Many faces of monogenic diabetes

Valerie M Schwitzgebel*

Pediatric Endocrine and Diabetes Unit, Department of Child and Adolescent Health, Children's University Hospital, Geneva, Switzerland

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[1]. The first description of a hereditary form dates back to 1928, when Cammidge identified families with autosomal dominant diabetes[2]. 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[3]. The first gene causally implicated was coded for the enzyme glucokinase (*GCK*)[4]. 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[5,6].

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
Nucleopathies 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 insufficiency[8]. Heterozygous carriers present with late-onset diabetes that can be misdiagnosed as type 2 diabetes[9]. *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 survival[10] and regulates β-cell susceptibility to endoplasmic reticulum (ER) stress[11]. 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 formation[12]. Interestingly, low C-peptide and insulin levels can be detected in the blood of patients with these homozygous mutations[13]. 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 diabetes[14], recessive mutations in a distal *PTF1A* enhancer are a frequent cause of pancreas agenesis in consanguineous families[15].

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 insufficiency[16,17]. *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 gut[18]. Therefore, many of the human cases have heart malformations, and gastrointestinal, pituitary and cognitive deficits[19,20]. 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 phenotype[21,22]. GATA factors bind the *PDX1* promoter and are involved in the proliferation of pancreatic
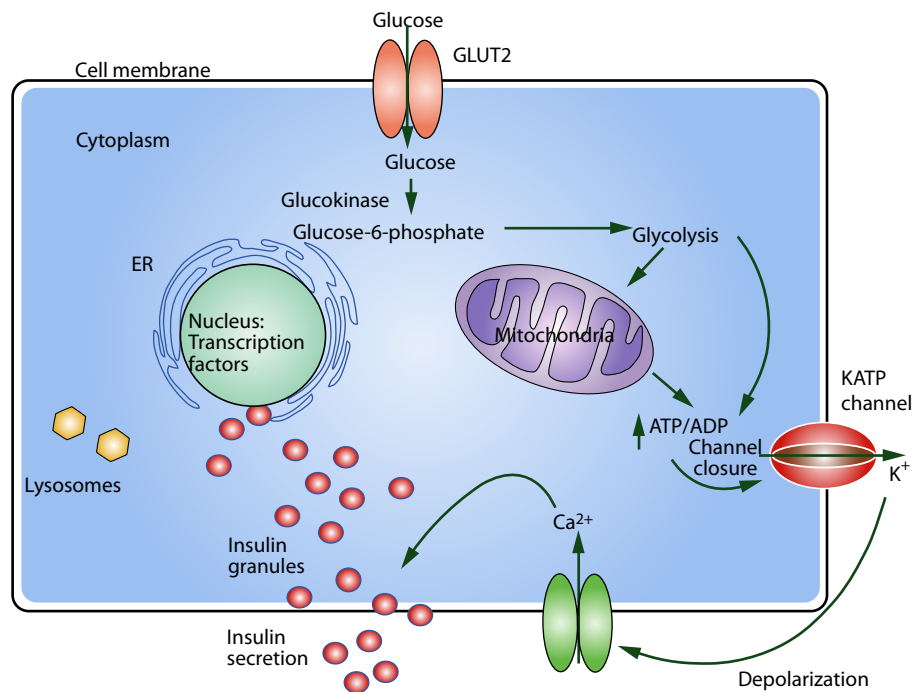

Figure 1 | Schematic β-cell. Subcellular localization of defects within the β-cell leading to monogenic diabetes. Starting at glucose uptake at the GLUT2 transporter, during phosphorylation by the enzyme glucokinase or during glycolysis. Dysfunction of the adenosine triphosphate-sensitive potassium (K_{ATP}) 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 Het	Pancreatic agenesis Adult onset	7–9
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
		Het	Adult onset diabetes	45
PAX6	Paired box protein Pax6	CHet	PNDM with brain anomaly	50
		Het	Diabetes and aniridia	51,52
PAX4	Paired box protein Pax4		Adult onset diabetes	54
HNF1B	Hepatocyte nuclear factor 1beta	Het	PNDM with pancreas hypoplasia, RCAD syndrome	55,57
MNX1	Motor neuron and pancreas homeobox protein 1	Hom	PNDM	66
		Het	Sacral dysgenesis without diabetes	68
KLF11	Krueppel-like factor 11	Het	Adult onset diabetes	84
HNF1A	Hepatocyte nuclear factor 1alpha	Het	Macrosomia and hypoglycemia at birth, adolescent onset diabetes	5
HNF4A	Hepatocyte nuclear factor 4 alpha	Het	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
		Hom	PNDM	73
SLC19A2	Thiamine transporter 1	Hom	PNDM or early onset, megaloblastic anemia, sensorineural deafness	96–98
Lysosome				
SLC29A3		Hom, CHet	Diabetes, pigmented hypertrichosis	101,103
Endoplasmic reticulum				
WFS1	Wolframin	CHet	Diabetes mellitus and insipidus, optic atrophy, deafness (Wolfram syndrome 1)	104
CISD2	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 (Wollcot-Rallison syndrome)	112,113
IER3IP1	Immediate early response 3 interacting protein 1	Hom	Microcephaly, epilepsy, PNDM (MEDS syndrome)	114
Insulin synthesis and secretion				

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
KCNJ11	KIR6.2	Het	PNDM, TNDM, adult onset	126
ABCC8	SUR1	Het	PNDM, TNDM, adult onset	127
Exocrine pancreas				
CEL	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.

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[23].

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[24]. 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[25]. 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 hyposecretion 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[26]. 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[27]. Interestingly, genome-wide association studies have identified GLIS3 as a candidate gene in type 1 diabetes and type 2 diabetes[28,29].

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[30]. 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[31,32]. 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[33,34]. Heterozygous NGN3 mutations rarely contribute to a type 2-like diabetes in Japanese and Indian subjects[35–37].

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[38]. In 2010, the cause of this syndrome was attributed to mutations in regulatory factor X-box binding 6 (RFX6) transcription factor[39]. All studied mutations except one were homozygous, and heterozygous parents had a normal oral glucose tolerance test[40]. 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[41]. 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

develop diabetes and die after birth[42]. NEUROD1 also functions as an activator of both GCK and insulin (INS)[43]. 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[44]. Malecki et al.[45] 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[46]. In several families, NEUROD1 diabetes has been associated with obesity, increasing the difficulties in clinically differentiating between monogenic diabetes and type 2 diabetes[47].

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[48]. PAX6 is also involved in the regulation of prohormone convertase 1/3 and contributes to proinsulin processing[49]. In humans, compound heterozygosity of PAX6 results in severe developmental defects in the brain with hypopituitarism and neonatal diabetes[50]. Heterozygous PAX6 mutations provoke aniridia associated with glucose intolerance[51,52]. Targeted disruption of the paired box gene 4 (PAX4) leads to an absence of β-cells[53]. Surprisingly, only rare autosomal dominant diabetes cases have been associated with heterozygous PAX4 mutations, especially in some Asian populations[54].

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[55]. The syndrome of renal cysts associated with diabetes (RCAD) sometimes includes genital tract abnormalities[56]. Defects in HNF1B can lead to neonatal diabetes with polycystic, dysplastic kidneys[57]. 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[58,59]. 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[60]. 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[61]. The β-cell-specific knockout of HNF1B confirmed the importance of HNF1B for glucose-stimulated insulin secretion, but not arginine-stimulated insulin secretion, which remains intact[62,63].

Severe non-diabetic renal disease can also be a phenotype of HNFB1 loss. Intriguingly, no phenotypic differences exist between large deletions, large genomic rearrangements and point mutations[64]. 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[65].

Motor neuron and pancreas homeobox 1 transcription factor (MMNX1; also called HLXB9) is expressed in the pancreas during embryogenesis. The first described homozygous mutation in humans leads to permanent neonatal diabetes with normal pancreas morphology[66]. Earlier work showed dorsal pancreatic agenesis in knockout mice with disorganized islets and a marked reduction in the number of β-cells[67]. Heterozygous deletions have been described in autosomal dominant sacral dysgenesis without diabetes[68].

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[63,69,70].

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[69]. The functional HNF1A protein forms a dimer that is able to homodimerize or heterodimerize with HNF1B[71]. HNF1A is an essential transcription factor for the glucose-stimulated insulin secretory response[63,72]. 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[75]. The presence of HNF1A binding sites in the C-reactive protein (CRP) promoter leads to a decrease in CRP levels when HNF1A is defective[76]. 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[77].

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[69], 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[78].

Subjects with HNF4A mutations can present with a dual phenotype, with hyperinsulinemic hypoglycemia at birth and diabetes many years later[79]. This paradoxical phenotype

might be explained by functionally different *HNF4A* targets with sequential temporal expression leading to fetal and perinatal hyperinsulinemia and adolescent hypoinsulinemia[80]. 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[81]. Reduced HNF4A activity in humans is also associated with decreased lipoprotein (a) and apolipoprotein A-II levels[82], because HNF4A regulates the expression of a large number of genes involved in lipid metabolism[83].

The transcription factor, Krüppel-like factor 11 (KLF11), is responsible for an autosomal dominant form of diabetes[84]. Functional analysis has shown that KLF11 regulates *PDX1* and *INS* transcription by binding to their respective promoters[85]. 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[86].

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[87,88]. In 1997, Santer *et al.*[89] 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[90]. Heterozygous mutations might lead to gestational diabetes[91] or only renal glycosuria[92].

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[93]. 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[4,29]. Patients with one of the two specific mutations (GCK G261R and L184P) have exceptionally high postprandial glucose levels, sometimes exceeding 13 mmol/L[94]. 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[73]. Activating mutations of the same enzyme have the opposite effect, leading to neonatal hyperinsulinemic hypoglycemia[95].

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[96,97]. Diabetes can appear during the neonatal period, and has been found to be associated with visual system disturbances, neurological deficits, and cardiac abnormalities[98]. Adequate intracellular thiamine levels are important for mitochondrial adenosine triphosphate (ATP) synthesis and cellular function[99].

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[100,101]. Intracellular localization seems to be cell-type dependent, and can involve lysosomes or mitochondria[102]. Mutation in *SLC29A3* can lead to the autosomal recessive disorder with pigmented hypertrichosis and insulin-dependent diabetes mellitus (PHID) manifesting in childhood[103].

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 wolframin protein, was not identified until 1998[104]. 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[105–108]. 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[109]. 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[110].

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

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

Insulin Synthesis and Secretion

Mutations in INS were first described in a patient with mild diabetes and hyperinsulinemia, resembling type 2 diabetes[117,118]. In 2007, the first series of neonatal diabetes as a result of heterozygous INS mutations was reported[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 Ins2), the ultrastructure of the β-cell is massively disrupted with dilatation of the ER, confirming increased ER stress and cell death[120,121].

INS mutations, together with mutations in ABCC8, KCNJ11 and GATA6, are the most frequent cause of neonatal diabetes. The average age at diagnosis is 9 weeks, usually with ketoacidosis. 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 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 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[122]. Screening of over 1000 diabetic patients showed that INS mutations are rare after the neonatal period[123]. Later-onset diabetes is mainly associated with mutations in the C-peptide and signal peptide regions.

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

Channelopathies

Mutations in KCNJ11 and ABCC8, which encode the subunits of the ATP-sensitive potassium (K_{ATP}) channel, lead to a similar phenotype as mutations in INS. Gain-of-function mutations that severely affect channel function result in permanent neonatal diabetes, and milder mutations result in transient neonatal diabetes[126,127]. All of the mutations impair K_{ATP} channel closure and, therefore, insulin secretion. As 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.

Exocrine Pancreas Defects Affecting Endocrine Function

The enzyme, carboxyl-ester lipase (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[128]. Protein misfolding with intracellular and extracellular aggregation probably exerts a cytotoxic effect and lead to sustained disease progression involving the islets of Langerhans[129].

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 (AIRE)[130,131]. Mutations in 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)[74,133]. 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.

Sirtuin1 (*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 UCP2[138]. 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 antidiabetics 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.

REFERENCES

1. Ledermann HM. Is maturity onset diabetes at young age (MODY) more common in Europe than previously assumed? *Lancet* 1995; 345: 648.
2. Cammidge PJ. Diabetes mellitus and heredity. *Br Med J* 1928; 2: 738–741.
3. Tattersall RB, Fajans SS. A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. *Diabetes* 1975; 24: 44–53.
4. Vionnet N, Stoffel M, Takeda J, *et al.* Nonsense mutation in the glucokinase gene causes early-onset non-insulin-dependent diabetes mellitus. *Nature* 1992; 356: 721–722.
5. Yamagata K, Oda N, Kaisaki PJ, *et al.* Mutations in the hepatocyte nuclear factor-1alpha gene in maturity-onset diabetes of the young (MODY3). *Nature* 1996; 384: 455–458.
6. Yamagata K, Furuta H, Oda N, *et al.* Mutations in the hepatocyte nuclear factor-4alpha gene in maturity-onset diabetes of the young (MODY1). *Nature* 1996; 384: 458–460.
7. Stoffers DA, Zinkin NT, Stanojevic V, *et al.* Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. *Nat Genet* 1997; 15: 106–110.
8. Schwitzgebel VM, Mamin A, Brun T, *et al.* Agenesis of human pancreas due to decreased half-life of insulin promoter factor 1. *J Clin Endocrinol Metab* 2003; 88: 4398–4406.
9. Stoffers DA, Ferrer J, Clarke WL, *et al.* Early-onset type-II diabetes mellitus (MODY4) linked to IPF1. *Nat Genet* 1997; 17: 138–139.

10. Ahlgren U, Jonsson J, Jonsson L, *et al*. beta-cell-specific inactivation of the mouse Ipf1/Pdx1 gene results in loss of the beta-cell phenotype and maturity onset diabetes. *Genes Dev* 1998; 12: 1763–1768.

11. Sachdeva MM, Claiborn KC, Khoo C, *et al*. Pdx1 (MODY4) regulates pancreatic beta cell susceptibility to ER stress. *Proc Natl Acad Sci USA* 2009; 106: 19090–19095.

12. Krapp A, Knöfler M, Ledermann B, *et al*. The bHLH protein PTF1-p48 is essential for the formation of the exocrine and the correct spatial organization of the endocrine pancreas. *Genes Dev* 1998; 12: 3752–3763.

13. Sellick GS, Barker KT, Stolte-Dijkstra I, *et al*. Mutations in PTF1A cause pancreatic and cerebellar agenesis. *Nat Genet* 2004; 36: 1301–1305.

14. Al-Shammari M, Al-Husain M, Al-Kharfy T, *et al*. A novel PTF1A mutation in a patient with severe pancreatic and cerebellar involvement. *Clin Genet* 2011; 80: 196–198.

15. Weedon MN, Cebola I, Patch A-M, *et al*. Recessive mutations in a distal PTF1A enhancer cause isolated pancreatic agenesis. *Nat Genet* 2013; 46: 61–64.

16. Allen HL, Flanagan SE, Shaw-Smith C, *et al*. GATA6 haploinsufficiency causes pancreatic agenesis in humans. *Nat Genet*. Nature Publishing Group; 2011; 44: 20–22.

17. De Franco E, Shaw-Smith C, Flanagan SE, International NDM Consortium, Hattersley AT, *et al*. GATA6 mutations cause a broad phenotypic spectrum of diabetes from pancreatic agenesis to adult-onset diabetes without exocrine insufficiency. *Diabetes* 2013; 62: 993–997.

18. Ketola I, Otonkoski T, Pulkkinen M-A, *et al*. Transcription factor GATA-6 is expressed in the endocrine and GATA-4 in the exocrine pancreas. *Mol Cell Endocrinol* 2004; 226: 51–57.

19. Bonnefond A, Sand O, Guerin B, *et al*. GATA6 inactivating mutations are associated with heart defects and, inconsistently, with pancreatic agenesis and diabetes. *Diabetologia* 2012; 55: 2845–2847.

20. Catli G, Abaci A, Flanagan SE, *et al*. A novel GATA6 mutation leading to congenital heart defects and permanent neonatal diabetes: a case report. *Diabetes Metab* [Internet]. Elsevier Masson SAS; 2013: 1–5. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=23639568&retmode=ref&cmd=prlinks

21. Xuan S, Borok MJ, Decker KJ, *et al*. Pancreas-specific deletion of mouse Gata4 and Gata6 causes pancreatic agenesis. *J Clin Invest* 2012; 122: 3516–3528.

22. Carrasco M, Delgado I, Soria B, *et al*. GATA4 and GATA6 control mouse pancreas organogenesis. *J Clin Invest* 2012; 122: 3504–3515.

23. D'Amato E, Giacopelli F, Giannattasio A, *et al*. Genetic investigation in an Italian child with an unusual association of atrial septal defect, attributable to a new familial GATA4 gene mutation, and neonatal diabetes due to pancreatic agenesis. *Diabetic Med* 2010; 27: 1195–1200.

24. Senée V, Chelala C, Duchatelet S, *et al*. Mutations in GLIS3 are responsible for a rare syndrome with neonatal diabetes mellitus and congenital hypothyroidism. *Nat Genet* 2006; 38: 682–687.

25. Kim Y-S, Kang HS, Takeda Y, *et al*. Glis3 regulates neurogenin 3 expression in pancreatic β-cells and interacts with its activator, Hnf6. *Mol Cells* 2012; 34: 193–200.

26. Dimitri P, Warner JT, Minton JAL, *et al*. Novel GLIS3 mutations demonstrate an extended multisystem phenotype. *Eur J Endocrinol* 2011; 164: 437–443.

27. Yang Y, Chang BH-J, Chan L. Sustained expression of the transcription factor GLIS3 is required for normal beta cell function in adults. *EMBO Mol Med* 2012; 5: 92–104.

28. Barrett JC, Clayton DG, Concannon P, *et al*. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. *Nat Genet* 2009; 41: 703–707.

29. Dupuis J, Langenberg C, Prokopenko I, *et al*. New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk. *Nat Genet* 2010; 42: 105–116.

30. Gradwohl G, Dierich A, LeMeur M, *et al*. Neurogenin3 is required for the development of the four endocrine cell lineages of the pancreas. *Proc Natl Acad Sci USA* 2000; 97: 1607–1611.

31. Pinney SE, Oliver-Krasinski J, Ernst L, *et al*. Neonatal diabetes and congenital malabsorptive diarrhea attributable to a novel mutation in the human neurogenin-3 gene coding sequence. *J Clin Endocrinol Metab* 2011; 96: 1960–1965.

32. Rubio-Cabezas O, Jensen JN, Hodgson MI, *et al*. Permanent neonatal diabetes and enteric anendocrinosis associated with biallelic mutations in NEUROG3. *Diabetes* 2011; 60: 1349–1353.

33. Wang J, Cortina G, Wu SV, *et al*. Mutant neurogenin-3 in congenital malabsorptive diarrhea. *N Engl J Med* 2006; 355: 270–280.

34. Jensen JN, Rosenberg LC, Heckser-Sørensen J, *et al*. Mutant neurogenin-3 in congenital malabsorptive diarrhea. *N Engl J Med* 2007; 356: 1781–1782 authorreply1782.

35. del Bosque-Plata L, Lin J, Horikawa Y, *et al*. Mutations in the coding region of the neurogenin 3 gene (NEUROG3) are not a common cause of maturity-onset diabetes of the young in Japanese subjects. *Diabetes* 2001; 50: 694–696.

36. Milord E, Gragnoli C. NEUROG3 variants and type 2 diabetes in Italians. *Minerva Med* 2006; 97: 373–378.

37. Jackson AE, Cassell PG, North BV, *et al*. Polymorphic variations in the neurogenic differentiation-1, neurogenin-3, and hepatocyte nuclear factor-1alpha genes contribute to glucose intolerance in a South Indian population. *Diabetes* 2004; 53: 2122–2125.

38. Mitchell J, Punthakee Z, Lo B, *et al*. Neonatal diabetes, with hypoplastic pancreas, intestinal atresia and gall bladder hypoplasia: search for the aetiology of a new autosomal recessive syndrome. *Diabetologia* 2004; 47: 2160–2167.

39. Smith SB, Qu H-Q, Taleb N, et al. Rfx6 directs islet formation and insulin production in mice and humans. *Nature*. Nature Publishing Group; 2010; 463: 775–780.

40. Spiegel R, Dobbie A, Hartman C, et al. Clinical characterization of a newly described neonatal diabetes syndrome caused by RFX6 mutations. *Am J Med Genet* 2011; 155A: 2821–2825.

41. Soyer J, Flasse L, Raffelsberger W, et al. Rfx6 is an Ngn3-dependent winged helix transcription factor required for pancreatic islet cell development. *Development* 2010; 137: 203–212.

42. Naya FJ, Huang HP, Qiu Y, et al. Diabetes, defective pancreatic morphogenesis, and abnormal enteroendocrine differentiation in BETA2/NeuroD-deficient mice. *Genes Dev* 1997; 11: 2323–2334.

43. Moates JM, Nanda S, Cissell MA, et al. BETA2 activates transcription from the upstream glucokinase gene promoter in islet beta-cells and gut endocrine cells. *Diabetes* 2003; 52: 403–408.

44. Rubio-Cabezas O, Minton JAL, Kantor I, et al. Homozygous mutations in NEUROD1 are responsible for a novel syndrome of permanent neonatal diabetes and neurological abnormalities. *Diabetes* 2010; 59: 2326–2331.

45. Malecki MT, Jhala US, Antonellis A, et al. Mutations in NEUROD1 are associated with the development of type 2 diabetes mellitus. *Nat Genet* 1999; 23: 323–328.

46. Liu L, Furuta H, Minami A, et al. A novel mutation, Ser159Pro in the NeuroD1/BETA2 gene contributes to the development of diabetes in a Chinese potential MODY family. *Mol Cell Biochem* 2007; 303: 115–120.

47. Gonsorcíková L, Průhová S, Cinek O, et al. Autosomal inheritance of diabetes in two families characterized by obesity and a novel H241Q mutation in NEUROD1. *Pediatr Diabetes* 2008; 9(4 Pt 2): 367–372.

48. Sander M, Neubuser A, Kalamaras J, et al. Genetic analysis reveals that PAX6 is required for normal transcription of pancreatic hormone genes and islet development. *Genes Dev* 1997; 11: 1662–1673.

49. Liu T, Zhao Y, Tang N, et al. Pax6 directly down-regulates Pcsk1n expression thereby regulating PC1/3 dependent proinsulin processing. Kulkarni R, editor *PLoS ONE* 2012; 7: e46934.

50. Solomon BD, Pineda-Alvarez DE, Balog JZ, et al. Compound heterozygosity for mutations in PAX6in a patient with complex brain anomaly, neonatal diabetes mellitus, and microophthalmia. *Am J Med Genet* 2009; 149A: 2543–2546.

51. Yasuda T, Kajimoto Y, Fujitani Y, et al. PAX6 mutation as a genetic factor common to aniridia and glucose intolerance. *Diabetes* 2001; 51: 224–230.

52. Nishi M, Sasahara M, Shono T, et al. A case of novel de novo paired box gene 6 (PAX6) mutation with early-onset diabetes mellitus and aniridia. *Diabet Med* 2005; 22: 641–644.

53. Sosa-Pineda B, Chowdhury K, Torres M, et al. The Pax4 gene is essential for differentiation of insulin-producing beta cells in the mammalian pancreas. *Nature* 1997; 386: 399–402.

54. Plengvidhya N, Kooptiwut S, Songtawee N, et al. PAX4 mutations in Thais with maturity onset diabetes of the young. *J Clin Endocrinol Metab* 2007; 92: 2821–2826.

55. Horikawa Y, Iwasaki N, Hara M, et al. Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. *Nat Genet* 1997; 17: 384–385.

56. Lindner TH, Njolstad PR, Horikawa Y, et al. A novel syndrome of diabetes mellitus, renal dysfunction and genital malformation associated with a partial deletion of the pseudo-POU domain of hepatocyte nuclear factor-1beta. *Hum Mol Genet* 1999; 8: 2001–2008.

57. Yorifuji T, Kurokawa K, Mamada M, et al. Neonatal diabetes mellitus and neonatal polycystic, dysplastic kidneys: phenotypically discordant recurrence of a mutation in the hepatocyte nuclear factor-1beta gene due to germline mosaicism. *J Clin Endocrinol Metab* 2004; 89: 2905–2908.

58. Haumaitre C. Severe pancreas hypoplasia and multicystic renal dysplasia in two human fetuses carrying novel HNF1/MODY5 mutations. *Hum Mol Genet* 2006; 15: 2363–2375.

59. Haldorsen IS, Vesterhus M, Raeder H, et al. Lack of pancreatic body and tail in HNF1B mutation carriers. *Diabet Med* 2008; 25: 782–787.

60. Cha JY, Kim H, Kim KS, et al. Identification of transacting factors responsible for the tissue-specific expression of human glucose transporter type 2 isoform gene. Cooperative role of hepatocyte nuclear factors 1alpha and 3beta. *J Biol Chem* 2000; 275: 18358–18365.

61. Cereghini S. Liver-enriched transcription factors and hepatocyte differentiation. *FASEB J* 1996; 10: 267–282.

62. Wang L, Coffinier C, Thomas MK, et al. Selective deletion of the Hnf1beta (MODY5) gene in beta-cells leads to altered gene expression and defective insulin release. *Endocrinology* 2004; 145: 3941–3949.

63. Pontoglio M, Sreenan S, Roe M, et al. Defective insulin secretion in hepatocyte nuclear factor 1alpha-deficient mice. *J Clin Invest* 1998; 101: 2215–2222.

64. Bellanné-Chantelot C, Clauin S, Chauveau D, et al. Large genomic rearrangements in the hepatocyte nuclear factor-1beta (TCF2) gene are the most frequent cause of maturity-onset diabetes of the young type 5. *Diabetes* 2005; 54: 3126–3132.

65. Raile K, Klopocki E, Holder M, et al. Expanded clinical spectrum in hepatocyte nuclear factor 1B-maturity-onset diabetes of the young. *J Clin Endocrinol Metab* 2009; 94: 2658–2664.

66. Bonnefond A, Vaillant E, Philippe J, et al. Transcription factor gene MNX1 is a novel cause of permanent neonatal diabetes in a consanguineous family. *Diabetes Metab* [Internet]. Elsevier Masson SAS; 2013: 1–5. Available at:

http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?
dbfrom=pubmed&id=23562494&retmode=ref&cmd=prlinks

67. Harrison KA, Thaler J, Pfaff SL, et al. Pancreas dorsal lobe agenesis and abnormal islets of Langerhans in Hlxb9-deficient mice. Nat Genet 1999; 23: 71–75.

68. Ross AJ, Ruiz-Perez V, Wang Y, et al. A homeobox gene, HLXB9, is the major locus for dominantly inherited sacral agenesis. Nat Genet 1998; 20: 358–361.

69. Nammo T, Yamagata K, Tanaka T, et al. Expression of HNF-4α (MODY1), HNF-1β (MODY5), and HNF-1α (MODY3) proteins in the developing mouse pancreas. Gene Expr Patterns 2008; 8: 96–106.

70. Lee YH, Sauer B, Gonzalez FJ. Laron dwarfism and non-insulin-dependent diabetes mellitus in the Hnf-1alpha knockout mouse. Mol Cell Biol 1998; 18: 3059–3068.

71. Edghill EL, Bingham C, Ellard S, et al. Mutations in hepatocyte nuclear factor-1beta and their related phenotypes. J Med Genet 2005; 43: 84–90.

72. Hagenfeldt-Johansson KA, Herrera PL, Wang H, et al. Beta-cell-targeted expression of a dominant-negative hepatocyte nuclear factor-1 alpha induces a maturity-onset diabetes of the young (MODY)3-like phenotype in transgenic mice. Endocrinology 2001; 142: 5311–5320.

73. Njolstad PR, Sovik O, Cuesta-Muñoz A, et al. Neonatal diabetes mellitus due to complete glucokinase deficiency. N Engl J Med 2001; 344: 1588–1592.

74. Bennett CL, Christie J, Ramsdell F, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 2001; 27: 20–21.

75. Steele AM, Shields BM, Shepherd M, et al. Increased all-cause and cardiovascular mortality in monogenic diabetes as a result of mutations in the HNF1A gene. Diabetic Med 2010; 27: 157–161.

76. Owen KR, Thanabalasingham G, James TJ, et al. Assessment of high-sensitivity C-reactive protein levels as diagnostic discriminator of maturity-onset diabetes of the young due to HNF1A mutations. Diabetes Care 2010; 33: 1919–1924.

77. Pontoglio M, Prié D, Cheret C, et al. HNF1alpha controls renal glucose reabsorption in mouse and man. EMBO Rep 2000; 1: 359–365.

78. Odom DT. Control of pancreas and liver gene expression by HNF transcription factors. Science 2004; 303: 1378–1381.

79. Pearson ER, Boj SF, Steele AM, et al. Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. Plos Med [Internet]. 2007; 4: e118. Available at: http://www.plosmedicine.org/article/fetchSingleRepresentation.action?uri=info:doi/10.1371/journal.pmed.0040118.sg001

80. Colclough K, Bellanné-Chantelot C, Saint-Martin C, et al. Mutations in the genes encoding the transcription factors hepatocyte nuclear factor 1 alpha and 4 alpha in maturity-onset diabetes of the young and hyperinsulinemic hypoglycemia. Hum Mutat 2013; 34: 669–685.

81. McDonald TJ, McEneny J, Pearson ER, et al. Lipoprotein composition in HNF1A-MODY: differentiating between HNF1A-MODY and Type 2 diabetes. Clin Chim Acta 2012; 413(9–10): 927–932.

82. Shih DQ, Dansky HM, Fleisher M, et al. Genotype/phenotype relationships in HNF-4alpha/MODY1: haploinsufficiency is associated with reduced apolipoprotein (AII), apolipoprotein (CIII), lipoprotein(a), and triglyceride levels. Diabetes 2000; 49: 832–837.

83. Stoffel M, Duncan SA. The maturity-onset diabetes of the young (MODY1) transcription factor HNF4alpha regulates expression of genes required for glucose transport and metabolism. Proc Natl Acad Sci USA 1997; 94: 13209–13214.

84. Neve B, Fernandez-Zapico ME, Ashkenazi-Katalan V, et al. Role of transcription factor KLF11 and its diabetes-associated gene variants in pancreatic beta cell function. Proc Natl Acad Sci USA 2005; 102: 4807–4812.

85. Fernandez-Zapico ME, van Velkinburgh JC, Gutiérrez-Aguilar R, et al. MODY7 gene, KLF11, is a novel p300-dependent regulator of Pdx-1 (MODY4) transcription in pancreatic islet beta cells. J Biol Chem 2009; 284: 36482–36490.

86. Bonnefond A, Lomberk G, Buttar N, et al. Disruption of a novel Kruppel-like transcription factor p300-regulated pathway for insulin biosynthesis revealed by studies of the c.-331 INS mutation found in neonatal diabetes mellitus. J Biol Chem 2011; 286: 28414–28424.

87. Fukumoto H, Seino S, Imura H, et al. Sequence, tissue distribution, and chromosomal localization of mRNA encoding a human glucose transporter-like protein. Proc Natl Acad Sci USA 1988; 85: 5434–5438.

88. Orci L, Thorens B, Ravazzola M, et al. Localization of the pancreatic beta cell glucose transporter to specific plasma membrane domains. Science 1989; 245: 295–297.

89. Santer R, Schneppenheim R, Dombrowski A, et al. Mutations in GLUT2, the gene for the liver-type glucose transporter, in patients with Fanconi-Bickel syndrome. Nat Genet 1997; 17: 324–326.

90. Yoo H-W, Shin Y-L, Seo E-J, et al. Identification of a novel mutation in the GLUT2 gene in a patient with Fanconi-Bickel syndrome presenting with neonatal diabetes mellitus and galactosaemia. Eur J Pediatr 2002; 161: 351–353.

91. Mueckler M, Kruse M, Strube M, et al. A mutation in the Glut2 glucose transporter gene of a diabetic patient abolishes transport activity. J Biol Chem 1994; 269: 17765–17767.

92. Sakamoto O, Ogawa E, Ohura T, et al. Mutation analysis of the GLUT2 gene in patients with Fanconi-Bickel syndrome. Pediatr Res 2000; 48: 586–589.

93. Dunn-Meynell AA, Routh VH, Kang L, et al. Glucokinase is the likely mediator of glucosensing in both glucose-

excited and glucose-inhibited central neurons. *Diabetes* 2002; 51: 2056–2065.

94. Cuesta-Munoz AL, Tuomi T, Cobo-Vuilleumier N, *et al*. Clinical heterogeneity in monogenic diabetes caused by mutations in the glucokinase gene (GCK-MODY). *Diabetes Care* 2010; 33: 290–292.

95. Osbak KK, Colclough K, Saint-Martin C, *et al*. Update on mutations in glucokinase (GCK), which cause maturity-onset diabetes of the young, permanent neonatal diabetes, and hyperinsulinemic hypoglycemia. *Hum Mutat* 2009; 30: 1512–1526.

96. Labay V, Raz T, Baron D, *et al*. Mutations in SLC19A2 cause thiamine-responsive megaloblastic anaemia associated with diabetes mellitus and deafness. *Nat Genet* 1999; 22: 300–304.

97. Fleming JC, Tartaglini E, Steinkamp MP, *et al*. The gene mutated in thiamine-responsive anaemia with diabetes and deafness (TRMA) encodes a functional thiamine transporter. *Nat Genet* 1999; 22: 305–308.

98. Shaw-Smith C, Flanagan SE, Patch A-M, *et al*. Recessive SLC19A2 mutations are a cause of neonatal diabetes mellitus in thiamine-responsive megaloblastic anaemia. *Pediatr Diabetes* 2012; 13: 314–321.

99. Depeint F, Bruce WR, Shangari N, *et al*. Mitochondrial function and toxicity: role of the B vitamin family on mitochondrial energy metabolism. *Chem Biol Interact* 2006; 163: 94–112.

100. Baldwin SA, Yao SYM, Hyde RJ, *et al*. Functional characterization of novel human and mouse equilibrative nucleoside transporters (hENT3 and mENT3) located in intracellular membranes. *J Biol Chem* 2005; 280: 15880–15887.

101. Edghill EL, Hameed S, Verge CF, *et al*. Mutations in the SLC29A3 gene are not a common cause of isolated autoantibody negative type 1 diabetes. *JOP.* 2009; 10: 457–458.

102. Govindarajan R, Leung GPH, Zhou M, *et al*. Facilitated mitochondrial import of antiviral and anticancer nucleoside drugs by human equilibrative nucleoside transporter-3. *Am J Physiol Gastrointest Liver Physiol* 2009; 296: G910–G922.

103. Cliffe ST, Kramer JM, Hussain K, *et al*. SLC29A3 gene is mutated in pigmented hypertrichosis with insulin-dependent diabetes mellitus syndrome and interacts with the insulin signaling pathway. *Hum Mol Genet* 2009; 18: 2257–2265.

104. Inoue H, Tanizawa Y, Wasson J, *et al*. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome) - Nature Genetics. *Nat Genet* 1998; 20: 143–148.

105. Ishihara H, Takeda S, Tamura A, *et al*. Disruption of the WFS1 gene in mice causes progressive beta-cell loss and impaired stimulus-secretion coupling in insulin secretion. *Hum Mol Genet* 2004; 13: 1159–1170.

106. Riggs AC, Bernal-Mizrachi E, Ohsugi M, *et al*. Mice conditionally lacking the Wolfram gene in pancreatic islet beta cells exhibit diabetes as a result of enhanced endoplasmic reticulum stress and apoptosis. *Diabetologia* 2005; 48: 2313–2321.

107. Lemaire K, Schuit F. Integrating insulin secretion and ER stress in pancreatic β-cells. *Nat Cell Biol*. Nature Publishing Group; 2012; 14: 979–981.

108. Fonseca SG, Urano F, Weir GC, *et al*. Wolfram syndrome 1 and adenylyl cyclase 8 interact at the plasma membrane to regulate insulin production and secretion. *Nat Cell Biol*. Nature Publishing Group; 2012; 14: 1105–1112.

109. Rigoli L, Lombardo F, Di Bella C. Wolfram syndrome and WFS1 gene. *Clin Genet* 2010; 79: 103–117.

110. Bonnycastle LL, Chines PS, Hara T, *et al*. Autosomal dominant diabetes arising from a wolfram syndrome 1 mutation. *Diabetes* 2013; 62: 3943–3950.

111. Amr S, Heisey C, Zhang M, *et al*. A homozygous mutation in a novel zinc-finger protein, ERIS, is responsible for Wolfram syndrome 2. *Am J Hum Genet* 2007; 81: 673–683.

112. Delepine M, Nicolino M, Barrett T, *et al*. EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. *Nat Genet* 2000; 25: 406–409.

113. Senée V, Vattem KM, Delépine M, *et al*. Wolcott-Rallison Syndrome: clinical, genetic, and functional study of EIF2AK3 mutations and suggestion of genetic heterogeneity. *Diabetes* 2004; 53: 1876–1883.

114. Abdel-Salam GMH, Schaffer AE, Zaki MS, *et al*. A homozygous IER3IP1mutation causes microcephaly with simplified gyral pattern, epilepsy, and permanent neonatal diabetes syndrome (MEDS). *Am J Med Genet* 2012; 158A: 2788–2796.

115. Gupta S, McGrath B, Cavener DR. PERK (EIF2AK3) regulates proinsulin trafficking and quality control in the secretory pathway. *Diabetes* 2010; 59: 1937–1947.

116. Zhang W, Feng D, Li Y, *et al*. PERK EIF2AK3 control of pancreatic beta cell differentiation and proliferation is required for postnatal glucose homeostasis. *Cell Metab* 2006; 4: 491–497.

117. Tager H, Given B, Baldwin D, *et al*. A structurally abnormal insulin causing human diabetes. *Nature* 1979; 281: 122–125.

118. Haneda M, Polonsky KS, Bergenstal RM, *et al*. Familial hyperinsulinemia due to a structurally abnormal insulin. Definition of an emerging new clinical syndrome. *N Engl J Med* 1984; 310: 1288–1294.

119. Støy J, Edghill EL, Flanagan SE, *et al*. Insulin gene mutations as a cause of permanent neonatal diabetes. *Proc Natl Acad Sci USA* 2007; 104: 15040–15044.

120. Wang J, Takeuchi T, Tanaka S, *et al*. A mutation in the insulin 2 gene induces diabetes with severe pancreatic beta-cell dysfunction in the Mody mouse. *J Clin Invest* 1998; 103: 27–37.

121. Herbach N, Rathkolb B, Kemter E, et al. Dominant-negative effects of a novel mutated Ins2 allele causes early-onset diabetes and severe -cell loss in Munich Ins2C95S mutant mice. *Diabetes* 2007; 56: 1268–1276.

122. Garin I, Edghill EL, Akerman I, et al. Recessive mutations in the INS gene result in neonatal diabetes through reduced insulin biosynthesis. *Proc Natl Acad Sci USA* [Internet]. 2010; 107: 3105–3110. Available at: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=20133622&retmode=ref&cmd=prlinks

123. Edghill EL, Flanagan SE, Patch AM, et al. Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood. *Diabetes* 2008; 57: 1034–1042.

124. Borowiec M, Liew CW, Thompson R, et al. Mutations at the BLK locus linked to maturity onset diabetes of the young and beta-cell dysfunction. *Proc Natl Acad Sci USA* 2009; 106: 14460–14465.

125. Bonnefond A, Yengo L, Philippe J, et al. Reassessment of the putative role of BLK-p.A71T loss-of-function mutation in MODY and type 2 diabetes. *Diabetologia* 2012; 56: 492–496.

126. Gloyn AL, Pearson ER, Antcliff JF, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. *N Engl J Med* 2004; 350: 1838–1849.

127. Babenko AP, Polak M, Cavé H, et al. Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. *N Engl J Med* 2006; 355: 456–466.

128. Ræder H, Johansson S, Holm PI, et al. Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. *Nat Genet* 2005; 38: 54–62.

129. Johansson BB, Torsvik J, Bjørkhaug L, et al. Diabetes and pancreatic exocrine dysfunction due to mutations in the carboxyl ester lipase gene-maturity onset diabetes of the young (CEL-MODY): a protein misfolding disease. *J Biol Chem* 2011; 286: 34593–34605.

130. Houtkooper RH, Pirinen E, Auwerx J. Sirtuins as regulators of metabolism and healthspan. *Nat Rev Mol Cell Biol* 2012; 13: 225–238.

131. Beier UH, Wang L, Bhatti TR, et al. Sirtuin-1 targeting promotes Foxp3+ T-regulatory cell function and prolongs allograft survival. *Mol Cell Biol* 2011; 31: 1022–1029.

132. Cheng MH, Anderson MS. Monogenic autoimmunity. *Annu Rev Immunol* 2012; 30: 393–427.

133. Biason-Lauber A, Lang-Muritano M, Vaccaro T, et al. Loss of kinase activity in a patient with Wolcott-Rallison syndrome caused by a novel mutation in the EIF2AK3 gene. *Diabetes* 2002; 51: 2301–2305.

134. Fontenot JD, Gavin MA, Rudensky AY. Foxp3 programs the development and function of CD4+CD25+ regulatory T cells. *Nat Immunol* 2003; 4: 330–336.

135. Khattri R, Cox T, Yasayko S-A, et al. An essential role for Scurfin in CD4+CD25+ T regulatory cells. *Nat Immunol* 2003; 4: 337–342.

136. Biason-Lauber A, Böni-Schnetzler M, Hubbard BP, et al. Identification of a SIRT1 mutation in a family with Type 1 diabetes. *Cell Metab*. Elsevier Inc; 2013; 17: 448–455.

137. Houtkooper RH, Auwerx J. Exploring the therapeutic space around NAD+. *J Cell Biol* 2012; 199: 205–209.

138. Moynihan KA, Grimm AA, Plueger MM, et al. Increased dosage of mammalian Sir2 in pancreatic beta cells enhances glucose-stimulated insulin secretion in mice. *Cell Metab* 2005; 2: 105–117.

139. Pearson ER, Flechtner I, Njølstad PR, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med* 2006; 355: 467–477.

140. Mlynarski W, Tarasov AI, Gach A, et al. Sulfonylurea improves CNS function in a case of intermediate DEND syndrome caused by a mutation in KCNJ11. *Nat Clin Pract Neurol.* 2007; 3: 640–645.

141. Riveline J-P, Rousseau E, Reznik Y, et al. Clinical and metabolic features of adult-onset diabetes caused by ABCC8 mutations. *Diabetes Care* 2012; 35: 248–251.

142. Pearson ER, Starkey BJ, Powell RJ, et al. Genetic cause of hyperglycaemia and response to treatment in diabetes. *Lancet* 2003; 362: 1275–1281.

143. Doliba NM, Fenner D, Zelent B, et al. Repair of diverse diabetic defects of β-cells in man and mouse by pharmacological glucokinase activation. *Diabetes Obes Metab* 2012; 14(Suppl 3): 109–119.

144. Meininger GE, Scott R, Alba M, et al. Effects of MK-0941, a novel glucokinase activator, on glycemic control in insulin-treated patients with type 2 diabetes. *Diabetes Care* 2011; 34: 2560–2566.

145. Amr S. Identification and Characterization of a Second Wolfram Syndrome Gene. Virginia Commonwealth University Richmond, Virginia, 2010.

146. Finnish-German APECED Consortium. An autoimmune disease, APECED, caused by mutations in a novel gene featuring two PHD-type zinc-finger domains. *Nat Genet* 1997; 17: 399–403.