



Global perspectives on monogenic forms of diabetes

James Russ-Silby¹ · Milena Teles^{2,3} · Samar S. Hassan^{4,5} · Nancy S. Elbarbary⁶ · Cấn Thị Bích Ngọc⁷ · Elisa De Franco¹

Received: 24 February 2025 / Accepted: 4 June 2025 / Published online: 16 July 2025
© The Author(s) 2025

Abstract

Monogenic forms of diabetes represent an uncommon but very heterogeneous subset of the disease, with variable associated clinical features and key differences in treatment options. In this review, we discuss how advances in precision medicine and genomic sequencing have enhanced our understanding of the aetiology and clinical variability of monogenic diabetes. We highlight current global challenges, including the over-representation of individuals of European genetic ancestry in research studies, which complicates diagnosis in non-European populations, and national disparities in genetic testing strategies, which influence diagnostic accuracy. Additionally, we address issues in variant interpretation stemming from the increased understanding of variable penetrance in monogenic diabetes and the need to expand current reference datasets to exclude common genetic variation. Finally, we explore future directions, including the potential benefits of ongoing genetic studies for under-represented populations, the benefits and potential pitfalls of newborn screening programmes, and the potential of stem cell-derived islet transplantation and glucagon-like peptide-1 receptor agonists as treatments for some forms of monogenic diabetes.

Keywords Diagnosis · Equity, diversity and inclusion · Genetic testing · Global challenges · MODY · Monogenic diabetes · Neonatal diabetes · Penetrance · Review

✉ Elisa De Franco
e.de-franco@exeter.ac.uk

¹ Department of Clinical and Biomedical Science, University of Exeter Medical School, Exeter, UK

² Grupo de Diabetes Monogênico, Unidade de Endocrinologia Genética (LIM25), Unidade de Diabetes, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil

³ Núcleo de Pesquisa e Desenvolvimento de Medicamentos, Programa de Pós-Graduação em Medicina Translacional, Universidade Federal do Ceará, Fortaleza, Brazil

⁴ Department of Pediatric Endocrinology, Gaafar Ibn Auf Pediatric Tertiary Hospital, Khartoum, Sudan

⁵ Sudan Childhood Diabetes Center, Khartoum, Sudan

⁶ Diabetes and Endocrine Unit, Department of Pediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt

⁷ Vietnam National Children's Hospital, Hanoi, Vietnam

Abbreviations

GLP-1 RA	Glucagon-like peptide-1 receptor agonist
MIDD	Maternally inherited diabetes and deafness
NDM	Neonatal diabetes mellitus
PNDM	Permanent neonatal diabetes mellitus
TNDM	Transient neonatal diabetes mellitus
TNGS	Targeted next-generation sequencing

Introduction

In the last 15 years, the study of monogenic diabetes subtypes, specifically neonatal diabetes and MODY, has increasingly become a global field (Fig. 1), strongly contributing to the understanding, diagnosis and management of individuals affected by these uncommon conditions. However, global challenges remain, including the identification of individuals

who should be referred for genetic testing, testing strategies, gene discovery and genetic interpretation. In this review, we explore recent advances and future challenges in monogenic diabetes from a global perspective.

Overview of the main monogenic diabetes subtypes

Neonatal diabetes

Clinical features of neonatal diabetes Neonatal diabetes mellitus (NDM) is defined as diabetes with onset in the first 6 months of life (see Text box, Summary of main monogenic diabetes subtypes). This clear diagnostic criterion is based on two studies showing that diabetes diagnosed before 6 months of age is most likely to have a monogenic cause rather than being due to polygenic autoimmunity [1, 2].

Summary of main monogenic diabetes subtypes

- Neonatal diabetes (NDM) is diagnosed before the age of 6 months. This very early onset means that it almost always has a monogenic aetiology.
- Some NDM genetic subtypes are responsive to targeted treatments that reduce or remove the need for insulin treatment, making a genetic diagnosis vital for optimal treatment.
- MODY is a form of monogenic diabetes with onset typically before 25 years of age, but it can occur later. Based on age of onset it is often misdiagnosed as type 1 or type 2 diabetes.
- Some MODY subtypes do not require insulin treatment and can be treated with sulfonylureas alone, and some do not require any medical intervention.

Clinically, NDM is categorised into three main types based on diabetes progression and additional extra-pancreatic features: permanent neonatal diabetes mellitus (PNDM), transient neonatal diabetes mellitus (TNDM) and syndromic neonatal diabetes [3]. Isolated PNDM is the most common type and requires lifelong therapy. TNDM is characterised by a period of remission in infancy, during which no treatment is required, but often relapses later in childhood or adolescence. Syndromic neonatal diabetes includes a range of

conditions in which NDM is one of several clinical features, reflecting a broader systemic involvement [3]. Examples of syndromic NDM subtypes include pancreatic agenesis, clinically defined as NDM and exocrine pancreatic insufficiency [4], and IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome, characterised by NDM, enteropathy and eczema [5].

Neonatal diabetes genetic testing The International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines recommend genetic testing for all individuals diagnosed with diabetes in the first 6 months of life [6]. To date, 43 different genetic causes of NDM have been described, including autosomal dominant, autosomal recessive and X-linked variants, as well as an imprinting disorder and a form of aneuploidy [7].

Neonatal diabetes treatment Identification of the genetic cause in individuals with NDM can result in improved treatment, highlighting the importance of precision medicine in the context of this disease (see Text box, Summary of main monogenic diabetes subtypes). Activating disease-causing variants in the genes encoding the ATP-dependent potassium (K_{ATP}) channel, *KCNJ11* and *ABCC8*, are the most common cause of NDM [8]. Individuals with these variants often respond to treatment with sulfonylureas such as glibenclamide [9, 10] rather than insulin, leading to improved management of glucose levels [11]. When insulin treatment for NDM is required, advanced insulin delivery technologies such as insulin pumps and hybrid closed-loop systems have been shown to be safe and effective and can lead to improved management of glucose levels over standard insulin injections [12]. However, because of the cost of these therapies, they may not frequently be an option for individuals with NDM.

Beyond diabetes management, a genetic diagnosis of NDM can improve treatment for extra-pancreatic features. In the case of individuals with NDM caused by K_{ATP} channel gene variants, timely intervention with glibenclamide can significantly improve neurodevelopmental outcomes [11] with early treatment in affected individuals associated with reduced neurodevelopmental impairment and greater independence in later life [13].

MODY

Clinical features of MODY In contrast to NDM, there is no single defining criterion for diagnosis of MODY. Traditionally, MODY has been defined as a subtype of diabetes characterised by a strong family history and early age of onset (typically <25 years of age). However, heterozygous MODY-causing variants can occur de novo and so a family

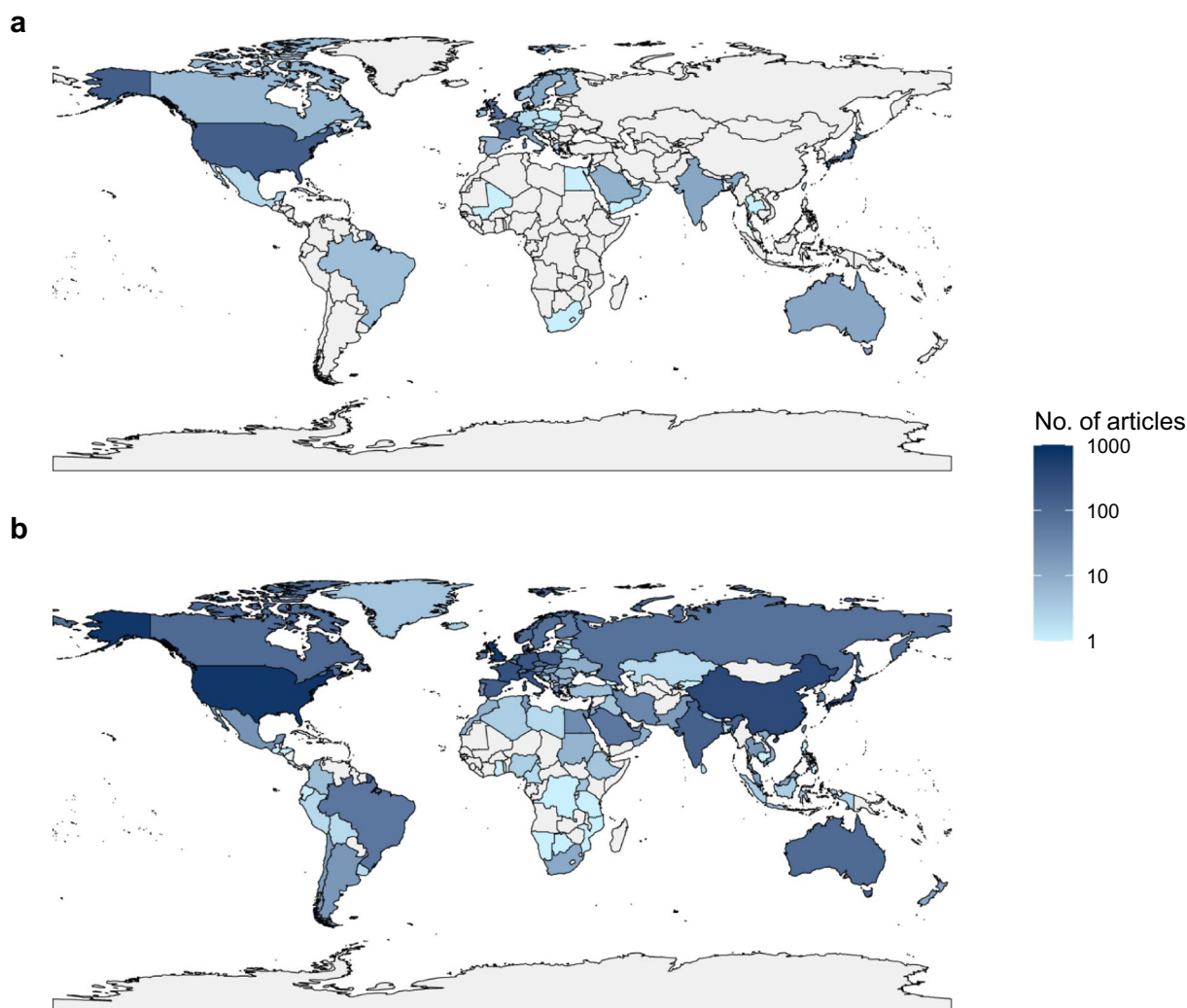


Fig. 1 Number of scientific journal articles matching the terms ‘monogenic diabetes’, ‘maturity-onset diabetes of the young’ or ‘neonatal diabetes’ (and variations of these terms) in the Scopus database (<https://www.scopus.com>) up to 2000 (a) and from 2000 onwards (b) by country (based on all named author affiliations). Authors from 114 different countries have published research on monogenic diabetes

since 2000 compared with authors from 41 countries prior to 2000, illustrating how, similar to other diseases, the study of monogenic diabetes has become an increasingly global field and why global perspectives on this disease are important. This figure is available as a [downloadable slide](#)

history of diabetes may not always be present. There is also increasing evidence from population databases and genetic testing of family members that onset of MODY after 25 years of age is not uncommon [14, 15]. Based on age at diagnosis, individuals with MODY are frequently misdiagnosed with either type 1 or type 2 diabetes [16] (see Text box, Summary of main monogenic diabetes subtypes).

MODY genetic testing ISPAD guidelines recommend considering genetic testing for MODY in people with a family history of diabetes whose clinical features do not clearly align with classical type 1 or type 2 diabetes [6]. Additional indicators include low levels or absence of islet autoantibodies, preserved C-peptide levels years after diagnosis and features suggestive

of specific MODY subtypes (e.g. mild stable fasting hyperglycaemia that does not progress in *GCK*-MODY, renal cysts in *HNF1B*-MODY or macrosomia in *HNF4A*-MODY) [17]. To aid the decision-making process around when MODY genetic testing is appropriate, MODY probability calculators based on family history of diabetes and clinical features are available [18, 19]. Strategies to identify individuals to refer for MODY testing have been reviewed elsewhere [17].

Monoallelic pathogenic variants in 11 genes are currently accepted as causative for MODY [20]. However, genetic testing panels for individuals with MODY will often include other genes, including those causing syndromic diseases that can include diabetes, such as Wolfram syndrome and mitochondrial maternally inherited diabetes and deafness (MIDD).

MODY treatment Similarly to NDM, a genetic diagnosis of MODY is essential to ensure optimal clinical management, with the most common genetic subtypes not requiring insulin treatment [20] (see Text box, Summary of main monogenic diabetes subtypes). Individuals with pathogenic variants in the *HNF1A* and *HNF4A* genes usually respond well to sulfonylurea therapy, although requirement for insulin treatment later in life has been reported in some cases [21], while individuals with dominant *GCK* variants have mild fasting hyperglycaemia from birth that does not require any treatment and it is not associated with long-term complications [22, 23]. Some forms of MODY include additional extra-pancreatic features, such as those caused by monoallelic pathogenic variants in *HNF1B*, which cause renal cysts [24]. It is important that individuals with syndromic forms of diabetes receive a genetic diagnosis to ensure proper management of the extra-pancreatic features of the disease.

Frequency of monogenic diabetes in different countries

Traditionally, NDM has been reported to affect 1 in 100,000 live births, while MODY is reported to affect 1 in 10,000 adults and 1 in 23,000 children (<https://www.orpha.net/>, accessed 5 Jun 2025). However, true disease prevalence can be difficult to accurately estimate, particularly in the case of NDM, where the genetic cause strongly influences life expectancy. Furthermore, the reported frequency of both diseases varies greatly in different populations. There are two primary explanations for this: population-specific differences in the frequencies of disease-causing variants and biases in clinical referrals for monogenic diabetes genetic testing [8, 25] (see Text box, Summary of frequency differences in monogenic diabetes).

Summary of frequency differences in monogenic diabetes

- The incidence of both NDM and MODY varies hugely between countries.
- Much of the variation in incidence observed for NDM is due to differences in the frequency of consanguineous marriage between populations, with autosomal recessive diseases more common in populations with high rates of consanguineous marriage.
- MODY is often underdiagnosed because of its clinical overlap with type 1 and type 2 diabetes, lack of awareness and insufficient genetic testing, resulting in wide variations in reported prevalence.

Population-specific differences in disease incidence

The reported incidence of NDM ranges from as low as 1 in 476,000 (0.00021%) births in the USA to as high as 1 in 22,938 (0.0044%) in Qatar and 1 in 20,833 (0.0048%) in Sudan [26–28]. The biggest driver of this observed difference is the rate of consanguineous marriages; 27 of 43 known genetic causes of NDM are recessively acting [29] and are therefore more likely to occur in countries in which consanguineous marriage is common. Consistent with this, in countries with higher rates of consanguineous marriage the most common NDM subtypes are primarily recessive. For example, among some Arabic populations where the rate of consanguineous marriage is 40–60%, the most common genetic subtype of NDM is Wolcott–Rallison syndrome, caused by biallelic variants in the *EIF2AK3* gene [28, 30]. Conversely, in countries with low rates of consanguineous marriage the most common NDM subtypes have autosomal dominant inheritance, with heterozygous variants in *KCNJ11*, *ABCC8* and *INS* accounting for more than 50% of NDM cases in the USA and Europe [31, 32].

Biases in referral rates

Biases in referral rates for monogenic diabetes testing are a key driver of the observed differences in the frequency of monogenic diabetes between countries. This is especially the case for MODY, where clinical overlap between MODY and type 1 and type 2 diabetes as well as a lack of awareness of the disease can lead to misdiagnosis and thus large variation in the reported frequency [25]. Within the UK it has been estimated that as many as 77% of MODY cases remain undiagnosed, with an estimated true case rate of 248 per million (0.025%) based on the prevalence in south-west England and Scotland, where disease awareness is high and similar prevalences have been reported [33]. A lower estimated prevalence has been reported in other European populations, such as the Netherlands (30 per million, 0.003% [34]) and Norway (92 per million, 0.0092% [35]), suggesting that similarly high proportions of cases may be undiagnosed.

To date, most studies on prevalence, genetics and clinical features of MODY have been conducted in European cohorts [25]. As a result, the prevalence of MODY in many non-European populations is currently unclear. This is further complicated by our current incomplete understanding of the differences in clinical features and genetic causes of MODY in non-European individuals, which impairs our ability to recognise the disease. Consequently, even within countries with higher referral rates such as the UK, significantly fewer non-European individuals are referred for MODY testing than would be expected based on the prevalence of diabetes in these groups [36].

Genetic testing for monogenic diabetes

Approaches to genetic testing

Traditionally, Sanger sequencing [37] of specific genes was used as the primary means of genetic testing for monogenic diabetes [8]. The development of next-generation sequencing and the discovery of more monogenic diabetes genes have led to replacement of this approach with methods that simultaneously test for all known genetic causes. However, Sanger sequencing is still the most affordable approach, especially for targeted testing in individuals with specific phenotypes (e.g. in cases of syndromic NDM) and as a first line of investigation to rapidly diagnose common genetic subtypes of monogenic diabetes that could result in treatment change.

Targeted next-generation sequencing (TNGS) of gene panels [38] enables sequencing of all genes and non-coding regions known to contain monogenic diabetes-causing genetic variants in a single assay [8] (see Text box, Summary of genetic testing in monogenic diabetes). The reduced cost of the assay compared with genome and exome sequencing, as well as the reduced data storage and processing costs, mean that TNGS has become one of the most popular methods for performing monogenic diabetes genetic testing worldwide. However, TNGS panels need to be constantly updated and redesigned as novel genetic aetiologies are identified.

Summary of genetic testing in monogenic diabetes

- Today, most monogenic diabetes genetic testing is performed using next-generation sequencing (NGS) methodologies.
- Testing strategy and choice of genes tested can heavily influence the ability of laboratories to identify the cause of an individual's monogenic diabetes.
- Variant interpretation poses a significant challenge in monogenic diabetes diagnosis, with the increasing output from NGS resulting in increasing numbers of variants of uncertain significance.
- International variant interpretation guidelines, such as the American College of Medical Genetics and Genomics guidelines [44], are essential to standardise reporting of variants in monogenic disease, including monogenic diabetes.
- Variant interpretation is hampered by unequal representation of different global populations in genetic databases.

Analysis of known monogenic diabetes genes can be performed through exome (capturing all protein-coding genes) and genome (capturing nearly all the genome) sequencing [39]. Genome sequencing is the most comprehensive option for analysis of known genes and reanalysis of data when new aetiologies are identified, without the need for additional samples and laboratory work. However, the approximately 100-fold increase in number of variants observed in genome sequencing compared with exome sequencing makes the processing and prioritisation of variants more complex [40]. These complexities combined with the increased sequencing and data storage costs mean that genome sequencing is currently not frequently used for monogenic diabetes diagnostic testing.

National differences in testing strategies

Different countries have adopted distinct testing strategies for monogenic diabetes based on healthcare infrastructure, funding and local expertise. While some countries have routine access to clinical exome or genome sequencing, others rely on more cost-effective approaches such as Sanger sequencing or TNGS. When local testing is not available, genetic analysis may sometimes be performed abroad at laboratories that accept international testing referrals, such as the Exeter Genomics Laboratory (<https://www.diabetesgenes.org>, accessed 5 Jun 2025), with charitable donations covering the costs of genetic testing of NDM when patients and their referring healthcare systems are unable to cover them. However, fewer funding opportunities exist for individuals with MODY from low-income countries.

The genetic testing strategy used heavily influences the rates of genetic diagnoses. When testing uses only Sanger sequencing or TNGS, the choice of genes tested is essential, as only variants in genes included in the test can be detected. Some genetic panels for MODY do not include genes causing syndromic forms of diabetes, such as *WFS1* (Wolfram syndrome 1) and *CISD2* (Wolfram syndrome 2) or the mitochondrial m.3243A>G variant causing MIDD, which may lead to missed diagnoses in cases where diabetes is the first manifestation of a syndrome [41]. Ideally, a consensus should be reached on the genes to be tested for all forms of monogenic diabetes. Similarly, the use of off-the-shelf exome sequencing assays that do not include non-coding regions can lead to missed diagnoses, as several non-coding regions have been implicated in monogenic diabetes [42]. This is a significant problem for individuals with NDM in countries such as Turkey, where non-coding variants in a distal regulatory element of the *PTF1A* gene are one of the leading causes of the disease [43].

The challenges of variant interpretation in the genomics era

As next-generation sequencing techniques have enabled examination of increasingly large amounts of genetic variation in individuals with disease, variant interpretation has become more complex. While the implementation of guidelines from bodies such as the American College of Medical Genetics and Genomics [44] has been instrumental in moving the field towards a standardised method for variant assessment, huge challenges remain, with different laboratories often classifying variants differently, leaving clinicians and patients without clear guidance while waiting for more definitive answers. At worst, misinterpretation of a variant of uncertain significance can lead to unnecessary medical interventions or the failure to treat a disease properly. The use of resources such as ClinVar [45], which provides information on variant classification from different laboratories that have identified variants previously, is essential to improve consistency in variant classification.

A key piece of evidence used in variant interpretation is the frequency of a variant in affected and unaffected populations. As population databases of genetic variation are over-represented for individuals of European genetic ancestry [46], variant interpretation is more challenging in individuals of non-European genetic ancestry. This issue is actively being addressed, with several projects aimed at sequencing under-represented populations and global biobank initiatives currently under way (summarised in Table 1). Integration of genetic variation data from these projects into variant interpretation pipelines has the potential to vastly improve our ability to interpret rare variation in individuals of non-European genetic ancestry.

Penetrance of monogenic diabetes and the monogenic–polygenic diabetes continuum

Identification and implications of variable penetrance in monogenic diabetes subtypes

Increased understanding of the genetics underlying monogenic diabetes has highlighted the variability in penetrance of some genetic subtypes (see Text box, Summary of penetrance in monogenic diabetes). Understanding the mechanisms underlying this variability is important to guide genetic counselling.

Summary of penetrance in monogenic diabetes

- There is increasing evidence for variable penetrance in monogenic diabetes.
- Variable penetrance has been reported in multiple subtypes of MODY but is uncommon in NDM.
- Some of this variable penetrance is due to an interplay between monogenic diabetes variants and polygenic risk.
- The observation of variable penetrance has key implications for unaffected family member testing and genetic screening programmes.

Variable penetrance has been especially well documented in MODY, with dominant *RFX6* loss-of-function variants and the hypomorphic *HNF4A* p.(Arg114Trp) variant reported to cause MODY with incomplete penetrance and variable expressivity [47, 48]. Recently, a study investigating the presence of disease-causing *HNF1A* and *HNF4A* variants

Table 1 Overview of large-scale sequencing projects currently under way in different populations

Project	Targeted group(s)	Projected sample size	Technology	Source
All of Us Research Program	Under-represented groups in the USA	>500,000	Array genotyping, genome sequencing	[79], https://allofus.nih.gov
OurDNA	Indigenous and non-European individuals in Australia	>7000	Genome sequencing	https://www.ourdna.org.au
Genes & Health	South Asian individuals in the UK	Up to 100,000	Array genotyping, exome sequencing	https://www.genesandhealth.org
Qatar Biobank	General Qatari population	60,000	Genome sequencing	[80]
Mexican Biobank	General Mexican population	6144	Array genotyping	[81]
Taiwan Biobank	General Taiwanese population	>150,000	Array genotyping	[82]

in large non-clinically selected cohorts showed that penetrance of monogenic diabetes is overestimated based on data in clinically selected cohorts [49]. Variation in penetrance and expressivity of disease-causing variants adds additional complexity to the diagnosis of MODY, as it can lead to a weaker family history of diabetes and increased challenges in classifying possible disease variants, as they may still be present in population databases [37].

Variable penetrance appears to be less extreme in NDM, with disease-causing NDM variants being largely absent or ultra-rare in population databases. However, variability in age at diagnosis and disease features has been reported for some NDM subtypes. This could be variant dependent, as is the case for K_{ATP} variants, where the phenotypic spectrum depends on the severity of the variant effect on the channel [50, 51] or be due to stochastic variation, for example for *GATA6* variants, which have been reported to cause a wide spectrum of disease, from syndromic NDM to isolated adult-onset diabetes, even within the same family [52].

Variants within the mitochondrial genome add an additional layer of complexity to penetrance assessment and variant interpretation because multiple copies of the mitochondrial genome exist in every cell, ranging from hundreds to thousands of copies depending on the tissue [53]. This means that a mitochondrial variant can be present at variable levels, a phenomenon called heteroplasmy. The mitochondrial variant most commonly linked to monogenic diabetes is the m.3243A>G variant causing MIDD. The same variant, however, is also known to cause the more severe phenotype of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) [54]. The level of heteroplasmy in the m.3243A>G variant has been shown to directly influence the phenotype [55]. A recent study observed that, in clinically unselected populations, mitochondrial variants, including m.3243A>G, are often present at low heteroplasmy levels. These variants were found to frequently have low penetrance, and penetrance and expressivity were highly correlated with the level of heteroplasmy [56].

Polygenic contributions to monogenic diabetes penetrance and expressivity

Emerging evidence suggests that common polygenic risk alleles can modulate the expression and severity of monogenic disease [57]. This observation highlights the possibility of a continuum between strictly monogenic and polygenic diabetes, in which both rare, highly penetrant variants and more common, lower penetrance variants interact to shape the clinical phenotype. Preliminary evidence from studies using the UK Biobank and US BioMe biobank have shown significant associations between polygenic risk for type 2 diabetes and phenotype in individuals with rare monogenic

diabetes variants, supporting a role for polygenic background in the penetrance and expressivity of MODY [58, 59].

An interplay between polygenic risk and monogenic diabetes has also been reported in monogenic autoimmune forms of diabetes, including subtypes presenting as NDM. Individuals with diabetes caused by pathogenic variants in the *AIRE*, *FOXP3*, *IL2RA*, *LRBA*, *STAT3* and *TNFAIP3* genes were found to have significantly higher type 1 diabetes genetic risk scores than healthy population-matched control individuals, while still having significantly lower scores than individuals with type 1 diabetes [60]. The mechanism by which the elevated risk influences development of autoimmune diabetes in individuals with these genetic subtypes is not yet understood.

Implications of screening unaffected individuals

The variable penetrance of certain monogenic diabetes subtypes has key implications for the genetic counselling of individuals with disease-causing variants and their families. Furthermore, it draws into question the appropriateness of testing asymptomatic family members, as well as the general population (e.g. as part of the newborn screening programme being undertaken in the UK [61]), as individuals harbouring variable penetrance disease-causing variants may not develop the disease. A more complete understanding of the penetrance and features of different monogenic diabetes subtypes will be vital to reach a consensus on when to report disease-causing variants in unaffected individuals. This is essential to negate the risk of unnecessary treatments, while maximising the potential benefits of treating the disease before the onset of severe or potentially life-threatening complications.

Future directions

Improving equitability in access to genetic testing for monogenic diabetes

Despite improvements in the cost and availability of next-generation sequencing, global access to genetic testing remains highly inequitable. Two primary barriers are the availability of genetic testing facilities and a lack of awareness of monogenic diabetes among clinical staff in some areas. Education will play a key role in addressing these issues.

Online training courses in monogenic diabetes, such as those offered by the Royal Devon University Healthcare NHS Foundation Trust (<https://www.diabetesgenes.org/training/>), have already been highly successful in raising awareness [33] and attract attendees from around the world.

However, their reach remains limited by language barriers and internet access. Expanding these courses to include in-person teaching in regions with lower awareness is vital to broadening their impact. Previously, the African Genomic Medicine Training Initiative [62] has successfully built a network of local trainers across Africa and trained thousands of doctors, nurses and scientists in genomic medicine. Replicating this model for monogenic diabetes training worldwide could greatly improve diagnostic equity. In addition to enhancing recognition of monogenic diabetes, such courses could also clarify options for genetic testing, including low-cost methods and available funding schemes.

Simplifying DNA sample collection could also significantly improve access to genetic testing. At present, DNA is primarily extracted from venous blood samples collected by primary healthcare workers; a process that can pose a major challenge for patients in remote regions, where the nearest clinic may be hours or even days away. This is additionally complicated by the need for DNA to be extracted within 7 days from venous blood sample collection. Optimising next-generation sequencing methods to use DNA from finger-prick capillary blood or saliva (akin to commercial direct-to-consumer genetic tests) would alleviate this barrier, as collection kits could be mailed directly to patients without requiring a healthcare worker's attendance. Saliva samples have already been shown to produce sufficient DNA for genome sequencing in most cases [63] and preliminary data on capillary blood shows a similar success rate [64].

One of the greatest barriers to equitable monogenic diabetes testing is the limited understanding of its presentation in non-European populations [65]. This gap is especially problematic for conditions such as MODY, which are challenging to distinguish from type 1 and type 2 diabetes. Conducting more research in understudied populations is essential to characterise phenotypic differences and refine disease classification. This can be achieved through the establishment of large biobanks integrating genotypic and phenotypic information in non-European populations [66] and by publication of case reports of monogenic diabetes in these populations. Such insights should then be integrated into decision-support tools that are easily accessible by primary healthcare providers, such as the MODY calculator, which simplify the choice of when to pursue genetic testing but which currently underperform in individuals of non-European genetic ancestry [67].

Undiagnosed individuals: gene discovery and polygenic phenocopies

Identifying the genetic causes of monogenic diabetes is essential to provide a genetic diagnosis and reveals essential information about the pathways that govern pancreatic beta cell development and function. By examining these

pathways, we can gain insights that impact individuals with all forms of diabetes.

Despite comprehensive genetic testing, some individuals still lack a genetic diagnosis. At present, approximately 85% of individuals referred for NDM testing [68] and 25% of individuals referred for MODY genetic testing [36] receive a genetic diagnosis. Ongoing research seeks to discover additional disease genes and identify cases that represent polygenic or environmental phenocopies.

Polygenic type 1 and type 2 diabetes is likely to be the underlying diagnosis for some individuals referred for NDM and MODY testing. Extreme early-onset type 1 diabetes has been proposed as being responsible for approximately 4% of NDM cases [69]. The difficulty in distinguishing type 1 and type 2 diabetes from MODY means that many referred but genetically undiagnosed individuals may instead have polygenic diabetes. Calculation of the type 1 diabetes genetic risk score has been shown to be effective in discriminating monogenic and type 1 diabetes [70]. However, methods to exclude type 2 diabetes based on genetic/polygenic risk remain far from perfect, with known genetic variation explaining only approximately 20% of type 2 diabetes heritability [71].

The ability to sequence the complete exomes and genomes of individuals with monogenic diabetes using next-generation sequencing has facilitated a paradigm shift in gene discovery, moving from a candidate gene-based approach to one that is entirely gene agnostic [72]. This means that researchers no longer need large family trees or prior knowledge of specific genes to pinpoint pathogenic variants. This has led to the discovery of at least 16 new genetic causes of NDM and MODY, marking a significant expansion in our understanding of these diseases (Table 2). Further genetic causes are likely to remain unidentified, with the main challenge now being the identification of the contribution of variants in the non-coding genome.

Novel monogenic diabetes treatments

In recent years, several new treatments for different forms of monogenic diabetes have been proposed. In MODY, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) such as dulaglutide and semaglutide have been highlighted as having strong therapeutic potential, with successful treatment reported in cases of *HNF1A*-, *HNF4A*- and *ABCC8*-MODY [73–75]. Early reports have also suggested that GLP-1 RAs may be effective for notoriously hard-to-treat syndromic forms of monogenic diabetes, such as *HNF1B*-MODY [76, 77]. These drugs, which have been shown to improve management of glucose levels and promote weight loss, are a promising new treatment for forms of monogenic diabetes in which some beta cell function is retained and are likely to continue to be trialled in different forms of monogenic diabetes.

When monogenic diabetes results from complete beta cell loss, transplantation of stem cell-derived islets is a promising new treatment option. The first successful application of this approach was recently reported in an individual with type 1 diabetes, with complete control of glucose levels from purely endogenous insulin detected at 75 days and no safety concerns after 1 year [78]. This exciting result highlights the potential of stem cell-derived islet transplantation to restore natural control of glucose levels and to revolutionise the treatment of subtypes of monogenic diabetes that currently can be treated only with exogenous insulin injections.

Final remarks

Monogenic diabetes spans a broad spectrum of disorders presenting at various stages of life with diverse clinical features and treatment needs. While advances in genetic testing have improved our understanding of the genetic basis of the disease, challenges remain in distinguishing monogenic diabetes from the more common polygenic forms, particularly given incomplete penetrance, referral biases and the influence of polygenic risk alleles on monogenic disease presentation. The increased use of next-generation sequencing for genetic testing and the generation of large-scale genome data in non-clinical populations will be critical to further understand the genetic causes of monogenic diabetes, discover factors underlying variable penetrance and improve

variant classification. These efforts are essential to ensure more accurate diagnoses, reduce misclassification and optimise care for individuals with these complex and uncommon forms of diabetes.

Supplementary Information The online version contains a slide of the figure for download available at <https://doi.org/10.1007/s00125-025-06495-3>.

Funding Work in the authors' laboratories is supported by the National Institute for Health and Care Research (NIHR) Exeter Biomedical Research Centre (BRC) and NIHR Exeter Clinical Research Facility. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. EDF is funded by a Diabetes UK RD Lawrence Fellowship (19/005971) and is the recipient of a European Foundation for the Study of Diabetes (EFSD)/Novo Nordisk Foundation Future Leaders Award.

Authors' relationships and activities The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement JR-S and EDF drafted the initial manuscript. All authors contributed to critical review and editing of the manuscript for important intellectual content. All authors approved the version to be published.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

Table 2 List of MODY and NDM aetiological genes identified through next-generation sequencing approaches

Gene/region ^a	Disease	Sequencing technology	Source
<i>KCNJ11</i>	MODY	Exome sequencing	[83]
<i>RFX6</i>	MODY	TNGS	[47]
<i>CNOT1</i>	NDM	Exome sequencing	[84]
<i>EIF2S3</i>	NDM	Exome sequencing	[85]
<i>FICD</i>	NDM	Genome sequencing	[86]
<i>GATA6</i>	NDM	TNGS	[4]
<i>LRBA</i>	NDM	TNGS	[87]
<i>NARS2</i>	NDM	Exome sequencing	[88]
<i>ONECUT1</i>	NDM	Genome sequencing	[89, 90]
<i>PD-L1 (CD274)</i>	NDM	Genome sequencing	[91]
<i>PDIA6</i>	NDM	Genome sequencing	[92, 93]
<i>PTF1A</i> enhancer	NDM	Genome sequencing	[94]
<i>TARS2</i>	NDM	Genome sequencing	[95]
<i>WFS1</i>	NDM	Exome sequencing	[96, 97]
<i>YIPF5</i>	NDM	Genome sequencing	[98]
<i>ZNF808</i>	NDM	Genome sequencing	[99]

^aOnly genes with variants identified in at least three families are included

References

1. Iafusco D, Stazi M, Cotichini R et al (2002) Permanent diabetes mellitus in the first year of life. *Diabetologia* 45(6):798–804. <https://doi.org/10.1007/S00125-002-0837-2>
2. Edghill EL, Dix RJ, Flanagan SE et al (2006) HLA genotyping supports a nonautoimmune etiology in patients diagnosed with diabetes under the age of 6 months. *Diabetes* 55(6):1895–1898. <https://doi.org/10.2337/DB06-0094>
3. Senaratne UD, De Franco E, Abdelmeguid Y, Lu ZX, Brown J (2020) Permanent neonatal diabetes mellitus. In: Rezaei N (ed) *Genetic syndromes: a comprehensive reference guide*. Springer International Publishing, Cham, Switzerland, pp 1–7
4. Allen HL, Flanagan SE, Shaw-Smith C et al (2011) *GATA6* haploinsufficiency causes pancreatic agenesis in humans. *Nat Genet* 44(1):20–22. <https://doi.org/10.1038/ng.1035>
5. Powell BR, Buist NRM, Stenzel P (1982) An X-linked syndrome of diarrhea, polyendocrinopathy, and fatal infection in infancy. *J Pediatr* 100(5):731–737. [https://doi.org/10.1016/S0022-3476\(82\)80573-8](https://doi.org/10.1016/S0022-3476(82)80573-8)
6. Greeley SAW, Polak M, Njølstad PR et al (2022) ISPAD Clinical Practice Consensus Guidelines 2022: The diagnosis and

- management of monogenic diabetes in children and adolescents. *Pediatr Diabetes* 23(8):1188–1211. <https://doi.org/10.1111/PEDI.13426>
7. Barbetti F, Deeb A, Suzuki S (2024) Neonatal diabetes mellitus around the world: update 2024. *J Diabetes Investig* 15(12). <https://doi.org/10.1111/JDI.14312>
 8. De Franco E, Flanagan SE, Houghton JAL et al (2015) The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: an international cohort study. *Lancet* 386(9997):957–963. [https://doi.org/10.1016/S0140-6736\(15\)60098-8](https://doi.org/10.1016/S0140-6736(15)60098-8)
 9. Zung A, Glaser B, Nimri R, Zadik Z (2004) Glibenclamide treatment in permanent neonatal diabetes mellitus due to an activating mutation in Kir6.2. *J Clin Endocrinol Metab* 89(11):5504–5507. <https://doi.org/10.1210/JC.2004-1241>
 10. Sagen JV, Røder H, Hathout E et al (2004) Permanent neonatal diabetes due to mutations in KCNJ11 encoding Kir6.2: patient characteristics and initial response to sulfonylurea therapy. *Diabetes* 53(10):2713–2718. <https://doi.org/10.2337/DIABETES.53.10.2713>
 11. Bowman P, Sulen Å, Barbetti F et al (2018) Effectiveness and safety of long-term treatment with sulfonylureas in patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. *Lancet Diabetes Endocrinol* 6(8):637–646. [https://doi.org/10.1016/S2213-8587\(18\)30106-2](https://doi.org/10.1016/S2213-8587(18)30106-2)
 12. Pezzotta F, Sarale N, Spacco G et al (2024) Safety and efficacy of using advanced hybrid closed loop off-label in an infant diagnosed with permanent neonatal diabetes mellitus: a case report and a look to the future. *Children (Basel)* 11(10). <https://doi.org/10.3390/CHILDREN11101225>
 13. Mlynarski W, Tarasov AI, Gach A et al (2007) Sulfonylurea improves CNS function in a case of intermediate DEND syndrome caused by a mutation in KCNJ11. *Nat Clin Pract Neurol* 3(11):640–645. <https://doi.org/10.1038/NCPNEURO0640>
 14. Campos Franco P, Santos de Santana L, Dantas Costa-Riquetto A, Santomauro Junior AC, Jorge AAL, Gurgel Teles M (2022) Clinical and genetic characterization and long-term evaluation of individuals with maturity-onset diabetes of the young (MODY): the journey towards appropriate treatment. *Diabetes Res Clin Pract* 187:109875. <https://doi.org/10.1016/J.DIABRES.2022.109875>
 15. Sharp L, Mirshahi L, Colclough K et al (2023) MODY in older onset diabetes is common and identification can improve treatment: analysis of >72,000 people. *Diabetologia* 66:S96–S97
 16. McDonald TJ, Colclough K, Brown R et al (2011) Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. *Diabetic Medicine* 28(9):1028–1033. <https://doi.org/10.1111/J.1464-5491.2011.03287.X>
 17. Colclough K, Patel K (2022) How do I diagnose maturity onset diabetes of the young in my patients? *Clin Endocrinol (Oxf)* 97(4):436–447. <https://doi.org/10.1111/CEN.14744>
 18. Shields BM, Carlsson A, Patel K et al (2024) Development of a clinical calculator to aid the identification of MODY in pediatric patients at the time of diabetes diagnosis. *Sci Rep* 14(1):1–9. <https://doi.org/10.1038/s41598-024-60160-0>
 19. Shields BM, McDonald TJ, Ellard S, Campbell MJ, Hyde C, Hattersley AT (2012) The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes. *Diabetologia* 55(5):1265–1272. <https://doi.org/10.1007/S00125-011-2418-8/TABLES/2>
 20. Zhang H, Colclough K, Gloyn AL, Pollin TI (2021) Monogenic diabetes: a gateway to precision medicine in diabetes. *J Clin Invest* 131(3). <https://doi.org/10.1172/JCI142244>
 21. Delvecchio M, Pastore C, Giordano P (2020) Treatment options for MODY patients: a systematic review of literature. *Diabetes Therapy* 11(8):1667–1685. <https://doi.org/10.1007/S13300-020-00864-4/TABLES/4>
 22. Shepherd MH, Shields BM, Hudson M et al (2018) A UK nationwide prospective study of treatment change in MODY: genetic subtype and clinical characteristics predict optimal glycaemic control after discontinuing insulin and metformin. *Diabetologia* 61(12):2520–2527. <https://doi.org/10.1007/S00125-018-4728-6/FIGURES/2>
 23. Steele AM, Shields BM, Wensley KJ, Colclough K, Ellard S, Hattersley AT (2014) Prevalence of vascular complications among patients with glucokinase mutations and prolonged, mild hyperglycemia. *JAMA* 311(3):279–286. <https://doi.org/10.1001/JAMA.2013.283980>
 24. Mateus JC, Rivera C, O'Meara M, Valenzuela A, Lizcano F (2020) Maturity-onset diabetes of the young type 5 a MULTISYSTEMIC disease: a CASE report of a novel mutation in the HNF1B gene and literature review. *Clin Diabetes Endocrinol* 6(1):1–8. <https://doi.org/10.1186/S40842-020-00103-6>
 25. Kleinberger JW, Pollin TI (2015) Undiagnosed MODY: time for action. *Curr Diab Rep* 15(12):1–11. <https://doi.org/10.1007/S11892-015-0681-7/TABLES/1>
 26. Al-Khawaga S, Mohammed I, Saraswathi S et al (2019) The clinical and genetic characteristics of permanent neonatal diabetes (PNDM) in the state of Qatar. *Mol Genet Genomic Med* 7(10):e00753. <https://doi.org/10.1002/MGG3.753>
 27. Kanakatti Shankar R, Pihoker C, Dolan LM et al (2012) Permanent neonatal diabetes mellitus: prevalence and genetic diagnosis in the SEARCH for diabetes in youth study. *Pediatr Diabetes* 14(3):174. <https://doi.org/10.1111/PEDI.12003>
 28. Hassan SS, Musa SA, De Franco E et al (2024) Incidence, phenotypes, and genotypes of neonatal diabetes: a 16-year experience the rare genetic etiologies of neonatal diabetes are common in Sudan. *Pediatr Diabetes* 2024(1):2032425. <https://doi.org/10.1155/2024/2032425>
 29. Ben-Omran T, Al Ghanim K, Yavarna T et al (2019) Effects of consanguinity in a cohort of subjects with certain genetic disorders in Qatar. *Mol Genet Genomic Med* 8(1):e1051. <https://doi.org/10.1002/MGG3.1051>
 30. Rubio-Cabezas O, Patch AM, Minton JAL et al (2009) Wolcott-Rallison syndrome is the most common genetic cause of permanent neonatal diabetes in consanguineous families. *J Clin Endocrinol Metab* 94(11):4162–4170. <https://doi.org/10.1210/JC.2009-1137>
 31. Rapini N, Delvecchio M, Mucciolo M et al (2024) The changing landscape of neonatal diabetes mellitus in Italy between 2003 and 2022. *J Clin Endocrinol Metab* 109(9):2349–2357. <https://doi.org/10.1210/CLINEM/DGAE095>
 32. Bowden TL, Letourneau-Freiberg LR, Kandasamy B et al (2021) Insight on diagnosis and treatment from over a decade of research through the university of Chicago monogenic diabetes registry. *Front Clin Diabetes Healthc* 2:735548. <https://doi.org/10.3389/FCDHC.2021.735548>
 33. Pang L, Colclough KC, Shepherd MH et al (2022) Improvements in awareness and testing have led to a threefold increase over 10 years in the identification of monogenic diabetes in the U.K. *Diabetes Care* 45(3):642. <https://doi.org/10.2337/DC21-2056>
 34. Weinreich SS, Bosma A, Henneman L et al (2014) A decade of molecular genetic testing for MODY: a retrospective study of utilization in The Netherlands. *Eur J Hum Genet* 23(1):29–33. <https://doi.org/10.1038/ejhg.2014.59>
 35. Søvik O, Irgens HU, Molnes J et al (2013) Monogenic diabetes mellitus in Norway. *Norsk Epidemiologi* 23(1):55–60. <https://doi.org/10.5324/NJE.V23I1.1603>
 36. Misra S, Shields B, Colclough K et al (2016) South Asian individuals with diabetes who are referred for MODY testing in the UK have a lower mutation pick-up rate than white European people. *Diabetologia* 59(10):2262–2265. <https://doi.org/10.1007/S00125-016-4056-7>

37. Sanger F, Nicklen S, Coulson AR (1977) DNA sequencing with chain-terminating inhibitors. *Proc Natl Acad Sci U S A* 74(12):5463. <https://doi.org/10.1073/PNAS.74.12.5463>
38. Ellard S, Lango Allen H, De Franco E et al (2013) Improved genetic testing for monogenic diabetes using targeted next-generation sequencing. *Diabetologia* 56(9):1958–1963. <https://doi.org/10.1007/S00125-013-2962-5>
39. Grada A, Weinbrecht K (2013) Next-generation sequencing: methodology and application. *J Investig Dermatol* 133(8):1–4. <https://doi.org/10.1038/JID.2013.248>
40. Lacey S, Chung JY, Lin H (2014) A comparison of whole genome sequencing with exome sequencing for family-based association studies. *BMC Proc* 8(Suppl 1):S38. <https://doi.org/10.1186/1753-6561-8-S1-S38>
41. Patel KA, Ozbek MN, Yildiz M et al (2022) Systematic genetic testing for recessively inherited monogenic diabetes: a cross-sectional study in paediatric diabetes clinics. *Diabetologia* 65(2):336–342. <https://doi.org/10.1007/S00125-021-05597-Y>
42. Arslan Ateş E, Türkyilmaz A, Yıldırım Ö et al (2021) Secondary findings in 622 Turkish clinical exome sequencing data. *J Hum Genet* 66(11):1113–1119. <https://doi.org/10.1038/S10038-021-00936-8>
43. Demirbilek H, Arya VB, Ozbek MN et al (2015) Clinical characteristics and molecular genetic analysis of 22 patients with neonatal diabetes from the South-Eastern region of Turkey: predominance of non-KATP channel mutations. *Eur J Endocrinol* 172(6):697–705. <https://doi.org/10.1530/EJE-14-0852>
44. Richards S, Aziz N, Bale S et al (2015) Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 17(5):405–424. <https://doi.org/10.1038/GIM.2015.30>
45. Landrum MJ, Chitipiralla S, Brown GR et al (2020) ClinVar: improvements to accessing data. *Nucleic Acids Res* 48(D1):D835–D844. <https://doi.org/10.1093/NAR/GKZ972>
46. Landry LG, Ali N, Williams DR, Rehm HL, Bonham VL (2018) Lack of diversity in genomic databases is a barrier to translating precision medicine research into practice. *Health Aff* 37(5):780–785. <https://doi.org/10.1377/HLTHAFF.2017.1595/ASSET/IMAGES/LARGE/FIGUREEX3.JPEG>
47. Patel KA, Kettunen J, Laakso M et al (2017) Heterozygous RFX6 protein truncating variants are associated with MODY with reduced penetrance. *Nat Commun* 8(1):1–8. <https://doi.org/10.1038/s41467-017-00895-9>
48. Laver TW, Colclough K, Shepherd M et al (2016) The common p.R114W HNF4A mutation causes a distinct clinical subtype of monogenic diabetes. *Diabetes* 65(10):3212. <https://doi.org/10.2337/DB16-0628>
49. Mirshahi UL, Colclough K, Wright CF et al (2022) Reduced penetrance of MODY-associated HNF1A/HNF4A variants but not GCK variants in clinically unselected cohorts. *Am J Hum Genet* 109(11):2018–2028. <https://doi.org/10.1016/J.AJHG.2022.09.014>
50. Demirbilek H, Galcheva S, Vurali D, Al-Khawaga S, Hussain K (2019) Ion transporters, channelopathies, and glucose disorders. *Int J Mol Sci* 20(10):2590. <https://doi.org/10.3390/IJMS20102590>
51. Cattoni A, Jackson C, Bain M, Houghton J, Wei C (2019) Phenotypic variability in two siblings with monogenic diabetes due to the same ABCC8 gene mutation. *Pediatr Diabetes* 20(4):482–485. <https://doi.org/10.1111/PEDI.12826>
52. De Franco E, Shaw-Smith C, Flanagan SE, Shepherd MH, Hattersley AT, Ellard S (2013) GATA6 mutations cause a broad phenotypic spectrum of diabetes from pancreatic agenesis to adult-onset diabetes without exocrine insufficiency. *Diabetes* 62(3):993–997. <https://doi.org/10.2337/DB12-0885/-DC1>
53. Rath SP, Gupta R, Todres E et al (2024) Mitochondrial genome copy number variation across tissues in mice and humans. *Proc Natl Acad Sci U S A* 121(33):e2402291121. https://doi.org/10.1073/PNAS.2402291121/SUPPL_FILE/PNAS.2402291121.SD01.XLSX
54. Li Yee M, Wong R, Datta M et al (2018) Mitochondrial disease: an uncommon but important cause of diabetes mellitus. *Endocrinol Diabetes Metab Case Rep* 2018(1):18–0091. <https://doi.org/10.1530/EDM-18-0091>
55. Grady JP, Pickett SJ, Ng YS et al (2018) mt DNA heteroplasmy level and copy number indicate disease burden in m.3243A>G mitochondrial disease. *EMBO Mol Med* 10(6). <https://doi.org/10.15252/EMMM.201708262>
56. Cannon SJ, Hall T, Hawkes G et al (2024) Penetrance and expressivity of mitochondrial variants in a large clinically unselected population. *Hum Mol Genet* 33(5):465–474. <https://doi.org/10.1093/HMG/DDAD194>
57. Fahed AC, Wang M, Homburger JR et al (2020) Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. *Nat Commun* 11(1):1–9. <https://doi.org/10.1038/s41467-020-17374-3>
58. Wei A, Border R, Fu B et al (2025) Investigating the sources of variable impact of pathogenic variants in monogenic metabolic conditions. *Nat Commun* 16(1):5223. <https://doi.org/10.1038/s41467-025-60339-7>
59. Leech JM, Beaumont RN, Arni AM et al (2025) Common genetic variants modify disease risk and clinical presentation in monogenic diabetes. *medRxiv* (Preprint). 21 Feb 2025. Available from: <https://doi.org/10.1101/2025.02.19.25322524>
60. Luckett AM, Hawkes G, Green HD et al (2025) Type 1 diabetes genetic risk contributes to phenotypic presentation in monogenic autoimmune diabetes. *Diabetes* 74(2):243–248. <https://doi.org/10.2337/DB24-0485>
61. Turnbull C, Firth HV, Wilkie AOM et al (2024) Population screening requires robust evidence—genomics is no exception. *Lancet* 403(10426):583–586. [https://doi.org/10.1016/S0140-6736\(23\)02295-X](https://doi.org/10.1016/S0140-6736(23)02295-X)
62. Nembaware V, Mulder N (2019) The African Genomic Medicine Training Initiative (AGMT): showcasing a community and framework driven genomic medicine training for nurses in Africa. *Front Genet* 10:490241. <https://doi.org/10.3389/fgene.2019.01209>
63. Yao RA, Akinrinade O, Chaix M, Mital S (2020) Quality of whole genome sequencing from blood versus saliva derived DNA in cardiac patients. *BMC Med Genomics* 13(1):1–10. <https://doi.org/10.1186/S12920-020-0664-7>
64. Miller E, Perez E, Nagy A, Mahanta L, Lebo M, Karlson E (2025) P736: an assessment of a novel capillary blood collection system for research sample collection in adults. *Genet Med Open* 3(Suppl 2):103105. <https://doi.org/10.1016/J.GIMO.2025.103105>
65. Mifsud F, Saint-Martin C, Dubois-Laforgue D, Bouvet D, Timsit J, Bellanné-Chantelot C (2022) Monogenic diabetes in adults: a multi-ancestry study reveals strong disparities in diagnosis rates and clinical presentation. *Diabetes Res Clin Pract* 188. <https://doi.org/10.1016/J.DIABRES.2022.109908>
66. Wilczewski CM, Obasohan J, Paschall JE et al (2023) Genotype first: clinical genomics research through a reverse phenotyping approach. *Am J Hum Genet* 110(1):3. <https://doi.org/10.1016/J.AJHG.2022.12.004>
67. Kreienkamp RJ, Shields BM, Pollin TI et al (2025) MODY calculator and clinical features routinely used to distinguish MODY from type 2 diabetes in adults perform poorly for youth clinically diagnosed with type 2 diabetes. *Diabetes Care* 48(1):e3–e5. <https://doi.org/10.2337/DC24-1565>
68. De Franco E (2021) Neonatal diabetes caused by disrupted pancreatic and β -cell development. *Diabetic Med* 38(12):e14728. <https://doi.org/10.1111/DME.14728>

69. Johnson MB, Patel KA, De Franco E et al (2020) Type 1 diabetes can present before the age of 6 months and is characterised by autoimmunity and rapid loss of beta cells. *Diabetologia* 63(12):2605–2615. <https://doi.org/10.1007/S00125-020-05276-4>
70. Patel KA, Oram RA, Flanagan SE et al (2016) Type 1 diabetes genetic risk score: a novel tool to discriminate monogenic and type 1 diabetes. *Diabetes* 65(7):2094–2099. <https://doi.org/10.2337/DB15-1690>
71. Vujkovic M, Keaton JM, Lynch JA et al (2020) Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 14 million participants in a multi-ancestry meta-analysis. *Nat Genet* 52(7):680–691. <https://doi.org/10.1038/s41588-020-0637-y>
72. De Franco E (2020) From biology to genes and back again: gene discovery for monogenic forms of beta-cell dysfunction in diabetes. *J Mol Biol* 432(5):1535–1550. <https://doi.org/10.1016/J.JMB.2019.08.016>
73. Nakhleh A, Goldenberg-Furmanov M, Goldstein R, Shohat M, Shehadeh N (2023) A beneficial role of GLP-1 receptor agonist therapy in ABCC8-MODY (MODY 12). *J Diabetes Complications* 37(9). <https://doi.org/10.1016/J.JDIACOMP.2023.108566>
74. Broome DT, Mehdi A, Chase C et al (2024) Use of a dual GIP/GLP-1 receptor agonist in HNF1A-MODY and HNF4A-MODY. *Diabetes Care* 47(9):e65–e66. <https://doi.org/10.2337/DC24-0730>
75. Broome DT, Tekin Z, Pantalone KM, Mehta AE (2020) Novel use of GLP-1 receptor agonist therapy in HNF4A-MODY. *Diabetes Care* 43(6):e65. <https://doi.org/10.2337/DC20-0012>
76. Almutair A, Almulhem B (2024) Semaglutide as a potential therapeutic alternative for HNF1B-MODY: a case study. *Front Endocrinol (Lausanne)* 15. <https://doi.org/10.3389/FENDO.2024.1294264>
77. Sue M, Watanabe M, Inoue A et al (2025) Maturity-Onset Diabetes of the Young (MODY) with HNF1B p.Glu105Lys mutation achieving significant insulin reduction on tirzepatide: a case report. *Clin Case Rep* 13(2):e70173. <https://doi.org/10.1002/CCR3.70173>
78. Wang S, Du Y, Zhang B et al (2024) Transplantation of chemically induced pluripotent stem-cell-derived islets under abdominal anterior rectus sheath in a type 1 diabetes patient. *Cell* 187(22):6152–6164.e18. <https://doi.org/10.1016/j.cell.2024.09.004>
79. Bick AG, Metcalf GA, Mayo KR et al (2024) Genomic data in the all of Us research program. *Nature* 627(8003):340–346. <https://doi.org/10.1038/s41586-023-06957-x>
80. Al Thani A, Fthenou E, Paparrodopoulos S et al (2019) Qatar biobank cohort study: study design and first results. *Am J Epidemiol* 188(8):1420–1433. <https://doi.org/10.1093/AJE/KWZ084>
81. Sohail M, Palma-Martínez MJ, Chong AY et al (2023) Mexican Biobank advances population and medical genomics of diverse ancestries. *Nature* 622(7984):775–783. <https://doi.org/10.1038/s41586-023-06560-0>
82. Feng YCA, Chen CY, Chen TT et al (2022) Taiwan Biobank: a rich biomedical research database of the Taiwanese population. *Cell Genomics* 2(11):100197. <https://doi.org/10.1016/J.XGEN.2022.100197>
83. Bonnefond A, Philippe J, Durand E et al (2012) Whole-exome sequencing and high throughput genotyping identified KCNJ11 as the thirteenth MODY gene. *PLoS One* 7(6):e37423. <https://doi.org/10.1371/JOURNAL.PONE.0037423>
84. De Franco E, Watson RA, Weninger WJ et al (2019) A specific CNOT1 mutation results in a novel syndrome of pancreatic agenesis and holoprosencephaly through impaired pancreatic and neurological development. *Am J Hum Genet* 104(5):985–989. <https://doi.org/10.1016/j.ajhg.2019.03.018>
85. Skopkova M, Hennig F, Shin BS et al (2017) EIF2S3 mutations associated with severe X-linked intellectual disability syndrome MEHMO. *Hum Mutat* 38(4):409–425. <https://doi.org/10.1002/HUMU.23170>
86. Perera LA, Hattersley AT, Harding HP et al (2023) Infancy-onset diabetes caused by de-regulated AMPylation of the human endoplasmic reticulum chaperone BiP. *EMBO Mol Med* 15(3). <https://doi.org/10.15252/EMMM.202216491>
87. Johnson MB, De Franco E, Allen HL et al (2017) Recessively inherited LRBA mutations cause autoimmunity presenting as neonatal diabetes. *Diabetes* 66(8):2316–2322. <https://doi.org/10.2337/DB17-0040>
88. Yagasaki H, Sano F, Narusawa H et al (2022) Compound heterozygous variants of the NARS2 gene in siblings with developmental delay, epilepsy, and neonatal diabetes syndrome. *Am J Med Genet A* 188(8):2466–2471. <https://doi.org/10.1002/AJMG.A.62873>
89. Philippi A, Heller S, Costa IG et al (2021) Mutations and variants of ONECUT1 in diabetes. *Nat Med* 27(11):1928–1940. <https://doi.org/10.1038/s41591-021-01502-7>
90. Russ-Silbsby J, Patel KA, Laver TW et al (2023) The role of ONECUT1 variants in monogenic and type 2 diabetes mellitus. *Diabetes* 72(11):1729–1734. <https://doi.org/10.2337/DB23-0498>
91. Johnson MB, Ogishi M, Domingo-Vila C et al (2024) Human inherited PD-L1 deficiency is clinically and immunologically less severe than PD-1 deficiency. *J Exp Med* 221(6):e20231704. <https://doi.org/10.1084/JEM.20231704>
92. Al-Fadhli FM, Afqi M, Sairafi MH et al (2021) Biallelic loss of function variant in the unfolded protein response gene PDIA6 is associated with asphyxiating thoracic dystrophy and neonatal-onset diabetes. *Clin Genet* 99(5):694–703. <https://doi.org/10.1111/CGE.13930>
93. De Franco E, Wakeling MN, Frew RD et al (2022) A biallelic loss-of-function PDIA6 variant in a second patient with polycystic kidney disease, infancy-onset diabetes, and microcephaly. *Clin Genet* 102(5):457–458. <https://doi.org/10.1111/CGE.14187>
94. Weedon MN, Cebola I, Patch AM et al (2013) Recessive mutations in a distal PTF1A enhancer cause isolated pancreatic agenesis. *Nat Genet* 46(1):61–64. <https://doi.org/10.1038/ng.2826>
95. Donis R, Patel KA, Wakeling MN et al (2024) A homozygous TARS2 variant is a novel cause of syndromic neonatal diabetes. *Diabet Med* 42(3):e15471. <https://doi.org/10.1111/DME.15471>
96. De Franco E, Flanagan SE, Yagi T et al (2017) Dominant ER stress-inducing WFS1 mutations underlie a genetic syndrome of neonatal/infancy-onset diabetes, congenital sensorineural deafness, and congenital cataracts. *Diabetes* 66(7):2044–2053. <https://doi.org/10.2337/DB16-1296>
97. Bonnycastle LL, Chines PS, Hara T et al (2013) Autosomal dominant diabetes arising from a wolfram syndrome 1 mutation. *Diabetes* 62(11):3943–3950. <https://doi.org/10.2337/DB13-0571>
98. de Franco E, Lytrivi M, Ibrahim H et al (2020) YIPF5 mutations cause neonatal diabetes and microcephaly through endoplasmic reticulum stress. *J Clin Invest* 130(12):6338–6353. <https://doi.org/10.1172/JCI141455>
99. De Franco E, Owens NDL, Montaser H et al (2023) Primate-specific ZNF808 is essential for pancreatic development in humans. *Nat Genet* 55(12):2075–2081. <https://doi.org/10.1038/s41588-023-01565-x>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.