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1 [Original Article]

2 **Clinical characteristics of *HNF1B*-related disorders in a Japanese population**

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1 **Abstract**

2 **Background** Hepatocyte nuclear factor 1 β (*HNF1B*), located on chromosome 17q12, causes renal cysts
3 and diabetes syndrome (RCAD). Moreover, various phenotypes related to congenital anomalies of the
4 kidney and urinary tract (CAKUT) or Bartter-like electrolyte abnormalities can be caused by *HNF1B*
5 variants. In addition, 17q12 deletion syndrome presents with multi-system disorders, as well as RCAD.
6 As *HNF1B* mutations are associated with different phenotypes and genotype–phenotype relationships
7 remain unclear, here, we extensively studied these mutations in Japan.

8 **Methods** We performed genetic screening of RCAD, CAKUT, and Bartter-like syndrome cases.
9 Heterozygous variants or whole-gene deletions in *HNF1B* were detected in 33 cases (19 and 14,
10 respectively). All deletion cases were diagnosed as 17q12 deletion syndrome, confirmed by multiplex
11 ligation probe amplification and/or array comparative genomic hybridization. A retrospective review of
12 clinical data was also conducted.

13 **Results** Most cases had morphological abnormalities in the renal–urinary tract system. Diabetes
14 developed in 12 cases (38.7%). Hyperuricemia and hypomagnesemia were associated with six (19.3%)
15 and 13 cases (41.9%), respectively. Pancreatic malformations were detected in seven cases (22.6%). Ten
16 patients (32.3%) had liver abnormalities. Estimated glomerular filtration rates were significantly lower in

the patients with heterozygous variants compared to those in patients harboring the deletion (median: 37.6 vs 58.8 ml/min/1.73 m²; p = 0.0091).

Conclusion We present the clinical characteristics of *HNF1B*-related disorders. To predict renal prognosis and complications, accurate genetic diagnosis is important. Genetic testing for *HNF1B* mutations should be considered for patients with renal malformations, especially when associated with other organ involvement.

Keywords

HNF1B, renal malformations, diabetes, hypomagnesaemia, gout, liver abnormality

1 **Introduction**

2 In humans, the hepatocyte nuclear factor-1 beta (*HNFI*B) gene is located on chromosome 17q12 and the
3 encoded protein contains an N-terminal dimerization domain, a homeobox and a POU A domain involved
4 in DNA binding, and a transactivation domain at the C-terminus [1]. *HNFI*B was initially identified as a
5 monogenic diabetes-related gene and the associated first mutation was described in a Japanese family
6 with maturity-onset diabetes of the young (MODY) in 1997 [2]. The encoded protein is a transcription
7 factor involved in the tissue-specific regulation of gene expression and the embryonic development of
8 various organs including the liver, kidney, intestine, pancreas, and genitourinary system [3]. In addition,
9 mutated *HNFI*B alleles are associated with a variety of disorders in renal development (congenital
10 anomalies of the kidney and urinary tract, CAKUT) including solitary functioning kidney, renal dysplasia,
11 glomerulocystic kidney disease, and oligomeganephronia [1, 4]. Moreover, mutations in *HNFI*B cause
12 renal cysts and diabetes syndrome (RCAD, OMIM#137920).

13 *HNFI*B-associated disease is generally considered to exhibit autosomal dominant inheritance;
14 however, de novo mutations and whole-gene deletions account for up to 50% of cases [5]. Further, the
15 phenotypes of *HNFI*B mutation-carriers are extremely variable and there is no clear evidence for a
16 genotype–phenotype relationship [6]. As we believe that these studies are necessary for the treatment and

prevention of complications associated with such diseases, we conducted extensive genetic /genotype–
phenotype analysis on *HNF1B* mutations in a Japanese population.

Materials and methods

Subjects

We analyzed *HNF1B* aberrations in 596 patients with clinically-diagnosed CAKUT, Bartter-like
syndrome, cystic kidneys, or an unknown cause of renal dysfunction from Sep 2010 to Dec 2018. A total
33 Japanese subjects with *HNF1B* mutations were recruited. The inclusion criterion was renal disease
without a defined etiology. Details regarding renal disease, the presence of diabetes in the probands or a
family member, and other clinical features were obtained from the referring clinician or the patient’s
hospital records.

Clinical diagnosis

The clinical conditions of the patients in this study were evaluated by their primary doctors according to
the following categories. CAKUT, pancreatic and hepatobiliary tract malformations were defined as any
abnormalities in the imaging tests including ultrasonographic examination, X-ray fluoroscopic
examination, computed tomography, or magnetic resonance imaging. Diabetes was diagnosed as patients
with chronic hyperglycemia meeting the following criteria repeatedly: (i) fasting plasma glucose level of

1 ≥ 126 mg/dl; (ii) 2-h value ≥ 200 mg/dl based on 75-g oral glucose tolerance test; (iii) casual plasma
2 glucose level of ≥ 200 mg/dl [7]. Hypomagnesemia was defined as serum magnesium less than 1.4
3 mEq/L. Hyperuricemia was defined as uric acid greater than 7.0 mg/dl. Genital abnormalities and
4 neurological abnormalities were diagnosed by primary doctors.

5 **Genetic analysis**

6 Genomic DNA was isolated from the peripheral blood leukocytes of patients and their family members
7 using the Quick Gene Mini 80 system (Wako Pure Chemical Industries, Ltd., Tokyo, Japan), in
8 accordance with the manufacturer's instructions. Direct sequencing or targeted sequencing using next-
9 generation sequencing (NGS) was conducted on genes responsible for inherited renal disease. NGS
10 samples were prepared using a HaloPlex target enrichment system kit (Agilent Technologies, Santa Clara,
11 CA), in accordance with the manufacturer's instructions. Briefly, 225 ng of genomic DNA was used for a
12 restriction reaction and hybridized at 54 °C for 16 h with NGS probes. All indexed DNA samples were
13 amplified by polymerase chain reaction (PCR) and sequenced using the MiSeq platform (Illumina, San
14 Diego, CA). We analyzed the data using SureCall 4.0, which is a desktop application combining
15 algorithms for end-to-end NGS data analysis, from alignment to the categorization of mutations (Agilent
16 Technologies). To determine copy number changes in a sample relative to a reference without copy
17 number alterations, we used pair analysis by SureCall [8].

1 **Multiplex ligation probe amplification**

2 We performed multiplex ligation probe amplification (MLPA) using SALSA P241, P357, or P463 for
3 *HNF1B*, as suggested by the manufacturer (MRC-Holland, Amsterdam, Netherlands). The MLPA test was
4 performed twice to confirm abnormal changes. Briefly, 50–100 ng of genomic DNA in 5 µl of deionized
5 water was denatured and hybridized overnight with the probe mix. Ligation was performed with the SALSA
6 Ligase 65 enzyme and finally PCR amplification was performed with the SALSA PCR Primer Mix.
7 Amplification products and the Size Standard 600 were mixed thoroughly and subjected to capillary
8 electrophoresis using the Gene Mapper v.3.7 (Thermo Fisher, Waltham, MA, USA).

9 **Array comparative genomic hybridization (aCGH)**

10 The Human Genome CGH Microarray (Agilent Technologies) was utilized and tests were carried out using
11 the SurePrint G3 Human CNV Microarray 400 K Kit or SurePrint G3 Human CGH Microarray 400 K, 180
12 K, or 60K Kit (Agilent Technologies), in accordance with the manufacturer's instructions. Briefly, 1 µg of
13 genomic DNA corresponding to either a human reference control (Promega) or test samples was fragmented
14 by heating it at 95 °C for 10 min. Fragmented DNA was labeled with Cy3 (reference DNA) and Cy5 (test
15 samples) fluorescent dUTPs, using the SureTag Complete Labeling Kit (Agilent Technologies). Purification
16 columns (Agilent) were used to remove the unincorporated nucleotides and dyes. The labeled samples along
17 with human Cot-1 DNA were added together and hybridized on the array slides. Hybridizations of labeled

DNA to array slides were performed in a hybridization oven at 65 °C with 20 rpm for 24 or 40 h. The slide was scanned at a resolution of 3 µm on an Agilent SureScan Microarray Scanner (Agilent Technologies). Agilent CytoGenomics software (Agilent Technologies) was used to visualize, detect, and analyze chromosomal patterns within the microarray profiles.

Statistical analysis

Results are presented as the median and intermediate quartile range (IQR). Whenever applicable, the independent samples Mann–Whitney U test was used to compare median differences between two experimental groups. The Kruskal–Wallis test was used to analyze mean differences between more than three groups. Statistical analysis was performed using standard statistical software (JMP version 10 for Windows; SAS Institute, Cary, NC). For all performed hypothesis tests, $P < 0.05$ was considered statistically significant.

Results (Table 1)

***HNF1B* mutations**

Heterozygous *HNF1B* alterations, thought to be pathogenic, were identified in 33 patients from 23 families (15 male and 18 female). Among them, 14 cases (42.4%) had a 17q12 deletion and 19 (57.6%) had variants in *HNF1B*. Thirteen different heterozygous small mutations (six missense (46.2%), three

nonsense (23.1%), one frameshift (7.7%), and three splice site mutations (23.1%)) were found in these 19 cases. Except for the frameshift, all missense mutations were localized to the DNA-binding domain (Fig 1). Among the point mutations, eight of 14 (57.1%) were novel (SC57, SC292, SC323, SC339, SC355, SC392, SC418, and SC487). A family history of a renal, pancreatic, liver, and/or genital tract abnormalities, suggestive of dominant inheritance, was reported in 11/23 cases (47.8%).

Clinicopathological characteristics of the kidneys

Most cases had morphological abnormalities in the renal–urinary tract system. Twenty-four had cystic kidneys, four of which had unilateral multi-cystic dysplastic kidneys. Nine cases had hypoplasia, and three had hydronephrosis and urinary tract abnormalities. One case had renal absence and one case had renal calcification.

One case progressed to stage 5 chronic kidney disease (CKD) during childhood, and renal transplantation commenced at the age of three. The eGFR (estimated glomerular filtration rate) was greater than 90 ml/min/1.73 m² (CKD stage 1) in four of 28 evaluable patients (13.8%), 60–89 ml/min/1.73 m² (CKD stage 2) in six (20.7%), 30–59 ml/min/1.73 m² (CKD stage 3) in 14 (48.3%), and less than 30 ml/min/1.73 m² (CKD stage 4 or 5) in four (13.7%) (Table 2). Thirteen patients (41.9%) had low serum Mg and six patients (19.4%) had hyperuricemia. Hyperparathyroidism occurred in five of seven patients for whom intact-PTH values were available.

Extra-renal symptoms

Twelve of 31 patients (38.7%) developed diabetes. Pancreatic malformations were detected in seven cases (22.6%), 10 (32.3%) had liver abnormalities, and seven patients (22.6%) had elevated concentrations of transaminase. Two cases had gallstones (the mother of SC448 and B222), and one case had gallbladder morphological abnormalities and cysts (SC226) [9]. Two of eighteen women (11.1%) had confirmed genital abnormalities; one had bicornate uterus and the other had cervical carcinoma. However, abnormal male genitalia were not detected. There was no case of esophageal malformations. Only one case was suspected pigmentary retinal degeneration and this patient had an arachnoid cyst.

Five patients had neurological complications, and all harbored a 17q12 deletion. One patient was reported to have autism and also had facial dysmorphism and joint contracture. Of the remaining patients, one had schizophrenia and three had intellectual disabilities.

HNF1B scores

The *HNF1B* score is calculated based on 17 items including antenatal discovery, family history, and organ involvement (kidney, pancreas, liver, and genital tract). It is a simple tool to provide a more rational approach to select patients for *HNF1B* screening [10]. The median *HNF1B* score was 14 (IQR: 10.5–17). Four individuals had a score below 8 and these individuals all harbored a heterozygous deletion of the entire *HNF1B* gene.

Genotype–phenotype correlations

When data were classified by mutation, eGFR levels were significantly lower in the patients who carried a heterozygous variant compared to those in patients who harbored a deletion, although the mean age for cases with a deletion was greater than that for patients with a gene variant (median: 37.6 ml/min/1.73 m² vs 58.8 ml/min/1.73 m², $p = 0.0091$; Fig 2). eGFR levels were associated either with deletions, missense mutations, or truncating mutations (median: 58.8 ml/min/1.73 m² vs 35.2 ml/min/1.73 m² vs 39.45 ml/min/1.73 m²; Fig 3).

Regarding other clinical characteristics (Table. 3), patients who carried a deletion had higher frequencies of hypomagnesemia ($p = 0.0002$) and neurological complications ($p = 0.0071$) than those who harbored variants.

Discussion

HNF1B mutations are associated with RCAD, which comprises renal cystic dysplasia, MODY, and hepatic, genital, and pancreatic abnormalities, with variabilities in renal and extra-renal defects [11, 12]. The phenotypes of *HNF1B* mutation-carriers are extremely variable and there is no clear evidence for a genotype–phenotype relationship [11]. Here, we described a large national cohort of 33 phenotyped patients with *HNF1B* mutations. From the Human Gene Mutation Database (HGMD, <http://www.hgmd.cf.ac.uk>), based on 240 mutation-positive cases, gross deletions (19.2%), missense or nonsense mutations (47.9%), splice-site mutations (7.1%), small deletions (14.6%), small insertions (7.1%), and indels (0.4%) were reported. In our cohort, we identified gross deletions (42.4%), missense or nonsense mutations (39.4%), small deletions or insertions (3.0%), and splice-site mutations (15.2%), indicating similar trends; however, our groups had a slightly larger number of large deletions and splice site mutations.

HNF1B is expressed in both maturing human collecting ducts and nephrons [13]. An *Hnf1b* deletion in mouse collecting ducts causes cysts [14, 15]. Furthermore, *Hnf1b* upregulates the transcription of uromodulin (*Umod*), polycystic kidney and hepatic disease 1 (*Pkhd1*), and polycystic kidney disease (*Pkd2*), the human homologues of which are respectively mutated in medullary cystic kidney disease type 2, autosomal recessive polycystic kidney disease, and a subset of autosomal dominant polycystic kidney

disease [15]. Previous reports suggest that renal malformations are the most common manifestation of *HNF1B* mutations. In fact, most cases in our cohort had renal morphological abnormalities. This is a convincing result from an embryological point of view.

In contrast, progression to end-stage kidney disease (ESKD) in the patients with *HNF1B* mutations seems rare [4]. In a larger cohort of 71 live births, only one was reported to have reached ESKD (age 3 months) [16]. However, in our report, one patient progressed to CKD stage 5 during childhood with eGFR levels below 90 ml/min/1.73 m² in 24 (86.2%). These levels were significantly lower in patients who harbored a heterozygous variant compared to those in patients with a deletion (median: 37.6 ml/min/1.73 m² vs 58.8 ml/min/1.73 m², $p = 0.0091$). A recent multicenter retrospective cohort study reported that patients with *HNF1B* mutations have poorer renal prognosis than those with a whole gene deletion, as evidenced by lower eGFR at follow-up and a higher frequency of CKD3–4 or ESKD [17]. Since our facility deals with hereditary renal disease, there is a possibility that patients with poor kidney function are overrepresented. However, it might also demonstrate the dominant-negative effect on kidney function.

Despite its initial identification as a diabetes-related gene, *HNF1B* variants also comprise a rare cause of MODY, accounting for < 2% of cases, compared to ~60% of cases attributed to *HNF1A* variants [18]. Indeed, in our cohort, nine patients had diabetes. *HNF1B* mutations are not usually associated with

1 diabetes in childhood. However, diabetes typically manifests in the third or fourth decade of life [19]. In
2 our study, onset occurred in teenagers in two cases, whereas the others were greater than 20 years of age.
3 Previously, in a different cohort of 21 patients, diabetes occurred in approximately one quarter of patients
4 during childhood, with the age at onset between 10 and 14 years [20]. We suggest that these variations
5 depend on the age at the time of diagnosis.

6 In this study, hyperuricemia, hypomagnesemia and hyperparathyroidism were identified in six,
7 13, and five patients, respectively. *HNF1B* regulates the transcription of *UMOD*, which plays a role in
8 renal urate transport, *FXYD2*, which plays a role in transcellular magnesium reabsorption, and *PTH*,
9 which encodes parathyroid hormone [21]. Therefore, these findings are important for patients with
10 *HNF1B* mutations. However, all patients with hyperuricemia or hyperparathyroidism had CKD higher
11 than stage 3, and thus, renal dysfunction also might affect hyperuricemia and hyperparathyroidism in this
12 study.

13 Recently, a more complicated score was developed based on 17 parameters, with renal hyper-
14 echogenicity and/or cysts and genital and pancreatic abnormalities scoring highest, followed by other
15 features such as abnormal fetal renal ultrasound, positive family history, renal hypoplasia or dysplasia,
16 and hypomagnesaemia. Using this score, the authors achieved a sensitivity of 98.2% and a specificity of

41.1% [10]. In our cohort, four cases had a score less than 8 and all of these were deletion cases. Thus, we believe that this screening method is useful before conducting genetic analysis, but is not perfect.

Based on phenotype–genotype correlations, patients with deletions were associated with hypomagnesemia and neurological complications. Therefore, in such cases, genetic testing that takes into account large deletions should be performed.

This study had several limitations. First, our study population was small, and it was a retrospective study. Second, the examination of individual patients relied entirely on the clinicians’ decisions, which implies that not all patients were evaluated for structural brain malformations or genital anomalies; lastly, most professional educational evaluations were not accessible.

Conclusion

In this study, we compared the genotypes and clinical findings for *HNF1B* mutations in Japanese individuals. Although renal symptoms are apparently the most common, we found that it is also necessary to consider other symptoms. Systematic screening for all potential abnormalities should be performed to better determine the frequency and characteristics of these complications. In the routine clinic, pediatrician and clinician awareness of these complications is important. To better understand this rare disease and develop potential interventions, good clinical registries are also needed.

Compliance with Ethical Standards

Ethical approval: All procedures performed for studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of Kobe University Graduate School of Medicine (IRB approval number 301) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Conflict of Interest

K.I has received grant support from Daiichi Sankyo CO., Ltd. and Zenyaku Kogyo Co., Ltd.

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Figure legends

Fig. 1 *HNF1B* gene and locations of the various mutations identified in this study.

Fig. 2 Comparison of age and estimated glomerular filtration rate (eGFR) between groups harboring *HNF1B* deletions and variants. Patients with heterozygous variants were younger than those with gene deletions (median: 11 years vs 32 years, $p = 0.005$) (a). Difference in eGFR between variant and deletion groups. eGFR levels were significantly lower in the group harboring variants (b).

Fig. 3 Comparison of age and estimated glomerular filtration rate (eGFR) among the groups harboring deletions, missense mutations, and truncating variants. Patients with missense and truncating mutations were younger than those with gene deletions (a); deletion: age 32 (19.5–45) years, missense: age 2.5 (0.5–10.75) years, truncating: age 12 (8.5–21) years. Type of *HNF1B* mutation (deletion, missense, truncating) according to the GFR (b); truncating vs missense: $p = 0.0338$, missense vs deletion: $p = 0.0073$, truncating vs deletion: $p = 0.0486$.

Table 1 Characteristics of patients

Patients with *HNF1B* mutations

Patient	Age	Sex	FH	Genome NM_000458.3	Amino acids	Method	Inheritance	Kidney disease	eGFR (ml/min/1.73m²)	CKD	Hypomagnesemia	Hyperuricemia	Hyperparathyroidism	Diabetes/ glucose intolerance	Pancreatic malformation	Liver abnormalities	Genital abnormalities	Neurological abnormality	HNF1B score	Other symptoms
SC57	11	M	-	c.130G>T	p.Glu44Ter	DS	maternal	b. cystic kidney	60.0	2	-	-	NA	-	-	-	-	-	16	bladder tumor
mother		F				DS	unknown	none	NA		NA	NA	NA	NA	NA	NA	NA	NA		
SC133	3	M	-	c.544+1G>A		DS	de novo	l. cystic kidney, r. MCDK	61.0	2	-	-	-	-	-	-	-	-	11	-
SC226	14	F	-	c.344+2T>C		DS	de novo	b. RHD	RT	T	-	-	NA	+	-	gallbladder anomaly	-	-	8	-
SC292	4m	F	+	c.865A>C	p.Asn289His	DS	paternal	r. RHD, l. MCDK	50.0	2	-	-	NA	-	-	-	-	-	14	-
father		M				DS		cystic kidney	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	8
SC323	1	M	-	c.455A>G	p.Gln152Arg	NGS	unknown	b. cystic kidney, l. hydronephrosis	37.3	3	-	-	NA	-	-	-	-	-	17	PDA, bicuspid aortic valve, aortic coarctation, short stature
SC339	2	M	-	c.508A>C	p.Thr170Pro	NGS	de novo	b. cystic kidney	17.0	4	-	-	NA	-	+	-	-	-	22	-
SC355	6	M	-	c.345-1G>T		NGS	unknown	b. cystic kidney	37.9	3	-	+	NA	-	-	-	-	-	16	-
SC392	12	F	+	c.1211_1212delCA	p.Ser404Cysfs*22	NGS	unknown	b. cystic kidney	11.2	5	-	-	+	-	-	-	bicornate uterus	-	14	arachnoid cyst, uveitis
SC396	11	M	+	c.884G>A	p.Arg295His	NGS	maternal	b. cystic kidney	67.4	2	-	-	NA	-	-	-	-	-	14	-
mother	50	F						l. cystic kidney, r. RA	59.0	3	-	-	NA	-	-	-	-	-	-	9
SC418	2m	M	+	c.493C>G	p.Arg165Gly	NGS	unknown	b. RHD	25.0	4	-	-	NA	-	-	-	-	-	14	short stature
sister	3	F						b. cystic kidney, RHD	32.0	3	-	-	NA	-	-	-	-	-	-	16
SC448	16	F	+	c.544+1G>T		DS	maternal	b. cystic kidney	69.0	2	+	-	NA	-	+	-	-	-	22	-
mother	50	F				DS		b. cystic kidney	41.0	3	-	-	NA	+	-	gallstone	cervical carcinoma	-	14	-
SC486	26	F	-	c.529C>T	p.Arg177Ter	DS	unknown	b. cystic kidney	23.2	4	+	+	+	+	+	+	-	-	22	ovarian failure
SC487	10	F	-	c.395A>G	p.His132Arg	DS	unknown	b. RHD, l. renal cyst, hydroureter, VUR r. ectopic kidney, double renal pelvis and ureter	33.1	3	-	-	NA	+	-	+	-	-	14	scoliosis (mild), short stature
SC581	12	F	+	c.826C>T	p.Arg276Ter	DS	paternal	b. cystic kidney	31.0	3	-	+	NA	-	+	-	-	-	28	-

Patients with 17q12 deletion

Patient	Age	Sex	FH	genome NM_000458.3	Amino acids	Method	Inheritance	Kidney disease	eGFR (ml/min/1.73m ²)	CKD	Hypomagnesemia	Hyperuricemia	Hyperparathyroidism	Diabetes/ glucose intolerance	Pancreatic malformation	Liver abnormalities	Genital abnormalities	Neurological abnormality	HNF1B score	Other symptoms
SC214	47	F	+	arr[GRCh37]17q12(34822500_36248918)x1		aCGH	maternal	l. MCDK, r. cystic kidney	46.8	3	+	+	NA	+	+	-	-	-	19	urinary bladder dysfunction
mother	78	F				aCGH		r. cystic kidney	45.5	3	+	-	NA	+	-	-	-	-	17	urinary bladder dysfunction
SC376	7m	M	-	arr[GRCh37] 17q12(34817422_36168104)x1		MLPA	unknown	r. MCDK, l. RHD	NA		-	-	NA	-	-	-	-	-	14	-
SC397	10	M	-	arr[GRCh37] 17q12(34822500_36248918)x1		aCGH	unknown	b. hydronephrosis	111.5	1	-	-	NA	-	-	-	-	autism	2	low set ears, mid facial dysplasia

SC412	30	F	+	arr[GRCh37] 17q12(34817422_36079369)x1	MLPA	unknown	l. cystic kidney, r. atrophy	52.9	3	+	+	+	+	+	-	-	-	18	-
sister	30	F			MLPA		l. cystic kidney, r. atrophy	36.8	3	+	+	+	+	+	-	-	-	13	-
SC457	10	M	-	heterozygous deletion; <i>HNFI1B</i> and <i>LHX1</i>	NGS, MLPA	unknown	b. cystic kidney	71.5	2	-	-	NA	-	-	-	-	-	16	pulmonary cyst, inguinal hernia, hydrocele testis
B222	43	M	+	heterozygous deletion; <i>HNFI1B</i>	MLPA	unknown	normal	40.5	3	+	-	+	+	-	gallstone	-	schizophrenia	9	-
B249	11	M	+	heterozygous deletion; <i>HNFI1B</i>	aCGH	de novo	calcinosis	99.7	1	+	-	NA	-	-	-	-	-	5	low set ears, mid facial dysplasia
B210	62	F	+	heterozygous deletion; <i>HNFI1B</i>	NGS	unknown	b.cystic kidney	58.8	3	+	-	NA	+	-	+	-	-	19	short stature
sister1	35	F			MLPA		l. RHD, r.cystic kidney	85.7	2	+	-	NA	+	-	+	-	ID	17	blindness
sister2	32	F			MLPA		NA	45.9	3	+	-	NA	-	-	+	-	ID	7	blindness
brother	28	M			MLPA		NA	111.9	1	+	-	NA	-	-	+	-	ID	7	-
B260	34	M	-	heterozygous deletion; <i>HNFI1B</i>	MLPA	unknown	b. cystic kidney	101.0	1	+	-	-	+	-	+	-	-	17	

FH: diabetes, renal anomaly, liver, pancreatic and/or genitourinary abnormalities

aCGH: array comparative genomic hybridization, CKD: chronic kidney disease, DS: direct sequence, eGFR: estimated glomerular filtration rate, ID: intellectual disability, MCDK: multicystic dysplastic kidney, MLPA: multiplex ligation-dependent probe amplification, NA: not available, NGS: next-generation sequencing, RA: renal agenesis, RHD: renal hypodysplasia, VUR: vesicoureteral reflux

Table 2 Number of patients by renal function stage

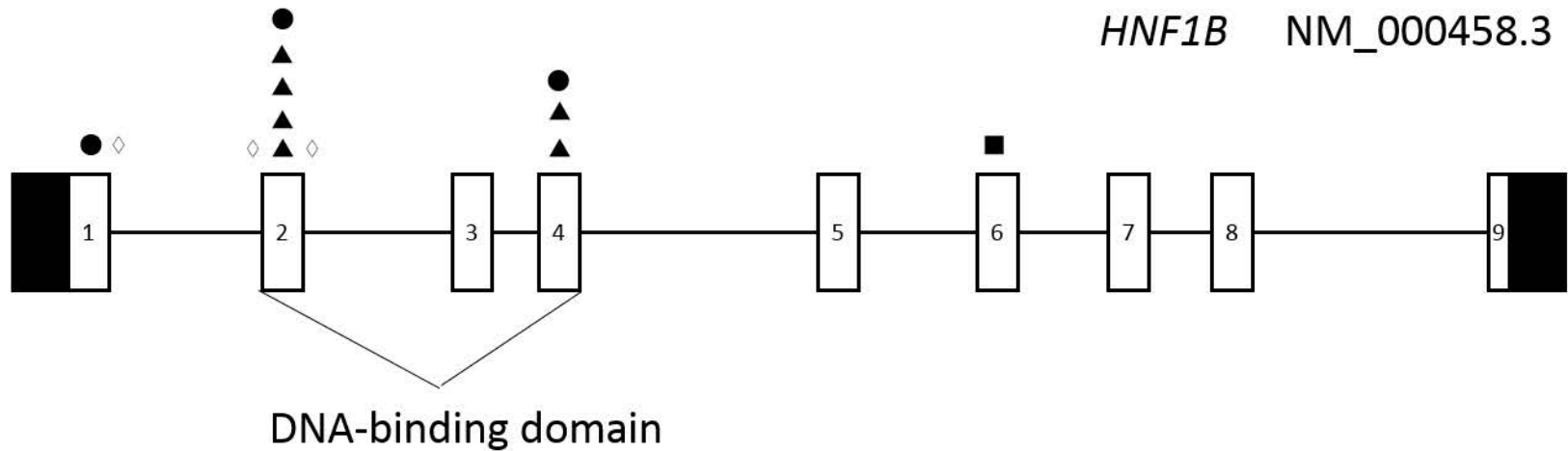
CKD stage	eGFR (ml/min/1.73 m²)	N (%)
1	≥ 90	4 (13.8)
2	60–89	6 (20.7)
3	30–59	14 (48.3)
4	15–29	3 (10.3)
5	< 15	1 (3.4)

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

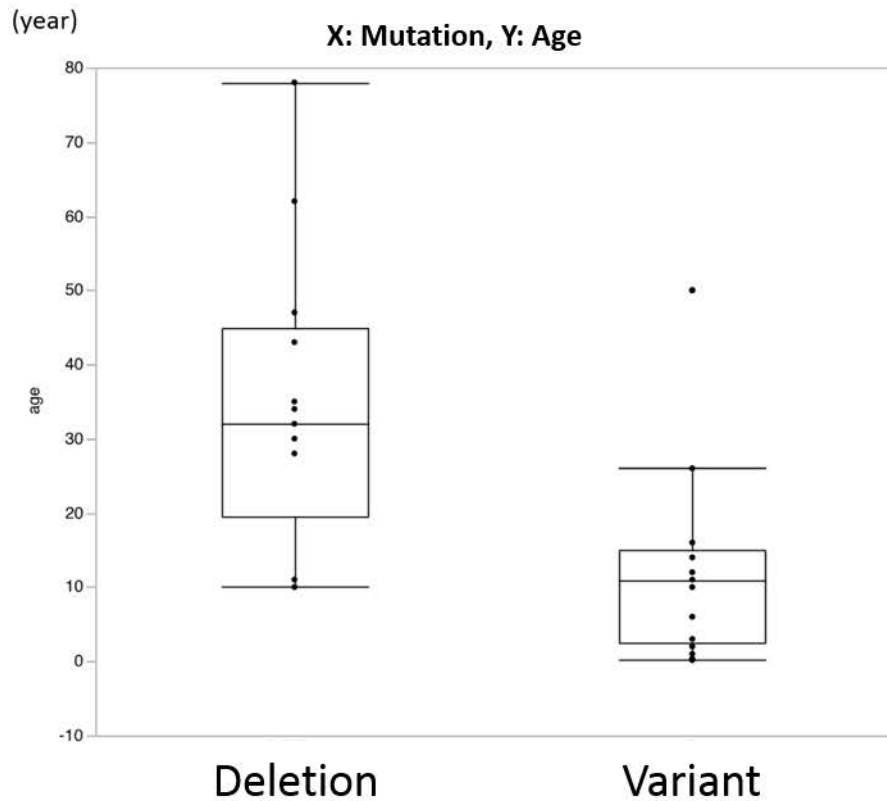
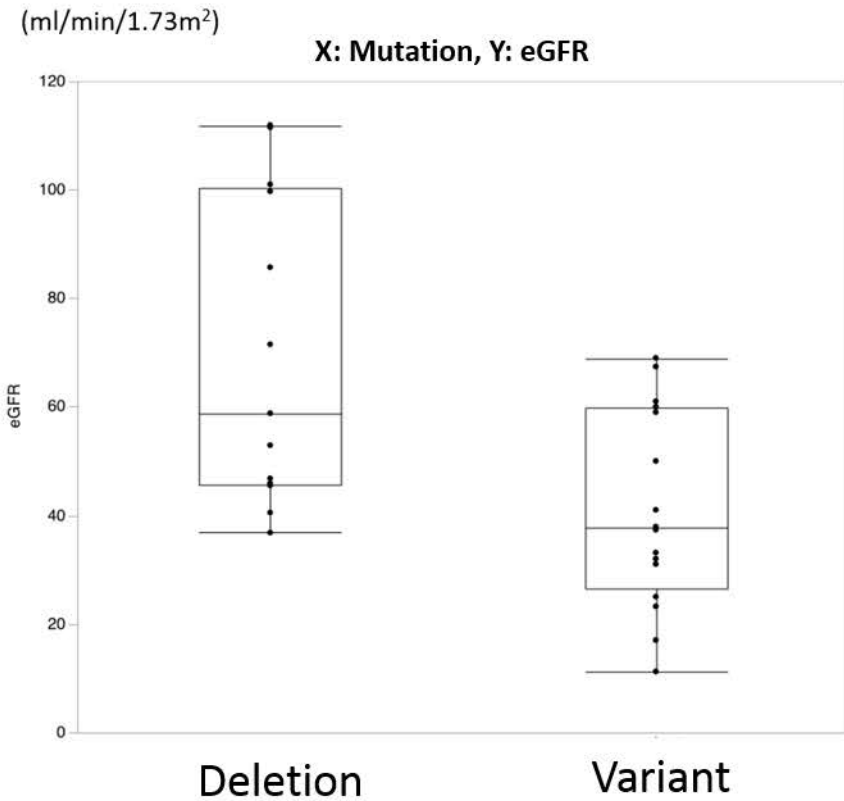
Table 3 Comparison of clinical phenotypes between patients with *HNF1B* variants and deletions

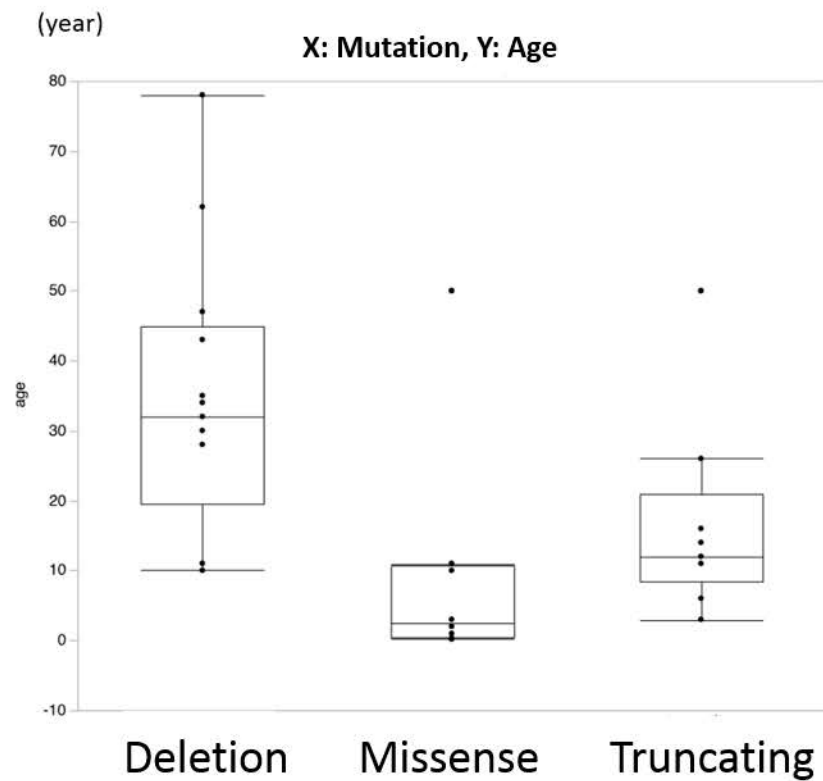
	Variant	Deletion	<i>p</i> value
Age*	11 (2.5–15)	32 (19.5–45)	0.005
Hypomagnesemia	2 /17	11 /14	0.0002
Hyperuricemia	3/17	3 /14	0.7908
Diabetes	4 /17	8 /14	0.0559
Pancreatic malformation	4 /17	3 /14	0.8893
Liver abnormalities	4 /17	6/14	0.252
Genital abnormalities	2 /17	0 /14	0.1845
Neurological abnormality	0 /17	5 /14	0.0071
<i>HNF1B</i> score*	14 (13.3–18.3)	15 (7–17.3)	0.4908

*median (IQR)



● nonsense, ◇ splice site, ▲ missense, ■ frameshift

a**b**

a**b**