feeds because of persistent hypoglycemia and feeding difficulty. Ongoing hypoglycemia prompted initiation of diazoxide for presumed hyperinsulinism on day of life 12, with subsequent stabilization of blood sugars. Critical hypoglycemia laboratory samples were not collected. His course was further complicated by hypotonia and difficulty feeding requiring admission to an inpatient rehabilitation facility, urinary tract infection complicated by hyperglycemia requiring readmission on day of life 42, and ongoing poor feeding requiring gastrostomy tube placement on day of life 64. He was discharged home on day of life 76 after successfully undergoing an 8-hour safety fast while taking diazoxide 5 mg/kg/d.

After discharge, diazoxide was titrated to a maximum of 10.5 mg/kg/d at the age of 4 months in response to recurrent hypoglycemia documented at home. Genetic testing (University of Chicago 17-gene congenital hyperinsulinism panel, 2020) revealed a missense mutation in *HNF1A* (c.794A>G, p.Tyr265Cys). This variant has been classified as both VUS and likely pathogenic by the reporting laboratory; however, upon expert review by the Monogenic Diabetes Variant Curation Expert Panel in June 2021 using new gene-specific curation guidelines,[12] it was classified as a VUS.

After delivering the infant, the mother transitioned to metformin monotherapy with an increase in the HbA1C level to 84 mmol/mol (9.8%). Glimepiride was added, with initial improvement in the HbA1C level to 48 mmol/mol (6.5%) but later an increase to 88 mmol/mol (10.2%) in the setting of weight gain and possible nonadherence. She was treated with metformin, glimepiride, and mixed insulins with an HbA1C level of 48 to 58 mmol/mol (6.5%-7.5%) for approximately 1 year before starting semaglutide. Initiation of semaglutide resulted in significant weight loss, improvements in hyperglycemia (HbA1C level, <7.0 mmol/mol [<6.0%]), and resolution of her insulin requirement. After her son's mutation was discovered, she underwent genetic testing by the same laboratory and was found to have the same variant in *HNF1A*.

Discussion

In this manuscript, we report 3 mother-child dyads in which the mothers had pregestational diabetes and genetic testing revealing *HNF1A* variants (2 pathogenic and 1 VUS) and their children experienced prolonged neonatal hypoglycemia, supporting the potential connection between *HNF1A* MODY variants and neonatal hypoglycemia.

HNF1A MODY has an autosomal dominant mode of inheritance, with penetrance estimated from clinically selected cohorts of approximately 70% by the age of 25 years and 97% by the age of 50 years.[13] Often patients are initially misdiagnosed with either T1D or T2D prior to receiving a genetic diagnosis[14]; these patients may initially be treated with insulin until eventually receiving a genetic diagnosis of *HNF1A* MODY and transitioning to noninsulin agents, including sulfonylureas, to which many patients are exquisitely sensitive leading to hypoglycemia even at low doses.[15] Sulfonylurea monotherapy may be sufficient to maintain glycemic control for years or decades, although patients may eventually progress to requiring insulin.[1,15,16] A recent trial has also suggested that glucagon-like peptide 1 receptor agonists are an effective treatment option.[17] *HNF1A* MODY is clinically similar to *HNF4A* MODY.[1,18]

The cases reported here (with key features summarized in Table 1) contribute to a limited literature composed predominantly

Table 1
Characteristics of Patients with *HNF1A* Variants During Pregnancy and Their Infants

Case	1	2	3
Maternal diabetes diagnoses (age at diagnosis)	T1D (8), T2D (9), *HNF1A* MODY (15)	T1D (22), *HNF1A* MODY (33)	GDM (22), T2D (23), possible *HNF1A* MODY (26)
Maternal BMI (kg/m^2), outside of pregnancy	28.8-29.6	22.8-24.0	30.4 (prior to pregnancy), 38.5-40.5 (postpartum)
Maternal glycemic control during pregnancy (HbA1C [mmol/mol, %] and either SMBG or CGM ranges [mg/dL])	HbA1C, 27-33 mmol/mol; 4.6%-5.2% Fasting: 60-110 mg/dL Postprandial: 100-184 mg/dL	HbA1C, 33 mmol/mol; 5.2% CGM mean ± SD glucose: 87-102 ± 22-29 mg/dL	HbA1C, 43-46 mmol/mol; 6.1%-6.4% Fasting: 90-125 mg/dL Postprandial: 85-200 mg/dL
Infant birth weight (percentile)	4.38 kg (>99th)	3.90 kg (>99th)	5.81 kg (>99th)
Infant glycemic phenotype (duration of hypoglycemic events)	Presumed congenital hyperinsulinism (hypoglycemia >1 y)	Neonatal hypoglycemia (<1 mo)	Presumed congenital hyperinsulinism (hypoglycemia >1 y)
Infant genetic testing result	*HNF1A* c.811C>T, p.Arg271Trp	*HNF1A* c.326+1G>T; splice donor	*HNF1A* c.794A>G, p.Tyr265Cys
HNF1A variant classification	Pathogenic	Pathogenic	VUS
Additional genetic variants found	None known	Mother only: VUS in *SLC2A2* (c.1068+5G>A)	None known
Additional infant phenotype	Feeding difficulty	Feeding difficulty	Feeding difficulty, hypotonia
Other potential etiologies of neonatal hypoglycemia or CHI	None found, although maternal diabetes control was slightly above goal	Maternal history of chorioamnionitis	None found, although maternal diabetes control was moderately above goal

Abbreviations: BMI = body mass index; CGM = continuous glucose monitoring; CHI = congenital hyperinsulinism; GDM = gestational diabetes; HbA1C = hemoglobin A1C; *HNF1A* = hepatocyte nuclear factor 1α; MODY = maturity-onset diabetes of the young; SMBG = self-monitoring of blood glucose; T1D = type 1 diabetes; T2D = type 2 diabetes; VUS = variant of uncertain significance.

of case reports and small case series linking heterozygous mutations in *HNF1A* and neonatal hypoglycemia attributed to CHI.[3-7,19] In fact, to our knowledge, there are only 6 unique cases reported in which an *HNF1A* variant currently classified as pathogenic or likely pathogenic in ClinVar has been associated with neonatal hypoglycemia or CHI (Table 2). Additionally, the fact that 2 of the mothers we report on have a definitive diagnosis of MODY (the third had a VUS in *HNF1A*) supports a more controversial relationship in which single variants may cause both *HNF1A* MODY and neonatal hypoglycemia, in contrast to the firmer connection between variants in *HNF4A* MODY and neonatal hypoglycemia.[2]

It is important to note that several factors can contribute to neonatal hypoglycemia, including maternal hyperglycemia and perinatal stress, making it challenging to definitively determine that a given genetic variant is responsible. Nevertheless, such environmental factors are more likely to cause transient hypoglycemia than persistent hypoglycemia extending beyond 7 days.[20] All infants described experienced prolonged hypoglycemia, with 2 cases extending beyond 1 year. Furthermore, although maternal glycemic control during pregnancy varied in each case, case 2 had particularly tight control with the CGM mean ± standard deviation glucose level: 87 to 102 ± 22 to 29 mg/dL throughout pregnancy. We also note that CHI was diagnosed and treated presumptively without confirmation with critical hypoglycemia laboratory samples; however, as described, there was documented hypoglycemia that resolved with diazoxide treatment.

The connection between variants in *HNF1A* and neonatal hypoglycemia has been controversial, as demonstrated by a large case series of kindreds with *HNF1A* MODY mutations, which did not identify an increased prevalence of neonatal hypoglycemia in infants who inherited the mutation (in contrast to kindreds with *HNF4A* MODY mutations).[2] Yet, a number of case reports have described patients with *HNF1A* mutations and persistent hypoglycemia, generally by examining infants with unexplained CHI.[3-7,19,21] Of these, 2 large case series of infants with confirmed CHI revealed multiple cases in which *HNF1A* variants were detected: in a series of 204 infants in a single U.S. institution, 7 were found to have variants in *HNF1A*,[5] and in a series of 40 infants in the Czech Republic, 5 were found to have variants in *HNF1A*.[19] Of note, some variants identified in these cases had not been curated using current standard of care guidelines,[22] and some have since been classified as VUS or likely benign. Furthermore, the mild and less persistent hypoglycemia described in some case reports,[19] as was observed in case 2, is more suggestive of transient neonatal hyperinsulinism than of CHI and makes it more difficult to distinguish *HNF1A*-associated hypoglycemia from hypoglycemia associated with maternal peripartum hyperglycemia. A similar spectrum of hypoglycemia severity has been described for *HNF4A*-associated hypoglycemic phenotypes.[2] It is possible that the location or characteristics of the specific variant leading to different degrees of protein dysfunction or incomplete penetrance may lead to different phenotypes in childhood and adulthood.

As noted, the co-occurrence of childhood CHI and adult *HNF1A* MODY in families sharing the same genetic variant has not been extensively described. In the available literature, the family members of infants with *HNF1A*-associated CHI who shared the same genetic variants had variable phenotypes, including euglycemia,[4,5,19] known MODY,[3] gestational diabetes only,[7,19] and diabetes not yet determined to be MODY.[4-7,19] Of the 7 infants with CHI from 5 parents found to have *HNF1A* mutations in the first large case series described earlier, each had a parent with the same genetic variant, but only 2 of these had any known glycemic abnormality.[5] In a second series, of 5 infants with CHI from 5 parents carrying the same variant, 4 of the 5parents had a known glycemic abnormality.[19] CHI has also been described in an infant with a pathogenic *HNF1A* variant whose father had *HNF1A* MODY (p.Arg159Gln).[3] We believe that our case 1 offers the strongest evidence in this case series for co-occurrence of persistent hypoglycemia (presumed CHI) and MODY due to the same genetic variants in *HNF1A* within a family.

Although examples of specific *HNF1A* mutations causing both neonatal hypoglycemia and MODY within a single individual at different stages of life are limited (eg, the mother in case 2 reported unprovoked, recurrent, and symptomatic childhood hypoglycemia, although objective data were not available), there is precedent for a single genetic variant causing both CHI in childhood and MODY in adulthood. This has been described for variants in both *ABCC8*[23,24] and *HNF4A*.[25,26]

It is paradoxical that 1 genetic variant could lead to both hyperinsulinism and defective insulin secretion. Although it is proposed that β-cell hyperresponsiveness leading to burnout, impaired incretin response,[26] or changes in transcription factor function[2]

Table 2
Previous Reports of *HNF1A*-Associated Neonatal Hypoglycemia or Congenital Hyperinsulinism

Publication citation	Variant(s) reported	ClinVar variant classification (for MODY)[a]	Duration of hypoglycemia (or age at which diazoxide was discontinued)	Presence of macrosomia or LGA birth weight	Report of MODY within the same individual, age at diagnosis
Brusgaard et al,[3] *Endocr Abstr* 2006 (abstract only)	**1. c.476G>A, p.Arg159Gln**	**1. Pathogenic**	**1. 3 y**	**1. Yes, 4378 g**	**1. Unclear**
Pearson et al[2], *PLoS Med* 2007	1. Mutation not reported	1. Unknown	1. <48 h	1. Not reported	1. Not reported
Stanescu et al,[4] *J Clin Endocrinol Metab* 2012	**1. c.94G>T, p.Glu32X** 2. c.871C>T, p.Pro291Ser	**1. Pathogenic** 2. Likely benign	**1. 6 y** 2. 36-42 mo	**1. Yes, 93rd percentile** 2. No, 7th percentile	**1. Not reported** 2. Not reported
Snider et al,[21] *J Clin Endocrinol Metabol* 2013	1. c.94G>T, p.Glu32* (previously included in the study by Stanescu et al[4], case 1) 2. c.871C>T, p.Pro291Ser (previously included in the study by Stanescu et al[4], case 2) 3. c.1541A>G, p.His514Arg	1. Pathogenic (duplicate) 2. Pathogenic (duplicate) 3. VUS vs benign	1. Not reported 2. Not reported 3. Not reported	1. Not reported 2. Not reported 3. Not reported	1. Not reported 2. Not reported 3. Not reported
Tung et al,[5] *Pediatr Diabetes* 2018	1. C.94G>T, p.Glu32 (previously included in the studies by Stanescu et al[4] and Snider et al[21], case 1) 2. c.871C>T, p.Pro291Ser (previously included in the studies by Stanescu et al[4] and Snider et al[21], case 2) **3. c.872dupC, p.Pro291fs** 4. c.654T>A, p.Tyr218 5. c.654T>A, p.Tyr218 **6. c.872dupC, p.Pro291fs** **7. c.872delC, p.Pro291fs**	1. Pathogenic (duplicate) 2. Benign **3. Pathogenic** 4. Not classified 5. Not classified **6. Pathogenic** **7. Pathogenic**	1. 6.8 y 2. 3.5 y **3. Continued on diazoxide at time of publication** 4. 7.3 y 5. Continued on diazoxide at time of publication **6. Continued on diazoxide at time of publication** **7. Continued on diazoxide at time of publication**	1. Yes, 4167g, 92nd percentile 2. No, 7th percentile **3. No, 71st percentile** 4. Not reported 5. No, 44th percentile **6. No, 84th percentile** **7. Yes, 97th percentile**	"At the time of analysis, the median age of the children in this cohort was 7.0 years (IQR = 2.3-13.5 years)… screening tests for diabetes [were performed] after age 10 and none of them had developed diabetes mellitus at the time of analysis."
Dusatkova et al,[6] *J Pediatric Endocrinol Metabol* 2011	**1. c.815G>A, p.Arg272His**	**4. Pathogenic/ likely pathogenic**	1. "At least 1 attack of symptomatic hypoglycemia in childhood" at the **age of 9 y** in the setting of fasting; experienced tonic-clonic convulsions repeatedly in childhood without blood glucose check but semiquantitative estimations of urine ketone bodies were positive (grades 3-4)	**1. Yes, 4750 g (+1.99 SD)**	**1. Yes, age 19 y**
Rozenkova et al,[19] *J Clin Endocrinol Metabol* 2015	1. p.Gly31Asp 2. p.Asn62* 3. p.Leu254Gln 4. p.Arg272His (previously included in the study by Dusatkova et al[6]) 5. p.Glu508Lys	1. Benign 2. VUS 3. Not classified 4. Pathogenic/likely pathogenic (duplicate) 5. VUS vs likely benign	1. Continued on diazoxide at time of publication, age of 6 y 2. Resolved in "infancy" 3. Resolved in "infancy" 4. Resolved in "childhood" 5. Continued on diazoxide at time of publication, age of 4 y	1. No 2. Yes 3. Yes 4. Yes 5. No	1. Not reported 2. Not reported 3. Not reported 4. Not reported 5. Not reported
Yau et al,[7] *Eur J Med Genet* 2020	1. c.-230_-101del 2. c.713G>T, p.Arg238Met	1. Not classified 2. Not classified	1. Continued on diazoxide at time of publication, age of "almost 6 y" 2. Continued on diazoxide at time of publication, age of 5 y	1. No, 4065 (+1.7 SD) 2. No, 4260 g (+1.7 SD)	1. No 2. No
Cromer et al, 2022 (infants)	**1. c.811C>T, p.Arg271Trp** **2. c.326+1G>T** 3. c.794A>G, p.Tyr265Cys	**1. Pathogenic** **2. Pathogenic** 3. VUS	**1. Continued on diazoxide at time of publication, age of 1 y** **2. 1 mo** 3. Continued on diazoxide at time of publication, age of 2 y	**1. Yes, 4380 g (>99th percentile)** **2. Yes, 3900 g (>99th percentile)** 3. Yes, 5810 g (>99th percentile)	**1. No** **2. No** 3. No

Abbreviations: LGA = large for gestational age; MODY = maturity-onset diabetes of the young; VUS = variant of uncertain significance.
Unique reports of cases with pathogenic or likely pathogenic variants are shown in bold
[a] Variant classification obtained from ClinVar database, June 29, 2022.[35] All variant classifications were based on clinical laboratory submissions and/or expert panel review after the publication of the 2015 American College of Medical Genetics variant classification criteria.[22]

may be the physiologic causes of these phenotypes, little data exist to support these hypotheses. Stem cell models of *HNF1A* deficiency in pancreatic islets demonstrate bias toward an alpha cell fate during differentiation and progressive impaired glucose-stimulated insulin response but no clear evidence of early hypersecretion.[27] Murine models of *HNF4A* deficiency have suggested disparate effects of defective *HNF4A* at different times of life—promoting insulin secretion in the fetal and neonatal periods while preventing insulin secretion and leading to beta cell loss in adulthood[2]—it is possible that *HNF1A* may have a similar pattern.

Still, the mechanism underlying these opposing phenotypes remains poorly understood.

Lastly, these cases suggest a possible association between variants in *HNF1A* and fetal macrosomia. Infants of women with *HNF1A* MODY, similar to infants of mothers with other forms of diabetes, are at risk of complications including fetal overgrowth and neonatal transitional hypoglycemia related to maternal glycemic control.[28,29] Although imperfect glycemic control during pregnancy may lead to increased fetal growth,[28] in our cases, each infant was strikingly large for gestational age (>99th percentile), despite one of the mothers reporting particularly tight glycemic control during pregnancy (case 2). Macrosomia independent of glycemic control is well described in infants with variants in *HNF4A* [2,30]; however, at least 1 case series suggested that this is not the case for infants with variants in *HNF1A*[2]: this series found no difference in birth weight among infants with *HNF1A* mutations and their unaffected family members, although notably only 1 infant in this series with an *HNF1A* variant experienced hypoglycemia.[2] In contrast to studies unselected for neonatal hypoglycemia, 2 case series in infants *with hyperinsulinism* found increased rates of large-for-gestational-age among infants with *HNF1A* mutations. In the first, infants with *HNF1A*-associated CHI weighed only 30 g less on average than those with *HNF4A*-associated CHI.[5] In the second, although infants with *HNF1A* mutations had lower birth weight on average than infants with *HNF4A* mutations (4100 ± 300 g, n = 2), their birth weights were 378 g heavier (3540 ± 884 g, n = 5), on average, than infants with hyperinsulinism without any mutations found (3162 ± 882 g, n 20); 60% of infants with *HNF1A*-associated CHI in this series were large for gestational age.[19] It should be noted, however, that both of these later case series included individuals with *HNF1A* variants that would no longer be classified as likely pathogenic or pathogenic using the most recent guidelines (only 4 of 7 in the first series and only 1 of 5 in the second series).[22] Still, the cases described in this report support that *HNF1A* mutations associated with neonatal hypoglycemia may contribute to fetal macrosomia independent of maternal glycemic control.

This study is strengthened by a detailed description of the genotype and phenotype of both mothers and their infants. However, as a retrospective case series, it is limited both by missing or self-reported data in some cases and by its small sample size. Furthermore, the absence of a critical sample collected at the time of hypoglycemia prevents the confirmation of hyperinsulinemic physiology in each these cases, although CHI is the leading cause of persistent hypoglycemia in infants and the natural history of their disease and response to treatment is consistent with CHI.[21,31-34]

In summary, we report 3 cases of mother-infant dyads with mutations in *HNF1A*. Although several factors can contribute to hypoglycemia and fetal macrosomia, these cases suggest that single mutations in *HNF1A* can cause both neonatal hypoglycemia and MODY. Long-term follow-up of neonatal hypoglycemia cases is needed to confirm whether a single mutation can result in both hypoglycemic and hyperglycemic phenotypes in a single individual at different stages of life.

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Author Contributions

S.J.C., A.C.S., C.P., D.M.M., and M.S.U. contributed to the conception and design of the study, with C.P. identifying and contributing several cases. S.J.C., A.C.S., E.R., and K.S. contributed to data collection. S.J.C. drafted the manuscript, with critical revisions by all authors. All authors give approval of the manuscript to be submitted.

Disclosure

S.J.C. reports employment of a close family member by Johnson & Johnson. D.M.M. has received consulting fees from Amolyt Pharma for unrelated work. All other authors have no multiplicity of interest to disclose.

References

1. Thanabalasingham G, Owen KR. Diagnosis and management of maturity onset diabetes of the young (MODY). *BMJ*. 2011;343(7828):d6044.
2. Pearson ER, Boj SF, Steele AM, et al. Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the *HNF4A* gene. *PLoS Med*. 2007;4(4):e118.
3. Brusgaard K, Christesen HBT, Hansen T, Njölstad P, Malec J, Brock JB. A TCF1 mutation may cause transient congenital hyperinsulinism followed by MODY3. *Endocrine Abstracts*. 2006;11. Accessed December 15, 2020. https://www.endocrine-abstracts.org/ea/0011/ea0011p283.
4. Stanescu DE, Hughes N, Kaplan B, Stanley CA, De León DD. Novel presentations of congenital hyperinsulinism due to mutations in the MODY genes: *HNF1A* and *HNF4A*. *J Clin Endocrinol Metab*. 2012;97(10):E2026–E2030.
5. Tung JY, Boodhansingh K, Stanley CA, De León DD. Clinical heterogeneity of hyperinsulinism due to *HNF1A* and *HNF4A* mutations. *Pediatr Diabetes*. 2018;19(5):910–916.
6. Dusatkova P, Pruhova S, Sumnik Z, et al. *HNF1A* mutation presenting with fetal macrosomia and hypoglycemia in childhood prior to onset of overt diabetes. *J Pediatr Endocrinol Metab*. 2011;24(3-4):187–189.
7. Yau D, Colclough K, Natarajan A, et al. Congenital hyperinsulinism due to mutations in *HNF1A*. *Eur J Med Genet*. 2020;63(6), 103928.
8. Flanagan SE, Kapoor RR, Mali G, et al. Diazoxide-responsive hyperinsulinemic hypoglycemia caused by *HNF4A* gene mutations. *Eur J Endocrinol*. 2010;162(5):987–992.
9. McGlacken-Byrne SM, Hawkes CP, Flanagan SE, Ellard S, McDonnell CM, Murphy NP. The evolving course of *HNF4A* hyperinsulinaemic hypoglycaemia—a case series. *Diabet Med*. 2014;31(1):e1–e5.
10. Kapoor RR, Flanagan SE, Arya VB, Shield JP, Ellard S, Hussain K. Clinical and molecular characterisation of 300 patients with congenital hyperinsulinism. *Eur J Endocrinol*. 2013;168(4):557–564.
11. Chèvre JC, Hani EH, Boutin P, et al. Mutation screening in 18 Caucasian families suggest the existence of other MODY genes. *Diabetologia*. 1998;41(9):1017–1023.
12. Monogenic diabetes variant curation expert panel. Clinical Genome Resource. Accessed September 3, 2021. https://www.clinicalgenome.org/affiliation/50016/#heading_documents.
13. Patel KA, Kettunen J, Laakso M, et al. Heterozygous RFX6 protein truncating variants are associated with MODY with reduced penetrance. *Nat Commun*. 2017;8(1):888.
14. Anık A, Çatlı G, Abacı A, Böber E. Maturity-onset diabetes of the young (MODY): an update. *J Pediatr Endocrinol Metab*. 2015;28(3-4):251–263.
15. Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT. Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet*. 2003;362(9392):1275–1281.
16. Shepherd M, Shields B, Ellard S, Rubio-Cabezas O, Hattersley AT. A genetic diagnosis of HNF1A diabetes alters treatment and improves glycaemic control in the majority of insulin-treated patients. *Diabet Med*. 2009;26(4):437–441.
17. Østoft SH, Bagger JI, Hansen T, et al. Glucose-lowering effects and low risk of hypoglycemia in patients with maturity-onset diabetes of the young when treated with a GLP-1 receptor agonist: a double-blind, randomized, crossover trial. *Diabetes Care*. 2014;37(7):1797–1805.
18. Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. *Nat Clin Pract Endocrinol Metab*. 2008;4(4):200–213.

19. Rozenkova K, Malikova J, Nessa A, et al. High incidence of heterozygous *ABCC8* and *HNF1A* mutations in Czech patients with congenital hyperinsulinism. *J Clin Endocrinol Metab*. 2015;100(12):E1540–E1549.
20. Kallem VR, Pandita A, Gupta G. Hypoglycemia: when to treat? *Clin Med Insights Pediatr*. 2017;11, 1179556517748913.
21. Snider KE, Becker S, Boyajian L, et al. Genotype and phenotype correlations in 417 children with congenital hyperinsulinism. *J Clin Endocrinol Metab*. 2013;98(2):E355–E363.
22. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405–424.
23. Koufakis T, Sertedaki A, Tatsi EB, et al. First report of diabetes phenotype due to a loss-of-function *ABCC8* mutation previously known to cause congenital hyperinsulinism. *Case Rep Genet*. 2019;2019, 3654618.
24. Khoriati D, Arya VB, Flanagan SE, Ellard S, Hussain K. Prematurity, macrosomia, hyperinsulinaemic hypoglycaemia and a dominant *ABCC*8 gene mutation. *BMJ Case Rep*. 2013;2013, bcr2013008767.
25. Stanik J, Skopkova M, Brennerova K, et al. Congenital hyperinsulinism and glycogenosis-like phenotype due to a novel *HNF4A* mutation. *Diabetes Res Clin Pract*. 2017;126:144–150.
26. Arya VB, Rahman S, Senniappan S, Flanagan SE, Ellard S, Hussain K. *HNF4A* mutation: switch from hyperinsulinaemic hypoglycaemia to maturity-onset diabetes of the young, and incretin response. *Diabet Med*. 2014;31(3):e11–e15.
27. González BJ, Zhao H, Niu J, et al. Human stem cell model of *HNF1A* deficiency shows uncoupled insulin to C-peptide secretion with accumulation of abnormal insulin granules. Preprint. Posted online January 26, 2021. bioRxiv. 2021.01.26.428260. doi:10.1101/2021.01.26.428260
28. Dickens LT, Naylor RN. Clinical management of women with monogenic diabetes during pregnancy. *Curr Diab Rep*. 2018;18(3):12.
29. Monsonego S, Clark H, Karovitch A, O'Meara P, Shaw T, Malcolm J. Management and outcomes of maturity-onset diabetes of the young in pregnancy. *Can J Diabetes*. 2019;43(8):647–654.
30. Colclough K, Bellanne-Chantelot C, Saint-Martin C, Flanagan SE, Ellard S. Mutations in the genes encoding the transcription factors hepatocyte nuclear factor 1 alpha and 4 alpha in maturity-onset diabetes of the young and hyperinsulinemic hypoglycemia. *Hum Mutat*. 2013;34(5):669–685.
31. Goel P, Choudhury SR. Persistent hyperinsulinemic hypoglycemia of infancy: an overview of current concepts. *J Indian Assoc Pediatr Surg*. 2012;17(3):99–103.
32. Lord K, Dzata E, Snider KE, Gallagher PR, De León DD. Clinical presentation and management of children with diffuse and focal hyperinsulinism: a review of 223 cases. *J Clin Endocrinol Metab*. 2013;98(11):E1786–E1789.
33. Congenital hyperinsulinism. National Organization for Rare Disorders. Accessed July 1, 2022. https://www.rarediseases.org/rare-diseases/congenital-hyperinsulinism/.
34. Skovrlj R, Marks SD, Rodd C. Frequency and etiology of persistent neonatal hypoglycemia using the more stringent 2015 Pediatric Endocrine Society hypoglycemia guidelines. *Paediatr Child Health*. 2019;24(4):263–269.
35. Landrum MJ, Lee JM, Benson M, et al. ClinVar: improving access to variant interpretations and supporting evidence. *Nucleic Acids Res*. 2018;46(D1):D1062–D1067.