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Case Report

Phenotypic heterogeneity and polygenic risk scores in a family of maturity-onset diabetes of the young

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Abstract

Diagnosis of a diabetes subtype leads to more precise management and informs the likelihood of diabetes in other family members. Patients with hepatocyte nuclear factor-1 alpha (*HNF1A*)-maturity-onset diabetes of the young (MODY) are highly sensitive to sulfonylureas, and a correct diagnosis can lead to more appropriate treatment. A patient may carry multiple genetic variants that contribute to the heterogeneity of phenotypes, trajectories, and outcomes. Polygenic risk score (PRS) is a useful tool to estimate an individual's genetic susceptibility to polygenic type 2 diabetes (T2D). Combining monogenic diabetes testing with PRS may explain the heterogeneity of phenotypes and clinical course among family members of patients with MODY. Herein, we report a nonobese Thai man with *HNF1A*-MODY due to a partial gene deletion. This has led to the same diagnosis in other family members diagnosed with T2D with heterogeneous presentations due to variable PRS and clinical risk factors.

Key Words hepatocyte nuclear factor-1 alpha, maturity-onset diabetes of the young, polygenic risk score, monogenic diabetes, heterogeneity, precision medicine

Abbreviations: A1C, glycated hemoglobin; BMI, body mass index; DPP4i, dipeptidyl peptidase 4 inhibitor; *HNF1A*, hepatocyte nuclear factor-1 alpha; MLPA, multiplex ligation-dependent probe amplification; MODY, maturity-onset diabetes of the young; PRS, polygenic risk score; SGLT, sodium-glucose cotransporter; T2D, type 2 diabetes mellitus.

Introduction

Maturity-onset diabetes of the young (MODY) is a group of monogenic diabetes with Mendelian mode of inheritance characterized by young age at diagnosis and dominant beta-cell dysfunction [1]. Patients with hepatocyte nuclear factor 1A (*HNF1A*-MODY, formerly known as MODY 3) are highly sensitive to low-dose sulfonylureas [2]. In Asia, 1 in 5 adults has young-onset diabetes (diagnosed <40 years), largely driven by interactions between genetic and environmental factors, including polygenic type 2 diabetes mellitus (T2D) variants. Genetic, environmental, and lifestyle factors underlie the heterogeneity in clinical course and treatment response in MODY [3-5].

Polygenic risk score (PRS), derived from the total number of causal variants mainly reported in genome-wide association studies (GWAS) can inform an individual's genetic predisposition to complex diseases [6]. Genetic discoveries in European and Asian populations have revealed inter-ethnic differences in location of loci, frequency of risk allele for the same locus or different effect sizes for the same risk allele, which are used to calibrate PRS in different populations [7].

Family history is a key risk factor for diabetes, especially T2D. Beyond clinical factors, PRS can help identify individuals at higher risk [8]. Herein, we report a case of *HNF1A*-MODY due to a partial gene deletion in a middle-aged Thai man, which has led to the same diagnosis in his father and older sister diagnosed with T2D. Despite all carrying the same variant, the differences in PRS and clinical risk factors contributed to their phenotypic heterogeneity. Timely *HNF*1A-MODY diagnosis through family screening, together with PRS and modifiable risk factor assessment, can improve diagnostic accuracy, prognosis, and therapy. This personalized information supports informed decision-making for providers, patients, and families, advancing precision medicine for better outcomes.

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Case presentation

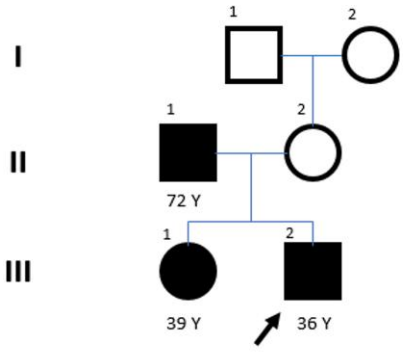
A 36-year-old, nonobese Thai man with a history of non-insulin-requiring T2D for 6 years came to our clinic due to worsening glycemic control. He was diagnosed as having T2D. When seen at our clinic, his fasting plasma glucose was 130 mg/dL (SI: 7.22 mmol/L) (reference range, <100 mg/dL [SI: <5.5 mmol/L]), glycated hemoglobin (A1C) 8.2% (66 mmol/mol) (reference range, ≤5.7% [SI: ≤39 mmol/L]) and urine was negative for ketones. His body mass index (BMI) was 21.6 kg/m^2. He did not drink alcohol or smoke and denied using any recreational drugs. When first diagnosed, his A1C was also 7.8% (SI: 62 mmol/mol) with glucosuria and he was treated with metformin 1000 mg daily, with A1C ranging from 6.7% to 8.1% (SI: 51-65 mmol/mol). Addition of sitagliptin, a dipeptidyl peptidase 4 inhibitor (DPP4i) dropped A1C to 7.5% (SI: 58 mmol/mol), which increased to 8.8% (SI: 73 mmol/mol) over a 12-month period. He had microalbuminuria but no retinopathy.

His father (aged 72) was diagnosed with nonobese T2D in his 50s, with A1C ranging from 7.1% (SI: 54 mmol/mol) to 8.7% (SI: 72 mmol/mol). The patient's older sister (aged 39) was diagnosed with T2D in her 30s and was treated with multiple oral glucose-lowering drugs with A1C ranging from 6.6% (SI: 49 mmol/mol) to 8.5% (SI: 69 mmol/mol). She also had hypertension and severe obesity with a BMI of 37.1 kg/m^2 (Fig. 1).

Diagnostic assessment

Fasting plasma C-peptide in the index patient showed adequate beta-cell function (0.86 ng/mL (0.28 nmol/L)) (reference range, 0.78-5.19 ng/mL [SI: 0.26-1.71 nmol/L]) (Immulite, Siemens Healthcare Diagnostics, USA), with a corresponding fasting plasma glucose of 151 mg/dL (SI: 8.3 mmol/L). Anti-islet autoantibodies were negative. Due to his lean BMI, positive family history, lack of autoimmune markers, and residual beta-cell function, we performed next-generation sequencing (NGS) using a panel including 33 monogenic diabetes-related genes (GemVCare, Shatin, Hong Kong) [9]. The sequencing regions covered exons and flanking regions within 25 base-pairs upstream and downstream of each exon. Multiplex ligation-dependent probe amplification (MLPA) assays were used to detect copy number variation (CNV) for glucokinase (*GCK)* and *HNF1A/4A/1B* genes. Sequence variations were reported according to the American College of Medical Genetics and Genomics (ACMG) standards and guidelines [10]. Heterozygous deletion of *HNF1A* exon 8-10 was detected and classified as a pathogenic variant confirming a diagnosis of *HNF1A*-MODY. The patient's father and older sister also underwent MLPA analysis of the *HNF1A* gene and were found to carry the same rare variant.

Due to their heterogeneous phenotypes (eg, age at diagnosis, obesity, and glycemic control), all affected family members underwent multiplex sequencing of a panel of 254 validated risk variants for T2D in Asians for computing a PRS. A proprietary algorithm including validated clinical and weighted genetic risk factors in Asians [6] was used to estimate the 10-year risk of T2D. The distribution of PRS for most complex polygenic disease such as T2D is nonlinear [11]. For this panel of 254 variants, individuals were ranked according to their clinical, genetic and combined risk scores by deciles with 70% to 80% of individuals who developed T2D in 10 years falling within the top 3 deciles, that is, 30% of population [12]. In a Chinese population, 40%, 30%, 20%, and 10% have low, moderate, high, and very high genetic risk for T2D, respectively (GemVCare, Shatin, Hong Kong). In this *HNF1A*-MODY family, the index case and his father both carried 130 variants, albeit with different combinations, putting them respectively in the top 30% and 20% rank for risk of T2D. The sister carried 135 variants, which put her in the top 10% rank for risk of T2D.



	III-2 (Index case)	III-1 (Sister)	II-1 (Father)
Age (years)	36	39	72
Age at diagnosis (years)	30	30	53
Disease duration (years)	6	9	19
Body mass index (kg/m^2)	21.6	39.1	23.9
Waist circumference (cm)	86	109	89
Diabetic complications	Albuminuria	Neuropathy	None
Insulin usage	No	No	No
***HNF1A* variant**	Yes	Yes	Yes
Percentile for polygenic risk scores	30th	10th	20th
Peak body weight (kg)	74	100	65
Smoking history	no	no	Ex
Physical inactivity	Yes	Yes	No
Treatment before diagnosis of MODY	Metformin Sitagliptin	Metformin Vildagliptin Luseogliflozin	Glipizide
A1C before diagnosis of MODY (%)	8.2%	8.5%	7.1%
Treatment after diagnosis of MODY	Metformin Empagliflozin Gliclazide	Metformin Luseogliflozin Glimepiride	Glipizide
Latest A1C after diagnosis of MODY (%)	6.8%	6.6%	7.6%

Figure 1 Family pedigree and clinical data in the index case and family members with *HNF1A*-MODY.

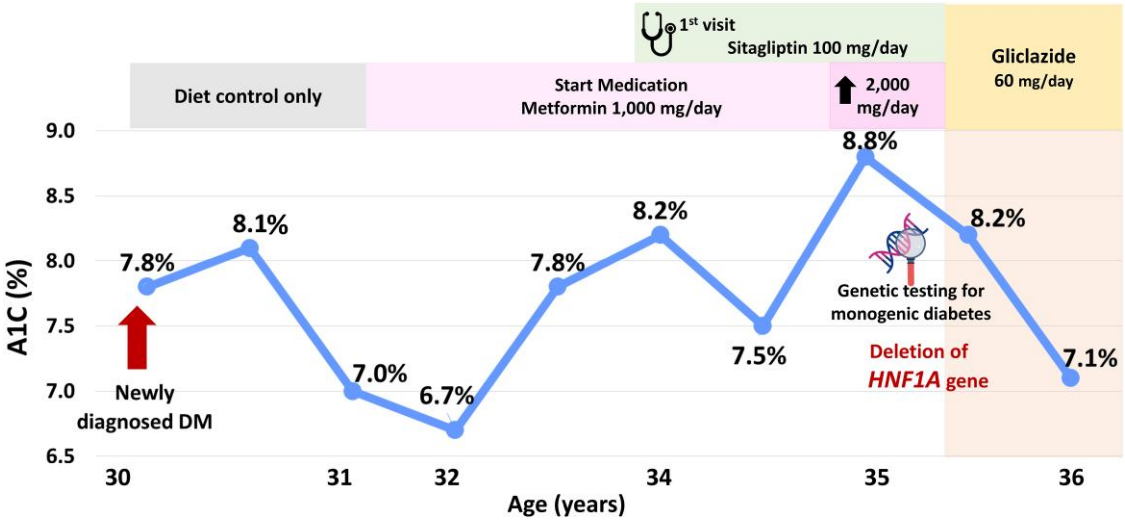


Figure 2 The clinical course and laboratory data of the index patient from empirical diagnosis of type 2 diabetes and after definitive diagnosis of *HNF1A*-MODY as a subtype of diabetes.

Treatment

The diagnosis of *HNF1A*-MODY led to the discontinuation of sitagliptin in the index patient. Sulfonylureas are considered as treatment of choice for *HNF1A*-MODY. He was started on gliclazide 30 mg once daily and titrated to 60 mg. His A1C decreased from 8.2% (SI: 66 mmol/mol) to 7.1% (SI: 54 mmol/mol) (Fig. 2).

Outcome and follow-up

In the following months, the index patient maintained his body weight and healthy behaviors while continuing gliclazide 60 mg once daily. Six months after the diagnosis of *HNF1A*-MODY and change to gliclazide, his A1C remained above 7% (SI: 53 mmol/mol). Due to the presence of albuminuria, he was initiated on a sodium-glucose cotransporter 2 (SGLT2) inhibitor and attained his glycemic target of 6.8% (SI: 51 mmol/mol).

The father was already on glipizide 5 mg once daily before the diagnosis of MODY. His latest A1C was 7.6% (SI: 60 mmol/mol). For his elder sister, after receiving glimepiride 1 mg once daily, her A1C decreased from 8.5% (SI: 69 mmol/mol) to 6.6% (SI: 49 mmol/mol) without any hypoglycemic symptoms.

Discussion

This *HNF1A*-MODY family illustrates the heterogeneity of clinical course, including different age at diagnosis among all 3 carriers of the same variant, in part due to varying contribution from genetic and nongenetic factors. In most series, depending on setting and other recruitment criteria, MODY accounts for 1% to 5% of patients diagnosed with T2D [1]. In a consecutive cohort of 1201 Chinese patients with non–type 1 diabetes (T1D) tested for rare variants of 33 genes for monogenic diabetes including *HNF1A*, 2.2% of patients had pathogenic or likely pathogenic variants [9]. There were only a few single-center studies on clinical and genetic characteristics of MODY in Thailand [13, 14]. The pathogenic deletion of *HNF1A* exon 8-10 in this family had not been reported. To this end, sequencing and bioinformatic analysis is needed to detect these structural variants.

The diagnosis of *HNF1A*-MODY in the index case improved his diabetes management and clarified the diagnosis in his father and sister through cascade screening. Incorporating PRS may help explain differences in their age at diagnosis, glycemic control, and complications. This personalized information also supports counseling, motivates behavioral change, and guides family screening for early detection and treatment [15].

The *HNF1A* gene is located at chromosome 12q24, consisting of 10 exons which encode 631 amino acids [16]. *HNF1A* plays a key role in maturation of pancreatic islets, thus, patients with *HNF1A* loss-of-function variants have reduced beta-cell capacity from birth. Given its autosomal dominant inheritance, a single copy of mutant protein is sufficient to cause diabetes. Although Individuals with the same variant have close phenotype-genotype correlation, different variants can affect protein structure and function with phenotypic heterogeneity among MODY patients [4, 6]. Furthermore, the background polygenic risk for T2D lowered the age at diagnosis of diabetes, suggesting that common variants may amplify the effects of rare variants [17]. Using a panel of 256 causal variants for T2D discovered and validated in East Asians [6, 18], the 3 affected members showed varied combinations of these variants, reflecting different polygenic risks. Differences in body weight, smoking status, and physical activity also influenced their age at diagnosis, disease duration, and complication risk.

HNF1A-MODY patients are highly sensitive to sulfonylureas. *HNF1A* pathogenic variants impair beta-cell function through various mechanisms [19]. Accurate diagnosis enables precision treatment, often allowing patients to stop insulin or switch therapies. However, sulfonylurea use has declined in Asia due to hypoglycemia risk and newer drug options. Delayed diagnosis and inappropriate treatment can worsen glucotoxicity and lead to insulin dependence.

In our *HNF1A*-MODY family, the index patient was treated with metformin and DPP4i with suboptimal control. In a randomized controlled trial, researchers had reported more time spent in

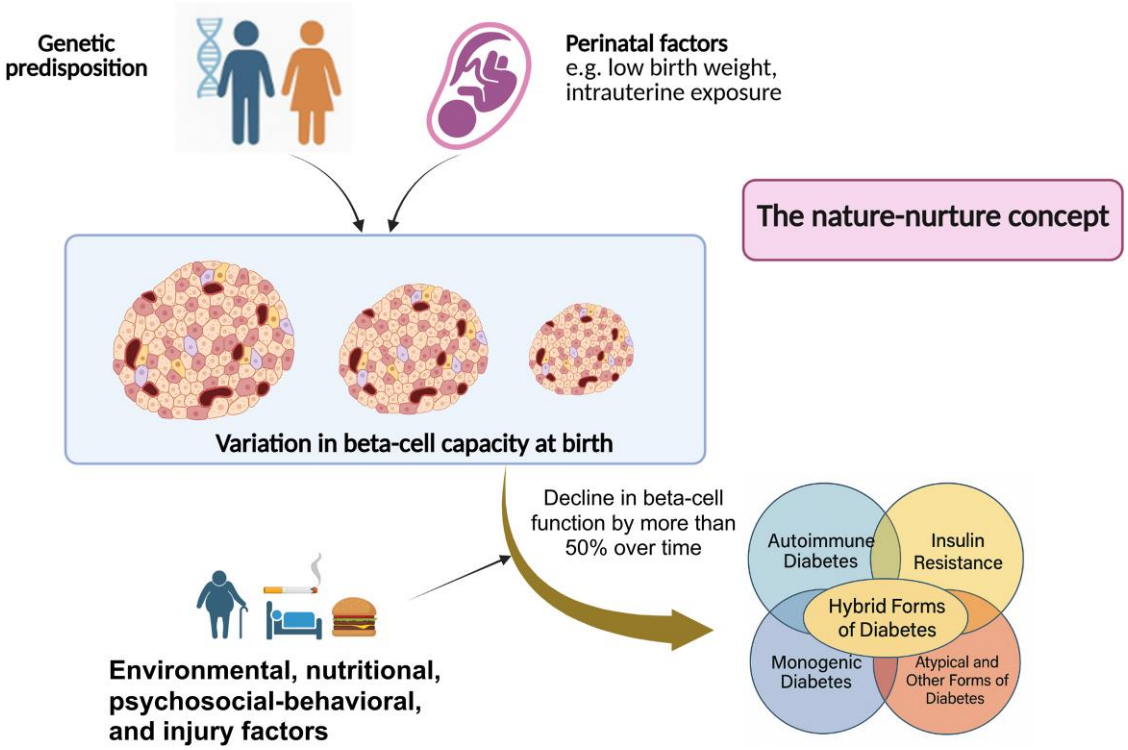


Figure 3 The nature-nurture concept—different beta-cell capacity at birth determined by ancestral or genetic and perinatal factors can interact with stressors during a life course giving rise to different trajectories of age-related decline in beta-cell function. For the same trajectory, individuals with different beta-cell capacity may have different ages at diagnosis of diabetes.

normoglycemia, higher postprandial C-peptide, lower glucagon level and postprandial blood glucose in patients with *HNF1A*-MODY treated with sulfonylurea plus DPP4i vs sulfonylurea only [20]. In our index patient, due to albuminuria, we added SGLT2i with improved A1C. Glucagon-like peptide-1 receptor agonists (GLP-1 RA) and SGLT2i have been used in patients with *HNF1A*-MODY with sustained glycemic control and without adverse events [21, 22].

The risk of complications in *HNF1A*-MODY is comparable to that in T1D and T2D [23]. The risk in *HNF1A*-MODY is strongly driven by glycemic exposure and diabetes duration. Given the legacy effect of glucose control on long-term outcomes, optimizing glycemic management from the outset remains essential [24]. In a propensity score matched cohort analysis including patients treated with metformin and sulfonylurea, the addition of DPP4i before A1C increased to 7.5% was associated with delayed insulin requirement and reduced risk of severe hypoglycemia, cardiovascular-kidney complications and all-cause death [25]. In the case of *HNF1A*-MODY, early diagnosis with use of sulfonylureas can transform the clinical course of the patient and his/her family members, analogous to the cascade screening with familial hypercholesterolemia for prevention of premature atherosclerosis and cardiovascular disease [26].

The concept of hybrid forms of diabetes, where insulin resistance coexists with autoimmune or monogenic diabetes, is increasingly recognized, especially in patients with young age at diagnosis. The distribution of genetic codes from both parents is random at birth with their expression subject to intrauterine exposure, perinatal events, and early pubertal development. Thus, each individual may be endowed with different organ capacities, including islets. Life course events including environmental, behavioral, nutritional, and injury factors can accelerate the age-related beta-cell loss, which accelerates once hyperglycemia sets in, yet this is modifiable by early diagnosis and intensive treatment. Depending on their beta-cell capacity, for the same trajectory, different individuals may have different thresholds for external stressors, such as obesity [27] and thus different age at diagnosis. This nature-nurture concept is particularly relevant to monogenic diabetes, given the marked reduction in beta-cell capacity from birth [15] (Fig. 3).

In conclusion, this *HNF1A*-MODY family highlights the phenotypic heterogeneity driven by interactions between genetic variants and modifiable risk factors. Advances in sequencing technology and therapeutics underscore the need for clinicians to apply this knowledge for early diagnosis and personalized care.

Learning points

- Genetic testing should be conducted to diagnose MODY especially in young patients with residual beta-cell function and positive family history to improve the precision of diagnosis and therapy, followed by cascade screening to ensure proper diagnosis of family members.
- Apart from single nucleotide variants, sequencing and bioinformatic analysis is needed to detect copy number variations (CNV), including partial or whole gene deletions that account for a small proportion of all variants in MODY genes.
- In families affected by MODY or monogenic diabetes, polygenic risk scores may serve as an additional tool to help

explain the phenotypic heterogeneity among family members carrying the same MODY variant.
- The interactions among common and rare variants along with other clinical risk factors (eg, obesity, age, and insulin resistance) in MODY families call for individualized treatment to attain multiple treatment targets and improve clinical outcomes.

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Contributors

All authors made individual contributions to authorship. W.C. and Y.T. were involved in the diagnosis and management of the index case. S.N. contributed to graphic preparation. C.L. performed the genetic testing. Y.T, T.H., and J.C. contributed to the discussions. All authors reviewed and approved the final draft.

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Informed patient consent for publication

Signed informed consent was obtained directly from the patient.

Data availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the present study.

References

1. Bonnefond A, Unnikrishnan R, Doria A, *et al.* Monogenic diabetes. *Nat Rev Dis Primers*. 2023;9(1):12.
2. Shepherd M, Shields B, Ellard S, Rubio-Cabezas O, Hattersley AT. A genetic diagnosis of HNF1A diabetes alters treatment and improves glycaemic control in the majority of insulin-treated patients. *Diabet Med*. 2009;26(4):437-441.
3. Valkovicova T, Skopkova M, Stanik J, Gasperikova D. Novel insights into genetics and clinics of HNF1A-MODY. *Endocr Regul*. 2019;53(2):110-134.
4. Ludwig-Słomczyńska AH, Seweryn MT, Radkowski P, *et al.* Variants influencing age at diagnosis of HNF1A-MODY. *Mol Med*. 2022;28(1):113.
5. Thewjitcharoen Y, Wanothayaroj E, Krittiyawong S, *et al.* Phenotypic and genetic heterogeneity in a Thai glucokinase MODY family reveals the complexity of young-onset diabetes. *Front Endocrinol (Lausanne)*. 2021;12:690343.
6. Yu G, Tam CHT, Lim CKP, *et al.* Type 2 diabetes pathway-specific polygenic risk scores elucidate heterogeneity in clinical presentation, disease progression and diabetic complications in 18,217 Chinese individuals with type 2 diabetes. *Diabetologia*. 2025;68(3):602-614.
7. O CK, Fan YN, Fan B, *et al.* Precision medicine to redefine insulin secretion and monogenic diabetes-randomized controlled trial (PRISM-RCT) in Chinese patients with young-onset diabetes: design, methods and baseline characteristics. *BMJ Open Diabetes Res Care*. 2024;12(3):e004120.
8. Murray Leech J, Beaumont RN, Arni AM, *et al.* Common genetic variants modify disease risk and clinical presentation in monogenic diabetes. *Nat Metab*. Published online September 9, 2025. Doi:10.1038/s42255-025-01372-0
9. Tsoi STF, Lim C, Ma RCW, *et al.* Monogenic diabetes in a Chinese population with young-onset diabetes: a 17-year prospective follow-up study in Hong Kong. *Diabetes Metab Res Rev*. 2024;40(5):e3823.
10. Richards S, Aziz N, Bale S, *et al.* Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17(5):405-424.
11. Khera AV, Chaffin M, Aragam KG, *et al.* Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat Genet*. 2018;50(9):1219-1224.
12. Zhang Y, Luk AOY, Chow E, *et al.* High risk of conversion to diabetes in first-degree relatives of individuals with young-onset type 2 diabetes: a 12-year follow-up analysis. *Diabet Med*. 2017;34(12):1701-1709.
13. Plengvidhya N, Boonyasrisawat W, Chongjaroen N, *et al.* Mutations of maturity-onset diabetes of the young (MODY) genes in Thais with early-onset type 2 diabetes mellitus. *Clin Endocrinol (Oxf)*. 2009;70(6):847-853.
14. Plengvidhya N, Tangjittipokin W, Teerawattanapong N, Narkdontri T, Yenchitsomanus PT. HNF1A mutation in a Thai patient with maturity-onset diabetes of the young: a case report. *World J Diabetes*. 2019;10(7):414-420.
15. Chan JCN, Chow E, Kong A, *et al.* Multifaceted nature of young-onset diabetes - can genomic medicine improve the precision of diagnosis and management? *J Transl Genet Genom*. 2024;8(1):13-34.
16. Lau HH, Ng NHJ, Loo LSW, Jasmen JB, Teo AKK. The molecular functions of hepatocyte nuclear factors - in and beyond the liver. *J Hepatol*. 2018;68(5):1033-1048.
17. Kettunen JLT, Rantala E, Dwivedi OP, *et al.* A multigenerational study on phenotypic consequences of the most

common causal variant of HNF1A-MODY. *Diabetologia*. 2022; 65(4):632-643.
18. Spracklen CN, Horikoshi M, Kim YJ, *et al.* Identification of type 2 diabetes loci in 433,540 East Asian individuals. *Nature*. 2020;582(7811):240-245.
19. Miyachi Y, Miyazawa T, Ogawa Y. HNF1A mutations and beta cell dysfunction in diabetes. *Int J Mol Sci*. 2022;23(6):3222.
20. Christensen AS, Hædersdal S, Støy J, *et al.* Efficacy and safety of glimepiride with or without linagliptin treatment in patients with HNF1A diabetes (maturity-onset diabetes of the young type 3): a randomized, double-blinded, placebo-controlled, crossover trial (GLIMLINA). *Diabetes Care*. 2020;43(9):2025-2033.
21. Müssig K. Novel treatment options in patients with maturity-onset diabetes of the young. *Exp Clin Endocrinol Diabetes*. 2025;133(01):51-58.
22. Hohendorff J, Szopa M, Skupien J, *et al.* A single dose of dapagliflozin, an SGLT-2 inhibitor, induces higher glycosuria in GCK- and HNF1A-MODY than in type 2 diabetes mellitus. *Endocrine*. 2017;57(2):272-279.
23. Bhattacharya S, Fernandez CJ, Kamrul-Hasan ABM, Pappachan JM. Monogenic diabetes: an evidence-based clinical approach. *World J Diabetes*. 2025;16(5):1047-1055.
24. Khunti K, Zaccardi F, Amod A, *et al.* Glycaemic control is still central in the hierarchy of priorities in type 2 diabetes management. *Diabetologia*. 2025;68(1):17-28.
25. Cheung JTK, Yang A, Wu H, *et al.* Association of dipeptidyl peptidase-4 inhibitor initiation at glycated haemoglobin<7.5% with reduced major clinical events mediated by low glycated haemoglobin variability. *Diabetes Obes Metab*. 2024;26(8):3339-3351.
26. Ned RM, Sijbrands EJ. Cascade screening for familial hypercholesterolemia (FH). *PLoS Curr*. 2011;3:RRN1238.
27. O CK, Chan JCN. Insights into optimal BMI from the GlasVEGAS study. *Nat Metab*. 2024;6(8):1435-1437.