Many faces of monogenic diabetes

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ABSTRACT
Monogenic diabetes represents a heterogeneous group of disorders resulting from defects in single genes. Defects are categorized primarily into two groups: disruption of β-cell function or a reduction in the number of β-cells. A complex network of transcription factors control pancreas formation, and a dysfunction of regulators high in the hierarchy leads to pancreatic agenesis. Dysfunction among factors further downstream might cause organ hypoplasia, absence of islets of Langerhans or a reduction in the number of β-cells. Many transcription factors have pleiotropic effects, explaining the association of diabetes with other congenital malformations, including cerebellar agenesis and pituitary agenesis. Monogenic diabetes variants are classified conventionally according to age of onset, with neonatal diabetes occurring before the age of 6 months and maturity onset diabetes of the young (MODY) manifesting before the age of 25 years. Recently, certain familial genetic defects were shown to manifest as neonatal diabetes, MODY or even adult onset diabetes. Patients with neonatal diabetes require a thorough genetic work-up in any case, and because extensive phenotypic overlap exists between monogenic, type 2, and type 1 diabetes, genetic analysis will also help improve diagnosis in these cases. Next generation sequencing will facilitate rapid screening, leading to the discovery of digenic and oligogenic diabetes variants, and helping to improve our understanding of the genetics underlying other types of diabetes. An accurate diagnosis remains important, because it might lead to a change in the treatment of affected subjects and influence long-term complications.

INTRODUCTION
The prevalence of monogenic diabetes is estimated at 2–5% of all patients with diabetes. The first description of a hereditary form dates back to 1928, when Cammidge identified families with autosomal dominant diabetes. In 1975, Maturity Onset Diabetes of the Young (MODY) was defined as diabetes occurring before the age of 25 years with autosomal dominant inheritance as a result of an intrinsic β-cell defect. The first gene causally implicated was coded for the enzyme glucokinase (GCK). A few years later, two other monogenic forms of diabetes, MODY1 and MODY3, were attributed to mutations in transcription factor genes; the hepatocyte nuclear factor 4 and 1 alpha (HNF4A, HNF1A), respectively.

Historically, the age at diabetes onset has been a criterion for classification. For example, neonatal diabetes is diagnosed within 6 months of birth, whereas MODY forms of diabetes occur before the age of 25 years. However, recent studies report that specific gene mutations occurring in the same family can present clinically as a neonatal form as well as ‘type 2-like’ or ‘type 1-like’ forms during adulthood.

Currently, many monogenic forms are missed or misclassified as type 2 or type 1 diabetes. Improved access to genetic testing will help determine the exact origin of diabetes. In the present review, I delineate the different gene defects using a functional approach, discussing developmental and cellular defects, glucose uptake at the cell surface, and then following the intracellular destiny of glucose molecules eliciting insulin secretion (Figure 1).

PATH TO MONOGENIC DIABETES
Nuleopathies Causing Developmental Pancreatic Defects
A network of nuclear transcription factors controls pancreatic development in humans and mice. Depending on their hierarchical position, defects lead to a severe phenotype, such as pancreatic agenesis with neonatal diabetes and exocrine insufficiency, or a milder phenotype, with diabetes onset during...
adolescence or adulthood. Pancreatic agenesis leads to severe intrauterine growth retardation as a result of the absence of insulin secretion, a major growth factor. Homozygous or compound heterozygous mutations usually cause more severe forms of diabetes, and many heterozygous mutations are associated with later-onset diabetes (Table 1). Numerous transcription factors play a pleiotropic role, leading to syndromic forms of diabetes associated with malformations in other organ systems, such as congenital heart defects and gastrointestinal defects.

The first gene defect described in human pancreatic agenesis was pancreatic duodenal homeobox gene 1 (PDX1/IPF1)7. Homozygous and compound heterozygous mutations lead to a severe phenotype with neonatal diabetes and exocrine pancreatic insufficiency8. Heterozygous carriers present with late-onset diabetes that can be misdiagnosed as type 2 diabetes9. PDX1 has dual functions. Early in embryogenesis, PDX1 is expressed in the forming pancreatic bud and controls the cell fate of pancreatic progenitors. During the postnatal period, PDX1 becomes restricted to β- and δ-cells, where it is involved in β-cell survival10 and regulates β-cell susceptibility to endoplasmic reticulum (ER) stress11. This change in function could explain why diabetes worsens over time in heterozygous carriers.

Similarly, homozygous mutations in the pancreas-specific transcription factor 1A gene (PTF1A) lead to pancreatic agenesis associated with cerebellar hypoplasia. PTF1A is important for pancreatic outgrowth in early embryogenesis and cerebellar formation12. Interestingly, low C-peptide and insulin levels can be detected in the blood of patients with these homozygous mutations13. The source of insulin production has not been elucidated in humans; but in mice, insulin is thought to be secreted by scattered ectopic β-cells in the spleen. Even if PTF1A mutations remain rare in human diabetes14, recessive mutations in a distal PTF1A enhancer are a frequent cause of pancreas agenesis in consanguineous families15.

Heterozygous mutations in the human GATA-binding protein 6 gene (GATA6) can lead to pancreatic agenesis with neonatal diabetes and exocrine pancreatic insufficiency, or to later-onset diabetes as well as type 2-like diabetes with variable exocrine insufficiency16,17. GATA6 is expressed before PDX1 in the developing endoderm, the pleiotropic effects are explained by the expression in the developing heart, lung, allantois, muscle and gut18. Therefore, many of the human cases have heart malformations, and gastrointestinal, pituitary and cognitive deficits19,20. Homozygous mutations are probably lethal. The functions of GATA6 and GATA4 have been studied extensively in mouse models, but only the double GATA6/4 knockout replicates the human phenotype19,20. GATA factors bind the PDX1 promoter and are involved in the proliferation of pancreatic cells.

Figure 1 | Schematic β-cell. Subcellular localization of defects within the β-cell leading to monogenic diabetes. Starting at glucose uptake at the GLUT2 transporter, during phosphorylation by the enzyme glucokinase or during glycolysis. Dysfunction of the adenosine triphosphate-sensitive potassium (KATP) channel with the KIR6.2 subunits (brown) and SUR1 subunits (red) will interfere with insulin secretion. Malfunction of the transcription factors located in the nucleus will lead to the nucleopathies and finally endoplasmic reticulum (ER) stress and lysosomal defects can also cause diabetes. ADP, adenosine diphosphate; ATP, adenosine triphosphate; GLUT2, glucose transporter 2.
Table 1 | Summary of mutations

| Gene               | Protein                                      | Mutation | Phenotype                                      | References |
|--------------------|----------------------------------------------|----------|-----------------------------------------------|------------|
| **Nucleus**        |                                              |          |                                               |            |
| PDX1/IPF1          | Pancreas/duodenum homeobox protein 1         | Hom, Chet| Pancreatic agenesis                           | 7–9        |
|                    |                                              | Het      | Adult onset                                   |            |
| PTF1A              | Pancreas transcription factor 1A             | Hom      | Pancreas and cerebellar agenesis              | 13         |
| PTF1A Enhancer     | Non-coding region                            | Hom, Chet| Pancreatic agenesis                           | 15         |
| GLIS3              | Zinc finger protein GLIS3                    | Hom      | PNDM and hypothyroidism                       | 24         |
| NGN3               | Neurogenin 3                                 | Hom, Chet| PNDM or later onset diabetes, congenital diarrhea | 31–33     |
| RFX6               | DNA binding protein RFX6                     | Hom      | PNDM, variable pancreas hypoplasia, intestinal atresia, gall bladder hypoplasia | 39         |
| GATA6              | Transcription factor GATA6                   | Het      | PNDM and adult onset diabetes, variable exocrine pancreatic insufficiency | 16,17      |
| GATA4              | Transcription factor GATA4                   | Het      | Possible pancreatic agenesis and cardiac defects | 23         |
| NEUROD1            | Neurogenic differentiation factor 1           | Hom      | PNDM, cerebellar hypoplasia, sensorineural deafness, retinal dystrophy | 44         |
| PAX6               | Paired box protein Pax6                      | Chet     | PNDM with brain anomaly                       | 50         |
| PAX4               | Paired box protein Pax4                      | Het      | Diabetes and anidria                          | 51,52      |
| HNF1B              | Hepatocyte nuclear factor 1beta              | Het      | PNDM with pancreas hypoplasia, RCAD syndrome  | 54,55,57   |
| MNX1               | Motor neuron and pancreas homeobox protein 1 | Hom      | PNDM                                          | 66         |
| KLF11              | Krueppel-like factor 11                      | Het      | Sacral dysgenesis without diabetes            | 68         |
| HNF1A              | Hepatocyte nuclear factor 1alpha             | Het      | Adult onset diabetes                          | 84         |
| HNF4A              | Hepatocyte nuclear factor 4 alpha            | Het      | Macrosomia and hypoglycemia at birth, adolescent onset diabetes | 5          |
|                    |                                              |          | Macrosomia and hypoglycemia at birth, adolescent onset diabetes | 6,79,80    |
| **Cell membrane and cytoplasm** |                  |          |                                               |            |
| SLC2A2             | Glucose transporter 2                        | Hom      | Fanconi Bickel syndrome PNDM, TNDM            | 87,88      |
| GCK                | Glucokinase                                  | Het      | Mild non-progressive hyperglycemia            | 4          |
| SLC19A2            | Thiamine transporter 1                       | Hom      | PNDM                                          | 73         |
|                    |                                              |          | PNDM or early onset, megaloblastic anemia, sensorineural deafness | 96–98     |
| **Lysosome**       |                                              |          |                                               |            |
| SLC29A3            |                                              |          |                                               |            |
| **Endoplasmic reticulum** |                  |          |                                               |            |
| WFS1               | Wolframin                                    | Chet     | Diabetes, pigmented hypertrichosis            | 101,103    |
|                    |                                              |          | Diabetes mellitus and insipidus, optic atrophy, deafness (Wolfram syndrome 1) | 104        |
| GSD2               | CDGSH iron-sulfur domain-containing protein 2| Hom      | Wolfram syndrome 2 without diabetes insipidus | 145        |
| EIF2AK3            | Eukaryotic translation initiation factor 2-alpha kinase 3 | Hom      | PNDM, skeletal defect, growth retardation (Wolclot-Rallison syndrome) | 112,113   |
| IER3P1             | Immediate early response 3 interacting protein 1 | Hom      | Microcephaly, epilepsy, PNDM (MEDS syndrome) | 114        |
| **Insulin synthesis and secretion** |                  |          |                                               |            |
progenitor cells; the double knockout has a reduced number of PDX1-positive cells during embryogenesis, resulting in pancreatic hypoplasia. During development, GATA4 is expressed in the pancreas, heart, liver and small intestine. Human GATA4 mutations mostly cause congenital heart malformations. A single report has associated an atrial septal defect with neonatal diabetes as a result of pancreatic agenesis and a heterozygous GATA4 mutation.

Defective GLIS family zinc finger 3 (GLIS3), acting downstream of PDX1 and PTF1A, leads to neonatal diabetes combined with hypothyroidism, congenital glaucoma, hepatic fibrosis and polycystic kidneys. GLIS3 directly transactivates the neurogenin 3 promoter, as well as the insulin promoter, and controls β-cell expansion through transcriptional control of the cell cycle gene CCND2. This explains why targeted disruption of GLIS3 causes defective islet cell differentiation with a marked reduction in β-cells. Intrauterine growth retardation points to insulin hyposcretion during pregnancy. Incomplete syndromes exist when residual transcripts are formed in a specific tissue, but neonatal diabetes and hypothyroidism persist throughout all families that have been described. GLIS3 is vital for adult β-cell function and mass, as conditional knockout of GLIS3 in adult β-cells results in apoptosis and fulminant diabetes. Interestingly, genome-wide association studies have identified GLIS3 as a candidate gene in type 1 diabetes and type 2 diabetes.

The transcription factor neurogenin 3 (NGN3), which acts downstream of PDX1, PTF1A and GLIS3 is the master gene controlling endocrine cell fate decisions in multipotent pancreatic endodermal progenitor cells. Targeted disruption leads to a failure of islet development, neonatal diabetes and early death. Therefore, NGN3 is required for the development of the four endocrine cell lineages. In humans, loss-of-function mutations, such as compound heterozygosity for E28X and L135P, or homozygous mutations in the coding region (E123X), are associated with neonatal diabetes and congenital malabsorption diarrhea as a result of enteric anendocrinosis. Thus, NGN3 is important in human islet and enteroendocrine cell development. Clinical characterization of these patients showed residual insulin secretion with a stimulated C-peptide level of up to 546 pmol/L during a mixed meal test; however, the glucagon levels were not measurable. Interestingly, incomplete loss of NGN3 function still leads to severe diarrhea, but only to later onset diabetes at the age of 8 years. Heterozygous NGN3 mutations rarely contribute to a type 2-like diabetes in Japanese and Indian subjects.

In 2004, several children from two different families were reported to have a syndrome comprising neonatal diabetes with a hypoplastic pancreas, intestinal atresia and gall bladder hypoplasia. In 2010, the cause of this syndrome was attributed to mutations in regulatory factor X-box binding 6 (RFX6) transcription factor. All studied mutations except one were homozygous, and heterozygous parents had a normal oral glucose tolerance test. The functional role of RFX6 was analyzed in mice harboring a targeted disruption of RFX6, these mice fail to generate islet cells, with the exception of pancreatic polypeptide (PP) cells. During development, RFX6 acts downstream of NGN3, and directs the β-cell fate. The size of the pancreas was reduced in most of the mice, as well as humans. The transcription factor, NEUROD1, plays a multisystemic role in brain and pancreas development, and lies downstream of NGN3. Targeted disruption of NEUROD1 in mice results in a 74% reduction of insulin-producing cells, as well as a 39% decrease in glucagon-producing cells. The newborn mice

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**Table 1** (Continued)

| Gene   | Protein       | Mutation | Phenotype                      | References |
|--------|---------------|----------|--------------------------------|------------|
|        |               |          |                                |            |
| INS    | Insulin       | Hom, Het | PNDM, TNDM, adult onset        | 119,122    |
|        |               | Het      | Adult onset                    | 117,118    |
| BLK    | Tyrosine-protein kinase Blk | Het | Adult onset diabetes           | 124        |
| KCN11  | Kir6.2        | Het      | PNDM, TNDM, adult onset        | 126        |
| ABCC8  | SUR1          | Het      | PNDM, TNDM, adult onset        | 127        |
| Exocrine pancreas cell | Bile salt-activated lipase         | Het | Adult onset progressive diabetes, exocrine insufficiency | 128 |
| Autoimmune diabetes | AIRE | Autoimmune regulator | Hom, Het | Systemic autoimmune disease | 146 |
|        | FOXP3         | FOXP3 protein | X-linked | PNDM, diarrhea, eczema, thyroid autoimmunity | 74 |
|        | SIRT1         | NAD-dependent protein deacetylase sirtuin-1 | Het | Adult onset autoimmune diabetes, insulin resistance | 136 |

CHet, compound heterozygous; Het, heterozygous; Hom, homozygous; MEDS, microcephaly, epilepsy and permanent neonatal diabetes syndrome; NAD, nicotinamide adenine dinucleotide; PNDM, permanent neonatal diabetes mellitus; RACD, renal cysts associated with diabetes; TNDM, transient neonatal diabetes mellitus.
develop diabetes and die after birth. NEUROD1 also functions as an activator of both GCK and insulin (INS). In humans, a homozygous mutation leads to permanent neonatal diabetes associated with cerebellar hypoplasia, learning difficulties, profound sensorineural deafness, and visual impairment as a result of severe myopia and retinal dystrophy. Malecki et al. were the first to describe a family with late onset diabetes associated with a heterozygous mutation in NEUROD1. More recently, a novel mutation was reported that led to autosomal dominant diabetes in a Chinese family with diabetes onset between 27 and 73 years-of-age. In several families, NEUROD1 diabetes has been associated with obesity, increasing the difficulties in clinically differentiating between monogenic diabetes and type 2 diabetes.

Paired box gene 6 (PAX6) is highly expressed in β-cells, the developing brain, and eyes. In mice, targeted disruption of PAX6 leads to microphthalmia and congenital diabetes with a reduction in the number of insulin-, glucagon-, somatostatin-, and PP-producing cells. PAX6 is also involved in the regulation of prohormone convertase 1/3 and contributes to proinsulin processing. In humans, compound heterozygosity of PAX6 results in severe developmental defects in the brain with hypopituitarism and neonatal diabetes. Heterozygous PAX6 mutations provoke aniridia associated with glucose intolerance. Targeted disruption of the paired box gene 4 (PAX4) leads to an absence of β-cells. Surprisingly, only rare autosomal dominant diabetes cases have been associated with heterozygous PAX4 mutations, especially in some Asian populations.

The first report implicating the transcription factor HNF1 homeobox B (HNF1B) was published in 1997 when Horikawa identified two Japanese families with diabetes associated with polycystic kidneys with heterozygous mutations. The syndrome of renal cysts associated with diabetes (RCAD) sometimes includes genital tract abnormalities. Defects in HNF1B can lead to neonatal diabetes with polycystic, dysplastic kidneys. Histopathological analysis of an affected fetus with heterozygous frameshift mutations in HNF1B has shown pancreas hypoplasia, disorganized islets with decreased β-cell density and a lack of GLUT2 expression. This presentation can be explained by the loss of transcriptional activation of GLUT2 by HNF1B on its binding to the GLUT2 promoter. This work led to the conclusion that HNF1B is essential for human β-cell maturation. During embryogenesis, HNF1B is expressed widely in the visceral endoderm of all PDX1-positive cells. After midgestation, HNF1B becomes a marker of ductal cells. In adults, HNF1B is expressed in the liver, stomach, ductal pancreatic cells, lungs and kidneys. HNF1B forms homodimers or heterodimers with the structurally similar HNF1A. The cell-specific knockout of HNF1B confirmed the importance of HNF1B for glucose-stimulated insulin secretion, but not arginine-stimulated insulin secretion, which remains intact.

Severe non-diabetic renal disease can also be a phenotype of HNF1B loss. Intriguingly, no phenotypic differences exist between large deletions, large genomic rearrangements and point mutations. One contiguous gene deletion syndrome combining mental retardation, severe growth deficit, eye abnormalities and immune deficiency with RCAD was recognized by the identification of a chromosomal microdeletion involving 1.3–1.7 Mb on Chr17q12.

Motor neuron and pancreas homeobox 1 transcription factor (MNMX1; also called HMXB9) is expressed in the pancreas during embryogenesis. The first described homozygous mutation in humans leads to permanent neonatal diabetes with normal pancreas morphology. Earlier work showed dorsal pancreatic agenesis in knockout mice with disorganized islets and a marked reduction in the number of β-cells. Heterozygous deletions have been described in autosomal dominant sacral dysgenesis without diabetes.

Nucleopathies Causing Functional Defects

Despite the expression of HNF1A and HNF4A during embryogenesis, their absence does not cause structural pancreatic defects, and diabetes manifests mostly during adolescence or young adulthood.

In early embryogenesis, HNF1A is expressed in most epithelial cells and follows the pattern of HNF4A. After birth, HNF1A is localized predominantly in exocrine cells with lower expression in islet cells. The functional HNF1A protein forms a dimer that is able to homodimerize or heterodimerize with HNF1B. HNF1A is an essential transcription factor for the glucose-stimulated insulin secretory response. Progressive hyperglycemia is the hallmark of this diabetes phenotype. As the human phenotype can vary, even in the same family, especially in regards to diabetes onset, several factors that influence the phenotype have been identified. For example, the presence of maternal diabetes during pregnancy leads to an earlier manifestation of diabetes in offspring by more than 10 years.

Despite a favorable lipid profile, an increased risk of vascular complications is present in HNF1A-diabetes. The presence of HNF1A binding sites in the C-reactive protein (CRP) promoter leads to a decrease in CRP levels when HNF1A is defective. Therefore, CRP can be used as a biomarker, with a cut-off for highly sensitive CRP levels of ≥0.2 mg/L, to distinguish HNF1A-diabetes from type 2 diabetes with a sensitivity of 79% and specificity of 83%. Because of the decreased renal glucose absorption, an action controlled by HNF1A, renal glycosuria can assist in making the diagnosis.

HNF4A is a nuclear transcription factor expressed in almost all PDX1-positive cells in the pancreatic bud at very early stages of embryogenesis. At the end of pancreas development, HNF4A is expressed in all endocrine cell types as well as exocrine cells, therefore mutations in HNF4A affect the function of the entire islet of Langerhans and is not restricted to the β-cell. HNF4A functions primarily as a homodimer, and binds to the HNF1B promoter and HNF1A promoter.

Subjects with HNF4A mutations can present with a dual phenotype, with hyperinsulinemic hypoglycemia at birth and diabetes many years later. This paradoxical phenotype...
might be explained by functionally different HNF4A targets with sequential temporal expression leading to fetal and perinatal hyperinsulinemia and adolescent hypoinsulinemia. Furthermore, progressive β-cell exhaustion might contribute to the later onset of diabetes. Clinical studies have shown a concomitant decrease of insulin, glucagon, PP and amylin secretion in humans with HNF4 mutations. Reduced HNF4A activity in humans is also associated with decreased lipoprotein (a) and apolipoprotein A-II levels, because HNF4A regulates the expression of a large number of genes involved in lipid metabolism.

The transcription factor, Krüppel-like factor 11 (KLF11), is responsible for an autosomal dominant form of diabetes. Functional analysis has shown that KLF11 regulates PDX1 and INS transcription by binding to their respective promoters. Interestingly, the diabetes-causing mutation, c-331, in the insulin gene promoter lies in the KLF11 binding site, showing the importance of KLF11 in humans.

Cellular Defects in Non-Nuclear Compartments
Defects in cellular structures, such as at the plasma membrane, the lysosome, the cytoplasm and the endoplasmic reticulum, are at the origin of many diabetes variants.

Glucose Uptake and Sensing
Glucose is taken up by the facilitative glucose transporter 2 (GLUT2) expressed at the surface of the human β-cell, liver, kidney and intestine. In 1997, Santer et al. reported the cause of Fanconi Bickel syndrome (FBS) as homozygous mutations in the solute carrier family 2 gene (SLC2A2) encoding the GLUT2 protein (Figure 1). FBS is an autosomal recessive disorder characterized by hyperglycemia, especially in the fed state, glycosuria and hepatorenal glycogen accumulation. Fasting hypoglycemia can also occur as a result of massive renal glucose loss. A defect in the glucose transporter leads to impaired monosaccharide uptake and accumulation in the blood. Furthermore, the rate limitation of glucose uptake by β-cells leads to a decrease in insulin secretion, amplifying postprandial hyperglycemia. Diabetes onset varies greatly, but neonatal diabetes associated with galactosemia has been described. Heterozygous mutations might lead to gestational diabetes or only renal glycosuria.

After glucose enters the β-cell, the enzyme GCK catalyzes the formation of glucose-6-phosphate and functions as a glucose sensor (Figure 1). GCK is also expressed in the liver and controls glycogen synthesis, gluconeogenesis, lipid synthesis and urea production. In the brain, GCK mediates glucose sensing. Heterozygous loss-of-function mutations lead to mildly elevated fasting blood glucose levels, up to 6.7 mmol/L with a postprandial increase of 2 mmol/L up to 8.6 mmol/L. Patients with one of the two specific mutations (GCK G261R and L184P) have exceptionally high postprandial glucose levels, sometimes exceeding 13 mmol/L. No worsening occurs over time, and no long-term complications have been described. However, homozygous inactivating mutations lead to severe neonatal diabetes, and insulin therapy is required. Activating mutations of the same enzyme have the opposite effect, leading to neonatal hyperinsulinemic hypoglycemia.

Cellular Metabolism
Solute carrier family 19 (thiamine transporter), member 2 (SLC19A2) encodes a high-affinity thiamine transporter that is expressed in the pancreas, heart, skeletal muscle, placenta, brain, liver, retina, bone marrow and fibroblasts. Therefore, a loss-of-function of SLC19A2 results in manifestations such as megaloblastic anemia, diabetes, and sensorineural deafness, called thiamine-responsive megaloblastic anemia (TRMA) or Rogers syndrome. Diabetes can appear during the neonatal period, and has been found to be associated with visual system disturbances, neurological deficits, and cardiac abnormalities. Adequate intracellular thiamine levels are important for mitochondrial adenosine triphosphate (ATP) synthesis and cellular function.

Lysosome
Solute carrier family 29 (nucleoside transporter), member 3 (SLC29A3) encodes a nucleoside transporter localized to intracellular membrane compartments and expressed in the endocrine and exocrine pancreas. Intracellular localization seems to be cell-type dependent, and can involve lysosomes or mitochondria. Mutation in SLC29A3 can lead to the autosomal recessive disorder with pigmented hypertrichosis and insulin-dependent diabetes mellitus (PHID) manifesting in childhood.

Endoplasmic Reticulum
Several forms of diabetes are due to dysfunction in the endoplasmic reticulum (ER); the first described form was Wolfram syndrome 1 (WFS1). WFS1 is an autosomal recessive, multisystem degenerative disorder also known as diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD). WFS1 was first reported in 1938, but the causative gene, WFS1, encoding the wolfram protein, was not identified until 1998. Wolframin is expressed in the ER in many cell types, including the pancreas, heart, retina, brain, placenta, lung, liver, skeletal muscle and kidney. The predominant role of this protein is to protect the cell from ER stress and subsequent death; in β-cells, wolframin associates with a cyclic adenosine monophosphate-generating enzyme, increasing insulin production and release. Generally, diabetes onset varies from age 3 weeks to 16 years, usually requiring insulin substitution. Optic atrophy starts around 11 years (range 6 weeks to 19 years), with most patients going blind. Diabetes insipidus presents at an average age of 14 years (range 3 months to 40 years), and sensorineural deafness at an average of 16 years (range 5–39 years). Neurodegenerative symptoms, including cerebellar ataxia, peripheral neuropathy and psychiatric illnesses, manifest in the fourth...
decade. Most patients are compound heterozygous for two mutations. A rare autosomal dominant form of WFS1 also exists\textsuperscript{110}.

Recently, \textit{CDGSH} iron sulfur domain 2 (\textit{CISD2}) was found to give rise to WFS2, a phenotype similar to WFS1, but without diabetes insipidus\textsuperscript{111}. Some patients also show a significant bleeding tendency as a result of defective platelet aggregation with collagen. \textit{CISD2} encodes a protein that localizes in the ER and is involved in calcium homeostasis.

The eukaryotic translation initiation factor 2-alpha kinase 3 (\textit{EIF2AK3}) and immediate early response 3 interacting protein 1 (\textit{IER3IP1}) are also located in the ER and play a role in the stress response. Gene defects in either of these genes leads to an overlapping autosomal recessive syndrome. Mutations in \textit{EIF2AK3} are associated with early onset diabetes, skeletal defects and growth retardation, also called Wolcott-Rallison syndrome (WRS)\textsuperscript{112,113}. Mutations in \textit{IER3IP1} lead to microcephaly, epilepsy and permanent neonatal diabetes (MEDS) in MEDS syndrome\textsuperscript{114}. In the mouse, the targeted disruption of \textit{EIF2AK3} results in proinsulin accumulation in the ER of $\beta$-cells and insulin deficiency. Therefore, \textit{EIF2AK3} seems to regulate ER-to-Golgi trafficking and proinsulin degradation in response to reduced insulin demand\textsuperscript{115}. The pancreas-specific knockout mouse model shows impaired $\beta$-cell differentiation and lower insulin content at birth with a 50% reduction in $\beta$-cell mass compared with wild type\textsuperscript{116}. Postnatal proliferation of $\beta$-cells is also reduced, leading to an 87% reduction in $\beta$-cell mass at weaning. In addition, the $\beta$-cells show a distended ER and squeezed mitochondria at birth. These results underline the importance of \textit{EIF2AK3} function in the prenatal and perinatal period.

\section*{Insulin Synthesis and Secretion}

Mutations in \textit{INS} were first described in a patient with mild diabetes and hyperinsulinemia, resembling type 2 diabetes\textsuperscript{117,118}. In 2007, the first series of neonatal diabetes as a result of heterozygous \textit{INS} mutations was reported\textsuperscript{119}. The dominance of these heterozygous mutations is explained by the misfolding of preproinsulin, leading to intracellular accumulation and ER stress. In two diabetes mouse models harboring human mutations (C96S or C96Y in \textit{Ins2}), the ultrastructure of the $\beta$-cell is massively disrupted with dilatation of the ER, confirming increased ER stress and cell death\textsuperscript{120,121}.

\textit{INS} mutations, together with mutations in \textit{ABCC8}, \textit{KCNJ11} and \textit{GATA6}, are the most frequent cause of neonatal diabetes. The average age at diagnosis is 9 weeks, usually with ketoadosis. However, some cases are diagnosed outside the neonatal period, between 6 months-of-age and 1 year. Over 80% of mutations are de novo. Interestingly, some family members carrying the same mutation have mild diabetes at the age of 30 years. Therefore, the phenotypic spectrum is quite broad. In 2010, recessive \textit{INS} mutations were reported to have a slightly different phenotype: neonatal diabetes is diagnosed earlier, at 1 week-of-age, and growth retardation as a result of decreased insulin secretion \textit{in utero} is more severe. Recessive mutations lead to decreased insulin biosynthesis through different mechanisms, such as a lack of translation initiation and decreased messenger ribonucleic acid stability. Recessive mutations might also cause transient neonatal diabetes, but these mutations are typically located in non-coding regions, such as the insulin promoter\textsuperscript{122}. Screening of over 1000 diabetic patients showed that \textit{INS} mutations are rare after the neonatal period\textsuperscript{123}. Later-onset diabetes is mainly associated with mutations in the C-peptide and signal peptide regions.

B lymphocyte kinase (\textit{BLK}) expressed in pancreatic islets is an enhancer of insulin secretion, and the first mutation was described to cosegregate with diabetes in several families\textsuperscript{124}. The human \textit{BLK} mutant, Ala71Thr, leads to blunted insulin secretion \textit{in vitro}, but \textit{BLK} has not been confirmed in other cohorts with autosomally dominant diabetes\textsuperscript{125}.

\section*{Channelopathies}

Mutations in \textit{KCNJ11} and \textit{ABCC8}, which encode the subunits of the ATP-sensitive potassium (\textit{K\textsubscript{ATP}}) channel, lead to a similar phenotype as mutations in \textit{INS}. Gain-of-function mutations that severely affect channel function result in permanent neonatal diabetes, and milder mutations result in transient neonatal diabetes\textsuperscript{126,127}. All of the mutations impair \textit{K\textsubscript{ATP}} channel closure and, therefore, insulin secretion. As \textit{KCNJ11} is also expressed in the brain and skeletal muscle, diabetes might be associated with speech delay, epilepsy and muscular hypotonia. This syndrome is called DEND for developmental delay, epilepsy and neonatal diabetes, or intermediate DEND (iDEND) without epilepsy.

\section*{Exocrine Pancreas Defects Affecting Endocrine Function}

The enzyme, carboxyl-ester lipase (\textit{CEL}), is involved in cholesterol ester hydrolysis in the duodenal lumen, and is expressed in the exocrine pancreas and lactating mammary glands, but not islet cells. A gene defect leads to pancreatic lipomatosis and exocrine pancreatic insufficiency in childhood, and progressive diabetes diagnosed at a mean age of 34 years\textsuperscript{128}. Protein misfolding with intracellular and extracellular aggregation probably exerts a cytotoxic effect and lead to sustained disease progression involving the islets of Langerhans\textsuperscript{129}.

\section*{Monogenic Autoimmune Diabetes}

The first single gene defect associated with a systemic autoimmune disease, autoimmune polyendocrine syndrome type 1 (APS1) including diabetes, was found in the autoimmune regulator gene (\textit{AIRE})\textsuperscript{130,131}. Mutations in \textit{AIRE} lead to the highly variable APS1, affecting the pancreas, as well as the parathyroid, adrenal, thyroid, liver, ovary, stomach and skin. Dysfunctional fungal immunity gives rise to mucocutaneous candidiasis. The transcription factor, AIRE, is mainly expressed in lymphoid tissues, and is essential for generating central tolerance through negative selection of autoreactive
T cells in the thymus. Mutant AIRE does not have the capability to maintain immunological tolerance, leading to the destruction of self, including β-cells.132

Similarly, forkhead box P3 (FOXP3) defects lead to a systemic autoimmune disease, called immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX)134,135. This severe syndrome recognized in the neonatal period by diarrhea, diabetes, eczema, thyroid autoimmunity and an exaggerated response to viral infections often leads to death early in life. FOXP3 is critical in the development of regulatory T cells and the suppression of autoimmunity.134,135 Female carriers have no established phenotype.

Sirtuins (SIRT1) is another gene responsible for a monogenic form of autoimmune diabetes associated with insulin resistance.136 SIRT1 belongs to the family of histone deacetylases, regulating complex metabolic processes.137 In β-cells, SIRT1 likely regulates insulin secretion in response to glucose through downregulation of UCP2138. SIRT1 deacetylates p53, thereby inhibiting apoptosis; therefore, loss-of-function favors apoptosis, which occurs in autoimmune diabetes. Furthermore, SIRT1 has been proposed to act as an insulin sensitizer, which fits the human model in which SIRT1 mutation leads to insulin resistance associated with β-cell destruction.

Implications for Treatment

Accurate diabetes diagnosis allows for improved treatment in at least five variants. Sulfonylurea drugs, such as glibenclamide, bind to the K_ATP channel and lead to channel closure thereby stimulating insulin secretion in β-cells. These oral drugs overcome the impaired channel closure, the hallmark of gain-of-function mutations in the KCNJ11 and ABCC8 genes. This explains why a switch from insulin to sulfonylurea treatment improves metabolic control in most cases. As dysfunction of KIR6.2 protein, encoded by KCNJ11, is thought to be responsible for the neurological phenotype, several reports show an amelioration of neurological functions, at least in children.139,140 In adults after decades of insulin treatment, a transfer to sulfonylurea can similarly restore endogenous insulin secretion.141

Patients carrying the HNF4A or HNF1A mutations are quite sensitive to sulfonylureas, these oral antiglycemics bypass the functional defect in β-cells by acting downstream of the metabolic steps eliciting insulin secretion.142 Thiamine-responsive diabetes as a result of decreased availability of cellular energy in the form of ATP responds to early substitution with thiamine, which enhances insulin secretion.

Finally, a new class of agents that activate GCK, enhancing glucose-stimulated insulin release, is being developed for GCK-deficient patients. These drugs could also be beneficial for type 2 diabetes.143 However, the first clinical trials of the compound, GKA MK-0941, were disappointing, reporting a loss of efficacy over time, and resulting in increased systolic blood pressure and serum triglycerides as a result of increased de novo lipogenesis.144

CONCLUSIONS

Over the past couple of years, discoveries about β-cell genes in monogenic diabetes have led to a better understanding of the human β-cell.

The availability of next-generation sequencing will help unravel the full spectrum of genetic diabetes, ranging from truly monogenic to digenic, oligogenic and polygenic traits. This tool will certainly offer deeper comprehension of the different diabetes variations and lead to optimized treatment of the specific forms. The discovery of modifier genes will also be useful to better understand the different diabetes phenotypes. Functional analyses in vitro and in vivo will also help define specific gene-related therapies. These results will prove to be relevant to the pathophysiology of β-cell defects in type 2 diabetes. Broader knowledge of human diabetes will lead to improved treatment, outcomes, prevention and hopefully a cure.

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