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Clinical features, complications and treatment of rarer forms of maturity-onset diabetes of the young (MODY) - A review

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ABSTRACT

Maturity onset diabetes of the young (MODY) is the most common form of monogenic diabetes and is currently believed to have 14 subtypes. While much is known about the common subtypes of MODY (MODY-1, 2, 3 and 5) little is known about its rare subtypes (MODY4, 6–14). With the advent of next-generation sequencing (NGS) there are several reports of the rarer subtypes of MODY emerging from across the world. Therefore, a greater understanding on these rarer subtypes is needed. A search strategy was created, and common databases were searched, and 51 articles finally selected. *INS*-(MODY10) and *ABCC8*-(MODY12) mutations were reported in relatively large numbers compared to the other rare subtypes. The clinical characteristics of the rare MODY subtypes exhibited heterogeneity between families reported with the same mutation. Obesity and diabetic ketoacidosis (DKA) were also reported among rarer MODY subtypes which presents as a challenge as these are not part of the original description of MODY by Tattersal and Fajans. The treatment modalities of the rarer subtypes included oral drugs, predominantly sulfonylureas, insulin but also diet alone. Newer drugs like DPP-4 and SGLT2 inhibitors have also been tried as new modes of treatment. The microvascular and macrovascular complications among the patients with various MODY subtypes are less commonly reported. Recently, there is a view that not all the 14 forms of 'MODY' are true MODY and the very existence of some of these rarer subtypes as MODY has been questioned. This scoping review aims to report on the clinical characteristics, treatment and complications of the rarer MODY subtypes published in the literature.

Contents

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1. Introduction

Monogenic diabetes is a rare form of diabetes caused by a single gene defect, which results in dysfunction of the pancreatic beta cells and affects insulin secretion. It is sub-classified into three main types: maturity-onset diabetes of the young (MODY), neonatal diabetes, and syndromic diabetes.

MODY is the most common type of monogenic diabetes, accounting for 1–2% of all diabetes cases in Europe.[1–5] In 1975, Tattersall and Fajans first proposed the clinical criteria for the diagnosis of MODY which included (i) early-onset of diabetes at <25 years of age, (ii) diabetes in at least two or ideally three family members (autosomal dominant mode of inheritance) (iii) non-insulin dependence (not requiring insulin even five years after diagnosis) (iv) absence of obesity (v) absence of diabetic ketoacidosis (DKA).[6] MODY was later reported to be a heterogeneous group of diseases caused by several molecular abnormalities in different genes but all of them associated with insulin secretion.[7] Genetic research studies started around 1992 and many subtypes of MODY continue to be reported.

According to the Online Mendelian Inheritance in Man (OMIM) database, MODY is currently categorised into 14 subtypes each caused by mutations in different genes,[8] described in Table 1.

The most commonly reported MODY subtypes, *HNF1A*-(MODY3), GCK-(MODY2), *HNF4A*-(MODY3) and *HNF1B*-(MODY5) (Table 1), together account for over 80% of all MODY cases. The other subtypes are referred to as the rarer subtypes.[2–4,7,9–11]

In recent years, next-generation sequencing (NGS) has helped to analyse many genes simultaneously with reduced cost.[12,13] This has led to the reporting of many of the rarer MODY genes shown in Table 1. Recently, two novel variants in the Regulatory Factor X6 (*RFX6*) gene were reported in the United Kingdom indicating this may be a new MODY gene with low penetrance.[14] In addition, the NK6 Homeobox 1 (NKX6-1) gene was reported from India as another possible novel MODY gene.[15] Therefore, while 14 MODY subtypes have officially been classified to date, more subtypes are continuing to be identified.

A karyogram of the common and rarer MODY mutations can be seen in Fig. 1.

1.1. Significance of diagnosis of MODY

A correct diagnosis of MODY is of great clinical significance to patients and their families. For example, patients with *GCK*-(MODY2) mutations may receive unnecessary pharmacotherapy for diabetes which can be withdrawn without any changes in glycaemic control.[11] Instead, these patients should be given reassurance about mild hyperglycaemia and assured about their low risk for vascular complications. Similarly, patients with *HNF1A*-(MODY3) and *HNF4A*-(MODY1) are best treated with oral sulfonylureas, and thus can avoid the unnecessary insulin therapy they are usually prescribed before a diagnosis of MODY is made.[12] These examples have highlighted the need for precision medicine in diabetes, providing individualised treatment to patients based on an accurate diagnosis.[16] In addition, the diagnosis of MODY in a patient often results in genetic testing and diagnosis of other family members resulting in earlier treatment of the rest of the family.[17]

1.2. Common forms of MODY

The most common subtype, *GCK*-(MODY2), presents with life-long, non-progressive fasting hyperglycaemia. The patients are often asymptomatic and are only diagnosed incidentally during pregnancy or during routine examinations.[18] Longitudinal studies of patients with *GCK*-(MODY2) have shown low prevalence of microvascular complications of diabetes despite long duration of mild hyperglycaemia.

The prevalence of *HNF1A*-(MODY3) is more common than *HNF4A*-(MODY1) but the clinical presentations are similar in both of these subtypes. They both present during adolescence or young adulthood[11] and patients with both subtypes are prone to micro- and macrovascular complications similar to type 1 and type 2 diabetes.[19]

Patients with *HNF1B*-(MODY5) present with extra-pancreatic features that affect the renal system resulting in a clinical syndrome of Renal Cysts and Diabetes (RCAD).[12] Apart from renal cysts, renal-tract malformations (horseshoe kidney) and familial hypoplastic glomerulocystic kidney diseases are also reported.[20] More than half of these patients develop end-stage renal failure before the age of

Table 1
Classification of the MODY subtypes (common and rarer subtypes). Source- Online Mendelian Inheritance in Man (OMIM).

Gene-(Locus name)	Locus
Common subtypes of MODY	
HNF4A-(MODY1)	20q13.12
GCK-(MODY2)	7p13
HNF1A-(MODY3)	20q24.31
HNF1B-(MODY5)	17cenq-21.3
Rarer subtypes of MODY	
IPF1/PDX1-(MODY4)	13q12
NEUROD1-(MODY6)	2q31.3
KLF11-(MODY7)	2p25.1
CEL-(MODY8)	9q34.13
PAX4-(MODY9)	7q32.1
INS-(MODY10)	11p15.5
BLK-(MODY11)	8p23.1
ABCC8-(MODY12)	11p15.1
KCNJ11-(MODY13)	11p15.1
APPL1-(MODY14)	3p14.3

45 years which may require renal transplant.[20] The majority of *HNF1B*-MODY patients are treated with insulin.[12]

The clinical features, treatment and complications of the common MODY subtypes *HNF1A*-(MODY3), *GCK*-(MODY2) and *HNF4A*-(MODY1) and *HNF1B*-(MODY5) have been well documented in the medical literature as review articles, case reports, and case series and have been studied extensively.[3,4,21,22] Hence the rest of this review focuses on the other rarer forms of MODY namely *IPF1/PDX1*-(MODY4), *NEUROD1*-(MODY6), *KLF11*-(MODY7), *CEL*-(MODY8), *PAX4*-(MODY9), *INS*-(MODY10), *BLK*-(MODY11), *ABCC8*-(MODY12), *KCNJ11*-(MODY13) and *APPL1*-(MODY14).

1.3. Rarer subtypes of MODY

In the last few years, the reporting of rarer MODY subtypes is increasing, with case reports or case series available. However, an exclusive review focussing on the clinical features, treatment and complications of the rarer MODY subtypes is not available in the literature. Thus, we believe that this scoping review provides an opportunity to review the literature and thus better understand the clinical and genetic profile of the rarer MODY subtypes. This review will also help researchers to broadly understand the increasingly reported rarer MODY subtypes and identify new areas of research. Finally, we will try to summarise the recent reports that some of these rarer forms of diabetes may not represent true MODY. There is a growing body of literature suggesting that only some of the MODY subtypes should be unequivocally accepted as MODY as by diagnosing these, suitable clinical action with respect to changing treatment could be done. It has been suggested that the other forms should not be reported as MODY until more evidence emerges to justify their classification as MODY.[18]

Table 2
Inclusion and exclusion criteria used for selection of studies.

Inclusion criteria	Exclusion criteria
• Studies reporting on the rarer types of MODY • Outcome including clinical characteristics, complications and/or treatment • English language	• Other types of monogenic diabetes (e.g. neonatal diabetes) • Animal studies • Publications not in English

2. Methods

Several methods of systematic review were considered for this study. However, considering the heterogeneity of the studies involved, to identify the key concepts and with the types of evidences available, a scoping review was chosen. A scoping review is a technique to provide a comprehensive coverage of a broad range of studies to map an area of relevant literature. This review considered the (i) clinical

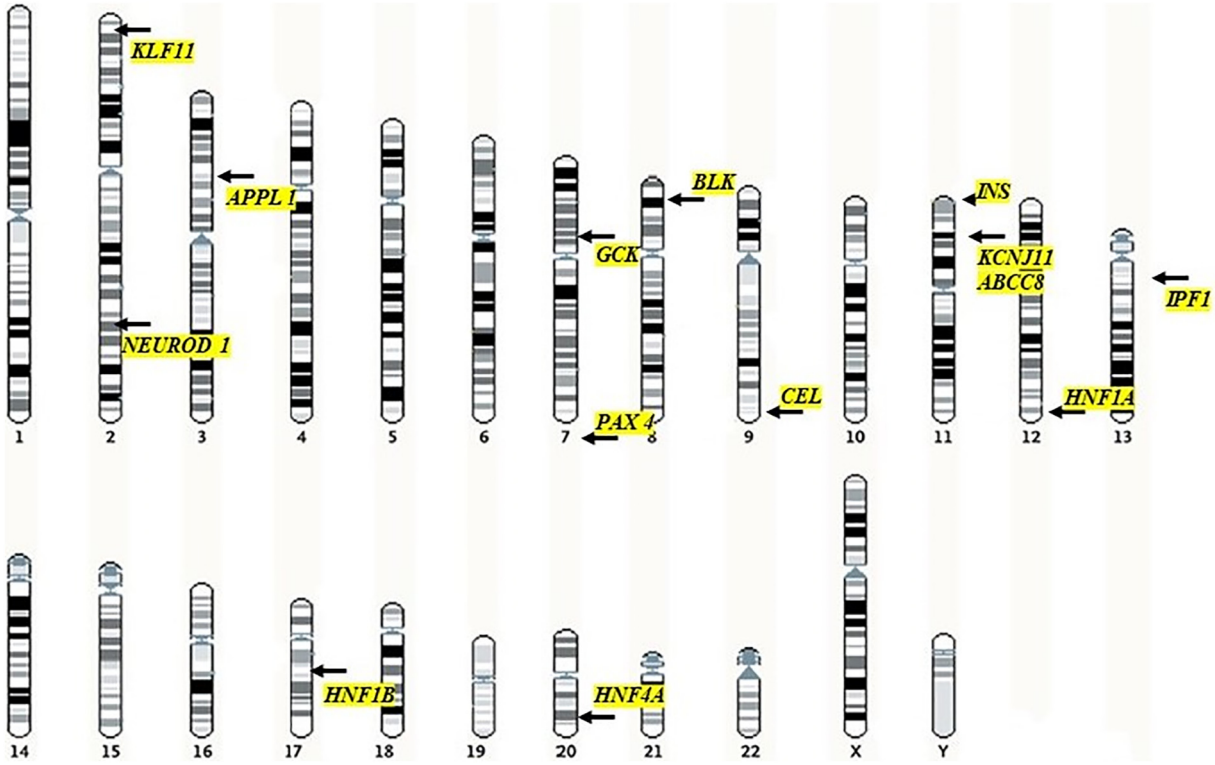

Fig. 1. A karyogram of the common and rarer types of MODY.

characteristics, (ii) treatment modalities, and (iii) complications related to rarer subtypes of MODY.

The methods for this scoping review were based on the five stages outlined in the Arksey and O'Malley Framework[23] and guidelines from the Joanna Briggs Institute.[24] We used the Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping Reviews (PRISMA-ScR).[25] The registration in the International Prospective Register of Systematic Reviews (PROSPERO) was not possible as registration of scoping reviews was not accepted during the time period of the review.

2.1. Stage 1: identifying the research questions

1. What are the clinical characteristics reported among patients with rarer MODY subtypes?
2. What are the treatments currently available to patients with rarer MODY subtypes?
3. What are the complications reported among patients with rarer MODY subtypes (e.g. microvascular or macrovascular complications)?

2.2. Stage 2: identifying the relevant studies

2.2.1. Search strategy

This review included all published original studies, case reports and reviews in the English language on the rarer MODY forms. Grey literature, which includes conference proceedings, dissertations and thesis reports, was also included. The inclusion and exclusion criteria are detailed in Table 2.

2.2.2. Databases used

The databases used for this review included: PubMed, EMBASE, SCOPUS and OVID-MEDLINE. The online databases were searched between February and June 2019. The results of each database search were imported to Covidence systematic review software, (Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org) a web-based software platform which helps to streamline the collection of articles. The back references of full-length publications were identified and screened for supplementary questions relevant to the objective. Where full articles were not available, attempts were made to contact the authors. Alerts were created in each database to ensure that new publications were not missed till December 2019. An outline of the search strategy used in one database is given as an example as Appendix A.

2.3. Stage 3: study selection

Two investigators were involved independently in the study selection process. AR ran the searches in the databases individually and screened the title by relevance in Covidence. Full text review was done by AR and AA independently and in case of any disagreement, a third reviewer (VM) was consulted as a subject expert.

2.4. Stage 4: charting the data

A template for data extraction is available in Appendix B.

2.5. Stage 5: collating, summarising and reporting the results

The process of study inclusion is presented as a PRISMA flow diagram in Fig. 2.

3. Results

As seen in Fig. 2, after an extensive search in the four databases, 4852 articles were imported for screening, out of which 3031 duplicated references were removed. Title/abstract screening of the remaining 1821 studies was done, and 1719 studies were removed due to non-relevance to the subject of this review. 98 full-text studies were examined in detail of which 47 were excluded due to missing clinical characteristics, treatment or complications of the rarer MODY mutations. Finally, 51 published reports were included in the scoping review.

During the review, it was noted that rarer MODY reports were missing from most African and Middle Eastern countries while more recently, the rarer MODY mutations have been commonly reported from Asia. An interesting finding from completing this review is that the criteria used for genetic testing among suspected MODY patients differed quite substantially. The summary of the review is presented in Appendix C and each of the rare MODY subtypes (detailed in Table 1) are described below in the same order.

3.1. IPF1/PDX1-(MODY4)

The clinical characteristics of *IPF1/PDX1*-MODY4 were reported among 13 families from Turkey, Brazil, Trinidad and Tobago, Italy, Sweden, India and China.[15,26–36] The age at onset of diabetes among those reported varied between 2 and 35 years with no difference in the gender distribution. Generally, these patients exhibited mild diabetes[26,28,29,33,37] with obesity reported in two families.[30,36] Two patients were initially diagnosed with type 1 diabetes[27,30] before genetic testing. One study noted that IPF1/*PDF1*-(MODY4) was found to coexist in families previously detected with HNF1A-(MODY3) suggesting that MODY3 genes may be acting as modifying genes.[34] Insulin Promoter Factor -1 is responsible for encoding a transcription factor necessary for regulating pancreatic function and development. However, even with its role in development, pancreatic agenesis (something that is common in neonatal diabetes mellitus) is relatively rare in *IPF1/PDX1*-(MODY4).[30] In fact, dorsal pancreatic agenesis has only been reported in two patients with *IPF1/PDX1*-(MODY4) from Brazil. A computed tomography (CT) scan of the proband and his son showed agenesis of the caudal pancreas with no sign of the main pancreatic duct of the segment. The proband also reported with reduced faecal elastase indicating exocrine pancreatic insufficiency while his son had normal faecal elastase levels.[27] In terms of other complications, hypertension

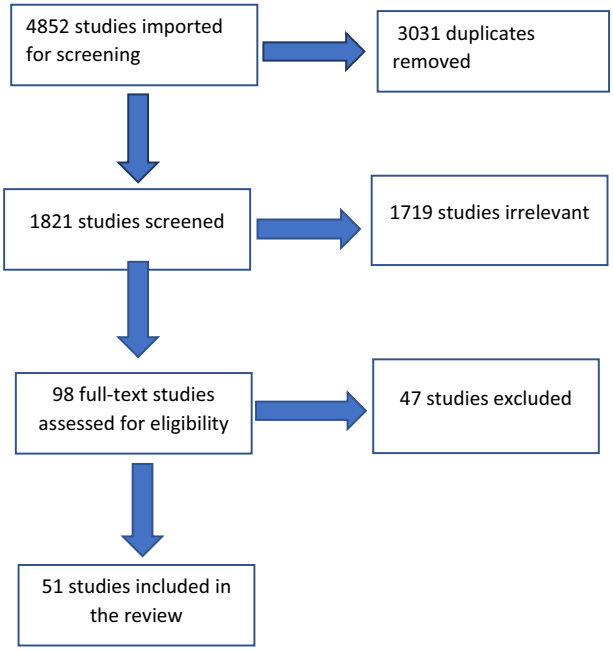

Fig. 2. PRISMA flow diagram of study inclusion.

was reported among two patients, a 2-year-old boy and a 26-year-old male.[26,32]

A large number of patients reported with *IPF1/PDX1*-(MODY4) were treated with insulin.[27–29,33] The insulin dosage was reduced in one patient after the genetic diagnosis and gliclazide was added to the treatment. Insulin was started after 7 and 5 years in two patients; however, their early treatment details were not reported.[34]

In a recent report, a 26-year old non-obese patient with *IPF/PDX1*-(MODY4) was started on a Dipeptidyl Peptidase-4 Inhibitor (DPP-4), Sitagliptin. The drug was introduced as the *IPF1/PDX1* mutation impairs the incretin pathway and DPP4 inhibition can activate this pathway. The patient initially responded to the drug but three months later had to be started on basal insulin, as the fasting plasma glucose levels began to rise. However, with significant improvement achieved in the glycaemic control, the authors proposed a targeted therapeutic modality for similar patients in the future.[32]

The complications among MODY-4 patients are rarely reported. Only one case of mild non-proliferative retinopathy was reported in a 52-year-old male patient from Brazil.[27]

3.2. NEUROD1-(MODY6)

NEUROD1 mutations have been reported among 16 families largely from the Asian region-area, China, India, Japan and Thailand,[29,33,38–40] as well as from other countries such as Iceland, Czech Republic and Poland.[41–43] The age at diagnosis varied between 10 and 33 years (mean 21.5 yrs) and the mutations are reported more commonly among women than men.[29,38] A case series from Japan reported four probands with *NEUROD1*-(MODY6) who inherited the mutation from their mothers.[38] The four probands had episodes of DKA which is seldom present among other MODY patients. Three of the four mothers who were carriers of the mutation had gestational diabetes during pregnancy. One proband and her mother with mutation were reported to have mental retardation and hippocampal hypoplasia.[38] Mental disability, hearing loss and convulsions were also reported in another proband's carrier mother. Such neuronal abnormalities are often reported in neonatal diabetes cases resulting from homozygous mutations,[44] however this is the first time they have been reported with a heterozygous MODY mutation.[45] Obesity was reported among a few subjects[29,33,41,42] which is also an unusual feature among MODY subjects. A milder form of diabetes was also reported in one patient.[39]

NEUROD1 is a transcription factor necessary for insulin synthesis and secretion and also plays an important role in the formation and function of the cerebellum, hippocampus, inner ear and retina.[45]

The treatment modalities reported for this mutation include mostly insulin. A few patients were treated with oral drugs alone[29,33,39] while two patients were initially started on oral drugs and later shifted to insulin after 3 and 5 years.[41] Alpha glucosidase inhibitors and DPP-4 inhibitors were also added to insulin in two patients.[45]

Microvascular complications including retinopathy, neuropathy and nephropathy are frequently reported with MODY-6.[41,42,45] Two of the proband's carrier mothers died due to chronic renal failure and second-stage nephropathy respectively.[45]

3.3. KLF 11-(MODY 7)

KLF11 regulates PDX1 transcription in beta cells[3] and was first described by Neve et al.[46] in three families with early-onset type 2 diabetes. In 2017, a p.A347S mutation in the KLF11 gene was reported as a single case in the "TODAY" clinical trial conducted among overweight/obese children in USA. The *KLF11* mutation was reported in a 16-year old Hispanic male, with an HbA1c value of 6.4%. The total cholesterol and triglyceride values were very high and LDL cholesterol was also high. The patient was treated with metformin and rosiglitazone; however, complications were not reported.[47]

3.4. CEL-(MODY8)

The *CEL*-(MODY8) has been reported in eight families.[15,48–51] Raedar et al. first described the *CEL*-(MODY8) mutation in two families from Norway identified with diabetes and exocrine pancreas dysfunction.[49] They identified a single-base deletion in the variable number of tandem repeats (VNTR) in exon 11 of the CEL gene. A six member family from Denmark was also reported with *CEL*-(MODY8) exhibiting diabetes and pancreatic exocrine dysfunction.[50] Recently, this mutation was reported from Siberia in a 37- year old female patient who was earlier treated as type 1 diabetes for five years and was reported to have an aggressive course of diabetes.[48] In a study from China, nine MODY probands (with biopsy-proven diabetic kidney disease) underwent whole-exome sequencing and two families with *CEL*-(MODY8) were described. The clinical characteristics included higher levels of albumin-to-creatinine ratio when compared with controls.[51]

Insulin is the only mode of treatment reported among the patients with this type of MODY.[48–50]

Microvascular complications such as non-proliferative diabetic retinopathy (NPDR) and peripheral neuropathy were reported in one patient.[48]

3.5. PAX4-(MODY9)

The *PAX4*-(*MODY9*) mutation was reported in eight families from Asia (China, India Japan, Singapore and Thailand)[29,51–55] and one from Siberia.[56] Two variants in the *PAX4* gene were first reported from Thailand in 2007.[54] The age of onset varied between six and 44 years (mean 24.2 years) and was reported to be more common in men. Insulin is the treatment modality for most of the patients.[29,51,53,55]

The diabetes reported in one case was severe and this patient presented with early onset renal complications.[53] Severe diabetic complications (retinopathy and nephropathy) were reported among family members from Thailand. Some of them died due to end-stage renal failure.[55]

3.6. INS-(MODY10)

Heterozygous *INS* mutations have been reported in 25 families across the world, in Australia, China, Czech Republic, Denmark, France, Italy, Norway and the USA; however, most reports come from the European region.[57–70] The mean age of onset of diabetes reported was 13.7 years. A mild form of diabetes was observed in few families[57,58,61,64,67] and gestational diabetes was reported in one proband's mother.[59] In one study, a R6C mutation was reported in a 15-year old proband, her mother and her grandmother with a milder form of diabetes.[60] Similarly, a single case of INS mutation was reported from the population-based Norwegian Childhood Diabetes Registry.[61] An *INS* mutation reported from Australia had a strong autosomal dominant form of diabetes which extended to four generations and was associated with mild ketoacidosis.[62] A 12- year old female proband was also reported from a cohort of overweight/obese children previously diagnosed with type 2 diabetes (TODAY trial).[63] A prediction program for type 1 diabetes patients at Czech Republic, PREDIA.CZ, also reported a case of *INS* mutation suggesting that MODY patients can also be hidden among families with type 1 diabetes.[66] Seven cases of INS mutation were reported from Japan presenting with early disease onset and DKA.[68] Two families with *INS* mutations were reported from China and one of the probands was earlier treated as a type 2 diabetes patient.[69,70]

The treatment modalities for patients with *INS*-(MODY10) have been; OHA treatment only,[63,64,69,70] patients who were started on OHA and later shifted to insulin[60,65] and patients treated only on insulin.[57,58,66,67] Two probands were shifted to insulin pump for better glycaemic control.[59,67] A 68 year old with duration of diabetes of 32 years was treated with multiple OHAs (metformin, sitagliptin and Glimepiride) as well as insulin.[59] One patient was on diet treatment only for 40 years before insulin was started and her mother, who was 65 years old, had been on diet treatment for eight years since diagnosis.[60] Several members of this family were started on insulin since diagnosis of diabetes.[62]

Complications with MODY10 have been reported in a few families. In one family, mild proliferative diabetic retinopathy (DR) was reported in a female proband and her mother underwent photocoagulation for retinopathy with neovascularisation.[59] Retinopathy, neuropathy and microalbuminuria was reported in a single proband,[64] while diabetic nephropathy, peripheral neuropathy and polycystic ovarian syndrome were reported in another.[69]

3.7. BLK-(MODY11)

The *BLK* gene is necessary for insulin synthesis and secretion and mutations in this gene are reported rarely in the literature.[33,71] Obesity is reported among three families reported with the *BLK* mutation.[71] Diabetogenic environment with an increased body weight plays an important role in the translation of BLK variant into diabetes as it is necessary for the translation of beta-cell abnormalities.[71]

Around 60% of the patients reported were treated with insulin. No complications have been reported among these patients.[71]

3.8. ABCC8-(MODY 12)

Mutations in *ABCC8* are related to both neonatal diabetes and MODY.[72] The heterozygous mutations related to MODY have been reported among 23 families across the world.[15,48,51,52,73–81] The mean age of diagnosis of the reported cases is 17.3 years and there is no difference in gender. Obesity is reported in few cases.[52,77,80] Seven probands were reported with heterozygous *ABCC8*-(MODY12) mutations. A response to sulphonylurea treatment is observed in these patients similar to *HNF1A*-(MODY3) and *HNF4A*-(MODY1).[73] In an interesting paper, a homozygous mutation was reported among two siblings. The mutation was inherited from both parents who were first cousins with heterozygous mutations and normal fasting glucose levels. The authors stressed the need for genetic testing to be done among consanguineous family members with negative autoantibodies.[74] Milder forms of diabetes were reported in a few families with an *ABCC8*-(MODY12) mutation.[75–77,81] Mild development delay and mild mental retardation was reported in a proband identified with a rare missense variant in the *ABCC8*-(MODY12) gene.[79] A study from South India reported *ABCC8* to be the most frequently mutated MODY gene from the region.[15] An aggressive type of diabetes from Russia reported a 29-year old man with convulsive seizures since childhood.[48]

The treatment for *ABCC8*-(*MODY12*) includes a shift from insulin to sulfonylurea drugs similar to the treatment of *HNF1A*-(*MODY3*)/*HNF4A*-(*MODY1*) mutations. In a case-report from Australia, the proband was started on sulfonylurea therapy after genetic testing and his insulin doses were reduced.[78] A large number of patients are treated with sulfonylureas and metformin[52,73,74,77–81] while one patient shifted to insulin after 6 years.[51] A patient from Russia with aggressive diabetes was sensitive to sulfonylurea drugs and a SGLT2 inhibitor (Dapagliflozin).[48]

The Russian patient was reported to have developed microvascular complications with peripheral neuropathy, pre-proliferative retinopathy, atherosclerotic changes of the brachiocephalic arteries, arterial hypertension and dyslipidaemia.[48] Two members of a family were reported with *COL4A3* variants associated with diabetes kidney disease (DKD). One among them was reported with end-stage kidney disease (ESKD) and diabetic retinopathy.[51]

3.9. KCNJ11–(MODY13)

To date, two families have been reported with *KCNJ11* mutations, from Singapore and Denmark.[52,82] The Danish study reported the mutation among 12 family members and three of the family members were treated with insulin while the rest were treated with oral drugs (name of the drug not mentioned), sulfonylureas and diet. The study from Singapore reported the mutation in a 43-year old female with a diabetes duration of 27 years. The patient was treated with oral drugs and insulin. The complications of diabetes were not reported in either of these studies.

3.10. APPL1-(MODY14)

A mutation in this gene has been reported in one American and one Italian family.[83] Twenty members of the Italian family and four family members of the American family were reported as carriers of this mutation. Eleven family members were diagnosed with diabetes and were treated with insulin and OHA. Diabetic complications were not reported in this study.

4. Discussion

This scoping review is one of the first attempts to study the clinical characteristics, treatment and complications reported among rarer MODY subtypes. The key findings from the study are as follows (i) different MODY criteria are used for genetic testing in different studies; (ii) *INS*-(MODY10) and *ABCC8*-(MODY12) mutations are the most commonly reported among the rarer MODY subtypes; (iii) significant clinical heterogeneity is present among members of the same family reported with rarer MODY mutations; (iv) characteristics thought to be

Table 3
Treatment management of the common and rarer MODY subtypes (adapted from reference[89]).

Common forms of MODY	Treatment options	
	Oral hypoglycaemic agents	Insulin
HNF1A-(MODY3)	Low-dose sulfonylureas	May be required after several years' duration
HNF4A-(MODY1)	Sensitive to sulfonylureas	May be required after several years' duration
HNF1B-(MODY5)	A minority respond to sulfonylureas	Commonly needed
GCK-(MODY2)	Rarely needed	Rarely needed except during pregnancy

Rarer forms of MODY	Diet	Oral hypoglycaemic agents	Insulin
ABCC8-(MODY12)		Sulfonylureas	May be required after several years' duration
INS-(MODY10)	Yes	Yes	Usually requires insulin
KCNJ11-(MODY13)	Yes	Sulfonylureas	Yes
NEUROD1-(MODY6)	Yes	Yes	Yes
IPF1/PDX1-(MODY4)	Yes	Yes	Yes
CEL-(MODY8)		Yes	Yes
BLK-(MODY11)	Yes	Yes	Yes
PAX4-(MODY9)	Yes	Yes	Yes
KLF11-(MODY7)		Yes	Yes
APPL1-(MODY14)	Yes	Yes	Yes

absent from MODY such as obesity and DKA are present among rarer MODY subtypes (v) insulin has largely been used in the treatment of rarer MODY subtypes but OHAs (including newer drugs like SGLT2 inhibitors and DPP4) have been attempted to treat patients and (vi) there is lack of data on microvascular and macrovascular complications among the rarer MODY subtypes. Although all the subtypes are loosely classified as MODY, some of them would definitely not fit into the original clinical criteria proposed by Tattersall and Fajans. Indeed, the very existence of some of these subtypes has not been established beyond doubt as is discussed below. These findings have significant clinical and research implications.

4.1. MODY-criteria have undergone changes from the original definition

In the past, most studies of MODY have largely used the Fajans and Tattersall criteria for genetic screening. However, in the studies reviewed here, modifications of the criteria such as a higher age of onset, presence of autoantibodies, absence of ketonuria etc. were used. Current guidelines for MODY insist that a genetic diagnosis must be made and hence MODY can only be diagnosed after the genetic studies.

The American Diabetes Association's *Standards of medical care in diabetes: Classification and diagnosis of diabetes-MODY*, The European Molecular Genetics Quality Network MODY group's *Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young* and The International Society for Pediatric and Adolescent Diabetes's *Clinical practice consensus guidelines for diagnosis and management of monogenic diabetes in children and adolescents* all have laid down strict criteria for diagnosis of MODY and these must be followed by future studies.

4.2. Sub-type reporting frequency

Among the rarer MODY subtypes reviewed, INS-MODY10, ABCC8-MODY12 and IPF1/PDX1-MODY4 are reported in large numbers. The other sub types such as *CEL*-(MODY8), *KLF 11*- (MODY 7), *APPL1*-(MODY14), *KCNJ11*–(MODY13) are much rarer forms.

4.3. Clinical characteristics

There exists significant clinical heterogeneity among the rarer MODY subtypes similar to what is seen in the common MODY subtypes. In addition, clinical heterogeneity exists among family members with the same mutation.

Although much clinical heterogeneity prevailed among the various MODY subtypes that were reported, it was observed that *IPF1*-(MODY4), *NEUROD1*-(MODY6) and *CEL*-(MODY 8) had some distinctive clinical characteristics. Dorsal pancreatic agenesis was reported in two *IPF1*/*PDX1*-(MODY4) cases.[27] However, as in the other reported *IPF1*/*PDX1*-(MODY4) cases pancreatic imaging has not been performed, it is not possible to determine whether this is a common feature of this MODY subtype or not. Given the possibility that this is a feature of this subtype, we suggest that *IPF1*/*PDX1*-(MODY4) patients are screened for this.

4.4. Non-traditional MODY characteristics

Obesity has previously been reported to be uncommon among MODY patients.[4,20] This is one of the important factors to distinguish between type 2 diabetes and suspected monogenic diabetes patients for genetic screening. However, we found that obesity was reported among patients with *IPF1*/*PDX1*-(MODY4), *NEUROD1*-(MODY6), *BLK*-(MODY 11) and *ABCC8*-(MODY12) mutations.[30,36,42,47,52,77,80] In recent years, obesity has also been reported in the more common MODY types (*HNF1A*/*HNF4A*-MODY).[47,84] Therefore, the occurrence of obesity in MODY may be more common than previously thought, likely due to the increase in obesity prevalence rates worldwide. Indeed, a longitudinal study conducted among overweight/obese children in the USA (the TODAY trial) observed that 4.5% of the children actually had monogenic diabetes which included *HNF1*-(MODY3), *HNF4A*-(MODY1), *GCK*-(MODY2), *INS*-(MODY10) and *KLF11*-(MODY7) mutations. The authors thus reported difficulty in differentiating youth-onset type 2 diabetes and MODY for sample selection since the study population selected was overweight/obese.[47]

Diabetic ketoacidosis (DKA) is also believed to be absent in MODY patients, and as DKA is used to help differentiate type 1 diabetes from MODY patients[19,20] this used to be a definite criteria for diagnosis of MODY. In this review, DKA was reported among patients with *PDX1*-(MODY4), *NEUROD1*-(MODY6), *HNF1A*-(MODY3) and *INS*-(MODY10) mutations[29,45,62,85,86] indicating that DKA may occasionally be present in MODY patients.

Therefore, using the absence of obesity and/or DKA as absolute criteria to suggest a patient does not have MODY no longer seems to be appropriate and this will need to be considered in the development of updated MODY screening guidelines.

4.5. Treatment

The treatment for rarer MODY subtypes, especially *IPF1*/*PDX1*-(MODY4), *CEL*-(MODY8), *INS*-(MODY10) and *APPL1*-(MODY14), includes largely insulin. ABCC8-(MODY12), patients tend to be shifted from insulin to sulfonylurea treatment. However, newer drugs have also been used in a few cases. Dapagliflozin, a SGLT2 inhibitor, was used along with a sulfonylurea in the treatment of a patient reported with ABCC8-(MODY12) mutation[48] and Sitagliptin, a DPP-4 inhibitor, was tried in a patient reported with *IPF1*/*PDX1*-(MODY4).[32] The use of Sitagliptin and Rosiglitazone was also reported in a patient with *HNF1A*-(MODY3) who was previously treated with insulin. Although HbA1c levels in the patient increased after 6 weeks, the authors suggest usage of these drugs among MODY3 patients despite failure in this one patient.[87] Similar findings were observed when *IPF1*/*PDF1*-(MODY4) patient was started on Sitagliptin.[32]

Table 4
Recent classification of the common, rare and doubtful MODY types (modified from reference.[18]).

a. Common or well-established forms of MODY (1% of MODY or greater)	*HNF1A*-(MODY3), *HNF4A*-(MODY1) and *GCK*-(MODY2), *HNF1B*-(MODY5), *ABCC8*-(MODY12), *KCNJ11*-(MODY13), *INS*-(MODY10)
b. Rare forms of MODY (Few families described but reasonable generic evidence for causing MODY)	*NEUROD1*-(MODY6), *IPF1/PDX1*-(MODY4), *CEL*-(MODY8), *WSF1* and *RFX6*
c. Genes reported as causal for MODY but evidence not compelling	*BLK*-(MODY11), *PAX4*-(MODY9) and *KLF11*-(MODY7), *APPL1*-(MODY14), *NKX6-1*

Table 5
When to order genetic testing for MODY?

1. Young age at onset
2. Strong family history of diabetes especially three-generation transmission of diabetes
3. Diabetes without typical features of type-1 or type-2 diabetes (negative diabetes-associated autoantibodies, non-obese, lacking other metabolic features)
4. Absence of ketoacidosis
5. Clinical features of a specific genetic subtype (example kidney abnormalities in HNF1B-(MODY5))

Overall, the literature on the use of different therapeutics with rarer MODY subtypes is still lacking and future studies should explore the possibilities of newer antidiabetic agents among such patients.

The ISPAD 2018 treatment guidelines support the use of sulfonylureas for *HNF1A*-(MODY3) and *HNF4A*-(MODY3) patients.[88] With increased reporting of rarer MODY subtypes it is important that similar guidelines be established based on evidence generated in these rarer forms of MODY.

The outline of the various treatment is seen in Table 3.

4.6. Complications

Complications among the rarer MODY subtypes are less documented when compared with patients with common MODY mutations. Patients with the common *HNF1A*-(MODY3) have an increased risk for cardiovascular mortality when compared with unaffected family members and hence early statin therapy is advised[90] while patients with the GCK-(MODY2) mutation have a low prevalence of microvascular and macrovascular complications.[22,91,92] Therefore, appropriately categorised treatment can be provided for these patients based on their subtype. However, there are very few reports on complications in rare MODY subtype patients. A few patients have been reported to develop severe complications such as nephropathy and retinopathy within 10 years of diabetes manifestation leading to renal failure and death.[41] However, longitudinal studies are required to study the complications among rarer MODY subtypes to develop a more complete picture of the likely, and not so likely, complications so that appropriate treatment guidelines can be generated.

4.7. Recent developments in rarer MODY subtypes: are some of these subtypes really MODY?

In recent years the widespread use of 'next generation' sequencing methods have helped understand the variations in human DNA sequence. However, difficulties are now faced in accurately differentiating the genetic differences between type 2 diabetes, monogenic diabetes and many variants which are reported to cause autosomal dominant disease. With no major new genes causing MODY identified in recent years, an accurate and quality interpretation of the genetic sequencing data for meaningful clinical translation is needed. There is an urgent need to consistently classify a gene as potentially causing monogenic diabetes,[93] especially in for rarer MODY subtypes so that their contribution as a true MODY-causing genes can be assessed. For instance, one study found that a previously reported MODY mutation in a population cohort was actually a common genetic variant.[8] Hence enough care should be taken in the interpretation of potential MODY gene variants which may otherwise lead to false positive interpretations.

4.8. Interpretation of true causal gene variants in MODY

One of the challenges in this area is the interpretation of genetic variants. Establishing the functional consequence of the variant based on experimental analysis can be time consuming and laborious. Databases like (i) Genome Aggregation Database (GnomAD), a resource developed by an international group of investigators to aggregate and harmonize exome and genome sequencing data, (ii) ClinVar, a freely accessible, public archive of reports of the relationships among human variations and phenotypes with supporting evidence, maintained by National Centre for Biotechnology Information-NCBI, (iii) Human Genome Mutation Database (HGMD), which collates all published gene lesions responsible for human inherited disease, can all be useful to make genetic testing for MODY more clinically meaningful. The GnomAD is the largest dataset of human genetic variation and characterises minor allele frequency (MAF) based on ancestry. It provides 125,748 exome sequences and 15,708 whole genome sequences from unrelated individuals and helps in understanding the clinical nature of a variant based on prediction from population prevalence of MODY. For example, allele frequencies that are common in GnomAD are most likely representative of benign conditions. Therefore, for a potential MODY variant it is important to compare MODY frequency with that in GnomAD before ascribing its causality.

4.9. Newer classification of MODY

Based on the genetic evidence studied in recent years, MODY mutations are now classified under three categories ***(i) common or well-established forms of MODY***- *HNF1A*-(MODY3), *HNF4A*-(MODY1), *GCK*-(MODY2), *HNF1B*-(MODY5), *ABCC8*-(MODY12), *KCNJ11*-(MODY 13) and *INS*-(MODY10), ***(ii) rarer forms of MODY-*** which have few families have been described but there is reasonable genetic evidence to call them as MODY- *NEUROD1*-(MODY6), *IPF1/PDX1*-(MODY4), *CEL*-(MODY8), *WSF1* and *RFX6* and ***(iii) genes reported as causal for MODY but evidence is not compelling*** which includes *BLK*-(MODY11), *PAX4*-(MODY9), *KLF11*-(MODY7), *APPL1*-(MODY14) and *NKX6-1* which is shown in Table 4 below:

Guidelines are now available from the American College of Medical Genetics and Genomics (ACMG) to assess the clinical significance of genetic variants.

We suggest that MODY testing is ordered if the following clinical features are seen as shown in Table 5 below.

The usual practice nowadays is to use the Next Generation Sequencing (NGS) to identify the presence and type of MODY. Once a MODY variant is identified, we suggest that the GnomAD and ACMG guidelines are followed so that patients are diagnosed correctly and false reporting of MODY cases can be avoided.[18]

5. Implications for future research

Registries like the Norwegian MODY registry, Norwegian Childhood Diabetes Registry (NCDR), PolPeDiabCollabration and the Molecular Genetic laboratory at Royal Devon and Exeter have built databases that help in studying the prevalence of MODY across Europe. It would also be useful for Asian countries including India and China, which have a high prevalence of diabetes, to undertake similar studies to understand the epidemiology of common and rarer MODY subtypes. From the evidence generated, the ISPAD treatment guidelines could be extended in the future to rarer MODY subtypes to improve the correct identification and best practice treatment for these patients.

6. Conclusions

This scoping review examined the existing literature about the clinical features, treatment and complications of rarer MODY subtypes reported across the world. In the recent years, increased reporting of unknown variants caused challenges in studying the pathogenesis or clinical significance of rare MODY subtypes. Hence, the authors support the recent reclassification of MODY by the Exeter team and suggest that this classification if followed could lead to better diagnosis and clinical management of patients with MODY worldwide.

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Declaration of competing interest

No conflict of interest to declare.

Appendix A. Search strategy used in PubMed

search term
1. #IPF-4/pancreas/duodenum homeobox protein 1(PDX1)
2. #Insulin promoter factor -4
3. #Maturity Onset Diabetes of the Young4
4. #Neurogenic differentiation 1
5. #NEUROD 1
6. #Maturity Onset Diabetes of the Young6
7. #Kruppel-like factor 11
8. #KLF 11
9. #Maturity Onset Diabetes of the Young7
10. #Carboxy-ester lipase (CEL)
11. #CEL
12. #Maturity Onset Diabetes of the Young 8
13. #Paired box gene 4 (PAX4)
14. #PAX4
15. #Maturity Onset Diabetes of the Young 9
16. #Insulin gene
17. #INS
18. #Maturity Onset Diabetes of the Young 10
19. #B-lymphocyte specific gene
20. #BLK gene
21. #Maturity Onset Diabetes of the Young 11
21. #ABCC8
22. #Maturity Onset Diabetes of the Young 12
23. #KCNJ11
24. #Maturity Onset Diabetes of the Young 13
25. #APPL1
26. #Maturity Onset Diabetes of the Young 14
27. #notanimals
28. #clinical features
29. #treatment
30. #complications
31. #1OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 AND 28 OR 29 OR 30 NOT 27

Appendix B. Description of data extracted from each included study

Study characteristics	Year of publication
	Authors
	Country of study
	MODY criteria used for genetic study (if available)
Type of rarer mutation reported	
Patient characteristics	Current age (years)
	Gender (male/female)
Clinical characteristics	Age of onset of diabetes (years)
	HbA1c (%)
	BMI (kg/m^2)
	Duration of diabetes (years)
	Fasting plasma glucose (mmol/l)
	C-peptide -fasting, stimulated (mmol/L, ng/mL, pmol/L)
	Serum creatinine (mg/d l)
	eGFR (ml/min)
	Fasting glucose level (ng/dl), (mg/dl) (mmol/l)
	Fasting insulin (μu/ml)
	2-h insulin (μu/ml)
	Total cholesterol (mmol/l) (mg/dl)
	Serum triglycerides (mmol/l) (mg/dl)
Complications	Retinopathy-classification if reported
	Neuropathy
	Nephropathy
Treatment	Oral hypoglycaemic drugs-
	name/dosage (if provided)
	Insulin (type/dosage if provided)

Appendix C. Summary of the clinical characteristics, treatment and complications of the rarer MODY subtypes

Rarer MODY mutation reported	Author/year/country/reference	Settings/participants	Clinical features	Treatment	Comorbidities/complications
IPF-1/PDX1-(MODY 4)	Ağladioğlu/2015/Turkey/[26]	MODY1–11 genes sequenced in 43 children Criteria used a. Age at diagnosis <25 yrs b. Positive family history c. Autosomal dominant inheritance across 3 generations d. Impaired insulin secretion reflected by C-peptide level - regardless of insulin treatment e. Absence of beta cell autoimmunity and DKA.	1 patient with PDX1 mutation: p.D76N **Clinical details** Male Age at diagnosis – 2 yrs Duration of diabetes – 1 yr HbA1c (%)- 6.4 (at diagnosis) Family history- 3 generations Renal function tests, renal Doppler ultrasonography, ECG and retinal examinations: normal	Diet + Anti-hypertensive	**Comorbidities:** Hypertension **Complications:** Not reported
	Caetano/2017/Brazil/[27]	Proband selected for NGS analysis. Criteria used a. Age of onset of diabetes <35 years b. Family history of diabetes c. Absence of obesity d. Negative pancreatic antibodies e. Detectable C -peptide levels 3–5 years after diabetes diagnosis.	Two patients (proband and his son) with PDX1 mutation: c.188delC/p.Pro63Argfs*60 **Clinical details** **1. Proband-** Male Age at diagnosis: 14 yrs Duration of diabetes: 38 yrs BMI (kg/m^2): 21.8 After long duration of diabetes had detectable C-peptide levels Caudal pancreatic agenesis with no signs of pancreatic duct of this segment Faecal elastase: Low **2. Proband's son** Age at diagnosis: 5 yrs Duration of diabetes: 1 yr BMI (kg/m^2): 16.3 Detected with IGT Caudal pancreatic agenesis Faecal elastase: Normal	**1.** Diagnosed with T1D, treated with low dose insulin After MODY diagnosis, SU and reduced insulin	**1. Comorbidities** None **Complications:** Mild non-proliferative retinopathy **2. Comorbidities** None **Complications:** None
	Chapla/2014/India/[29]	NGS of MODY1–10 genes in 80 subjects of Asian Indian origin Criteria used a. Age of diagnosis <35 years b. Autosomal dominant inheritance c. Absence of beta-cell autoimmunity d. Absence of DKA	1 patient PDX1 gene mutation: V177M **Clinical details** Male Age at diagnosis (yrs)- 26 Duration of diabetes (yrs) - 14 BMI (kg/m^2)-24.4	Insulin	**Complications:** Not reported
	Cockburn/2004/Trinidad and Tobago/[28]	Western blot analysis of IPF1/PDX1 in 264 patients: Criteria used a. Type 2 diabetes diagnosis at <40 yrs b. History of T2D in at least two generations	Two patients with IPF1/PDX1 mutation: E224K **Clinical details** **1. Proband** Female Age at diagnosis: 21 yrs Duration of diabetes: 2 yrs BMI (kg/m^2): 36.8 Fasting blood glucose (mmol/l): 7.6 2hBG (mmol/l): 16.6 **2. Proband's father (deceased)** Age at diagnosis: 17 yrs	**1.** Insulin **2.** Insulin	**Complications:** Not reported
	Deng/2019/China[30]	Whole-exome detection by next generation sequencing (NGS) American College of Medical Genetics and Genomics (ACMG) followed	Three patients with IPF1/PDX1 mutation: (p.Arg155Ser) **Clinical details** **1. Proband (first visit):** Male Current age- 14 yrs	1. **At first visit:**	**Complications:** Not reported

Fajans/2010/USA[36]	5 generation Michigan-Kentucky pedigree family -110 individuals. The Michigan -Kentucky pedigree includes members with permanent neonatal diabetes, MODY 4 and type 2 diabetes.	BMI (kg/m^2)-24.4 HbA1c (%)-10.7 Glycated albumin (GA%)- 23.5 **Clinical details** Obesity (BMI >30) and Islet cell antibody (ICA) negative **IPF1 mutation** **Clinical details** Sole Proband Age of diagnosis (yrs) – 16 DKA (no. of episodes) – 3 BMI (kg/m^2)-21.75 HbA1c (%)-4.5 Cholesterol (mg/dl)-174 (Reference value -240) Triglycerides (mg/dl)- 80 (Reference value -150) **2. Father of the proband** Basal C-peptide (ng/ml)-1.3 Age at diagnosis -34 yrs BMI (kg/m^2)-25 Glycosylated Hb -normal Creatinine and lipase -normal **Clinical details** Proband-Male Age - 26 yrs BMI (kg/m^2)-23 Non-fasting glucose(mg/dl)-511 C-peptide (ng/mL)- 1.6 HbA1c (%)-9.3 Islet cell and GAD antibodies-negative	Not reported Insulin-23 units/day. He was later changed to only metformin 0.5 g QD and had occasional hypoglycaemia Diet **2. Father of the proband** Metformin 0.25 g TID Initial treatment Metformin+ Pioglitazone- improvement in glycaemic control after a month of therapy (twice daily blood sugars- 120-220(mg/dl)) He became intolerant to metformin and shifted to glyburide 5 mg with pioglitazone This worsened the glycaemic control with blood sugars – 200-300 mg/dl After genetic testing positive to IPF-1 and to avoid insulin therapy the patient was started on 100 mg Sitagliptin, discontinue sulfonylureas and continue thiazolidinedione. The patient noticed improved glycaemic control with improvement in postprandial glucose readings. However his fasting glucose began to rise to start basal insulin 10 units of glargine each morning	**Complications:** Not reported **Complications:** Not reported Associated comorbidity Hypertension **Complications:** Not reported
Gragnoli/2005/Italy[37]	40 Italian families (22 men and 18 women) and 50 healthy Italian subjects (26 men and 24 women) were recruited around Rome. 40 probands were screened for mutations in the IPF1/PDX1 gene Criteria used a. Early-onset diabetes type 2 diabetes (age of onset <40 years)	**PDX1 mutation** **P33T mutation** **Clinical details** Sole Proband Age of diagnosis (yrs) – 16 DKA (no. of episodes) – 3 BMI (kg/m^2)-21.75 HbA1c (%)-4.5 Cholesterol (mg/dl)-174 (Reference value -240) since the diagnosis. Later his BMI increased to Triglycerides (mg/dl)- 80 (Reference value -150) **2. Father of the proband** Basal C-peptide (ng/ml)-1.3 Age at diagnosis -34 yrs BMI (kg/m^2)-25 Glycosylated Hb -normal Creatinine and lipase -normal **Clinical details** Proband-Male Age - 26 yrs BMI (kg/m^2)-23 Non-fasting glucose(mg/dl)-511 C-peptide (ng/mL)- 1.6 HbA1c (%)-9.3 Islet cell and GAD antibodies-negative	Diet	**Complications:** Not reported
Mangrum/2015/USA[32]	26-year-old male with PDX1 mutation who was treated with DPP-4 inhibitor	**PDX1 mutation** **C.694_695delCG** **Clinical details** Proband-Male Age - 26 yrs BMI (kg/m^2)-23 Non-fasting glucose(mg/dl)-511 C-peptide (ng/mL)- 1.6 HbA1c (%)-9.3 Islet cell and GAD antibodies-negative	Initial treatment Metformin+ Pioglitazone- improvement in glycaemic control after a month of therapy (twice daily blood sugars- 120-220(mg/dl)) He became intolerant to metformin and shifted to glyburide 5 mg with pioglitazone This worsened the glycaemic control with blood sugars – 200-300 mg/dl After genetic testing positive to IPF-1 and to avoid insulin therapy the patient was started on 100 mg Sitagliptin, discontinue sulfonylureas and continue thiazolidinedione. The patient noticed improved glycaemic control with improvement in postprandial glucose readings. However his fasting glucose began to rise to start basal insulin 10 units of glargine each morning	Associated comorbidity Hypertension **Complications:** Not reported
Mohan/2017/India[15]	Subjects recruited from a large diabetes centre in Chennai. All patients who met the MODY clinical criteria MODY criteria met Criteria set by Fajans and Tattersal a. Age at diagnosis – 30 years or less b. Control of hyperglycaemia for a minimum period of 2 years without insulin c. Negative for autoantibodies d. Absence of ketonuria any time e. Evidence of autosomal dominant inheritance including a three-generation family history of diabetes	Mutation in a single patient-K147R **Clinical details** Age at onset(yr)- 15–20 HbA1c (%)-7.6 BMI (kg/m^2)-30.0 FPG (mmol/dl)-136 C-peptide (fasting)—Not available Creatinine- Not available	Not reported	**Complications:** Not reported
Mruthyunjaya/2017/India[33]	Women recruited with pregnancy complicated with hyperglycaemia from September 2012 to 2013 Christian Medical College South India Criteria used Pregnant women with a. any degree of glucose intolerance with an age of onset of disease ≤35 years and b. BMI ≤ 30 (kg/m^2)	**PDX1 mutation- 1 patient** **C.670G>A** **Clinical details** Current age-26 yrs Age at diagnosis –10 yrs Duration of diabetes-16 yrs Type- preGDM BMI (kg/m^2)-23.6 Autoantibodies-negative History of ketoacidosis at onset The proband delivered a pre-term male	Insulin	**Complications:** Not reported

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Rarer MODY mutation reported	Author/year/country/reference	Settings/participants	Clinical features	Treatment	Comorbidities/complications
		Control subjects were selected from a homogenous population if Dravidian ethnic origin. The control subjects had normal Oral Glucose Tolerance Test (OGTT) with a HbA1c (%) <5.7. The subjects were without any known history of diabetes.	baby with low birth weight(2240 g) and was negative for PDX1 pathogenic variant Proband's mother is a carrier of the mutation and has impaired fasting glucose (IFG)		
	Stoffers/1997/USA[35]	Next generation sequencing (NGS) was used 5-Generation pedigree – Virginia family	**IPF1/PDX1 mutation** **Pro63fsdelC** The parents were heterozygous carriers and father had diabetes. The proband was a female infant with homozygous mutation. Eight family members were heterozygous carriers. Consanguinity was observed The average age of onset is 35 years (17–67 years)	Six of the eight affected members were treated with diet or oral hypoglycaemic agents	**Complications:** Not reported
	Weng/Sweden/2001[34]	IPF1/PDX1 mutation screening of 115 Scandinavian families with early-onset diabetes, with at least two members with onset of diabetes younger than 40 years.	**Mutation was reported in two families-(P239Q and D76N)** IPF1-D76N variant was found in one proband **Clinical details** 1. Proband- Female Current age -34 yrs Age of onset - 21 yrs P239Q mutation was identified in two patients **Clinical details** **1. Proband – female** Current age-59 yrs Age of onset- 15 yrs 2. Proband-Male Current age-36 yrs Age of onset- 15 yrs	1. Proband of one family Insulin started after 7 years 2. Proband of second family Started on insulin treatment after 5 and 2 years	**Complications:** Not reported
NEUROD1-(MODY 6)	Chapla/2014/India[29]	Reported earlier	**Mutation reported in two patients- p. His241Gln, p.Glu59Gln** **Clinical details** Proband -Female Age – 35 yrs Age of onset- 24 yrs BMI (kg/m^2)-39.7 **Clinical details** Proband –Male Age – 30 yrs Age of onset- 30 yrs BMI (kg/m^2)-19.3	**Proband-1** Metformin and Glimeperide **Proband-2** Glimeperide	**Complications:** Not reported
	Gonsorcikova/2008/ Czech Republic[41]	30 unrelated Czech probands with a clinical diagnosis of MODY (median age at testing -18 yr, median age at the recognition of hyperglycaemia-16 yr) were investigated for mutations in the NEUROD1 and IPF-1 genes. All of them had previously tested negative for mutations in HNF-1 alpha, glucokinase and HNF-4 alpha	H241Q mutation was identified in two unrelated families **Clinical details** Family 1 Age of diagnosis – 20 years Sex- Female	**Family 1** First three years- OHA, later with insulin **Others in the family** All obese and on insulin **Family 2**	**Family 1** Developed serious complications -nephropathy, neuropathy and retinopathy within 10 years of diabetes manifestation Her complications led to chronic renal failure and premature death at

		BMI (kg/m^2)-34.0 Fasting serum C peptide- 1540 pmol/l at an ambient plasma glucose of 6.1 mmol/l **Others in the family** Six were positive for the variant- four were diagnosed with diabetes. (Age of onset of diabetes- 25, 19, 20 and 20 yrs) **Clinical details** **Family 2** Proband- Male Age of diagnosis – 20 years BMI (kg/m^2)-36.8 Fasting serum C peptide- 1262 pmol/l at an ambient plasma glucose of 5.0 mmol/l	Diet/OHA for the first 5 years later shifted to insulin	44 years **Others in family 1** Developed serious late complications-proliferative retinopathy, peripheral neuropathy and nephropathy **Family 2** Not reported
Horikawa/2017/Japan[38]	275 subjects suspected with MODY and negative for MODY 1–5 mutations referred from 155 medical institutions throughout Japan. Non-obese early-onset diabetes patients regardless of family history were included to miss any low penetrant cases. Criteria used: a. Age of onset 35 years or less b. Autoimmune antibody negative c. No obesity- (BMI < 25 kg/m^2) d. Family history was not included in order to not miss any sporadic or low penetrant cases Direct sequencing of all exons and flanking regions of NEUROD1 was performed	**NEUROD1** Four heterozygous mutations were reported- His206ProfsTer38, Pro245ArgfsTer17, L157R, H206TfsTer56 **Family -1** The mutation was found in proband and her mother, grandfather **Clinical details** Proband- Female Age at diagnosis – 14 years Eleven months following the medical treatment developed Diabetic ketoacidosis (DKA) and the cause was unknown. Insulin therapy was immediately begun. Autoantibodies – negative Insulin secretory capacity was reduced at glucagon load examination. **Family- 2** Mutation was found in proband and her mother **Clinical details** Proband- Female Age at diagnosis – 11 years She was diagnosed with diabetic ketosis and insulin was started. Autoantibodies were negative **Proband Mother- deceased** Gestational diabetes-34 years Also had slight mental retardation Age at diagnosis- 34 yrs	**Family 1** OHA -alpha glucosidase inhibitor (Initial treatment) Insulin (Current treatment) **Proband's mother** Metformin 750 mg/day Mitiglinide calcium hydrate 15 mg/day **Proband's grandfather** Glimepiride 0.5 mg **Family 2** **Proband** Insulin **Proband Mother-deceased** Not available	**Family 1** **Complications:** Not reported **Proband's mother** No complications **Proband's grandfather** Peripheral neuropathy of lower limbs **Family-2** Comorbidities **Proband** Mental retardation at 1–2 years. Webbed neck, low hairline, slightly high-arched palate, cubitus valgus, bilateral brachydactylia of the fifth digit, bilateral complete dactylosymphysis of the third and fourth digit, Joint contracture of left ankle Neurological abnormalities Developmental delay Mild cerebellar dysfunction Dysplasia of hippocampus Multiple deformity MRI- brain – dysplasia of the right hippocampus but no abnormality of cerebellum **Proband Mother-**slight mental retardation **Complications** **Proband Mother-deceased** Nephropathy,

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Rarer MODY mutation reported	Author/year/country/reference	Settings/participants	Clinical features	Treatment	Comorbidities/complications
					Simple diabetic retinopathy On haemodialysis from 52 years
			Family 3 Mutation found in proband and her mother **Clinical details** Proband – Female Age at diagnosis – 10 years Admitted for diabetic ketoacidosis at 20 years Abnormalities of the central nervous system were no apparent **Proband mother-deceased** Age at diagnosis- Not available Her intelligence level was low, hearing loss and seizures several times. At 55, she became bed-ridden and had diffuse brain atrophy found by CT scan at 56 yrs. She died at 58 – brain stem haemorrhage.	**Family 3** **Proband** Insulin 46 Units/day Metformin 1500 mg/day Sitagliptin 50 mg/day **Proband mother-deceased** Admitted to the hospital with complaints of foot ulcer at 42 years and insulin was started	**Family 3** **Proband** Second stage nephropathy Albuminuria **Proband mother-deceased** Developed proliferative retinopathy, nephropathy – fourth stage, haemodialysis
			Family 4 The mutation was found in the proband and her mother **Clinical details** Proband – Female Age at diagnosis – 12 years Ketosis at 20 years **Proband mother** Had gestational diabetes 27 years Age at onset – 33 years	**Family 4** **Proband** Nateglinide -90 mg/day Voglibose 0.4 mg/day Insulin 4 units/day **Proband mother** OHA (at initiation) glibenclamide+voglibose Insulin (at present)-16 units/day	**Family 4** **Complications** Not Reported
	Kristinsson/2001/Iceland[42]	To investigate the clinical and genetic causes of MODY in Iceland Mutation detection was carried out by sequencing the NEUROD1 and *HNF1A* genes.	Mutation reported in a single family -E110K mutation **NEUROD1 mutation- 1 family** **Clinical details** 5 of the 14 affected were diagnosed before 25 years of age The mean BMI (kg/m^2)– 24.1 One was underweight, Four overweight, one obese	Diet/OHA/Insulin	Retinopathy- 3 Peripheral neuropathy-5 Nephropathy-2
	Liu/2007/China[39]	85 unrelated early-onset and 95 late onset type 2 diabetes patients diagnosed according to the 2003 criteria of the American Diabetes Association and 87 unrelated non-diabetic control subjects in Shanghai, China Criteria used: a. Two consecutive generations of type 2 diabetes with at least one member diagnosed <25 years c. Negative for GAD and IA2 antibodies Of these generations, at least three members were affected	Mutation reported in five family members-Ser159 Pro **Clinical details** Proband-Male Age at onset (yr)- 27 BMI (kg/m^2) – 23.7 Proband's father, aunt, uncle and uncle's daughter have the mutation	OHA	**Complications** Not Reported
	Mruthyunjaya/2017/India[33]	As reported earlier	Mutation reported in one patient-c.953A>G	Metformin + SU	

			Clinical details Proband- Female Current age-29 yrs Age at diagnosis –27 yrs Duration of diabetes -2 yrs Type- preGDM BMI (kg/m^2)-30		**Complications** Not Reported
	Plengvidhya/2009/ Thailand[40]	51 unrelated probands with early onset type 2 diabetes, 21 of them who fit the classic MODY criteria were analysed Criteria used: a. The proband and at least one first degree relative diagnosed with type 2 diabetes before age 35 b. Two or more generations affected by diabetes c. Diabetes treatment with diet and/or oral agents for at least 2 years d. No history of diabetic ketoacidosis e. Absence of anti-GAD antibody PCR-SSCP method by direct DNA sequencing	**Mutations reported in two persons- NEUROD1-1972G>A, NEUROD1-A322N** Proband 1 **Clinical details** Age at onset-20 yrs Duration of diabetes-4 yrs BMI (kg/m^2)-32 HbA1c(%)- 12.6 Fasting C-peptide (mmol/l)-0.35 S. Creatinine (μmol/l)-53.04 Total cholesterol (mmol/l)-5.83 Triglyceride (mmol/l)-1.33 LDL (mmol/l)-3.89 HDL (mmol/l)-0.78 Proband 2 **Clinical details** Age at onset-14 yrs Duration of diabetes-17 yrs BMI (kg/m^2)-22.23 HbA1c(%)- 7.60 Fasting C-peptide (mmol/L)-NA S. Creatinine (μmol/l)-88.40 Total cholesterol (mmol/l)-8.62 Triglyceride (mmol/l)-3.60 LDL (mmol/l)-6.19 HDL (mmol/l)-0.78	Not reported	**Complications** Not Reported
	Szopa/2016/Poland[43]	Included 156 diabetic probands of MODY families among them 52 patients earlier tested for GCK-MODY and/for *HNF1A*-MODY by Sanger sequencing. Genetic testing was now performed using targeted NGS sequencing	Mutation identified in one patient and 10 of his family members- Arg103Pro 1. Proband- Female **Clinical details** Current age- 66 yrs Age at diagnosis- 23 yrs BMI (kg/m^2)-28 Deceased	Insulin (started after 14 years of diagnosis)	**Complications** Not reported
KLF11- (MODY 7)	Kleinberger/ 2017/USA[47]	Sequencing using a custom genetic diabetes gene panel was done among 488 overweight/obese adolescents with type 2 diabetes in the Treatment Options for Type 2 Diabetes in Adolescent and Youth (TODAY)	Mutation reported in one patient-p.A347S 1. Proband- Male **Clinical details** Age - 16 yrs BMI z-score Mean ± SD 1.49 DXA fat (%) 23.9 Fasting glucose (mmol/l) 11.6 Fasting insulin(pmol/l) 164.6 Total cholesterol (mmol/l) 6.4 HDL cholesterol (mmol/l) 0.83 LDL cholesterol (mmol/l) 3.34 Triglycerides (mmol/l) 6.09	Metformin + Rosiglitazone	**Complications** Not reported

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Rarer MODY mutation reported	Author/year/country/reference	Settings/participants	Clinical features	Treatment	Comorbidities/complications
	Mohan/2018/India[15]	Reported earlier	KLF11 mutation reported in one patient-R465H Proband **Clinical details** Age at onset(yr)- 20–25 HbA1c (%)-15.4 BMI (kg/m^2)-26.3 FPG (mmol/dl)-134 C-peptide (fasting)—3.0 Creatinine- 0.7	Not reported	**Complications** Not reported
CEL-(MODY 8)	Mohan/2018/India[15]	Reported earlier	CEL mutation reported in one patient Proband **Clinical details** Age at onset- 10-15 yrs HbA1c (%)-6.9 BMI (kg/m^2)-26.1 FPG (mmol/dl)-134 C-peptide (fasting)—1 Creatinine- 0.5	Not reported	**Complications** Not reported
	Ovsyannikova/ 2017/Siberia[48]	20 patients with clinical diagnosis of MODY were examined.	**Mutation was reported in one patient**-p. Gly299Cys Proband- Female **Clinical details** Current age -37 yrs Age at diagnosis -32 yrs c-peptide (ng/ml)-1.9 BMI (kg/m^2)-23.6 HbA1c (%)- 7.5	Basal bolus regimen of insulin therapy (Lantus 8 Units, Humalog 10 Units per day)	Patient developed non-proliferative retinopathy and peripheral neuropathy
	Raeder/2006/Norway[49]	A large family autosomal dominant diabetes detected before 40 years of age. The age of onset was before 40 years was selected	**Characteristics of mutation carries in both families with CEL mutation** Total number of subjects/number of males- 17/8 Present age (yr)-49 ± 12 BMI (kg/m^2)-24 ± 2.9 CT scan of the pancreas in the ten mutation carriers showed decreased pancreatic X-ray attenuation that was similar to visceral fat. The abnormal pancreatic morphology was observed in all mutation carriers. Several family members complained of abdominal pain and loose stools.	Insulin- 10 OHA- 5 Insulin/OHA - 2	**Complications** Not reported
	Torsvik/2010/Norway/ Denmark/United Kingdom[50]	A total of 56 members of the two previously identified Norwegian families with mutation in the CEL VNTR were screened using the multiplex PCR. A total of 241 proband (95 Denmark, 146 from UK) with diabetes who met the minimal diagnostic criteria for MODY were analysed. All probands had tested negative for mutations in seven known MODY genes and therefore classified as MODYX. A total of 223 population-based controls with unknown diabetes status were also included.	**CEL VNTR mutation- 3-repeat CEL VNTR allele** 6 members from a Denmark family were identified with the mutation. **Characteristics of the family** Total number/male- 6/2 Present age(yr) - 52 ± 19 BMI (kg/m^2)-26.5 ± 1.2 Endocrine pancreas dysfunction Mean age at diagnosis(yr) - 27 ± 18 HbA1c (%)- 8.2 ± 1.9 Fasting plasma glucose (mmol/l)- 10.5 ± 5.1	Insulin	**Complications** Not reported

			Exocrine pancreas dysfunction Faecal elastase-1,μg/g -326 ± 211		
	Wang/2018/China[51]	355 patients with diabetes mellitus underwent kidney biopsy at Sichuan University and genetic information of 120 patients was obtained. Among them, 30 families had a family history of diabetes. After taking clinical and genetic characteristics into account nine patients were diagnosed into MODY and regarded as probands. The diagnosis of diabetes of the recommendations of the American Diabetes Association. Criteria used: a. Diagnosis of diabetes at an early age (<40 years old) b. Strong family history of diabetes c. Negative diabetes associated antibodies d. Non-obese and lacking other metabolic diseases e. Pathogenic variants in known MODY genes Whole-exome sequencing was done on nine proband's families to identify suspected MODY probands and their families related to diabetic kidney disease (DKD) and the susceptibility genes were reviewed. Immunofluorescence staining of COL4A3 was performed in kidney specimens of patients with DKD.	All the participants belonged to Han ethnicity. Clinical characteristics and the number of DKD variants of probands Age, yr, Median (IQR)- 44 (30–51) Duration of diabetes yr, Median (IQR)- 13.0 (10–17.5) Initial proteinuria, g/24 h, Median (IQR)- 6.0(1.3–10.8) Urine albumin-to-creatinine, mg/g, Median (IQR)- 3161(2107–6034) Serum Creatinine, mg/dl, Median (IQR)- 1.3(1.0–1.7) eGFR, ml/min per1.73 m^2, Median (IQR)- 56(46–94) ESKD, %(n) – 33(3) Number of DKD variants - 99	Insulin (6 years to insulin) Oral drugs	**Complications** Not reported
PAX4-(MODY 9)	Ang/2016/Singapore[52]	84 potential probands identified with the following criteria Criteria used: a. Age of onset <45 years b. No signs of acanthosis nigricans c. Negative GAD status d. Positive family history e. Preserved endogenous pancreatic beta cell insulin production (i.e. No history of unprovoked diabetic ketoacidosis) The main idea was to exclude obvious young-onset type 1 and type 2 diabetes while looking for MODY	Mutation reported in one patient: R52C Proband -Male **Clinical details** Race- Malay Age at diagnosis-35 yrs Diabetes duration- 3 yrs Family history- positive BMI- 28.1(kg/m^2) HbA1c(%)-9.2	**1.** OHA	**Complications** Not reported
	Chapla/2014/India[29]	Reported earlier	Mutation reported in one person: R31L mutation Proband-Male **Clinical details** Age of onset- 14 yrs BMI (kg/m^2)-23 GAD/IA2- negative Grandmother and mother diagnosed with diabetes at 45 years.	Glimepiride and Insulin	**Complications** Not reported
	Jo/2011/Japan[53]	Hokkaido University School of Medicine,	Mutation in proband and his father-	**1. Proband**	

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Rarer MODY mutation reported	Author/year/country/reference	Settings/participants	Clinical features	Treatment	Comorbidities/complications
		Sapporo Japan	(c.374–412 del39) 1. Proband-Male **Clinical details** Age at onset- 15 years Fasting glucose level(mg/dl)- 642 HbA1c(%)- 14.5 C-peptide ng/ml (Fasting)- 1.08 C-peptide ng/ml (post-prandial)- 1.25 CT scan- Kidneys and pancreas normal **Proband's father** **Clinical details** Father diagnosed with diabetes at 30 years BMI (kg/m^2)-32	Insulin – 0.5 Units/kg **Proband's father** Diet therapy	**Complications** Not reported
	Plengvidhya/2007/ Thailand[54]	PAX4 coding sequence in 46 MODY probands without mutations in known MODY genes and in 74 non diabetic controls using PCR Criteria used: a. The proband and at least one first-degree relative diagnosed with type 2 diabetes before 35 years of age b. two or more generations affected by diabetes c. diabetes treatment with diet and/or oral agents d. No history of diabetic ketoacidosis e. Absence of glutamic acid decarboxylase activity	**PAX4 mutation** Two novel variants were identified-(R164W and IVS7-1G>A) **R164W proband-** Female Age at onset- 20 yrs **Proband's father** Age at onset – 50 yrs **IVS7-1G>A proband** Clinical details not provided	**R164W proband** OHA **Proband's father** OHA **IVS7-1G>A proband** Not reported	**R164W proband** Complications not reported **IVS7-1G>A proband** The members were reported with severe complications
	Sujjitjoon/2015/Thailand[55]	PAX4 mutation studied in a family PCR-RFLP method was used.	**IVS7-1G>A** mutation identified in a family-proband and his daughter Proband-Female **Clinical details** Age at diagnosis - 44 yrs Deceased **Proband's daughter** **Clinical details** Age at diagnosis – 30 yrs Diagnosed with gestational diabetes at 24 years	**Proband's daughter** Insulin	Pedigree analysis revealed severe complications in diabetic family members. Some of them died due to end-stage renal failure. Proband's younger sister suffered with diabetic retinopathy at 30 years and nephropathy 10 years after diabetes diagnosis.
	Wang/2018/China[51]	Reported earlier	The clinical characters of the proband is explained earlier PAX4 mutation reported in two families.	Family 1-proband Insulin (7 years to insulin) Oral drugs Family 2-proband Not reported	Family 1-proband Diabetic retinopathy End stage renal disease (ESRD) Family 2-Proband Diabetic retinopathy End stage renal disease (ESRD)
	Zubkova/2017/Russia[56]	Federal State Budgetary Institution, Endocrinological Scientific Center of the Ministry of Health of Russia INS was sequenced in 116 maturity-onset diabetes	**Mutation reported in two patients** - c.55C>Tp.R19W c.596C>Tp.T199l Proband- Male **Clinical details** Age at diagnosis- 6 years HbA1c (%)-7.3 Mutation detected in proband and his mother **2**. Age at diagnosis- 16 years HbA1c (%)-4.1 INS – 2 patients	**Case-1** Diet only **Case-2** Not reported **Proband-1**	**Complications** Not reported

INS-(MODY 10)	Bonfanti/2009/Italy[58] Boesgaard/2010/ Denmark[57]	[illegible: overprinted text — 326 clinical criteria / MODY X patients / type 1 diabetes / autoantibodies] b. No treatment with insulin and/or measurable C-peptide at least one year after diagnosis c. Autosomal dominant inherited diabetes with known diabetes in at least two consecutive generations	[illegible: overprinted text] Proband 2 **Clinical details** Ethnicity-Czech **Clinical details** Sex-Male Age at diagnosis-13 years Age at onset- 6 years 8 months Duration of diabetes-4 years BMI-16.4 (kg/m^2)- 50th centile for corresponding age C-peptide -0.49 mg/ml HbA1c(%)-6.4	**Proband-1** Insulin- 0.7 units/kg/day **Proband 2** Insulin was started and continued for 6 months. The patient was on and off insulin several times (a pattern that may resemble the so-called honeymoon phase of type1 diabetes) Current treatment Insulin dose- 0.17 units/kg/day	**Complications** Not reported
	Dustakova/2015/ Czech Republic[59]	Charles University in Prague	INS mutation detected in two families **Family 1** (c.233delA) Mutation was found in the proband, his mother and maternal grandfather 1. Proband-Male **Clinical details** Current age – 20 years Age of diagnosis – 14 years 2 Six years after insulin treatment BMI (kg/m^2)-27.4 HbA1c (%)-6.3 C-peptide still detected Diabetic ketoacidosis- NIL GAD- negative **Family 2** c.188-31G>A Mutation in the proband and her mother **2.** Proband-Female **Clinical details** Current age – 29 years Age of diagnosis – 17 years BMI (kg/m^2)-22.3 Diabetic ketoacidosis- NIL GAD- negative Current clinical measurements HbA1c (%)-8.2 Insulin autoantibodies-positive GAD and IA2- autoantibodies -negative	**Family 1** **Proband** Insulin-0.8 IU units/kg/day **Family 2-proband** Following two weeks of insulin therapy she achieved complete remission and remained untreated and normoglycemic for 3 years. Her condition resembled type 1 diabetes since she received multiple doses of insulin injections. Insulin dose increased during adolescence and currently on insulin pump	**Family 2** **Proband** Mild proliferative retinopathy
	Edghill/2008/The Neonatal Diabetes International Collaborative Group[60]	INS gene was sequenced in 296 probands with maturity-onset diabetes of the young in addition to 285 patients with diabetes diagnosed before 2 years of age and 463 patients with young-onset type 2 diabetes (nonobese, diagnosed <45 years)			**1. Complications** Not reported

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Rarer MODY mutation reported	Author/year/country/reference	Settings/participants	Clinical features	Treatment	Comorbidities/complications
		Minimal diagnostic criteria were used a. At least two generations affected b. at least one subject diagnosed before 25 years of age			
			Mutation in three members of the family: R6C (c.16C>T,p.Arg6Cys) proband, probands' mother and maternal grandmother 1. Proband **Clinical details** Current age-not given Age of diagnosis – 15 years BMI (kg/m^2)-24.1 **2. Proband's mother** **Clinical details** Age of diagnosis – 15 years BMI (kg/m^2)-26.9 **3. Proband's grandmother** **Clinical details** Age of diagnosis – 65 years BMI (kg/m^2)-29.3	**1. Proband** Diet – 10 years then on OHA before starting on insulin (0.2 IU/kg/day) **2. Proband's mother** Diet for 40 years before starting oral drugs at 55 years **3. Proband's grandmother** Diet 8 years since diagnosis	
	Irgens/2013/Norway[61]	2756 children aged 0–14 years with newly diagnosed diabetes were recruited to the nationwide population-based Norwegian Childhood Diabetes Registry (NCDR) from July 2002 to March 2012. Criteria used: a. All children who had at least one parent with diabetes and b. GAD- negative and IA-2 -negative, c.HbA1c(%)- <7.5, no insulin requirement	**Mutation reported in one patient;** c.163C>T/p.Arg55Cys **Clinical details** 1. Age of diagnosis – 10 years Sex- not reported C-peptide(nmol/l) - 0.5 BMI (kg/m^2)-20.8 HbA1c (%)-9.1 GAD- <1 IA2- <1 Family history - positive	**1.** Insulin	**1. Complications** Not reported
	Johnson/2018/Australia[62]	Case report	**Mutation reported in four generations**	**Initial treatment**	

Molven/2008/Norway[65]	Screened for INS in 62 probands with MODY, 30 probands with suspected MODY and 223 from Norwegian Childhood Diabetes Registry selected on the basis of autoantibody negativity or family history of diabetes Physicians refer to the **Norwegian MODY registry based on at least two criteria** a. First-degree relative with diabetes b. Insulin level < 0.5 units/kg/day c. Diabetes diagnosed between 25 years and 40 years of age or unusual type 1 diabetes (low insulin requirement, no antibodies or atypical history)	**c.227C>A (p.Pro76Gln) in three family members; (R46Q)** Proband, mother, brother and sister proband, father, paternal aunt 1. Proband: Female **Clinical details** Clinical details Clinical details Age at diagnosis-11 yrs Age at diagnosis-20 yrs BMI (kg/m^2)-22.9 HbA1c (%)-5.9 (current) GAD/IA2 antibody-negative **2. Proband's father** Age of diagnosis-18 yrs ce:bold>3. Proband's paternal aunt Age of diagnosis -17 yrs	In Proband Initial treatment Current treatment Insulin dose (current)-0.8 units/kday **2. Proband's father** **Initial treatment** Sulfonyl urea **Current treatment** Insulin-0.25 Units/kg/day **3. Proband's paternal aunt** Diet	**1. Complications** No comorbid condition Detected with bipolar disorder **1. Complications** Not reported **2. Proband's father** Neuropathy 3. **Complications** Not reported
Kleinberger/2017/USA[63]	Reported earlier	**Mutation in one patient;**p.R6H **1.** Female Age – 12 yrs Three mutation identified in two French and one Danish patients; c.88C>GG-p.L30M; c.163C>T-p.R55C; L30M mutation **1.** Age at diagnosis- 17 yrs HbA1c (%)- 5–9 **2.** Age at diagnosis-20 yrs 3. Age at diagnosis- 17 yrs BMI (kg/m^2)-19–25.5	**INS mutation** Metformin **1.** OHA- Glibenclamide Insulin (after 9 yrs of onset) **2.** Diet+OHA **3.** OHA	**Not reported**
Meur/2010/France[64]	16 probands of French families based on MODY criteria. 95 patients diagnosed with non-autoimmune diabetes before 35 years and at least one affected first degree relative were included. Additional three families- one French, One Danish The clinically defined MODY based on two criteria a. Diabetes diagnosed before 25 years (range of diagnosis- 15-23) without requirement of exogenous insulin in the first 2 years and an autosomal dominant inheritance of type 2 diabetes			**1.** No microangiopathy or macroangiopathy was detected in -the patient after 24 years **2.** Retinopathy Neuropathy Microalbuminuria
Petruzelkova/2015/ Czech Republic[66]	53 families who had one or more family members with diabetes were chosen for direct sequencing with the following genes- GCK, *HNF1A*, HNF4A, INS genes The 2008 best practices guidelines for the molecular diagnosis of MODY was used	One patient reported with mutation **1**. Proband-Female **Clinical details** Age at onset- 7 yrs HbA1c (mmol/mol, IFCC)-49 4 patients carrying the mutation: **c.125T>C** Proband's father, his brother and sister carry the mutation.	Insulin treatment	**Complications** Not reported
Piccini/2016/Italy[67]	34 patients recruited at the Genetic unit and Diabetology unit of Meyer Children's Hospital during 2012–2014 were investigated. Criteria used: a. Early onset of diabetes (<25 years), b. Three generation positive family history of AD diabetes with at least one parent or sibling with diabetes according to ISPAD guidelines.	1. Proband-Male **Clinical details** Age at diagnosis-6 yrs HbA1c(%)- 6.4 GADA< IA2, IAA0- negative 2. Proband's brother **Clinical details** Age at diagnosis(yr)-10 BMI (kg/m^2)-15.5 Proband's sister Age at diagnosis(yr)-3	**1. Proband** **Initial treatment** Basal bolus-therapy with multiple daily injections (MDI) resulted in good metabolic control **2. Proband brother** Insulin replacement therapy with insulin glargine given subcutaneously once daily. After 16 months MDI with basal bolus therapy was started resulting in adequate metabolic control (initial treatment) After genetic results, the brothers were shifted to Repaglinide and insulin glargine The brothers and sister are on continuous subcutaneous insulin pump (CSII pump) to get a better glycaemic control and quality of life.	**1. Comorbid condition** At birth presented with posterior urethral valves Surgically treated at two months of life. Abdominal ultrasound – dilated pelvis **Complications** Screening for complications was negative in 2015
	Mutations in 30 genes were screened using	Seven patients were identified with the	Not reported	

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Rarer MODY mutation reported	Author/year/country/reference	Settings/participants	Clinical features	Treatment	Comorbidities/complications
		next-generation sequencing All participants required insulin therapy and satisfied the following criteria Criteria used: a. Recruited by JSGIT between January 2008 and June 2013 b. Diagnosed with type -1 diabetes on the criteria of the World Health Organisation (WHO) c. Diagnosed between the age of 0.5 to 16 years d. Had detailed medical records including all details including height and weight e. Showed negative results for all diabetes associated with autoantibodies examined.	above mutations INS (p.C31Y), INS (p.V42A) INS (p.G75C), INS (p.R89C) INS (p.C96F), INS (p.C96R) **Clinical characteristics of INS mutation carriers** **Clinical details** Male/Female- 5/2 Age at diagnosis - 2.3 (1.5–4) yrs Diabetes duration- 3.0 (1.5–5.2) yrs Parenteral history of diabetes- 3/7 DKA at diagnosis- 2/5 HBA1c (%)- 9.7		**Complications** Not reported
	Ushijima/2017/Japan[68] Xiao/2019/China[69]	The Second Xiangya Hospital Centre South University, Hunan, China National Clinical Research Centre for Metabolic Diseases, Changsa, Hunan, China	**Mutation reported in three generations:** c.212dupG(p.Gly73fs) Mutation reported in three generations – proband, her mother, maternal uncle, maternal aunt, maternal female cousin **Clinical details** BMI (kg/m^2)-23.3 HbA1c (%)-12.3 Fasting glycaemia (mmol/l)-12.02 C-peptide (FCP) (pmol/l)-115.8 2-h postprandial C-peptide (pmol/L)-325.1 GAD- <1 IA2- <1 Zinc transporter antibody-negative Family history - positive **2. Proband's mother clinical features** BMI (kg/m^2)-23.9 Metabolic cataract	**1.** Metformin and gliclazide (Initial treatment) Metformin and Insulin (Current treatment) 2. **Proband's mother** Premixed insulin- twice a day	**1. Comorbid condition** Metabolic cataract Polycystic ovarian syndrome **1. Complications** Diabetic nephropathy Peripheral neuropathy
	Yan/2017/China[70]	31 patients were selected for whole exome sequencing from 3140 patients with type 2 diabetes previously genotyped in Shanghai Diabetes Institute Inpatients Database. Criteria used: a. Positive family history of type 2 diabetes b. Earlier onset-age of diabetes (< 50 years) c. Lower BMI (≤ 26) d. Negative for autoantibodies	**Mutation reported in one patient p.Ala2Thr** **1**. Proband-Male **Clinical details** Age of onset- 31 years Fasting plasma glucose- 16 (mmol/l) Autoimmune antibodies-negative	Gliclazide and Acarbose	**Complications** Not reported
BLK-(MODY 11)	Borowiec/2009/ Poland[71]		**Mutation in three families: Ala71Thr mutation** **Clinical features of the BLK mutation carriers:** Families 3 Male/Female- 9/12 Age at diagnosis 31 ± 16 yrs Age at examination 45 ± 20 yrs BMI (kg/m^2) 28.7 ± 5	Diet only (%) -18.2 Oral agents (%) -22.7 Insulin (%)-59.1	**Complications** Not reported

			HbA1c(%) 7.7 ± 1.6 Fasting glucose (mg/dl) 166 ± 60 Fasting C-peptide(ng/ml) 0.87 ± 0.4		
	Mruthyunjaya/ 2017/India[33]	Reported earlier	**BLK mutation – 1 patient** c.1252G>A **Proband** **Clinical details** Current age(yr)-23 Age at diagnosis(yr) –23 Type- preGDM BMI (kg/m^2)-30	**BLK mutation** Metformin+Insulin	**Complications** Not reported
ABCC8-(MODY 12)	Ang/2016/Singapore[52]	Reported earlier	**Mutation in one patient: R1493G** Proband-Male **Clinical details** Race- Chinese Age at diagnosis-30 yrs Diabetes duration- 5 yrs Family history- positive BMI- 30.3(kg/m^2) HbA1c(%)-6.0	OHA	**Complications** Not reported
	Bowman/2012/ United Kingdom[73]	85 patients with BMI < 30 $kg/m^{2,}$ no family history of neonatal diabetes and who were sensitive to SU were taken. All were tested negative for *HNF1A* and HNF4A genes PCR analysis was carried out	Mutation in seven patients **Clinical features of the seven patients** Male/Female-3/4 Age at diagnosis - 21.4 ± 11.4 yrs Age at examination -30.5 ± 11.3 yrs HbA1c (%) 7.5 ± 1.5	**Proband1-**Gliclazide 20 mg with meals **Proband 2-** Repaglinide 2 mg TDS **Proband 3-** Insulin. Initially gliclazide. Poor glycaemic control **Proband 4-** Insulin. Previously Gliclazide 40 mg BD and Metformin 2 g MR **Proband 5** Gliclazide 40 mg daily dose **Proband 6** Glibenclamide 2.5 mg BD **Proband 7** Tolbutamide 2.5 mg/day Metformin 2 g/day Levemir 2 g/day 10–18 U OD	**Complications** Not reported
	Cattoni/2018/ United Kingdom[74]	University of Exeter, London Targeted NGS sequencing carried out	Mutation reported in 1 patient: c.188delC/p.Pro63Argfs*60 1. Proband-Male **Clinical details** Age of onset – 3 yrs Insulin levels- 1.7μUI/ml, C-peptide – 43.5 ng/dl Blood glucose level- 370.8 mg/dl	Glibenclamide. Post insulin switch over, significant improvement in blood glucose control was observed after a year. No episodes of hyper or hypoglycaemia was observed.	**Complications** Not reported
	Gioeva/2016/Russia[75]	Molecular genetic study was conducted in 256 patients (149 boys and 107 girls) aged 3 months to 25 years using next generation sequencing	No clinical details elicited, though the clinical details of the patient are similar to MODY 1 and MODY 3 patients	Metformin Currently hospitalised for change of treatment	**Complications** Not reported
	Gonsorcikova/2011/ Czech Republic[76]	Proband recruited from a cohort of patients of Czech Caucasian origin with autosomal dominant transmission of diabetes or hyperglycaemia first recognised in childhood, adolescence or early adulthood.	**Mutation in one patient: V**84I mutation 1. Proband-Male **Clinical details** Age of diagnosis – 19 yrs Mild hyperglycaemia was detected at 12 years. Clinical signs of diabetes were absent. The fasting and C-peptide levels were 8.38	No treatment reported	**Complications** Not reported

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Rarer MODY mutation reported	Author/year/country/reference	Settings/participants	Clinical features	Treatment	Comorbidities/complications
			and 50.2 mIU/l for insulin and 496 ad 1620 pmol/l for C-peptide		
	Johansson/2012/ Norway[77]	Exome sequencing for a molecular diagnosis in nine patients suspected with MODY with negative candidate genes recruited from Norwegian MODY Registry Criteria used: a. Diabetes in at least three generations b. Age of diagnosis – 11- 28 years for at least 1 family member	**Mutation in one patient: p.A1366T** Proband-Female **Clinical details** Current age- 38 yrs Age at diagnosis-25 yrs BMI (kg/m^2)-29.9 HbA1c (%)-9.0	Sulfonylurea and Metformin	**Complications** Not reported
	Johnson/2018/Australia[78]	Case report of ABCC8 mutation	**Mutation reported in 3 patients (c.4196C>T,p.Ala390Val)** Proband, his mother and his maternal uncle were reported with the mutation Proband -Male **Clinical details** Age at diagnosis- 27 yrs	**1.** After genetic diagnosis, the proband was stared on Glyclazide-160 mg/daily (SU). The dose of insulin was reduced from 25 units to <10 units over three months and maintained good glycaemic control. He was lost to follow-up precluding further insulin reduction. **2. Proband's mother** Diet **3. Proband's maternal uncle** Shifted to gliclazide -160 mg/daily. Insulin requirements reduced from 130 units to 10 units daily and reported improvement in the quality of life	**Complications** Not reported
	Kwak/2016/South Korea[79]	Whole exome sequencing in 28 patients with early onset diabetes	**Mutation in one patient:p.Arg74Gln** Proband-Female **Clinical details** Current age – 17 yrs Age at onset – 9 yrs BMI (kg/m^2)-23.6	Metformin Insulin Time to insulin – 6 yrs	**Complications** Not reported
	Mohan/2018/India[15]	Reported earlier	**Mutation in five patients:** (N781S, G1009S, A1473T,E971V,K1023Q) **Clinical details** Age at onset - 5-30 yrs HbA1c (%)-7.46 BMI (kg/m^2)-22.36 FPG (mmol/dl)-98.6 C-peptide (fasting)—0.56 Creatinine- 0.74	Not reported	**Complications** Not reported
	Ovsyannikova/ 2017/Siberia[48]	Reported earlier	**Mutation reported in two patients:** p. Ala1457Thr Proband-Male **Clinical details** Current age -29 yrs Age at diagnosis -27 yrs c-peptide (ng/ml)-0.7 HbA1c (%)- 6.6 The proband had convulsive seizures during his childhood **2. Proband's mother** **Clinical details** Age at diagnosis (yr)- 30 HbA1c(%)-7.8	**1.** Basic bolus regimen of insulin – 24 U/day After genetic diagnosis- Gliclazide and Dapagliflozin The glycaemic control was achieved in 3 months. 2. **Proband's mother** Metformin (Initial treatment) Gliclazide and empagliflozin (current)	**Comorbid conditions** Dyslipidaemia Arterial hypertension **ABCC8 proband** Early signs of diabetic retinopathy (2 years of onset)
	Ozdemir/2018/Turkey[80]	NGS was performed in 106 patients with a clinical	**Mutation in 1 patient: (c.1252T>C(p.**	Insulin +Metformin	

		diagnosis of MODY for the mutation for seven MODY genes. The variants were evaluated according to ACMG	**C418R))** Proband-Female **Clinical details** Age at diagnosis- 13 yrs Fasting glucose (mg/dl)-322 HbA1C(%)-12 C-peptide (ng/ml)-4.64 BMI (kg/m^2)-30.3		**Complications** Not reported
	Shepherd/2016/ United Kingdom[81]	808 patients <20 years of age with diabetes attending the six pediatric clinics in South West England and Tayside, Scotland were studied.	**Mutation in one patient: c.4139G>A** Proband-Female **Clinical details** Age at diagnosis – 11 yrs Duration of diabetes – 8 yrs GAD/IA2 - negative	OHA (Initial treatment) OHA (Current treatment)	**Complications** Not reported
	Wang/2018/China[51]	Reported earlier	**Variant in one patient**: c.824G>Ap.R275Q	Insulin (after 6 years of diagnosis)	**Complication** Diabetic retinopathy
KCNJ11- (MODY 13)	Ang/2016/Singapore[52]	Reported earlier	**Mutation in 1 patient: I131T** Proband-Female **Clinical details** Race – Chinese Age at diagnosis-16 Diabetes duration- 27 yrs BMI- 23.1(kg/m^2) HbA1c (%)-8.1	Both OHA/insulin	**Complications** Not reported
	Bonneford/2012/ Denmark[82]	Reported earlier	Mutation carriers in the French family-12 members Age of onset of diabetes 13–47 years HbA1c varies 5–8.6 (%)	Insulin- 3 patients SU- 1 patient OHA-2 patients OHA/diet-1 patient OHA/SU-2 patients	**Complications** Not reported
APPL1- (MODY 14)	Prudente/2015/USA/Italy[83]	Whole-exome sequencing done	**Mutation reported in two families-Italian and American** **APPL1-** **(c.1655T>A[p.Leu552*])** **(c.280G>A[p.Asp94Asn])** **1. Italian Family** Mutation carrier 20 Affected with diabetes- 8 **2. American family** Mutation carriers 4 Affected with diabetes- 3	**1. Italian Family** Insulin/OHA/diet **2. American family** Insulin	**Comorbidities** None **Complications** Not reported

BMI- body mass index, T2DM- type-diabetes mellitus, HbA1c- glycated haemoglobin, GAD/IA2-glutamic acid decarboxylase, insulinoma antibodies 2, FPG- fasting plasma glucose, eGFR- end glomerular filtration rate, ESKD- end stage kidney disease, DKD- diabetic kidney disease, HDL- high density lipoprotein, LDL- low density lipoprotein, 2hBG- 2 hour blood glucose, IGT- impaired glucose tolerance, OHA-oral antihyperglycemic agents, SU- sulfonylureas, NGS- next generation sequence.

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