Monogenic Diabetes:

Implementation of translational genomic research towards precision medicine

Running title: Translational genomics in monogenic diabetes

Martine VAXILLAIRE,[1,2,3] and Philippe FROGUEL,[1,2,3,4]

[1]CNRS-UMR 8199, Integrative Genomics and Modelling of Metabolic Diseases, Pasteur Institute of Lille, Lille, France

[2]Lille University, Lille, France

[3]European Genomic Institute for Diabetes (EGID), FR-3508, Lille, France

[4]Department of Genomics of Common Diseases, School of Public Health, Imperial College London, Hammersmith Hospital, London, United Kingdom

Correspondence:

Martine Vaxillaire, PharmD, PhD

CNRS UMR 8199, Institut Pasteur de Lille, 1 rue du Professeur Calmette, 59019 Lille, France

Tel: +33 320 87 10 68 Fax: +33 320 87 10 31

Email: martine.vaxillaire@good.ibl.fr

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Abstract

Various forms of early-onset non-autoimmune diabetes are recognized as monogenic diseases, each subtype being caused by a single highly penetrant gene defect at the individual level. Monogenic diabetes (MD) is clinically and genetically heterogeneous, including maturity-onset diabetes of the young (MODY), infancy-onset and neonatal diabetes mellitus, which are characterized by functional defects of insulin-producing pancreatic β-cells and hyperglycemia early in life. Depending on the genetic cause, MD differs in ages at diabetes onset, the severity of hyperglycemia, long-term diabetic complications and extra-pancreatic manifestations. In this review, we discuss the many challenges of molecular genetic diagnosis of MD in the face of a substantial genetic heterogeneity; as well as the clinical benefit and cost-effectiveness of an early genetic diagnosis as demonstrated by simulation models based on lifetime complications and treatment costs. We also discuss striking examples of proof-of-concept of genomic medicine, which enabled to remarkably improve patients' care and long-term evolution. Recent advances in genome editing and pluripotent stem-cell reprogramming technologies provide new opportunities for *in vitro* diabetes modelling and the discovery of novel drug targets and cell-based diabetes therapies. A review of these future directions makes the case for exciting translational research for further understanding early-onset diabetes pathophysiology.

Keywords:

Diabetes, Genetics, Genomic medicine, Insulin secretion, Monogenic diabetes, MODY, Mutation, Next-generation sequencing, pancreatic β-cell.

Genetic subtypes and clinical spectrum of monogenic diabetes

Monogenic diabetes (MD) is caused by a rare single-gene defect that strongly contributes to the disease phenotype without or not much environmental contribution (meaning that is each individual DNA mutation or genome structural abnormality has a high or almost complete penetrance).[1] MD encompasses a broad spectrum of clinically and genetically highly heterogeneous forms of non-autoimmune diabetes, which are mainly characterized by functional defects of pancreatic β-cells resulting in insulin deficiency and moderate to severe hyperglycemia early in life.[1,2] MD includes maturity-onset diabetes of the young (MODY), early-infancy onset and neonatal diabetes mellitus (NDM), and many rare forms of atypical diabetes.[1-3] Decades of genetic and clinical research to decipher etiological mechanisms underlying MODY, NDM and early-infancy diabetes led to identify major genes and molecular pathways relevant to β-cell physiology, that allowed to better understand the sustained genetic and clinical heterogeneity among the different MD subtypes in young people.

MODY subtypes

MODY usually presents in lean young individuals before age 25-30 years, as a dominantly inherited familial form of diabetes, and it may account for at least ~1-2% of all cases with type 2 diabetes.[4,5]

Epidemiology of MODY. Although MODY has been very well studied in selected areas of the world (mainly in European countries thanks to availability of clinical reports and research policies), epidemiological studies are lacking in many countries and ethnicities across the world, making difficult to accurately estimate the worldwide prevalence of MODY. Furthermore, such observations and estimation of MODY prevalence or subtype distribution are largely dependent on the referral inclusion criteria of nation-wide patient registries, physician practices and healthcare systems' policies. From a retrospective study in the UK population (between 1996-2009), the prevalence of MODY was reported to be ~100 cases/10^6, with a large variability among UK provinces.[6] Other estimations from population-based childhood diabetes registries are between 2.5-5 cases/100 000 in

several European countries;[7-9] and 2.1 cases/100 000 in American children from the SEARCH for Diabetes in Youth Study.[10] A high frequency (>20%) of clinically suspected MODY was reported among patients with type 2 diabetes (T2D) younger than 25 years in south India,[11] but no genetic characterization was done. The epidemiology of MODY in many important geographical areas, like in African, Latino and Middle Eastern populations, is largely under-studied.[12] More detailed information on the current situation of epidemiological studies related to MODY can be found in the recent report by Kleinberger & Pollin.[12]

Molecular genetic bases of MODY. Genetics of MODY was fully investigated since the 1990's with the identification of two major genes, *GCK* (encoding glucokinase) and *HNF1A* (encoding hepatocyte nuclear factor-1α).[13,14] The inverse genetic approach based on familial linkage studies in large MODY families (mostly of French, UK and german origins) led to successfully and extensively characterize the various molecular and cellular defects involved in the major subtypes of MODY (**Tables 1 and 2**). These defects are mainly due to either decreased glucose phosphorylation or impaired activity of pancreatic β-cell expressed transcription factors or impaired insulin biosynthesis.[2] Since these proof-of-concept discoveries from genetics, an expanding amount of research findings has revealed a marked genetic heterogeneity with 14 MODY-associated genes reported so far (details on all genes are given in **Table 2**).[4,15] Most of the MODY genes encode pancreatic β-cell expressed proteins with key roles in the fetal development of pancreas and β-cells, in the maturation and maintenance of β-cell function (like transcription factors of the HNF family, HNF-1α [*HNF1A*/MODY3], -1β [*HNF1B*/MODY5], -4α [*HNF4A*/MODY1], or IPF1/*PDX1*/MODY4, *NEUROD1/*MODY6*, PAX4/*MODY9), or in the regulation of glucose sensing by the pancreatic β-cell (through glucokinase [*GCK*/MODY2] activity) and of β-cell signaling to insulin secretion.[4,5] Heterozygous mutations, and more rarely partial or whole gene deletions, in these MODY genes affect key processes in the pancreatic β-cell physiology, which results in moderate chronic hyperglycemia (typical of MODY2/*GCK* subtype) or more severe phenotypes with marked insulin deficiency with regard to the *in vivo* fasting and/or post-prandial hyperglycemia levels (as in the majority of other MODY subtypes).[4,5] As it is outlined

below, there are many clinical differences within and among the different MODY subtypes, which may differ not only in age at diabetes onset or the pattern of hyperglycemia, but also in the responses to hypoglycemic treatment, long-term diabetic complications or extra-pancreatic manifestations depending on the genetic defect (**Table 2; Figure 1**).

Overall, genetic diagnosis reports worldwide showed numerous young-onset diabetic cases with a MODY-like phenotype do not have a defined genetic etiology (notably in the USA, Indian or Asian populations).[12] Further genetic investigations in those unresolved cases are highly recommended to identify new genetic etiologies and molecular defects of MD (with information on each of the deleterious mutations involved, particularly in purely monogenic cases); this may also highlight still unrecognized genetic mechanisms (for ex. in case of digenic inheritance, or when a single nucleotide mutation is not involved).

NDM and early-infancy diabetes subtypes

NDM (incidence estimated at 1:100,000 live births) is diagnosed within the first 6 months of life reflecting severe β-cell dysfunction that can be either permanent or transient (in ~half of cases). NDM is genetically highly heterogeneous with >25 known genetic causes, which are associated with a range of pancreatic and non-pancreatic phenotypes (**Tables 1 and 3**).[3,16] Both dominant and recessive inheritance patterns occur, and *de novo* mutations are also frequent in NDM genetic etiology. The most frequent NDM genetic subtypes include mutations in *KCNJ11*/Kir6.2 and *ABCC8*/SUR1, which encode the two subunits forming the hetero-octameric ATP-dependent K+ (K-ATP) channel, in *INS* and *ZFP57* genes, or chromosome 6q24 anomalies).[16,17] Other rarer genetic defects, mostly reported in consanguineous families, cause either isolated permanent NDM (homozygote mutations of *GCK*), or syndromic forms of NDM, mostly involving transcription factor gene abnormalities, such as homozygous mutations in *PDX1* and *PTF1A* responsible for pancreas agenesis/hypoplasia, in *NEUROG3* and *RFX6* causing NDM and intestinal development anomalies

(**Table 3**). Heterozygous mutations in *GATA6* are associated with heart defects and inconsistently with pancreas agenesis/hypoplasia and diabetes (**Table 3**).

Heterozygous gain-of-function mutations in *KCNJ11* and *ABCC8* cause a spectrum of diabetic phenotypes ranging from transient or permanent NDM (diabetes onset in the first 6 months of life) to later onset diabetes developing in the 3rd or 4th decades of life and resembling MODY in a few families.[18,19] These *KCNJ11*/*ABCC8* mutations impair the K_{ATP} channel closure, by reducing ATP-binding affinity on Kir6.2 or altering channel gating via the interaction of Mg^2-ADP with SUR1, which lead to persistent channel overactivity, β-cell membrane hyperpolarization, and consequently to a severe reduction of insulin secretion. In some NDM cases with *KCNJ11* mutations that severely affect channel function, diabetes may be associated with speech and developmental delay, epilepsy and muscular hypotonia, known as DEND or iDEND syndrome.[2,3]

Another frequent cause of NDM may arise from heterozygous missense mutations of the *INS* gene, which are mainly located at amino acids in the signal peptide, the B-chain and A-chain regions and pairs of basic residues that flank the C-peptide, and thereby affect formation of the disulfide bonds or cleavage of the signal peptide.[20] These dominantly-acting mutations cause diabetes via another mechanism of proteotoxicity due to misfolded proinsulin molecules overload in endoplasmic reticulum (ER) causing ER stress and ultimately β-cell apoptosis and death.[20] In some rarer cases, homozygous mutations in the promoter or 5'-UTR region of *INS* result in impaired transcriptional regulation of the *INS* gene and decreased insulin biosynthesis,[21] whereas a few homozygous intronic mutations create unstable mutant transcripts undergoing nonsense and non-stop-mediated decay resulting in insulin production deficiency and diabetes without β-cell death.[22]

Precision medicine and clinical implementation of genomic research

Apart clinical specificities and metabolic features of MD subtypes according to the genetic and molecular defects, marked differences in drug therapy response have been shed light, which is particularly relevant for a personalized treatment of MODY patients (**Figure 1**).

The fasting hyperglycemia associated with *GCK* mutations is most often mild and stable over the patient's lifetime, despite the sustained pancreatic and liver defects. As HbA1c levels are mildly increased, the risk of developing microvascular diabetic complications is very low in MODY2 patients compared to the other MODY subtypes and late-onset T2D.[5,23] However, the development of insulin resistance with age may impact on the long-term glucose tolerance status in MODY2 patients, as it is largely reported in the general population.[24] Overall, the MODY2 patients are usually well responsive to diet alone and do not require any pharmacotherapy, while low-carbohydrate diets are recommended for a good glycemic control in GCK-MODY.[25] There is no deterioration in HbA1c levels in MODY2 patients when treatment is stopped after diagnosis of GCK-MODY, and the consensus is that antidiabetic drugs can be stopped in most MODY2 patients. The case of treating women during pregnancy, where fetal macrosomia is suspected, is still under debate although insulin treatment may help to control fetal growth. Therefore, it is crucial to make a genetic diagnosis of MODY2 at a young age to provide patient's best clinical care, as they may be misdiagnosed with type 1 or type 2 diabetes.

In contrast, the diabetic phenotype of *HNF1A*-MODY3 and *HNF4A*-MODY1 patients is more severe at diagnosis and most often quickly progressive with a deterioration throughout life, especially when superimposed environmental factors are present.[2,5] Typically, *HNF1A* or *HNF4A* mutation carriers are oftentimes normoglycemic in childhood but have a progressively impaired insulin secretion, and diabetes is usually diagnosed in the second to fourth decades. Effectiveness of oral sulfonylurea (SU) treatment is a feature of both *HNF1A*-MODY3 and *HNF4A*-MODY1 patients, and consensus guidelines for their diabetes management recommended low dose SU as the first-line treatment (**Figure 1**). According to animal and cellular models of HNF1α and HNF4α deficiency, the pancreatic β-cell defect is upstream of the pancreatic K_{ATP} channel, where SU molecules directly bind the SUR1 channel

regulatory subunit and lead to K_{ATP} channel closure thereby stimulating insulin release from pancreatic β-cells. Subsequently, this effect can result in symptomatic hypoglycaemia in some hyper-responsive patients. Otherwise, the hypersensitivity to SU means that MODY patients who have been misdiagnosed as type 1 diabetes and treated with insulin from diagnosis can be switched safely and successfully to oral SU with an improved glycemic control in most cases.[26] A good control may be maintained for many years, although SU treatment may become insufficient in many MODY3 patients requiring a combined therapy with insulin most often or the new class of dipeptidyl peptidase-IV (DPP-IV) inhibitors. Indeed, DPP-IV inhibitors acting by prolonging the activity of circulating incretins are also an effective adjuvant therapy in *HNF1A*- and *HNF4A*-MODY patients who failed to respond to SU monotherapy.[27] In contrast, MODY5 patients with *HNF1B* mutations are unsensitive to SU treatment, and early insulin therapy is generally required from diabetes diagnosis to prevent long-term complications. Another good example of successful genomic medicine in MD is diabetes caused by K_{ATP} channel-mutations, where patients can almost always be treated with inexpensive oral SU therapy alone in place of daily insulin injections enabling a long-term excellent glycemic control, as well as correction or improvement of neuro-psychomotor abnormalities (in young patients).[16,17,28,29] Although, some patients may require highly variable doses of SU or additional medications to optimise glycemic normalization over time. Importantly, a retrospective cohort study using data from 58 NDM patients with a *KCNJ11* mutation demonstrated that an earlier age at initiation of SU treatment is associated with improved response to SU therapy,[29] supporting the need for early genetic diagnosis and appropriate personalized treatment particularly in NDM cases. The *in vitro* functional effect as per the mutation may also determine the rate of successful transfer to SU monotherapy.[30]

New research fields targeting the human genome-metabolome relationships, and enabling to examine whole-body metabolism variation, have recently emerged with the potential to identify novel circulating biomarkers related to gene regulation networks.[31,32] Beyond, such studies provide insightful clinical translation for improved patient stratification. Interestingly, a non-targeted metabolomic profiling study from serum samples of patients with *HNF4A*-MODY1, *GCK*-MODY2,

HNF1A-MODY3, including T2D and healthy individuals, revealed that *GCK*-MODY patients present a normal or supernormal metabolic control characterized by lower FFA and triglycerides levels (a 52% decrease in FFA compared with healthy controls), which is usually a sign of high insulin sensitivity, despite chronic high fasting glucose levels.[33] In contrast, the other forms of diabetes differed markedly from healthy controls in their metabolite profiles.[33] These findings evidenced that GCK-MODY is a metabolically normal condition, which may explain the lack of microvascular complications and the non progressive nature of MODY2. Alternatively, other "omics" approaches such as proteomic or lipidomic approaches might be powerful in identifying robust biomarkers for monogenic diabetes subtype discrimination.

Other circulating molecules such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are potent regulators of gene expression, which are potentially involved in pancreas development and β-cell differentiation, as well as in insulin production, secretion and action;[34] lncRNAs being essentially studied in cancer research.[35] One representative study investigated changes in miRNA expression in INS-1 insulinoma cells inducibly expressing the *HNF1A*-Pro291fsinsC hot-spot mutation and in serum from 31 cases with *HNF1A*-MODY.[36] Two miRNAs, miR-103 and miR-224, were significantly up-regulated upon suppression of endogenous HNF1α function in the INS-1 cell line, and both miRNAs were found strongly elevated in the serum of *HNF1A*-MODY patients when compared with family controls (mean levels 47- and 293-fold higher, respectively).[36] Furthermore, miR-103 may distinguish *HNF1A*-MODY patients from HbA1c-matched T2D subjects. Both miR-103 and miR-224 were further assessed in urine samples of a large cohort of *HNF1A*-MODY mutation carriers (and of other types of diabetes including type 1 diabetes samples), and they were found to be differentially highly expressed in *HNF1A*-MODY samples; miR-224 was also highly expressed in the urine of T1D patients, which could support its detection as a biomarker of β-cell demise, whereas high expression of miR-103 was found in all participants with diabetes (as it was previously reported consistently deregulated in diabetes across multiple tissues).[37] Findings from this study may promote

further translational research for the diagnosis and treatment of diabetes through novel biomarkers useful in the clinical setting.

Current challenges in molecular genetic diagnosis of MD

Making an accurate genetic diagnosis will provide a molecular confirmation for a clinical diagnosis of MD (defining a discrete genetic subtype either of MODY, NDM or other infancy-onset diabetes). Importantly, this will guide the most appropriate clinical management and pharmacological treatment depending on the specific genetic subtype (notably for *GCK*-MODY, *HNF1A/HNF4A*-MODY or NDM and MODY associated with *ABCC8/KCNJ11* mutations). A molecular diagnosis will also help to anticipate long-term clinical evolution and risk level of complications. Besides, a genetic counseling in the family may trigger molecular testing in other family members, which may be important in children with incidental hyperglycemia or in undiagnosed patients; or it can eventually lead to reclassify diabetes in patients misdiagnosed with type 1 or type 2 diabetes with beneficial effects upon therapeutic adaptation.

Notwithstanding, the lack of a family history of diabetes in some clinically defined MODY cases is an important issue questioning the usual practices of genetic testing, as to whether to test or not patients with a clinical suspicion of MODY apart from a familial inheritance of diabetes. *De novo* mutations in the most prevalent MODY genes (*GCK, HNF1A* and *HNF4A*) were found to be more frequent than previously thought. In a systematic analysis of a target group of 150 patients without a family history of diabetes, who fulfilled the remaining diagnostic criteria for MODY (representing 16.3% of the referrals for MODY testing from two national MD registries), 11 cases with *de novo* mutations were identified (6 *GCK*, 4 *HNF1A* and 1 *HNF4A*) accounting for 7.3% of the probands tested.[38] A report from the Young Diabetes in Oxford (YDX) study also showed that less than 50% of probands identified with a mutation fulfilled all the diagnostic criteria for MODY.[39] These two studies clearly support that MODY genetic diagnosis should be extended beyond current guidelines (**Box 1**), particularly when age at diagnosis is below 30 years.

The issues of genetic testing costs and healthcare benefits are recurrently debated as to improve practical guidelines for both patients' care and educational perspectives.[40] A simulation model for diabetes complications was used to evaluate the cost-effectiveness of a genetic testing policy for mutations in *GCK*-, *HNF1A*-, and *HNF4A*-MODY in a hypothetical case cohort with a MODY prevalence of 2%.[41] With a conservative interpretation of cost-effectiveness and based on incremental cost-effectiveness ratio thresholds in the US, model sensitivity analysis showed that small increases in MODY prevalence in the case cohort (from 2% to 6%) made the genetic screening policy cost-effective.[41] Moreover, as genetic testing costs are markedly decreasing with the recent progress made in high-throughput sequencing technologies, a broader screening for all the currently known MD subtypes can be provided, particularly in case of infancy-onset diabetes besides strict clinical criteria of MODY. Consequently, a genuine precision genomic medicine will be established in the next future for improved diabetes prevention and management in young people.

New-generation sequencing (NGS) at the heart of diagnostic odyssey in MD

In the past years, before the advent of NGS, molecular genetic diagnosis of MD relied on Sanger sequencing of a few potentially candidate genes selected on the basis of knowledge and availability of phenotype information (for ex. presence of a renal disease in *HNF1B*-MODY, macrosomia and/or neonatal hypoglycemia in *HNF4A*-MODY), but this greatly hampered the etiological diagnosis in a number of the tested patients. Given the high genetic heterogeneity of MD, the ability to use NGS approaches for evaluating all possible candidate genes simultaneously has proven to be a reliable, rapid and cost-effective means compared to previous screening methods.[42-45]

Among the NGS platforms and existing enrichment methods usable for targeted gene panel sequencing, there are marked differences in sequencing coverage of the targets between available exon capture methods (which are based on DNA sonication or enzymatic DNA fragmentation).[42-44] Furthermore, for an accurate genetic diagnosis, these methods require high sensitivity and reliability for all the genes tested in a set of patients. The study by Bonnefond et al. reported that the

microdroplet-based PCR enrichment RainDance technology coupled with Illumina sequencing has great performance and advantages to accurately detect all the causal mutations previously identified in 40 patients with MD or obesity (except one complex indel variant) from a custom panel of 43 genes, and notably with most of the targeted coding regions perfectly sequenced in all participants.[42] This NGS method was found highly sensitive, very fast and cost-effective for mutation screening based on a targeted multi-gene panel analysis.[42] The question of which NGS technique yields the highest diagnosis rate is frequently discussed and is still opened.[46] From our NGS experience, the RainDance enrichment and SureSelect exon-capture methods provided the best results in terms of high quality of sequencing and sensitivity of rare variant detection.[47]

Actually, the targeted NGS methods may serve as first-screening tools before using a broader or almost complete genome sequencing, which has the potential of discovering new disease-causing genes. Given the extensive genetic heterogeneity of MD, the alternative approach is to carry out whole-exome sequencing (WES) in place of testing specific genes, which will allow a first evaluation of a large pre-defined set of genes implicated in glucose metabolism.[45] Improvements in sequence coverage for disease-associated genes have been made, allowing to perform sequencing of a 'medical exome' as a fully optimized diagnostic tool.[48] Furthermore, the hypothesis-free WES approach allows to identify a significantly larger number of variants of unknown clinical significance, as well as variants of incidental findings, which requires development of integrated and sophisticated analysis pipelines (including filtering out the vast majority of known variants from various public databases, and comprehensive functional annotation of the novel potentially deleterious mutations). For diagnosis purposes, the increased number of genes tested will result in a higher detection rate of pathogenic mutations associated with MD; this may also lead to identify cases of possible digenic presentation, as this was evidenced in two recent reports by the co-inheritance of two pathogenic *HNF1A* and *GCK* variants in two MODY families.[49,50]

From our previous studies or from other datasets, it was estimated that ~25-30% of MODY, and a number of NDM or atypical forms of early-onset non-autoimmune diabetes are still unresolved,

hampering a full understanding of diabetes pathophysiology in those patients and the setting up of a pathogenesis-oriented treatment. A recent study by using whole-genome sequencing and linkage analysis in a consanguineous family reported the identification of a novel deletion in *PCBD1* (encoding pterin-4 alpha-carbinolamine dehydratase, also known as dimerization cofactor of hepatocyte nuclear factor-1 alpha) associated early-onset antibody-negative diabetes; subsequently, three additional biallelic *PCBD1* mutations were found in three patients from independent families, who presented with mild neonatal hyperphenylalaninemia and *HNF1A*-MODY-like diabetes.[51] Interestingly, a morpholino-mediated *PCBD1* knockdown in Xenopus revealed that Pcbd1 activity is required for proper establishment of early pancreatic fate within the endoderm.[51] Otherwise, patients with *PCBD1* deficiency can be detected through a newborn screening for phenylketonuria, and subsequently they can be treated with SU or glinide instead of insulin.

In the next future, thanks to whole-genome sequencing and a better understanding of regulatory DNA sequences, we can expect that non-coding mutations will be identified in some of MD cases. Altogether, new findings from these studies will improve our current knowledge of disease mechanisms, and may lead to optimized mechanistic-based therapeutic options for specific subtypes of diabetes. In this contect, integrative functional genomics and system biology approaches will be pivotal to help delineate new gene-related therapies.

Perspectives and challenges of diabetes modelling in the era of iPSC biology

Pluripotent stem cells (PSCs), as embryonic stem cells (ESCs) and induced PCSs (iPSCs), have a great potential to differentiate into all cell types, and to re-establish the disease phenotype *in vitro*.[52] Several iPSC lines have been generated from patients with different types of diabetes, including several MODY subtypes, and some of these cell lines were shown to differentiate into insulin-secreting β cells.[53-57] These biotechnological advances seem to be essential to better evaluate the pathogenic mechanisms and pathophysiological events leading to diabetes. A few representative cutting edge studies in the field are summarized here.

The proof-of-concept of this approach was provided by Hua et al. with hiPSCs derived from MODY2 patients who carry GCK mutations.[54] Those cells have been differentiated into mature β-cells with similar efficiency as control counterparts, and they recapitulated well the clinical phenotype of the patients. Another study has successfully generated hiPSC lines from patients with different types of MODY including HNF4A-MODY1, GCK-MODY2, HNF1A-MODY3, HNF1B- MODY5 and CEL-MODY8, although these lines were not differentiated into pancreatic cells.[53] The generation of MODY patient-specific iPSCs is important to investigate the role played by the MODY genes in pancreatic development and islet-cell dysfunction in diabetes. However, the extent to which these cells are representative of functionally mature adult β-cells remains unclear. Pagliuca et al. reported a novel *in vitro* differentiation approach leading to the generation of functional human pancreatic β-cells, and a gene expression analysis showed that those cells are more similar to adult rather than fetal β-cells.[55] In short, they obtained stem cell-derived glucose-responsive and mono-hormonal insulin-producing cells with features of mature adult β-cells.[55] These new approaches used for generating patient-specific hiPSC lines will enable the direct comparison of mutated and corrected cells sharing the same genetic background, which is very relevant in case of an established single-gene defect.[52]

Interestingly, the study by Shang et al. took a cell biology approach after having successfully generated *in vitro* iPSC-derived β-cells from skin cells of WS patients to assess the role of *WFS1* in insulin production, insulin secretion and protection against ER stress in β-cells.[56] The "WS-iPSC-derived β-cells" displayed increased ER stress levels and decreased insulin content, and an impaired insulin processing and defective insulin secretion in response to glucose (and other secretagogues) were seen upon exposure to experimental ER stress.[56] Moreover, this study showed that a chemical protein folding and trafficking chaperone (4-phenyl butyric acid, 4PBA) can restore normal insulin synthesis and the ability to up-regulate insulin secretion in this WS-derived β-cell model,[56] suggesting that 4PBA and potentially other chemical chaperones might protect β-cells from death arising from ER stress. Otherwise, such β-cell model could be used to test the efficacy of other

candidate drugs, that may be effective in preventing or delaying β-cell dysfunction, and ultimately to develop novel treatments applicable to other forms of diabetes.

The pathogenic mechanisms and/or the defective molecular targets at stake in the pathophysiological processes behind MD clinical outcome are yet not fully understood, mainly due to the poor accessibility of affected tissues, most notably the pancreatic β-cells. Thus, the generation of patient-specific iPSCs towards glucose-responsive insulin-secreting cells represents a pivotal key step to address many important issues of diabetes cellular models and of human cell-based diabetes therapy in the near future of precision and regenerative medicine. To overcome the limitations of host immune responses to exogeneous implants or of adverse effects of immunosuppression, strategies using immunoisolation of insulin-producing cells (like with biomaterials functioning as an immune barrier) could be tested. A recent study reported for the first time long-term glycemic control using polymer-encapsulated human SC-derived β-cells in immune-competent C57BL/6J mice treated with streptozotocin.[58] These implants induced glycemic correction without any immunosuppression for 174 days (the longest duration of sustained normoglycemia using this kind of encapsulated human cells in a robust rodent model), and human C-peptide concentrations and *in vivo* glucose responsiveness demonstrated a therapeutically relevant glycemic control.[58]

Conclusion and future prospects

Over the past 25 years, the scientific community has been strongly committed to investigate the genetic determinants and pathophysiological mechanisms of MD through powerful human genomics and cell biology-based approaches. Outstanding achievements and insightful information from these studies greatly broadened our knowledge of both normal and altered β-cell biology, and of the many faces of the dynamically and temporally controlled insulin secretion in humans.

State-of-the-art genomics and integrative biology approaches are key to further decipher genetic mechanisms of unresolved atypical early-onset diabetes. A timely and accurate clinical translation of new genetic findings is also crucial to guide improved diagnosis, prevention and therapeutic policies.

In the next future, we can expect the rapidly expanding fields of integrative genomic research and translational biology will open new ways towards a broader knowledge of human diabetes. Hopefully, time is there to foster trans-disciplinary researches for mechanistic-based therapies of diabetes.

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Disclosure

The authors have no conflict of interest to declare.

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Box 1. **Best practice consensus guidelines for MODY genetic testing**

Recommendations by the European Molecular Genetics Quality Network (EMGQN) MODY group allow to assist physicians in their decision to test for a MODY diagnosis, and also to improve the rate of a positive molecular diagnosis,[59] following established clinical criteria of MODY:

i/ a family history of diabetes in one parent and first degree relatives although isolated MODY cases with *de novo* mutations may exist (those may be recognized on clinical criteria of early-onset diabetes despite a negative family history of diabetes),

ii/ age at diagnosis usually before 25-30 years,

iii/ lack of islet autoantibodies (to make difference with type 1 diabetes at a young age),

iv/ low or no insulin requirements 2 years after diagnosis,

v/ absence of obesity (based on BMI value at diagnosis and follow-up examination).

Practically , a validated MODY calculator is proposed to assess the probability that a particular patient has MODY with a probability score, taking into account age at diagnosis, BMI, HbA1c level, treatment with insulin or oral hypoglycemic agents, and whether a parent has or not diabetes.[60] This calculator can be found for direct use online at: http://www.diabetesgenes.org/content/mody-probability-calculator (in English); and at: http://files-good.ibl.fr/childhood-obesity-fr (in French).

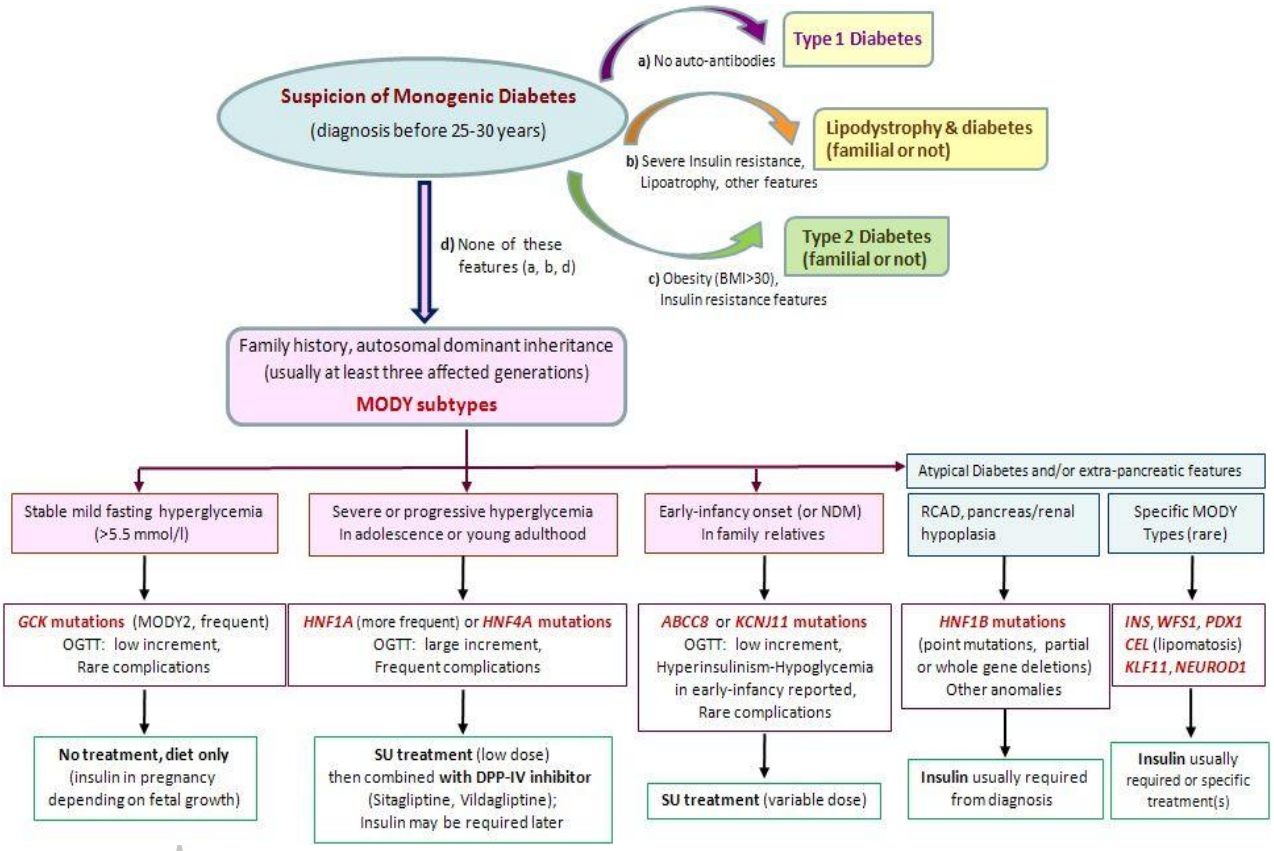

Figure 1. Diagnostic criteria and clinical features for differentiating the main genetic subtypes of MODY, and impact of the genetic defect on the recommended therapeutic options. Criteria for differentiating MODY with other types of diabetes are pointed out on the top-right part (as in either a) or b) or c) case). Gene symbol names are described in Table 2. NDM, neonatal diabetes mellitus; OGTT, oral glucose tolerance test; RCAD, renal cysts and diabetes; SU, sulfonylurea.

Table 1. Genes involved in the different subtypes of monogenic diabetes (MODY, NDM and MDI) and their implication in the pancreatic β-cell physiology.

	MODY	NDM/MDI	Syndromic NDM/MDI
Nucleus, regulation of gene transcription and transcriptional networks			
	HNF1A, HNF4A, KLF11, PAX4	*MNX1, ZFP57, PLAGL1/ZAC (6q24), PCBD1/DCoH*[#]	*GATA4, GATA6, GLIS3, HNF1B, NEUROD1, NEUROG3, NKX2.2, PAX6, PTF1A, RFX6*
	HNF1B, NEUROD1, PDX1		
Glucose uptake and phosphorylation, cellular metabolism and insulin secretion			
	BLK	*SLC2A2*	*SLC19A2*
	GCK		
Endoplasmic reticulum, insulin production and secretion			
	WFS1		*CISD2, EIF2AK3, IER3IP1, PPP1R15B, TRMT10A, WFS1*
	INS		
$K_{(ATP\text{-}sensitive)}$ *channel, insulin secretion*			
	ABCC8, KCNJ11		
Exocrine pancreas, lipase enzymatic activity			
	CEL		

Genes indicated in bold are known to contribute to a continuum of early-onset diabetes phenotypes from NDM to MODY,

depending on the severity of functional defects and the nature of the mutation.[1,2]

[#]Biallelic *PCBD1/DCoH* mutations were identified as causing early-onset antibody-negative diabetes in consanguineous families.[51]

NDM, neonatal diabetes mellitus; MDI, monogenic diabetes of infancy

Table 2. Main characteristics of the MODY genetic subtypes

MODY type	Gene name and locus	Protein/Function	Phenotypes/Syndromes	OMIM[#]	Association with T2D (low-frequency or common variants)[§]
MODY1	*HNF4A* 20q12	HNF-4α Transcription factor	Diabetes in adolescence or early adulthood (and neonatal hyperinsulinism)	125850 600281	+
MODY2	*GCK* 7p13	Glucokinase Glycolytic enzyme	Mild hyperglycemia (onset in early childhood, and life-long) [frequent]	138079 125851	+
MODY3	*HNF1A* 12q24.2	HNF-1α Transcription factor	Diabetes in adolescence or early adulthood [frequent]	600496 142410	+
MODY4	*PDX1* 13q12.1	IPF1 Transcription factor	Diabetes in early adulthood (similar to *HNF1A* but rare)	606392 600733	+
MODY5	*HNF1B* 17q21	HNF-1β Transcription factor	Diabetes in early adulthood, renal cysts and diabetes (RCAD)	137920 189907	+
MODY6	*NEUROD1* 2q31.3	NeuroD1 or Beta2 Transcription factor	Diabetes in early adulthood (similar to *HNF1A* but rare)	606394 601724	
MODY7	*KLF11* 2p25	Krüppel-like factor 11 Transcription factor	Diabetes in childhood and early-adulthood	603301 610508	+
MODY8	*CEL* 9q34	carboxyl-ester lipase enzyme	Diabetes in early-adulthood Pancreatic exocrine insufficiency,	114840 609812	

			pancreatic atrophy and lipomatosis		
MODY9	*PAX4* 7q32	Paired box gene 4 Transcription factor	Diabetes in early-adulthood	167413 612225	+
MODY10	*INS* 11p15.5	Preproinsulin, insulin Hypoglycemic hormone, effect on anabolism	Diabetes in childhood and early-adulthood	613370 176730	
MODY11	*BLK* 8p23	B lymphocyte kinase non-receptor tyrosine kinase	Diabetes in early-adulthood	191305 613375	+
MODY12	*ABCC8* 11p15.1	SUR1 (sulfonylurea receptor) K_{ATP} channel regulatory subunit	Diabetes in childhood and early-adulthood	600509	+
MODY13	*KCNJ11* 11p15.1	Kir6.2 K_{ATP} channel pore-forming subunit	Diabetes in childhood and early-adulthood	600937	+
MODY14	*WFS1* 4p16	Wolfram syndrome 1 Wolframin	Diabetes in early-adulthood	606201 222100	+

[#]The OMIM (Online Mendelian Inheritance in Man) numbers depict the phenotype and/or gene MIM numbers.

[§]The sign '+' denotes the presence of low-frequency or common variants associated with common forms of T2D.[61,62]

K_{ATP}, ATP-sensitive potassium channel; RCAD, renal cysts and diabetes.

Table 3. Main characteristics of NDM and MDI genetic subtypes

Gene name and locus	Protein/Function	Phenotypes/syndromes	OMIM #	Association with T2D (low-frequency or common variants)[51]
PLAGL1 6q24.2	Pleiomorphic adenoma gene-like 1, zinc finger protein or ZAC tumor suppressor	TNDM; Chromosome 6q structural anomalies with imprinting mechanisms (methylation defects)	601410 603044	
ZFP57 6p22.1	Zinc-finger protein 57, role in maintenance of imprinted DNA methylation	TNDM with macroglossia, developmental delay, umbilical defect, visual impairment, CHD	601410 612192	
KCNJ11 11p15.1	Kir6.2 Inward rectifier K+ channel pore-forming subunit	PNDM (more often), TNDM (less often) DEND (rarely)	600937	+
ABCC8 11p15.1	Sulfonylurea receptor 1 (SUR1) subunit of K_{ATP} channel	TNDM (more often), PNDM (less often) DEND (very rare)	606176 600509	+
INS 11p15.5	Preproinsulin, insulin Hypoglycemic hormone, effect on anabolism	PNDM and early-infancy diabetes; Heterozygous mutations in *INS* coding regions, homozygous mutations in *INS* regulatory regions	606176 176730	
GCK 7p13	Glucokinase Glycolytic enzyme	PNDM (homozygous or compound heterozygous mutations)	606176 138079	+
PDX1	Pancreatic duodenal homeobox	PNDM with pancreas agenesis/hypoplasia	260370	+

13q12	protein 1 (PDX1) or IPF1 Transcription factor	for homozygous mutations	600733	
MNX1 *7q36*	Motor Neuron and Pancreas Homeobox 1; also known as HB9 or HLXB9	PNDM (homozygous mutations)	142994	
NDM/MDI associated with developmental anomalies and/or extra-pancreatic features				
EIF2AK3 2p12	Eukaryotic translation initiation factor 2-α kinase 3, or pancreatic eIF2-α kinase (PERK)	Wolcott Rallison syndrome (diabetes associated with epiphyseal dysplasia)	226980 604032	
FOXP3 Xp11.23	Forkhead box protein P3 (FoxP3) or Scurfin Transcription factor	X-linked IPEX syndrome (Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) with diffuse aut immunity	304790 300292	
GATA6 *18q11*	GATA binding protein 6	Diabetes, pancreas agenesis/hypoplasia, in association with congenital heart defects (autosomal dominant)	601656 600001	
GLIS3 9p24.2	GLI-similar family zinc finger 3 transcription factor	PNDM with congenital Hypothyroidism, glaucoma (NDH syndrome)	610199 610192	+
HNF1B 17q21	HNF-1β Transcription factor	TNDM/PNDM with pancreatic atrophy and/or renal abnormalities (GCKD: renal cysts) or renal dysplasia	189907	+

IER31P1 18q21.1	Immediate early response 3 interacting protein 1	PNDM with microcephaly, severe infantile epileptic encephalopathy	614231
NEUROD1 2q31.3	NeuroD1 or Beta2 Transcription factor	PNDM with cerebellar hypoplasia, sensorineural deafness, visual impairment and developmental delay	601724
NEUROG3 10q22.1	NeuroG3 or NGN3 Transcription factor	PNDM with severe diarrhea, absence of intestinal enteroendocrine cells	610370 604882
PAX6 11p13	Paired box 6 containing Transcription factor	PNDM with brain malformations, microcephaly, microphtalmia, panhypopituitarism	165550 607108
PPP1R15B 1q32.1	Protein phosphatase 1, regulatory subunit 15B, or CREP	Diabetes, short stature, microcephaly and intellectual disability	613257 616817
PTF1A 10p12	Pancreas transcription factor 1, Subunit α	PNDM with pancreatic and cerebellar hypoplasia	609069 607194
RFX6 6q22.2	Regulatory factor X, 6 Transcription factor	PNDM with pancreatic hypoplasia, intestinal atresia, gall bladder hypoplasia or aplasia, diarrhea	601346 612659
SLC19A2 1q24.2	Thiamine transporter 1 Solute carrier family 19 member	TRMA syndrome (megaloblastic anemia) Sensorineural deafness, occasional heart defect, NDM or later-onset diabetes	249270 603941

SLC2A2 3q26.2	GLUT2 Facilitated glucose transporter	Fanconi-Bickel syndrome, NDM or IGT or diabetes in infancy/childhood	227810 138160	
TRMT10A 4q23	tRNA methyltransferase 10 Homolog A	Diabetes, short stature, microcephaly, intellectual disability and epilepsy	616013 616033	
WFS1 4p16.1	Wolframin Membrane glycoprotein	Wolfram syndrome (DIDMOAD) Diabetes insipidus, diabetes mellitus, optic atrophy, deafness	222300 606201	+

The OMIM (Online Mendelian Inheritance in Man) numbers depict the phenotype and/or gene MIM numbers.

CHD, congenital heart defect; CREP, constitutive reverter of eIF2α phosphorylation; DEND, developmental delay, epilepsy, neonatal diabetes; DIDMOAD, diabetes insipidus, diabetes mellitus, optic atrophy, deafness; GCKD, glomerulocystic kidney disease; IGT, impaired glucose tolerance; K_{ATP}, ATP-sensitive potassium channel; MDI, monogenic diabetes of infancy; NDH, neonatal diabetes and congenital hypothyroidism; NDM, neonatal diabetes mellitus; PNDM, permanent neonatal diabetes mellitus; RCAD, renal cysts and diabetes; TNDM, transient neonatal diabetes mellitus; TRMA, thiamine-responsive megaloblastic anemia; T2D, type 2 diabetes; UPD6, uniparental disomy of chromosome 6.