



**HAL**  
open science

## Monogenic diabetes

Amélie Bonnefond, Ranjit Unnikrishnan, Alessandro Doria, Martine Vaxillaire, Rohit Kulkarni, Viswanathan Mohan, Vincenzo Trischitta, Philippe Froguel

► **To cite this version:**

Amélie Bonnefond, Ranjit Unnikrishnan, Alessandro Doria, Martine Vaxillaire, Rohit Kulkarni, et al.. Monogenic diabetes. Nature reviews Disease primers, 2023, 9 (1), pp.12. 10.1038/s41572-023-00421-w . inserm-04303664

**HAL Id: inserm-04303664**

**<https://inserm.hal.science/inserm-04303664>**

Submitted on 23 Nov 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

# 1 Monogenic diabetes

---

2  
3 Amélie Bonnefond<sup>1,2,3</sup>, Ranjit Unnikrishnan<sup>4</sup>, Alessandro Doria<sup>5,6</sup>, Martine  
4 Vaxillaire<sup>1,2</sup>, Rohit N. Kulkarni<sup>5,6</sup>, Viswanathan Mohan<sup>4</sup>, Vincenzo Trischitta<sup>7,8</sup>,  
5 Philippe Froguel<sup>1,2,3</sup>

6  
7 <sup>1</sup>Inserm UMR1283, CNRS UMR8199, European Genomic Institute for Diabetes (EGID), Institut  
8 Pasteur de Lille, Lille University Hospital, Lille, France

9 <sup>2</sup>Université de Lille, Lille, France

10 <sup>3</sup>Department of Metabolism, Imperial College London, London, UK

11 <sup>4</sup>Department of Diabetology, Madras Diabetes Research Foundation, Indian Council of Medical  
12 Research Centre for Advanced Research on Diabetes and Dr Mohan's Diabetes Specialities Centre,  
13 Chennai, India

14 <sup>5</sup>Research Division, Joslin Diabetes Center, Boston, MA, USA

15 <sup>6</sup>Department of Medicine, Harvard Medical School, Boston, MA, USA

16 <sup>7</sup>Research Unit of Diabetes and Endocrine Diseases, Fondazione IRCCS Casa Sollievo Della  
17 Sofferenza, San Giovanni Rotondo, FG, Italy

18 <sup>8</sup>Department of Experimental Medicine, Sapienza University, Rome, Italy

19  
20  
21  
22 Corresponding authors: Philippe Froguel ([philippe.froguel@cncrs.fr](mailto:philippe.froguel@cncrs.fr)), Amélie Bonnefond  
23 ([amelie.bonnefond@cncrs.fr](mailto:amelie.bonnefond@cncrs.fr))

24  
25  
26

27 **Abstract**

28

29 Monogenic diabetes includes several clinical conditions generally characterized by  
30 early-onset diabetes, like neonatal diabetes, maturity-onset diabetes of the young  
31 (MODY) and diabetes-associated syndromes. However, patients with apparent type  
32 2 diabetes may actually have monogenic diabetes. Indeed, the same monogenic  
33 diabetes gene depending of the functional impact of its variants can contribute to  
34 different forms of diabetes with early or late onset. Same spectrum of diabetes  
35 phenotypes can also be observed for a single specific pathogenic mutation shared by  
36 different carriers, even of the same family. Monogenic diabetes is mostly due to  
37 impaired function or development of pancreatic islets with defective insulin secretion  
38 in absence of obesity. The most prevalent monogenic diabetes form is MODY that  
39 may account for 0.5–5% of patients diagnosed with non-autoimmune diabetes, but is  
40 probably underdiagnosed due to insufficient genetic testing. Most cases with  
41 neonatal diabetes or MODY have an autosomal dominant form of diabetes. More  
42 than 40 monogenic forms of diabetes have been identified so far, the most prevalent  
43 being deficiencies for *GCK* (glucokinase) and *HNF1A* (hepatocyte nuclear factor 1  
44 alpha). Some of these genes (including *GCK* and *HNF1A*) are actionable, namely  
45 carriers of a pathogenic mutation should benefit from precision medicine. This  
46 precision medicine includes specific treatments of hyperglycemia, the monitoring of  
47 associated extrapancreatic phenotypes, and/or the follow up of clinical trajectories  
48 especially during pregnancy, which increases patients' quality of life. Next-generation  
49 sequencing has made affordable and cost efficient the genetic diagnosis of  
50 monogenic diabetes that enables effective genomic diabetic medicine.

## 51 **Introduction**

52 Monogenic diabetes is a heterogeneous group of disorders that include various  
53 clinical conditions associated with hyperglycemia, which are mostly due to impaired  
54 function or altered development of islets of Langerhans (including pancreatic beta  
55 cells that secrete insulin) and are linked to a single, pathogenic, genetic event.  
56 Monogenic diabetes comprises a large spectrum of clinical conditions, such as  
57 neonatal diabetes (a very rare form of monogenic diabetes at 1 in 90,000 live births  
58 that occurs within the first 6 months of life), maturity-onset diabetes of the young  
59 (MODY), an early-onset diabetes occurring during childhood, adolescence or young  
60 adulthood (age of onset under 25 years according to the original definition) with  
61 strong family history, and diabetes-associated syndromes (e.g. Wolfram syndrome,  
62 Wolcott-Rallison syndrome and Mitchell-Riley Syndrome), the common denominator  
63 of which is early-onset diabetes. Diabetes-associated syndromes are multisystem  
64 diseases that cause neonatal diabetes or diabetes with a later onset<sup>1</sup>. Diabetes may  
65 be not recognized as a first manifestation of these syndromes<sup>1</sup>.

66 The first gene identified to cause monogenic diabetes (*GCK*, encoding glucokinase, a  
67 glucose sensor for the pancreas) was discovered in 1992<sup>2,3</sup>. Since then, several  
68 dozens of genes harboring rare, coding or even non-coding mutations causing  
69 monogenic diabetes have been identified, following various modes of inheritance  
70 (Table 1). Some of these genes are medically actionable, which means that  
71 pathogenic mutations in these genes are related to health conditions with known  
72 medical recommendations to act upon with the carriers (e.g. follow-up of clinical  
73 trajectories, treatment of hyperglycemia). This advocates for an enhanced screening  
74 for monogenic diabetes worldwide.

75 Monogenic diabetes phenotypes overlap with both type 1 and 2 diabetes mellitus,  
76 and same genes can confer risk to a common form of diabetes or can cause  
77 monogenic diabetes in another inherited context. Type 1 diabetes is due to  
78 autoimmune beta-cell destruction, usually leading to absolute insulin deficiency, and  
79 results from polygenic predisposition<sup>4</sup>. Mutations in several genes linked to  
80 autoimmune diabetes have been found to cause monogenic diabetes (i.e. apparent  
81 type 1 diabetes), mostly with a recessive pattern of inheritance (Figure 1). On the  
82 other hand, type 2 diabetes is due to a progressive loss of adequate beta-cell insulin  
83 secretion (i.e. mostly seen in adults) frequently on the background of insulin

84 resistance, and results from polygenic predisposition like type 1 diabetes<sup>4</sup>.  
85 Nonetheless, the dominant deficiency of many genes causing monogenic diabetes  
86 has been found in patients with apparent type 2 diabetes, namely with age of onset  
87 above 40 years<sup>5</sup>. In fact, the diagnosis of type 2 diabetes can be referred as a  
88 diagnosis of exclusion and therefore type 2 diabetes is very heterogeneous.  
89 Research on monogenic diabetes has truly revolutionized our understanding of the  
90 pathophysiology of diabetes and the genetics of common diseases<sup>6</sup>. Furthermore,  
91 monogenic diabetes has provided one of the best examples of the vision of precision  
92 medicine so far. This Primer focuses on monogenic forms of diabetes primarily due  
93 to impaired function or development of pancreatic islets. It does not address potential  
94 diabetes due to monogenic forms of insulin resistance such as lipodystrophy.

## 95 **Epidemiology**

96 MODY may account for about 2–5% of patients diagnosed with non-autoimmune  
97 diabetes (as estimated in European patient cohorts, mainly from childhood diabetes  
98 registries), with a global prevalence of ~100 per million in white European  
99 populations<sup>7</sup>. However, the true prevalence of monogenic diabetes is still unknown. It  
100 may be largely underestimated in many countries due to poor access to genetic  
101 testing, no access to this diagnostic procedure or lack of awareness. In fact, genetic  
102 testing is not widely available even in most affluent countries: for instance, it was  
103 estimated that >80% of MODY cases in the United Kingdom (UK) may go  
104 undiagnosed<sup>8</sup>. Hopefully, recent access in next-generation sequencing facilities has  
105 improved MODY discovery rates at least in young patients with typical MODY clinical  
106 features<sup>9</sup>. In the UK, the apparent prevalence of MODY is four times higher in South  
107 West of England, where genetic testing is more widely implemented than in other UK  
108 regions such as Northern Ireland where it is not the case<sup>8</sup>. It is unlikely that ethnic  
109 differences explain these differences, but rather lower doctors' awareness of MODY  
110 in some UK regions. In the general population from the United States, 3 in 200  
111 individuals from the general population have been shown to carry a variant that has  
112 been reported previously to cause MODY although the majority of them were not  
113 known to have diabetes yet<sup>10</sup>.

114 A recent study in different countries around the Mediterranean Sea has screened for  
115 pathogenic mutations in genes linked with monogenic diabetes in patients with an

116 early age of diagnosis: in the entire study population, a genetic diagnosis of  
117 monogenic diabetes was established in 18% of the participants. In most countries,  
118 the pathogenic mutations were mostly harboured by *GCK* (7%) and *HNF1A* (5%).  
119 However, diagnosis rates differed widely by country of inclusion, with the highest  
120 rates observed in Greece (40%), Algeria (30%) and France (28%), and the lowest in  
121 Tunisia (8%) and Turkey (12%) while no variant of interest were found in the  
122 Moroccan patients<sup>11</sup>. Differences in ethnicity, but also in patients' ascertainment, may  
123 explain this variability, knowing that the inclusion criterion was an age below 40 years  
124 at diabetes diagnosis (without insulin treatment and obesity at diagnosis, and with no  
125 autoantibodies to at least three islet cell antibody tests), or self-reported family history  
126 of diabetes consistent with autosomal dominant inheritance.

127 Recently, a comprehensive genetic investigation in South India revealed a  
128 monogenic etiology in 15% of the cases: however, in contrast to European  
129 populations, the distribution of MODY genes was very different with a lack of  
130 pathogenic mutations in *GCK*<sup>12</sup>.

131 Although the true prevalence of monogenic diabetes is still unclear in adult patients  
132 with history of early-onset diabetes and absence of obesity, its putative occurrence  
133 among patients with typical type 2 diabetes (*i.e.* with age of onset > 40 years and  
134 overweight or obesity) has been largely ignored until recently. In a recent study, 6%  
135 of patients of European origin with apparent type 2 diabetes followed by a French  
136 diabetes clinic were found to carry pathogenic mutations in genes linked to  
137 monogenic diabetes<sup>5</sup>. These patients with MODY mutations were impossible to  
138 identify using clinical criteria as they did not differ from other patients with T2D<sup>5</sup>.  
139 Furthermore, among them, 2% carried pathogenic mutations in actionable MODY  
140 genes (*i.e.* their discovery should lead to an attempt to change diabetes care)<sup>5</sup>. In  
141 addition, in an Italian study, ~3% of adult patients with early-onset type 2 diabetes  
142 carried pathogenic mutations in MODY genes<sup>13</sup>. This was in line with a recent study  
143 done in US children with type 2 diabetes<sup>14</sup>. The main conclusion is that hidden  
144 MODY exists among patients with apparent type 2 diabetes and only genetic  
145 diagnosis can recognize them, and when possible can enable precision medicine.

## 146 **Mechanisms/pathophysiology**

147

148 Pancreatic islets, or islets of Langerhans, are islands of endocrine cells scattered  
149 throughout the pancreas<sup>15</sup>. Human pancreatic islets include 60% beta cells that  
150 produce insulin in response to a glucose challenge, 30% alpha cells that produce  
151 glucagon, with the remainder 10% made up of delta cells (somatostatin-producing),  
152 PP cells (pancreatic polypeptide-producing), and epsilon cells (ghrelin-producing)<sup>15</sup>.  
153 Endocrine cells are randomly distributed in human islets<sup>15</sup>. In pancreatic beta cells,  
154 insulin is packaged into secretory granules and released in response to high glucose  
155 (and other nutrient) levels, neurotransmitters (that are released in response to food)  
156 and incretin hormones<sup>15</sup>.

157 Many genes causing monogenic diabetes have been found via multiple genetic  
158 strategies and technologies that have evolved according to the state-of-the-art in  
159 genetics (Table 1; Box 1). MODY inheritance mostly follows an autosomal dominant  
160 mode whereas neonatal diabetes and diabetes-associated syndromes can be  
161 dominant or recessive disorders. Linkage analyses (mostly using microsatellites),  
162 followed by Sanger sequencing of candidate genes in diabetes-associated linkage  
163 genomic peaks were very successful in the discovery of various types of MODY (e.g.  
164 dominant *GCK*-, *HNF1A*-, *HNF4A*- or *CEL*-diabetes)<sup>2,3,16-18</sup>. In suspected recessive  
165 forms of monogenic diabetes, linkage analyses were mostly based on the discovery  
166 of runs of homozygosity (ROH), which are genomic regions where identical  
167 haplotypes are inherited from each (consanguineous) parent. Surprisingly perhaps,  
168 single candidate gene strategy (using Sanger sequencing), which requires a prior  
169 functional hypothesis that particular genes of interest contain pathogenic mutations  
170 that may cause monogenic diabetes, was also very successful. More recently, the  
171 advent of next-generation sequencing technology (including whole-exome and  
172 whole-genome sequencing) has enabled the discovery of new monogenic diabetes  
173 genes. It is striking that the vast majority of monogenic diabetes genes are well  
174 expressed in pancreatic islets and beta cells, and play an important role in the  
175 development and/or function of pancreatic beta cells, notably insulin secretion (Table  
176 2; Figure 2). In fact, all compartments of the pancreatic beta cells can be impacted in  
177 monogenic diabetes. We are showing below the main genes causing monogenic  
178 diabetes compartment by compartment.

## 179 **Nucleus**

180 A plethora of genes whose mutations cause monogenic diabetes encode  
181 transcription factors that are highly expressed in pancreatic islets and beta cells.  
182 Among these, the most frequently mutated is *HNF1A*, whose deficiency leads to  
183 MODY or even to adult-onset non-autoimmune diabetes. *HNF1A* is mainly expressed  
184 in pancreatic beta cells and in hepatocytes. Pathogenic mutations in this gene lead to  
185 impaired transactivation function, protein expression, DNA binding, and/or subcellular  
186 (nuclear) localization<sup>19</sup>. *HNF1A* is an important transcription factor for the  
187 maintenance of beta-cell function, as well as for the development and maturation of  
188 pancreatic islets<sup>20</sup>. *HNF1A* directly binds to the promoter region of the insulin gene  
189 *INS*, positively regulating the transactivation of the latter<sup>20</sup>. Importantly, the bi-allelic  
190 deficiency of *PDX1* or *PTF1A*, and the dominant deficiency of *GATA6* cause neonatal  
191 diabetes linked with pancreatic agenesis, along with a spectrum of extrapancreatic  
192 features. However, penetrance can be incomplete<sup>21</sup>. *PDX1*, *PTF1A* and *GATA6* are  
193 transcription factors that play a key role in pancreatic development and pancreatic  
194 cell fate specification<sup>22–24</sup>. Notably, *PTF1A* does not seem to be expressed in adult  
195 and fetal pancreatic beta cells; however, it is expressed in the very early stages of  
196 pancreatic development, being required for pancreatic specification and exocrine  
197 *versus* endocrine fate decision<sup>23</sup>.

## 198 **Endoplasmic reticulum**

199 Several monogenic diabetes genes (*i.e.* *WFS1*, *CISD2*, *MIA3* [previously called  
200 *TANGO1*], *MANF*, *YIPF5*, *DNAJC3*, *EIF2AK3*, *EIF2B1*, *PPP1R15B* and *IER3IP1*;  
201 **Table 1**) encode proteins that play a key role in endoplasmic reticulum, in particular  
202 in the maintenance of endoplasmic calcium homeostasis (**Figure 2**). Strikingly, all  
203 these genes are ubiquitously expressed and their bi-allelic deficiency systematically  
204 causes severe early-onset diabetes associated with extrapancreatic features  
205 including deafness, hearing loss, renal tract abnormalities, short stature, hepatic  
206 dysfunction, microcephaly, epilepsy and other neurodevelopmental disorders. It has  
207 been shown that the deficiency of these genes results in endoplasmic reticulum  
208 stress indicative of increased unfolded protein response (UPR) signaling, leading to  
209 insulin secretion failure or even apoptosis of pancreatic beta cells<sup>25,26</sup>. Recent  
210 studies (focused on the deficiency of *YIPF5* and *MIA3*) have also suggested that  
211 endoplasmic reticulum stress may be caused by impaired transport from the  
212 endoplasmic reticulum through the Golgi apparatus<sup>26</sup>.



## 213 **Plasma membrane**

214 Several monogenic diabetes genes encode channel subunits (*ABCC8*, *KCNJ11*, and  
215 *KCNK16*) or transporters (*SLC2A2*, *SLC19A2*) that are embedded in the plasma  
216 membrane (Figure 2). *ABCC8* and *KCNJ11* encode the subunits of an ATP-sensitive  
217 potassium channel that are highly expressed in the pancreatic islets and beta cells,  
218 although their expression is also high in other organs and tissues such as the  
219 cerebellum and pituitary (Table 2). The ATP-sensitive potassium channel encoded by  
220 *KCNJ11* and *ABCC8* plays a key role in insulin granule exocytosis from pancreatic  
221 beta cells. Indeed, an increase in glucose metabolism leads to an increase in  
222 intracellular ATP/ADP ratio due to enhanced glycolysis and Krebs cycle activity,  
223 which in turn results in closure of the ATP-sensitive potassium channel and  
224 membrane depolarization<sup>7</sup>. This activates voltage-dependent calcium channels  
225 leading to a rise in intracellular calcium, which stimulates insulin release. Activating  
226 (or gain-of-function) homozygous or heterozygous mutations in *ABCC8* or *KCNJ11*  
227 lead to neonatal diabetes, MODY or even late-onset diabetes, since the mutated  
228 ATP-sensitive potassium channel remains open despite high glucose levels, thereby  
229 leading to inhibition of insulin secretion in mutation carriers<sup>7</sup>. An activating mutation in  
230 *KCNK16* encoding another potassium channel has recently been suggested to cause  
231 MODY<sup>27</sup>. Contrary to *ABCC8* and *KCNJ11*, the expression of this gene is specific to  
232 pancreatic beta cells. A pathogenic mutation in this gene was found to cause a  
233 profound increase in potassium current, altering beta-cell calcium flux, and  
234 decreasing glucose-stimulated insulin secretion<sup>27</sup>. Very rare forms of monogenic  
235 diabetes were attributed to pathogenic mutations in *SLC2A2* and *SLC19A2* encoding  
236 glucose and thiamine transporters<sup>28,29</sup>. Recessive *SLC2A2*- and *SLC19A2*-diabetes  
237 (known as Fanconi-Bickel syndrome and Rogers syndrome, respectively) lead to  
238 severe extrapancreatic features including failure to thrive, hepatomegaly secondary  
239 to glycogen accumulation, galactose intolerance, proximal tubular nephropathy,  
240 phosphaturia, aminoaciduria and hypophosphatemia for *SLC2A2* deficiency, and  
241 megaloblastic anaemia, and sensorineural deafness for *SLC19A2* deficiency<sup>28,29</sup>.  
242 Isolated early-onset diabetes was also reported in dominant-*SLC19A2* deficiency<sup>30</sup>.

## 243 **Mitochondria**

244 The mitochondrial m.3243A>G mutation is one of the most frequent point mutations  
245 of the mitochondrial DNA<sup>31</sup>. This mutation causes a syndrome known as MELAS for

246 Mitochondrial Encephalopathy with Lactic Acidosis and Stroke-like episodes, or  
247 MIDD for Maternally-Inherited Diabetes and Deafness. This mutation can actually  
248 lead to a broad spectrum of phenotypes more or less severe, including hearing loss,  
249 diabetes, seizure, stroke-like episodes, muscle weakness and heart disease<sup>31</sup>. The  
250 molecular mechanisms underlying m.3243A>G-associated phenotypes may be due  
251 to a complex interplay between m.3243A>G mutant load, mitochondrial DNA copy  
252 number, nuclear genetic factors, epigenetics, and environmental exposures<sup>32</sup>.

## 253 **[H2] Cytosol**

254 In the cytosol, the most commonly mutated gene in dominant monogenic diabetes is  
255 *GCK* encoding glucokinase, which is the predominant glucose-phosphorylating  
256 enzyme in pancreatic beta cells and in hepatocytes<sup>33</sup>. *GCK* has a relatively low  
257 affinity for glucose and displays positive cooperativity for this substrate, despite the  
258 fact that it is a monomeric enzyme<sup>33</sup>. Functional analyses of the kinetic properties of  
259 the *GCK* mutants found in MODY have shown that the relative enzymatic activity was  
260 impaired, leading to a decrease in the glycolytic flux in pancreatic beta cells<sup>33</sup>. This  
261 translates *in vivo* as a glucose-sensing defect and a right shift in the dose response  
262 curve of glucose-induced insulin secretion<sup>33</sup>. *GCK* mutations are pathogenic through  
263 different mechanisms including impaired enzymatic activity, altered protein stability  
264 and/or increased interaction with the glucokinase regulatory protein<sup>34,35</sup>. In the liver, a  
265 decrease in glycogen synthesis and storage, and an increase in gluconeogenesis  
266 after standard meals were reported in patients deficient for *GCK*; contributing to  
267 postprandial hyperglycemia<sup>33</sup>. Pathogenic homozygous mutations in *GCK* also cause  
268 neonatal diabetes<sup>36</sup>.

## 269 **Insulin granules**

270 Dominant or bi-allelic pathogenic mutations in *INS* were found to cause “neonatal”  
271 diabetes, (usually in infancy rather than in the first months of life), MODY or even  
272 late-onset diabetes. Most of the pathogenic, coding *INS* mutations described so far  
273 have been shown to cause severe proinsulin misfolding, endoplasmic reticulum  
274 retention, increased UPR signaling and pancreatic beta-cell apoptosis<sup>37</sup>.  
275 Homozygous, pathogenic, non-coding *INS* mutations were reported in patients with  
276 neonatal diabetes<sup>38,39</sup>. These mutations decreased insulin biosynthesis through  
277 distinct mechanisms, including *INS* gene deletion, severe dysfunction of  
278 transcriptional activity due to mutations located in the *INS* promoter, lack of the

279 translation initiation signal, and altered mRNA stability because of the disruption of a  
280 polyadenylation signal<sup>38,39</sup>.

## 281 **Exocrine pancreas**

282 A dominantly inherited monogenic form of diabetes is caused by mutations in *CEL*  
283 encoding the carboxyl ester lipase, which is expressed by pancreatic acinar cells<sup>18,40</sup>.  
284 Patients with a pathogenic *CEL* mutation develop childhood-onset exocrine pancreas  
285 dysfunction followed by diabetes during adulthood. Clinical investigations have  
286 reported that pre-diabetic mutation carriers exhibit significantly reduced first-phase  
287 insulin response with early  $\beta$ -cell dysfunction prior to development of diabetes<sup>18</sup>.  
288 However, it is unclear how *CEL* mutations cause diabetes. Studies with *in vitro* and *in*  
289 *vivo* human pluripotent stem cell-based disease models and pancreatic cell lines  
290 have demonstrated co-localization of insulin and CEL protein in mutant beta-like  
291 cells, which supports a crosstalk between exocrine and endocrine compartments<sup>41</sup>.  
292 The presence of the mutant CEL in insulin-expressing cells from patients with this  
293 form of diabetes provides further evidence that an abnormal relationship between  
294 pancreatic exocrine and endocrine cells likely underlies the beta-cell dysfunction in  
295 this form of diabetes<sup>41</sup>. Specifically, the mutant CEL protein is taken up and remained  
296 insoluble in beta cells with consequent development of endoplasmic reticulum stress  
297 that contributes to defects in secretory function and proliferation<sup>40,41</sup>. Whether CEL is  
298 taken up by beta cells through a paracrine or endocrine pathway within the pancreas  
299 and if circulating CEL in human plasma is preferentially taken up by beta cells  
300 compared to other cell types requires further investigation.

## 301 **Diagnosis, screening and prevention**

### 302 **Clinical presentation**

303 According to its original definition, MODY is inherited following an autosomal  
304 dominant pattern (*i.e.* 50% of offspring are carriers of heterozygous, pathogenic DNA  
305 mutations and are in theory affected) and occurs in lean individuals before the age of  
306 25 years who do not always need insulin therapy<sup>42</sup>. Hyperglycemia and related  
307 symptoms can be mild especially at disease onset and can deteriorate with  
308 increasing disease duration, depending on the gene and the nature of the mutations  
309 causing hyperglycemia<sup>7,43</sup>.

310 In practice, MODY should be strongly suspected in children and young adults with  
311 mild hyperglycemia at onset in the absence of typical features of both type 1 and type  
312 2 diabetes. The former includes the coexistence of autoimmunity and the need of  
313 insulin treatment at diagnosis (possibly presenting with ketoacidosis), while obesity  
314 and other features related to insulin resistance including acanthosis nigricans, and  
315 sometimes early-onset atherogenic dyslipidemia and essential hypertension are  
316 among the latter<sup>6,7,33,44</sup>. Finally, although the possibility of a *de novo* mutation should  
317 always be considered, a strong family history of diabetes reinforces the suspicion of  
318 MODY. While these criteria are valid, they are far from exhaustive. Indeed, several  
319 reports have now made it clear that the picture is much more heterogeneous, with  
320 MODY also occurring in patients (both children and adults) with excess adiposity and  
321 other features of insulin resistance and/or in middle-aged individuals<sup>7,45</sup>. As a  
322 consequence, the “old definition”<sup>42</sup> misses at least a quarter of patients with MODY  
323 and therefore should be abandoned<sup>8,46,47</sup>.

324 The marked heterogeneity in the clinical presentation of MODY is largely the  
325 consequence of the multiple genetic etiologies of this form of diabetes. However,  
326 pathogenic, heterozygous mutations in several genes, including *ABCC8*, *KCNJ11*,  
327 *INS*, *HNF1B*, *GATA4* and *GATA6*, are involved in MODY but also in severe cases of  
328 neonatal diabetes (Table 1); at the same time, rare and frequent variants in some of  
329 these genes also contribute to shaping the risk for common multifactorial type 2  
330 diabetes. Thus, the different forms non-autoimmune diabetes belongs to a  
331 continuous spectrum of disease rather than being distinct entities<sup>6,48</sup>. In fact, it has  
332 been shown that, even in the same family, the same heterozygous mutation can lead  
333 to neonatal diabetes, MODY, late-onset non-autoimmune diabetes or even normal  
334 glucose tolerance at an advanced age<sup>21,49–51</sup>, an observation that clearly highlights  
335 the incomplete penetrance of pathogenic mutations in monogenic diabetes. Notably,  
336 a high polygenic risk score, summarizing the effect of several hundred genetic  
337 variants associated with type 2 diabetes, was found to be a significant determinant of  
338 an earlier age of diabetes diagnosis in patients with a pathogenic mutation of  
339 *HNF1A*<sup>51</sup>. Therefore, the polygenic background (as captured by a polygenic risk  
340 score for common type 2 diabetes) could be one of the causes of this variable  
341 penetrance of rare, pathogenic mutations in monogenic diabetes.

342 Furthermore, very recently, it was reported that approximately 20% of the pathogenic  
343 mutations found in patients indicated as having MODY were actually harbored by

344 genes or loci typically associated with syndromic presentations; these particularly  
345 include the (i) maternally inherited mitochondrial m.3243A>G variant, (ii)  
346 heterozygous, pathogenic mutations in *HNF1B* and (iii) bi-allelic, pathogenic  
347 mutations in *WFS1*<sup>44,52,53</sup>. These observations challenge the concept of MODY and  
348 diabetes-associated syndromes being distinct clinical entities. It is now clear that  
349 MODY (especially due to *WFS1*, *SLC19A2* and *GCK* deficits) without any atypical  
350 presentation can be recessively inherited (*i.e.* with homozygous mutations or  
351 compound heterozygous pathogenic variants), especially but not exclusively in  
352 population with high rates of consanguinity<sup>54</sup>. As mentioned above, these new  
353 findings are likely the consequences of the variable penetrance and expressivity of  
354 mutations in genes causing monogenic diabetes and further support the existence of  
355 a continuous spectrum of disease, with very blurred boundaries between each of the  
356 different diabetes subtypes thus far described as distinct entities<sup>45,55</sup>.  
357 All this indicates the need to reconsider the current classification of monogenic  
358 diabetes which appears to be too rigid and inconsistent with both clinical and  
359 molecular evidence. A practical proposal is to group the various forms of diabetes  
360 due to genetic mutations under the deliberately generic umbrella of “monogenic  
361 diabetes”, to which the following notations are added consistently with each specific  
362 case: (i) the disease-causing gene; (ii) the type of hereditary transmission (*e.g.*  
363 dominant, recessive) and (iii) the peculiar features of clinical presentation (*e.g.*  
364 neonatal onset of hyperglycemia, presence of syndromic features). For example,  
365 MODY due to pathogenic, heterozygous mutations in *GCK* would be “dominant *GCK*-  
366 diabetes” while neonatal hyperglycemia due to pathogenic, homozygous mutations in  
367 *GCK* would be “recessive, neonatal, *GCK*-diabetes”. As an additional example,  
368 diabetes due to pathogenic, heterozygous mutations in *HNF1B* would be defined as  
369 “dominant *HNF1B*-diabetes” or “dominant, syndromic *HNF1B*-diabetes” depending  
370 on the absence or presence of renal, urinary, genital or gonadal abnormalities.

### 371 **Identification of patients for genetic screening**

372 The traditional approach to identifying candidates for MODY genetic screening  
373 utilized the original clinical criteria for diagnosis<sup>42</sup>. However, these criteria are neither  
374 sensitive nor specific enough for identifying the majority of individuals with  
375 monogenic forms of diabetes. Large cases series have shown that in some  
376 populations pathogenic mutations are found in only 10% of all individuals suspected

377 to have MODY by clinical criteria (e.g. early-onset non-autoimmune diabetes with  
378 normal weight)<sup>12,56</sup>. Subsequently, attempts were made to further refine the diagnosis  
379 of MODY using a risk calculator, mainly developed in populations of European origin.  
380 This MODY risk calculator, utilizing variables such as current age, age at diagnosis,  
381 gender, ongoing treatment, duration of insulin treatment, family history of diabetes,  
382 body mass index, and glycated hemoglobin A1c (HbA1c) levels<sup>57</sup>, tend to perform  
383 well in distinguishing individuals with MODY from those with type 1 diabetes.  
384 However, they are less useful in differentiating MODY from type 2 diabetes,  
385 particularly in populations (e.g. South Asian) with a high prevalence of youth-onset  
386 type 2 diabetes<sup>58</sup>.

387 Considering the limitations of available diagnostic criteria and risk scores, and the  
388 fact that universal genetic screening of all youth-onset diabetes is unfortunately  
389 impractical in large parts of the world, the identification of candidates for screening is  
390 best achieved using a combination of phenotypic and biochemical variables. There is  
391 some evidence, albeit based on models with inherent assumptions, that a phenotype-  
392 based screening strategy for monogenic diabetes is cost-effective<sup>59</sup>; however, this  
393 needs confirmation with larger studies.

#### 394 **Patient age**

395 Diabetes diagnosed within the first 6 months of life is most likely due to monogenic  
396 defects, as autoimmune type 1 diabetes is rare at this age<sup>60</sup>. More than 50% of  
397 children with neonatal diabetes have been found to carry pathogenic mutations in  
398 *ABCC8*, *KCNJ11* or *INS*<sup>60,61</sup>. Diabetes due to these mutations is mostly diagnosed  
399 within the first 6 months, although it can occasionally present beyond 6 months<sup>60</sup>.  
400 Diabetes due to pathogenic mutations in *HNF1A* and *HNF4A* tend to present with  
401 hyperglycemia before the age of 25 years, although the penetrance of disease by this  
402 age is only around 60%<sup>62</sup>. Individuals with dominant *GCK*-diabetes may be  
403 diagnosed at any age, and depending on this, may be treated as type 1 diabetes,  
404 type 2 diabetes or even gestational diabetes. The phenotype of nonprogressive  
405 hyperglycemia in these cases only becomes apparent with the passage of time. They  
406 are not at risk of developing chronic complications of diabetes<sup>43</sup>.

#### 407 **Family history of diabetes**

408 According to the originally described clinical criteria, MODY is characterised by  
409 severe young-onset diabetes and a positive family history of young-onset diabetes in

410 several consecutive generations. However, the majority of patients with type 2  
411 diabetes will also report a positive family history of diabetes in either or both  
412 parents<sup>13</sup>. Even so, a family history of non-insulin treated young onset diabetes in an  
413 individual diagnosed with type 1 diabetes should raise the suspicion of monogenic  
414 diabetes.

#### 415 **Obesity and markers of insulin resistance**

416 Presence of overweight or obesity, and markers of insulin resistance (e.g. acanthosis  
417 nigricans and skin tags) would suggest a diagnosis of type 2 diabetes rather than  
418 monogenic diabetes in such cases. It should, however, be noted that type 2 diabetes  
419 can occur even in the absence of obesity or clinically evident insulin resistance,  
420 particularly in ethnic groups such as South Asians.

#### 421 **Presence of extrapancreatic features**

422 Presence of multi-organ involvement (e.g. renal cysts in dominant *HNF1B*-diabetes;  
423 hepatic, renal and skeletal abnormalities in Wolcott-Rallison syndrome; deafness,  
424 optic atrophy, diabetes insipidus and genitourinary abnormalities in Wolfram  
425 syndrome; deafness and megaloblastic anemia in Rogers' syndrome) should prompt  
426 genetic testing for elucidation of the molecular defect. Most of these syndromic forms  
427 of diabetes are due to bi-allelic, pathogenic mutations (in *EIF2AK3* [Wolcott-Rallison  
428 syndrome], *WFS1/CISD2* [Wolfram syndrome] and *SLC19A2* [Rogers' syndrome]  
429 genes, respectively) but also heterozygous, pathogenic mutations in *HNF1B* (Table  
430 1). As diabetes may be the first manifestation of many of these syndromes and may  
431 remain the only manifestation for a considerable period of time<sup>53</sup>, it is important to  
432 look for mutations in syndromic diabetes genes in all patients with suspected  
433 monogenic diabetes<sup>44</sup>. On the contrary, extra pancreatic features such as kidney  
434 failure and pancreatic exocrine dysfunction may precede diabetes by decades in  
435 dominant *HNF1B*-diabetes and dominant *CEL*-diabetes, respectively<sup>18,63</sup>.

#### 436 **Biochemical variables**

437 Absence of islet autoantibodies, presence of endogenous insulin production (as  
438 evidenced by detectable C-peptide levels distant from the time of diagnosis) and  
439 modestly elevated blood glucose levels have been suggested as criteria for selection  
440 of individuals for genetic testing<sup>47,64–66</sup>. However, another study concluded that no  
441 single clinical criterion was able to identify all patients with monogenic diabetes<sup>67</sup>. It

442 should also be noted that while these criteria have been shown to perform well in  
443 distinguishing monogenic diabetes from type 1 diabetes, they are unlikely to reliably  
444 distinguish monogenic diabetes from type 2 diabetes. Some studies have even  
445 suggested that offering genetic screening for MODY could be considered for all  
446 children with diabetes irrespective of other clinical characteristics<sup>68</sup>. This approach,  
447 however, is not practical in resource-constrained settings.

448

449 Some clinical pointers to differentiate between monogenic diabetes and the more  
450 common type 1 and type 2 diabetes are given in **Figure 3**.

### 451 **Genetic screening for monogenic diabetes**

452 In the candidates described above, genetic screening for monogenic diabetes is  
453 carried out by sequencing the coding parts of genes known to be involved in this  
454 disease. In the 2000s and even before, this screening was performed via Sanger  
455 sequencing which was very labor-intensive and expensive. Since the advent of next-  
456 generation sequencing, genetic screening for monogenic diabetes has become  
457 increasingly cost-effective and less laborious. In this context, two sequencing  
458 technologies are mostly used today in genetic diagnostic laboratories: (i) targeted  
459 enrichment of a set of genes (or gene panels) known to be involved in monogenic  
460 diabetes; and (ii) whole-exome sequencing (*i.e.* sequencing of ~2 % coding part of  
461 the genome). Thanks to their targeted nature, gene panels inherently lead to a  
462 smaller amount of data to handle and lower cost, and decrease the risk of secondary  
463 findings when compared to whole-exome sequencing<sup>69,70</sup>. However, as new genes  
464 are discovered, the gene panel must be re-designed and re-validated. This is not  
465 necessary with whole-exome sequencing. Also, while whole-exome sequencing  
466 leads to bioinformatic challenges resulting from the large amount of data, it enables  
467 the identification of pathogenic variants in genes that were not considered at  
468 prescription (*i.e.* years after the initial assessment) and it fuels research of new  
469 monogenic diabetes genes. Gene panels and whole-exome sequencing are both  
470 limited in their capacity to detect copy-number variations (*e.g.* the deletion of one or  
471 several entire exons which are common in dominant *HNF1B*-diabetes) or low-level  
472 heteroplasmic mitochondrial variants (*e.g.* m.3243A>G variant causing monogenic  
473 diabetes)<sup>69,71</sup>. Therefore, multiplex ligation-dependent probe amplification (MLPA)  
474 and Sanger sequencing of mitochondrial DNA are often used to supplement these



475 techniques<sup>69,71</sup>. It is likely that whole-genome sequencing will substitute these  
476 technologies in the next five years, although the issues of cost and large amount of  
477 data need to be solved.

478 Since 2015, the standards and guidelines of the American College of Medical  
479 Genetics and Genomics (ACMG) have enabled a rigorous interpretation of sequence  
480 variants, which have been followed by all genetic diagnostic laboratories worldwide<sup>72</sup>.  
481 These criteria use various types of variant evidence including population data (e.g.  
482 extremely low frequency of variants in the Genome Aggregation Database),  
483 computational data (e.g. use of *in silico* predictive programs of variants), functional  
484 data (by *in vitro* or *in vivo* assays), and segregation data<sup>72</sup>. More specific guidelines  
485 have been gathered by the ClinGen Monogenic Diabetes Expert Panel VCEP for  
486 interpreting mutat. In dominant monogenic diabetes, it has recently been  
487 recommended to exclude *BLK*, *KLF11* and *PAX4* from monogenic diabetes testing as  
488 the evidence in support of these gene-disease associations is still controversial;  
489 furthermore, it was recommended that all variants with a frequency higher than 0.001  
490 in any ancestry included in the Genome Aggregation Database should be excluded  
491 from the analysis<sup>73</sup>.

## 492 **Prevention of monogenic diabetes**

493 Prevention in the classical sense of the term is not possible for monogenic diabetes  
494 at present. The identification of a pathogenic mutation early in life give the  
495 opportunity of diets low on fast acting carbohydrates. That may delay the onset of  
496 diabetes and hence lower risk for diabetes-associated late complications. It is indeed  
497 likely that environmental influences might play a role in the development of diabetes  
498 in many of these cases. For instance, an individual harbouring a mutation in *HNF1A*  
499 (involved in pancreas development) might develop diabetes at an earlier age (and  
500 therefore be at higher risk of complications) if the beta cell reserve is placed under  
501 strain by the development of obesity and insulin resistance. Correction of these  
502 environmental factors might favourably modify the presentation of monogenic  
503 diabetes at least in some cases. No studies looking at this issue have been reported  
504 to our knowledge.

## 505 **Management**

506 The optimal treatment of young patients with emerging MODY has been discussed  
507 since the 1970s<sup>74</sup>. In 1991, one year before the discovery of *GCK* deficiency in  
508 MODY, it was noted that MODY was very heterogeneous with some patients  
509 responding well to sulfonylureas (*i.e.* the only diabetes treatment along with insulin  
510 therapy in the USA at that time) and others not<sup>75</sup>. It remains, that at that time nearly  
511 all children discovered worldwide with hyperglycemia were immediately treated with  
512 insulin by pediatricians. That included the numerous children that carried pathogenic  
513 mutations in *GCK* who were mistakenly treated with daily injections of insulin with  
514 poor results<sup>3</sup>.

515 Progressively, the recognition of MODY as an entity different from type 1 diabetes  
516 and the identification of subtypes of MODY and other monogenic forms of diabetes  
517 has led to a better understanding of monogenic diabetes pathophysiology and  
518 elucidated clinical characteristics and trajectory of patients with monogenic diabetes.  
519 From this point, specific treatments based on the nature of the genetic defect have  
520 emerged and have been progressively introduced as the genetic diagnosis of  
521 monogenic diabetes became more popular among the diabetes community (Figure  
522 4). Given the outstanding efficiency of this personalized treatment, monogenic  
523 diabetes can be seen as a one-of-a-kind achievement of precision medicine that is  
524 only limited by the lack of provider knowledge of genetics and consequent lack of  
525 availability of genetic counseling and testing in many territories.

### 526 **Dominant *GCK*-diabetes**

527 Dominant *GCK*-diabetes is characterized by sustained and non-manageable modest  
528 fasting and post prandial hyperglycemia, which occurs in the very first years of life  
529 and is actually only modulated by age. Indeed, it is not rare that elderly patients  
530 deficient for *GCK* show HbA1c (*i.e.* a metric that reflects glucose control in the last  
531 couple of months) higher than 7.5%, which is above the HbA1c targets of an optimal  
532 diabetes treatment<sup>43</sup>. This has led to an avalanche of non-useful medications given to  
533 these patients in absence of genetic diagnosis, which are expensive and with  
534 potential adverse effects.

535 Diabetes treatment in patients deficient for *GCK* is unnecessary for two reasons.  
536 First, in these patients, no treatment can modify blood glucose that is firmly controlled  
537 by *GCK* enzymatic activity. Second, it has been unambiguously demonstrated that  
538 these patients do not develop any typical complications of diabetes (*e.g.* retinopathy,

539 nephropathy)<sup>43</sup>; thus, there is no reason to manage a form of diabetes that is not  
540 harmful for health. Remarkably, discontinuation of diabetes treatment does not  
541 change glucose homeostasis or other medical outcomes of these patients, whatever  
542 the duration of the condition before genetic recognition<sup>76</sup>. Asymptomatic, mild fasting  
543 hyperglycaemia (usually 5.6–8.0 mmol/l) related to dominant *GCK*-diabetes should  
544 be only monitored without any attempt to fix it. However, dominant *GCK*-diabetes  
545 should be taken seriously in the management of pregnancies.

546 Indeed, when a mother with diabetes carries a pathogenic *GCK* mutation while the  
547 fetus does not carry the mutation, maternal hyperglycemia causes fetal  
548 hyperinsulinemia and increased risk of macrosomia<sup>77</sup>. On the contrary, when the  
549 mother and her fetus share the same pathogenic *GCK* mutation, the glucose  
550 threshold to trigger insulin secretion is similar in the mother and her fetus, leading to  
551 normal fetal insulin levels and average birth weight<sup>77</sup>. Furthermore, if the mother  
552 presents with normal blood glucose levels and the father carries a pathogenic *GCK*  
553 mutation that was transmitted to the fetus, maternal blood glucose levels are  
554 insufficient to stimulate adequate fetal insulin secretion to sustain optimal growth,  
555 leading to increased risk of low birth weight<sup>78</sup>. Finally, if the mother presents with  
556 normal blood glucose levels and the father carries a pathogenic *GCK* mutation that  
557 was not transmitted to the fetus, fetal insulin secretion and birth weight are normal<sup>77</sup>.  
558 Therefore, insulin therapy should be given to a pregnant woman deficient for *GCK*  
559 only when frank hyperglycemia occurs and/or when diagnostic ultrasonography  
560 shows accelerated fetal growth (as elevated fetal insulin secretion leads to increased  
561 risk of fetal macrosomia and associated obstetric complications)<sup>7</sup>. In fact, it would be  
562 important to diagnose dominant *GCK*-diabetes in all women with gestational diabetes  
563 (which is rarely done unfortunately), as the optimal diabetes care greatly depends on  
564 whether the fetus has inherited the pathogenic *GCK* mutation or not, rather than the  
565 degree of maternal blood glucose. It has been stated that around 5% of women with  
566 gestational diabetes carry a pathogenic mutation causing MODY (and not only in  
567 *GCK*)<sup>79</sup>, but actually no large genetic study of women with GDM has systematically  
568 addressed this issue yet.

569 Dominant *GCK*-diabetes should be considered in pregnant women with mild fasting  
570 hyperglycemia (5.6–8.0 mmol/L), often during the first trimester, and with normal  
571 body mass index. If fasting hyperglycemia is found in the second trimester, MODY  
572 might be suspected in case abnormal 120-min oral glucose tolerance test above 7.5

573 mmol/l with HbA1c being either normal or moderately increased (5.6–7.6%). These  
574 patients usually present with a history of gestational diabetes in a previous  
575 pregnancy, a record of mild hyperglycemia before conception or after the delivery  
576 and a strong family history of type 2 diabetes at early ages. It is also possible to  
577 suspect dominant *GCK*-diabetes with history of fetal macrosomia in previous  
578 pregnancies, or of insulin therapy only during the previous pregnancy that has been  
579 removed after delivery<sup>79</sup>.

### 580 **Dominant *HNF1A*- or *HNF4A*-diabetes**

581 *HNF4A* and *HNF1A* encode two key transcription factors for insulin secretion control.  
582 Dominant *HNF1A*- or *HNF4A*-diabetes often causes severe, early-onset diabetes,  
583 which is frequently revealed at puberty (*i.e.* when insulin resistance can appear)<sup>33</sup>. In  
584 absence of genetic diagnosis, patients deficient for *HNF4A* or *HNF1A* are  
585 unfortunately generally treated by insulin injections<sup>7</sup>. If glucose homeostasis is badly  
586 controlled, dominant *HNF1A*- or *HNF4A*-diabetes shares the same long-term risks as  
587 type 1 diabetes, namely diabetic kidney disease and retinal complications. However,  
588 as both *HNF4A* and *HNF1A* modulate the liver metabolism of sulfonylureas, the  
589 intake of oral sulfonylureas has been shown to be particularly efficient at low dosage  
590 in the patients deficient for *HNF4A* or *HNF1A*, which diminishes the risk of  
591 hypoglycemia<sup>80</sup>. These two forms of monogenic diabetes are thus optimally treated  
592 with low-dose sulfonylureas because of their increased insulin secretion and their  
593 increased insulin sensitivity.

594 Unfortunately, as the genetic diagnosis is often much delayed in age, the current  
595 practice is still to introduce oral sulfonylureas after decades of insulin therapy,  
596 especially when diabetes occurs in adolescence or young adulthood and is confused  
597 with type 1 diabetes. This is tragic as it is important to perform the switch from insulin  
598 to sulfonylureas as early as possible. Indeed, at any age, the successful switch of  
599 insulin therapy into sulfonylureas in patients deficient for *HNF1A* or *HNF4A* is highly  
600 dependent of the residual insulin secretion that can be measured by the C-peptide  
601 which is the residue of the processing of proinsulin to insulin, reflecting insulin  
602 endogenous production<sup>81</sup>. Furthermore, body mass index, disease duration and  
603 HbA1c levels help predict the efficacy of sulfonylureas in patients deficient for *HNF1A*  
604 or *HNF4A*<sup>76</sup>. As insulin secretion progressively declines in these patients, it is of  
605 paramount importance to recognize these conditions as early as possible. When the

606 treatment with sulfonylureas is not sufficiently efficient, it has been proposed to treat  
607 these patients with glucagon-like peptide 1 (GLP1) analogs that may work well  
608 according to recent studies<sup>82</sup>.

609 With regard to pregnancy, fetal growth is affected by maternal glycemic control in  
610 dominant *HNF1A*-diabetes, and by both fetal mutation status and maternal  
611 hyperglycemia in dominant *HNF4A*-diabetes<sup>79</sup>. Importantly, sulfonylureas cross the  
612 placental barrier and can lead to macrosomia and hyperinsulinemic hypoglycemia,  
613 particularly in the third trimester<sup>79</sup>. Therefore, it is recommended to switch to insulin  
614 at pre-pregnancy (when possible) or to switch to insulin at the end of the first  
615 trimester if the glucose control is adequate during the first months of pregnancy. The  
616 overall principles of insulin treatment in these pregnant women with dominant  
617 *HNF1A*- or *HNF4A*-diabetes are actually similar to the treatment of other pregnant  
618 women with diabetes. However, due to the risk of higher birth weight and fetal  
619 macrosomia, the pregnancy of these women should be regularly monitored by  
620 sonography to detect the fetal growth since 28<sup>th</sup> week of gestation every two weeks<sup>79</sup>.  
621 If macrosomia is identified, induction of delivery or caesarian between 35 and 38<sup>th</sup>  
622 week of gestation should be considered<sup>79</sup>.

623 Importantly, dominant *HNF1A*-diabetes can be associated with liver adenomatosis (in  
624 6.5% of the cases according to a study), a rare disease that can lead to severe  
625 abdominal hemorrhage<sup>83</sup>. Therefore, it is recommended to screen carriers in the  
626 families for liver tumours, as preventive surgical or non-surgical procedures can be  
627 discussed to prevent the risk of liver bleeding, especially when adenomas are  
628 numerous or large<sup>83</sup>.

### 629 **Dominant *KCNJ11*- or *ABCC8*-diabetes**

630 As mentioned above, pathogenic, activating, heterozygous mutations in the two ATP-  
631 dependent potassium channel genes *KCNJ11* and *ABCC8*, which cause neonatal  
632 diabetes, can also lead to MODY or even typical type 2 diabetes. Their treatment of  
633 choice is relatively high dosage of sulfonylureas as SUR1 (encoded by *ABCC8*) is  
634 the ligand of this class of drugs which generally enables long-term excellent glucose  
635 control<sup>84,85</sup>. However, if the transfer from insulin is successful for most patients with  
636 dominant *KCNJ11*-diabetes, the good response to sulfonylurea is best predicted by  
637 the *in vitro* response of the specific mutation and the duration of diabetes<sup>86</sup>. This  
638 result strongly supports the early genetic testing and early treatment change<sup>86</sup>.

639 Neurological features, especially epilepsy, impaired cognition, motor function and  
640 muscular tone, visuo-motor integration, and attention deficits are frequent in children  
641 and adults carrying pathogenic mutations in *KCNJ11* or *ABCC8*<sup>87</sup>. A recent meta-  
642 review of 34 publications showed that the sulfonylurea glibenclamide significantly  
643 improved neurological abnormalities in these patients, but earlier treatment initiation  
644 was associated with greater benefits. Hypotonia was the symptom that responded  
645 best<sup>87</sup>.

### 646 **Other forms of monogenic diabetes**

647 There is no specific treatment for the other types of monogenic diabetes. These  
648 patients are often treated with insulin injections<sup>88</sup>. This is the case for dominant  
649 *HNF1B*-diabetes. Unlike patients with dominant *HNF1A*- or *HNF4A*-diabetes, those  
650 deficient for *HNF1B* do not respond adequately to treatment with sulfonylureas,  
651 possibly due to comorbid pancreatic hypoplasia and some degree of hepatic insulin  
652 resistance<sup>89</sup>. However, the genetic diagnosis of monogenic diabetes should be  
653 carefully followed in many cases by the monitoring of extra-pancreatic development  
654 abnormalities: more commonly in heart in patients deficient for *GATA4* or *GATA6*,  
655 and in the renal and genitourinary organs in patients deficient for *HNF1B*<sup>21,49,63</sup>. It is  
656 noteworthy that in many cases the impaired development of the heart found in  
657 *GATAs* mutations has led to surgery at birth, a history that should be elicited while  
658 evaluating early-onset diabetes in order to guide the genetic screening.

659 Specific lifestyle and dietary modifications are not different from common forms of  
660 type 1 diabetes and type 2 diabetes with reasonable physical activity (avoiding  
661 hypoglycemia) and a balanced diet avoiding high glycemic index food<sup>90</sup>. Of note,  
662 most patients with monogenic diabetes are not obese (Figure 3), and thus weight  
663 loss is generally not an issue to be fixed by lifestyle modifications.

### 664 **Quality of life**

665 Monogenic diabetes is genetically and phenotypically heterogeneous and the clinical  
666 care of its different subtypes is diversely demanding. However, the genetic diagnosis  
667 of monogenic diabetes usually increases the quality of life of patients and their family  
668 and decreases their anxiety about their future children<sup>91,92</sup>. This is obvious for  
669 dominant *GCK*-diabetes, as the prognosis of glucokinase deficiency is benign and,  
670 thus, diagnosing this mild form of hyperglycemia is “good news”. However, the

671 condition should not be forgotten especially in women considering future  
672 pregnancies. For dominant *HNF1A*- and *HNF4A*-diabetes, low dosage sulfonylureas  
673 with or without GLP1 analogues has greatly improved the quality of life of these  
674 patients<sup>7</sup>, and it is likely that it will be beneficial for the long-term health of these  
675 patients. The situation is the same for patients dominant *KCNJ11*- or *ABCC8*-  
676 diabetes. Indeed, in contrast to patients with common type 2 diabetes, there is no  
677 long-term beta-cell desensitization to sulfonylureas and excellent glucose control  
678 remains for decades<sup>85</sup>. Unfortunately, for patients with one of the other forms of  
679 monogenic diabetes, insulin therapy is generally required which is as challenging as  
680 in patients with type 1 diabetes. With regard to long-term disability, the most worrying  
681 situation concerns dominant *HNF1B*-diabetes as infertility and even end-stage renal  
682 failure are possible<sup>63</sup>. Close follow up of these patients is necessary.

683 Studies in 2011 and 2014 have evaluated the cost-effectiveness of neonatal diabetes  
684 and MODY genetic testing, respectively<sup>91,92</sup>. Main outcome measures were costs and  
685 quality-adjusted life years (QALYs) based on lifetime risk of complications and  
686 treatments, expressed as the incremental cost-effectiveness ratio (ICER). Genetic  
687 diagnosis targeting *KCNJ11* and *ABCC8* was particularly cost-efficient with a good  
688 0.32 QALYs at 10 years and 0.70 at 30 years, along with an ICER of \$200,000 per  
689 QALY<sup>92</sup>. Testing *GCK*, *HNF1A* and *HNF4A* in patients between the ages of 25–40  
690 years with presumed type 2 diabetes yielded an average gain of 0.012 QALY and  
691 resulted in an ICER of \$205,000 per QALY, considering a MODY prevalence of 2%<sup>92</sup>.  
692 An increase in MODY prevalence from 2 to 6% would lead to an ICER of about  
693 \$50,000 per QALY, which is frequently used as the threshold for assessing cost-  
694 effectiveness of a health intervention<sup>91</sup>. It is noteworthy that this study was based on  
695 the expensive and labor-intensive Sanger sequencing (*i.e.* \$2,580 per individual  
696 tested). The decrease in the cost of genetic testing (*e.g.* using next-generation  
697 sequencing methodologies that are much more economical and quick to run) from  
698 \$2,580 to \$700 led to an ICER of \$50,000 per QALY<sup>91</sup>. A more recent article has  
699 confirmed that the widespread implementation of genetic diagnosis along with  
700 screening of biomarkers (*i.e.* negativity for islet cell autoantibodies and positivity for  
701 C-peptide) could improve the lives of patients with MODY while saving the health  
702 system money (increased average quality of life [0.0081 QALY] and decreased costs  
703 [-\$735] per patient)<sup>93</sup>. Adding cascade genetic testing (*i.e.* testing first-degree

704 relatives of probands) further improved the lives of patients and substantially  
705 decreased costs<sup>93</sup>.

## 706 **Outlook**

707 Monogenic diabetes research has truly revolutionized our understanding of the  
708 pathophysiology of diabetes and the genetics of common diseases<sup>6</sup>: it has been one  
709 of the first proof of concepts that a very prevalent and complex disorder could be  
710 caused by a single gene defect. Later on, further models of complex traits including  
711 obesity but also heart diseases or Alzheimer disease have emerged, showing a  
712 continuum between rare and common forms of diseases. As mentioned above,  
713 depending of the nature of the DNA variant, the same monogenic diabetes genes  
714 can contribute to different forms of diabetes with early or late onset. This spectrum of  
715 diabetes phenotypes can also be observed for a single specific pathogenic mutation  
716 shared by different carriers. Therefore, a boundary between monogenic diabetes and  
717 type 2 diabetes is less obvious than the community thought 20 years ago. These new  
718 findings have dramatic consequences on diabetes management: a non-negligible  
719 part of patients with “typical” common forms of type 2 diabetes actually carry a  
720 pathogenic mutation in a monogenic diabetes gene, and thus they may potentially be  
721 treated differently than those who have common, truly polygenic type 2 diabetes<sup>5</sup>.

722 Monogenic diabetes research (along with genome-wide association studies related to  
723 type 2 diabetes) has also radically modified our understanding of the pathophysiology  
724 of non-autoimmune diabetes. Indeed, before 1992, when dominant *GCK*-diabetes  
725 was discovered, insulin resistance was considered as the primary abnormality  
726 eventually leading to abnormal glucose control with secondary exhaustion of  
727 pancreatic insulin-secreting cells. Monogenic diabetes research has demonstrated  
728 for the first time that inherited defects in insulin secretion can cause diabetes, even at  
729 a young age, without the need for severe insulin resistance or concurring obesity. Far  
730 later, genome-wide association studies (in combination with other genomic analyses  
731 or *in vitro* assays) have also shown that (i) type 2 diabetes-associated single  
732 nucleotide polymorphisms (SNPs) are enriched in regulatory regions that are active  
733 in pancreatic islets and not in tissues related to insulin resistance<sup>94,95</sup>; (ii)  
734 susceptibility genes for common type 2 diabetes (*i.e.* close to type 2 diabetes-  
735 associated SNPs) are involved in insulin secretion far more frequently than in insulin



736 resistance<sup>96</sup>. In this respect, monogenic diabetes genes and susceptibility genes for  
737 common type 2 diabetes are mostly involved in the development and function of  
738 pancreatic beta cells.

739 If monogenic diabetes research in the past 30 years has been very successful,  
740 several gaps remain to be filled. Several hypotheses could explain why the etiology  
741 of hyperglycemia in some patients with atypical diabetes remain unclear even after  
742 state-of-the-art attempt of genetic diagnosis:

743 (i) These patients may actually have a polygenic form of type 2 diabetes with very  
744 early age of onset (*e.g.* due to the presence of type 2 diabetes in both paternal and  
745 maternal lineages). Polygenic risk scores for type 2 diabetes derived from genome-  
746 wide association studies should be systematically analyzed as these MODY-like  
747 patients maybe in the upper range of the polygenic risk scores, which borders the  
748 risk scores for diabetes of pathogenic mutations in monogenic diabetes genes<sup>97</sup>.

749 (ii) Alternatively, these patients may carry a deleterious mutation in a non-coding  
750 regulatory region of a monogenic diabetes gene. An elegant study showed that  
751 deleterious homozygous non-coding mutations in a distal *PTF1A* enhancer led to  
752 neonatal diabetes due to pancreatic agenesis<sup>98</sup>. Therefore, whole-genome  
753 sequencing (along with genomic analyses) would be the only way to elucidate these  
754 cases.

755 (iii) Of course, it is possible that other, as yet unknown but very rare monogenic  
756 diabetes genes remain to be identified.

757 That advocates for a graded approach in the diagnosis of monogenic diabetes  
758 including, first, whole-exome sequencing with a focus on known monogenic diabetes  
759 genes. If negative, the mutation analysis should be extended to candidate genes for  
760 diabetes or should be included in a gene-centric analysis, including other  
761 unelucidated cases and elderly normal glucose controls, in order to find new  
762 monogenic diabetes genes. In parallel, whole-genome sequencing and DNA  
763 microarray genotyping may be performed. The situation is quite different in non-  
764 European ancestries (*e.g.* Asians, Africans) where only a minority of cases have  
765 been elucidated, so far<sup>11</sup>. A specific effort of screening these populations by all  
766 possible means (*i.e.* whole-exome sequencing, whole-genome sequencing, DNA  
767 microarrays) is needed to make further progress in these ethnicities.

768 Despite strong initial hopes with GCK activators<sup>99</sup>, no drug directly derived from  
769 monogenic diabetes research has been developed yet and introduced into the

770 market. GCK activators failed since their effect on insulin secretion was modest (with  
771 diminished long-term efficacy) and they had adverse effects on the liver, with the  
772 development of steatosis and hypertriglyceridemia directly linked to increased liver  
773 glucokinase activity<sup>100</sup>. To our knowledge, no other promising drug target directly  
774 coming from monogenic diabetes research has emerged so far. Ironically, the first  
775 ever anti-diabetic drug family, the sulfonylureas, which directly targets SUR1  
776 encoded by *ABCC8*, has a much better long term efficacy in monogenic diabetes  
777 than in patients with common type 2 diabetes<sup>45</sup>. Of note, families where three  
778 generations of patients with apparent type 2 diabetes are well controlled by  
779 sulfonylureas may actually carry a mutation in *ABCC8*, *KCNJ11*, *HNF1A* or *HNF4A*<sup>55</sup>.  
780 Further efforts may provide new clues. This is very important since the majority of  
781 patients with type 2 diabetes fail to achieve treatment objectives (in term of glucose  
782 control, weight management etc.), and innovative molecules restoring normal insulin  
783 secretion are lacking. More efforts directed to the pathways involving monogenic  
784 diabetes genes in pancreatic beta cells may reveal novel drug targets.

785 The priorities for basic and clinical research and precision medicine centered on  
786 monogenic diabetes may be summarized as follows: (i) developing economical, quick  
787 and reliable gene screening methodologies and high throughput pipelines that can be  
788 disseminated in every country to diagnose most of the patients with monogenic  
789 diabetes whatever their age is and their phenotype looks like; (ii) making more  
790 progress in developing specific treatments for monogenic diabetes gene mutation  
791 carriers as their long-term health (especially in dominant *HNF1A*- or *HNF4A*-  
792 diabetes) is still uncertain – an effort that implies having an efficient follow-up of  
793 every patient diagnosed with monogenic diabetes; (iii) further advancing our  
794 knowledge on pancreatic beta-cell biology by leveraging the outcomes of monogenic  
795 diabetes research.

796

797 **Acknowledgements**

798 A.B. is supported by the European Research Council (ERC OπO: 101043671). A.B.,  
799 M.V. and P.F. are supported by the National Center for Precision Diabetic Medicine –  
800 PreciDIAB, which is jointly supported by the French National Agency for Research  
801 (ANR-18-IBHU-0001), by the European Union (FEDER), by the Hauts-de-France  
802 Regional Council and by the European Metropolis of Lille (MEL). V.M. and R.U.  
803 would like to acknowledge the support of M/S Servier Laboratories to their work on  
804 monogenic diabetes as part of the PAN INDIA STUDY ON MODY  
805 (CTRI/2019/12/022394 & CTRI/2020/03/023968).

806 **Author Contributions**

807 Introduction (A.B., M.V.); Epidemiology (P.F.); Mechanisms/Pathophysiology (A.B.,  
808 A.D., M.V.); Diagnosis/Screening/Prevention (A.B., R.U., V.M., V.T.); Management  
809 (P.F., V.M., V.T.); Quality of life (P.F., A.B.), Outlook (P.F.). Overview of Primer (A.B.,  
810 P.F.).

811 **Conflict of Interest**

812 The authors declare no competing interests.

813

814 **References**

- 815 1. Riddle, M. C. *et al.* Monogenic Diabetes: From Genetic Insights to Population-Based Precision in  
816 Care. Reflections From a Diabetes Care Editors' Expert Forum. *Diabetes Care* **43**, 3117–3128  
817 (2020).
- 818 2. Froguel, P. *et al.* Close linkage of glucokinase locus on chromosome 7p to early-onset non-  
819 insulin-dependent diabetes mellitus. *Nature* **356**, 162–164 (1992).
- 820 3. Vionnet, N. *et al.* Nonsense mutation in the glucokinase gene causes early-onset non-insulin-  
821 dependent diabetes mellitus. *Nature* **356**, 721–722 (1992).
- 822 4. American Diabetes Association Professional Practice Committee. 2. Classification and Diagnosis  
823 of Diabetes: *Standards of Medical Care in Diabetes—2022*. *Diabetes Care* **45**, S17–S38 (2022).
- 824 5. Bonnefond, A. *et al.* Pathogenic variants in actionable MODY genes are associated with type 2  
825 diabetes. *Nat Metab* **2**, 1126–1134 (2020).
- 826 6. Yang, Y. & Chan, L. Monogenic Diabetes: What It Teaches Us on the Common Forms of Type 1  
827 and Type 2 Diabetes. *Endocr Rev* **37**, 190–222 (2016).
- 828 7. Vaxillaire, M., Froguel, P. & Bonnefond, A. How Recent Advances in Genomics Improve  
829 Precision Diagnosis and Personalized Care of Maturity-Onset Diabetes of the Young. *Curr Diab  
830 Rep* **19**, 79 (2019).
- 831 8. Shields, B. M. *et al.* Maturity-onset diabetes of the young (MODY): how many cases are we  
832 missing? *Diabetologia* **53**, 2504–2508 (2010).
- 833 9. Donath, X. *et al.* Next-generation sequencing identifies monogenic diabetes in 16% of patients  
834 with late adolescence/adult-onset diabetes selected on a clinical basis: a cross-sectional  
835 analysis. *BMC Medicine* **17**, 132 (2019).
- 836 10. Flannick, J. *et al.* Assessing the phenotypic effects in the general population of rare variants in  
837 genes for a dominant Mendelian form of diabetes. *Nat. Genet.* **45**, 1380–1385 (2013).
- 838 11. Vaxillaire, M. *et al.* Monogenic diabetes characteristics in a transnational multicenter study  
839 from Mediterranean countries. *Diabetes Res Clin Pract* **171**, 108553 (2021).
- 840 12. Mohan, V. *et al.* Comprehensive genomic analysis identifies pathogenic variants in maturity-  
841 onset diabetes of the young (MODY) patients in South India. *BMC Med Genet* **19**, 22 (2018).
- 842 13. Pezzilli, S. *et al.* Pathogenic variants of MODY-genes in adult patients with early-onset type 2  
843 diabetes. *Acta Diabetol* **59**, 747–750 (2022).
- 844 14. Todd, J. N. *et al.* Monogenic Diabetes in Youth With Presumed Type 2 Diabetes: Results From  
845 the Progress in Diabetes Genetics in Youth (ProDiGY) Collaboration. *Diabetes Care* dc210491  
846 (2021) doi:10.2337/dc21-0491.
- 847 15. Da Silva Xavier, G. The Cells of the Islets of Langerhans. *J Clin Med* **7**, E54 (2018).
- 848 16. Yamagata, K. *et al.* Mutations in the hepatocyte nuclear factor-1alpha gene in maturity-onset  
849 diabetes of the young (MODY3). *Nature* **384**, 455–458 (1996).
- 850 17. Yamagata, K. *et al.* Mutations in the hepatocyte nuclear factor-4alpha gene in maturity-onset  
851 diabetes of the young (MODY1). *Nature* **384**, 458–460 (1996).
- 852 18. Raeder, H. *et al.* Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic  
853 exocrine dysfunction. *Nat Genet* **38**, 54–62 (2006).
- 854 19. Malikova, J. *et al.* Functional Analyses of HNF1A-MODY Variants Refine the Interpretation of  
855 Identified Sequence Variants. *J Clin Endocrinol Metab* **105**, dgaa051 (2020).
- 856 20. Li, L.-M., Jiang, B.-G. & Sun, L.-L. HNF1A : From Monogenic Diabetes to Type 2 Diabetes and  
857 Gestational Diabetes Mellitus. *Front Endocrinol (Lausanne)* **13**, 829565 (2022).
- 858 21. Bonnefond, A. *et al.* GATA6 inactivating mutations are associated with heart defects and,  
859 inconsistently, with pancreatic agenesis and diabetes. *Diabetologia* **55**, 2845–2847 (2012).
- 860 22. Jonsson, J., Carlsson, L., Edlund, T. & Edlund, H. Insulin-promoter-factor 1 is required for  
861 pancreas development in mice. *Nature* **371**, 606–609 (1994).
- 862 23. Duque, M., Amorim, J. P. & Bessa, J. Ptf1a function and transcriptional cis-regulation, a  
863 cornerstone in vertebrate pancreas development. *FEBS J* **289**, 5121–5136 (2022).

- 864 24. Tiyaboonchai, A. *et al.* GATA6 Plays an Important Role in the Induction of Human Definitive  
865 Endoderm, Development of the Pancreas, and Functionality of Pancreatic  $\beta$  Cells. *Stem Cell*  
866 *Reports* **8**, 589–604 (2017).
- 867 25. Rouzier, C. *et al.* A novel CISD2 mutation associated with a classical Wolfram syndrome  
868 phenotype alters Ca<sup>2+</sup> homeostasis and ER-mitochondria interactions. *Hum Mol Genet* **26**,  
869 1599–1611 (2017).
- 870 26. Shrestha, N., De Franco, E., Arvan, P. & Cnop, M. Pathological  $\beta$ -Cell Endoplasmic Reticulum  
871 Stress in Type 2 Diabetes: Current Evidence. *Front Endocrinol (Lausanne)* **12**, 650158 (2021).
- 872 27. Graff, S. M. *et al.* A *KCNK16* mutation causing TALK-1 gain-of-function is associated with  
873 maturity-onset diabetes of the young. *JCI Insight* (2021) doi:10.1172/jci.insight.138057.
- 874 28. Santer, R. *et al.* Mutations in *GLUT2*, the gene for the liver-type glucose transporter, in patients  
875 with Fanconi-Bickel syndrome. *Nat. Genet.* **17**, 324–326 (1997).
- 876 29. Labay, V. *et al.* Mutations in *SLC19A2* cause thiamine-responsive megaloblastic anaemia  
877 associated with diabetes mellitus and deafness. *Nat. Genet.* **22**, 300–304 (1999).
- 878 30. Jungtrakoon, P. *et al.* Loss-of-Function Mutation in Thiamine Transporter 1 in a Family With  
879 Autosomal Dominant Diabetes. *Diabetes* **68**, 1084–1093 (2019).
- 880 31. Mancuso, M. *et al.* The m.3243A>G mitochondrial DNA mutation and related phenotypes. A  
881 matter of gender? *J Neurol* **261**, 504–510 (2014).
- 882 32. Pickett, S. J. *et al.* Phenotypic heterogeneity in m.3243A>G mitochondrial disease: The role of  
883 nuclear factors. *Ann Clin Transl Neurol* **5**, 333–345 (2018).
- 884 33. Vaxillaire, M. & Froguel, P. Monogenic diabetes in the young, pharmacogenetics and relevance  
885 to multifactorial forms of type 2 diabetes. *Endocr Rev* **29**, 254–264 (2008).
- 886 34. Raimondo, A. *et al.* Phenotypic severity of homozygous GCK mutations causing neonatal or  
887 childhood-onset diabetes is primarily mediated through effects on protein stability. *Hum Mol*  
888 *Genet* **23**, 6432–6440 (2014).
- 889 35. Rees, M. G. *et al.* A panel of diverse assays to interrogate the interaction between glucokinase  
890 and glucokinase regulatory protein, two vital proteins in human disease. *PLoS One* **9**, e89335  
891 (2014).
- 892 36. Njølstad, P. R. *et al.* Neonatal Diabetes Mellitus Due to Complete Glucokinase Deficiency. *N*  
893 *Engl J Med* **344**, 1588–1592 (2001).
- 894 37. Meur, G. *et al.* Insulin gene mutations resulting in early-onset diabetes: marked differences in  
895 clinical presentation, metabolic status, and pathogenic effect through endoplasmic reticulum  
896 retention. *Diabetes* **59**, 653–661 (2010).
- 897 38. Garin, I. *et al.* Recessive mutations in the *INS* gene result in neonatal diabetes through reduced  
898 insulin biosynthesis. *Proc Natl Acad Sci U S A* **107**, 3105–3110 (2010).
- 899 39. Bonnefond, A. *et al.* Disruption of a novel Kruppel-like transcription factor p300-regulated  
900 pathway for insulin biosynthesis revealed by studies of the c.-331 *INS* mutation found in  
901 neonatal diabetes mellitus. *J Biol Chem* **286**, 28414–28424 (2011).
- 902 40. Johansson, B. B. *et al.* The role of the carboxyl ester lipase (*CEL*) gene in pancreatic disease.  
903 *Pancreatology* **18**, 12–19 (2018).
- 904 41. Kahraman, S. *et al.* Abnormal exocrine-endocrine cell cross-talk promotes  $\beta$ -cell dysfunction  
905 and loss in *MODY8*. *Nat Metab* **4**, 76–89 (2022).
- 906 42. Tattersall, R. B. & Fajans, S. S. A difference between the inheritance of classical juvenile-onset  
907 and maturity-onset type diabetes of young people. *Diabetes* **24**, 44–53 (1975).
- 908 43. Steele, A. M. *et al.* Prevalence of vascular complications among patients with glucokinase  
909 mutations and prolonged, mild hyperglycemia. *JAMA* **311**, 279–286 (2014).
- 910 44. Di Paola, R., Marucci, A. & Trischitta, V. The Need to Increase Clinical Skills and Change the  
911 Genetic Testing Strategy for Monogenic Diabetes. *Diabetes* **71**, 379–380 (2022).
- 912 45. Zhang, H., Colclough, K., Gloyne, A. L. & Pollin, T. I. Monogenic diabetes: a gateway to precision  
913 medicine in diabetes. *J Clin Invest* **131**, 142244 (2021).
- 914 46. Kleinberger, J. W. *et al.* Monogenic diabetes in overweight and obese youth diagnosed with  
915 type 2 diabetes: the TODAY clinical trial. *Genet Med* **20**, 583–590 (2018).

- 916 47. Thanabalasingham, G. *et al.* Systematic assessment of etiology in adults with a clinical diagnosis  
917 of young-onset type 2 diabetes is a successful strategy for identifying maturity-onset diabetes  
918 of the young. *Diabetes Care* **35**, 1206–1212 (2012).
- 919 48. Flannick, J., Johansson, S. & Njølstad, P. R. Common and rare forms of diabetes mellitus:  
920 towards a continuum of diabetes subtypes. *Nat Rev Endocrinol* **12**, 394–406 (2016).
- 921 49. Shaw-Smith, C. *et al.* GATA4 mutations are a cause of neonatal and childhood-onset diabetes.  
922 *Diabetes* **63**, 2888–2894 (2014).
- 923 50. Bonnefond, A. *et al.* Whole-exome sequencing and high throughput genotyping identified  
924 KCNJ11 as the thirteenth MODY gene. *PLoS ONE* **7**, e37423 (2012).
- 925 51. Kettunen, J. L. T. *et al.* A multigenerational study on phenotypic consequences of the most  
926 common causal variant of HNF1A-MODY. *Diabetologia* **65**, 632–643 (2022).
- 927 52. Saint-Martin, C., Bouvet, D., Bastide, M. & Bellanné-Chantelot, C. Gene Panel Sequencing of  
928 Patients With Monogenic Diabetes Brings to Light Genes Typically Associated With Syndromic  
929 Presentations. *Diabetes* **71**, 578–584 (2022).
- 930 53. Colclough, K., Ellard, S., Hattersley, A. & Patel, K. Syndromic Monogenic Diabetes Genes Should  
931 Be Tested in Patients With a Clinical Suspicion of Maturity-Onset Diabetes of the Young.  
932 *Diabetes* **71**, 530–537 (2022).
- 933 54. Patel, K. A. *et al.* Systematic genetic testing for recessively inherited monogenic diabetes: a  
934 cross-sectional study in paediatric diabetes clinics. *Diabetologia* **65**, 336–342 (2022).
- 935 55. Bonnefond, A. & Semple, R. K. Achievements, prospects and challenges in precision care for  
936 monogenic insulin-deficient and insulin-resistant diabetes. *Diabetologia* (2022)  
937 doi:10.1007/s00125-022-05720-7.
- 938 56. Chapla, A. *et al.* Maturity onset diabetes of the young in India - a distinctive mutation pattern  
939 identified through targeted next-generation sequencing. *Clin. Endocrinol. (Oxf)* **82**, 533–542  
940 (2015).
- 941 57. Shields, B. M. *et al.* The development and validation of a clinical prediction model to determine  
942 the probability of MODY in patients with young-onset diabetes. *Diabetologia* **55**, 1265–1272  
943 (2012).
- 944 58. Misra, S. *et al.* South Asian individuals with diabetes who are referred for MODY testing in the  
945 UK have a lower mutation pick-up rate than white European people. *Diabetologia* **59**, 2262–  
946 2265 (2016).
- 947 59. Carroll, R. W. & Murphy, R. Monogenic diabetes: a diagnostic algorithm for clinicians. *Genes*  
948 (*Basel*) **4**, 522–535 (2013).
- 949 60. Rubio-Cabezas, O. & Ellard, S. Diabetes mellitus in neonates and infants: genetic heterogeneity,  
950 clinical approach to diagnosis, and therapeutic options. *Horm Res Paediatr* **80**, 137–146 (2013).
- 951 61. Pipatpolkai, T., Usher, S., Stansfeld, P. J. & Ashcroft, F. M. New insights into KATP channel gene  
952 mutations and neonatal diabetes mellitus. *Nat Rev Endocrinol* **16**, 378–393 (2020).
- 953 62. Shepherd, M. *et al.* Predictive genetic testing in maturity-onset diabetes of the young (MODY).  
954 *Diabet Med* **18**, 417–421 (2001).
- 955 63. Dubois-Laforgue, D. *et al.* Diabetes, Associated Clinical Spectrum, Long-term Prognosis, and  
956 Genotype/Phenotype Correlations in 201 Adult Patients With Hepatocyte Nuclear Factor 1B  
957 (HNF1B) Molecular Defects. *Diabetes Care* **40**, 1436–1443 (2017).
- 958 64. Shepherd, M. *et al.* Systematic Population Screening, Using Biomarkers and Genetic Testing,  
959 Identifies 2.5% of the U.K. Pediatric Diabetes Population With Monogenic Diabetes. *Diabetes*  
960 *Care* **39**, 1879–1888 (2016).
- 961 65. Shields, B. M. *et al.* Population-Based Assessment of a Biomarker-Based Screening Pathway to  
962 Aid Diagnosis of Monogenic Diabetes in Young-Onset Patients. *Diabetes Care* **40**, 1017–1025  
963 (2017).
- 964 66. Carlsson, A. *et al.* Absence of Islet Autoantibodies and Modestly Raised Glucose Values at  
965 Diabetes Diagnosis Should Lead to Testing for MODY: Lessons From a 5-Year Pediatric Swedish  
966 National Cohort Study. *Diabetes Care* **43**, 82–89 (2020).

- 967 67. Pihoker, C. *et al.* Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of  
968 the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for  
969 Diabetes in Youth. *J Clin Endocrinol Metab* **98**, 4055–4062 (2013).
- 970 68. Johnson, S. R. *et al.* Comprehensive genetic screening: The prevalence of maturity-onset  
971 diabetes of the young gene variants in a population-based childhood diabetes cohort. *Pediatr*  
972 *Diabetes* **20**, 57–64 (2019).
- 973 69. Dillon, O. J. *et al.* Exome sequencing has higher diagnostic yield compared to simulated disease-  
974 specific panels in children with suspected monogenic disorders. *Eur J Hum Genet* **26**, 644–651  
975 (2018).
- 976 70. Xue, Y., Ankala, A., Wilcox, W. R. & Hegde, M. R. Solving the molecular diagnostic testing  
977 conundrum for Mendelian disorders in the era of next-generation sequencing: single-gene,  
978 gene panel, or exome/genome sequencing. *Genetics in Medicine* **17**, 444–451 (2015).
- 979 71. Montagne, L. *et al.* CoDE-seq, an augmented whole-exome sequencing, enables the accurate  
980 detection of CNVs and mutations in Mendelian obesity and intellectual disability. *Mol Metab*  
981 **13**, 1–9 (2018).
- 982 72. Richards, S. *et al.* Standards and guidelines for the interpretation of sequence variants: a joint  
983 consensus recommendation of the American College of Medical Genetics and Genomics and  
984 the Association for Molecular Pathology. *Genet. Med.* **17**, 405–424 (2015).
- 985 73. Ellard, S., Colclough, K., Patel, K. A. & Hattersley, A. T. Prediction algorithms: pitfalls in  
986 interpreting genetic variants of autosomal dominant monogenic diabetes. *J. Clin. Invest.* **130**,  
987 14–16 (2020).
- 988 74. Fajans, S. S. Heterogeneity of insulin responses in maturity-onset type diabetes (MOD) and in  
989 maturity-onset type diabetes of young people (MODY). *Adv Exp Med Biol* **119**, 171–175 (1979).
- 990 75. Tattersall, R. B. & Mansell, P. I. Maturity onset-type diabetes of the young (MODY): one  
991 condition or many? *Diabet Med* **8**, 402–410 (1991).
- 992 76. Shepherd, M. H. *et al.* A UK nationwide prospective study of treatment change in MODY:  
993 genetic subtype and clinical characteristics predict optimal glycaemic control after  
994 discontinuing insulin and metformin. *Diabetologia* **61**, 2520–2527 (2018).
- 995 77. Timsit, J., Ciangura, C., Dubois-Laforgue, D., Saint-Martin, C. & Bellanne-Chantelot, C. Pregnancy  
996 in Women With Monogenic Diabetes due to Pathogenic Variants of the Glucokinase Gene:  
997 Lessons and Challenges. *Front Endocrinol (Lausanne)* **12**, 802423 (2021).
- 998 78. Shields, B. M. *et al.* Mutations in the glucokinase gene of the fetus result in reduced placental  
999 weight. *Diabetes Care* **31**, 753–757 (2008).
- 1000 79. Urbanová, J., Brunerová, L., Nunes, M. & Brož, J. Identification of MODY among patients  
1001 screened for gestational diabetes: a clinician’s guide. *Arch Gynecol Obstet* **302**, 305–314 (2020).
- 1002 80. Bosselaar, M., Hattersley, A. T. & Tack, C. J. J. [High sensitivity to sulphonylurea treatment in 2  
1003 patients with maturity-onset diabetes of the young type 3]. *Ned Tijdschr Geneesk* **146**, 726–  
1004 729 (2002).
- 1005 81. Stankute, I. *et al.* Systematic Genetic Study of Youth With Diabetes in a Single Country Reveals  
1006 the Prevalence of Diabetes Subtypes, Novel Candidate Genes, and Response to Precision  
1007 Therapy. *Diabetes* **69**, 1065 (2020).
- 1008 82. Broome, D. T., Tekin, Z., Pantalone, K. M. & Mehta, A. E. Novel Use of GLP-1 Receptor Agonist  
1009 Therapy in HNF4A-MODY. *Diabetes Care* **43**, e65 (2020).
- 1010 83. Haddouche, A. *et al.* Liver adenomatosis in patients with hepatocyte nuclear factor-1 alpha  
1011 maturity onset diabetes of the young (HNF1A-MODY): Clinical, radiological and pathological  
1012 characteristics in a French series. *J Diabetes* **12**, 48–57 (2020).
- 1013 84. Bowman, P. *et al.* Effectiveness and safety of long-term treatment with sulfonylureas in  
1014 patients with neonatal diabetes due to KCNJ11 mutations: an international cohort study. *Lancet*  
1015 *Diabetes Endocrinol* **6**, 637–646 (2018).
- 1016 85. Iafusco, D. *et al.* No beta cell desensitisation after a median of 68 months on glibenclamide  
1017 therapy in patients with KCNJ11-associated permanent neonatal diabetes. *Diabetologia* **54**,  
1018 2736–2738 (2011).

- 1019 86. Babiker, T. *et al.* Successful transfer to sulfonylureas in KCNJ11 neonatal diabetes is determined  
1020 by the mutation and duration of diabetes. *Diabetologia* **59**, 1162–1166 (2016).
- 1021 87. de Gouveia Buff Passone, C. *et al.* Sulfonylurea for improving neurological features in neonatal  
1022 diabetes: A systematic review and meta-analyses. *Pediatr Diabetes* **23**, 675–692 (2022).
- 1023 88. Aarthy, R. *et al.* Clinical features, complications and treatment of rarer forms of maturity-onset  
1024 diabetes of the young (MODY) - A review. *J Diabetes Complications* **35**, 107640 (2021).
- 1025 89. Urakami, T. Maturity-onset diabetes of the young (MODY): current perspectives on diagnosis  
1026 and treatment. *Diabetes Metab Syndr Obes* **12**, 1047–1056 (2019).
- 1027 90. Asif, M. The prevention and control the type-2 diabetes by changing lifestyle and dietary  
1028 pattern. *J Educ Health Promot* **3**, 1 (2014).
- 1029 91. Naylor, R. N. *et al.* Cost-effectiveness of MODY genetic testing: translating genomic advances  
1030 into practical health applications. *Diabetes Care* **37**, 202–209 (2014).
- 1031 92. Greeley, S. A. W. *et al.* The cost-effectiveness of personalized genetic medicine: the case of  
1032 genetic testing in neonatal diabetes. *Diabetes Care* **34**, 622–627 (2011).
- 1033 93. GoodSmith, M. S., Skandari, M. R., Huang, E. S. & Naylor, R. N. The Impact of Biomarker  
1034 Screening and Cascade Genetic Testing on the Cost-Effectiveness of MODY Genetic Testing.  
1035 *Diabetes Care* **42**, 2247–2255 (2019).
- 1036 94. Pasquali, L. *et al.* Pancreatic islet enhancer clusters enriched in type 2 diabetes risk-associated  
1037 variants. *Nat. Genet.* **46**, 136–143 (2014).
- 1038 95. Gaulton, K. J. *et al.* Genetic fine mapping and genomic annotation defines causal mechanisms at  
1039 type 2 diabetes susceptibility loci. *Nat. Genet.* **47**, 1415–1425 (2015).
- 1040 96. Ndiaye, F. K. *et al.* Expression and functional assessment of candidate type 2 diabetes  
1041 susceptibility genes identify four new genes contributing to human insulin secretion. *Mol*  
1042 *Metab* **6**, 459–470 (2017).
- 1043 97. Khera, A. V. *et al.* Genome-wide polygenic scores for common diseases identify individuals with  
1044 risk equivalent to monogenic mutations. *Nat. Genet.* **50**, 1219–1224 (2018).
- 1045 98. Weedon, M. N. *et al.* Recessive mutations in a distal PTF1A enhancer cause isolated pancreatic  
1046 agenesis. *Nat Genet* **46**, 61–64 (2014).
- 1047 99. Rees, M. G. & Gloyn, A. L. Small molecular glucokinase activators: has another new anti-diabetic  
1048 therapeutic lost favour? *Br J Pharmacol* **168**, 335–338 (2013).
- 1049 100. Sharma, P. *et al.* Targeting human Glucokinase for the treatment of type 2 diabetes: an  
1050 overview of allosteric Glucokinase activators. *J Diabetes Metab Disord* **21**, 1129–1137 (2022).
- 1051 101. Stoffers, D. A., Ferrer, J., Clarke, W. L. & Habener, J. F. Early-onset type-II diabetes mellitus  
1052 (MODY4) linked to IPF1. *Nat. Genet.* **17**, 138–139 (1997).
- 1053 102. Horikawa, Y. *et al.* Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with  
1054 MODY. *Nat. Genet.* **17**, 384–385 (1997).
- 1055 103. Malecki, M. T. *et al.* Mutations in NEUROD1 are associated with the development of type 2  
1056 diabetes mellitus. *Nat. Genet.* **23**, 323–328 (1999).
- 1057 104. Bowman, P. *et al.* Heterozygous ABCC8 mutations are a cause of MODY. *Diabetologia* **55**, 123–  
1058 127 (2012).
- 1059 105. Bonnycastle, L. L. *et al.* Autosomal dominant diabetes arising from a Wolfram syndrome 1  
1060 mutation. *Diabetes* **62**, 3943–3950 (2013).
- 1061 106. Igoillo-Esteve, M. *et al.* tRNA methyltransferase homolog gene TRMT10A mutation in young  
1062 onset diabetes and primary microcephaly in humans. *PLoS Genet.* **9**, e1003888 (2013).
- 1063 107. Simate, D. *et al.* Recessive mutations in PCBD1 cause a new type of early-onset diabetes.  
1064 *Diabetes* **63**, 3557–3564 (2014).
- 1065 108. Prudente, S. *et al.* Loss-of-Function Mutations in APPL1 in Familial Diabetes Mellitus. *Am. J.*  
1066 *Hum. Genet.* **97**, 177–185 (2015).
- 1067 109. Patel, K. A. *et al.* Heterozygous RFX6 protein truncating variants are associated with MODY with  
1068 reduced penetrance. *Nat Commun* **8**, 888 (2017).



- 1069 110. Iacovazzo, D. *et al.* MAFA missense mutation causes familial insulinomatosis and diabetes  
1070 mellitus. *Proceedings of the National Academy of Sciences* 201712262 (2018)  
1071 doi:10.1073/pnas.1712262115.
- 1072 111. Philippi, A. *et al.* Mutations and variants of ONECUT1 in diabetes. *Nat Med* **27**, 1928–1940  
1073 (2021).
- 1074 112. Yorifuji, T. *et al.* Neonatal diabetes mellitus and neonatal polycystic, dysplastic kidneys:  
1075 Phenotypically discordant recurrence of a mutation in the hepatocyte nuclear factor-1beta  
1076 gene due to germline mosaicism. *J Clin Endocrinol Metab* **89**, 2905–2908 (2004).
- 1077 113. Gloyn, A. L. *et al.* Activating mutations in the gene encoding the ATP-sensitive potassium-  
1078 channel subunit Kir6.2 and permanent neonatal diabetes. *N. Engl. J. Med.* **350**, 1838–1849  
1079 (2004).
- 1080 114. Babenko, A. P. *et al.* Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. *N.*  
1081 *Engl. J. Med.* **355**, 456–466 (2006).
- 1082 115. Støyr, J. *et al.* Insulin gene mutations as a cause of permanent neonatal diabetes. *Proc. Natl.*  
1083 *Acad. Sci. U.S.A.* **104**, 15040–15044 (2007).
- 1084 116. the International Pancreatic Agenesis Consortium *et al.* GATA6 haploinsufficiency causes  
1085 pancreatic agenesis in humans. *Nat Genet* **44**, 20–22 (2012).
- 1086 117. van den Ouweland, J. M. *et al.* Mutation in mitochondrial tRNA(Leu)(UUR) gene in a large  
1087 pedigree with maternally transmitted type II diabetes mellitus and deafness. *Nat Genet* **1**, 368–  
1088 371 (1992).
- 1089 118. Nagamine, K. *et al.* Positional cloning of the APECED gene. *Nat Genet* **17**, 393–398 (1997).
- 1090 119. Finnish-German APECED Consortium. An autoimmune disease, APECED, caused by mutations in  
1091 a novel gene featuring two PHD-type zinc-finger domains. *Nat Genet* **17**, 399–403 (1997).
- 1092 120. Stoffers, D. A., Zinkin, N. T., Stanojevic, V., Clarke, W. L. & Habener, J. F. Pancreatic agenesis  
1093 attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. *Nat.*  
1094 *Genet.* **15**, 106–110 (1997).
- 1095 121. Inoue, H. *et al.* A gene encoding a transmembrane protein is mutated in patients with diabetes  
1096 mellitus and optic atrophy (Wolfram syndrome). *Nat. Genet.* **20**, 143–148 (1998).
- 1097 122. De Franco, E. *et al.* Dominant ER Stress-Inducing WFS1 Mutations Underlie a Genetic Syndrome  
1098 of Neonatal/Infancy-Onset Diabetes, Congenital Sensorineural Deafness, and Congenital  
1099 Cataracts. *Diabetes* **66**, 2044–2053 (2017).
- 1100 123. Delépine, M. *et al.* EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated  
1101 in patients with Wolcott-Rallison syndrome. *Nat. Genet.* **25**, 406–409 (2000).
- 1102 124. Bennett, C. L. *et al.* The immune dysregulation, polyendocrinopathy, enteropathy, X-linked  
1103 syndrome (IPEX) is caused by mutations of FOXP3. *Nat. Genet.* **27**, 20–21 (2001).
- 1104 125. Sellick, G. S. *et al.* Mutations in PTF1A cause pancreatic and cerebellar agenesis. *Nat. Genet.* **36**,  
1105 1301–1305 (2004).
- 1106 126. Senée, V. *et al.* Mutations in GLIS3 are responsible for a rare syndrome with neonatal diabetes  
1107 mellitus and congenital hypothyroidism. *Nat Genet* **38**, 682–687 (2006).
- 1108 127. Yasuda, T. *et al.* PAX6 mutation as a genetic factor common to aniridia and glucose intolerance.  
1109 *Diabetes* **51**, 224–230 (2002).
- 1110 128. Kofoed, E. M. *et al.* Growth hormone insensitivity associated with a STAT5b mutation. *N Engl J*  
1111 *Med* **349**, 1139–1147 (2003).
- 1112 129. Amr, S. *et al.* A homozygous mutation in a novel zinc-finger protein, ERIS, is responsible for  
1113 Wolfram syndrome 2. *Am J Hum Genet* **81**, 673–683 (2007).
- 1114 130. Smith, S. B. *et al.* Rfx6 directs islet formation and insulin production in mice and humans.  
1115 *Nature* **463**, 775–780 (2010).
- 1116 131. Rubio-Cabezas, O. *et al.* Homozygous mutations in NEUROD1 are responsible for a novel  
1117 syndrome of permanent neonatal diabetes and neurological abnormalities. *Diabetes* **59**, 2326–  
1118 2331 (2010).
- 1119 132. Rubio-Cabezas, O. *et al.* Permanent Neonatal Diabetes and Enteric Anendocrinosis Associated  
1120 With Biallelic Mutations in NEUROG3. *Diabetes* **60**, 1349–1353 (2011).

- 1121 133. Poulton, C. J. *et al.* Microcephaly with simplified gyration, epilepsy, and infantile diabetes linked  
1122 to inappropriate apoptosis of neural progenitors. *Am J Hum Genet* **89**, 265–276 (2011).
- 1123 134. Boonen, S. E. *et al.* Transient neonatal diabetes, ZFP57, and hypomethylation of multiple  
1124 imprinted loci: a detailed follow-up. *Diabetes Care* **36**, 505–512 (2013).
- 1125 135. Bonnefond, A. *et al.* Transcription factor gene MNX1 is a novel cause of permanent neonatal  
1126 diabetes in a consanguineous family. *Diabetes & Metabolism* **39**, 276–280 (2013).
- 1127 136. Synofzik, M. *et al.* Absence of BiP co-chaperone DNAJC3 causes diabetes mellitus and  
1128 multisystemic neurodegeneration. *Am. J. Hum. Genet.* **95**, 689–697 (2014).
- 1129 137. Flanagan, S. E. *et al.* Activating germline mutations in STAT3 cause early-onset multi-organ  
1130 autoimmune disease. *Nat. Genet.* **46**, 812–814 (2014).
- 1131 138. Flanagan, S. E. *et al.* Analysis of transcription factors key for mouse pancreatic development  
1132 establishes NKX2-2 and MNX1 mutations as causes of neonatal diabetes in man. *Cell Metab.* **19**,  
1133 146–154 (2014).
- 1134 139. Kerns, S. L. *et al.* A novel variant in CDKN1C is associated with intrauterine growth restriction,  
1135 short stature, and early-adulthood-onset diabetes. *J Clin Endocrinol Metab* **99**, E2117-2122  
1136 (2014).
- 1137 140. Abdulkarim, B. *et al.* A missense mutation in PPP1R15B causes a syndrome including diabetes,  
1138 short stature and microcephaly. *Diabetes* db150477 (2015) doi:10.2337/db15-0477.
- 1139 141. Johnson, M. B. *et al.* Recessively Inherited LRBA Mutations Cause Autoimmunity Presenting as  
1140 Neonatal Diabetes. *Diabetes* **66**, 2316–2322 (2017).
- 1141 142. Şıklar, Z. *et al.* Monogenic Diabetes Not Caused By Mutations in Mody Genes: A Very  
1142 Heterogenous Group of Diabetes. *Exp Clin Endocrinol Diabetes* **126**, 612–618 (2018).
- 1143 143. Stekelenburg, C. *et al.* Exome sequencing identifies a de novo FOXA2 variant in a patient with  
1144 syndromic diabetes. *Pediatr Diabetes* **20**, 366–369 (2019).
- 1145 144. De Franco, E. *et al.* A Specific CNOT1 Mutation Results in a Novel Syndrome of Pancreatic  
1146 Agenesis and Holoprosencephaly through Impaired Pancreatic and Neurological Development.  
1147 *The American Journal of Human Genetics* S0002929719301144 (2019)  
1148 doi:10.1016/j.ajhg.2019.03.018.
- 1149 145. De Franco, E. *et al.* YIPF5 mutations cause neonatal diabetes and microcephaly through  
1150 endoplasmic reticulum stress. *J Clin Invest* **130**, 6338–6353 (2020).
- 1151 146. De Franco, E. *et al.* De Novo Mutations in EIF2B1 Affecting eIF2 Signaling Cause Neonatal/Early  
1152 Onset Diabetes and Transient Hepatic Dysfunction. *Diabetes* db191029 (2019)  
1153 doi:10.2337/db19-1029.
- 1154 147. Lekszas, C. *et al.* Biallelic TANGO1 mutations cause a novel syndromal disease due to hampered  
1155 cellular collagen secretion. *eLife* **9**, e51319 (2020).
- 1156 148. Chaimowitz, N. S., Ebenezer, S. J., Hanson, I. C., Anderson, M. & Forbes, L. R. STAT1 Gain of  
1157 Function, Type 1 Diabetes, and Reversal with JAK Inhibition. *N Engl J Med* **383**, 1494–1496  
1158 (2020).
- 1159 149. Montaser, H. *et al.* Loss of MANF Causes Childhood-Onset Syndromic Diabetes Due to Increased  
1160 Endoplasmic Reticulum Stress. *Diabetes* **70**, 1006–1018 (2021).
- 1161 150. Blodgett, D. M. *et al.* Novel Observations From Next-Generation RNA Sequencing of Highly  
1162 Purified Human Adult and Fetal Islet Cell Subsets. *Diabetes* **64**, 3172–3181 (2015).
- 1163 151. Alonso, L. *et al.* TIGER: The gene expression regulatory variation landscape of human pancreatic  
1164 islets. *Cell Reports* **37**, 109807 (2021).
- 1165 152. Bansal, V. *et al.* Spectrum of mutations in monogenic diabetes genes identified from high-  
1166 throughput DNA sequencing of 6888 individuals. *BMC Med* **15**, 213 (2017).
- 1167 153. Goodrich, J. K. *et al.* Determinants of penetrance and variable expressivity in monogenic  
1168 metabolic conditions across 77,184 exomes. *Nat Commun* **12**, 3505 (2021).
- 1169

## 1170 Highlighted References

1171 Vionnet, N. *et al.* Nonsense mutation in the glucokinase gene causes early-onset  
1172 non-insulin-dependent diabetes mellitus. *Nature* **356**, 721–722 (1992). **First original**  
1173 **article that highlighted pathogenic mutations in *GCK* leading to one of the most**  
1174 **prevalent forms of monogenic diabetes**

1175  
1176 Yamagata, K. *et al.* Mutations in the hepatocyte nuclear factor-1alpha gene in  
1177 maturity-onset diabetes of the young (MODY3). *Nature* **384**, 455–458 (1996). **First**  
1178 **original article that highlighted pathogenic mutations in *HNF1A* leading to one**  
1179 **of the most prevalent forms of monogenic diabetes**

1180  
1181 Steele, A. M. *et al.* Prevalence of vascular complications among patients with  
1182 glucokinase mutations and prolonged, mild hyperglycemia. *JAMA* **311**, 279–286  
1183 (2014) **Original article that showed a very low prevalence of vascular**  
1184 **complications in patients with long-term dominant *GCK*-diabetes**

1185  
1186 Bonnefond, A. *et al.* Pathogenic variants in actionable MODY genes are associated  
1187 with type 2 diabetes. *Nat Metab* **2**, 1126–1134 (2020). **Recent original article that**  
1188 **highlighted the incomplete penetrance of pathogenic mutations in monogenic**  
1189 **diabetes genes. Indeed, these mutations were found in patients with a**  
1190 **suspicion of typical type 2 diabetes.**

1191  
1192 Saint-Martin, C., Bouvet, D., Bastide, M. & Bellanné-Chantelot, C. Gene Panel  
1193 Sequencing of Patients With Monogenic Diabetes Brings to Light Genes Typically  
1194 Associated With Syndromic Presentations. *Diabetes* **71**, 578–584 (2022). **Recent**  
1195 **original article that highlighted the incomplete penetrance of pathogenic**  
1196 **mutations in syndromic monogenic diabetes genes. Indeed, these mutations**  
1197 **were found in patients with a suspicion of non-syndromic monogenic diabetes.**

1198  
1199 Colclough, K., Ellard, S., Hattersley, A. & Patel, K. Syndromic Monogenic Diabetes  
1200 Genes Should Be Tested in Patients With a Clinical Suspicion of Maturity-Onset  
1201 Diabetes of the Young. *Diabetes* **71**, 530–537 (2022). **Recent original article that**  
1202 **highlighted the incomplete penetrance of pathogenic mutations in syndromic**  
1203 **monogenic diabetes genes. Indeed, these mutations were found in patients**  
1204 **with a suspicion of non-syndromic monogenic diabetes.**

1205 **Tables**1206 **Table 1 | Identification and inheritance mode of monogenic diabetes**  
1207 **genes**

Gene	Inheritance mode	Location	Ref.
<b>MODY (without other atypical features)</b>			
<i>GCK</i>	AD/AR	7p13	2,3
<i>HNF1A</i>	AD	12q24.31	16
<i>HNF4A</i>	AD	20q13.12	17
<i>PDX1</i>	AD	13q12.2	101
<i>HNF1B</i>	AD	17q12	102
<i>NEUROD1</i>	AD	2q31.3	103
<i>CEL</i>	AD	9q34.13	18
<i>INS</i>	AD	11p15.5	37
<i>ABCC8</i>	AD	11p15.1	104
<i>KCNJ11</i>	AD	11p15.1	50
<i>GATA6</i>	AD	18q11.2	21
<i>WFS1</i>	AD/AR	4p16.1	105
<i>TRMT10A</i>	AR	4q23	106
<i>PCBD1</i>	AR	10q22.1	107
<i>GATA4</i>	AD	8p23.1	49
<i>APPL1</i>	AD	3p14.3	108
<i>RFX6</i>	AD	6q22.1	109
<i>MAFA</i>	AD	8q24.3	110
<i>SLC19A2</i>	AD/AR	1q24.2	30
<i>ONECUT1</i>	AD	15q21.3	111
m.3243A>G	maternally	Mitochondria	52
<i>KCNK16</i>	AD	6p21.2	27
<b>Neonatal Diabetes (without other atypical features)</b>			
<i>HNF1B</i>	AD	17q12	101
<i>GCK</i>	AR	7p13	36
<i>KCNJ11</i>	AD/AR	11p15.1	113
<i>ABCC8</i>	AD/AR	11p15.1	114
<i>INS</i>	AD/AR	11p15.5	115
<i>GATA6</i>	AD	18q11.2	116
<i>GATA4</i>	AD	8p23.1	49
<b>Syndrome including Neonatal/Early-Onset Diabetes</b>			
m.3243A>G	maternally	Mitochondria	117
<i>HNF1B</i>	AD	17q12	102
<i>AIRE*</i>	AR/AD	21q22.3	118,119
<i>PDX1</i>	AR	13q12.2	120
<i>SLC2A2</i>	AR	3q26.2	28
<i>WFS1</i>	AR/AD	4p16.1	121,122
<i>SLC19A2</i>	AR	1q24.2	29
<i>EIF2AK3</i>	AR	2p11.2	123
<i>FOXP3*</i>	XR	Xp11.23	124
<i>PTF1A</i>	AR	10p12.2	125
<i>GLIS3</i>	AR	9p24.2	126
<i>CEL</i>	AD	9q34.13	18
<i>PAX6</i>	AR	11p13	127
<i>STAT5B*</i>	AR	17q21.2	128
<i>CISD2</i>	AR	4q24	129
<i>RFX6</i>	AR	6q22.1	130
<i>NEUROD1</i>	AR	2q31.3	131
<i>NEUROG3</i>	AR	10q22.1	132
<i>IER3IP1</i>	AR	18q21.1	133
<i>ZFP57</i>	AR	6p22.1	134
<i>MNX1</i>	AR	7q36.3	135
<i>GATA6</i>	AD	18q11.2	21
<i>DNAJC3</i>	AR	13q32.1	136
<i>STAT3*</i>	AD	17q21.2	137
<i>TRMT10A</i>	AR	4q23	106

<b>GATA4</b>	AD	8p23.1	49
<b>NKX2-2</b>	AR	20p11.22	138
<b>CDKN1C</b>	AD	11p15.4	139
<b>PPP1R15B</b>	AR	1q32.1	140
<b>LRBA*</b>	AR	4q31.3	141
<b>IL2RA*</b>	AR	10p15.1	142
<b>FOXA2</b>	AD	20p11.21	143
<b>CNOT1</b>	AD	16q21	144
<b>YIPF5</b>	AR	5q31.3	145
<b>EIF2B1</b>	AD	12q24.31	146
<b>MIA3</b>	AR	1q41	147
<b>STAT1*</b>	AD	2q32.2	148
<b>MANF</b>	AR	3p21.2	149
<b>ONECUT1</b>	AR	15q21.3	111

- 1208 **AD**, autosomal dominant inheritance; **AR**, autosomal recessive inheritance; **XR**, X-
- 1209 linked recessive inheritance
- 1210 \*Genes causing auto-immune diabetes
- 1211 Additional MODY genes have been described in *BLK*, *KLF11* and *PAX4* but the
- 1212 evidence in support of these gene-disease associations has been refuted<sup>73</sup>.

1213  
1214

**Table 2. | Expression of monogenic diabetes genes and nature/location of encoded proteins**

Gene	Protein type	Location	TPM adult beta cell	TPM fetal beta cell	TPM adult islet	Other hits
<i>ABCC8</i>	Channel subunit	Membrane	1010	232	226	Brain (cerebellum), pituitary
<i>KCNJ11</i>	Channel subunit	Membrane	34	28	11	Skeletal muscle, pancreas, brain (cerebellum), heart, thryroid, stomach, pituitary
<i>KCNK16</i>	Channel subunit	Membrane	182	97	68	None
<i>SLC2A2</i>	Transporter	Membrane	10	1	10	Liver, Small intestine
<i>SLC19A2</i>	Transporter	Membrane	9	9	11	Ubiquitous
<i>GCK</i>	Enzyme	Cytosol	30	68	25	Liver
<i>APPL1</i>	Protein binding	Cytosol	42	17	14	Ubiquitous
<i>CEL</i>	Enzyme	Cytosol	-	-	86	Pancreas
<i>CNOT1</i>	Protein/RNA binding	Cytosol	-	-	71	Ubiquitous
<i>LRBA*</i>	Protein binding	Cytosol	62	43	19	Ubiquitous
<i>INS</i>	Hormone	Granule	205700	83300	37000	None
<i>PAX6</i>	Transcription factor	Nucleus	261	333	122	Brain (cerebellum)
<i>PCBD1</i>	Enzyme	Nucleus	53	113	48	Ubiquitous
<i>RFX6</i>	Transcription factor	Nucleus	79	107	18	None
<i>PDX1</i>	Transcription factor	Nucleus	118	105	18	Pancreas
<i>CDKN1C</i>	Protein binding	Nucleus	107	27	54	Ubiquitous
<i>NKX2-2</i>	Transcription factor	Nucleus	104	42	16	Brain, pituitary
<i>NEUROD1</i>	Transcription factor	Nucleus	189	167	31	Brain (cerebellum)
<i>GLIS3</i>	Transcription factor	Nucleus	136	111	35	Thyroid
<i>STAT3*</i>	Transcription factor	Nucleus	110	32	81	Ubiquitous
<i>FOXA2</i>	Transcription factor	Nucleus	42	43	23	Liver, lung, stomach, pancreas, colon, thyroid
<i>NEUROG3</i>	Transcription factor	Nucleus	0	35	0	Brain (hippocampus), small intestine, colon
<i>MAFA</i>	Transcription factor	Nucleus	97	13	26	Skeletal muscle, testis
<i>STAT5B*</i>	Transcription factor	Nucleus	26	18	17	Ubiquitous
<i>STAT1*</i>	Transcription factor	Nucleus	43	10	68	Ubiquitous
<i>MNX1</i>	Transcription factor	Nucleus	35	21	9	Pancreas, colon, pituitary, stomach, small intestine
<i>HNF1B</i>	Transcription factor	Nucleus	5	23	16	Kidney, liver, lung, pancreas, bladder, colon, small intestine, stomach, testis
<i>HNF1A</i>	Transcription factor	Nucleus	10	22	5	Liver, kidney, pancreas, colon, small intestine, stomach
<i>HNF4A</i>	Transcription factor	Nucleus	5	12	15	Liver, kidney, pancreas, colon, small intestine, stomach
<i>GATA6</i>	Transcription factor	Nucleus	-	-	14	Ubiquitous
<i>GATA4</i>	Transcription factor	Nucleus	1	0	3	Pancreas, ovary, heart, testis, stomach, artery
<i>TRMT10A</i>	Enzyme	Nucleus	2	2	4	Ubiquitous
<i>ONECUT1</i>	Transcription factor	Nucleus	-	-	4	Liver, pancreas, testis
<i>FOXP3*</i>	Transcription factor	Nucleus	0	2	0	Blood, testis, spleen, skin, small intestine, lung, liver
<i>PTF1A</i>	Transcription factor	Nucleus	0	0	0	Pancreas
<i>ZFP57</i>	Transcription factor	Nucleus	0	0	0	Brain (spinal cord, substantia nigra)
<i>AIRE*</i>	Transcription factor	Nucleus	-	-	0	Brain
<i>IL2RA*</i>	Protein binding	Nucleus	0	0	1	Spleen, small intestine, lung
<i>WFS1</i>	Protein binding	ER	112	19	28	Ubiquitous
<i>MANF</i>	Protein/RNA binding	ER	93	46	86	Ubiquitous
<i>PPP1R15B</i>	Protein binding	ER	56	71	35	Ubiquitous
<i>IER3IP1</i>	Protein binding	ER	49	8	23	Ubiquitous
<i>EIF2B1</i>	Protein binding	ER	42	29	19	Ubiquitous
<i>MIA3</i>	Protein binding	ER	43	21	37	Ubiquitous
<i>DNAJC3</i>	Protein binding	ER	59	21	47	Ubiquitous
<i>YIPF5</i>	Protein transport	ER	-	-	41	Ubiquitous
<i>CISD2</i>	Protein binding	ER	15	8	28	Ubiquitous
<i>EIF2AK3</i>	Protein binding	ER	15	12	24	Ubiquitous

1215 \*Genes causing auto-immune diabetes

1216 TPM in adult and fetal pancreatic beta cells are shown according to RNA-seq data published  
1217 in ref<sup>150</sup>. TPM in adult pancreatic islets are shown according to RNA-seq data published in  
1218 ref<sup>151</sup>.  
1219 **ER**, endoplasmic reticulum; **TPM**, transcript per million

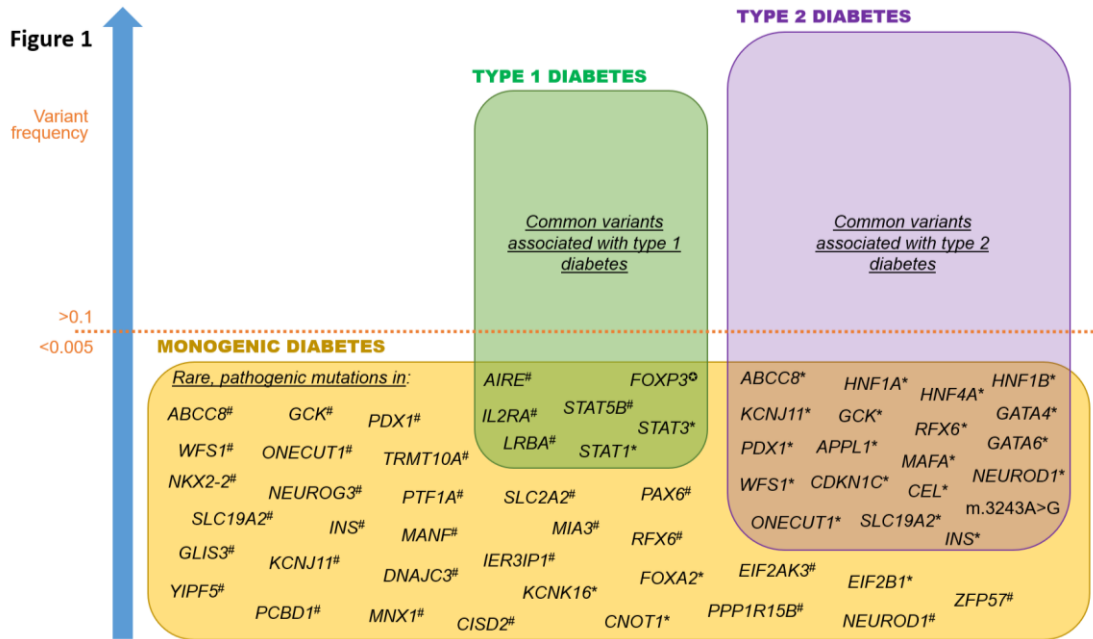
1220

1221

1222 **Figure 1 | Overlapping between monogenic diabetes, type 1 diabetes and**  
 1223 **type 2 diabetes**

1224 Genes harbouring rare pathogenic mutations leading to monogenic diabetes, type 1  
 1225 diabetes and/or type 2 diabetes. #autosomal recessive inheritance; \*autosomal  
 1226 dominant inheritance; ♂X-linked recessive inheritance

1227



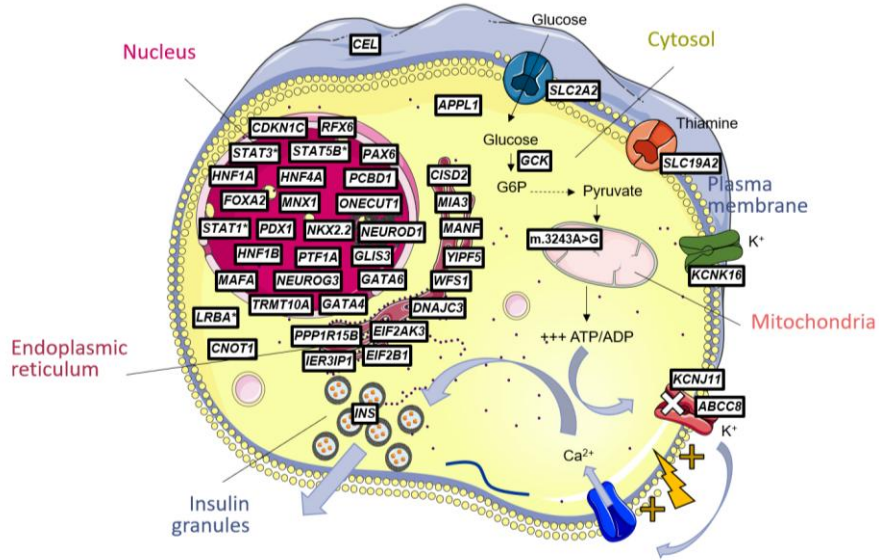
1228

1229



1230 **Figure 2. | Monogenic diabetes genes in pancreatic beta cells**  
 1231 Monogenic diabetes genes impact all compartments of pancreatic beta cells  
 1232 including nucleus, endoplasmic reticulum, plasma membrane, mitochondria etc.  
 1233 \*Genes linked with auto-immune diabetes. Only genes that are expressed in human  
 1234 islets or beta cells are shown in this figure

Figure 2



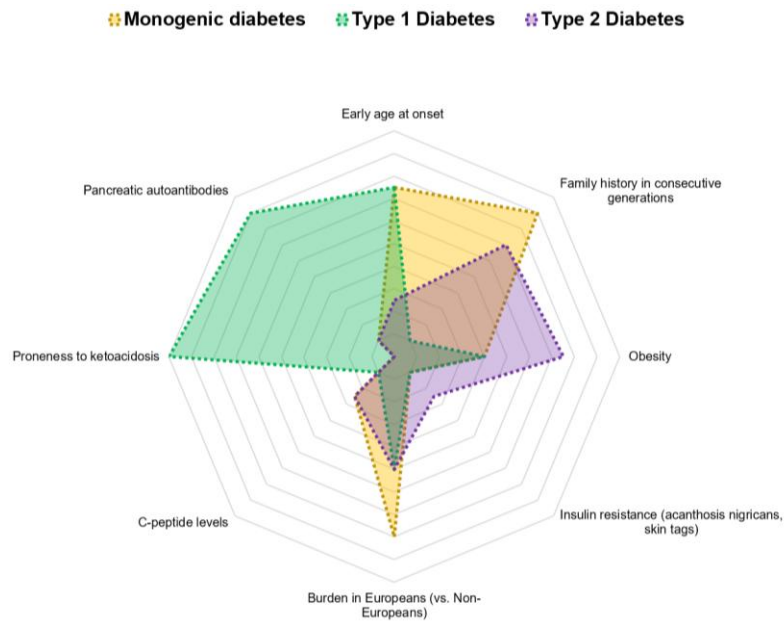
1235

1236

1237 **Figure 3 | Differentiation between monogenic diabetes, type 1 diabetes**  
1238 **and type 2 diabetes, based on clinical presentation and ancestry**

1239 Clinical presentation features that differentiate monogenic diabetes, type 1 diabetes  
1240 and type 2 diabetes at the time of diagnostic. Ideas of magnitude have been shown  
1241 in this flow chart based on multiple articles in the literature<sup>5,9,11,152,153</sup> and on the  
1242 definition of type 1 diabetes, type 2 diabetes and monogenic diabetes.

Figure 3



1243

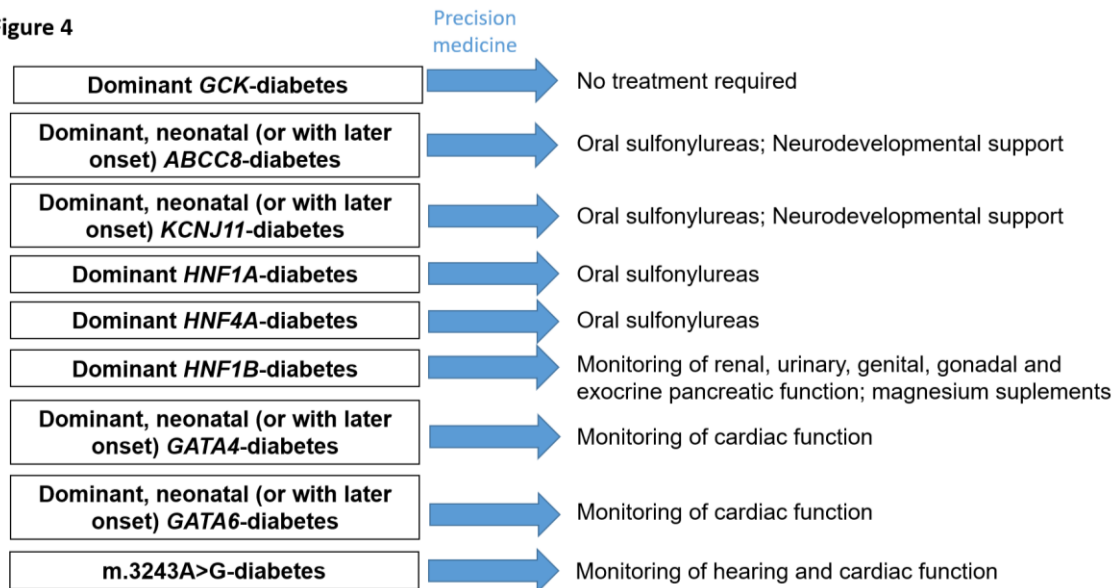
1244

1245  
1246

## Figure 4 | Actionable genes linked with monogenic diabetes

Precision medicine can be applied in several monogenic forms of diabetes.

Figure 4



1247

1248 **Boxes**

1249

1250 **Box 1 | Monogenic diabetes-associated genes and technology used for**  
1251 **their discovery**

1252

- 1253 • **Linkage analyses followed by Sanger sequencing of candidate genes in**  
1254 **diabetes-associated linkage genomic peaks**

1255 *GCK, HNF1A, HNF4A, CEL, INS, WFS1, SLC19A2, CISD2, IER3IP1*

- 1256 • **Candidate gene strategy**

1257 *PDX1, HNF1B, NEUROD1, KCNJ11, ABCC8, GATA4, NEUROG3, AIRE,*  
1258 *SLC2A2, PAX6, STAT5B, ZFP57*

- 1259 • **Homozygosity mapping followed by Sanger sequencing of candidate**  
1260 **genes in runs of homozygosity (ROH)**

1261 *EIF3AK3, FOXP3, PTF1A, GLIS3*

- 1262 • **Candidate variant strategy**

1263 *m.3243A>G*

- 1264 • **Next-generation sequencing**

1265 *GATA6, MNX1, DNAJC3, STAT3, APPL1, MAFA, KCNK16, PPP1R15B,*  
1266 *LRBA, IL2RA, FOXA2, CNOT1, YIPF5, EIF2B1, MIA3, STAT1, MANF*

- 1267 • **Linkage analyses and next-generation sequencing**

1268 *TRMT10A, PCBD1, CDKN1C*

- 1269 • **Homozygosity mapping and next-generation sequencing**

1270 *RFX6, NKX2-2, ONECUT1*