



# Genetics and Pathophysiology of Maturity-onset Diabetes of the Young (MODY): A Review of Current Trends

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## ARTICLE INFO

### Article history:

Received: 8 December 2018

Accepted: 4 February 2019

### Online:

DOI 10.5001/omj.2020.44

### Keywords:

Diabetes Mellitus; Genes; Hyperglycemia; Insulin; Mutation.

## ABSTRACT

Single gene mutations have been implicated in the pathogenesis of a form of diabetes mellitus (DM) known as the maturity-onset diabetes of the young (MODY). However, there are diverse opinions on the suspect genes and pathophysiology, necessitating the need to review and communicate the genes to raise public awareness. We used the Google search engine to retrieve relevant information from reputable sources such as PubMed and Google Scholar. We identified 14 classified MODY genes as well as three new and unclassified genes linked with MODY. These genes are fundamentally embedded in the beta cells, the most common of which are HNF1A, HNF4A, HNF1B, and GCK genes. Mutations in these genes cause  $\beta$ -cell dysfunction, resulting in decreased insulin production and hyperglycemia. MODY genes have distinct mechanisms of action and phenotypic presentations compared with type 1 and type 2 DM and other forms of DM. Healthcare professionals are therefore advised to formulate drugs and treatment based on the causal genes rather than the current generalized treatment for all types of DM. This will increase the effectiveness of diabetes drugs and treatment and reduce the burden of the disease.

Maturity-onset diabetes of the young (MODY) is a monogenic and non-autoimmune form of diabetes mellitus (DM) with characteristic pancreatic  $\beta$ -cell destruction and disrupted insulin biosynthesis.<sup>1,2</sup> The disease usually appears between the teen ages and early adulthood, < 25 years.<sup>3,4</sup> MODY was discovered by Robert Tattersall in 1974 as a distinct form of DM after discovering young non-insulin dependent diabetic individuals two-years post-diagnosis.<sup>5,6</sup> The condition was later named MODY by Fajans Stefan after a series of studies.<sup>5,6</sup> However, this classification may be confusing due to the similar pathophysiology of MODY and type 2 DM (T2DM). Many physicians and researchers often considered and misdiagnosed MODY as a subset of T2DM.<sup>7</sup> It was estimated that at least 90% of MODY diabetics are misdiagnosed as having T2DM due to lack of awareness on the differences between the two.<sup>2,8,9</sup> Some distinct characteristics of MODY include less significant weight gain, the absence of pancreatic autoantibodies, and lack of insulin resistance or

elevated fasting glucose.<sup>10</sup> However, these symptoms are often unrecognized due to the low incidence of MODY, which is estimated to account for 1–5% of DM cases.<sup>11–13</sup>

MODY genes disrupt insulin production processes, culminating in hyperglycemia, which with time, may damage organs such as eyes, kidneys, nerves, and blood vessels.<sup>14</sup> The phenotypic expressions of MODY depend on the causal gene. Individuals with certain types of mutations may show a slightly raised blood sugar for life with mild or no symptoms of DM.<sup>14</sup> These individuals may not also develop long-term complications, and their high blood glucose levels may only be discovered during routine blood tests.<sup>14</sup> People with other mutation types require specific treatment with either insulin or a type of oral DM medication called sulfonylureas.<sup>14</sup> In the past, people with MODY had generally not been overweight or obese, or have other risk factors for T2DM, such as high blood pressure or abnormal blood fat levels.<sup>14</sup> However, as more people become overweight or obese, especially in the US, people with MODY may also be overweight or obese.<sup>14</sup> Although

both T2DM and MODY can have a family history, such inheritance is autosomal dominant in MODY, meaning that, it does not skip any generation.<sup>14</sup>

DM is a major public health problem worldwide.<sup>15,16</sup> The number of people with DM has quadrupled in the past three decades.<sup>17</sup> DM is now the ninth primary cause of death, accounting for about 1 in 11 adults with DM.<sup>17</sup> In 2019, about 463 million people were diagnosed with DM and this number was projected to reach 578 million by 2030, and 700 million by 2045.<sup>18</sup> More information and awareness are needed to contain the disease effectively. To this end, this study was conceived to provide current information on the already identified MODY genes with their mechanism of actions and phenotypic presentations. This will enable healthcare providers to formulate effective drugs and treatment methods for various forms of MODY.

### ***MODY genes***

We identified 14 classified MODY genes as well as three new and unclassified genes linked with MODY. The identities of these genes with various mechanisms of action and phenotypic features are presented in Table 1.

### ***Common MODY genes***

Using linkage analysis, restriction fragment length polymorphism, and DNA sequencing,<sup>6</sup> scientists have identified mutations in the hepatocyte nuclear factor 1-alpha (HNF1A), 4-alpha (HNF4A), 1-Beta (HNF1B), and glucokinase (GCK) genes as the most common cause of MODY.<sup>48</sup> Depending on the country, these genes account for over 80% of all MODY cases.<sup>49-51</sup>

### ***The HNF1A gene***

The HNF1A gene provides instructions for the synthesis of the HNF1A protein.<sup>52,53</sup> The protein plays a vital role in the development of beta cells and the expression of many genes embedded in the liver.<sup>52,53</sup> These roles enable the pancreas to produce insulin normally in childhood, which decreases as one ages.<sup>22</sup> Thus, mutations in this gene may lower the amount of insulin produced,<sup>22</sup> and have been implicated in the pathogenesis of MODY type 3 (MODY3).<sup>52,53</sup> MODY3 is the commonest form of MODY, accounting for about 70% of cases.<sup>52,53</sup>

Several single nucleotide polymorphisms (SNPs) have been identified in the HNF1A gene

of MODY patients, which could suggest the pathophysiology and possible treatment options. In a study, the coding and promoter regions of the HNF1A gene were screened for mutations in 34 unrelated Iranian patients with MODY. The study identified one novel missense mutation (C49G), two novel polymorphisms, and eight recently identified SNPs.<sup>22</sup> In another study, mutations identified in 356 unrelated MODY3 patients, including 118 novel mutations, were analyzed, and the correlation was drawn between the variants and age of onset of DM. Missense mutations were observed in 74% of cases, while 62% of patients had truncating mutations.<sup>54</sup> Most mutations (83%) were found in exons 1–6, wherein all three HNF1A isoforms are located and are thus affected.<sup>54</sup> The age of onset of DM was lower in patients with truncating mutations than in those with missense mutations.<sup>54</sup> It was also observed that the higher the number of HNF1A isoforms with missense mutations, the lower the age of diagnosis of DM in the patients.<sup>54</sup> These findings indicate that MODY3 patients may express variable clinical features depending on the type and location of the HNF1A mutations.<sup>54</sup> Aside from the liver and pancreas, HNF1A is embedded in the kidney, isolated islets, and intestines. So, the clinical presentations of individuals with HNF1A mutation may also depend on the tissues and its developmental stage.<sup>55,56</sup>

### ***The HNF4A gene***

The HNF4A gene codes for a transcription protein embedded in the liver.<sup>57,58</sup> The HNF4A gene regulates the expression of several liver-specific genes. Thus, some liver functions may be enabled or disabled, depending on the expression or otherwise of this gene.<sup>57,58</sup> In addition, HNF4A controls the expression of the HNF1A gene, which in turn regulates the expression of several important genes in the liver.<sup>57</sup> The HNF4A gene is also found in the pancreas, kidneys, and intestines and, together with transcription factors such as HNF1A and HNF1B, control gene expression in developing embryos.<sup>59,60</sup> Specifically, in the pancreatic beta cells, this group of transcription factors controls the expression of the insulin gene. These genes also regulate the expression of several other genes involved in insulin secretion, such as the genes that are involved in glucose transport and metabolism.<sup>59,61</sup> Considering these functions, mutations in the HNF4A gene would lead to several problems.

**Table 1:** Maturity-onset diabetes of the young (MODY) genes showing chromosomal location and pathophysiology.

Gene/function	Full name	Locus	MODY type	Pathophysiology
HNF4A/transcription factor	Hepatocyte nuclear factor-4 alpha	20q12	MODY 1	Causes progressive beta-cell dysfunction, leading to macrosomia and hyperinsulinemic hypoglycemia. <sup>8,19</sup>
GCK/glycolytic enzyme	Glucokinase	7p15	MODY 2	Disrupts glucose sensing, leading to hyperglycemia. <sup>20,21</sup>
HNF1A/transcription factor	Hepatocyte nuclear factor-1 alpha	12q24.31	MODY 3	Causes gradual beta-cell dysfunction, leading to reduced insulin production and progressive hyperglycemia. <sup>21,22</sup>
IPFI/PDX1/transcription factor	Insulin promoter factor /Pancreatic duodenal homeobox	13q27.92	MODY 4	Causes pancreatic agenesis, beta-cell developmental errors, and defective insulin secretion. <sup>23,24</sup>
HNF1B/transcription factor	Hepatocyte nuclear factor 1B	17q12	MODY 5	Results in dysfunctional pancreatic embryonic development, the formation of kidney cyst, and suppresses cytokine signaling. <sup>3,25,26</sup>
NEURODI/transcription factor	Neurogenic differentiation 1 factor	2q31.3	MODY 6	Impairs pancreatic morphogenesis and beta-cell differentiation. <sup>27,28</sup>
KLF11/transcription factor	Krüppel-like factor 11	2p25.1	MODY 7	Disrupts the activation of some insulin promoters. It also suppresses the expression of certain free radical scavengers such as catalase and superoxide dismutase, disrupting pancreatic beta-cell function. <sup>29,30</sup>
CEL/Lipase	Carboxyl ester lipase	9q34	MODY 8	Alters C-terminal sequencing. It can also disrupt exocrine and endocrine functioning of pancreas. <sup>6,31</sup>
PAX4/Transcription factor	Paired box 4	7q32.1	MODY 9	Truncates embryonic beta-cell development, inhibiting beta-cell differentiation. <sup>32,33</sup>
INS/Insulin synthesis	Insulin hormone	11p15.5	MODY 10	Causes molecular defects in the $\beta$ -cell and increases endoplasmic reticulum (ER) stress, resulting in the synthesis of structurally altered (pre) proinsulin molecules and low insulin biosynthesis. <sup>34,35</sup>
BLK/B-cell receptor signaling and development, stimula	B-lymphocyte kinase	8p23.1	MODY 11	Suppresses MIN6 B-cells, disrupting beta-cell functions. <sup>36,37</sup>
ABCC8/regulates insulin secretion	ATP binding cassette subfamily C member 8	11p15.1	MODY 12	Causes congenital hyperinsulinism, adversely affecting the biogenesis and insulin trafficking of $K_{ATP}$ channels. <sup>38,39</sup>
KCNJ11/regulates insulin secretion	Inward-rectifier potassium channel, subfamily J, member 11	11p15.1	MODY 13	Causes congenital hyperinsulinism, adversely affecting the biogenesis and insulin trafficking of $K_{ATP}$ channels. <sup>39,40</sup>
APPL1/regulates cell proliferation, cellular signaling pathways	Adaptor protein, Phosphotyrosine interacting with PH domain and Leucine Zipper 1	3p14.3	MODY 14	Starts off the beta-cell structural abnormality and gradual death, leading to developmental delay. It can also suppress the insulin-uptake regulatory role of AKT2. <sup>41,42</sup>
ISL-1/transcription factor, INS enhancer	ISL LIM homeobox 1	5q11	-	Interferes with the expression of several genes, including insulin gene, also causes poor islet differentiation and proliferation. <sup>43,44</sup>
RFX6/Regulatory factor (regulates the transcription factors involved in beta-cell maturation and function)	Regulatory factor X	6q22.1	-	Causes beta-cell dysfunction, leading to reduced insulin secretion and hyperglycemia. <sup>45,46</sup>
NK6-1/transcription factor	NK6 homeobox 1	4q21.23	-	Beta-cell dysfunction. <sup>47</sup>

Among the likely consequence of mutation in the HNF4A gene is the development of DM. The pancreatic beta-cell is sensitive to the population of HNF4A present, and certain HNF4A haplotypes are being linked with altered insulin secretion.<sup>62</sup> In particular, mutations in the gene are suspected in the pathogenesis of MODY type 1 (MODY1).<sup>8</sup> Individuals with MODY1 respond normally to insulin, but express an impaired response to secreting insulin in the presence of glucose.<sup>8</sup> If this condition remained unchecked, insulin secretion decreases, leading to DM.<sup>8</sup>

Several types of nonsense and missense mutations in HNF4A characterized by a shortfall in insulin secretion have been observed to cause MODY1.<sup>62</sup> Similarly, the variant of the HNF4A gene inherited may influence the function of beta cells, increasing or decreasing insulin secretion.<sup>62</sup> A British study identified a haplotype that was linked with reduced disease risk.<sup>62</sup> Individuals with the 'reduced-risk' haplotype were strongly associated with increased insulin secretion and lower fasting glucose levels.<sup>63</sup> These findings suggest that a certain HNF4A haplotype might have the ability for increased insulin secretion and protective effects on DM.<sup>63</sup> This protective variant was identified upstream of the HNF4A coding region in an alternative promoter called P2, which lies 46 kb upstream of the P1 promoter. Though the two promoters help in the transcription of HNF4A, they play different roles in different cells. Both P1 and P2 are embedded in the pancreas, but P2 is the main transcription site in the beta cells, and a mutation of P2 is a cause of MODY.<sup>63</sup>

How HNF4A mutations cause  $\beta$ -cell dysfunction or lipid profile disruption in MODY1 is not fully understood. However, based on its role in glucose transport and glycolysis as well as lipid metabolism,<sup>64</sup> loss of function of the gene could result in low triglyceride. This could end in less expression of some genes involved in glucose biosynthesis and metabolism.<sup>64</sup> Mice with a mutated HNF4A gene have been reported to show impaired glucose-stimulated insulin secretion and altered intracellular calcium response, characteristic of MODY1.<sup>65</sup> These observations were suggestive of loss of insulin regulatory function of  $K_{ATP}$  channel in the pancreatic  $\beta$ -cells of the mutated mice.<sup>65</sup>

### ***The HNF1B gene***

The HNF1B gene encodes a protein (called a

transcription factor) that attaches to certain parts of DNA and modulates the expression of other genes.<sup>66,67</sup> The HNF1B protein is found in many organs and tissues, including the lungs, livers, intestines, pancreas, kidneys, reproductive system, and urinary tract.<sup>66,67</sup> Researchers suggest that the protein may be instrumental in the development of these body parts;<sup>66</sup> hence, its inactivation may initiate a lot of diseases. Notable among the diseases linked to mutations in the HNF1B gene is the MODY type 5 (MODY5).<sup>66</sup>

To prove the association between HNF1B and MODY5, a team of researchers compared pluripotent stem cell lines from MODY5 individuals with cells grown from unaffected family members and healthy controls.<sup>25</sup> In MODY5, children who inherited the mutation from one parent grew a malformed and small pancreas, indicating that they developed DM usually aged < 25 years.<sup>25</sup> The use of pluripotent stem cells allowed researchers to replicate human pancreas development in cell culture.<sup>25</sup> The scientists observed that HNF1B gene mutation disrupted the embryonic pancreas development of the cell cultures, leading to beta-cell dysfunction and impaired insulin biosynthesis.<sup>25</sup> It was also observed that mutations in this gene initiated DM independently of other DM genes.<sup>25</sup> However, the differentiating cells up-regulated other pancreatic development genes to compensate for the HNF1B inactivation.<sup>25</sup> These cellular events were observed in numerous MODY5 cell lines compared with healthy family members and non-related healthy controls.<sup>25</sup> The scientists were of the opinion that these findings and a greater understanding of beta-cell development and disruption could lead to improved DM treatments. This discovery once again shows the diabetic population could be stratified into subgroups and treated individually based on the mechanism of the causal gene rather than the current generalized treatment methods.<sup>25</sup>

As HNF1B is expressed in several tissues during embryonic development, diabetic conditions associated with HNF1B mutations can stem from extra-pancreatic abnormalities. The commonly afflicted organ is the kidney, usually affected by renal cysts, which precede diabetic conditions.<sup>68-70</sup> Renal dysplasia and renal tract malformations had also been reported to precede diabetic syndrome in individuals with HNF1B gene mutations.<sup>68-70</sup> Other precursors of MODY1 include hypomagnesemia, mild genital



tract anomalies, abnormal liver morphology, and enzymes, especially alanine aminotransferase (ALT) and gamma-glutamyl transferase.<sup>68-70</sup>

### **GCK gene**

The GCK gene encodes the enzyme glucokinase, a member of the hexokinase family.<sup>71</sup> The gene plays a central role in carbohydrate metabolism in that it catalyzes the first reaction of the glycolytic pathway, the conversion of glucose to glucose 6-phosphate.<sup>71</sup> Glucokinase is expressed along with glucose transporter 2 (GLUT2) by the pancreatic  $\beta$ -cells and catalyzes the production of glucose, enabling it to act as a glucose sensor for the beta cells.<sup>71,72</sup> Compared with other hexokinase members, glucokinase has a high uninterrupted transport capacity for glucose.<sup>71</sup> Glucokinase works together with the GLUT2 receptor in the liver and beta-cell and enhances rapid insulin-independent entry and metabolism of glucose.<sup>71</sup> This allows the liver to act as a reservoir for circulating glucose as well as helps the glucose sensing mechanism of the beta cells.<sup>71</sup>

Mutations in the GCK gene have been demonstrated to cause abnormal glucose sensing, resulting in a raised threshold for initiation of glucose-stimulated insulin secretion. This ends in stable and mild hyperglycemia without any threat of DM complications.<sup>73,74</sup> This form of DM is known as GCK-MODY, otherwise known as MODY type 2 (MODY2). However, the clinical presentation of the MODY may vary based on the type of mutation. Heterozygous inactivating mutations cause mild fasting hyperglycemia (the hallmark of GCK-MODY), while the homozygous inactivating mutations cause a more severe condition, resembling permanent neonatal diabetes mellitus.<sup>73,74</sup> Other GCK mutations up-regulate insulin production, characterized by hyperinsulinemic hypoglycemia. In contrast to other forms of DM, hyperglycemia in MODY2 does not deteriorate with age.<sup>75</sup>

GCK expression is tissue-specific. In the liver, GCK synthesis is directly proportional to the concentration of insulin, which rises and falls with the nutritive state of the body.<sup>76</sup> On the other hand, glucagon, another liver hormone, suppresses GCK expression.<sup>76</sup> In the  $\beta$ -cells, GCK expression is relatively constant regardless of the body's food intake and, by extension, insulin levels.<sup>76</sup> Considering the roles of GCK in glucose metabolism and insulin

release, GCK mutations are expected to cause both hyperglycemia and hypoglycemia.<sup>77</sup> Heterozygous mutations in the gene may result in a reduced phosphorylation rate in the liver, decreasing the concentration of glycogen synthesized, and disrupting postprandial glucose regulation.<sup>78</sup> In  $\beta$ -cells, loss of function of the gene will impair insulin secretion regulation.<sup>79</sup>

### **Selection of individuals for MODY genetic testing**

Due to the overlapping characteristics of various forms of DM, some of the discussed MODY pathophysiology might be observed in individuals with type 1 DM (T1DM) and T2DM, making the selection for genetic testing difficult. However, diabetic teens and young adults with a multi-generational history, as well as non-ketotic insulin-sensitive hyperglycemia and the absence of autoantibodies, should consider testing for MODY.<sup>80,81</sup> Additionally, middle-aged with autosomal dominant history and symptoms and signs of T2DM, but showing no obesity, insulin resistance and fatty liver, should also consider MODY testing.<sup>81,82</sup>

A MODY probability calculator developed by researchers at Exeter, UK, can also be used as a guide to select diabetics for genetic screening.<sup>83</sup> In the model, diabetics below 35 years old are scored based on their responses to eight questions. These questions include sex, age at diagnosis and referral, body mass index (BMI), treatment option taken, time insulin treatment begins, glycated hemoglobin (HbA<sub>1c</sub>) level, and diabetic status of the parents.<sup>83,84</sup> For MODY to be considered against T1DM, HbA<sub>1c</sub> must be lower, at least one of the parents must be affected, and the age of diagnosis must be older.<sup>83,84</sup> MODY will be considered against T2DM if the BMI is lower, the age of diagnosis is younger, HbA<sub>1c</sub> is lower, and if the affected has a diabetic parent(s).<sup>83,84</sup> MODY will also be suspected against T2DM if the diabetic does not respond to oral hypoglycemic drugs or insulin.<sup>83,84</sup>

In advanced countries, some organizations have compiled major clinical features of MODY and employed them as guidelines for the selection of diabetics for MODY testing. Notable among these organizations/guidelines include European Molecular Genetics Quality Network Best Practice Guidelines<sup>82</sup> and the Clinical Practice Consensus

Guidelines by the International Society for Pediatric and Adolescent Diabetes.<sup>85</sup>

However, comparing all these selection methods with the large numbers of MODY pathophysiology described in this study shows the methods lack adequate information to detect MODY accurately. This suggests that many MODY patients are still currently being misdiagnosed as T1DM or T2DM. Thus, the MODY population worldwide could be higher than those reported in several studies.

### ***Genetic testing techniques for MODY***

When there are means and sufficient information that an individual has MODY, the next step is to choose a screening procedure or technique. For effective prevention and management of genetic diseases, including MODY, genetic testing should begin during the intrauterine life, which is termed prenatal genetic testing.<sup>86</sup> Prenatal testing can be carried out to detect genetic errors related to MODY during fetal development. Genetic testing for GCK-MODY is particularly important during pregnancy to confirm the presence or otherwise of macrosomia, which may help in the choice of therapies.<sup>87,88</sup> Genetic testing can also be done immediately after birth to detect MODY mutations that can be corrected if detected early. This form of genetic testing is called newborn testing.<sup>86</sup> Predictive and pre-symptomatic testing is also conducted a few years after birth<sup>86</sup> to identify the MODY risk of an individual, especially those with a family history of MODY. Diagnostic testing is another test that can be conducted at any time when certain biomarkers or pathophysiology of MODY are observed in an individual. The test is often used to confirm the status of a specific genetic or chromosomal condition.<sup>86</sup>

A couple of biological techniques are available for genetic testing, notable among which are gene-targeted testing (serial single gene or multigene panel) and whole-exome sequencing.<sup>89</sup>

### ***Gene-targeted testing (serial single gene or multigene panel)***

Gene-targeted testing, such as Sanger sequencing, is genetic testing in which specific genes, based on the clinical presentations of the person with diabetes, are selected for testing.<sup>90</sup> The technique is most suitable when the patient expresses some signs related to a few known MODY types. The test is carried out serially in which a sequence analysis of the probable

genes is carried out first.<sup>89</sup> For a patient showing the classical features of MODY, HNF1A is screened first, followed by HNF4A and GCK. However, if the diabetic phenotype is mild and fasting glucose is between 5.5 and 8.5 mmol/L, GCK should be tested first, then HNF1A and HNF4A in that order.<sup>12,91</sup> If the patient has renal and pancreatic dysfunction as well as a urogenital problem, HNF1B should be tested first.<sup>12,91</sup> If no SNP was discovered, deletion/duplication analysis should be done to detect such genes as CEL, GCK, HNF1A, HNF1B, and HNF4A.<sup>89</sup> Generally, the gene-targeted approach is time-consuming and expensive. Complete genetic testing for HNF1A, HNF4A, and GCK involves sequencing 31 exons in which each gene is sequenced separately.<sup>92</sup>

Alternatively, a MODY multigene panel that contains the 14 known MODY genes and other suspect genes can be employed to detect the genetic cause of a MODY. This is cost-effective as it targets several genes at a time and precludes testing unnecessary variants.<sup>90,93</sup>

### ***Whole-exome capture and high-throughput sequencing***

When a MODY patient does not show sufficient or clear clinical features, in-depth genomic screening such as whole-exome sequencing could be the best genetic testing option.<sup>89</sup> In exome sequencing, the selection of probable genes for testing is not needed. Because of these reasons, exome sequencing has some advantages over gene-targeted sequencing in that it can detect MODY genes beyond the reach of the latter.<sup>92</sup> In some cases, exome sequencing is used as a further diagnostic tool where gene-targeted sequencing is ineffective due to insufficient clinical expressions it needs to work with. Whole-exome sequencing is relatively new and could be improved upon in the near future to expand its search coverage and potential.<sup>92</sup> If this is done, it will make MODY diagnosis easier and better.

### ***Cost-effectiveness of genetic testing for MODY***

For individuals, the huge cost of genetic testing for MODY could be burdensome. However, if done accurately, it will improve the quality of life. Testing for MODY genes in a family with the disease may help detect MODY variants in predisposed members and proffer treatment before it degenerates to glucose imbalance and DM. Accurate genetic

screening may help predict the likelihood and types of complications and, in turn, reduce expenditures. For instance, HNF1A and HNF4A MODY are characterized by microvascular complications, which can be managed with a low dose of sulfonylureas instead of rigorous insulin therapy<sup>94</sup> typified by T1DM. On the other hand, GCK-MODY shows less microvascular complications and may not need any treatment.<sup>92</sup> So, accurate diagnosis of MODY type could prevent a wrong treatment choice, culminating in reduced healthcare cost.<sup>95,96</sup>

In a society where there is insurance cover or policy for testing, the cost-effectiveness of genetic testing for MODY depends on the frequency of the condition in the population.<sup>97,98</sup> In a stimulated study carried out in the US by Naylor et al,<sup>98</sup> genetic testing for MODY was non-cost-effective when the frequency of the disease was as low as 2%. However, when the population of MODY was increased to 6% with improved screening techniques and expanded pathophysiology, testing was found to be cost-effective.<sup>98</sup> Moreover, genetic testing was found to be cost-effective in the population, with a 2% prevalence of MODY when the cost of testing was reduced.<sup>98</sup> The study also demonstrated that if the MODY population is increased to 31%, through advanced testing techniques, the genetic testing policy for MODY becomes cost-saving.<sup>98</sup> In brief, the cost-effectiveness of a genetic testing policy depends on the frequency of MODY in society and the cost of the test.

## CONCLUSION

An autosomal dominant mutation in certain genes involved in insulin biosynthesis and metabolism may cause MODY. This form of DM has distinct pathogenic and clinical presentations. Thus, its treatment may require a different approach from other types of disease. As such, healthcare providers are advised to formulate MODY drugs and treatment methods based on the identified mechanism of action and phenotypic presentations of its subtypes.

### Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

### REFERENCES

1. Heuvel-Borsboom H, de Valk HW, Losekoot M, Westerink J. Maturity onset diabetes of the young: Seek

and you will find. *Neth J Med* 2016 Jun;74(5):193-200.

2. Bansal V, Gassenhuber J, Phillips T, Oliveira G, Harbaugh R, Villarasa N, et al. Spectrum of mutations in monogenic diabetes genes identified from high-throughput DNA sequencing of 6888 individuals. *BMC Med* 2017 Dec;15(1):213.
3. Ziegler R, Neu A. Diabetes in childhood and adolescence. *Dtsch Arztebl Int* 2018 Mar;115(9):146-156.
4. Pihoker C, Gilliam LK, Ellard S, Dabelea D, Davis C, Dolan LM, et al; SEARCH for Diabetes in Youth Study Group. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. *J Clin Endocrinol Metab* 2013 Oct;98(10):4055-4062.
5. Fajans SS, Bell GI. MODY: history, genetics, pathophysiology, and clinical decision making. *Diabetes Care* 2011 Aug;34(8):1878-1884.
6. Firdous P, Nissar K, Ali S, Ganai BA, Shabir U, Hassan T, et al. Genetic testing of maturity-onset diabetes of the young current status and future perspectives. *Front Endocrinol (Lausanne)* 2018 May;9:253.
7. Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? *Diabetologia* 2010 Dec;53(12):2504-2508.
8. Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. *N Engl J Med* 2001 Sep;345(13):971-980.
9. Kleinberger JW, Copeland KC, Gandica RG, Haymond MW, Levitsky LL, Linder B, et al. Monogenic diabetes in overweight and obese youth diagnosed with type 2 diabetes: the TODAY clinical trial. *Genet Med* 2018 Jun;20(6):583-590.
10. Naylor R, Philipson LH. Who should have genetic testing for maturity-onset diabetes of the young? *Clin Endocrinol (Oxf)* 2011 Oct;75(4):422-426.
11. Irgens HU, Molnes J, Johansson BB, Ringdal M, Skriverhaug T, Undlien DE, et al. Prevalence of monogenic diabetes in the population-based Norwegian Childhood Diabetes Registry. *Diabetologia* 2013 Jul;56(7):1512-1519.
12. Molven A, Njølstad PR. Role of molecular genetics in transforming diagnosis of diabetes mellitus. *Expert Rev Mol Diagn* 2011 Apr;11(3):313-320.
13. Shepherd M, Shields B, Hammersley S, Hudson M, McDonald TJ, Colclough K, et al; UNITED Team. Systematic population screening, using biomarkers and genetic testing, identifies 2.5% of the UK. pediatric diabetes population with monogenic diabetes. *Diabetes Care* 2016 Nov;39(11):1879-1888.
14. National Institute of Diabetes and Digestive and Kidney Disease. NIDDK. Monogenic diabetes (Neonatal diabetes mellitus & MODY). [cited 2018 Oct 20]. Available from: <https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/monogenic-neonatal-mellitus-mody>.
15. Al-Yaarubi S, Ullah I, Sharef SW, Al Shidhani A, Al Hanai S, Al Kalbani R, et al. Demographic and clinical characteristics of type 1 diabetes mellitus in omani children - single center experience. *Oman Med J* 2014 Mar;29(2):119-122.
16. Al-Lawati JA. Diabetes mellitus: a local and global public health emergency! *Oman Med J* 2017 May;32(3):177-179.
17. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. *Nat Rev Endocrinol* 2018 Feb;14(2):88-98.
18. International Diabetes Federation. IDF Diabetes Atlas 9th Edition, 2019. [cited 2020 April 19]. Available from: [https://www.diabetesatlas.org/upload/resources/2019/IDF\\_Atlas\\_9th\\_Edition\\_2019.pdf](https://www.diabetesatlas.org/upload/resources/2019/IDF_Atlas_9th_Edition_2019.pdf).



19. Arya VB, Rahman S, Senniappan S, Flanagan SE, Ellard S, Hussain K. HNF4A mutation: switch from hyperinsulinaemic hypoglycaemia to maturity-onset diabetes of the young, and incretin response. *Diabet Med* 2014 Mar;31(3):e11-e15.
20. Bonfig W, Hermanns S, Warncke K, Eder G, Engelsberger I, Burdach S, et al. GCK-MODY (MODY 2) caused by a novel p.Phe330Ser mutation. *ISRN Pediatr* 2011;2011:676549.
21. Noorian S, Sayarifard F, Farhadi E, Barbetti F, Rezaei N. GCK mutation in a child with maturity onset diabetes of the young, type 2. *Iran J Pediatr* 2013 Apr;23(2):226-228.
22. Moghbeli M, Naghibzadeh B, Ghahraman M, Fatemi S, Taghavi M, Vakili R, et al. Mutations in HNF1A gene are not a common cause of familial young-onset diabetes in Iran. *Indian J Clin Biochem* 2018 Jan;33(1):91-95.
23. Caetano LA, Santana LS, Costa-Riquetto AD, Lerario AM, Nery M, Nogueira GF, et al. PDX1 -MODY and dorsal pancreatic agenesis: New phenotype of a rare disease. *Clin Genet* 2018 Feb;93(2):382-386.
24. Doddabelavangala Mruthyunjaya M, Chapla A, Hesarghatta Shyamasunder A, Varghese D, Varshney M, Paul J, et al. Comprehensive maturity onset diabetes of the young (MODY) gene screening in pregnant women with diabetes in India. *PLoS One* 2017 Jan;12(1):e0168656.
25. Agency for Science Technology and Research. ASTAR. Genetic mutation during embryonic development could hold the key to a lifetime living with diabetes. [cited 2018 Sept 22]. Available from: <https://medicalxpress.com/news/2016-08-genetic-mutation-embryonic-key-lifetime.html#nRlv>.
26. Mancusi S, La Manna A, Bellini G, Scianguetta S, Roberti D, Casale M, et al. HNF-1 $\beta$  mutation affects PKD2 and SOCS3 expression causing renal cysts and diabetes in MODY5 kindred. *J Nephrol* 2013 Jan-Feb;26(1):207-212.
27. Malecki MT, Jhala US, Antonellis A, Fields L, Doria A, Urban T, et al. Mutations in NEUROD1 are associated with the development of type 2 diabetes mellitus. *Nat Genet* 1999 Nov;23(3):323-328.
28. Kim SH. Maturity-onset diabetes of the young: what do clinicians need to know? *Diabetes Metab J* 2015 Dec;39(6):468-477.
29. Neve B, Fernandez-Zapico ME, Ashkenazi-Katalan V, Dina C, Hamid YH, Joly E, et al. Role of transcription factor KLF11 and its diabetes-associated gene variants in pancreatic beta cell function. *Proc Natl Acad Sci U S A* 2005 Mar;102(13):4807-4812.
30. Robertson RP, Harmon J, Tran PO, Poytout V. Beta-cell glucose toxicity, lipotoxicity, and chronic oxidative stress in type 2 diabetes. *Diabetes* 2004 Feb;53(Suppl 1):S119-S124.
31. Raeder H, Johansson S, Holm PI, Haldorsen IS, Mas E, Sbarra V, et al. Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. *Nat Genet* 2006 Jan;38(1):54-62.
32. Shimajiri Y, Sanke T, Furuta H, Hanabusa T, Nakagawa T, Fujitani Y, et al. A missense mutation of Pax4 gene (R121W) is associated with type 2 diabetes in Japanese. *Diabetes* 2001 Dec;50(12):2864-2869.
33. Bignon-Lauber A, Boehm B, Lang-Muritano M, Gauthier BR, Brun T, Wollheim CB, et al. Association of childhood type 1 diabetes mellitus with a variant of PAX4: possible link to beta cell regenerative capacity. *Diabetologia* 2005 May;48(5):900-905.
34. Meur G, Simon A, Harun N, Virally M, Dechaume A, Bonnefond A, et al. Insulin gene mutations resulting in early-onset diabetes: marked differences in clinical presentation, metabolic status, and pathogenic effect through endoplasmic reticulum retention. *Diabetes* 2010 Mar;59(3):653-661.
35. Nishi M, Nanjo K. Insulin gene mutations and diabetes. *J Diabetes Invest* 2011 Apr;2(2):92-100.
36. Borowiec M, Liew CW, Thompson R, Boonyasrisawat W, Hu J, Mlynarski WM, et al. Mutations at the BLK locus linked to maturity onset diabetes of the young and  $\beta$ -cell dysfunction. *Proc Natl Acad Sci U S A* 2009 Aug;106(34):14460-14465.
37. Borowiec M, Liew CW, Thompson R, Boonyasrisawat W, Hu J, Mlynarski WM, et al. Mutations at the BLK locus linked to maturity onset diabetes of the young and beta-cell dysfunction. *Proc Natl Acad Sci U S A* 2009 Aug;106(34):14460-14465.
38. Huopio H, Reimann F, Ashfield R, Komulainen J, Lenko HL, Rahier J, et al. Dominantly inherited hyperinsulinism caused by a mutation in the sulfonylurea receptor type 1. *J Clin Invest* 2000 Oct;106(7):897-906.
39. Taschenberger G, Mougey A, Shen S, Lester LB, LaFranchi S, Shyng SL. Identification of a familial hyperinsulinism-causing mutation in the sulfonylurea receptor 1 that prevents normal trafficking and function of K<sub>ATP</sub> channels. *J Biol Chem* 2002 May;277(19):17139-17146.
40. Dean L, McEntyre J, Bethesda MD. The genetic landscape of diabetes. national center for biotechnology information (US). [Cited 2018 Nov 22]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1665/>.
41. Prudente S, Jungtrakoon P, Marucci A, Ludovico O, Buranasupkajorn P, Mazza T, et al. Loss-of-function mutations in APPL1 in familial diabetes mellitus. *Am J Hum Genet* 2015 Jul;97(1):177-185.
42. Schenck A, Goto-Silva L, Collinet C, Rhinn M, Giner A, Habermann B, et al. The endosomal protein Appl1 mediates Akt substrate specificity and cell survival in vertebrate development. *Cell* 2008 May;133(3):486-497.
43. Zhang H, Wang WP, Guo T, Yang JC, Chen P, Ma KT, et al. The LIM-homeodomain protein ISL1 activates insulin gene promoter directly through synergy with BETA2. *J Mol Biol* 2009 Sep;392(3):566-577.
44. Peng SY, Wang WP, Meng J, Li T, Zhang H, Li YM, et al. ISL1 physically interacts with BETA2 to promote insulin gene transcriptional synergy in non-beta cells. *Biochim Biophys Acta* 2005 Dec;1731(3):154-159.
45. Patel KA, Kettunen J, Laakso M, Stančáková A, Laver TW, Colclough K, et al. Heterozygous RFX6 protein truncating variants are associated with MODY with reduced penetrance. *Nat Commun* 2017 Oct;8(1):888.
46. Morales S. New type of diabetes caused by gene mutation discovered. [cited 2018 Dec 5]. Available from: <https://www.diabetesdaily.com/blog/new-type-of-diabetes-caused-by-gene-mutation-discovered-498141/>.
47. Kanna R. Gene for rare form of diabetes found. [cited 2018 Dec 5]. Available from: <https://www.thehindu.com/sci-tech/health/gene-for-rare-form-of-diabetes-found/article22847084.ece>.
48. Chambers C, Fouts A, Dong F, Colclough K, Wang Z, Batish SD, et al. Characteristics of maturity onset diabetes of the young in a large diabetes center. *Pediatr Diabetes* 2016 Aug;17(5):360-367.
49. McDonald TJ, Ellard S. Maturity onset diabetes of the young: identification and diagnosis. *Ann Clin Biochem* 2013 Sep;50(Pt 5):403-415.
50. Weinreich SS, Bosma A, Henneman L, Rigter T, Spruijt CM, Grimbergen AJ, et al. A decade of molecular genetic testing for MODY: a retrospective study of utilization in The Netherlands. *Eur J Hum Genet* 2015 Jan;23(1):29-33.
51. Delvecchio M, Ludovico O, Menzaghi C, Di Paola R, Zelante L, Marucci A, et al. Low prevalence of HNF1A mutations after molecular screening of multiple MODY genes in 58 Italian families recruited in the pediatric or adult diabetes clinic from a single Italian hospital. *Diabetes Care* 2014 Dec;37(12):e258-e260.
52. Genetic Home Reference GH. HNF1A gene: your guide to understanding genetic condition. [cited 2018 Oct 10]. Available from: <https://ghr.nlm.nih.gov/gene/HNF1A>.
53. Balamurugan K, Bjørkhaug L, Mahajan S, Kanthimathi S, Njølstad PR, Srinivasan N, et al. Structure-function studies of HNF1A (MODY3) gene mutations in South



- Indian patients with monogenic diabetes. *Clin Genet* 2016 Dec;90(6):486-495.
54. Bellanné-Chantelot C, Lévy DJ, Carette C, Saint-Martin C, Riveline JP, Larger E, et al; French Monogenic Diabetes Study Group. Clinical characteristics and diagnostic criteria of maturity-onset diabetes of the young (MODY) due to molecular anomalies of the HNF1A gene. *J Clin Endocrinol Metab* 2011 Aug;96(8):E1346-E1351.
  55. Servitja J-M, Pignatelli M, Maestro MÁ, Cardalda C, Boj SF, Lozano J, et al. Hnf1 $\alpha$  (MODY3) controls tissue-specific transcriptional programs and exerts opposed effects on cell growth in pancreatic islets and liver. *Mol Cell Biol* 2009 Jun;29(11):2945-2959.
  56. Harries LW, Ellard S, Stride A, Morgan NG, Hattersley AT. Isoforms of the TCF1 gene encoding hepatocyte nuclear factor-1 alpha show differential expression in the pancreas and define the relationship between mutation position and clinical phenotype in monogenic diabetes. *Hum Mol Genet* 2006 Jul;15(14):2216-2224.
  57. Genetic Home Reference GH. HNF4A gene: your guide to understanding genetic condition. [cited 2018 Nov 15]. Available from: <https://ghr.nlm.nih.gov/gene/HNF4A>.
  58. Bolotin E, Liao H, Ta TC, Yang C, Hwang-Verslues W, Evans JR, et al. Integrated approach for the identification of human hepatocyte nuclear factor 4alpha target genes using protein binding microarrays. *Hepatology* 2010 Feb;51(2):642-653.
  59. Stoffel M, Duncan SA. The maturity-onset diabetes of the young (MODY1) transcription factor HNF4alpha regulates expression of genes required for glucose transport and metabolism. *Proc Natl Acad Sci U S A* 1997 Nov;94(24):13209-13214.
  60. Laver TW, Colclough K, Shepherd M, Patel K, Houghton JA, Dusatkova P, et al. The common p.R114W HNF4A mutation causes a distinct clinical subtype of monogenic diabetes. *Diabetes* 2016 Oct;65(10):3212-3217.
  61. Wang H, Maechler P, Antinozzi PA, Hagenfeldt KA, Wollheim CB. Hepatocyte nuclear factor 4alpha regulates the expression of pancreatic beta-cell genes implicated in glucose metabolism and nutrient-induced insulin secretion. *J Biol Chem* 2000 Nov;275(46):35953-35959.
  62. Barroso I, Luan J, Middelberg RP, Harding AH, Franks PW, Jakes RW, et al. Candidate gene association study in type 2 diabetes indicates a role for genes involved in beta-cell function as well as insulin action. *PLoS Biol* 2003 Oct;1(1):E20-E20.
  63. Thomas H, Jaschowitz K, Bulman M, Frayling TM, Mitchell SM, Roosen S, et al. A distant upstream promoter of the HNF-4alpha gene connects the transcription factors involved in maturity-onset diabetes of the young. *Hum Mol Genet* 2001 Sep;10(19):2089-2097.
  64. Lehto M, Bitzén PO, Isomaa B, Wipemo C, Wessman Y, Forsblom C, et al. Mutation in the HNF-4 $\alpha$  gene affects insulin secretion and triglyceride metabolism. *Diabetes* 1999 Feb;48(2):423-425.
  65. Miura A, Yamagata K, Kakei M, Hatakeyama H, Takahashi N, Fukui K, et al. Hepatocyte nuclear factor-4 $\alpha$  is essential for glucose-stimulated insulin secretion by pancreatic  $\beta$ -cells. *J Biol Chem* 2006 Feb;281(8):5246-5257.
  66. Genetic Home Reference GH. HNF1B gene: your guide to understanding genetic condition. [cited 2018 May 16]. Available from: <https://ghr.nlm.nih.gov/gene/HNF1B#synonyms>.
  67. Lu P, Li Y, Gorman A, Chi YI. Crystallization of hepatocyte nuclear factor 1 $\beta$  in complex with DNA. *Acta Crystallogr Sect F Struct Biol Cryst Commun* 2006 Jun;62(Pt 6):525-529.
  68. Anik A, Çatlı G, Abacı A, Böber E. Maturity-onset diabetes of the young (MODY): an update. *J Pediatr Endocrinol Metab* 2015 Mar;28(3-4):251-263.
  69. Edghill EL, Bingham C, Ellard S, Hattersley AT. Mutations in hepatocyte nuclear factor-1 $\beta$  and their related phenotypes. *J Med Genet* 2006 Jan;43(1):84-90.
  70. Chen Y-Z, Gao Q, Zhao X-Z, Chen YZ, Bennett CL, Xiong XS, et al. Systematic review of TCF2 anomalies in renal cysts and diabetes syndrome/maturity onset diabetes of the young type 5. *Chin Med J (Engl)* 2010 Nov;123(22):3326-3333.
  71. National Center for Biotechnology. GCK glucokinase [Homo sapiens (human)]. [cited 2020 April 12]. Available from: <https://www.ncbi.nlm.nih.gov/gene/2645>.
  72. Gloyn AL. Glucokinase (GCK) mutations in hyper- and hypoglycemia: maturity-onset diabetes of the young, permanent neonatal diabetes, and hyperinsulinemia of infancy. *Hum Mutat* 2003 Nov;22(5):353-362.
  73. Stride A, Vaxillaire M, Tuomi T, Barbetti F, Njølstad PR, Hansen T, et al. The genetic abnormality in the beta cell determines the response to an oral glucose load. *Diabetologia* 2002 Mar;45(3):427-435.
  74. Martin D, Bellanné-Chantelot C, Deschamps I, Froguel P, Robert JJ, Velho G. Long-term follow-up of oral glucose tolerance test-derived glucose tolerance and insulin secretion and insulin sensitivity indexes in subjects with glucokinase mutations (MODY2). *Diabetes Care* 2008 Jul;31(7):1321-1323.
  75. Pearson ER, Velho G, Clark P, Stride A, Shepherd M, Frayling TM, et al. beta-cell genes and diabetes: quantitative and qualitative differences in the pathophysiology of hepatic nuclear factor-1alpha and glucokinase mutations. *Diabetes* 2001 Feb;50(1)(Suppl 1):S101-S107.
  76. Iynedjian PB. Molecular physiology of mammalian glucokinase. *Cell Mol Life Sci* 2009 Jan;66(1):27-42.
  77. Osbak KK, Colclough K, Saint-Martin C, Beer NL, Bellanné-Chantelot C, Ellard S, et al. Update on mutations in glucokinase (GCK), which cause maturity-onset diabetes of the young, permanent neonatal diabetes, and hyperinsulinemic hypoglycemia. *Hum Mutat* 2009 Nov;30(11):1512-1526.
  78. Adeva-Andany MM, González-Lucán M, Donapetry-García C, Fernández-Fernández C, Ameneiros-Rodríguez E. Glycogen metabolism in humans. *BBA Clin* 2016 Feb;5:85-100.
  79. Bae JS, Kim TH, Kim MY, Park JM, Ahn YH. Transcriptional regulation of glucose sensors in pancreatic  $\beta$ -cells and liver: an update. *Sensors (Basel)* 2010;10(5):5031-5053.
  80. Gardner DS, Tai ES. Clinical features and treatment of maturity onset diabetes of the young (MODY). *Diabetes Metab Syndr Obes* 2012;5:101-108.
  81. Juszczak A, Pryse R, Schuman A, Owen KR. When to consider a diagnosis of MODY at the presentation of diabetes: aetiology matters for correct management. *Br J Gen Pract* 2016 Jun;66(647):e457-e459.
  82. Sequeiros J, Martindale J, Seneca S, Giunti P, Kämäräinen O, Volpini V, et al; European Molecular Quality Genetics Network. EMQN Best Practice Guidelines for molecular genetic testing of SCAs. *Eur J Hum Genet* 2010 Nov;18(11):1173-1176.
  83. Njølstad PR, Molven A. To test, or not to test: time for a MODY calculator? *Diabetologia* 2012 May;55(5):1231-1234.
  84. Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, Hattersley AT. The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. *Diabetologia* 2012 May;55(5):1265-1272.
  85. Hattersley AT, Greeley SA, Polak M, Rubio-Cabezas O, Njølstad PR, Mlynarski W, et al. ISPAD Clinical Practice Consensus Guidelines 2018: The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* 2018 Oct;19(Suppl 27):47-63.
  86. US National Library of Medicine. What are the types of genetic tests? Genetic Home Reference, 2019 [cited 2018 Nov]. Available from: <https://ghr.nlm.nih.gov/primer/testing/uses>.

87. Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. *Nat Clin Pract Endocrinol Metab* 2008 Apr;4(4):200-213.
88. Spyer G, Macleod KM, Shepherd M, Ellard S, Hattersley AT. Pregnancy outcome in patients with raised blood glucose due to a heterozygous glucokinase gene mutation. *Diabet Med* 2009 Jan;26(1):14-18.
89. Naylor R, Knight Johnson A, del Gaudio D. Maturity-Onset Diabetes of the Young Overview. 2018 May 24. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al, editors. *GeneReviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019.
90. Ellard S, Lango Allen H, De Franco E, Flanagan SE, Hysenaj G, Colclough K, et al. Improved genetic testing for monogenic diabetes using targeted next-generation sequencing. *Diabetologia* 2013 Sep;56(9):1958-1963.
91. Hattersley A, Bruining J, Shield J, Njolstad P, Donaghue KC. The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* 2009 Sep;10(Suppl 12):33-42.
92. Johansson S, Irgens H, Chudasama KK, Molnes J, Aerts J, Roque FS, et al. Exome sequencing and genetic testing for MODY. *PLoS One* 2012;7(5):e38050.
93. Alkorta-Aranburu G, Sukhanova M, Carmody D, Hoffman T, Wysinger L, Keller-Ramey J, et al. Improved molecular diagnosis of patients with neonatal diabetes using a combined next-generation sequencing and MS-MLPA approach. *J Pediatr Endocrinol Metab* 2016 May;29(5):523-531.
94. Naylor R, Philipson LH. Who should have genetic testing for maturity-onset diabetes of the young? *Clin Endocrinol (Oxf)* 2011;75(4):422-426.
95. Schnyder S, Mullis PE, Ellard S, Hattersley AT, Flück CE. Genetic testing for glucokinase mutations in clinically selected patients with MODY: a worthwhile investment. *Swiss Med Wkly* 2005 Jun;135(23-24):352-356. doi:10.7892/boris.45687.
96. Pinelli M, Acquaviva F, Barbetti F, Caredda E, Coccozza S, Delvecchio M, et al; Italian Study Group on Diabetes of the Italian Society of Pediatric Endocrinology and Diabetology. Identification of candidate children for maturity-onset diabetes of the young type 2 (MODY2) gene testing: a seven-item clinical flowchart (7-iF). *PLoS One* 2013 Nov;8(11):e79933.
97. Stride A, Hattersley AT. Different genes, different diabetes: lessons from maturity-onset diabetes of the young. *Ann Med* 2002;34(3):207-216.
98. Naylor RN, John PM, Winn AN, Carmody D, Greeley SA, Philipson LH, et al. Cost-effectiveness of MODY genetic testing: translating genomic advances into practical health applications. *Diabetes Care* 2014;37(1):202-209.