Number of Supplementary tables: 5

Number of Supplementary figures: 4

Table S1. Rare variants of the *HNF1A* gene identified in this study

Occurrence	Cohort	Condon change	Amino acid change	Reference*
1	1	ACG>ATG	Thr10Met	Ellard (2006) Hum Mutat [1]
1	1	CCG>CTG	Pro33Leu	Bellanne-Chantelot (2008) Diabetes [2]
2	1&2	CGG>TGG	Arg131Trp	Glucksmann (1997) Diabetes [3]
1	1	CAG>TAG	Gln176Ter	Xu (2002) Diabetologia [4]
1	2	CGG>TGG	Arg200Trp	Chevre (1998) Diabetologia [5]
2	1	CGT>CAT	Arg203His	Ng (1999) Diabet Med [6]
1	2	GAA>GTA	Glu240Val[#]	Klupa (2002) Diabetes Care [7]
1	2	CGT>TGT	Arg263Cys	Iwasaki (1997) Diabetes [8]
1	1	-	Gly292Argfs*25	Novel
2	1	GCC>GAC	Ala311Asp	Xu (2005) Eur J Hum Genet [9]
1	2	CAG>TAG	Gln324Ter	Bellanne-Chantelot (2008) Diabetes [2]
1	1	CCT>ACT	Pro379Thr	Bellanne-Chantelot (2008) Diabetes [2]
1	1	G>A	IVS2+1 G>A	Frayling (2001) Diabetes [10]
1	1	CCG>CTG	Pro519Leu	Frayling (1997) Diabetes [11]
1	1	GAG>GGG	Gln541Ter	Novel
1	1	GTC>ATC	Val567Ile	Tonooka N (2002) Diabetologia [12]
1	1	ATC>ATG	Ile618Met	Ng (1999) Diabet Med [6]
1	2	G>A	IVS8-1	Frayling (2001) Diabetes [10]
1	2	-	Arg159fs	Novel
1	2	GAG>GGG	Glu548Gly[†]	Novel
1	2	CCG>CTG	Pro112Leu	Bjørkhaug (2000) BBRC [13]
1	2	GGG>CGG	Gly47Arg[†]	Colclough (2013) Hum Mutat [14]

HNF1A gene Accession No. (NM_000545.5). Reference*: References reporting that this variant causes *HNF1A*-MODY. The variant Glu240Val[#] is novel; but located at a locus where a mutation had been reported to cause *HNF1A*-MODY. The variants Glu548Gly[†] and Gly47Arg[†] are predicted to be benign, neutral and tolerated by PROVEAN, Ployphen-2 and SIFT, respectively.

Table S2. Classifying the rare variants in this study according to the standards and guidelines recommended by the ACMG [15]

Variant	PVS1	PS3	PS4	PM1	PM2	PM5	PP1	PP3	PP4	Classification
The10Met				a [16]	√			√	√	Likely pathogenic
Pro33Leu				a [2,16]	√			√	√*[2]	Likely pathogenic
Arg131Trp		*[17]	*[3,7,10,17]	a [7]	√	*[18,19]	*[3,7]	√	√*	Pathogenic
Gln176Ter	√	*[4]		b	√			√	√*[9]	Pathogenic
Arg203His			√	b	√	*[20,21]	*[6,9]	√	√*[6]	Pathogenic
Gly292Rfs	√				√			√	√	Pathogenic
Ala311Asp			√*[9]		√			√	√*[9]	Likely pathogenic
Pro379Thr			* [2]		√	*[2,9,19,22]		√	√	Pathogenic
IVS2+1 G>A	√				√		*[10]	√	√*[10]	Pathogenic
Pro519Leu				c[23]	√		*[10]	√	√*[10]	Likely pathogenic
Gln541Ter	√			c[23]	√			√	√	Pathogenic
Val567Ile				c[23]	√			√	√*[12]	Likely pathogenic
Ile618Met				c[23]	√			√	√*[6]	Likely pathogenic
Arg200Trp			*[5,10]	b [5]	√		*[5]	√	√*	Pathogenic
Glu240Val#					√	*[7]		√	√	Likely pathogenic
Arg263Cys					√	*[24]		√	√*[8]	Likely pathogenic
Gln324Ter	√				√			√	√*[2]	Pathogenic
IVS8-1	√				√		*[10]		√*	Pathogenic
Arg159fs	√				√			√	√	Pathogenic
Glu548Gly#					√					Uncertain significance

Pro112Leu	*[13,17]	*[4,17]	√	*[13]	√	√*	Pathogenic
Gly47Arg			√			√	Uncertain significance

Novel variant identified in the present study; √ evidence obtained from the present study; * evidence obtained from other studies; a indicates dimerization and DNA binding domains; b indicates the DNA recognition domain (homeodomain) of the DNA binding region; and c indicates the transactivation domain. We used three in silico predictive algorithms [PROVEAN (http://provean.jcvi.org), Polyphen2 (http://g

Table S3. Clinical characteristics of 150 normal subjects (cohort 2) without any abnormal components of metabolic syndrome in the Pinggu cohort.

Characteristic	Normal subjects (n = 150)
Sex, male/female	55/95
Age, mean (SD), years	34.4 (6.4)
BMI, mean (SD), kg/m^2	21.6 (2.2)
SBP, mean (SD), mmHg	111.3 (9.3)
DBP, mean (SD), mmHg	73.6 (7.2)
Waist circumference, mean (SD), cm	
Male	79.8 (5.7)
Female	70.9 (4.4)
FPG, median (IQR), mmol/L	5.09 (4.84, 5.35)
HbA1c, mean (SD), mmol/mol	33.3 (3.15)
HbA1c, mean (SD), %	5.23 (0.26)
Fins, median (IQR), pmol/L	37.71 (26.46, 52.57)
HOMA-IR, median (IQR)	1.19 (0.86, 1.72)
HOMA-ß, median (IQR)	72.34 (52.91, 94.93)
TC, mean (SD), mmol/L	4.51 (0.71)
LDL-c, mean (SD), mmol/L	2.41 (0.67)
HDL-c, mean (SD), mmol/L	
Male	1.21 (0.19)
Female	1.52 (0.20)
Triglycerides, median (IQR), mmol/L	0.65 (0.48, 0.87)
CRE, mean (SD), μmol/L	55.01 (11.40)
UA, mean (SD), μmol/L	
Male	287.79 (62.68)
Female	220.36 (47.51)
ACR, median (IQR), mg/g	3.11 (0.96, 7.30)

Data are presented as means (standard deviations, SD) or medians (interquartile ranges, IQRs). Categorical variables are presented as no. (%). T2DM, type 2 diabetes; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; CRE, serum creatinine; ACR, urinary albumin/creatinine ratio; UA, uric acid; hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate (mL/min per 1.73 m^2) = $175 \times \text{CRE(mg/dL)}^{-1.234} \times \text{age (years)}^{-0.179} \times 0.79$ (if female).

Table S4. Clinical characteristics of the patients with other monogenetic diabetes excluded in cohort 3

Gene	mitochondria	mitochondria	GCK	HNF4A
Variants	A3243G	A3243G	Ser445Arg	Gln357Ter
Sex	male	male	male	male
Age at recruitment, years	43	39	29	34
Age at diagnosis, years	27	32	25	34
Therapy	Insulin, OHA	OHA	Insulin	OHA
Family history of diabetes	Y	Y	Y	N
BMI, kg/m^2	19.1	23.5	19.6	25.6
Waist circumference, cm	84.0	83.0	-	93.0
Blood pressure, mmHg	130/80	108/73	120/70	108/70
FPG, mmol/L	8.63	7.01	6.11	5.86
Fins, pmol/L	112.23	43.41	-	84.38
HbA1c, mmol/mol	77	90	50	46
HbA1c, %	9.2	10.4	6.7	6.4
TC, mmol/L	4.85	4.61	3.64	4.58
TG, mmol/L	1.76	1.57	0.42	2.51
LDL-c, mmol/L	2.90	3.26	1.63	2.79
HDL-c, mmol/L	0.87	0.77	1.89	0.99
UA, µmol/L	299	320	279	395
CRE, µmol/L	69	70	79	68
hs-CRP, mg/L	2.49	1.89	0.25	1.38
ACR, mg/g	10.2	4.1	1.84	9.73
Diabetic retinopathy	Y	N	N	N
Hearing loss	Y	Y	N	N

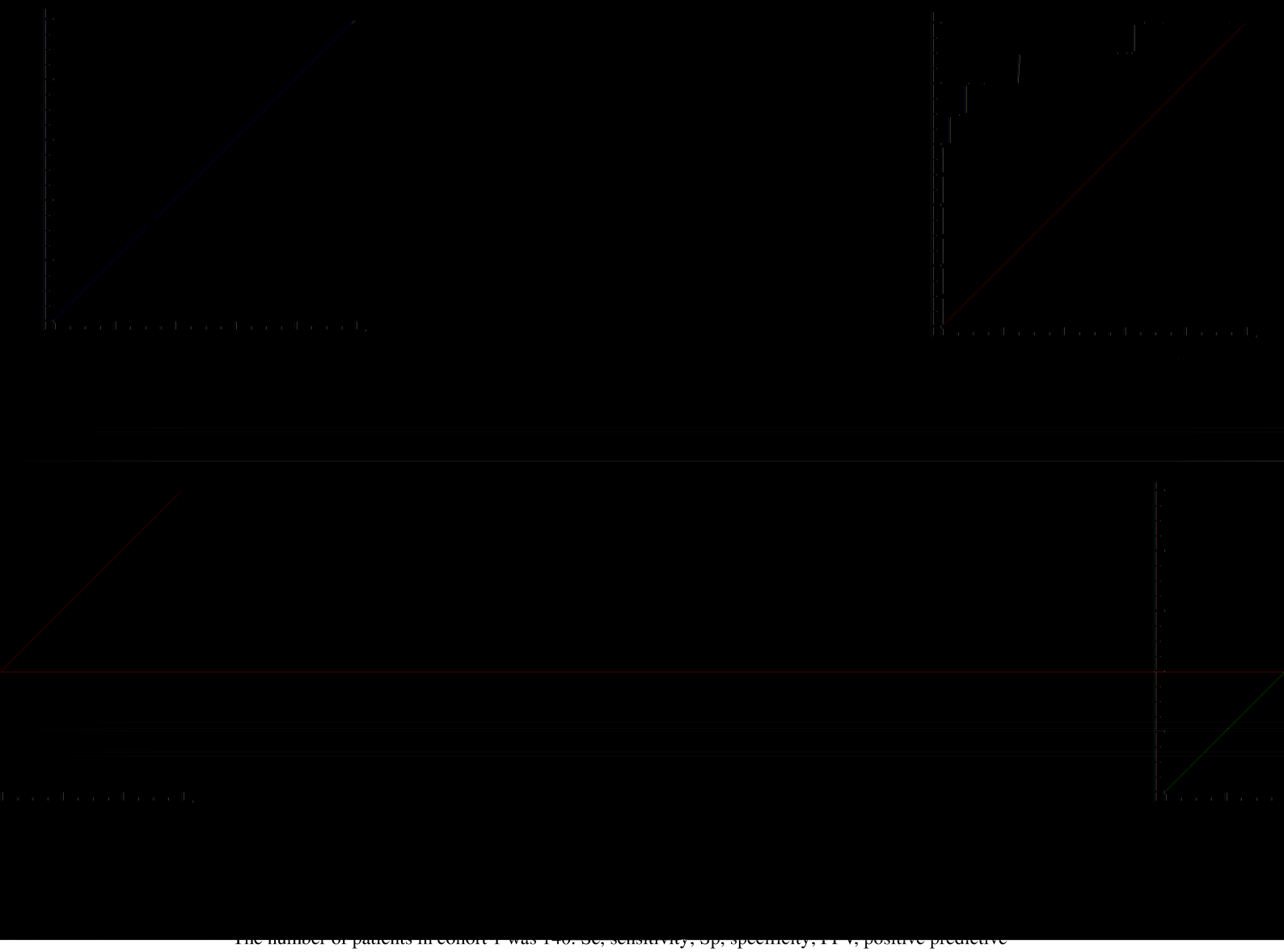
BMI, body mass index; N, no; Y, yes; OHA, oral hypoglycemic agents; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; Fins, fasting serum insulin; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; TG, triglycerides; UA, uric acid; CRE, serum creatinine; ACR, urinary albumin/creatinine ratio, hs-CRP, high-sensitivity C-reactive protein. SI/non-SI conversion calculate: glucose, mmol/L *18.02 = mg/dl; insulin, pmol/L = µU/ml*6.945; TC, mmol/L*38.61 = mg/dl; HDL, mmol/L*38.61 = mg/dl; LDL, mmol/L*38.61 = mg/dl; TG, mmol/L*88.50 = mg/dl; UA, µmol/L = mg/dl*59.485; CRE, µmol/L = mg/dl*88.4.

Table S5. Clinical characteristics of the patients with *HNF1A*-MODY identified in cohort 3

Variants	Arg263Cys	Glu240Val	Arg131Trp	Arg200Trp	Arg200Trp[1]	Ivs8-1G>A	Arg159fs	Gln324Ter	Pro112Leu
Sex	female	female	male	female	female	female	male	female	male
Age at recruitment, years	15	31	34	15	41	29	33	27	31
Age at diagnosis, years	14	13	33	11	18	13	32	22	29
Therapy	Insulin, OHA	insulin	OHA	OHA	OHA	insulin	OHA	insulin	OHA
Family history of diabetes	Y	Y	Y	Y	Family member	Y	N	Y	Y
BMI, kg/m^2	22.8	20.7	18.0	21.9	20.8	22.7	21.6	21.8	17.5
Waist circumference, cm	73.0	64.0	75.5	86.0	83	86.0	91.0	73.0	-
Blood pressure, mmHg	95/65	100/60	100/67	102/64	116/57	95/60	159/101	140/85	110/80
FPG, mmol/L	6.04	4.19	7.28	5.43	6.44	8.96	7.62	9.57	8.12
Fins, pmol/L	-	-	26.88	42.43	91.00	-	49.03	-	25.49
HbA1c, mmol/mol	151	36	58	79	43	61	61	60	52
HbA1c, %	16.0	5.4	7.5	9.4	6.1	7.7	7.7	7.6	6.9
TC, mmol/L	4.24	4.05	3.98	4.49	3.12	4.28	6.15	7.51	4.26
TG, mmol/L	0.88	0.43	1.05	1.01	0.86	1.18	1.54	1.88	1.51
LDL-c, mmol/L	2.59	1.66	2.33	2.65	2.72	2.55	3.88	4.70	2.52
HDL-c, mmol/L	1.32	1.75	1.35	1.39	1.69	1.50	1.25	1.53	1.26
UA, μmol/L	257	350	350	272	358	231	475	283	369
CRE, μmol/L	39	54	69	45	84	47	112	94	76
hs-CRP, mg/L	0.10	0.17	0.10	0.11	0.14	0.44	0.20	1.22	0.18
ACR, mg/g	8.10	10.87	15.26	7.66	12.47	2.25	3776.94	2065.58	5.67
eGFR, mL/min/1.73 m^2	233.72	137.36	126.38	195.89	75.74	164.99	69.89	71.05	115.56

Diabetic retinopathy	N	Y	N	N	Y	N	Y	N	N

1, Mother of proband carrying the variant Arg200Trp. BMI, body mass index; N, no; Y, yes; OHA, oral hypoglycemic agents; FPG, fasting plasma glucose; HbA1c, haemoglobin A1c; Fins, fasting serum insulin; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; TG, triglycerides; UA, uric acid; CRE, serum creatinine; ACR, urinary albumin/creatinine ratio, hs-CRP, high-sensitivity C-reactive protein; eGFR, estimated glomerular filtration rate (mL/min per 1.73 m^2) = $175\times CRE(mg/dL)^{-1.234}\times age\ (years)^{-0.179}\times 0.79$ (if female).



The number of patients in cohort 1 was 148. Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

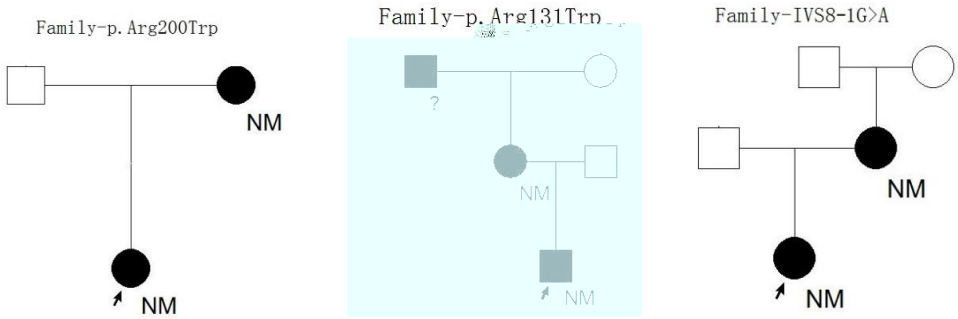
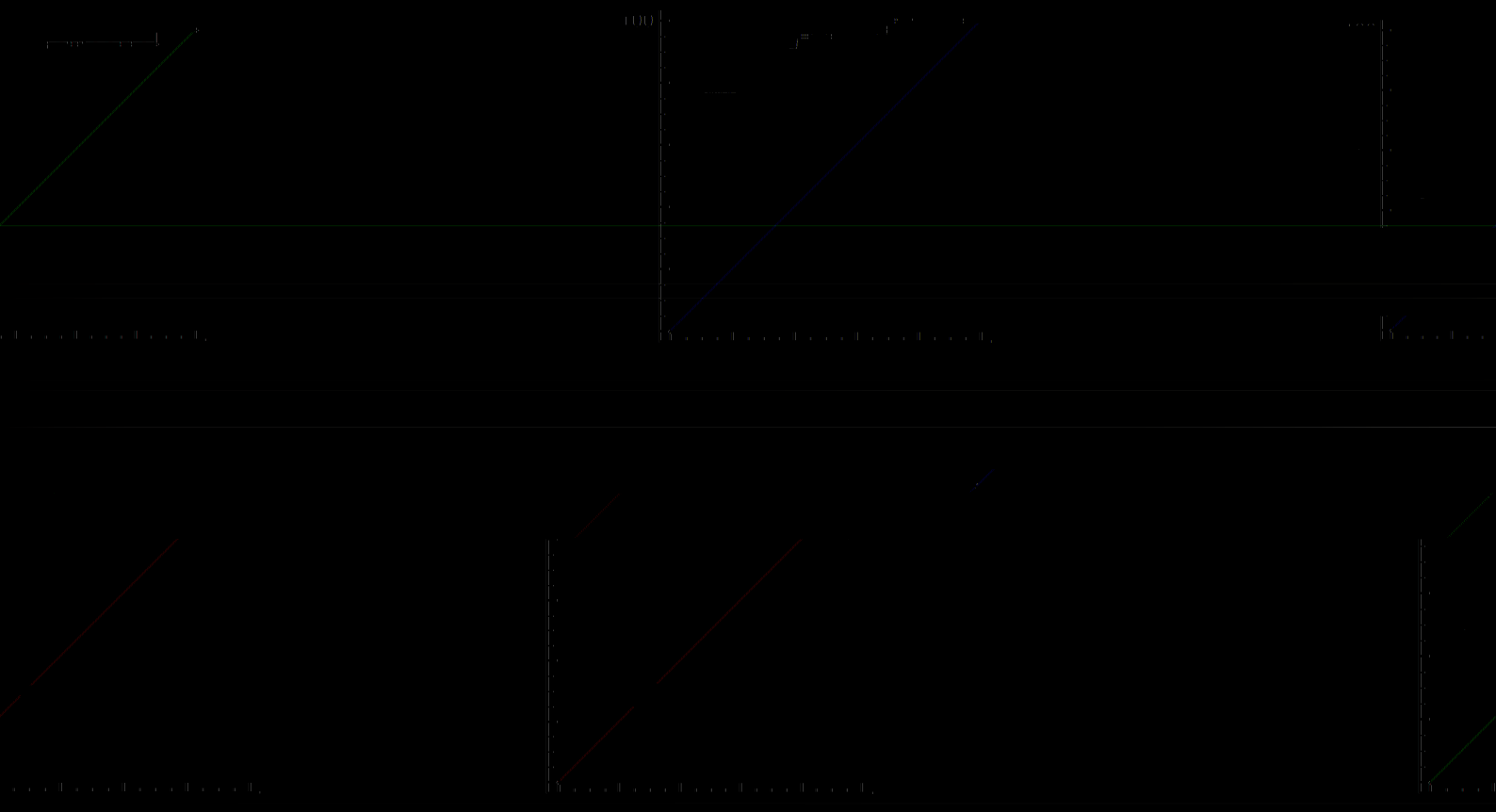
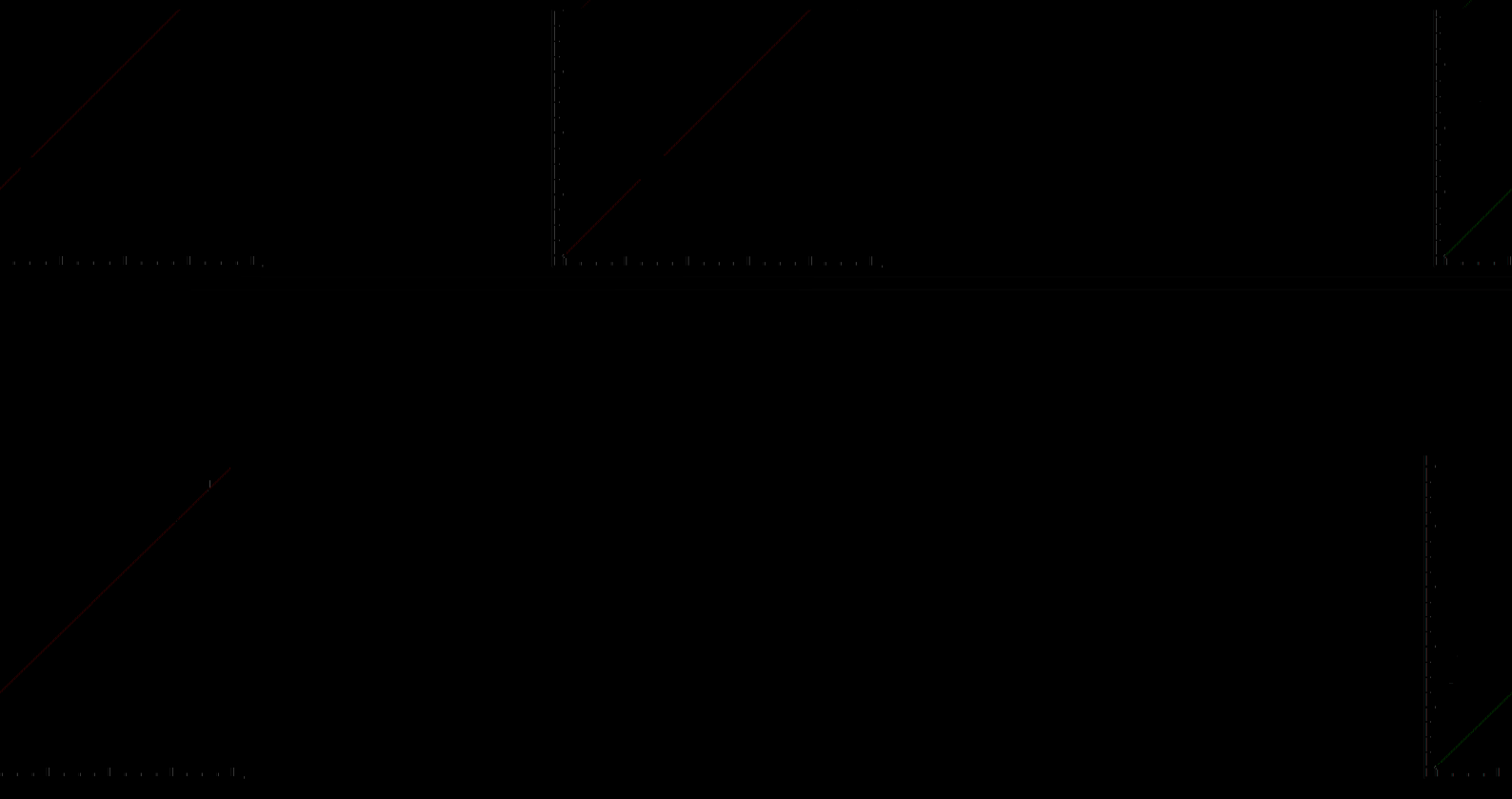


Figure S2. Three pedigrees of carriers of *HNF1A* variants from cohort 3.
In the *HNF1A* variant alleles, N denotes no variant and M denotes a variant. The squares indicate males and the circles indicate females. The arrow indicates the proband. Individuals with diabetes are indicated with filled symbols; normoglycemic individuals are indicated with open symbols. The question marks denote untested family members.





the number of patients in cohorts 1 and 3 was

SSI_S, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value; F, indicates the number of patients with HMP1A-MOD1 who were included in the analysis.

three or four criteria, and *HNF1A*-CSS2 indicates that patients meet four criteria.

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