NCDによる外科医療レベルの発信

- 肝切除
  2011年7732例の検討　J Am Coll Surg 2014
- 膵頭十二指腸切除
  2011年8575例の検討　Ann Surg
- 結腸切除
  2011年19070例の検討　J Gastroenterol
- 心臓血管外科データベース機構＋NCD
  Ann Thorac Surg, J Cardiothorac Surg, J Am Coll Cardiolog, など多数

診断・治療法評価(臨床研究)へのStep

- 臨床の発展に寄与する診断・治療法に関する特定の因果関係の解明に向けたプロジェクト
  - 投薬や医療機器，手術手技，検査，治療適応の判断など
    - 第IV相試験が簡単に企画できる
  - より詳細な情報やより長期の追跡期間が必要
    - 実施期間・参加施設・対象症例について条件の設定が必要
  - 領域横断的な臨床研究の実施
    - 肥満と手術合併症など

登録データを駆使した評価のあり方

- 全数把握が原則となるDBと連動することで、母集団の分布にもとづいた研究デザインを設計
  - 費用対効果は非常に高い
- 限られた施設、限られた時間内にデータを収集
  - 介入研究でありあらたにICは必要
- 倫理的にランダム化が不可能な別の臨床研究を支援するために、NCDに登録された症例を比較対照群として設定し、効果を検証することも可能

登録データを駆使した評価のあり方

- 臓器がん登録を一例とした評価のあり方
  - 医療水準評価
    - 周術期における診療科のアウトカム分析
    - 適応のある臨床プロセスの実施状況
  - 診断・治療法評価
    - 癌取り扱い規約とTNM分類の整合性検討
    - 抗がん剤治療の効果評価
    - 特定手術におけるアプローチ別の影響の検討
    - ガイドラインと対応した標準治療法の推奨
- 課題は長期フォローアップに向けた仕組みの構築
  - より簡便な追跡方法について検討が必要

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CASE REPORT Open Access

Focal form of congenital hyperinsulinism clearly detectable by contrast-enhanced computed tomography imaging

Yukiko Hashimoto[1*], Azumi Sakakibara[1], Rie Kawakita[1], Yuki Hosokawa[1], Rika Fujimaru[1], Tetsuro Nakamura[2], Hiroko Fukushima[3], Aiko Igarashi[4], Michiya Masue[5], Hironori Nishibori[5], Nobuyoshi Tamagawa[6], Akiko Murakami[6], Kazue Hatake[6] and Tohru Yorifuji[1,6]

Abstract

The focal form of congenital hyperinsulinism (CHI) is characterized by a cluster of abnormal insulin-oversecreting β cells within a restricted area of the pancreas. Although identification of the focal lesion is very important in the management of CHI, it has been reported that imaging studies, including computed tomography (CT), magnetic resonance imaging (MRI) scans, or angiography, are not helpful in identifying the focal lesion. Currently, fluorine-18-L-dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA PET) is believed to be the only imaging modality that can identify the focal lesions. In this report, however, we present a case of a 7-month-old girl with the focal form of CHI, caused by a loss-of-function mutation in the *ABCC8* gene, whose lesion was clearly visible as a hyperenhancing nodule on contrast-enhanced CT and dynamic MRI imaging.

Background

Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in the neonatal/infantile period which often requires pancreatectomy when unresponsive to medical treatments [1–7].

There are two known histological forms of CHI: diffuse and focal. The focal form is characterized by a cluster of abnormal insulin-oversecreting β cells within a restricted area of the pancreas, whereas in the diffuse form, abnormal β cells are scattered throughout the pancreas. Focal CHI arises in individuals with a paternally inherited monoallelic mutation in one of the genes coding for pancreatic ATP-sensitive potassium channel (K_{ATP} channel), *KCNJ11* or *ABCC8*, both located side-by-side in the chromosomal 11p15.1 region [8, 9]. When a second event of paternal uniparental disomy at chromosome 11p15 occurs in a β cell during the development of the pancreas, that particular cell loses the K_{ATP} channel activity, and also loses the activity of *H19* and *CDKN1C*, which are adjacent imprinted tumor suppressor genes, expressed only from the maternal allele. Moreover, in 11p15.5, there is an oppositely imprinted growth factor gene, *IGF2*, which is expressed only from the paternal allele. The gene dosage of *IGF2* would be doubled when paternal uniparental disomy takes place. Consequently, the insulin-oversecreting abnormal β cell acquires a growth advantage, eventually forming a focus of abnormal β cells [10–12].

Since the focal form of CHI can be cured by partial pancreatectomy without postsurgical diabetes mellitus, when a patient is unresponsive to conservative therapy, identification of the focal lesion is very important. It has been reported that imaging studies, including computed tomography (CT), magnetic resonance imaging (MRI) scans, or angiography, are not helpful in identifying focal lesions, since they do not distort the surrounding normal pancreatic structure, and also lack significant vascularization [13, 14]. Localization of the focal form, therefore, has been identified only by fluorine-18-L-dihydroxyphenylalanine positron emission tomography (^{18}F-DOPA PET) scans or by invasive diagnostic procedures such as arterial stimulation with venous

* Correspondence: yukko930@gmail.com
[1]Department of Pediatric Endocrinology and Metabolism, Children's Medical Center, Osaka City General Hospital, 2-13-22 Miyakojima-hondori, Miyakojima, Osaka 534-0021, Japan
Full list of author information is available at the end of the article

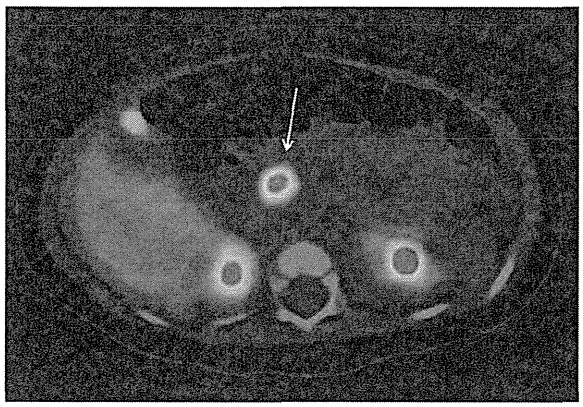

Fig. 1 ^{18}F-DOPA PET scan. A focal lesion was identified in the head of the pancreas (arrow)

sampling (ASVS) or transhepatic portal venous sampling (THPVS) [15–17].

In this report, however, we present a case of a 7-month-old girl with the focal form of K_{ATP} channel CHI whose lesion was clearly visible as a hyperenhancing nodule on contrast-enhanced CT and dynamic MRI imaging corresponding to the site detected by ^{18}F-DOPA PET scan.

Case presentation

The patient was a 7-month-old Japanese girl who was born after 39 weeks of an uneventful pregnancy, with a birth weight of 3792 g (+2.4 standard deviation [SD]) and length 54 cm (+2.7 SD). Both parents were healthy and there was no family history of hypo- or hyperglycemia. On the second day of life, she presented with hypothermia associated with hypoglycemia. A diagnosis of hyperinsulinemic hypoglycemia was made, based on the characteristic findings at the time of hypoglycemia: plasma glucose 1.6 mmol/L with serum insulin 26.7 pmol/L, undetectable ketone bodies, normal lactate, and normal ammonia. She was unresponsive to diazoxide at a dose of 20 mg/kg/day, and required 8.6 mg/kg/min of intravenous glucose infusion to maintain normoglycemia. From the 15th day of life, continuous subcutaneous octreotide infusion was started, and at 25 μg/kg/day of octreotide, glucose infusion could be stopped. However, hypoglycemic episodes persisted quite often despite frequent feedings. Fortunately, her psychosocial growth and psychomotor development remained within the normal range despite frequent hypoglycemic episodes.

Mutational analysis revealed that she had a paternally inherited monoallelic mutation in the *ABCC8* gene (c.2506C > T, p.Arg836*). ^{18}F-DOPA PET performed at 4 months of age revealed focal uptake in a single region in the head of the pancreas (Fig. 1). Based on these results, surgical resection of the focus was scheduled at 7 months of age. Since an enlargement in the head of the pancreas was suspected by preoperative abdominal ultrasound, further studies using other imaging modalities were performed. Unexpectedly, a contrast-enhanced CT scan revealed a clearly enhancing nodule at the head of the pancreas, corresponding to the site of the focus detected by the ^{18}F-DOPA PET scan (Fig. 2). Dynamic MRI imaging also detected a hyperenhancing nodule on the arterial phase. On T1- and T2-weighted imaging, the nodule showed an isointense signal, compared with the surrounding pancreatic parenchyma.

On laparotomy, a firmer focal lesion, measuring about 9 mm in diameter, was visible in the head of the pancreas which could be easily resected (Fig. 3). Microscopically, the lesion contained hyperplastic islets separated by thin fibrovascular bands. The islets were adenoma-like, and some of the β cells within the lesion had enlarged nuclei typical of the focal form of CHI (Fig. 4). Insulin immunostaining showed increased insulin producing β cells within the lesion (Fig. 4). The islets in the surrounding pancreas were normal.

DNA was extracted from the abnormal islets obtained by laser microdissection. Sequencing analysis of the *ABCC8* gene revealed predominance of a mutated paternal allele from these abnormal islets, confirming the diagnosis of the focal form of K_{ATP} channel CHI (Fig. 5).

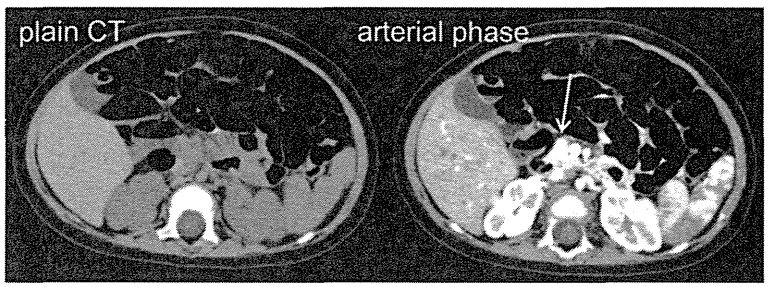

Fig. 2 CT scan. A hyperenhancing nodule was identified on the arterial phase

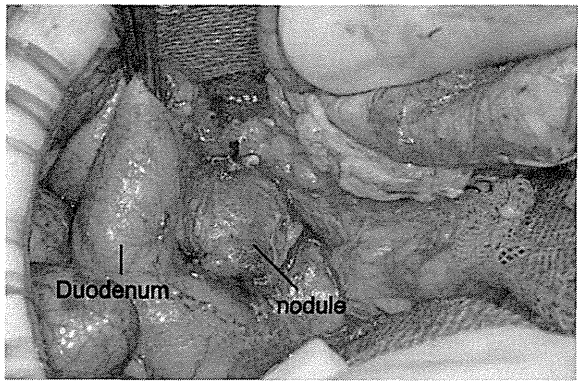

Fig. 3 Macroscopic finding of the focus. A nodule with a clear margin was identified in the head of the pancreas at laparotomy

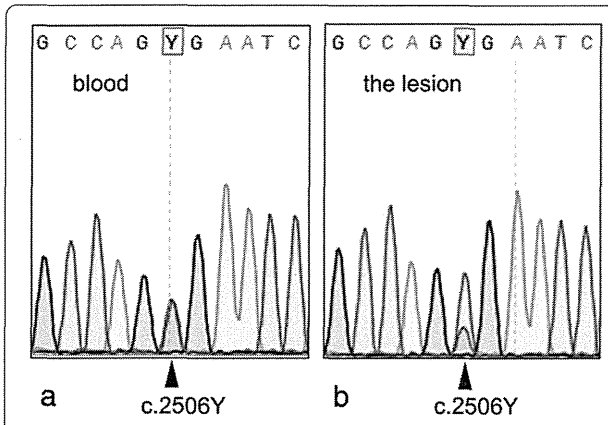

Fig. 5 Mutational analysis of the *ABCC8* gene. **a** DNA obtained from the peripheral blood leukocytes of the patient. A c.2506C > T mutation was detected in the heterozygous state with the wild type allele. The mutation was found to be of paternal origin (data not shown). **b** DNA obtained from the focus by laser microdissection. A loss of the wild type maternal allele was evident. The reduced peak of the wild type allele probably reflects the normal tissue within the focus

Molecular analysis

Mutational analysis was performed as described previously [18]. Briefly, all exons and exon-intron boundaries of the K_{ATP} channel genes were amplified from genomic DNA and directly sequenced. Laser microdissection was performed using the Arcturus PIXCELL IIe (Life Technologies, Carlsbad, CA) instrument, as described in the manufacturer instructions. The study protocol was approved by the Institutional Review Board (No. 743), and written informed consent was obtained from the guardians of the patient.

Discussion

Contrary to the previous belief, our report shows that some of the focal K_{ATP}-channel CHI can be visualized by conventional imaging modalities such as contrast-enhanced CT or dynamic MRI imaging. Although CT scans are not advisable for infants in view of the risk of irradiation, MRI imaging might be worth trying especially where ^{18}F-DOPA PET scans are not easily available.

The reason why the focal lesion of our patient could be clearly visualized by contrast-enhanced CT and MRI scans is not clear. Generally, for pancreatic nodules to be visualized by these imaging modalities, they need to grow fast enough to have a mass effect. In addition, they need to have a higher vascularity, or higher vascular permeability, to be enhanced by the contrast media. The focal lesion of our patient somehow attained both of these properties. In contrast, the size and cell density of the lesion do not appear to be critical factors for visualization by these techniques [19, 20].

Since the tumor suppressor activity of our patient is presumed to be lost as in all other cases of focal CHI, the higher growth potential of the focal lesion in this case might be explained by a difference in the growth promoting activity of the *IGF2* gene, although no

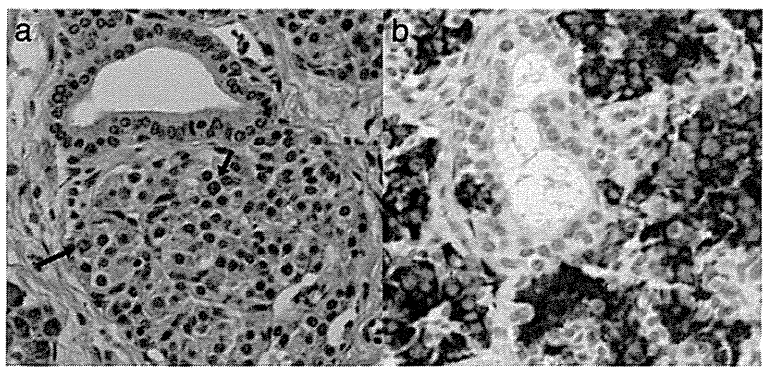

Fig. 4 Histological findings of the resected focus. **a** Hematoxylin eosin staining (×400). Some of the β cells within the lesion had enlarged nuclei (arrow). **b** Insulin staining (× 400). An increased number of insulin-positive β cells were observed within the lesion

mutations could be identified in the coding region of *IGF2* in our patient (data not shown).

Microscopically, the vascularity in the focal lesion of our patient was not particularly different from that of other patients with the focal form of CHI. However, if the focal lesion has higher growth potential, capillary dilatation without angiogenesis could follow [21], which might explain the contrast enhancement observed in our patient.

Conclusions

We report the unprecedented findings in a case of a focal form of CHI whose lesion was clearly visible as a hyperenhancing nodule on contrast-enhanced CT and dynamic MRI imaging. The mechanism leading to the visualization of the focal lesion in our patient needs further investigation.

Consent

Written informed consent was obtained from the parents of the patient for publication of this Case Report and the accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AI first diagnosed the patient. YH took over the treatment and drafted the manuscript. TY was instrumental in coordinating this report and guides the genetic analysis on the patient. KH, NT, AM carried out the molecular genetic studies, and participated in the sequence alignment. TN and HF advised on interpreting the histological findings. MM and HN carried out the ^{18}F-DOPA PET scan and interpreted the result. AS, RK, YH and RF participated in the clinical care of the patient and revised the manuscript. All authors read and approved the final manuscript.

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Author details

[1]Department of Pediatric Endocrinology and Metabolism, Children's Medical Center, Osaka City General Hospital, 2-13-22 Miyakojima-hondori, Miyakojima, Osaka 534-0021, Japan. [2]Department of Pediatric Surgery, Osaka City General Hospital, Osaka, Japan. [3]Department of Pathology, Osaka City General Hospital, Osaka, Japan. [4]Department of Pediatrics, Faculty of Medical Sciences, University of Fukui, Fukui, Japan. [5]Department of Pediatrics, Kizawa Memorial Hospital, Chubu Medical Center for Prolonged Traumatic Brain Dysfunction, Minokamo, Japan. [6]Clinical Research Center, Osaka City General Hospital, Osaka, Japan.

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International Diabetes Federation

Two patients with *HNF4A*-related congenital hyperinsulinism and renal tubular dysfunction: A clinical variation which includes transient hepatic dysfunction

Chikahiko Numakura [a,*], *Yukiko Hashimoto* [b], *Takashi Daitsu* [a], *Kiyoshi Hayasaka* [a], *Tetsuo Mitsui* [a], *Tohru Yorifuji* [b]

[a] *Department of Pediatrics, Yamagata University School of Medicine, Yamagata, Japan*

[b] *Department of Pediatric Endocrinology and Metabolism, Children's Medical Center, Osaka City General Hospital, Osaka, Japan*

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ABSTRACT

The *HNF4A* p.R76W mutation causes congenital hyperinsulinism with Fanconi syndrome. Here, we report two cases who also presented with increased urinary calcium excretion and one had a transient hepatic dysfunction with hepatomegaly. Clinical variations including transient liver dysfunction is a likely mutation-specific clinical characteristic.

1. Introduction

Heterogeneous, loss-of-function mutations of the hepatocyte nuclear factor 4 gene (*HNF4A*) cause congenital hyperinsulinism (CHI) with macrosomia at birth, or a form of maturity-onset diabetes of the young (MODY1) later in life. In 2012, Stanescu et al. [1] reported a single case with a p.R76W mutation in *HNF4A*, who presented with CHI associated with Fanconi syndrome (FS). Recently, Hamilton et al. [2] reported six patients from four families with a p.R76W mutation in *HNF4A* who presented with an unusual phenotype of CHI with FS. Therefore, CHI with FS is likely a p.R76W mutation-specific phenotype. In addition, the six patients reported by Hamilton et al. [2] had nephrocalcinosis and the patient reported by Stanescu et al. [1] showed transient hepatic dysfunction with hepatomegaly.

In this report, we present two new cases of the p.R76W mutation, both of whom presented with CHI and FS. Our patients did not have nephrocalcinosis, however, they had increased urinary calcium excretion and one had transient hepatic dysfunction with hepatomegaly. These cases suggest that clinical variations including transient liver dysfunction is a specific characteristic of the p.R76W mutation.

* Corresponding author. Tel.: +81 236285329; fax: +81 236285332.
E-mail address: cnumakur@med.id.yamagata-u.ac.jp (C. Numakura).

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0168-8227/

Table 1 – Laboratory findings in patient follow-up visits.

Age	25 d	5 m	7 m	1 y2 m	2 y0 m	3 y0 m	3 y8 m	3 y11 m
AST (IU/L)	54	210	274	141	79	61	40	43
ALT (IU/L)	27	98	152	122	67	54	29	30
LDH (IU/L)	297	273	300	232	224	213	183	210
GGT (IU/L)	1333	98	146	92	67	63	40	56
ALP (IU/L)	3306	3237	2284	1973	1757	1395	1353	1117
Calcium (mg/dL)	ND	11.0	9.9	10.2	10.5	9.9	9.4	9.3
iP (mg/dL)	ND	4.4	4.4	3.4	3.7	4.8	3.9	3.2
Magnesium (mg/dL)	ND	2.5	2.7	ND	ND	2.3	2.3	2.2
Creatinine (mg/dL)	0.49	0.40	0.36	0.32	0.43	0.58	0.54	0.53
Urate (mg/dL)	3.2	2.5	2.7	2.1	3.9	2.4	2.1	1.9
U-Ca/Cr* (mg/mgCr)	ND	0.09	0.11	0.16	0.10	0.08	0.57	0.53
Liver enlargement**	ND	4 cm	7 cm	3 cm	2.5 cm	NP	NP	NP
Alphacalcidol (μg/day)		0.4	0.25	0.25	0.25	0.25	Discon.	

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), inorganic phosphate (iP), urinary calcium/creatinine ratio (U-Ca/Cr), no data (ND), not palpable (NP), discontinuation (Discon).

* U-Ca/Cr is still elevated after discontinuation of alphacalcidol.

** Below the right costal margin.

2. Case report

Patient 1 was a Japanese boy born after 37 weeks of an uneventful pregnancy with a birth weight of 3355 g (+2.04 SDS for gestational age). The parents were nonconsanguineous. Four hours after delivery, he was found to have apneic episodes associated with hypoglycemia (1.0 mmol/L). Continuous hypertonic glucose infusion (11 mg/kg/min) was required to maintain euglycemia, and serum insulin levels of 9.5 mU/L measured during hypoglycemia (2.7 mmol/L) led to a diagnosis of CHI. Hypoglycemia was controlled by diazoxide. Laboratory tests at 14 months of age revealed elevated serum alkaline phosphatase (2118 IU/L), aspartate aminotransferase (40 IU/L), and magnesium levels (2.7 mg/dL) associated with a decrease in inorganic phosphorus (3.3 mg/dL). Further investigation revealed renal tubular dysfunction with renal glycosuria, aminoaciduria, hypophosphatemic rickets, and renal tubular acidosis. Nephrocalcinosis was not detected on ultrasonography, however, urinary calcium excretion was mildly elevated with urinary calcium/creatinine (U-Ca/Cr) levels at 0.35 mg/mg Cr. There was no hepatomegaly during follow-up.

Patient 2 was born at 38 weeks of gestation with a birth weight of 3672 g (+2.42 SDS for gestational age) from nonconsanguineous parents. Twelve hours after birth, he developed hypoglycemia (1.9 mmol/L) associated with hyperinsulinemia (45.3 mU/L). Initially, glucose infusion at 12 mg/kg/min was required to maintain euglycemia. However, glucose requirements gradually decreased and the infusion was stopped on day 17 leading to a final diagnosis of transient CHI.

He had gradually increasing levels of serum transaminases and gamma-glutamyl transpeptidase with progressive hepatomegaly reaching 7 cm below the right costal margin at 7 months of age (Table 1). The hepatomegaly and liver dysfunction gradually improved and normalized by 3 years of age (Table 1).

At 8 months of age, failure to thrive was apparent. Laboratory tests revealed a moderate metabolic acidosis with normal anion gap, proteinuria, glucosuria and aminoaciduria, which lead to the diagnosis of FS. Alfacalcidol was administrated from 5 months of age due to decreased serum 25-hydroxy vitamin D level (6 ng/mL) and increased serum alkaline phosphatase level. Alfacalcidol administration was stopped at 3 years and 8 months of age due to a gradual increase in U-Ca/Cr. However, the level of U-Ca/Cr did not decrease after that (Table 1). Ultrasonography did not show any signs of renal calcification at 8 months and 3 years of age.

3. Mutational analysis

After informed consent was provided from the guardians, *HNF4A* mutational analysis was performed as described previously [3]. Both cases carried a heterozygous p.R76W mutation in *HNF4A* according to conventional cDNA numbering [4]. Their parents did not have the mutation.

4. Discussion

We present two patients carrying the p.R76W mutation of *HNF4A*, who had CHI and FS similar to those reported previously [1,2]. Neither of our patients showed nephrocalcinosis, which was a characteristic feature of the p.R76W mutation reported by Hamilton et al. [2]. However, our patients had increased levels of urinary calcium excretion and were younger than the patients described by Hamilton et al. [2]. They may have nephrocalcinosis in the future.

It is interesting to note that patient 2 showed a transient liver enlargement with increases in serum transaminases at 5 months of age followed by spontaneous regression at age 3. Stanecau et al. [1] reported a similar case, suggesting that a transient liver enlargement could be a mutation-specific characteristic of p.R76W. The p.R76W mutation is predicted to alter the structure of HNF4α DNA binding motif [2,5] leading to change in the transcriptional activity. Interestingly, liver-specific *HNF4A* knock-out mice show hepatomegaly [6]. Moreover, *HNF4A* regulates the expression of *SLC2A2* [1,7], a mutation which is a cause of Fanconi–Bickel syndrome, a form

of FS with liver enlargement [8]. By contrast, patient 1 and the patients described by Hamilton et al. [2] did not show liver enlargement. Transient liver dysfunction with hepatomegaly is likely one of the clinical variations of p.R76W mutation.

In conclusion, the *HNA4A* p.R76W mutation shows age-dependent and clinically variable manifestations. In the neonatal period, macrosomia and CHI are apparent. Some patients have liver dysfunction with hepatomegaly in early infancy, which resolves by age 5. Growth failure due to FS may be apparent in late infancy, and nephrocalcinosis can occur post-school age. Some patients develop diabetes during adulthood.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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V. 研究班名簿

小児期発症の希少難治性肝胆膵疾患における包括的な診断・治療ガイドライン作成に関する研究班

	氏　名	所　属　等	職　名
研究代表者	仁尾　正記	東北大学大学院医学系研究科・小児外科学分野	教　授
研究分担者	松井　陽	聖路加国際大学・看護学部	特任教授
	橋本　俊	名古屋市立大学大学院医学研究科・分子神経生物学	研究員
	安藤　久實	愛知県心身障害者コロニー・発達障害研究所・小児外科（小児肝・胆・膵）	総　長
	北川　博昭	聖マリアンナ医科大学・外科学・小児外科	教　授
	虻川　大樹	宮城県立こども病院総合診療科・小児科学・小児肝臓消化器病学	科　長
	林田　真	九州大学病院・小児外科	共同研究員
	佐々木　英之	東北大学病院・小児外科	講　師
	島田　光生	徳島大学大学院消化器・移植外科	教　授
	神澤　輝実	東京都立駒込病院	副院長
	藤井　秀樹	山梨大学	理　事
	遠藤　格	横浜市立大学消化器・腫瘍外科学	教　授
	濵田　吉則	関西医科大学・小児外科	教　授
	窪田　正幸	新潟大学医歯学総合研究科・小児外科学分野	教　授
	鈴木　達也	藤田保健衛生大学・小児外科	教　授
	漆原　直人	静岡県立こども病院・外科系診療部	部　長
	須磨崎　亮	筑波大学医学医療系・小児科	教　授
	田口　智章	九州大学大学院医学研究院・小児外科学分野	教　授
	前田　貢作	神戸大学大学院医学研究科・小児外科学	客員教授
	近藤　宏樹	近畿大学医学部奈良病院・小児科	講　師
	木下　義晶	九州大学大学病院・総合周産期母子医療センター	准教授
	岡田　忠雄	北海道教育大学教育学部札幌校・養護教育専攻医科学看護学分野	教　授
	位田　忍	地方独立行政法人大阪府立病院機構大阪府立母子保健総合医療センター・消化器・内分泌科	診療局長（内科）
	清水　俊明	順天堂大学医学部・小児科	教　授
	松藤　凡	聖路加国際大学・聖路加国際病院・小児外科	副院長
	玉井　浩	大阪医科大学・小児科	教　授
	八木　実	久留米大学医学部外科学講座・小児外科部門	主任教授
	工藤　豊一郎	国立成育医療研究センター・肝臓内科	医　長
	黒田　達夫	慶應義塾大学医学部・外科学（小児）	教　授
	杉浦　時雄	名古屋市立大学大学院医学研究科　新生児・小児医学分野	助　教
	村上　潤	鳥取大学周産期・小児医学	講　師
	韮澤　融司	杏林大学医学部・小児外科学	教　授
	呉　繁夫	東北大学大学院医学系研究科・小児病態学分野	教　授
	坂本　修	東北大学大学院医学系研究科・小児病態学分野	准教授
	田尻　仁	大阪府立急性期・総合医療センター・小児科	主任部長
	乾　あやの	済生会横浜市東部病院・小児肝臓消化器科	部　長
	虫明　聡太郎	近畿大学医学部奈良病院・小児科	教　授
	米倉　竹夫	近畿大学医学部奈良病院・小児外科	教　授
	依藤　亨	大阪市立総合医療センター・小児内分泌代謝病学	部　長
	鹿毛　政義	久留米大学病院・病理診断科・病理部	教　授
	原田　憲一	金沢大学　医薬保健研究域医学系	教　授
	猪股　裕紀洋	熊本大学大学院・小児外科学・移植外科学分野	教　授
	岩中　督	東京大学大学院医学系研究科・小児外科	特任研究員
研究協力者	石橋　広樹	徳島大学病院小児外科・小児内視鏡外科	教　授
	伊藤　玲子	国立成育医療研究センター・肝臓内科	医　師
	風間　理郎	東北大学病院・小児外科	助　教
	金森　豊	国立成育医療研究センター外科	医　長
	新開　真人	神奈川県立こども医療センター外科	部　長
	鈴木　光幸	順天堂大学医学部・小児科	助　教
	田川　学	筑波大学附属病院・小児科	病院講師
	田中　拡	東北大学病院・小児外科	助　教
	谷川　健	久留米大学病院・病理診断科・病理部	助　教
	戸川　貴夫	名古屋市立大学大学院医学研究科新生児・小児医学分野	大学院生
	中澤　温子	東海大学医学部基盤診療学系病理診断学	准教授
	林　久允	東京大学大学院・薬学系研究科分子薬物動態学教室	助　教
	別所　一彦	大阪大学・小児科	講　師
	細村　直弘	山梨大学医学部外科学講座第１教室	助　教
	松田　政徳	山梨大学医学部外科学講座第１教室	准教授
	矢田　圭吾	徳島大学病院小児外科・小児内視鏡外科	助　教
	吉田　雅博	化学療法研究所附属病院・人工透析・一般外科	教　授
	和田　宏来	筑波大学大学院人間総合科学研究科	大学院生
	渡邊　智彦	東北大学大学院医学系研究科・小児外科学分野	大学院生