# MODY5 Hepatocyte Nuclear Factor 1ß (HNF1ß)-Associated Nephropathy: experience from a regional monogenic diabetes referral centre in Singapore

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## Abstract

From our monogenic diabetes registry set-up at a secondary-care diabetes center, we identified a nontrivial subpopulation (~15%) of maturity-onset diabetes of the young (MODY) among people with young-onset diabetes. In this report, we describe the diagnostic caveats, clinical features and long-term renal-trajectory of people with *HNF1B* mutations (HNF1B-MODY). Between 2013 and 2020, we received 267 referrals to evaluate MODY from endocrinologists in both public and private practice. Every participant was subjected to a previously reported structured evaluation process, high-throughput nucleotide sequencing and gene-dosage analysis. Out of 40 individuals with confirmed MODY, 4 (10%) had HNF1B-MODY (harboring either a *HNF1B* whole-gene deletion or duplication). Postsequencing follow-up biochemical and radiological evaluations revealed the known HNF1B-MODY associated systemic-features, such as transaminitis and structural renal-lesions. These anomalies could have been missed without prior knowledge of the nucleotide-sequencing results. Interestingly, preliminary longitudinal observation (up to 15 years) suggested possibly 2 distinct patterns of renal-deterioration (albuminuric vs. nonalbuminuric chronic kidney disease). Monogenic diabetes like HNF1B-MODY may be missed among young-onset diabetes in a resource-limited routine-care clinic. Collaboration with a MODY-evaluation center may fill the care-gap. The long-term renal-trajectories of HNF1B-MODY will require further studies by dedicated registries and international consortium.

## Keywords

HNF1B-associated nephropathy, HNF1B-MODY, MODY5, renal anomalies, renal trajectory

## Introduction

Mutations in the hepatocyte nuclear factor-1B (HNF1B) gene was first reported in 1997 as a rare genetic cause of monogenic diabetes or maturity-onset diabetes of the young (MODY) by Horikawa Y et al.[1] MODY is characterized by young-onset diabetes (typically <30 years old), lean, absence of beta cell autoimmunity, noninsulin dependence, and nonketotic prone hyperglycemia.[2] It is a form of Mendelian dominantly inherited disease primarily caused by underlying genetic defects in more than 20 different genes identified to date,[3] including the *HNF1B* gene.

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Genetic defects in *HNF1B* account for 2% to 6% of all MODY cases and affected individuals usually present with extra-renal features, including multicystic dysplastic kidneys, glomerulocystic kidney disease, renal agenesis, renal hypoplasia, and renal interstitial fibrosis.[4,5] *HNF1B* belongs to the homeobox-containing family of transcription factors and plays an essential role in the development and function of epithelia in the pancreas, kidneys, liver, and genitourinary tract.[5] Till date, more than 50 different variants have been described within the *HNF1B* gene,[6] located on chromosome 17q12. The most common genetic defect, occurring in 50% of HNF1B-MODY patients, is a whole-gene deletion. In fact, virtually all *HNF1B* whole-gene deletions have been associated with the 17q12 recurrent deletion syndrome (due to a 1.4 Mb heterozygous recurrent deletion at chromosome 17q12 which contains 15 genes, including *HNF1B*).[7,8] This syndrome is characterized by variable combinations of clinical features including young-onset diabetes (MODY), neurodevelopmental, or neuropsychiatric disorders (ie, developmental delay, intellectual disability, autism spectrum disorder, schizophrenia, anxiety, and bipolar disorder), structural lesion of the intra-abdominal organs involving the pancreas and genital-tract, renal tubule-interstitial disease, and congenital abnormalities of the kidney and urinary tract (CAKUT).[9] The recently proposed *HNF1B* risk score[10] is a useful discriminative tool which relies on a combination of clinical, imaging and biological variables, in selecting patients for *HNF1B* genetic testing. However, a crucial determinant of this risk score is to radiologically detect intra-abdominal organ defects, which may not be routinely ordered without prior suspicion, even in specialist diabetes clinics, thereby limiting the adoption of the scoring system even among diabetes care-providers.

HNF1B-MODY is uniquely susceptible to chronic kidney disease (CKD). This is because of the dual vulnerability conferred by CAKUT and early-onset diabetes. Importantly, the heterogeneity and longitudinal renal trajectory of HNF1B-associated nephropathy has not been well described. In this report, we describe the clinical presentation, long-term renal outcomes (up to 15 years) and therapeutic management of 4 selected HNF1B-MODY patients harboring either a *HNF1B* whole-gene deletion or duplication. Notably, 2 out of 4 patients, receiving care at a secondary-care diabetes center, were referred for MODY candidate genes nucleotide-sequencing primarily because of atypical diabetes, instead of known CAKUT. Therefore, the *HNF1B* risk score was not applied prior to gene sequencing.

## Materials and Methods

Participants were selected for MODY evaluation based on previously described clinical criteria.[11,12] Briefly, these include age of diabetes onset ≤35 years, body mass index (BMI) <32.5 kg/m$^2$ (threshold motivated by the BMI value

collected often after long duration of diabetes rather than observed upon diabetes onset), absence of diabetic ketoacidosis (DKA) and negative glutamic acid decarboxylase antibodies (GADA). Massively parallel targeted-gene sequencing for 16 MODY-associated genes and gene dosage analysis using multiplex ligation-dependent probe amplification (MLPA) method combined with MRC-Holland kit P241-E1 for 5 MODY genes (as described by Ang SF et al) were carried out.[12] Chromosomal microarray using whole genome Infinium CytoSNP-850K v1.2 Illumina BeadChip or MLPA using the SALSA MLPA Probemix P297 Microdeletion Syndromes-2 assay (MRC-Holland) was used to detect the recurrent micro-aberration at chromosome 17q12.

Glycated hemoglobin A1c (HbA1c), lipids (cholesterol, triglyceride, LDL-, and HDL-cholesterol), urinary albumin-to-creatinine ratio (uACR) were measured by the American College of Pathology certified Department of Laboratory Medicine at the Khoo Teck Puat Hospital, Singapore. Estimated glomerular filtration rate (eGFR) was calculated from age and serum creatinine using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. This study is approved by the Singapore National Healthcare Group Domain Specific Review Board (DSRB Study Reference No. 2011/00232, 2012/01131 and 2017/00276). Informed consent was obtained from all study participants.

## Results

Among 267 individuals eligible for genetic testing, 40 (~15%) were diagnosed with MODY. From those with MODY, we identified 4 patients with either a *HNF1B* whole-gene deletion (NM_000458.4 [*HNF1B*]: c.195_1868del p.[Met1_Trp557del]) or duplication (NM_000458.4 [*HNF1B*]: c.195_1868dup p.[Met1_Trp557dup]). Further genetic workup by chromosomal microarray or MLPA suggests a recurrent deletion or duplication at chromosome 17q12 respectively. Table 1 shows the baseline clinical characteristics and key features associated with HNF1B-MODY of all 4 patients upon referral for genetic evaluation. Notably, all 4 patients presented with early-onset diabetes (between 19 and 35 years old) and fairly optimal glucose control (HbA1c between 6.6% and 7.3%; 49 to 56 mmol/mol) at point of referral. Among those with family history available (3 out of 4), all had either first or second degree family history of diabetes. Of note, HNF1B-associated features, especially those that are not routinely measured or performed in a diabetes clinic (eg magnesium concentration, parathyroid hormone, hypo-plastic pancreas, and genital abnormalities), were mostly not assessed before genetic diagnosis. Subsequent targeted diagnostic workup by abdominal or renal ultrasound revealed structural abnormalities of the kidney (multicystic dysplastic kidney, unilateral renal agenesis, or multiple cysts) that were not different from previously reported cases.

The first patient, a 48-year-old female, was diagnosed with diabetes at age 19 and was referred for MODY evaluation 26

**Table 1.** Evaluation of HNF1B-MODY Associated Clinical Features and Baseline Characteristics of Four Selected Patients Diagnosed With HNF1B-MODY.

| Characteristic | Patient 1 Before | Patient 1 After | Patient 2 Before | Patient 2 After | Patient 3 Before | Patient 3 After | Patient 4 Before | Patient 4 After |
|---|---|---|---|---|---|---|---|---|
| Evaluation of HNF1B-MODY associated clinical features before and after genetic diagnosis | | | | | | | | |
| Renal cysts | Not assessed | No | Yes[a] | Yes | Yes[b] | Yes | Not assessed | Yes[c] |
| Diabetes | Yes | | Yes | | Yes | | Yes | |
| Reduced renal function | Yes | Yes | No | Yes | No | No | Yes | Yes |
| CAKUT | Not assessed | Yes[d] | No | No | Yes[e] | Yes | Not assessed | No |
| Hyperechogenicity | Not assessed | No | No | No | Yes[f] | Yes | Not assessed | Yes[g] |
| Hypomagnesemia | Not assessed | Yes | Not assessed | Yes | Not assessed | Yes | Not assessed | |
| Hyperuricemic/gout | Not assessed | No | Not assessed | No | Not assessed | No | Not assessed | No |
| Elevated liver enzymes | Not assessed | Yes | Not assessed | No | Not assessed | Yes | Not assessed | No |
| Exocrine pancreatic disease | No | No | No | No | No | No | No | No |
| Urinary tract malformation | Not assessed | Yes[h] | Not assessed | No | No | No | Not assessed | No |
| Genital malformations | Not assessed | | Not assessed | | No | | Not assessed | |
| Neurodevelopmental/ neuropsychiatric disorder | Not formally assessed | | Not formally assessed | | No^ | | Not formally assessed | |
| Hyperparathyroidism | Not assessed | No | Not assessed | No | Not assessed | No | Not assessed | No |
| Baseline clinical characteristics at point of referral for MODY evaluation | | | | | | | | |
| Sex | Female | | Male | | Male | | Male | |
| Family history of diabetes (first and second degree) | Yes | | Yes | | Yes | | Not available | |
| Age at presentation (at diabetologist), year | 19 | | 23 | | 29 | | 35 | |
| BMI (kg/m$^2$) | 26.2 | | 17.2 | | 14.5 | | 22.6 | |
| HbA1c (%; mmol/mol) | 6.8; 51 | | 7.3; 56 | | 6.6; 49 | | 7.0; 53 | |
| Systolic blood pressure (mmHg) | 128 | | 123 | | 147 | | 133 | |
| Diastolic blood pressure (mmHg) | 73 | | 87 | | 101 | | 79 | |
| Total cholesterol (mM) | 4.44 | | 5.12 | | 5.00 | | 4.68 | |
| HDL-C (mM) | 1.79 | | 1.56 | | 1.50 | | 1.13 | |
| LDL-C (mM) | 2.48 | | 3.56 | | 3.28 | | 2.89 | |
| Triglycerides (mM) | 1.23 | | 0.77 | | 1.26 | | 2.30 | |
| CKD-Epi-eGFR (ml/min/1.73 m$^2$) | 62 | | 92 | | 111 | | 34.2 | |
| Pharmacological treatment | | | | | | | | |
| Insulin | Yes | | Yes | | Yes | | No | |
| OHA | Yes | | No | | No | | Yes | |
| *HNF1B* mutation | Whole-gene deletion | | Whole-gene deletion | | Whole-gene deletion | | Whole-gene duplication | |
| Diagnostic delay | 26 years | | 10 years | | 10 months | | 38 years | |
| *HNF1B* score at presentation[1] | 4, 10 (re-evaluation) | | 12, 14 (re-evaluation) | | 14, 18 (re-evaluation) | | 4, 16 (re-evaluation) | |
| MODY probability (Shields BM et al)[2] | 8.2% | | 1.9% | | 4% | | 4.6% | |
| MODY probability (Ang SF et al)[3] | 12.9% | | 51.8% | | Not available* | | 20.6% | |

Abbreviations: *HNF1B-MODY*, Hepatocyte Nuclear Factor-1B-maturity-onset diabetes of the young; CAKUT, congenital abnormalities of the kidney and urinary tract; BMI = body mass index; OHA, oral hypoglycemic agents.

[1]Based on *HNF1B* score developed by Faguer S et al.[10]
[2]Based on MODY probability calculator developed by Shields BM et al.[13]
[3]Based on MODY probability calculator developed by Ang SF et al.[12]
[a]Postgenetic diagnosis, abdominal ultrasonography revealed multiple cysts in both kidneys.
[b]Pregenetic diagnosis, renal ultrasonography revealed multiple cysts in the left kidney.
[c]Postgenetic diagnosis, abdominal ultrasonography revealed multiple cysts in the left kidney.
[d]Postgenetic diagnosis, abdominal ultrasonography revealed unilateral renal agenesis of the right kidney.
[e]Pregenetic diagnosis, renal ultrasonography revealed multicystic dysplastic right kidney which preceded diabetes onset.
[f]Pregenetic diagnosis, renal ultrasonography revealed increased echogenicity in the left kidney.
[g]Postgenetic diagnosis, abdominal ultrasonography revealed increased echogenicity in both kidneys.
[h]Postgenetic diagnosis, abdominal ultrasound revealed presence of mild hydronephrosis in the left kidney suggesting distal urinary tract obstruction.
^Patient presented with congenital lateral rectus palsy during adolescent.
*Unable to derive probability due to insufficient clinical data required by the calculator.
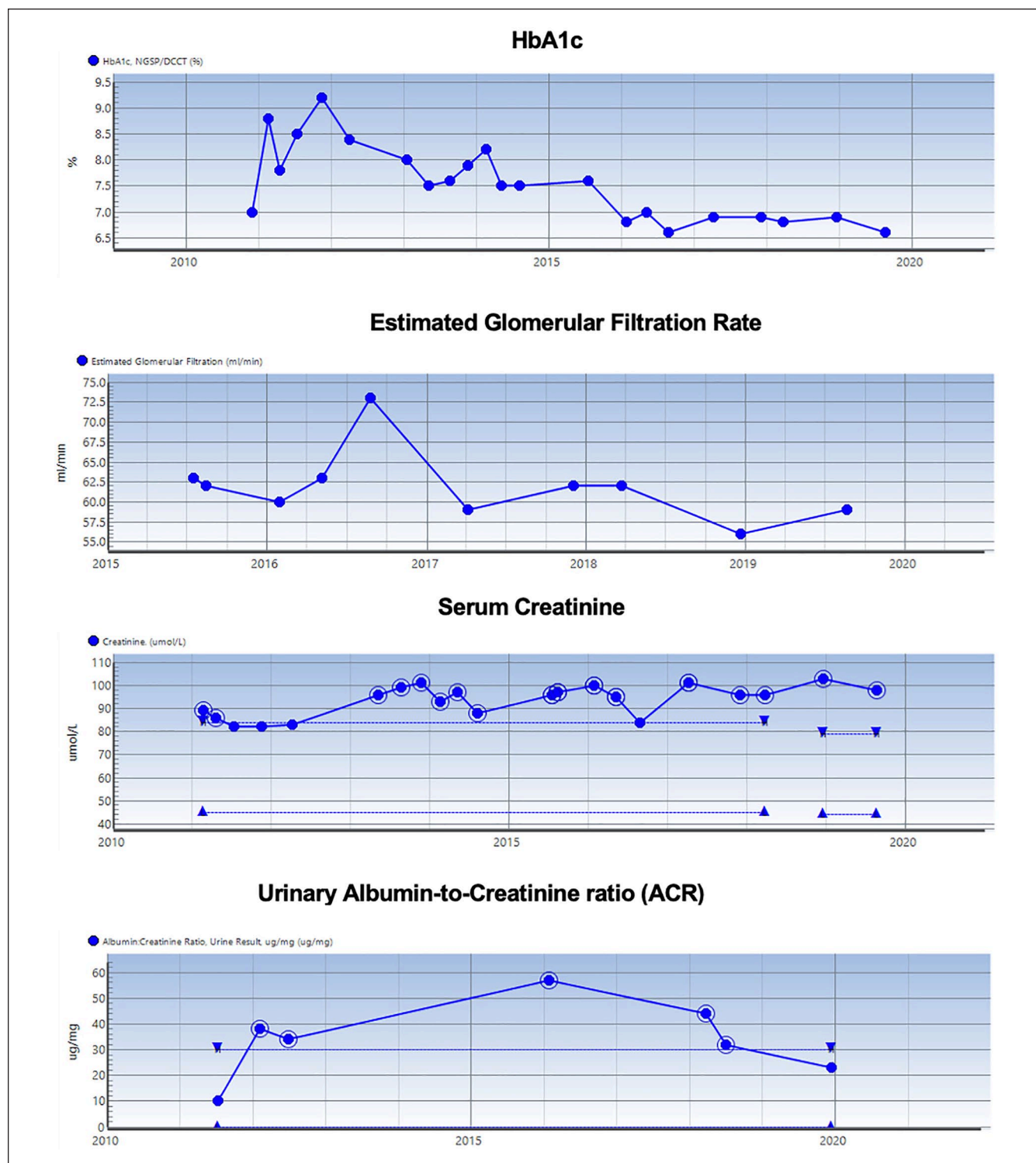
**Figure 1.** Longitudinal renal trajectory of Patient 1 based on HbA1c (%), eGFR (mL/min/1.73 m$^2$), serum creatinine (μmol/L), and urinary ACR (μg/mg).
Abbreviation: ACR, albumin-to-creatinine ratio.

years after diabetes onset. At the point of referral, she was on Metformin as well as multiple daily insulin injections with NPH Insulin and Insulin Actrapid with total daily dose of 64 units/day or 1 unit/kg of short and intermediate-acting insulin

therapy. Postgenetic diagnosis, abdominal ultrasonography carried out in this patient revealed unilateral agenesis of the right kidney and the presence of mild hydronephrosis in the left kidney suggested distal urinary tract obstruction.
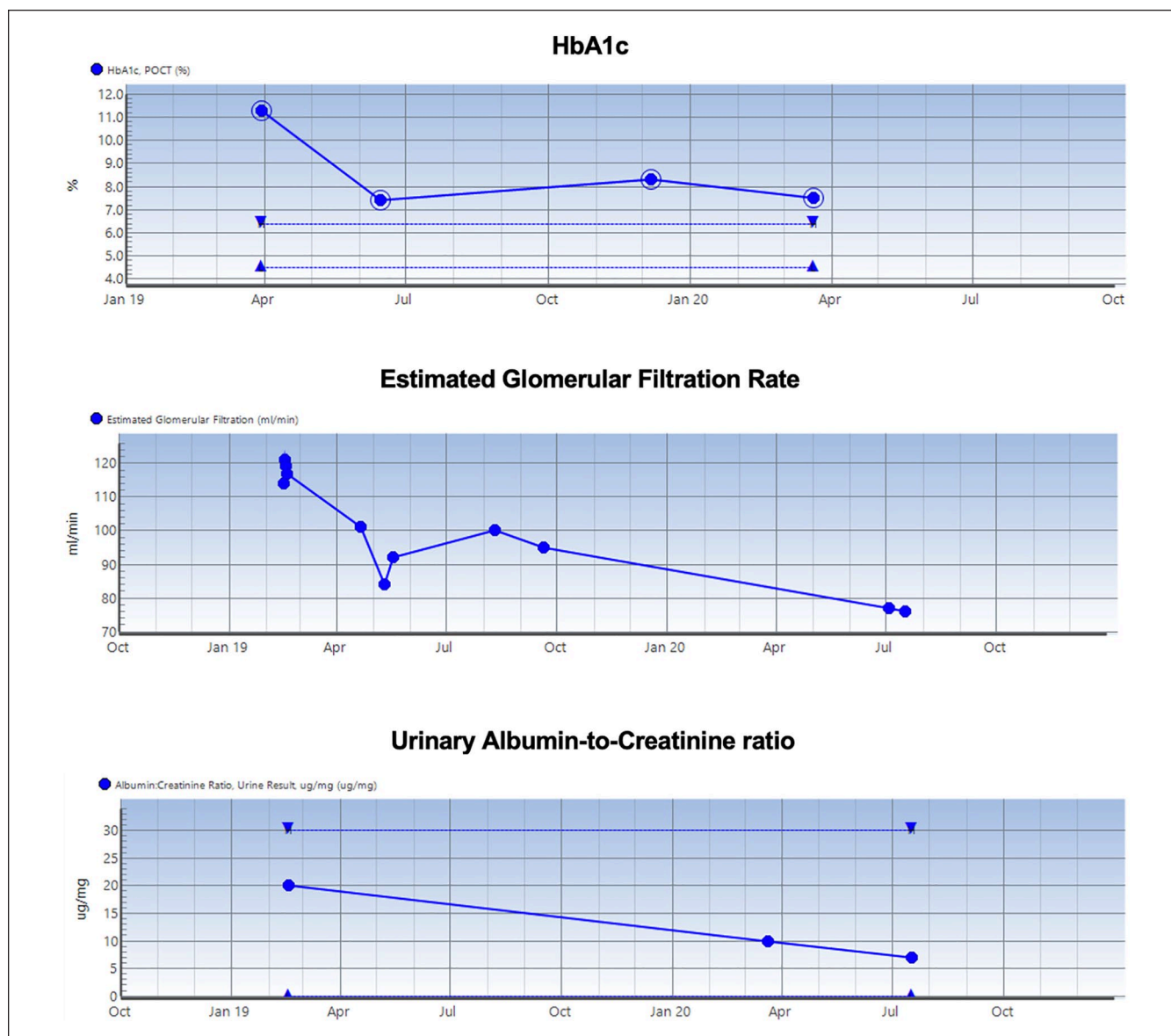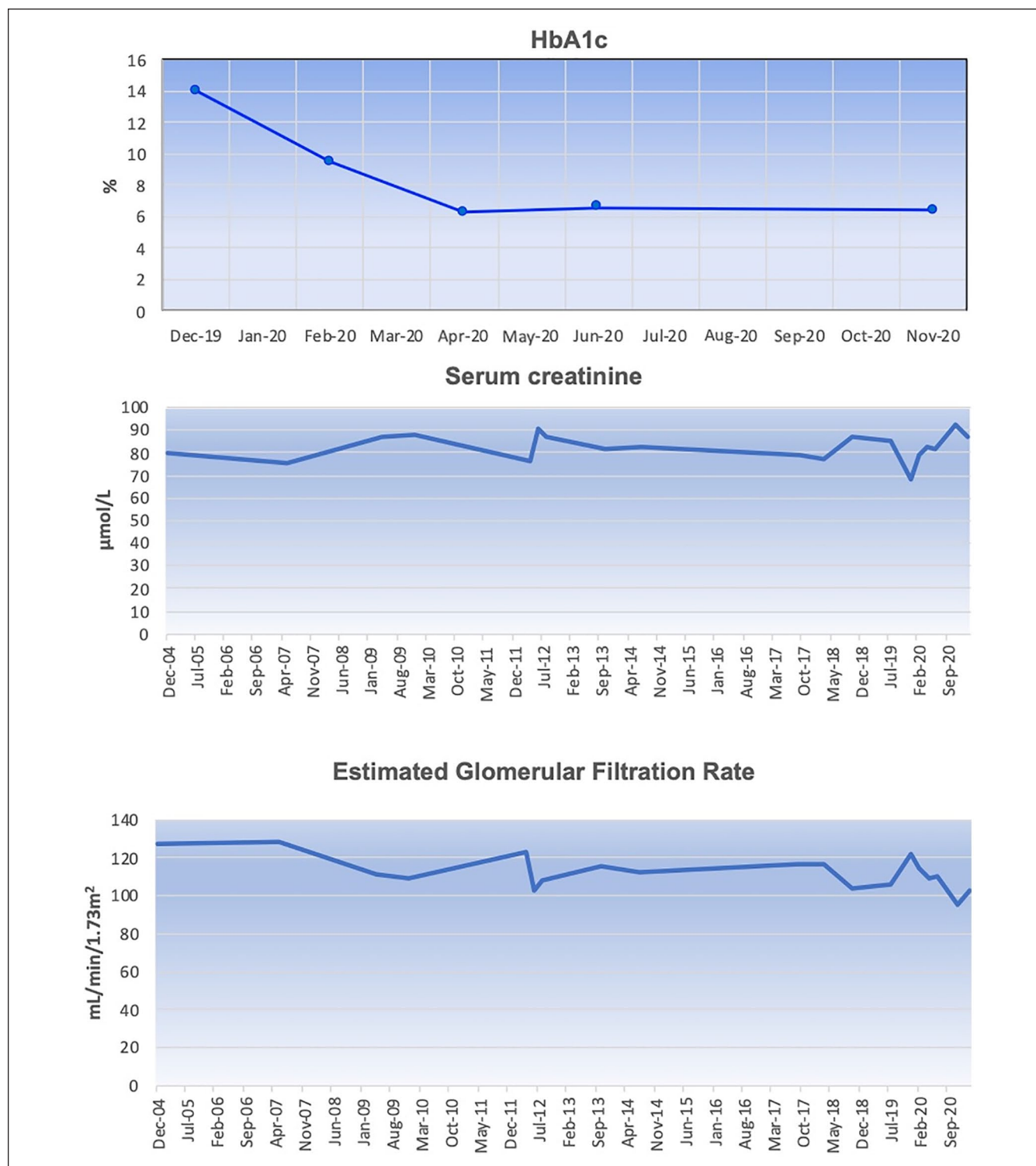
**Figure 2.** Longitudinal renal trajectory of Patient 2 based on HbA1c (%), eGFR (mL/min/1.73 m$^2$), and urinary ACR (μg/mg). Abbreviation: ACR, albumin-to-creatinine ratio.

Glycemic control was variable and mostly suboptimal, with HbA1c ranging between 7% and 9.3% (53-78.1 mmol/mol) over several years (Figure 1). After genetic diagnosis in 2017, she had optimal glucose control, with HbA1c between 6.5% and 7% (48 to 53 mmol/mol). Kidney function evaluation suggest CKD based on eGFR of <60 mL/min/1.73 m$^2$ for more than 2 years, elevated serum creatinine levels and prolonged microalbuminuria based on uACR between 10 and 60 μg/mg, initially attributed to uncontrolled glycemic burden by the primary physician. Notably, in recent years, her rate of eGFR decline was -2.26 mL/min/1.73 m$^2$ per year.

The second patient, a 34-year-old male, diagnosed with diabetes at age 23 years was referred for MODY evaluation 10 years after diabetes onset while on multiple daily insulin injections with insulin glargine and insulin glulisine with total daily dose of 27 units/day or 0.5 unit/kg. Notably, he presented with multicystic kidneys in utero and had chronic hypomagnesemia and hypokalemia during childhood. A few foci of parenchymal calcification were observed in the kidneys but hydronephrosis was not detected. He had stable renal function for several years after diabetes onset but recently, his eGFR began to decline rapidly at -4.67 mL/min/1.73 m$^2$ per year, accompanied by suboptimal glycemic control with HbA1c between 7.0% and 8.5% (53 to 69.4 mmol/mol) albeit absence of albuminuria (uACR <30 μg/mg), suggesting nonalbuminuric CKD (Figure 2). In addition, recent ophthalmological examination ruled out diabetic retinopathy, suggesting non-diabetes-related CKD.

**Figure 3.** Longitudinal renal trajectory of Patient 3 based on HbA1c (%), serum creatinine (μmol/L), and eGFR (mL/min/1.73 m$^2$).
Abbreviation: eGFR, Estimated glomerular filtration rate.

The third patient, a 29-year-old male, presented with congenital lateral rectus palsy in his right eye and dysplastic right kidney at 9-year-old which precedes diabetes onset 20 years later. He was subsequently referred for MODY evaluation (particularly HNF1B-MODY) upon diagnosis of diabetes. Renal ultrasound performed prior to genetic diagnosis suggested that his left kidney is normal in size with increased echogenicity and several cysts present. There was

no hydronephrosis nor calcification in both kidneys. Upon diagnosis of diabetes with HbA1c of 14.0% (130 mmol/mol) in 2019, he was started on multiple daily insulin injections with insulin glargine and glulisine with total daily dose of 32 units/day or 0.8 unit/kg. He achieved good glycemic control over 7 months upon treatment with HbA1c between 6.3 and 6.6% (45 to 49 mmol/mol) (Figure 3). Based on his renal trajectory, his kidney function is presently well-preserved (eGFR >90 mL/min/1.73 m$^2$) with absence of albuminuria. It would be noteworthy to continually observe his long-term renal outcome. Notably, genital examination excluded structural genital malformations.

The fourth patient, a 74-year-old male, was diagnosed with diabetes at age 35 and evaluated for MODY 38 years after diabetes onset. Renal-trajectory over 15 years suggests progressive decline in renal function based on declining eGFR at 1.125 mL/min/1.73 m$^2$ per year and presence of prolonged macroalbuminuria (uACR >300 µg/mg). The onset and progression of renal-injury was most probably attributable to long standing diabetes (more than 30 years) and long-term variable HbA1c and off-target glucose control (Figure 4).[14] Abdominal ultrasound showed that both kidneys were normal in size but with increased echogenicity and well-defined cysts in the left kidney. However, no focal mass or hydronephrosis was detected. He is currently treated with dual oral anti-diabetic agents of metformin and a sulphonylurea, along with an angiotensin receptor blocker for the albuminuria.

Taken together, there appears to be 2 patterns of renal deterioration. Patients 1 and 2 showed the atypical features of fairly steep decline in eGFR, despite relatively modest albuminuria. In contrast, patient 4 experienced progressive albuminuria and gradual eGFR decline, which is the more classical pattern expected of diabetic kidney disease (DKD).

We also evaluated the 17-item *HNF1B* risk score developed by Faguer et al[10] in all 4 patients. Particularly, 2 of the patients had a risk score <8 (cutoff of 8 was reported to be the optimal threshold with a sensitivity of 98.2%, a specificity of 41.1%, and a positive predictive value [PPV] of 19.8%) at the point of initial presentation. Importantly, after the genetic diagnosis has been ascertained by nucleotide-sequencing, subsequent re-evaluation of their clinical features (eg, abdominal imaging, biochemistry tests) led to a re-assignment of higher risk scores. This suggested that the extent of evaluation prompted by clinical indications (eg, with or without abdominal imaging), will affect the performance of such a risk score. This highlights the limitation of the current *HNF1B* risk score, because of its reliance upon information on intra-abdominal organs structural abnormalities, that is often not routinely or adequately assessed in real-world resource-limited diabetes clinics, unless CKD or other indications such as rapid renal function decline or recurrent urinary tract infections are present or HNF1B-related disease is strongly suspected. In addition, the MODY probability calculators developed by Shields et al[13] and Ang et al[12] (optimal Youden index-informed cutoff of 17.5%, will yield a sensitivity of

76.0%, specificity of 72.6% and PPV of 37.3%, NPV of 93.4% and accuracy of 73.2%), were also evaluated (Table 1).

## Discussion

A nontrivial subpopulation of people with young-onset atypical diabetes has MODY.[11,12] Our experience suggested that a structured clinical-algorithm, supported by candidate-genes massively parallel high-throughput nucleotide sequencing could identify a meaningful proportion (~15%) of individuals with major subtypes of MODY. Notably, among these 40 individuals, 4 (10%) were diagnosed with HNF1B-MODY attributable to *HNF1B* gene mutations. However, given the rarity of HNF1B-MODY, it is largely undiagnosed in the diabetes clinics. We wish to describe 3 important clinical observations. First, our data suggested that the proposed 17-item *HNF1B* risk score may not work well in the diabetes clinic because of its heavy reliance on documenting intra-abdominal organ structural abnormalities (eg, CAKUT), which is not part of real-world routine diabetes care, without prior indication for such abdominal imaging. In addition, liver abnormalities and high uric acid levels are nonspecific and electrolytes such as magnesium and even parathyroid hormones are not routinely measured. The MODY probability calculators developed by Shields et al and Ang et al were based on different MODY subtypes and therefore, are not specifically targeted at HNF1B-MODY. Nevertheless, the adoption of poly-genetic risk score[15] may help to identify T1D and T2D among individuals with young-onset diabetes, thereby enriching the remaining subjects for monogenic diabetes gene testing such as HNF1B-MODY. Second, HNF1B-MODY is unique because of its distinctive genetic architecture, that is, *HNF1B* whole-gene deletion, as part of the chromosome 17q12 syndrome in about 50% of affected individuals.[7,8] This results in a myriad of clinical phenotype, which includes structural kidney anomalies, that compounds the susceptibility to CKD, given the context of on-going long-term diabetes-mediated metabolic injury. Third, the longitudinal renal trajectory of people with HNF1B-MODY has not been well described. Our preliminary data suggested 2 possible patterns: (1) eGFR decline in-tandem with incremental albuminuria, conforming with classical DKD, largely attributable to long-term suboptimal glycemic control and (2) fairly rapid eGFR decline with no or minimal albuminuria, atypical of diabetic nephropathy (DN).[16] Therefore, the latter atypical pattern of renal progression, which is uncommon among Asians (estimated ~5% of our diabetic population),[17] may prompt the request for renal-imaging to search for unexpected diagnosis like HNF1B-MODY associated renal lesions.

Nonetheless, subsequent biochemistry lab tests revealed hypomagnesemia in 3 out of 4 patients and abnormalities of the liver in the form of elevated concentrations of transaminases (alanine aminotransferase and aspartate aminotransferase) in 2 out of 4 patients. Neurodevelopmental or neuropsychiatric disorder which is another common feature
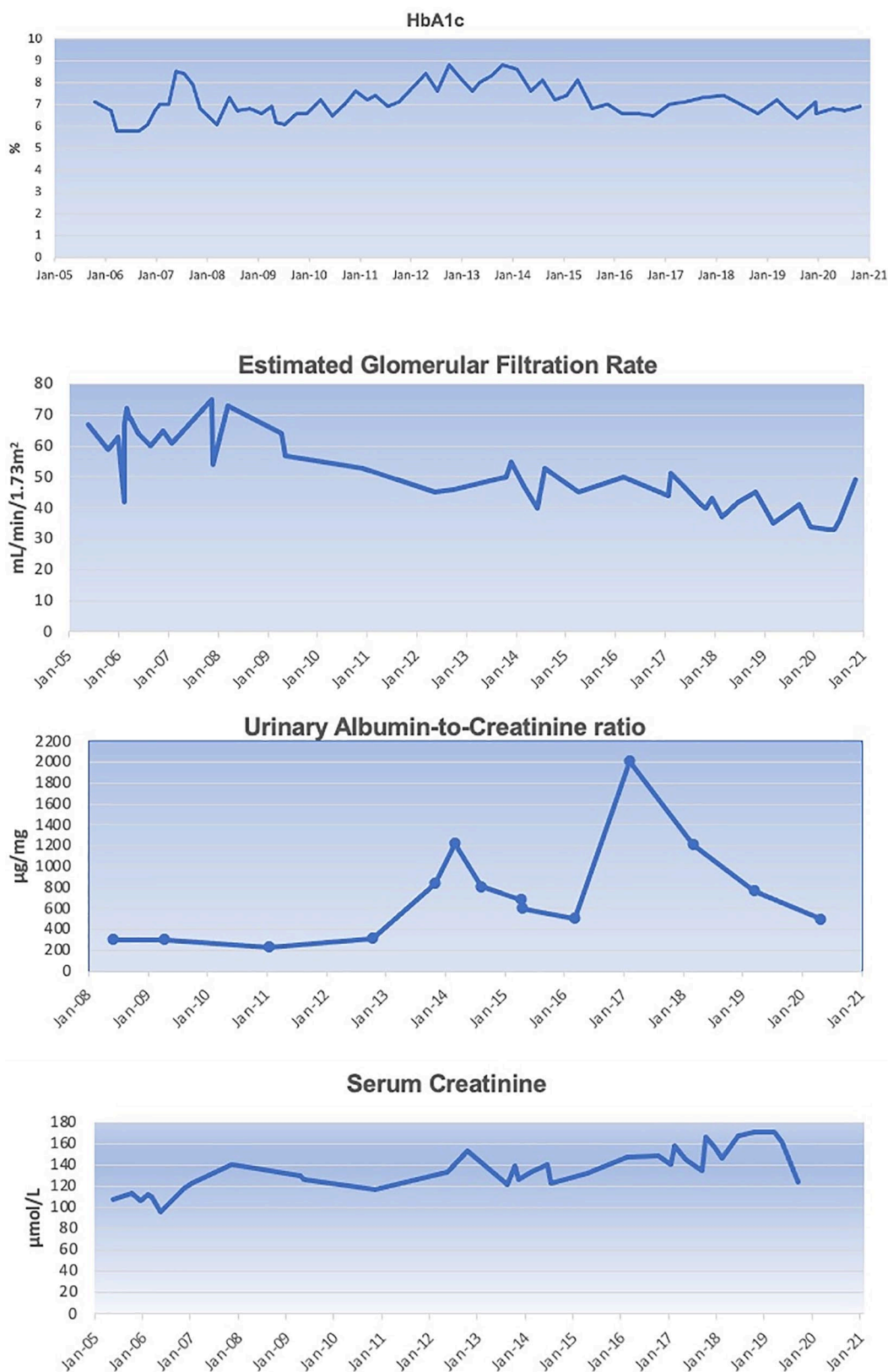
**Figure 4.** Longitudinal renal trajectory of Patient 4 based on HbA1c (%), eGFR (mL/min/1.73 m$^2$), urinary ACR (μg/mg), and serum creatinine (μmol/L).
Abbreviations: eGFR, Estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio.

(>50% occurrence) related to the 17q12 syndrome was either absent or not formally assessed. The increased risk for neurodevelopmental and neuropsychiatric disorders, such as developmental delay, intellectual disability, autism, and schizophrenia are thought to be attributed by genes other than *HNF1B* in the 17q12 region, namely *LHX1* and *ACACA*.[18-20] Conversely, the lack of individuals with neurological disease associated with mutations in either of these two candidate genes and the variable severity or absence of neurological disease among 17q12 deletion carriers support a more complex disease model.[7,21] Assessing the extent to which 17q12 genomic disarrangement is associated with neuropsychological disorders will require comprehensive evaluation in all affected patients.

Taken together, the recognition and diagnosis of HNF1B-associated nephropathy is even more challenging when CKD accompanied by diabetes is frequently misdiagnosed as common garden DN and CKD in combination with renal cysts is easily misdiagnosed as autosomal dominant tubulointerstitial disease (ADTKD).[22] This is further complicated when the phenotypes associated with *HNF1B* mutations partly overlap with mutations in other genes (eg, *REN, UMOD, PKD1, PKD2* and *MUC1*).[23] Furthermore, *HNF1B* has recently been identified as a modifier gene in autosomal dominant polycystic kidney disease (ADPKD)—caused by mutations in the *PKD1* or *PKD2* genes.[24] Therefore, the use of tolvaptan may be explored in HNF1B-MODY patients to slow down the formation of cysts and protect kidney function.[25,26] Additionally, the therapeutic role of SGLT2 inhibitor (a highly effective treatment for CKD) in HNF1B-associated nephropathy is unclear, given the concern of increased susceptibility to uro-genital sepsis (a known contraindication for SGLT2 inhibitor) in the presence of CAKUT.[27] Hence, future studies will be needed to address these important clinical issues.

## Conclusion

HNF1B-MODY is often a serious multi-systemic disease, partly because of its unique genetic architecture, for example, chromosomal microdeletion with multiple gene-loss. However, the diagnosis can be easily missed among young-onset diabetes in a resource-limited routine-care clinic. Hence, collaboration with a MODY-evaluation center may fill the clinical care-gap.

Additionally, HNF1B-MODY is uniquely vulnerable to CKD due to concomitant CAKUT and early-onset diabetes. Therefore, the long-term renal trajectories of HNF1B-MODY will require further studies by dedicated registries and international consortium.

In the era of precision medicine, the accurate molecular diagnosis of HNF1B-MODY is a feasible and realizable goal, to provide personalized care for affected patients and their families.

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