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A brief history of diabetes genetics: insights for pancreatic beta-cell development and function

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Abstract

Since the discovery of insulin 100 years ago, our knowledge and understanding of diabetes have grown exponentially. Specifically, with regards to the genetics underlying diabetes risk, our discoveries have paralleled developments in our understanding of the human genome and our ability to study genomics at scale; these advancements in genetics have both accompanied and led to those in diabetes treatment. This review will explore the timeline and history of gene discovery and how this has coincided with progress in the fields of genomics. Examples of genetic causes of monogenic diabetes are presented and the continuing expansion of allelic series in these genes and the challenges these now cause for diagnostic interpretation along with opportunities for patient stratification are discussed.

Keywords

diabetes; pancreas; genomics; b-cell development

Introduction

It was in the 1930s, after the discovery and first use of insulin, that Harold Percival Himsworth first made the distinction between type 1 and type 2 diabetes (Bryder & Harper 2013). However, it was not until the 1970s, following decades of observation, that both Stefan Fajans and Robert Tattersall extended this classification to recognize the existence of diabetes subtypes inherited in an autosomal dominant manner (Tattersall 1974, Tattersall & Fajans 1975) (Fig. 1). This dominantly inherited form of diabetes was originally reported as ‘mild familial diabetes with dominant inheritance’, and subsequently ‘maturity-onset diabetes of the young (MODY)’, to distinguish it from juvenile onset type 1 diabetes and indicate its similarities in clinical presentation to maturity-onset diabetes (now known as type 2) (Tattersall & Fajans 1975). In recent years, we have seen a gradual move toward using the broader term ‘monogenic diabetes’ to encompass other genetic types of

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Declaration of interest

A L G declares that her spouse is an employee of Genentech and hold stock options in Roche. J K declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

diabetes, such as neonatal or syndromic diabetes. Fueled by steady improvements in our understanding of the human genome, and coupled with technological advancement, we have seen the careful dissection of the genetic causes of these monogenic forms of diabetes. This has provided numerous insights into the machinery responsible for making and maintaining functional insulin-secreting pancreatic β-cells (Fig. 2). In this review, we focused on how these discoveries have shaped our understanding of insulin secretion across the phenotypic spectrum of diabetes and provided a model for precision medicine in diabetes.

Recognition of autosomal dominantly inherited diabetes

Maturity-onset diabetes of the young (MODY) is defined as autosomal, dominantly inherited diabetes which is characterized by non-insulin dependence, with an early age of onset (at least one affected family member with an onset before 25 years of age) and pancreatic β-cell dysfunction. In the 1950s, Fajans and Conn were attempting to develop a method for earlier detection of diabetes; whilst on this quest, they discovered ‘unsuspected diabetes’ in about 20% of subjects who had a close relative with diabetes. They noted that not only was the unsuspected ‘chemical diabetes’ distinct from juvenile-onset diabetes (now known as type 1 diabetes) but also that the inheritance was different (Fajans & Conn 1959).

Given what we now know, it is particularly fascinating that the early descriptions of MODY in the literature indicate that subjects were often treated with sulfonylureas to maintain their glucose levels (Fajans & Brown 1993). Even before the various subtypes of MODY were genetically dissected, it was apparent that there were families with distinct clinical phenotypes. Some cases were characterized by years of mild fasting hyperglycemia, whereas others progressed to persistent fasting hyperglycemia, often preceded by varying degrees of glucose intolerance (Fajans 1987, 1990). Of course, this now fits perfectly with our understanding of the differences in the underlying pathophysiology of glucokinase (GCK) vs transcription factor (HNF1A/HNF4A/HNF1B) MODY.

At the time of writing this article, the number of genetic subtypes causing MODY differs depending on the source of information. Online Mendelian inheritance in man (OMIM) lists 14 genetic subtypes; however, not all of these meet the American College of Medical Genetics criteria and a shorter list of 10 subtypes is more broadly acknowledged (Zhang *et al.* 2021). While there are multiple genetic causes, most cases in the clinical setting are due to mutations in three of these genes (*HNF1A*, *HNF4A*, *GCK*) which can collectively account for up to 95% of all MODY cases (Shields *et al.* 2010).

Subtypes of monogenic diabetes

Although we still use the name maturity-onset diabetes of the young (MODY), the field has moved in recent years to rebrand these conditions to the broader monogenic diabetes and to use the names of the genes responsible, for example, ‘glucokinase diabetes’ or ‘transcription factor diabetes’ (Ellard *et al.* 2008, McDonald & Ellard 2013). This shift in naming convention reflects our broadening understanding of the wide phenotypic spectrum which can result from a given gene mutation, leading to blurred boundaries between historic non-genetic nomenclature which relied on the age of diagnosis (e.g. MODY vs neonatal

diabetes). As we unravel the genetic causes for monogenic diabetes (Fig. 1), the rational for this shift in thinking will become apparent along with the emerging themes of monogenic forms of pancreatic β-cell dysfunction – largely arising from either an intrinsic defect in β-cell function (e.g. *GCK*, *KCNJ11*), pancreas development (e.g. *PDX1*, *HNF1A*) or β-cell proliferation and mass (e.g. *INS*). This review will focus on the most common genes connected with monogenic diabetes while also highlighting a selection of less commonly seen genes to illustrate additional pathologic mechanisms.

Hepatocyte nuclear factor 4 alpha (HNF4A-MODY, MODY1)

In 1992, a locus on chromosome 20p containing *HNF4A* was identified by linkage analysis in a large pedigree, known as the RW pedigree (Bowden *et al.* 1992). However, it was not until 1996 that back-to-back publications reported the positional cloning of the genes responsible for both MODY1 (*HNF4A*) and MODY3 (*HNF1A*). Prior to this discovery, both transcription factors had recognized roles in the liver but these studies unearthed a previously unknown role in the regulation of pancreatic β-cell development and function (Yamagata *et al.* 1996*a*,b).

HNF4A belongs to a group of hepatocyte nuclear transcription factors, some of which are important in regulating insulin secretion (including *HNF1A* and *HNF1B* discussed below) (Yamagata *et al.* 1996*a*). As the name suggests, these transcription factors were originally described in the liver but they also function within the pancreatic β-cell to directly regulate the gene expression important for both pancreatic islet-cell development as well as glucose metabolism, including the insulin gene itself (Yamagata *et al.* 1996*a*).

Patients with heterozygous loss-of-function mutations in *HNF4A* have a progressive decline in β-cell function, with most carriers developing diabetes in adolescence or early adulthood. Because *HNF4A* also has a role in cholesterol and fatty acid metabolism, individuals with HNF4A-MODY may have unique changes in cholesterol and triglyceride levels (Pearson *et al.* 2005). Importantly, a diagnosis of HNF4A-MODY has implications for treatment as patients can often be successfully treated with oral sulfonylureas rather than insulin (Pearson *et al.* 2003, Hattersley *et al.* 2018).

Glucokinase (GCK-MODY, MODY2)

Shortly after the reports of linkage on chromosome 20p, linkage to chromosome 7p, where the gene for the key glycolytic enzyme *glucokinase* (*GCK*) resides, was described in both French and UK pedigrees in 1992 (Froguel *et al.* 1992, Hattersley *et al.* 1992) (Fig. 1). The demonstration of linkage was quickly followed by characterization of the *GCK* human gene and the detection of diabetes-causing mutations (Stoffel *et al.* 1992). GCK is a member of the hexokinase family of enzymes and is largely expressed in hepatocytes and pancreatic β-cells where it is responsible for catalyzing the transfer of phosphate from ATP to glucose, generating glucose-6-phosphate (Magnuson *et al.* 1989). This catalytic transfer is the first, rate-limiting step in glucose metabolism, and as such GCK is often considered the glucose sensor of the β-cell (Bedoya *et al.* 1986). A single inactivating mutation in GCK impairs that glucose sensor, as well as the β-cell ability to respond to increasing glucose concentrations, ultimately leading to MODY. Thus, hyperglycemia in

individuals with GCK-MODY is essentially caused by increasing the glucose set point that is necessary to induce insulin secretion (Velho *et al.* 1992). To date, *in vitro* studies have indicated mutation-specific variation in the severity of the functional defect; however, in the clinical setting, heterozygous inactivating mutations result in strikingly similar phenotypes, irrespective of the specific mutation (Stride *et al.* 2002). This observation is explained by compensation by the WT allele, which is post-translationally upregulated in response to the elevated circulating glucose levels (Gloyn *et al.* 2004*c*). In contrast, activating *GCK* mutations lead to over-secretion of insulin and hypoglycemia, and given the lack of compensation by the WT allele, the phenotype is more varied (Glaser *et al.* 1998, Gloyn 2003, Cuesta-Muñoz *et al.* 2004).

Patients with GCK-MODY have stable mild fasting hyperglycemia throughout their lifespan; however, due to the mild degree of hyperglycemia, and the low incidence of micro- or macrovascular complications, individuals with GCK-MODY typically do not require pharmacological treatment (Steele *et al.* 2014). The exception to this is during pregnancy, where glucose-lowering medications may be considered in the case of increased fetal growth observed on ultrasound (Chakera *et al.* 2015).

Hepatocyte nuclear factor 1 alpha (HNF1A-MODY, MODY3)

Positional cloning of the linkage signal on chromosome 12p, which had been identified in multiple families with monogenic diabetes, identified another liver transcription factor gene, *hepatocyte nuclear factor 1 alpha* (*HNF1A*), as a major cause of monogenic diabetes (Yamagata *et al.* 1996*b*). Like HNF4A, HNF1A functions as an important transcriptional regulator of insulin and other genes involved in islet-cell development and glucose metabolism. HNF1A is also a key transcriptional regulator of the sodium-glucose transporter in the kidney (*SGLT2*), therefore, patients with HNF1A-MODY have a low renal threshold for glucose (Pontoglio *et al.* 2000).

Functional studies have demonstrated that protein-truncating mutations result in haploinsufficiency (Harries *et al.* 2004), whilst missense variants lead to loss of function through a variety of mechanisms (Althari *et al.* 2020). More recently, our appreciation for the role of *HNF1A* in MODY has been expanded, as homozygous hypomorphic variants have also been identified as a cause of MODY (Misra *et al.* 2020). These observations fit with a growing body of evidence demonstrating that genetic variation across the functional severity spectrum corresponds to phenotype (Althari *et al.* 2020).

HNF1A-MODY is characterized by normal glucose tolerance early in childhood, with progressive hyperglycemia developing in adolescence or adulthood. Because of the progressive nature of HNF1A-MODY, these individuals are at risk for microvascular complications and do require glucose-lowering therapy (Lee *et al.* 1999, Hattersley *et al.* 2018). Importantly, as with a diagnosis of HNF4A-MODY, patients with HNF1A-MODY can usually be treated with oral sulfonylureas rather than insulin (Pearson *et al.* 2003, Hattersley *et al.* 2018).

Pancreatic duodenal homeobox factor 1 (PDX1-MODY, MODY4)

Pancreatic duodenal homeobox factor 1 (*PDX1*), previously referred to as *insulin promoter factor 1* (*IPF1*), is yet another transcription factor involved in monogenic diabetes. Located on chromosome 13, *PDX1* plays a central role in determining cell fate in embryonic pancreatic development, and also in the differentiation, maturation, and function of pancreatic β-cells (Stoffel *et al.* 1995, Inoue *et al.* 1996). In 1997, Stoffers and colleagues shed light on this critical transcription factor first by demonstrating that homozygous loss resulted in pancreatic agenesis and neonatal diabetes (NDM) (Stoffers *et al.* 1997*b*) and secondly, that heterozygous carriers of these mutations had defective insulin secretion, consistent with previously described MODY phenotypes (Stoffers *et al.* 1997*a*).

PDX1-MODY is characterized by often having a slightly later age of onset than other forms of MODY (Stoffers *et al.* 1997*a*). Some patients have only mildly impaired glucose tolerance while others have fulminant diabetes requiring daily insulin injections. Although early reports suggested that variants in *PDX1* were associated with increased risk of diabetes due to impaired PDX1-mediated *INS* expression (Ahlgren *et al.* 1998), larger genome-wide studies have not substantiated these early findings (Edghill *et al.* 2011). Since there is variation in phenotype within PDX1-MODY, the treatment must be tailored to the individual patient; options range from dietary changes alone to sulfonylureas or insulin (Hattersley *et al.* 2018, Delvecchio *et al.* 2020).

Hepatocyte nuclear factor 1 beta (HNF1B-MODY, MODY5)

HNF1B is closely related to HNF1A and in fact actually dimerizes with it (Mendel *et al.* 1991). Unsurprisingly, it plays a similarly important function in pancreatic embryonic development but unlike HNF1A, it also has a vital role in nephron embryonic development (Horikawa *et al.* 1997). This leads to a wide spectrum of phenotypes which may include diabetes or kidney disease alone or a combination of the two. Kidney disease, typically renal cysts, is somewhat unique to HNF1B-MODY, and so should be expected in young patients presenting with both diabetes and kidney disease. HNF1B-MODY can also be complicated by urogenital tract malformations, hyperuricemia, and gout (Firdous *et al.* 2018). Interestingly, patients with HNF1B-MODY display both defects in insulin secretion and insulin sensitivity (Pearson *et al.* 2004).

Neurogenic differentiation-1 (NEUROD1-MODY, MODY6)

Neurogenic differentiation-1 (NEUROD1, also known as BETA2) is a helix-loop-helix (HLH) transcription factor that functions as a regulatory switch for pancreatic and neuronal development. One important role of NEUROD1 is in directly regulating insulin gene (*INS*) expression by binding to a critical E-box motif on the *INS* promoter (Malecki *et al.* 1999). NEUROD1 also has important roles in activating other genes encoding components of the insulin secretion pathway within the β-cell, including *ABCC8*, *GCK*, and *PAX6* (Kim *et al.* 2002, Marsich *et al.* 2003, Moates *et al.* 2003).

In 2001, Kristinsson and colleagues confirmed that heterozygous *NEUROD1* mutations are a rare cause of MODY (Kristinsson *et al.* 2001), while homozygous loss-of-function mutations lead to NDM and neurological impairment (Rubio-Cabezas *et al.* 2010).

NEUROD1-MODY can be diagnosed throughout the lifespan, as early as childhood and into the seventh decade most likely reflecting the incomplete penetrance of some variants and requirement for additional environmental or genetic risk factors. As with many of the other MODY subtypes, clinical presentation and course can be quite variable even within a single family (Delvecchio *et al.* 2020); approximately 20% of patients require insulin therapy, whilst others may respond well to dietary modifications alone or in combination with oral glucose-lowering agents.

Genetic causes of monogenic diabetes outside the β-cell

Mutations in *CEL*, encoding *carboxy-ester lipase*, cause young-onset diabetes coupled with exocrine pancreas dysfunction (CEL-MODY), which is characterized by low fecal elastase levels (Raeder *et al.* 2006). It is notable that the disease-causing mutations are caused by alterations in the variable number of tandem repeats (VNTR) region rather than in the protein-coding sequence (Raeder *et al.* 2006). This variety of monogenic diabetes is unusual as it does not appear to directly involve defects in the β-cell rather it involves the acinar cells of the pancreas and may involve defects in mitogen-activating protein kinase (MAPK) signaling (Ræder *et al.* 2014). This atypical monogenetic diabetes may prove to be a paradigm for other types of diabetes as multiple recent studies have suggested a role for the exocrine pancreas in mediating genetic association signals for both type 1 and type 2 diabetes (Ng *et al.* 2019, Chiou *et al.* 2021).

Monogenic diabetes diagnosed in the first 6 months of life

Many of the early strides in identifying genetic diabetes, particularly in describing key MODY genes, relied on chromosomal linkage analysis. In 2001, the Human Genome Project published the first complete sequence for the human genome, and with that, sparked a new era in genetic discoveries (Lander *et al.* 2001). As our genetic capabilities continued to progress, so did our understanding of genetic regulation of insulin secretion and related disorders, specifically in regards to neonatal diabetes mellitus (NDM). NDM was first described in 1852 by J F Kitselle and is often complicated by poor *in utero* growth and neonatal failure to thrive (Shield 2000). NDM is a heterogeneous disease defined as diabetes with onset during the first 6 months of life with a monogenic cause identifiable in up to 85% of cases (Letourneau & Greeley 2018). NDM exists on a spectrum, with mild forms being transient (TNDM) and resolving spontaneously by 18 months of life, permanent forms (PNDM) which do not resolve, and syndromic forms that may be accompanied by a number of other complications. It is worth noting that many of the genes described above in causing MODY can also be related to NDM, with a strong genotype-phenotype correlation. Of the >80% of NDM cases with a known genetic cause, more than 18 causative genes have been described in the literature but many of these are very rare and only seen in a small number of families (Delépine *et al.* 2000, Gloyn *et al.* 2004*c*, Babenko *et al.* 2006, Støy *et al.* 2007, Flanagan *et al.* 2014, De Franco *et al.* 2015, 2017, 2019, 2020*a*, Johnson *et al.* 2017, De Franco 2020). In this review, we highlight the most common varieties and those which have informed our current thinking on β-cell biology and the continuums of risk in diabetes.

ATP-sensitive potassium channel (K_{ATP}) defects (K_{ATP}-NDM)

Mutations in pancreatic K_{ATP} channel genes are the most common known causes of NDM. These channels, composed of four SUR1 subunits (encoded by *ABCC8*) and four Kir6.2 subunits (encoded by *KCNJ11*), are critical for regulating membrane excitability and insulin secretion by the β-cell (Shimomura & Maejima 2017). At low plasma glucose concentration, K_{ATP} channels are normally open, the cell membrane is hyperpolarized, and voltage-dependent calcium channels (VDCCs) are closed, thus inhibiting insulin secretion. Glucose metabolism increases the intracellular (ATP)/(ADP) ratio, closing K_{ATP} channels, leading to membrane depolarization, calcium influx through VDCCs, and triggering insulin release.

The role of these two K_{ATP} channel subunits in NDM was first appreciated in 2004 when heterozygous activating mutations in the *KCNJ11* gene were reported as a major cause of permanent neonatal diabetes (Gloyn *et al*. 2004*b*). A number of additional causative mutations were subsequently identified in *KCNJ11* (Gloyn *et al*. 2004*a*, Sagen *et al*. 2004, Yorifuji *et al*. 2005). The physiologic role of these specific mutations was further confirmed by co-expressing mutated Kir6.2 and demonstrating a significant decrease in response to ATP by the K_{ATP} channel (Gloyn *et al*. 2004*a*,b, Tammaro *et al*. 2005). In 2005, it was further demonstrated that distinct mutations in *KCNJ11* can also lead to transient, or remitting, diabetes, suggesting that certain abnormalities within this channel can lead to a fluctuating phenotype (Gloyn *et al*. 2005). Shortly after, it was also demonstrated that some patients with particular *KCNJ11* mutations have diabetes complicated by additional neurological features, a syndrome which has been termed developmental delay, epilepsy and neonatal diabetes (DEND) (Gloyn *et al*. 2006). Around this same time, Babenko *et al*. identified seven novel activating mutations in *ABCC8*, which also lead to NDM (Babenko *et al*. 2006). In direct contrast to the activating mutations leading to NDM, inactivating mutations in these same genes result in reduced K_{ATP} channel activity, β-cell hyperexcitability, and excessive insulin secretion (Kane *et al*. 1996, Nichols *et al*. 1996, Thomas *et al*. 1996, Dunne *et al*. 1997, Huopio *et al*. 2000).

The discovery linking the K_{ATP} channel mutations to neonatal diabetes was critical for patient care – prior to this knowledge, individuals with neonatal diabetes required lifelong treatment with insulin for survival. However, since this pathology is directly due to a failure of the K_{ATP} channels to close in response to ATP generated by glucose metabolism, the majority of patients with this variety of diabetes are responsive to oral sulfonylureas, which act on SUR1 to close the channel in an ATP-independent manner restoring insulin secretion (Gloyn *et al*. 2004*a*, Sagen *et al*. 2004). This discovery has enabled many affected patients to discontinue insulin use with great success, and often achieving better glycemic control with sulfonylureas than with their prior insulin therapy. More recent studies have shown that the majority of these patients still had excellent glycemic control at 10 year follow-up, confirming sulfonylureas as a safe and effective approach over the long-term (Bowman *et al*. 2018). This responsiveness to oral medication, along with a strong genotype-phenotype correlation (Flanagan *et al*. 2006) which can guide medical decision-making and family counseling, makes an early molecular diagnosis for NDM imperative.

INS-PNDM

It was really only a matter of time before mutations in the *insulin* gene (*INS*) were discovered as a cause of diabetes. The search had been on for many years but the first descriptions were in patients with hyperproinsulinemia and not diabetes (Gruppuso *et al.* 1984). The reason for this, as often is the case, is the site and consequence of the mutation. In 2007 a team led by Graeme Bell, who had cloned the gene back in the early 1980s (Bell *et al.* 1980), combined linkage analysis with a candidate gene approach to identify first diabetes-causing *INS* mutation, and subsequently identified nine additional mutations in a total of 16 probands with NDM (Støy *et al.* 2007, Hodish *et al.* 2010). In this cohort, subjects had a median age of diabetes presentation at 9 weeks and were often complicated by ketoacidosis. Due to the mutation being within the insulin gene itself, predicted to prevent normal folding and secretion, these individuals are not eligible for treatment with sulfonylureas, which acts on the secretory pathway rather than the insulin protein itself. It has been observed that mice with similarly misfolded insulin proteins may actually have increased β-cell death due to extreme endoplasmic reticulum (ER) stress (Støy *et al.* 2007). Large-scale screening of patients with PNDM identified *INS* mutations as one of the most common causes of this disease, secondly only to K_{ATP} channel mutations (Edghill *et al.* 2008). A recent study by Balboa *et al.* demonstrated β-like cells generated from *in vitro* differentiated induced pluripotent stem cells (iPSCs) from individuals carrying *INS* mutations have diminished β-cell proliferation, leading to a decreased β-cell mass, likely playing a role in diabetes pathogenesis (Balboa *et al.* 2018). Recessively inherited *INS* mutations have also been shown to cause PNDM due to a contrasting pathogenic mechanism of decreased insulin biosynthesis through a variety of regulatory mechanisms (Garin *et al.* 2010).

GCK-PNDM

Glucokinase, discussed in detail above as a MODY-causing gene when it presents as a heterozygous mutation, can also cause permanent NDM when presenting with homozygous or compound heterozygous mutations (Njølstad *et al.* 2001, 2003). These individuals have similar traits to those with K_{ATP}-related NDM, including intrauterine growth restriction, low birth weights, and insulin requirements shortly after birth (Njølstad *et al.* 2003). Not all homozygous or compound heterozygous inactivating *GCK* mutations cause NDM though. A relatively recent study demonstrated the importance of protein stability as a major contributor to the severity of inactivating *GCK* mutations. This became apparent through the study of a homozygous *GCK* mutation which presented as diabetes in young-adolescence rather than at birth (Raimondo *et al.* 2014).

PDX1-PNDM

PDX1 is another MODY-causing gene that is also a rare, but important, cause of permanent neonatal diabetes. *PDX1* is critical for pancreatic development (Jonsson *et al.* 1994), and some individuals with *PDX1* mutations have little or no development of functional pancreatic islets (Stoffers *et al.* 1997*b*). Although most cases are confirmed to have pancreatic hypoplasia or agenesis, there are some reports in patients with a normally formed pancreas that may still be affected by permanent NDM due to a *PDX1* mutation (De Franco

et al. 2013). By regulating the expression of a number of important islet transcripts (insulin, glucokinase, somatostatin), *PDX1* serves as a master regulator of gene expression within the islet (Hui & Perfetti 2002). Additional genes important for pancreatic development, including *NKX2–2*, *GATA4*, *GATA6*, *GLIS3*, *RFX6*, and *PTF1A*, have also been identified as rare causes of NDM (Wang *et al*. 2004, Senée *et al*. 2006, Doyle & Sussel 2007, Chen *et al*. 2008, Fukuda *et al*. 2008, Smith *et al*. 2010, Allen *et al*. 2011, Carrasco *et al*. 2012, Stanescu *et al*. 2015, Xuan & Sussel 2016).

GLIS3-PNDM

Gli-similar 3 (GLIS3) is a Krüppel-like zinc finger transcription factor that is important during cell specification and patterning during pancreatic development. GLIS3 interacts with other important β-cell transcription factors including PDX1 and NEUROD1 and binds directly to the insulin promoter to positively regulate gene expression. In mice, deletion of both copies of *Glis3* leads to neonatal diabetes (Kang *et al*. 2009, Yang *et al*. 2009). GLIS3 is also important in humans, as homozygous mutations in *GLIS3* are responsible for a syndrome characterized by neonatal diabetes, congenital hypothyroidism, polycystic kidneys, and facial anomalies (Senée *et al*. 2006). At least one patient with compound heterozygous *GLIS3* mutations has been described; this patient has isolated NDM but none of the other features (Dimitri *et al*. 2011). Genome-wide association studies (GWAS) have also demonstrated variants at the *GLIS3* locus which are associated with both type 1 and type 2 diabetes (Aylward *et al*. 2018).

Syndromic monogenic diabetes

Neonatal diabetes has also been identified as a component of a number of multi-system syndromes, many of which have identified genetic causes. The majority of these syndromes are rare, and because of variable presentation, are at risk for late or missed diagnosis. Despite the heterogeneous nature of these conditions, the genetic dissection of these conditions and molecular understanding of the underlying pathophysiology make it apparent that there are some shared clinical features and biological mechanisms. For example, a large number of patients with NDM also have neurological symptoms (e.g. epilepsy, developmental delay) (De Franco *et al*. 2015, 2020*b*). Neurons and β-cells have similar electrophysiology and signaling mechanisms, making this frequent association between defects in glucose homeostasis and neurology unsurprising (De Franco *et al*. 2020*a*,b). A majority of the genes implicated in these syndromes are transcription factors with key roles in the development of both cell types (ex. *PTF1A*, *NEUROD1*, *MNX1*, and *NKX2–2*).

Other causative gene mutations are related to ER stress, either due to mutations in important checkpoints in controlling the ER stress response, or due to mutations that directly result in protein-misfolding, and subsequently, lead to ER stress (ex. *EIF2AK3*, *SLC19A2*, *IER3IP1*, *WFS1*, *TRMT10A*, *PPP1R15B*, *EIF2S3*) (De Franco *et al*. 2020*b*). Clinical presentation with diabetes can be diagnosed beyond the neonatal period well into adolescence for some of these etiologies. One example of NDM caused by ER stress is Wolcott–Rallinson syndrome (WRS); the most common cause of syndromic NDM in areas with high consanguinity (Rubio-Cabezas *et al*. 2009). It is an autosomal recessive condition and is

often accompanied by skeletal dysplasia, poor growth, and liver dysfunction, in addition to NDM. Homozygous or compound heterozygous mutations in eukaryotic translation initiation factor 2-α kinase 3 (*EIF2AK3*), a critical component of the ER stress response, are responsible for WRS (Delépine *et al.* 2000).

Blurring the boundaries of NDM genes in MODY

As with *PDX1*, where mutations were first described in neonatal diabetes (NDM), additional genes which are major causes of NDM have been reported as the cause of diabetes outside of infancy, consistent with MODY. These include those encoding the ATP-sensitive potassium channel subunits (*ABCC8* and *KCNJ11*). In 2012, Bonnefond and colleagues used whole-exome sequencing (WES) to study some of the 30% of French-MODY patients without a genetic diagnosis. This analysis identified a *KCNJ11* mutation, specifically, p.E227K, as the cause of MODY in a single-family (Bonnefond *et al.* 2012). In that same year, Bowman and colleagues found four novel *ABCC8* mutations within a cohort of sulfonylurea responsive MODY patients (Bowman *et al.* 2012). The term MIDY (mutant *INS*-gene induced diabetes of youth) has also been used to describe patients with *INS* mutations presenting outside the neonatal period (Liu *et al.* 2010, 2012).

Expanding the spectrum of the role of monogenic diabetes genes in type 2 diabetes (T2D) risk

The early type 2 diabetes (T2D) genetics literature is plagued by both poorly designed and executed genetic association studies (Siontis *et al.* 2010). With a few exceptions, most earlier findings failed to replicate when expanded to large, well-powered studies. Of the early studies which have stood the test of time, it is notable that two of three such studies include genes (*PPARG*, *KCNJ11*, and *TCF7L2*) involved in monogenic forms of diabetes (Altshuler *et al.* 2000, Gloyn *et al.* 2003, Grant *et al.* 2006). In the late 2000s, people began to explore the utility of genome-wide association studies (GWAS) for understanding complex diseases and traits. GWAS compare multiple individual genomes to identify associations between specific genetic changes and a given disease or trait. International efforts for both type 1 and type 2 diabetes have been terrifically successful in uncovering hundreds of association signals. As has been the case for most complex traits, the vast majority of GWAS signals for both T1D and T2D exert their impact through non-coding variants with a presumed regulatory impact (Mahajan *et al.* 2018). A consistent finding has also been the identification of signals in or close to genes with known roles in monogenic diabetes, such as *HNF1A* and *KCNJ11*. A number of these also have coding variants across the frequency spectrum, which are associated with altered risk for T2D: sometimes they are specific to a population (e.g. p.E508K in *HNF1A*) (SIGMA Type 2 Diabetes Consortium *et al.* 2014) whilst others are common in the population (e.g. p.E23K in *KCNJ11*) (Gloyn *et al.* 2003). The field has also uncovered common regulatory variants near monogenic diabetes genes which likely have an impact in a tissue and developmental time-specific manner (e.g. *HNF4A*) (Kathiresan *et al.* 2009). These findings bring into focus a continuum between normal function and complete loss of function in these genes – an allelic spectrum – where the relationship between the specific variant and subsequent disease presentation is not necessarily straightforward

(Althari *et al.* 2020). The genetic characterization of large Biobanks (e.g. UKBioBank, BioMe) will facilitate the studies required to fully understand both the relationship between genetic variation in monogenic diabetes genes and clinical phenotype as well as the impact of common genetic variation (e.g. T2D genetic risk scores) on altering the presentation of variants in these genes. Genetics has certainly delivered precision medicine for monogenic forms of diabetes; the challenge for the next decade is extending this to all types of diabetes.

Outlook

Moving forward, our expanding knowledge surrounding the genetic changes underlying both monogenic and polygenic forms of diabetes will continue to advance our potential for personalized medicine through both precision diagnostics and therapeutics. These genetic breakthroughs, in combination with clinical biomarkers, will allow us to refine our classification and diagnosis of diabetes subtypes and provide evidence-based care to determine optimal management and decrease morbidity and mortality associated with these conditions. The importance of molecular diagnosis of MODY and NDM is quite apparent on its own; however, the groundwork laid in understanding them will continue to provide insight and guidance for more complex forms of diabetes as well.

Closing remarks

The careful dissection of the genetic etiology of monogenic forms of diabetes has created a framework of potential mechanisms to understand how common genetic variants could exert their effect and lead to increased risk for complex forms of diabetes such as type 1 and type 2 diabetes. There are now documented examples of single-gene defects causing alterations in glucose sensing, insulin secretion, pancreas development and β-cell mass, and for each of these examples of how these same mechanisms influence type 1 and type 2 diabetes. As we mark the centenary of the discovery of insulin, it is remarkable to see the speed at which its discovery was translated into changes in clinical practice. With the exception of the remarkable efforts with the COVID19 vaccinations, this is not often witnessed. Progress in understanding the genetic basis of pancreatic islet-cell dysfunction in diabetes has also had an incredible century but we have some way to go before we have the same impact as Banting, Best, Collip, and Mcleod.

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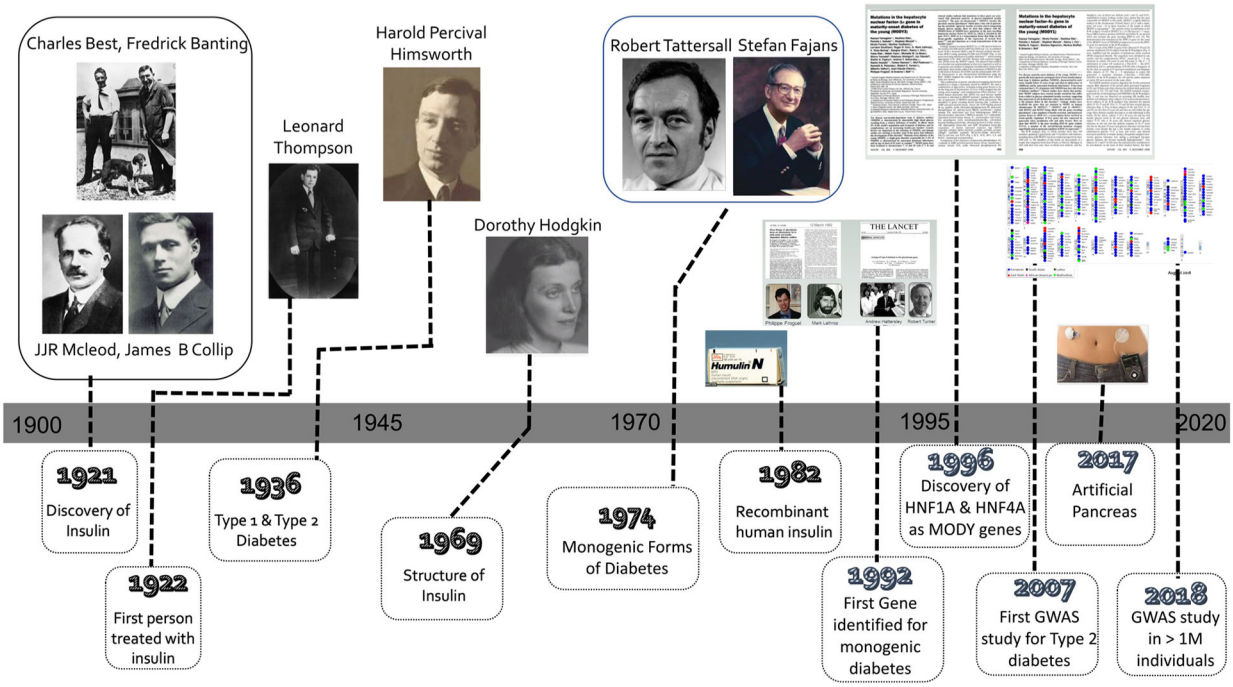

Figure 1.

Timeline indicating key genetic discoveries in the context of our understanding of the hormone insulin and its use therapeutically.

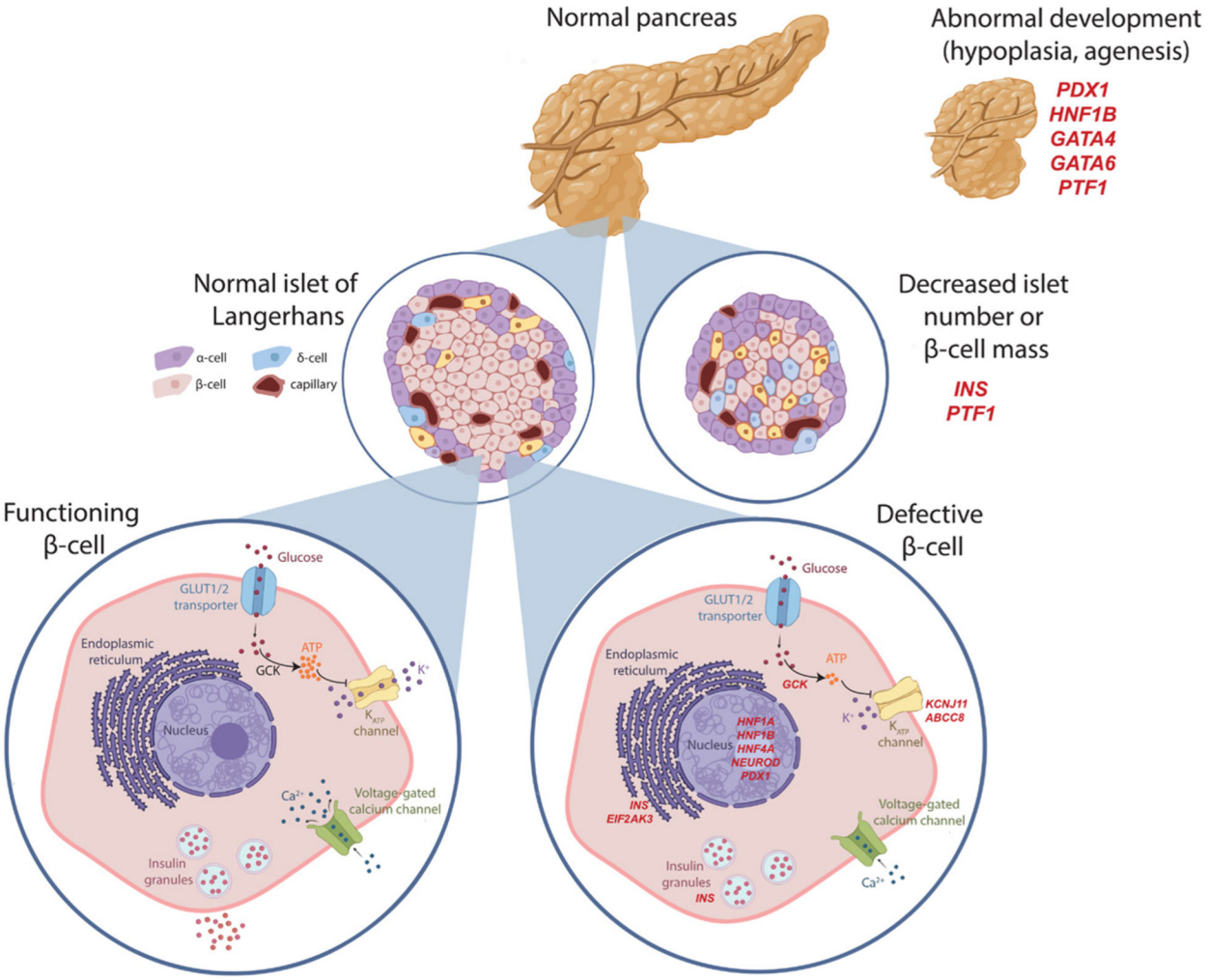

Figure 2.

Schematic representation of the pancreatic β-cell illustrating the three main mechanisms by which monogenic diabetes arises. Gene defects of selected representative genes at each stage indicated in red italics. Defect in pancreas/β-cell development leading to pancreatic agenesis or hypoplasia (*PDX1*, *HNF1B*, *GATA4*, *GATA6*, *PTF1A*), decreased β-cell mass or proliferations (*INS*, *PTF1A*) or β-cell dysfunction, including glucose sensing (*GCK*), ATP responsiveness (*ABCC8*, *KCNJ11*), ER stress (*INS*, *EIF2AK3*), and transcriptional regulation (*HNF1A*, *HNF1B*, *HNF4A*, *NEUROD1*, *PDX1*). Created with BioRender.com.