OUTLOOK

# Rethinking HNF1A-MODY: HNF1A at the crossroads of development and multiorgan metabolic disease

**Julie Warin[1] and Anne Grapin-Botton[1,2,3,4,5]**

[1]Max Planck Institute of Molecular Cell Biology and Genetics, Dresden 01307, Germany; [2]Center for Systems Biology Dresden, Dresden 01307, Germany; [3]Cluster of Excellence Physics of Life, Technische Universität Dresden Dresden, Dresden 01062, Germany; [4]Paul Langerhans Institute Dresden of the Helmholtz Munich at University Hospital Carl Gustav Carus, Dresden 01307, Germany; [5]Faculty of Medicine, Technische Universität Dresden, Dresden 01307, Germany

**In this issue of *Genes & Development*, Unger and colleagues (doi:10.1101/gad.353153.125) combined human pluripotent stem cell-derived in vitro models with targeted in vivo mouse models to reveal multiple developmental defects triggered by *HNF1A* mutations causing maturity-onset diabetes of the young. This work paints the picture of a disorder that starts well before diabetes manifests, highlighting its complexity arising from the diverse roles of HNF1A across distinct cell types, each potentially differentially impacted by different mutations.**

Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes caused by mutations affecting key regulators of pancreatic β-cell identity and function. The most prevalent form, caused by mutations in the transcription factor *HNF1A*, has long been regarded as a disorder characterized by impaired insulin secretion from adult pancreatic β-cell, accompanied by hepatic dysfunction (Zhao et al. 2022). However, this perspective struggles to account for the clinical heterogeneity observed in patients and is increasingly challenged by emerging evidence of developmental abnormalities. Hundreds of pathogenic variants in *HNF1A* have been identified (Fig. 1A; Çubuk and Yalçın Çapan 2021), leading to a broad spectrum of clinical phenotypes that are not fully captured by models focusing solely on β-cell dysfunction. In this issue of *Genes & Development*, Unger et al. (2026) show that HNF1A-MODY starts far earlier than previously appreciated, at the level of fundamental cell fate decisions during development. Their work contributes to repositioning HNF1A-MODY as a developmental disorder whose trajectory may be shaped long before diabetes becomes clinically apparent.

[*Keywords*: GLI3; HNF1A; duodenal fate; intestinal elongation; pancreatic fate; pancreatic progenitors]
**Corresponding author: botton@mpi-cbg.de**
Article published online ahead of print. Article and publication date are online at http://www.genesdev.org/cgi/doi/10.1101/gad.353709.126. Freely available online through the *Genes & Development* Open Access option.

Over the past decades, mouse models of HNF1A deficiency have provided important mechanistic insights; however, they only partially mirror the human condition, as heterozygous mutations are sufficient to cause progressive diabetes in humans but not in rodents. These limitations have spurred the development of human pluripotent stem cell (hPSC) systems. These models, leveraging differentiation protocols that recapitulate pancreatic development, have been instrumental in interrogating mutation-specific effects and revealing early developmental defects associated with *HNF1A* mutations that are difficult to capture in vivo (Cardenas-Diaz et al. 2019; Low et al. 2021; Cujba et al. 2022; Hermann et al. 2023). By recapitulating key stages from the definitive endoderm to the posterior foregut, pancreatic progenitors, and endocrine lineages (Rezania et al. 2014), hPSC-based frameworks allow precise identification of the developmental windows at which HNF1A dysfunction exerts its effects. They have shown that HNF1A mutations can lead to a reduced number of pancreatic progenitors (Low et al. 2021; Cujba et al. 2022), impaired differentiation resulting in perturbed α-cell to β-cell ratios (Cardenas-Diaz et al. 2019; Cujba et al. 2022; González et al. 2022), and reduced insulin secretion (Cardenas-Diaz et al. 2019; Low et al. 2021; Cujba et al. 2022; González et al. 2022) and glucose sensing (Cardenas-Diaz et al. 2019; Low et al. 2021; González et al. 2022). Several of these defects have been reported in mutants, leading to *HNF1A* total deletion (Cardenas-Diaz et al. 2019), truncations (Cujba et al. 2022), or mutations in the DNA-binding domain (González et al. 2022). In contrast, gain-of-function mutations impairing DNA binding and transactivation resulted in insulin hypersecretion (Hermann et al. 2023). Unger et al. (2026) show that new lines with the truncated mutation studied previously (Cujba et al. 2022) have an earlier effect on development and interfere with Hedgehog (HH)

signaling, a fundamental pathway in lineage segregation in the posterior foregut during embryonic patterning.

Using both CRISPR-edited and patient-derived hPSC models focusing on the truncating p291fsinsC mutation, Unger et al. (2026) demonstrate that HNF1A deficiency perturbs developmental programs as early as the posterior foregut stage (Fig. 1B). They uncover a regulatory feedback loop in which full-length HNF1A is required for the proper processing of GLI3R, a repressor of the HH pathway, which in turn is necessary to sustain *HNF1A* expression and ensure effective repression of HH signaling. In cells expressing truncated HNF1A, this loop is disrupted, leading to reduced GLI3R activity, diminished expression of the fate determinant *HHEX*, and a developmental diversion away from pancreatic progenitor identity toward intestinal and hepatic lineages. Although later differentiation steps enrich for pancreatic endocrine cells, this early mispatterning leaves a lasting imprint. Indeed, progenitor cells with intestinal gene signatures are maintained up to the stage of islet production in HNF1A-deficient cells. In addition, they display a persistent bias toward glucagon-producing α cells over insulin-producing β cells, though it is not clear if it is a consequence of the early patterning defects or an independent role of HNF1A. Notably, similar α-cell biases have been reported in hPSC models carrying truncating mutations in other regions of the *HNF1A* gene (Cardenas-Diaz et al. 2019; González et al. 2022), whereas this phenotype is absent in a model expressing full-length but transcriptionally inactive HNF1A (Hermann et al. 2023), underscoring the importance of mutation-specific mechanisms.

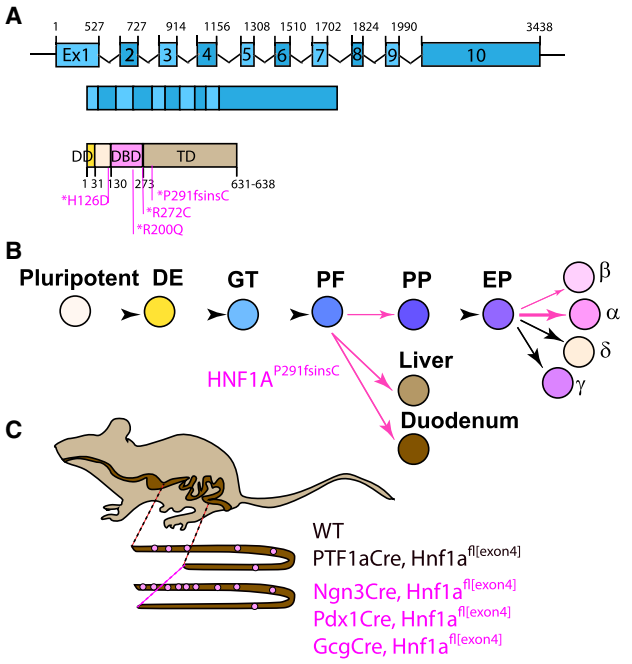


**Figure 1.** HNF1A truncating mutations affect multiple steps of development. (*A*) Structure of the *HNF1A* gene (exons [in blue] and introns), transcripts (multiple schematized as one), and proteins (several schematized as one). The dimerization domain (DD), DNA-binding domain (DBD), and transactivation domain (TA) are shown, as well as the few human mutations on which human pluripotent stem cell models have been studied (pink). (*B*) Effect of HNF1A$^{P291fsinC}$ mutation on in vitro differentiation steps from pluripotent stem cells to endocrine cells. The steps affected are shown with pink arrows marking either a decrease or increase in efficiency, encoded by the arrow size. (DE) Definitive endoderm, (GT) primitive gut tube, (PF) posterior foregut, (PP) pancreas progenitors, (EP) endocrine progenitors. The different endocrine cell types are denoted by their Greek symbol. (*C*) An increase of glucagon/glucagon-like peptide (GCG/GLP1)-expressing cells is observed in mice with *Hnf1a*$^{fl[exon4]}$ conditional truncating mutations driven by different Cre lines targeting the pancreas as well as intestinal elongation. Ptf1aCre targets the pancreas, Pdx1Cre targets the pancreas/intestine/posterior stomach, Ngn3Cre targets pancreatic endocrine and enteroendocrine cells, and GcgCre targets α cells and GLP1/GCG-expressing enteroendocrine cells.

Crucially, using mouse models carrying four different Cre-inducible deletions of exon 4 that generate a truncated but stable HNF1A protein, Unger et al. (2026) confirmed and further characterized their human in vitro observations (Fig. 1C). They found that *HNF1A* deficiency in endocrine progenitors of the pancreas reduces β-cell differentiation and increases α cells. As this was observed upon mutation induction in endocrine progenitors, this effect is not a consequence of the early HH-driven patterning defects seen in humans but an independent role in endocrine progenitors. Moreover, by systematically comparing multiple lineage-restricted Cre drivers, the study identifies expression of truncated HNF1A in glucagon/GLP-expressing enteroendocrine cells as a driver of intestinal elongation through increased epithelial proliferation, independently of pancreatic dysfunction. While gut elongation may in principle be caused by the increase in intestinal lineage seen in the human model, this is an additional later effect, as the mutation was introduced in mice after the patterning stage. Together, these findings establish HNF1A as a regulator of multiple early developmental patterning decisions that shape both endocrine lineage allocation and intestinal architecture, with consequences that persist despite later differentiation and tissue maturation. Further functional and differentiation defects of enteroendocrine cells that may have secondary effects on diabetes would be worth investigating. They also show the importance of HH control downstream from HNF1A, which raises the question of the relation between the effect of the truncation on HH signaling and the previously reported effect mediated by a dimerization with HNF1B. Further investigations with mutations that cannot heterodimerize should help with disentangling this.

By demonstrating that HNF1A-MODY has deep developmental roots, this work strongly suggests that disease trajectories may be established well before clinical diagnosis, potentially opening windows for earlier and more targeted interventions. The findings also highlight critical questions for the field. First, to what extent do these early lineage biases and intestinal phenotypes manifest in human patients? While in vitro models show a clear shift toward α cells, this has rarely been reported in patients

(Østoft et al. 2014), underscoring the complex interplay between mutation type, protein stability, and gene dosage. Moreover, intestinal elongation may be a readout of interest for patient stratification. Future studies must directly assess endocrine and intestinal characteristics in HNF1A-MODY patients to bridge the gap between bench and bedside. Finally, the models used here, while powerful, represent homozygous HNF1A deficiency rather than the heterozygous state typical of MODY, highlighting the need for mutation-matched and dosage-matched systems, as well as multilineage hPSC models capable of capturing extrapancreatic manifestations.

Taken together, Unger et al. (2026) provide a compelling, multisystem investigation that reframes HNF1A-MODY as a developmental disorder rather than a solely pancreatic β-cell dysfunction. By integrating sophisticated hPSC and in vivo models, they reveal how a single mutation can disrupt fundamental patterning decisions, with consequences that ripple through to the mature endocrine system and beyond. This work not only provides a new conceptual framework for HNF1A-MODY but also goes beyond, as some HNF1A variants also predispose to type 2 diabetes. It thus lays out a clear and challenging road map for future research aimed at translating these developmental insights into clinical practice.

## Competing interest statement

The authors declare no competing interests.

## Acknowledgments

We thank the Max Planck Society for funding.

## References

Cardenas-Diaz FL, Osorio-Quintero C, Diaz-Miranda MA, Kishore S, Leavens K, Jobaliya C, Stanescu D, Ortiz-Gonzalez X, Yoon C, Chen CS, et al. 2019. Modeling monogenic diabetes using human ESCs reveals developmental and metabolic deficiencies caused by mutations in HNF1A. *Cell Stem Cell* **25:** 273–289.e5. doi:10.1016/j.stem.2019.07.007

Çubuk H, Yalçın Çapan Ö. 2021. A review of functional characterization of single amino acid change mutations in HNF transcription factors in MODY pathogenesis. *Protein J* **40:** 348–360. doi:10.1007/s10930-021-09991-8

Cujba A-M, Alvarez-Fallas ME, Pedraza-Arevalo S, Laddach A, Shepherd MH, Hattersley AT, Watt FM, Sancho R. 2022. An HNF1α truncation associated with maturity-onset diabetes of the young impairs pancreatic progenitor differentiation by antagonizing HNF1β function. *Cell Rep* **38:** 110425. doi:10.1016/j.celrep.2022.110425

González BJ, Zhao H, Niu J, Williams DJ, Lee J, Goulbourne CN, Xing Y, Wang Y, Oberholzer J, Blumenkrantz MH, et al. 2022. Reduced calcium levels and accumulation of abnormal insulin granules in stem cell models of HNF1A deficiency. *Commun Biol* **5:** 779. doi:10.1038/s42003-022-03696-z

Hermann FM, Kjærgaard MF, Tian C, Tiemann U, Jackson A, Olsen LR, Kraft M, Carlsson P-O, Elfving IM, Kettunen JLT, et al. 2023. An insulin hypersecretion phenotype precedes pancreatic β cell failure in MODY3 patient-specific cells. *Cell Stem Cell* **30:** 38–51.e8. doi:10.1016/j.stem.2022.12.001

Low BSJ, Lim CS, Ding SSL, Tan YS, Ng NHJ, Krishnan VG, Ang SF, Neo CWY, Verma CS, Hoon S, et al. 2021. Decreased GLUT2 and glucose uptake contribute to insulin secretion defects in MODY3/HNF1A hiPSC-derived mutant β cells. *Nat Commun* **12:** 3133. doi:10.1038/s41467-021-22843-4

Østoft SH, Bagger JI, Hansen T, Pedersen O, Holst JJ, Knop FK, Vilsbøll T. 2014. Incretin effect and glucagon responses to oral and intravenous glucose in patients with maturity-onset diabetes of the young—type 2 and type 3. *Diabetes* **63:** 2838–2844. doi:10.2337/db13-1878

Rezania A, Bruin JE, Arora P, Rubin A, Batushansky I, Asadi A, O'Dwyer S, Quiskamp N, Mojibian M, Albrecht T, et al. 2014. Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. *Nat Biotechnol* **32:** 1121–1133. doi:10.1038/nbt.3033

Unger L, Larsen U, Legøy TA, Hossain MK, Gudmestad JH, Friestad A, Sharmine S, Njølstad PR, Ræder H, Herrera PL, et al. 2026. Defective HNF1A hinders GLI3 processing favoring duodenal versus pancreatic fate, thus leading to intestinal elongation in vivo. *Genes Dev* (this issue). doi:10.1101/gad.353153.125

Zhao Q, Ding L, Yang Y, Sun J, Wang M, Li X, Liu M. 2022. Clinical characteristics of patients with HNF1-α MODY: a literature review and retrospective chart review. *Front Endocrinol* **13:** 900489. doi:10.3389/fendo.2022.900489

# Rethinking HNF1A-MODY: HNF1A at the crossroads of development and multiorgan metabolic disease

Julie Warin and Anne Grapin-Botton

*Genes Dev.* published online April 22, 2026
Access the most recent version at doi:10.1101/gad.353709.126