Genetics in Maturity-Onset Diabetes of the Young

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Diabetes is a heterogeneous group of metabolic disorders, defined by persistent hyperglycemia due to both defects in insulin secretion and action, culminating in abnormal glucose metabolism with lifelong micro- and macro-vascular complications that develop from chronic hyperglycemia. It constitutes a significant cause of social, psychological, and financial burdens, along with an increased overall risk of premature death. Diabetes with early-onset hyperglycemia diagnosed in a patient under 25 years old, with an autosomal dominant transmission with at least three affected generations, a partially conserved pancreatic β-cell function, and the absence of autoantibodies are the characteristics of maturity-onset diabetes of the young (MODY). This subtype of genetically transmitted diabetes is suspected to be the most frequent type of monogenic diabetes, with a prevalence of 21–45 in 1,000,000 children and 100 patients in 1,000,000 individuals. Fourteen subtypes of MODY were identified and are currently acknowledged.

diabetes mellitus MODY3 insulin

1. HNF1A-MODY (MODY3)

HNF1A-MODY accounts for approximately 30%–50% of the maturity-onset diabetes of the young (MODY) cases, with nearly 414 mutations detected in 1247 families diagnosed. Such pathogenic variants are more frequently observed in exons 2 and 4, with a specific mutation (p.Gly292fs) accounting for nearly 10% to 15% of cases [1] Since patients with variants in the ending exons (8–10) are diagnosed, on average, eight years earlier than the ones with mutations in exons 1 to 6, studies show that the age at diagnosis can be partly pre-determined. The majority of pathogenic variants detected in the HNF1A gene are classified as mutations of high penetrance, once their presence is responsible for 63% of patients developing diabetes by the age of 25, 79% at 35 years old, and 96% by age 55 [2]. Heterozygous mutations in HNF1A are known to originate from MODY3, the most common form of MODY, characterized by a failure in glycaemic control with progressive impaired β-cell function. Individuals with heterozygous mutations are normoglycemic with the sufficient sensibility to insulin in the early stages, however, over time, typically occurring before the 25 years old, individuals with HNF1Apatohenic variants acquire an impaired glucose tolerance, and ultimately diabetes [3][4].

Similar to humans, HNF1A-null mice exhibit abnormal glucose-stimulated insulin secretion and develop diabetes two weeks after birth, expressing low levels of insulin and insulin-like growth-factor-1 (Igf1).

Therefore, the pathophysiology of HNF1A-MODY focuses on a severe reduction in insulin secretion in response to glucose. HNF1A has been shown to play a vital role as a transcription factor of the INS gene and GLUT2, encoded by the SLC2A2 gene, thus explaining the pancreatic-related disorders [5].

In the pancreatic β cell, GLUT2 acts as a glucose sensor that detects small changes in glucose levels leading to increased insulin secretion, and the lack of such transporters in the immature pancreas are likely to impact the β cell's response to hyperglycemia. While the role of GLUT2 in mouse β cells has been well-established, the role of GLUT2 in human β cells has remained debatable. Unlike in rodent β cells, where GLUT2 is the predominantly expressed glucose transporter, human β cells predominantly express GLUT1 and GLUT3, thereby suggesting that it may not be the principal glucose transporter in human β cells. However, despite the purported irrelevance of GLUT2 in human β cells, the association of GLUT2 mutations in Fanconi–Bickel syndrome and diabetes pathology supports the imperative role played by GLUT2 in human β cells, regardless of its lower abundance [6].

More evidence confirmed the extra-pancreatic effect of HNF1A mutations. MODY3 patients suffer from renal dysplasia, growth hormone deficiency, and hypothyroidism, which is similar to homozygous HNF1A knockout mice, which exhibit stunted growth, reduced size, and weight 50%–60% less than their wild-type counterparts [7]. Less frequently, patients show an infantile uterus and unidentifiable ovaries, which are responsible for infertility [8].

2. HNF4A-MODY (MODY1)

HNF4A-MODY is present in 5%–10% of MODY patients, and is caused by more than 103 mutations identified in 173 families. Typically, pathogenic variants are often found in exons 7 and 8 of the HNF4A gene.

HNF4A-MODY patients usually exhibit a phenotype, clinical presentation, and sensitivity to sulfonylureas, which are similar to those found in HNF1A-MODY, therefore the genetic test to confirm the presence of a mutation in HNF4A is only performed if a pathogenic mutation in HNF1A is not identified. Inactivating mutations in HNF4A result in MODY1, in addition to the similar insulin secretory defects showed in MODY3, as explained by the fact that HNF1A regulates the expression of the HNF4A gene.

Studies show that HNF4a-null mice exhibit several liver-related alterations, such as affected hepatic epithelium, steatosis, severe disruption of gluconeogenesis, and hepatocellular carcinoma. Those alterations can be explained by the role that HNF4A plays as a transcription factor, regulating the expression of many genes involved in hepatic function by interaction with promoters of such genes, as apolipo- and metabolic proteins (APOA, APOB, PAH, and FABP1), as demonstrated by studies performed in liver-specific HNF4A-null mice. All the features mentioned pinpoint the crucial role played by HNF4A in the expression of genes implicated in regulating serum cholesterol levels in mice [9]. These observations are comparable to MODY1 patients that exhibit liver disorders, for example, reduced HDL cholesterol, apolipoprotein A1 and A2, and triglyceride levels, unlike LDL cholesterol levels, which are increased and constitute a differential phenotype between MODY1 and MODY3. It is worth mentioning that differential factors between HNF4A-MODY and HNF1A-MODY, besides altered cholesterol and triglycerides profiles, include the MODY1 patient's progressive hyperglycemia associated with impaired insulin secretion that

worsens with time and normal renal threshold for glucose. MODY1 patients typically exhibit an absence of glycosuria, increased birth weight (macrosomia), transient hypoglycemia and/or diazoxide-responsive hyperinsulinemia at birth, highlighting the different pathways that give rise to the MODY1 and MODY3 subtypes [10] [11].

3. HNF1B-MODY (MODY5)

MODY5 accounts for 1%–5% of all cases and results from heterozygous HNF1B inactivating mutations, with more than 65 pathogenic variants being associated with MODY5 so far. Moreover, de novo mutations are frequent, comprising as much as half of all cases, meaning family history may be absent and approximately 28% of individuals present full allele deletion.

Due to HNF1B's network and crucial role in embryo development, as well as liver, pancreas, and kidney differentiation, slight alterations in HNF1B expression results in multiple organ disorders. Starting in embryo development, HNF1B-null embryos fail to mature at the early stage of the blastocyst (E3.5) due to abnormal or absent extraembryonic endoderm, while HNF1B-null embryos rescued via tetraploid complementation failed to grow a ventral pancreas, with only a small dorsal pancreas [12]. As previously mentioned, the complex OC1-HNF1B cross-regulatory network in the pancreas development, where the expression of Oc1 in the pancreatic precursor cells is activated by HNF1B, leads to the expression of PDX1, which is critical for the specification of pancreatic cell fate, and at later stages, the regulation of pancreatic endocrine differentiation via the Ngn3 expression by Oc1. Therefore, mutations in HNF1B disturb the OC1-HNF1B, with consequent unsuccessful activation of such genes required for endocrine cell differentiation, with a consequent absence of endocrine cells and abnormal β-cell development [13].

Additionally, regarding the impact on the pancreas, impaired expression of HNF1B is also responsible for kidney alterations in relation to its target expression levels and function. As observed in MODY5 patients who are usually affected by renal cysts and diabetes (RCAD) syndrome, young mice with conditional knockout of HNF1B show polycystic kidneys, whereas knockout of HNF1B at P10 or later, results in significantly delayed cyst formation. The consequent results from the incapable binding of HNF1B to the proximal promoter of the mouse Pkhd1 gene contains an evolutionarily-conserved HNF-1-binding site located near a region of deoxyribonuclease hypersensitivity [14]. Regarding the Pkd2 gene, one of the cystic disease genes, responsible for the Ca^{2+}-permeable cation channel Polycystin-2 (PC2), is strongly affected by HNF1B. PC2 interacts with polycystin-1 (PC1) in the primary cilium, and as the name suggests, facilitates Ca^{2+} entry, which is necessary for cAMP level regulation. Mutations in HNF-1β are associated with downregulation and consequently altered functioning of PC2, resulting in decreased Ca^{2+} entry, activation of the Ca^{2+}-inhibitable adenylyl cyclases AC5 and AC6, and elevated cAMP levels in an indirect manner. Such increased levels of cAMP stimulate cell proliferation and fluid secretion, thus promoting cyst growth [15]. cAMP levels can also be increased directly by HNF1B regulation in phosphodiesterase 4C (PDE4C) expression. PDE4C, which catabolizes cAMP in the primary cilium, is downregulated in Hnf1b mutant kidney cells and mice [15].

Despite renal cysts being the most common abnormality, renal dysplasia, renal tract malformations, like horseshoe kidney, and/or familial hypoplasia glomerulocystic kidney disease have been reported, which in some severe cases ultimately led to end-stage renal failure. Moreover, less than 6% of HNF1B-MODY patients had a normal renal function and about half had end-stage renal failure.

Additionally, occasional genital tract abnormalities like vaginal aplasia or azoospermia, have also been reported, but penetrance is incomplete. Other associated anomalies are abnormal liver function, gallbladder dysfunction, hyperuricemia, and hypomagnesemia [16].

Regardless of the similarity between HNF1A and HNF1B, which share a highly conserved DNA-binding domain and a more divergent C-terminal transactivation domain, and could act as either homodimers or as heterodimers, the mechanisms by which mutations in HNF1B are responsible for the development of MODY5, phenotype and treatment are diverse, and are not entirely comparable.

Unlike the other MODY subtypes originated by alteration in HNF genes, in approximately 50% of HNF1B mutation carriers, diabetes results from a combination of β-cell dysfunction and insulin resistance.

Haumaitre et al. showed that the truncated R112fsdel and P472fsins, which causes a frameshift and a truncated protein-lacking part of the POU-specific domain (POUS), and premature stop codon and the insertion of 35 novel amino acids at the C-terminus of the transactivation domain, respectively, resulted in truncated protein by the formation of non-functional heterodimers and decreased transactivation capacity [17].

The aforementioned mechanisms can be responsible for early-onset diabetes in MODY5 patients, such as GLUT2 deficiency associated with reduced glucose uptake and diminished insulin secretion. Several studies have shown the connection between HNF1B mutations, namely R112fsdel or P472fsins (which disrupt its DNA binding domain), GLUT2, a potential direct target of HNF1B, and the MODY5 phenotype [17][18].

Moreover, MODY5 patients present a reduced insulin reserve, requiring early insulin therapy, unlike MODY1 and the three patients that respond to sulfonylureas treatment [17][19][20][21].

4. GCK—MODY (MODY2)

To date, nearly 600 mutations have been associated with MODY2 in 1441 families and are most frequently detected in exons 7 and 9 [22].

Asymptomatic mildly stable hyperglycemia, present from birth, characterize GCK-MODY or MODY2. Such asymptomatic and non-progressive, hyperglycemia often remains undetected or misdiagnosed as T2DM or gestational diabetes (GDM) [23][24].

Mild and minor phenotypes result from heterozygous loss-of-function mutations, as stated by Grupe et al. based on mutant GCK heterozygotes mice, which develop mild early-onset diabetes that resembles GCK-MODY in humans

[25].

Heterozygous pathogenic variants in the GCK gene ultimately leads to alterations in the GCK conformational state, causing a decreased phosphorylation rate, consequent impairment of glycogen synthesis. Additionally, such mutations are responsible for two differential effects, depending on the target cells. In hepatocytes, a blockage of postprandial glucose regulation occurs, while in β-cells, a diminished insulin secretion regulation with a new and higher glycaemic threshold for insulin release being established is observed.

An example of such a mechanism is the c.766G>A (p.Glu256Lys) variant [26][27]. This variant has been reported in numerous countries, and since Glu256 is located in GCK's active site, conformational changes induced in GCK's active site, as well as the whole structure, resulted in decreased glucose binding and a downstream loss of catalytic activity, thus explaining the hyperglycaemic phenotype [22].

Characterized by total GCK deficiency, MODY2 patients with compound heterozygous loss-of-function mutations display permanent insulin-requiring diabetes mellitus (PNDM) with neonatal onset. This more severe phenotype is also observed in individuals with homozygous mutations that cause GCK loss-of-function, although such mutations are witnessed in a small percentage of MODY2 individuals [22].

Hypoglycemia has also been established in MODY2 individuals and is associated with hyperinsulinemia when GCK changes from an inactive super-open conformation to a catalytically active closed conformation, even at lower glucose concentrations [22][24][28].

Unlike MODY1 and MODY3, treatment with oral hypoglycemic agents (OHA) or insulin therapy in MODY2 may be ineffective, since GCK mutations result in a deficient recognition of glucose. Therefore, the administration of exogenous insulin may trigger a compensatory response, with a decreased secretion of endogenous insulin [29].

The exception to insulin therapy in MODY2 is for pregnant women, in whom higher-than-standard doses may be required to prevent fetal overgrowth. In the case of pregnant women presenting heterozygous loss-of-function mutations and an unaffected child, the increased insulin secretion and insulin-stimulated growth secondary to maternal hyperglycemia can increase the risk of fetal macrosomia. However, if the baby inherits the mutation from the father and the mother is unaffected, due to the high glucose threshold, there will not be enough glucose to stimulate the appropriate insulin secretion for normal fetal growth, and the child will be born underweight. If both the mother and fetus carry mutations, the baby will have the necessary glucose to stimulate the proper insulin secretion for healthy fetal growth [30].

Unlike the elevated number of GCK-MODY cases is observed in European countries, explained by the increased number of routine monitoring in pediatric cases, pregnancy, and asymptomatic young individuals, the exact occurrence of GCK-MODY in different geographic locations and ethnic groups is poorly known [31][32][33][34][35][36][37][38][39]. Large-scale studies in different ethnic groups and more awareness to the mild symptoms, seem to be the path to recognize GCK-MODY.

5. PDX1-MODY (MODY 4)

While pancreatic agenesis in human subjects is attributable to homozygosity for an inactivating mutation of the PDX1 gene, heterozygous carriers of PDX1 pathogenic variants develop MODY 4.

MODY4 was first described by Stoffers et al., who reported a homozygous single cytosine deletion within codon 63 (Pro63fsdelC) of the human PDX1 gene, previously attributed to the PNDM syndrome. Despite the similarity between MODY4 and PNDM pancreatic exocrine insufficiency, Stoffers and colleagues rectified this heterozygous pathogenic mutation as MODY4-causing. It is considered to be family-related when individuals developed diabetes over six generations, with an average age at onset of 35 years. Six of eight affected heterozygotes were treated with diet or oral hypoglycaemic agents and lacked ketosis or other indications of severe insulin deficiency.

Two pathogenic variants, E164D and E178K in the human PDX1 gene, also individually lead to PNDM and pancreatic exocrine insufficiency [40][41].

In 2011, in a family where the parents were carriers of the heterozygous form Pro63fsx60 of pathogenic variant, Fajans et al. found the presence of the homozygous form in a child with neonatal diabetes and exocrine pancreatic insufficiency. The authors established that in the carriers of this mutation, the onset of diabetes may occur at more advanced ages (around the age of 35), compared to other MODY subtypes [42]. Gragnoli et al. detected a Pro to Thr substitution (P33T) in the IPF1 transactivation domain, in an Italian family, with the clinical phenotype going from gestational diabetes, namely MODY4 to T2DM [43].

6. NEUROD1-MODY (MODY6)

Other than permanent neonatal diabetes, NEUROD1-MODY patients usually display a range of neurological abnormalities, which include physical alterations such as cerebellar hypoplasia, as well as cognition disability relating to learning difficulties, and an alteration in two of the five senses, including sensorineural deafness and visual impairment [44].

Very few cases of a homozygous mutation have been reported, and this kind of condition usually leads to neonatal diabetes [45]. Recently, Rubio-Cabezas et al. reported two cases with homozygous frameshift NEUROD1 mutations (c.364dupG; p.Asp122Glyfs*12 and c.427_428del; p.Leu143Alafs*55) and both mutations introduced a frameshift to produce a prematurely truncated protein lacking the activation domain at the C terminus. These patients were diagnosed with permanent diabetes, and both exhibited a normal morphological pancreas and normal exocrine functioning. Moreover, patients had severe neurological abnormalities, including developmental delay, cerebellar hypoplasia, sensorineural deafness, and visual impairment [46]. Recently, a homozygous missense NEUROD1 mutation (c.449T>A; p.I150N) was reported with the same phenotype [47].

Approximately 20 families have been reported so far with heterozygous loss-of-function mutations in *NEUROD1.* The first pathogenic variant E110K was reported in an Icelandic MODY6 family, and following the missense

variants, S159P, H241Q, and R103P in *NEUROD1* were identified worldwide [48].

Among the 20 families reported, there are 86 mutation carriers, of which 68 (79.1%) are glucose intolerant, nevertheless the several subjects remain glucose tolerant. Therefore, the overall phenotype of MODY6 is a broad clinical spectrum that ranges in patients with typical MODY features, to the incomplete penetrance of diabetes.

As mentioned, NEUROD1 forms a heterodimer with the ubiquitous HLH protein E47 to transactivate INS expression by binding to a critical E-box motif on the promoter. Most of the reported mutations are present in the bHLH domain or the transactivation domain, thus causing disruption of DNA recognition of downstream target genes. Mechanistically, pathogenic variants in the NEUROD1 gene, located in this domain, abolish the E-box binding activity of NEUROD1 and significantly compromise INS transcription in pancreatic β-cells. Alternatively, the transactivation domain interacts with the cellular coactivator p300, possibly affecting the stimulation of target gene activation [49].

MODY6 individuals are equally treated with insulin therapy and oral glucose-lowering agents or diet, showing that the optimal therapeutic approach is yet to be disclosed, since the related literature suggesting OAD or insulin therapy is scarce.

Along with the endocrine phenotype, MODY6 may also be accompanied with neurological abnormalities, such as intellectual disability, although this is very rarely.

7. MODY-KLF11 (MODY7)

In 2005, Neve and colleagues reported KLF11 as a causative gene for MODY7 with the identification of two KLF11 variants, p.Ala347Ser and p.Thr220Met, in individuals diagnosed with early-onset T2DM, which were shown to significantly impair the transcriptional activity of KLF11.

Over the years, several studies have allowed for the identification of new pathogenic variants associated with MODY7, leading to the development of late-onset diabetes. Ushijima et al. identified a heterozygous KLF11 (p.His418Gln) variant in a family that was clinically diagnosed with early childhood-onset diabetes [34]. The combination of several studies allowed for an understanding of KLF11 function and diabetes outcome. Utilizing cells transfected with KLF11-WT and mutant plasmid with (c.1061G > T) mutation, KLF11-C354F-transfected cells, the authors concluded that this pathogenic variant impaired insulin promoter regulation activity and insulin expression and secretion in pancreatic beta cells, even upon stimulation with high glucose when compared to KLF11-WT cells. Authors predicted that such a decreased expression of INS could be a consequence of exposure on the surface of the protein, altering the protein activity, suggesting that the site is located in a larger transcriptional blocking domain, thereby affecting the transcriptional functions of INS [50][51].

The study showed that KLF11 is both a transcriptional repressor, as well as an activator, and such transcription activity can be mediated by p300. As mentioned in regards to other MODY subtypes, this coactivator has been

shown to have a powerful coregulatory activity in 90% of MODY genes, hypothesizing that p300 recruitment is affected in MODY-causing variants [52].

KLF11 was proposed as a cause of MODY, with a candidate gene approach, in 2005 and a possible mechanism of action was suggested for the variants via the gain of function, which causes increased KLF11 repression activity [53].

However, Laver et al. (2022) examined variant-level genetic evidence (co-segregation with diabetes and frequency in the population) for published putative pathogenic variants after concern has been raised about whether variants in KLF11, PAX4, and BLK1 cause MODY.

Given the high frequency of KLF11 variants in the population, poor cosegregation with diabetes in the families, and a lack of enrichment of rare variants in a MODY cohort, the authors conclude that such variants were not disease-causing [54].

8. CEL-MODY (MODY 8)

In 2006, Ræder, H. et al. reported single-base deletion (DEL) in the exon 11 of the CEL gene, comprised of the VNTR region, c.1686delT and c.1785delC. Such identification was only possible by focusing the study on patients with deficient exocrine pancreatic function. Functional studies demonstrated that, in spite of the similar in vitro catalytic activity, the enzyme resultant of the mutated gene was more instable and less secreted. The authors were able to conclude that the exocrine pancreatic dysfunction observed was due to the pathogenic variants detected in patients that fulfilled the MODY criteria [55].

The current literature supports the involvement of CEL exocrine and endocrine pancreatic dysfunction associated with another MODY subtype, however the pathophysiological mechanisms underlying this connection are yet to be fully understood.

After this first study, many have followed and claimed to identify new CEL pathogenic variants, nonetheless only one was strongly associated with MODY8 in an Italian individual [55][56].

Additionally, to the identification of the first CEL VNTR single-bp deletions, Ræder et al. characterized the MODY8 patients. The authors observed that, in addition to pancreatic phenotypes, such as pancreatic exocrine dysfunction in early childhood, diabetes, and pancreatic cysts, MODY8 individuals developed clinical malabsorption, deficient absorption of nutrients, as well as pancreatic fatty tissue accumulation [55].

Animal studies failed to dissect the disease mechanism of MODY8, however in vitro studies were able to indicate that the CEL VNTR single-bp deletions contain a different and shorter tail region, altered biochemical properties, and reduced O-glycosylation potential, concluding that CEL protein is misfolded. Altered CEL protein has a high propensity to form both intracellular and extracellular aggregates with cellular reuptake followed by lysosomal

degradation, leading to impaired pancreatic cell line viability. The misfolded CEL protein has a major impact on endoplasmic reticulum (ER) stress, the stimulus of the unfolded protein response, and subsequent apoptosis [57][58].

More recently, El Jellas et al. (2022) uncovered the existence of two new CEL VNTR single-base pair deletions in the proximal part at the exon 11, in two different families, from Sweden and Czech Republic displaying the criteria for MODY [59].

Therefore, MODY8 is associated with pancreatic atrophy, fibrosis, and lipomatosis, together with exocrine insufficiency and later endocrine dysfunction and diabetes.

9. PAX4-MODY (MODY9)

Knowledge of the molecular basis of PAX4 mutations causing diabetes remains incomplete. It is recognized that PAX4 predominantly represses the glucagon promoter activity in α-cells and weakly inhibits insulin promoter activity in β-cells by its transcriptional factor role [60].

To determine whether PAX4 mutations contributed to MODY, more specifically in the Thai population, Plengvidhya et al. examined PAX4 coding sequences in 46 MODY probands lacking mutations in other known MODY genes. The authors observed the first association of mutations in PAX4 to MODY diabetes by finding two possible pathogenic mutations of PAX4, R164W and IVS7–1G>A in patients with MODY, but not in nondiabetic controls and healthy subjects [61]. The altered protein R164W resulted in decreased PAX4 repression activity, while the guanine to adenine change at IVS7-1G>A intronic variant disrupted mRNA splicing and resulted in an in-frame deletion p.Gln250del (exon 8) with the repression of both insulin and glucagon's promoter in α-cells. Complementary studies indicated that this pathogenic variant enhanced cell susceptibility to apoptosis upon cytokine or high glucose exposure. Conversely, the forced expression of wild-type PAX4 has been shown to protect against cytokine-induced β-cell death in isolated human islets [61][62][63].

Later, two new pathogenic variants were found by the same authors, namely PAX4 R192H and (C.374–412 del 39), as reported by Jo et al. and associated with MODY9 [64].

In vitro studies showed that the transcriptional repressor capacity on human insulin and glucagon promoters was reduced in cell lineages transfected with PAX4 R192H plasmid when compared to those of wild-type PAX4, suggesting that PAX4 R192H polymorphism generated a protein with a defect in transcriptional repressor activities on its target genes, leading to β-cell dysfunction associated with MODY and the early onset-age of T2D.

Regarding the 39-bp deletion in exon 3, this pathogenic variant caused exon 3 skipping and a truncated protein lacking part of the homeodomain and repressor domain in the carboxy terminus. This defective protein failed to repress the insulin and glucagon promoters [64][65].

Over the years, other missense mutations, including p.Arg31Leu14 and p.Arg52Cys,15 were found in an Indian and Malay patient, respectively, and both exhibited clinical hallmarks of monogenic diabetes.

PAX4 mutations can be located in the paired domain, the homeodomain, or between the paired domain and homeodomain, thus damaging its transcriptional repressor activity.

Persistent and severe β-cell dysfunction, flexible clinical features, and ketosis-prone diabetes (KPD) characterize PAX4-related MODY 9.

Mauvais-Jarvis and colleagues first reported that PAX4 homozygous R133W and heterozygous R37W mutations are associated with KPD [66]. Subsequent studies performed by Balasubramanyam et al. concluded that approximately 30% of the KPD patient subgroup had variants in HNF1A, PDX1, and PAX4 genes, suggesting that these variants may be the origin of β-cell dysfunction in a fraction of patients with A-β KPD [67].

On the whole, most MODY patients are submitted to sulfonylureas, metformin, or insulin treatment.

Despite the incomplete knowledge of the molecular basis of PAX4 mutations causing diabetes, new evidence has shed a light on possible treatments. Recent studies documented the efficacy of GLP-1 receptor agonists and dipeptidyl peptidase-IV inhibitors in MODY9 patients through their glucagon-inhibiting actions [68][69][70][71].

As previously mentioned, Laver et al. (2022) recently examined variant-level genetic evidence (co-segregation with diabetes and frequency in the population) for published putative pathogenic variants after concern has been raised about whether variants in KLF11, PAX4, and BLK1 cause MODY. While Plengvidhya et al. used the control subjects from the same population as the case subjects and researchers now know that p.R192H is common in East Asians. Additionally, despite the authors observing the impairment of the repressor activity of PAX4 on the insulin and glucagon promoters, the authors disclosed that the impairment was relatively modest, thus the reduction may be insufficient to result in a clinical phenotype. Until now, no large MODY pedigrees with cosegregation for a variant in PAX4 have been described since the initial report [54][61].

10. INS-MODY (MODY10)

Heterozygous pathogenic variants in the INS gene result in MODY 10, which is a monogenic form of diabetes. Such genetic alterations result in a severe folding defect, which is an abnormal response to unfolded proteins, ß-cell apoptosis, and variable-onset diabetes mellitus. Dominant misfolding mutations in the INS gene are a frequent cause of isolated (PNDM). Therefore, it is only normal to verify decreased β-cell mass and gradual loss of insulin secretion in individuals displaying INS mutations [72][73].

Molven et al. reported the *INS* pathogenic variants, namely c.137G>A (R46Q), in a MODY10 family and c.163C>T (R55C) in a T1D family displaying ketoacidosis and insulin dependency. In vitro studies showed that the R46Q mutation disrupted a critical hydrogen bond formation, impairing the insulin molecule stability [74].

Soon after, Garin et al. and Carmody et al. identified *INS* mutations outside the exonic regions that are usually associated with diabetes. For example, mutations such as heterozygous c.188–31G>A (259) and homozygous c.187+241G>A were found to cause PNDM [75]. The intronic c.188–31G>A mutation ultimately results in an aberrant transcript producing misfolded proteins to induce ER stress and β-cell death [75][76]. Later, the c.188–31G>A mutation was also reported to cause MODY in one family [77].

After this, Dusatkova and colleagues unraveled a novel heterozygous single nucleotide deletion (c.233delA) leading to a frameshift mutation (Q78fs) in the *INS* gene in a MODY family. This mutation produces an aberrant proinsulin that lacks the native structures of the C-peptide and α-chain [78].

Complications with MODY10 have been reported in a few families, such as mild proliferative diabetic retinopathy, neuropathy, peripheral neuropathy, and polycystic ovarian syndrome.

At the time of diagnosis, diet or OADs may be used as a treatment for patients with MODY, but they eventually become insulin dependent [48][49].

11. BLK-MODY (MODY11)

Not all carriers of BLK pathogenic variants exhibit diabetes, and thus BLK-MODY has incomplete penetrance. The reason why a small proportion of the mutation carriers remain normoglycemic is unclear and is thought to result from environmental as well as genetic modifiers [79]. Borowiec and colleagues observed that the penetrance of a specific haplotype (three mutations occurred as a haplotype) was higher among carriers with a BMI greater than or equal to 28. Therefore, β-cell abnormalities caused by this haplotype might only come to light when in the presence of a diabetogenic environment conferred by increased body weight [80].

Recently, Laver et al. examined variant-level genetic evidence (co-segregation with diabetes and frequency in the population) for published putative pathogenic variants after concern has been raised about whether variants in *BLK* cause MODY [54]. The only BLK coding variant (p.A71T) reported to cause MODY was later found to be very common in normoglycemic individuals, showing that the variant is too common to cause MODY, raising doubt over the aetiological role of BLK. Additionally, since the initial report, no MODY pedigrees with consegregation of BLK pathogenic variants have been described [81].

Given the lack of evidence for coding variants in BLK as a cause of MODY, it is unlikely that noncoding variants would be pathogenic [54][80].

12. ABCC8-MODY (MODY12)

The *ABCC8* gene is responsible for at least 1% of MODY cases in the literature and there are about 700 pathogenic variants of the *ABCC8* gene in the HGMD database, with more than half of them being missense and nonsense variations.

Bowman et al. first reported that MODY12 is caused by ABCC8 gene mutation in 2012. Until now, only 55 ABCC8 variants were associated with MODY12 [82].

Data showed that four patients were heterozygous for previously reported mutations and four novel mutations, E100K, G214R, Q485R, and N1245D, were identified. Only four probands fulfilled the MODY criteria, with two diagnosed after 25 years and one patient, who had no family history of diabetes as a result of a proven de novo mutation. The four unique mutations were found in susceptible MODY patients with diverse clinical manifestations associated with overweight or obesity and with no significant hypertriglyceridemia and hypercholesterolemia. Despite the residues being highly conserved, suggesting a pathogenic impact, the authors stated the need for functional studies to show that the mutations increase KATP channel activity and cause diabetes. Both activating and inactivating pathogenic variants of the ABCC8 gene were found to trigger MODY 12 [83].

Pathogenic variants in the *ABCC8* gene ultimately lead to membrane hyperpolarization and impaired insulin secretion, due to augmented binding of Mg-nucleotide to nucleotide-binding domains of SUR [84].

ABCC8 gene mutations can result in congenital hyperinsulinism, which can be caused by dominantly inherited inactivating mutations. As a result of activating mutations or recessive loss-of-function mutations, ABCC8 gene mutations can lead to other forms of monogenic diabetes, such as permanent or transient neonatal diabetes (PNDM or TNDM, respectively) [85].

Rafiq et al. proposed that, in adulthood, all ABCC8 mutation carriers could be switched to sulfonylureas since sulfonylureas specifically bind to the SUR1 subunit of the K_{ATP} channel and shut down the channel to release insulin in a non-ATP-dependent manner, with MODY being sensitive to sulfonylureas. In fact, the treatment switch from insulin to sulfonylureas was proven to improve patients' glycemic control, as well as decrease the risk of hypoglycemia episodes [86].

13. KCNJ11-MODY (MODY13)

Molecularly, MODY 13 corresponds to the existence of activating mutations in KCNJ11, which is associated with decreased ATP sensitivity to the Kir6.2 subunit characterized by the prolonged open state of the channel and indirectly influencing ATP sensitivity, thereby compromising the insulin secretory response.

KCNJ11 gene screening is currently indicated by guidelines in all patients who present with diabetes diagnosed before 6–12 months of age since some studies reported that families of patients with a transient or permanent form of NDM can also include individuals with childhood or later-onset diabetes. However, no previous study has described a family with a well-defined MODY due to a *KCNJ11* mutation.

Bonnefond et al., by focusing on variants of interest, found 69 mutations in KCNJ11 in the three affected relatives and not present in the control population. Subsequently, only one mutation (p.Glu227Lys in KCNJ11) co-segregated with diabetes in the family. Data confirmed that *KCNJ11* mutations can be associated with a large

spectrum of diabetes phenotypes and cannot completely penetrant as one of the identified members of the French MODY family that carries the *KCNJ11* p.Glu227Lys mutation, has normal fasting plasma glucose level at 39 years. This large phenotype spectrum has also been reported in carriers of pathogenic variants in *ABCC8* and the *INS*, which together with *KCNJ11*, represent the most frequently mutated genes in patients with NDM. Other modifier, genetic effects such as epigenetics could explain the substantial difference in both diabetes onset and clinical expression between NDM and MODY patients [87].

Gloyn and colleagues revealed, in 2004, the existence of six new heterozygous missense mutations in 10 out of 29 patients, and among these four patients, exhibit p.Arg201His pathogenic variants. They concluded that neonatal diabetes was caused by heterozygous mutations of the KCNJ11, with variable onset and the severity of diabetes [88]. Later, another group of studies uncovered the occurrence of five different heterozygous mutations, including two novel mutations in the KCNJ11 gene in eight Italian patients, concluding that KCNJ11 gene mutations are the common cause of PNDM [89].

As with INS-related MODY (MODY 10) and ABCC8-related MODY (MODY 12), MODY 13 is associated with neonatal diabetes, which is also sensitive to sulfonylurea therapy.

14. APPL1-MODY (MODY 14)

MODY 14 is a rare subtype. Heterozygous loss-of-function mutations in this gene result in diminished insulin secretion in response to glucose stimulation and increasing β-cell apoptosis [90]. In 2015, Prudente et al. reported two loss-of-function mutations (c.1655T>A [p.Leu552∗] and c.280G>A [p.Asp94Asn]) in APPL1, identified by whole-exome sequencing in two large families with a high prevalence of diabetes. Both mutations caused APPL1 to lose function. The authors observed that the p.Leu552∗ pathogenic variant caused deletion of most of the PTB domain, thereby making APPL1 unable to bind to AKT and abolishing APPL1 protein expression in HepG2 transfected cells [91]. The missense p.Asp94Asn alteration affected the aspartic acid residue at position 94, located on the concave surface of the APPL1 BAR domain, and is highly conserved among various species, causing a noteworthy reduction of the insulin-stimulated AKT2 and GSK3β phosphorylation, in comparison to wild-type APPL1 transfection. In APPL1 WT cells, APPL1 binds to AKT2, which is a key molecule in the insulin signaling pathway, thereby enhancing insulin-induced AKT2 activation and downstream signaling and leading to insulin action and secretion. Therefore, these findings reaffirm the critical role of APPL1 in glucose homeostasis [91].

More recently, Ivanoshchuk and colleagues observed that rs11544593 may contribute to the earlier onset of carbohydrate metabolism disorders with an association of rs11544593 with blood glucose concentration revealed in the MODY group [92]. Schenck et al. detected that, in pathogenic variants in APPL1 in tissues where this gene is highly expressed, there is increased apoptosis [90].

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