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Hypertriglyceridemia as a main feature associated with 17q12 deletion syndrome-related hepatocyte nuclear factor 1β-maturity-onset diabetes of the young

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Summary

Hepatocyte nuclear factor 1β (*HNF1B*) gene is located on chromosome 17q12. It is a transcription factor implicated in the early embryonic development of multiple organs. *HNF1B*-associated disease is a multi-system disorder with variable clinical phenotypes. There are increasing reports suggesting that the 17q12 deletion syndrome should be suspected in patients with maturity-onset diabetes of the young type 5 (MODY5) due to the deletion of *HNF1B* gene. In contrast to classical 17q12 syndrome in childhood with neurological disorders and autism, patients with *HNF1B*-MODY deletion rarely had neuropsychological disorders or learning disabilities. The diagnosis of 17q12 deletion syndrome highlighted the phenotypic heterogeneity of *HNF1B*-MODY patients. In this study, we report the clinical course of a Thai woman with young-onset diabetes mellitus and hypertriglyceridemia as a predominant feature due to *HNF1B* deletion as part of the 17q12 deletion syndrome. Our findings and others suggest that hypertriglyceridemia should be considered a syndromic feature of *HNF1B*-MODY. Our case also highlights the need to use sequencing with dosage analyses to detect point mutations and copy number variations to avoid missing a whole deletion of *HNF1B*.

Learning points:

- Maturity-onset diabetes of the young type 5 (MODY5) may be caused by heterozygous point mutations or whole gene deletion of *HNF1B*. Recent studies revealed that complete deletion of the *HNF1B* gene may be part of the 17q12 deletion syndrome with multi-system involvement.
- The length of the deletion can contribute to the phenotypic variability in patients with *HNF1B*-MODY due to whole gene deletion.
- Using next-generation sequencing alone to diagnose MODY could miss a whole gene deletion or copy number variations. Specialized detection methods such as microarray analysis or low-pass whole genome sequencing are required to accurately diagnose *HNF1B*-MODY as a component of the 17q12 deletion syndrome.
- Molecular diagnosis is necessary to distinguish other acquired cystic kidney diseases in patients with type 2 diabetes which could phenocopy *HNF1B*-MODY.
- Hypertriglyceridemia is a possible metabolic feature in patients with *HNF1B*-MODY due to 17q12 deletion syndrome.

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Background

Maturity-onset diabetes of the young (MODY) is often misdiagnosed as type 1 (T1D) or type 2 diabetes (T2D) resulting in patients with mutations in actionable MODY genes receiving inappropriate treatments. Hepatocyte nuclear factor 1β (*HNF1B*)-MODY or MODY5 is a multisystem disorder. It is one of the less common subtypes of MODY accounting for less than 5% of confirmed cases (1). In 1997, a heterozygous pathogenic mutation in *HNF1B* was first described as a cause of *HNF1B*-MODY in one Japanese family (2). Subsequently, other point mutations in the *HNF1B* gene were detected in patients with the 'Renal Cysts And Diabetes' syndrome (RCAD, OMIM 137920) (3). Other reports had described syndromic features including extra-pancreatic manifestations involving the liver and genital tract in addition to congenital anomalies of the kidneys and urinary tract where *HNF1B* is expressed (4). With advanced sequencing technology and bioinformatics analysis, there are increasing number of reports of *HNF1B*-MODY due to whole gene deletion as part of the 17q12 deletion syndrome. To this end, heterozygous deletions of chromosome 17q12 involving at least 15 genes including *HNF1B* are now recognized as a distinct entity (5).

Among individuals with *HNF1B*-MODY, dyslipidemia has been rarely reported. In a register of patients with atypical diabetes, eight of nine carriers with *HNF1B* point mutations or deletions had hypertriglyceridemia (6). Herein, we report a sporadic case of *HNF1B*-MODY related to the 17q12 deletion syndrome associated with hypertriglyceridemia. Our case also highlights the need to use sequencing with dosage analyses to detect both point mutations and structural variations in order not to miss a diagnosis of *HNF1B*-MODY due to whole gene deletion.

Case presentation

A 35-year-old Thai woman diagnosed with early onset non-autoimmune diabetes mellitus returned to our diabetes clinic after default for 2 years. At the age of 30 years, she was diagnosed with T2D based on 75-g oral glucose tolerance test (OGTT) at our hospital due to high fasting plasma glucose during annual medical check-up. At that time, she was asymptomatic and her BMI was 21.4 kg/m^2. The post-load plasma glucose was 219 mg/dL (12.2 mmol/L) and glycated hemoglobin (HbA1c) was 6.3% (43 mmol/mol). Fasting lipid profiles showed isolated hypertriglyceridemia (plasma total cholesterol: 233 mg/dL; 6.0 mmol/L, plasma triglyceride: 598 mg/dL; 6.8 mmol/L, plasma HDL-C: 44 mg/dL; 1.1 mmol/L, and plasma LDL-C: 110 mg/dL; 2.9 mmol/L). Oral metformin of 1000 mg/day and gemfibrozil of 300 mg/day were given with regular follow-up for 2 years. She then got pregnant for the second time and all medications were stopped. Throughout her pregnancy, she had good glycemic control treated with diet alone. She gave birth to a healthy boy with a birth weight of 3980 g. There was no perinatal complication and she defaulted follow up after delivery.

When she returned to our clinic at the age of 35, she remained well and was not on any medication. Detailed history taking revealed normal childhood development without learning difficulty and she completed her bachelor's degree education. Menarche occurred at the age of 11 without menstrual problems. She was diagnosed to have atrophic left kidney during an ultrasonographic study at the age of 12 as a part of urinary tract infection investigations. Her renal function remained normal. At the age of 31, she had her first pregnancy with spontaneous abortion requiring curettage at the gestational age of 8 weeks. She had no history of steatorrhea or abdominal discomfort. She neither smoke nor drink alcohol. Her height was 170 cm and her weight was 62.2 kg with a BMI of 21.3 kg/m^2. Clinical examination did not reveal any dysmorphic features and she did not have xanthomas, lipemia retinalis, or neurological deficits. She had no known family history of lipid disorders or premature cardiovascular disease or death. Diabetes mellitus was present on the paternal side (Fig. 1). Her father (present age of 63 years) was diagnosed to have T2D at the age of 39 during the medical check-up. He was overweight (BMI: 25.6 kg/m^2) with hypertension and hypercholesterolemia but did not have hypertriglyceridemia. He received multiple oral glucose-lowering drugs with HbA1c level of 6.0–6.9% (42–52 mmol/mol). At the age of 55 years, he had a routine ultrasound scan and was found to have a 2.2-cm hemangioma in the right hepatic lobe and a 5.4-cm simple cyst in the right renal cortex.

During the 2 years of medical default, she occasionally checked her glycemic and lipid control at a nearby hospital. Her HbA1c level varied from 5.8–6.8% (40–51 mmol/mol) without any medications, but her plasma triglyceride level remained high at 264 mg/dL (3.0 mmol/L). Figure 2 summarizes the clinical course and laboratory data from the time of diagnosis of diabetes to when she returned for medical consultation. She had variable hypertriglyceridemia with a range of 180–598 mg/dL (2.0–6.8 mmol/L) but consistently normal plasma LDL-C levels. Given the patient's young-onset diabetes, left renal atrophy, and paternal history of diabetes, the possibility of *HNF1B*-MODY or other subtypes of MODY was suspected.

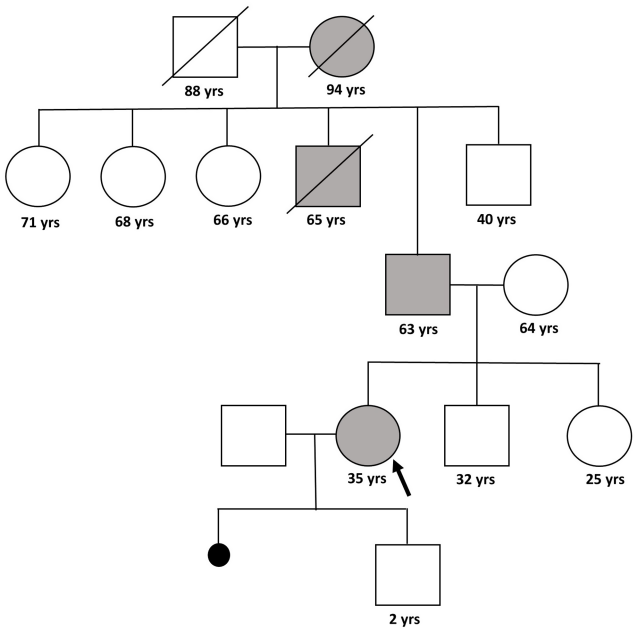

Figure 1
A family pedigree of the index patient. Squares, circles, and arrows indicate males, females, and the patient, respectively. Gray color indicates the presence of diabetes mellitus.

Investigation

Next-generation sequencing (NGS) panel for monogenic diabetes including 34 monogenic diabetes-related genes (Table 1 and Supplementary material, see section on supplementary materials given at the end of this article) and a mitochondrial mutation for maternally inherited deafness and diabetes (MIDD, mt A3243G) (GemVCare, Shatin, Hong Kong) revealed negative results in both patient and her father. However, heterozygous deletion of exons 1–9 of *HNF1B* gene was detected using multiplex ligation-dependent probe amplification (MLPA) in the patient. Further MLPA testing for *HNF1B* in her parents, her younger siblings, and her son showed no deletion of *HNF1B*. Therefore, a diagnosis of *de novo* deletion of *HNF1B* was made in this patient. Since most whole-gene deletions of *HNF1B* gene formed part of the 17q12 deletion syndrome, we performed low-pass whole genome sequencing (performed by the Department of Obstetrics and Gynecology, The Chinese University of Hong Kong) to detect copy number variants (CNVs). The sequencing analysis identified the loss of a copy of chromosome band 17q12 of approximately 1.6 Mb, encompassing 34 genes (first gene: TBC1D3L exons 1–2; last gene: LOC101929950 exons 2–6). No other pathogenic CNVs were detected.

Whole exome sequencing was performed to detect mutations of other candidate genes for triglyceride-related disorders but yielded no mutations. Based on reports of 17q12 deletion syndrome, we performed additional laboratory investigations (Table 1). We found hypomagnesemia due to renal loss of magnesium, mild hyperuricemia, and vitamin D insufficiency. Thyroid function tests and serum intact parathyroid hormone levels were normal. Assessment of beta-cell function by OGTT showed peak stimulated plasma C-peptide level at 2.3 ng/mL (0.8 nmol/L) and negative islet autoantibodies (anti-glutamic acid decarboxylase and anti-tyrosine phosphatase-related islet antigen 2). The OGTT-derived hepatic insulin resistance index (HIRI) calculated as the area under the curve of fasting plasma insulin and glucose levels between 0 and 30 min after OGTT (7) indicated hepatic insulin resistance (HIRI: 4.3, normal < 2.0). CT scan of the abdomen and pelvis showed Riedel's lobe of the liver (a normal anatomical variant referring to a tongue-like projection extending caudally from the right lobe of liver), hypoplasia of the body and tail of the pancreas, and atrophic dysplastic left kidney (Fig. 3). No abnormalities of genitourinary system were found.

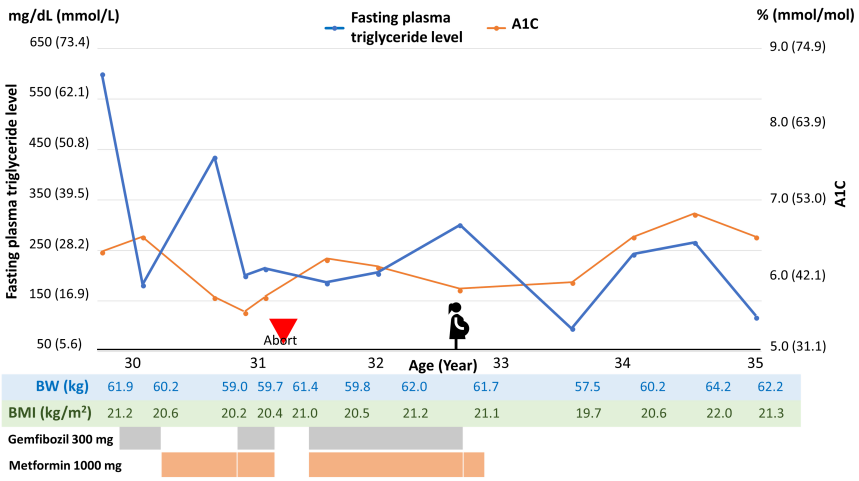

Figure 2
The clinical course and laboratory data of the patient from the diagnosis of diabetes mellitus to the time when *HNF1B*-MODY was confirmed by genetic testing.

Table 1 Laboratory investigations of the index patient with HNF1B-MODY related to 17q12 deletion syndrome.

Parameters	Normal values	Results
BUN		
mg/dL	6–20	10
mmol/L	2.1–7.1	3.6
Creatinine		
mg/dL	0.5–1.0	0.7
µmol/L	44.2–88.4	61.9
Sodium (mEq/L)	136–145	141
Potassium (mEq/L)	3.5–5.1	4.2
Chloride (mEq/L)	98–107	100
Bicarbonate (mEq/L)	22–29	26
AST (U/L)	0–32	24
ALT (U/L)	0–33	22
ALP (U/L)	35–104	77
Total bilirubin		
mg/dL	0–1.2	0.6
µmol/L	0–20.5	10.3
Direct bilirubin		
mg/dL	0–0.3	0.2
µmol/L	0–5.1	3.4
Amylase (U/L)	40–140	59
Lipase (U/L)	13–60	54
Calcium		
mg/dL	8.6–10.0	9.1
mmol/L	2.2–2.5	2.3
Phosphate		
mg/dL	2.5–4.5	4.2
mmol/L	0.8–1.5	1.4
Magnesium		
mg/dL	1.6–2.6	1.1
mmol/L	0.7–1.1	0.5
Uric acid		
mg/dL	2.4–5.7	6.3
mmol/L	143–339	374
25-OH vitamin D		
ng/dL	≥30	18
nmol/L	≥75	45
Intact PTH		
pg/dL	15–65	40
ng/L	15–65	40
FE calcium (%)	0–0.13	0.01
FE phosphate (%)	0–16	12.3
FE magnesium (%)	2–4	8.8
FE uric acid (%)	5–9	7.6
Fasting plasma glucose		
mg/dL	<100	110
mmol/L	<5.6	6.1
Fasting plasma insulin		
µIU/mL	2.6–24.9	8.5
pmol/L	18.7–178.7	61.0
Post-load OGTT		
Plasma glucose at 30 min		
mg/dL	<200	234
mmol/L	<11.1	13.0

AST, aspartate aminotransferase; ALT, alanine aminotransferase; FE, fractional excretion; HOMA-IR, homeostatic model assessment for insulin resistance; OGTT, oral glucose tolerance test.

Treatment

Her glycemic control was satisfactory with HbA1c level <6.5% (48 mmol/mol) on diet alone. She was prescribed fenofibrate for her hypertriglyceridemia and given vitamin D2 supplementation 60 000 units per week to correct her vitamin D deficiency. The patient was advised to maintain her body weight and healthy lifestyle with regular assessment and medical review to detect silent deterioration of cardiometabolic risk factors and complications.

Outcome and follow-up

During her last follow-up visit, 1 year after the diagnosis of *HNF1B* deletion syndrome, her HbA1c was 6.2% (44 mmol/mol) and plasma triglyceride level was 167 mg/dL (1.9 mmol/L) while on diet alone. She maintained her body weight at 62 kg. Plasma magnesium level was still low at 1.2 mg/dL (0.5 mmol/L), but she had no symptoms. Her liver function and glomerular filtration rate remained normal.

Discussion

Our report highlights the importance of proper genetic testing in patients suspected to have MODY. The 17q12 deletion syndrome is often detected in patients with complete *HNF1B* gene deletion. Although *HNF1B* is implicated in embryonic organ development, most patients with point mutations or deletions of *HNF1B* did not have dysmorphic features or neuropsychological disorders. Our patient had hypertriglyceridemia in the absence of poor glycemic control or obesity suggesting that hypertriglyceridemia might be a feature of the contiguous gene deletion syndrome or *HNF1B*-related functional defect. Interestingly, despite a history of young-onset diabetes on the paternal pedigree, her father did not have point mutation or deletion of *HNF1B*.

In a multicenter cohort involving 201 patients with mutations or deletions of *HNF1B*-MODY, half of them were *de novo* (1). Therefore, the absence of family history of renal disease or diabetes did not exclude the possibility of *HNF1B*-MODY. In the latest series of 1280 patients suspected to have MODY, m.3243A>G and *HNF1B* were among the top mutations with or without syndromic features (8). Given the many genes implicated in the 17q12 deletion syndrome, *HNF1B*-MODY due to deletions may have complex clinical presentation. However, compared with children diagnosed with 17q12 deletion syndrome, dysmorphic features (high forehead, high arched eyebrows, and long face) and neurodevelopmental disorders were rare

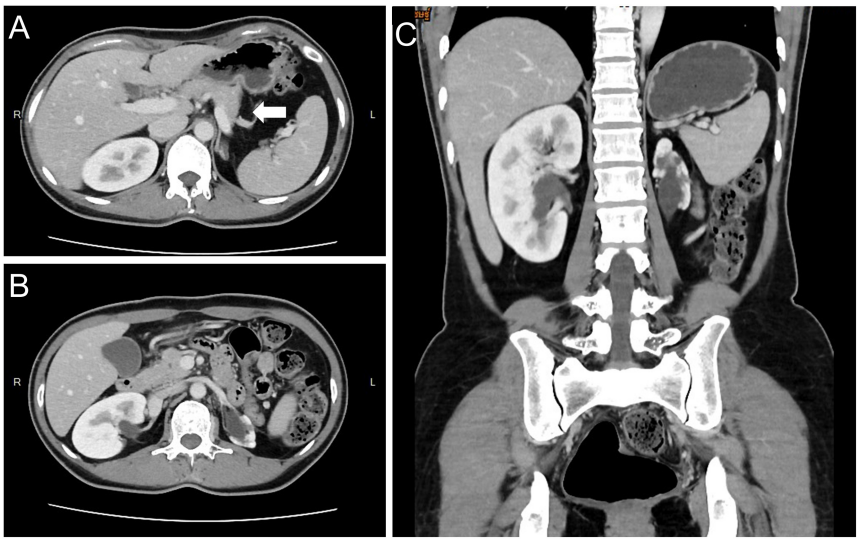

Figure 3
Abdominal contrast-enhanced CT showing (A) hypoplasia of body and tail of pancreas (arrow) with slightly atrophic pancreatic head (B and C) severe hypoplasia of left kidney in the index patient with *HNF1B*-MODY.

in young adults with *HNF1B*-MODY as part of the 17q12 deletion syndrome (5).

Classically, *HNF1B*-MODY was suspected in patients with familial young-onset diabetes in the presence of kidney abnormalities although there is a diversity of extra-pancreatic and extra-renal manifestations. In most of the cohorts of *HNF1B*-MODY, lipid profiles have not been systematically evaluated. In a pediatric case series, dyslipidemia has emerged as an important clinical feature of *HNF1B*-MODY (6). This metabolic abnormality could be attributable to the deletion of genes implicated in lipid metabolism in the 17q12 region or unexplored roles of *HNF1B* in lipid metabolism. Rare variants or CNVs disrupting triglyceride metabolic pathway had been reported in individuals with mild-to-moderate hypertriglyceridemia (9). There are close relationships between lipid and glucose metabolism where reduced insulin sensitivity and/or insulin secretion can lead to non-suppression of hepatic triglyceride synthesis with increased secretion of triglyceride-rich very low-density lipoproteins manifest as high plasma triglyceride levels. Hepatic insulin resistance is a common feature in *HNF1B*-MODY although this may be confounded by glycemic control and insulin status. In our patient, serum triglyceride was disproportionately high given her good glycemic control and normal body weight. More studies are needed to explore the roles of *HNF1B* or contiguous genes in the 17q12 region and their interactions with common genetic variants in the regulation of lipid metabolism.

Pediatric patients with *HNF1B*-MODY often have insulin secretion defects and insulin resistance (4). In these young individuals, the detection of renal abnormalities usually pre-date the diagnosis of diabetes with a mean age of 24 years, ranging from the neonatal period to late middle age. By the time diabetes was diagnosed, many patients had significant loss of beta-cell function with many of them requiring insulin therapy soon after the diagnosis (4). Our patient with *HNF1B*-MODY had an atypical clinical course with preserved endogenous insulin secretion 5 years after the diagnosis of diabetes. However, close monitoring is required to detect glycemic deterioration for the early start of glucose-lowering medications.

Diagnosing *HNF1B*-MODY related to 17q12 deletion syndrome in a clinic setting can be challenging requiring sequencing and special methods to detect heterozygous gene deletions. We used low-pass whole genome sequencing to detect CNVs and microdeletions in our patient. This method offers advantages over chromosomal microarray analysis with increased sensitivity and accuracy. Using low-pass whole genome sequencing to detect CNVs is now the preferred technology which is offered as a high-resolution cytogenetic tool for prenatal diagnostic testing (10). Identification of the precise localization of the breakpoints is necessary to ascertain the deleted genes and gene networks for the evaluation of genotype–phenotype associations.

In conclusion, our patient illustrates the importance of diagnosing *HNF1B*-MODY as part of the 17q12 deletion syndrome. In addition to pancreatic and renal manifestations, hypertriglyceridemia might be an important feature of this syndrome. Clinical acumen, detailed phenotyping, and molecular analysis are needed in patients with atypical or syndromic diabetes for personalized management and genetic counseling.

Supplementary materials
This is linked to the online version of the paper at https://doi.org/10.1530/EDM-22-0297.

Declaration of interest

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Patient consent

Written informed consent for publication of the clinical details and/or clinical images was obtained from the patient.

Author contribution statement

Y Thewjitcharoen wrote the first draft of the article. He was also the attending endocrinologist of the patient for investigation, review and treatment. S Nakasatien was responsible for collecting data from the patient and her family. C L and T T were responsible for genetic examination analysis. All authors contributed to the editing process and approved the submitted version. The authors are extremely grateful for the collaboration of the patient and her families. Dr Veekij Veerasomboonsin provided expert opinion on all radiological investigations. We also acknowledge the proofreading and editing by Dr Tinapa Himathongkam.

References

1 Dubois-Laforgue D, Cornu E, Saint-Martin C, Coste J, Bellanné-Chantelot C, Timsit J & Monogenic Diabetes Study Group of the Société Francophone du Diabète. Diabetes, associated clinical spectrum, long-term prognosis, and genotype/phenotype correlations in 201 adult patients with hepatocyte nuclear factor 1B (HNF1B) molecular defects. *Diabetes Care* 2017 **40** 1436–1443. (https://doi.org/10.2337/dc16-2462)

2 Horikawa Y, Iwasaki N, Hara M, Furuta H, Hinokio Y, Cockburn BN, Lindner T, Yamagata K, Ogata M, Tomonaga O, *et al.* Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. *Nature Genetics* 1997 **17** 384–385. (https://doi.org/10.1038/ng1297-384)

3 Bingham C, Bulman MP, Ellard S, Allen LI, Lipkin GW, Hoff WG, Woolf AS, Rizzoni G, Novelli G, Nicholls AJ, *et al.* Mutations in the hepatocyte nuclear factor-1beta gene are associated with familial hypoplastic glomerulocystic kidney disease. *American Journal of Human Genetics* 2001 **68** 219–224. (https://doi.org/10.1086/316945)

4 Raile K, Klopocki E, Holder M, Wessel T, Galler A, Deiss D, Müller D, Riebel T, Horn D, Maringa M, *et al.* Expanded clinical spectrum in hepatocyte nuclear factor 1b-maturity-onset diabetes of the young. *Journal of Clinical Endocrinology and Metabolism* 2009 **94** 2658–2664. (https://doi.org/10.1210/jc.2008-2189)

5 Roehlen N, Hilger H, Stock F, Gläser B, Guhl J, Schmitt-Graeff A, Seufert J & Laubner K. 17q12 deletion syndrome as a rare cause for diabetes mellitus type MODY5. *Journal of Clinical Endocrinology and Metabolism* 2018 **103** 3601–3610. (https://doi.org/10.1210/jc.2018-00955)

6 Craven ME, Bamba V, Calabria AC & Inney SE. 16-OR: endocrine manifestations of pediatric HNF1B-MODY (MODY 5). *Diabetes* 2021 **70** (Supplement 1) 16. (https://doi.org/10.2337/db21-16-OR)

7 Abdul-Ghani MA, Matsuda M, Balas B & DeFronzo RA. Muscle and liver insulin resistance indexes derived from the oral glucose tolerance test. *Diabetes Care* 2007 **30** 89–94. (https://doi.org/10.2337/dc06-1519)

8 Colclough K, Ellard S, Hattersley A & Patel K. Syndromic monogenic diabetes genes should be tested in patients with a clinical suspicion of maturity-onset diabetes of the young. *Diabetes* 2022 **71** 530–537. (https://doi.org/10.2337/db21-0517)

9 Dron JS, Wang J, McIntyre AD, Cao H & Hegele RA. The polygenic nature of mild-to-moderate hypertriglyceridemia. *Journal of Clinical Lipidology* 2020 **14** 28.e2–34.e2. (https://doi.org/10.1016/j.jacl.2020.01.003)

10 Chau MHK, Wang H, Lai Y, Zhang Y, Xu F, Tang Y, Wang Y, Chen Z, Leung TY, Chung JPW, *et al.* Low-pass genome sequencing: a validated method in clinical cytogenetics. *Human Genetics* 2020 **139** 1403–1415. (https://doi.org/10.1007/s00439-020-02185-9)

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