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Heterozygous Recurrent *HNF4A* variant p.Arg85Trp Causes Fanconi Renotubular Syndrome 4 with Maturity Onset Diabetes of the Young, an Autosomal Dominant Phenocopy of Fanconi Bickel Syndrome with Colobomas

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Abstract

Heterozygous pathogenic variants in *HNF4A* cause hyperinsulinism, maturity onset diabetes of the young type 1, and more rarely Fanconi renotubular syndrome. Specifically, the recurrent point pathogenic variant c.253C >T (p.Arg85Trp) has been associated with a syndromic form of hyperinsulinism with additional features of macrosomia, renal tubular nephropathy, hypophosphatemic rickets, and liver involvement. We present an affected mother, who had been previously diagnosed clinically with Fanconi Bickel Syndrome, and her affected son. The son's presentation expands the clinical phenotype to include multiple congenital anomalies, including penile chordee with hypospadias and coloboma. This specific pathogenic variant should be considered in the differential diagnosis of Fanconi Bickel Syndrome when genetics are negative or the family history is suggestive of autosomal dominant inheritance. The inclusion of HI and MODY changes the management of this syndrome and the recurrence risk is distinct. Additionally, this family also emphasizes the importance of genetic confirmation of clinical diagnoses, especially in adults who grew up in the pre-molecular era that are now coming to childbearing age. Finally, the expansion of the phenotype to include multiple congenital anomalies suggests that the full spectrum of *HNF4A* is likely unknown.

Keywords

HNF4A; hyperinsulinism; Fanconi renotubular syndrome; maturity onset diabetes of the young (MODY)

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INTRODUCTION

Hepatocyte nuclear factor 4 alpha (*HNF4A*) is a transcription factor that is important in the development of the liver, kidneys, and intestines, as well as the function of pancreatic beta cells. Heterozygous pathogenic variants in this gene have been associated with autosomal dominant maturity-onset diabetes of the young (MODY), type 1 (MIM# 125850), as well as hyperinsulinism (Kapoor et al., 2008; Pearson et al., 2007; Pingul, Hughes, Wu, Stanley, & Gruppuso, 2011). The *HNF4A* pathogenic missense variant c.253C >T (p.Arg85Trp) was first reported as a novel pathogenic variant in 2010 (Flanagan et al., 2010). Since then, this recurrent pathogenic variant c.253C >T (p.Arg85Trp) (NM_000457.3; p.Arg76Trp (Chartier, Bossu, Laudet, Fruchart, & Laine, 1994); p.Arg63Trp NM_175914.3) has been reported in 18 cases, eight cases were unrelated probands, to cause a more complex condition known as "Fanconi renotubular syndrome 4 with maturity onset diabetes of the young (OMIM# 616026)" characterized by hyperinsulinism that transitions to MODY, macrosomia, tubular nephropathy with resulting hypophosphatemic rickets and liver involvement (Clemente et al., 2017; Hamilton et al., 2014; Improda et al., 2016; Liu, Shen, Li, & Xu, 2018; Numakura et al., 2015; Stanescu, Hughes, Kaplan, Stanley, & De León, 2012; Walsh et al., 2017). This variant is also absent in gnomAD. We present a mother who had been previously clinically diagnosed with Fanconi Bickel Syndrome. Fanconi Bickel Syndrome (OMIM # 227810) is characterized by fasting hypoglycemia, short stature proximal tubular nephropathy, hepatomegaly due to glycogen accumulation, glucose and galactose intolerance (Santer et al., 1998). Later the mother was correctly diagnosed after having an affected son they both had Fanconi renotubular syndrome 4 and hyperinsulinism that in the mother evolved to maturity onset diabetes of the young due to the c.253 C >T (p.Arg85Trp) pathogenic variant in the *HNF4A* gene. This case also expands the phenotype to include colobomas and penile chordee with hypospadias.

Informed Consent and Data Sharing.

The patient's family provided informed consent for publication of identifiable photographs. The data are not publicly available due to privacy restrictions.

CLINICAL REPORT

The mother had a clinical diagnosis of Fanconi Bickel Syndrome due to a renal tubular nephropathy, hypophosphatemic rickets requiring multiple orthopedic surgeries and hepatosplenomegaly with liver, renal and splenic cysts. However, her spleen was not as large as expected and urine galactitol was not elevated. In addition, she had multiple features not fully explained by Fanconi Bickel Syndrome. She had a history of normal birth weight and hyperinsulinism at birth. Her initial plasma glucose was 0 mg/dl. Her fasting insulin level was 51 u/ml. She required a maximum glucose infusion rate (GIR) of 31 mg/kg/min to maintain plasma glucose from 80-100 mg/dl. She was discharged after a 28 day neonatal intensive care unit (NICU) stay when she was able to maintain adequate blood glucose levels without supplementation. She had similar facial features to the proband at birth, including excess nuchal skin (Sup. Fig. 1B). Her initial NICU stay also included a normal head ultrasound and normal abdominal ultrasound. Around 8 months old, as part of a failure to

thrive work up, she had an abdominal ultrasound, which showed 3 hepatic cysts, 1 splenic cyst, gallstones, and no pelviectasis. Repeat abdominal ultrasound showed no changes. At 13 years of age, she developed diabetes and was started on insulin therapy. She also developed nephrocalcinosis. Her adult height was 145 cm (Z = −2.85). Genetic testing for Fanconi Bickel Syndrome had not been performed. Her mother was 150 cm tall (Z = −1.7) and had preeclampsia during pregnancy but no other issues. Her father was healthy.

The mother married a healthy partner with non-contributory family history. Due to this family history, the mother was counseled that with a nonconsanguineous partner recurrence in her offspring was highly unlikely due to the autosomal recessive inheritance of Fanconi Bickel Syndrome.

The couple had a male infant born at 36 weeks gestational age following spontaneous rupture of membranes to a 30-year-old gravida 2 para 0 to 1 mother. His birth head circumference (33.5 cm), length (47.5 cm), weight (3.1 kg) were 75 percentile for 36 weeks gestational age. Delivery was by C-section for fetal bradycardia. The pregnancy was notable for normal prenatal ultrasounds and well controlled maternal diabetes with HgbA1c 4.8% mmol/mol.

Shortly after birth, he had persistent hypoglycemia requiring a maximum glucose infusion rate of 25 mg/kg/min with laboratory investigations confirming hyperinsulinism (critical sample: plasma glucose 47 mg/dl, insulin 132 uU/mL, growth hormone 32 ng/ml, beta hydroxybutyrate 0.07 mmol/L, cortisol 4.9 mcg/dl, with positive glucagon response indicated by plasma glucose increase from 45 mg/dl to 82 mg/dl). His hyperinsulinism was treated with diazoxide. Echocardiogram showed hypertrophic cardiomyopathy without obstruction, which spontaneously resolved by day of life (DOL) 12 and was attributed to hyperinsulinism. He had hyperbilirubinemia requiring phototherapy. He had difficulty feeding orally and required total parenteral nutrition, nasogastric tube feeding and ultimately percutaneous gastronomy tube placement. His physical exam at DOL 12 was notable for broad forehead with high anterior hairline, bitemporal narrowing, full cheeks, mildly low set ears with thick helices and lobes, anterior earlobe creases, short depressed nasal bridge, mild anteversion of the nares, no macroglossia, mild excess nuchal skin, palpable liver edge, penile chordee with hypospadias, tuft of hair on sacrum, symmetric extremities and bilateral sandal gap (Sup. Fig. 1A,B). His eye exam showed iris and chorioretinal colobomas. His hearing exam was significant for mild conductive hearing loss for 2000 Hz in the right ear. Laboratory investigation showed hypophosphatemia (3.1 mg/dL) with elevated alkaline phosphatase (747 U/L). Carnitine and cholesterol levels were within normal limits for age. Urinalysis showed glucosuria, proteinuria, phosphaturia but no galactosuria. His abdominal US on DOL 12 and spine US were normal.

Given his phenotype and family history, a hyperinsulinism panel, including *HNF4A*, Beckwith-Wiedemann Syndrome (BWS) methylation and *CDKN1C* sequencing, microarray and *SLC2A2* sequencing and deletion/duplication studies were sent initially on the proband. *SLC2A2* showed no variants, casting doubt on the maternal diagnosis of Fanconi Bickel syndrome. BWS testing was negative. SNP microarray was normal male. The hyperinsulinism panel showed a heterozygous maternally inherited pathogenic variant in

HNF4A: c.253C>T, p.Arg85Trp, which is located in the DNA binding domain. This variant is not observed in ~ 6500 individuals of European and African American ancestry in the NHLBI Exome Sequencing Project. This is a non-conservative amino acid substitution (arginine to tryptophan) that affects the charge and hydrophobicity affecting the DNA binding domain. This variant was not present in the maternal grandmother. This variant was previously reported in 18 patients.

Given the proband's hearing loss, colobomas and genital anomalies, exome sequencing was sent to confirm that there was not a second genetic etiology contributing to his phenotype. This showed no additional variants.

At follow up at 16-months-old, he continued diazoxide for glycemic control and gastronomy tube feeds for nutritional support. His growth parameters were height was at 50th percentile for a 6 month old (70 cm) and weight was at the 50th percentile for a 4 month old (7.245 kg). He was developmentally appropriate for social, fine motor, and language skills. He had gross motor delay. He was cruising, but not walking. Early intervention was involved for physical therapy, speech therapy, learning support and vision therapy. Abdominal US showed hepatomegaly (9.7 cm from 6.4 cm) with mildly increased echogenicity throughout the liver. The gallbladder, kidneys, and spleen had normal appearance and size. He continues to follow with Endocrinology for management of his hyperinsulinism, risk for hypophosphatemic rickets, Biochemical Genetics for care coordination, Gastroenterology for feeding, and Nephrology for renal Fanconi syndrome. He had been discharged from Audiology on repeat evaluation.

DISCUSSION

The heterozygous c.253C >T (p. Arg85Trp) pathogenic missense variant in *HNF4A* has a distinct presentation characterized by hyperinsulinism and atypical renal Fanconi syndrome (tubulopathy of phosphate, proteins, bicarbonates, glucose, calcium and magnesium). Additional features that are noted are macrosomia at birth in 7 out 14 patients (Sup. Fig. 1E). Six out of ten patients have gone on to develop maturity onset diabetes of the young. Interestingly, one patient is a grandfather who developed diabetes at age 55 and found to be mosaic ~23% of leukocytes (Hamilton et al., 2014). Other features include hypophosphatemic rickets (diagnosed as early as 1 y.o.) and liver involvement ranging from mild constant elevation in transaminases to liver cysts.

Fanconi Bickel Syndrome (glycogen storage disease type XI) is due to biallelic pathogenic variants in *SLC2A2*. There is impaired utilization of glucose and galactose and galactitol elevations, which is not seen with this *HNF4A* pathogenic missense variant. Overlapping features include renal Fanconi syndrome with subsequent hypophosphatemic rickets and severe short stature, beta cell insensitivity leading to diabetes, increased glycogen storage in liver and kidney resulting in hepatomegaly and nephromegaly, and ketotic hypoglycemia. Furthermore, hyperinsulinism and nephrocalcinosis are not generally seen in Fanconi Bickel syndrome compared to Fanconi renotubular syndrome 4 with maturity onset diabetes of the young (MIM# 616026) due to *HNF4A*.

In this case, the family history suggested autosomal dominant inheritance and there was congenital hyperinsulinism making us suspicious that Fanconi Bickel Syndrome was not the correct diagnosis. Genetics confirmed a diagnosis of Fanconi renotubular syndrome 4 with maturity onset diabetes of the young (MIM# 616026) in the mother and her son. This case demonstrates the overlap of these two syndromes and the consideration of the other when one is in the differential diagnosis. This case also highlights the importance of confirming a molecular diagnosis in adults previously given a clinical diagnosis, as this impacts recurrence risk and medical care for both the patient and his or her offspring. This couple has subsequently gone on to have an unaffected daughter testing prenatally and postnatally for the familial variant.

The phenotype of our patients' is similar to those previously published with the *HNF4A* pathogenic missense variant c.253C >T (p. Arg85Trp) with a few exceptions. Only one patient previously was reported to have hearing loss (Liu et al., 2018). Although other studies in the literature suggest a true relationship (Groth, Kao, Briët, & Stankovic, 2016), the proband reported here did not have hearing loss on repeat evaluation. However, his colobomas and penile chordee with hypospadias have not been reported previously. Notably, microarray and exome sequencing did not identify any other genetic etiologies to explain these findings. The patient's mother had well-controlled insulin dependent MODY during pregnancy, thus it is unlikely the additional congenital malformations are due to this. Interestingly, genitourinary anomalies, including urethral stenosis and cystic kidney dysplasia, congenital unilateral dysplasia and a bicornuate uterus, and renal cysts, were seen out of 3 out of 5 patients with MODY due to *HNF1A* mutations (Raile et al., 2009). One of these patients also had colobomas.

HNF4A binds to the promoter of *HNF1A* to upregulate its transcription (Eeckhoute, Formstecher, & Laine, 2004). HNF1A binds to the HNF regulatory response element of SLC2A2 to upregulate its transcription (Bae, Kim, Kim, Park, & Ahn, 2010). As this pathogenic variant in *HNF4A* is predicted to affect the DNA binding domain, we hypothesize that this leads to decreased binding of HNF4A to the *HNF1A* promoter, thus leading to a decrease in the transcriptional activity of *HNF1A* and therefore also a decrease in the transcriptional activity of *SLC2A2*, causing a similar phenotype to Fanconi Bickel Syndrome and leading to the expanded phenotype in our patient, including features that had previously been reported in patients with pathogenic variants in *HNF1A* (Sup. Fig. 2).

In conclusion, we present a mother and son with Fanconi renotubular syndrome 4 with maturity onset diabetes of the young due to a recurrent *HNF4A* c.253C >T (p. Arg85Trp) pathogenic variant. This causes a phenotype similar to Fanconi Bickel syndrome with renal Fanconi syndrome, hypophosphatemic rickets, severe short stature, hyperinsulinism and MODY. Molecular testing should be performed to confirm clinical diagnoses for adult patients for recurrence risk counseling and prognostication of the child's health. The son expands the phenotype to include multiple congenital anomalies such as penile chordee with hypospadias and iris and chorioretinal colobomas. The *HNF4A* c.253C >T (p. Arg85Trp) pathogenic variant should be considered in the differential diagnosis for syndromic hyperinsulinism and Fanconi Bickel Syndrome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References

Bae J-S, Kim T-H, Kim M-Y, Park J-M, & Ahn Y-H (2010). Transcriptional regulation of glucose sensors in pancreatic β-cells and liver: an update. Sensors (Basel, Switzerland), 10(5), 5031–5053. 10.3390/s100505031

Chartier FL, Bossu JP, Laudet V, Fruchart JC, & Laine B (1994). Cloning and sequencing of cDNAs encoding the human hepatocyte nuclear factor 4 indicate the presence of two isoforms in human liver. Gene, 147(2), 269–272. [PubMed: 7926813]

Clemente M, Vargas A, Ariceta G, Martínez R, Campos A, & Yeste D (2017). Hyperinsulinaemic hypoglycaemia, renal Fanconi syndrome and liver disease due to a mutation in the HNF4A gene. Endocrinology, Diabetes & Metabolism Case Reports, 2017, 29–5. 10.1530/EDM-16-0133

Eeckhoute J, Formstecher P, & Laine B (2004). Hepatocyte nuclear factor 4alpha enhances the hepatocyte nuclear factor 1alpha-mediated activation of transcription. Nucleic Acids Research, 32(8), 2586–2593. 10.1093/nar/gkh581 [PubMed: 15141028]

Flanagan SE, Kapoor RR, Mali G, Cody D, Murphy N, Schwahn B, et al. (2010). Diazoxide-responsive hyperinsulinemic hypoglycemia caused by HNF4A gene mutations. European Journal of Endocrinology, 162(5), 987–992. 10.1530/EJE-09-0861 [PubMed: 20164212]

Groth JB, Kao S-Y, Briët MC, & Stankovic KM (2016). Hepatocyte nuclear factor-4 alpha in noise-induced cochlear neuropathy. Developmental Neurobiology, 76(12), 1374–1386. 10.1002/dneu.22399 [PubMed: 27112738]

Hamilton AJ, Bingham C, McDonald TJ, Cook PR, Caswell RC, Weedon MN, et al. (2014). The HNF4AR76W mutation causes atypical dominant Fanconi syndrome in addition to a β cell phenotype. Journal of Medical Genetics, 51(3), 165–169. 10.1136/jmedgenet-2013-102066 [PubMed: 24285859]

Improda N, Shah P, Güemes M, Gilbert C, Morgan K, Sebire N, et al. (2016). Hepatocyte Nuclear Factor-4 Alfa Mutation Associated with Hyperinsulinaemic Hypoglycaemia and Atypical Renal Fanconi Syndrome: Expanding the Clinical Phenotype. Hormone Research in Paediatrics, 86(5), 337–341. 10.1159/000446396 [PubMed: 27245055]

Kapoor RR, Locke J, Colclough K, Wales J, Conn JJ, Hattersley AT, et al. (2008). Persistent hyperinsulinemic hypoglycemia and maturity-onset diabetes of the young due to heterozygous HNF4A mutations. Diabetes, 57(6), 1659–1663. 10.2337/db07-1657 [PubMed: 18268044]

Liu J, Shen Q, Li G, & Xu H (2018). HNF4A-related Fanconi syndrome in a Chinese patient: a case report and review of the literature, 1–5. 10.1186/s13256-018-1740-x

Numakura C, Hashimoto Y, Daitsu T, Hayasaka K, Mitsui T, & Yorifuji T (2015). Two patients with HNF4A-related congenital hyperinsulinism and renal tubular dysfunction: A clinical variation which includes transient hepatic dysfunction. Diabetes Research and Clinical Practice, 108(3), e53–e55. 10.1016/j.diabres.2015.03.005 [PubMed: 25819479]

Pearson ER, Boj SF, Steele AM, Barrett T, Stals K, Shield JP, et al. (2007). Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. PLoS Medicine, 4(4), e118. 10.1371/journal.pmed.0040118 [PubMed: 17407387]

Pingul MM, Hughes N, Wu A, Stanley CA, & Gruppuso PA (2011). Hepatocyte nuclear factor 4α gene mutation associated with familial neonatal hyperinsulinism and maturity-onset diabetes of the

young. The Journal of Pediatrics, 158(5), 852–854. 10.1016/j.jpeds.2011.01.003 [PubMed: 21353246]

Raile K, Klopocki E, Holder M, Wessel T, Galler A, Deiss D, et al. (2009). Expanded Clinical Spectrum in Hepatocyte Nuclear Factor 1B-Maturity-Onset Diabetes of the Young. The Journal of Clinical Endocrinology & Metabolism, 94(7), 2658–2664. 10.1210/jc.2008-2189 [PubMed: 19417042]

Santer R, Schneppenheim R, Suter D et al. Fanconi-Bickel syndrome – the original patient and his natural history, historical steps leading to the primary defect, and a review of the literature. Eur J Pediatr 157, 783–797 (1998). 10.1007/s004310050937 [PubMed: 9809815]

Stanescu DE, Hughes N, Kaplan B, Stanley CA, & De León DD (2012). Novel Presentations of Congenital Hyperinsulinism due to Mutations in the MODY genes: HNF1Aand HNF4A. The Journal of Clinical Endocrinology & Metabolism, 97(10), E2026–E2030. 10.1210/jc.2012-1356 [PubMed: 22802087]

Walsh SB, Unwin R, Kleta R, Van't Hoff W, Bass P, Hussain K, et al. (2017). Fainting Fanconi syndrome clarified by proxy: a case report. BMC Nephrology, 18(1), 230. 10.1186/s12882-017-0649-8 [PubMed: 28693455]