SUPPLEMENTARY DATA

Absence of islet autoantibodies and modestly raised glucose values at diabetes diagnosis should lead to testing for MODY: Lessons from a 5-year pediatric Swedish national cohort study.

Short running title: Identifying MODY at diabetes diagnosis

Authors

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Supplementary Table 1. Clinical characteristics of subjects.

	All Patients		Autoantibody +ve		Autoantibody -ve		
Phenotype	N	mean (SD) or % (N)	N	mean (SD) or % (N)	N	mean (SD) or % (N)	P
Clinical features							
N			3471		462		
Sex (% female)	3933	45 (1755)	3471	45 (1566)	462	41 (189)	0.09
Age at diagnosis (yrs)	3933	10.1 (4.4)	3471	9.9 (4.4)	462	11.6 (4.5)	$5x10^{-14}$
Parental Diabetes (%)	3933	13 (500)	3471	11 (379)	462	26 (121)	$4x10^{-17}$
Polyuria (%)	3608	94 (3392)	3233	96 (3104)	375	77 (288)	$2x10^{-33}$
Polydipsia (%)	3597	93 (3363)	3225	95 (3077)	372	77 (286)	$1x10^{-29}$
Weight loss (%)	3487	75 (2625)	3129	77 (2423)	358	56 (202)	$2x10^{-16}$
BMI (SDS)	3378	-0.35 (1.55)	3020	-0.44 (1.49)	358	0.43 (1.83)	$1x10^{-16}$
Acanthosis Nigricans (%)	3490	1 (44)	3136	1 (17)	354	8 (27)	$8x10^{-17}$
Investigations- early							
Plasma glucose (mmol/L)	3569	26.5 (9.1)	3198	26.9 (8.9)	371	23.1 (10.8)	$1x10^{-15}$
HbA1c (%)	3541	10.6 (4.5)	3161	10.7 (4.5)	380	9.9 (5.1)	$9x10^{-8}$
DKA (%)	3933	15 (601)	3471	17 (574)	462	6 (27)	$6x10^{-11}$
Investigations – delayed							
High risk HLA (%)	3876	69 (2693)	3419	73 (2486)	457	45 (207)	$2x10^{-30}$
C peptide (nmol/mol)	3596	0.35 (0.44)	3184	0.28 (0.23)	412	0.85 (0.98)	$3x10^{-36}$
C Peptide <0.2 (nmol/mol) (%)	3596	40 (1434)	3184	42 (1337)	412	24 (97)	$1x10^{-13}$

Plasma glucose and C peptide results based on log10 transformation.

SUPPLEMENTARY DATA

Supplementary Table 2. Comparing the research genetically tested autoantibody negative group with those not tested to assess if representative.

	Research tested Autoantibody negative		Not tested Autoantibody negative		
Phenotype	N	mean (SD) or % (N)	N	mean (SD) or % (N)	P value *
Clinical features					
N	227		159		
Sex (% female)	227	37 (85)	159	42 (66)	0.46
Age at diagnosis (yrs)	227	12.06 (4.47)	159	10.88 (4.57)	0.01
Parental Diabetes (%)	227	25 (56)	159	15 (24)	0.03
Polyuria (%)	189	79 (150)	122	87 (106)	0.10
Polydipsia (%)	186	80 (149)	122	85 (104)	0.29
Weight loss (%)	178	58 (104)	118	69 (81)	0.09
BMI (SDS)	178	0.42 (1.96)	118	0.28 (1.85)	0.55
Acanthosis Nigricans (%)	178	9 (16)	115	8 (9)	0.83
Investigations- early					
Plasma glucose (mmol/L)	186	23.6 (10.2)	121	25.9 (11.2)	0.05
HbA1c (%)	186	10.3 (5.0)	123	10.3 (5.1)	0.88
DKA (%)	227	6 (13)	159	8 (13)	0.41
Investigations - delayed					
High risk HLA (%)	226	46 (103)	155	53 (82)	0.18
C peptide (nmol/mol)	213	0.86 (1.01)	131	0.83 (1.07)	0.08

Plasma glucose and C-peptide results based on log10 transformation.
* To correct for the 13 variables analysed a p value of < 0.004 should be considered significantly different.

SUPPLEMENTARY DATA

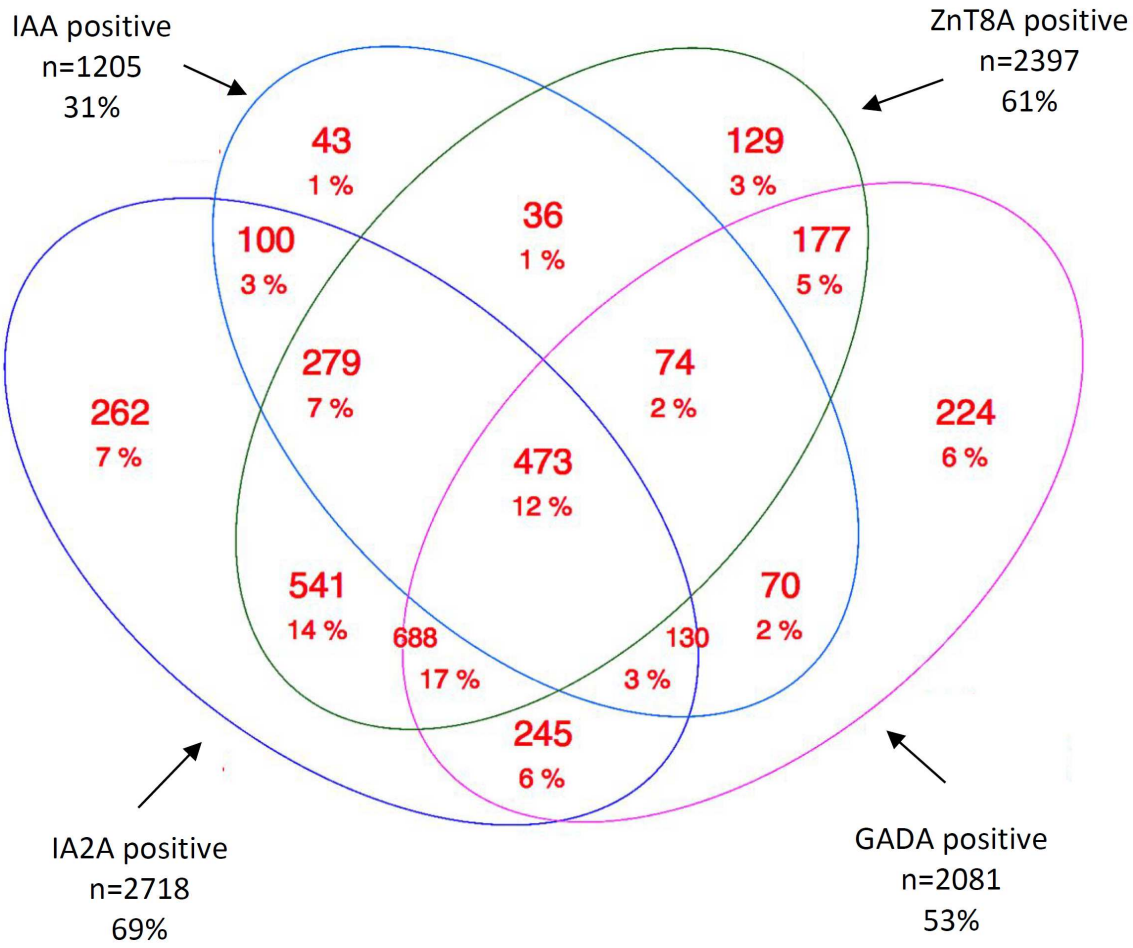
Supplementary Table 3. Comparing the research tested autoantibody positive group with those not tested to assess if representative.

	Research tested Autoantibody positive		Not tested Autoantibody positive		
Phenotype	N	mean (SD) or % (N)	N	mean (SD) or % (N)	P value *
Clinical features					
N	177		3294		
Sex (% female)	177	49 (87)	3294	45 (1479)	0.28
Age at diagnosis (yrs)	177	9.54 (4.43)	3294	9.91 (4.39)	0.27
Parental Diabetes (%)	177	8 (15)	3294	11 (364)	0.32
Polyuria (%)	156	95 (148)	3077	96 (2956)	0.40
Polydipsia (%)	156	94 (147)	3069	95 (2930)	0.43
Weight loss (%)	146	73 (107)	2983	78 (2316)	0.22
BMI (SDS)	143	-0.17 (1.56)	2877	-0.45 (1.49)	0.03
Acanthosis Nigricans (%)	154	1 (2)	2982	1 (15)	0.20
Investigations- early					
Plasma glucose (mmol/L)	155	25.3 (7.4)	3043	27.0 (8.9)	0.02
HbA1c (%)	154	10.5 (4.5)	3007	10.7 (4.5)	0.22
DKA (%)	177	12 (21)	3294	17 (553)	0.10
Investigations - delayed					
High risk HLA (%)	177	72 (128)	3242	73 (2358)	0.93
C peptide (nmol/mol)	166	0.34 (0.263)	3018	0.28 (0.231)	$4x10^{-4}$
Antibodies					
1 antibody +ve	177	23 (40)	3294	19 (618)	0.20
2 antibody +ve	177	35 (61)	3294	34 (1108)	0.81
3 antibody +ve	177	31 (54)	3294	34 (1117)	0.37
4 antibody +ve	177	12 (22)	3294	14 (451)	0.74

Plasma glucose and C peptide results based on log10 transformation.
* To correct for the 17 variables analysed a p value of < 0.003 should be considered significantly different.

SUPPLEMENTARY DATA

Supplementary Figure 1. Breakdown of autoantibody positivity in 3933 individuals tested
Venn diagram produced using venndiag stata package



SUPPLEMENTARY DATA

Supplementary Table 4. Characteristics of the patients referred for genetic testing (and not referred for genetic testing) by clinicians. Plasma glucose and C peptide results based on log10 transformation.

	Patients Tested Clinically		Patients Not Tested Clinically		
Phenotype	N	mean (SD) or % (N)	N	mean (SD) or % (N)	P
Clinical features					
N	81		3852		
Sex (% female)	81	49 (40)	3852	45 (1715)	0.43
Age at diagnosis (yrs)	81	11.8 (4.02)	3852	10.1 (4.44)	$3x10^{-4}$
Parental Diabetes (%)	81	54 (44)	3852	12 (456)	$1x10^{-19}$
Polyuria (%)	69	54 (37)	3539	95 (3355)	$5x10^{-22}$
Polydipsia (%)	69	55 (38)	3528	94 (3325)	$1x10^{-19}$
Weight loss (%)	67	31 (21)	3420	76 (2604)	$2x10^{-14}$
BMI (SDS)	67	0.78 (1.46)	3311	-0.37 (1.55)	$2x10^{-8}$
Acanthosis Nigricans (%)	66	3 (2)	3424	1 (42)	0.20
Investigations- early					
Plasma glucose (mmol/L)	69	17.0 (8.9)	3500	26.7 (9.0)	$3x10^{-13}$
HbA1c (%)	76	8.2 (4.8)	3465	10.7 (4.5)	$9x10^{-12}$
DKA (%)	81	1 (1)	3852	16 (600)	$3x10^{-5}$
Investigations – delayed					
4 Autoantibody negative (%)	81	94 (76)	3852	10 (386)	$9x10^{-67}$
High risk HLA (%)	81	28 (23)	3795	70 (2670)	$2x10^{-14}$
C peptide (nmol/mol)	72	0.85 (0.69)	3524	0.34 (0.43)	$2x10^{-12}$
C Peptide < 0.2 (nmol/mol) (%)	72	13 (9)	3524	40 (1425)	$5x10^{-7}$

SUPPLEMENTARY DATA

Supplementary Table 5: Pathogenic MODY gene variants identified in the cohort

Study Number	Gene	DNA description*	Protein Description*	Predicted Effect	No. of heterozygotes in GnomAD†	Variant Classification‡	References	Clinician requested test?
BDD0024	*GCK*	c.772G>T	p.(Gly258Cys)	Missense	0/123027	Pathogenic	Mantovani (2003) Hum Mutat 22, 338	No
BDD0068	*GCK*	c.571C>T	p.(Arg191Trp)	Missense	2/123005	Pathogenic	Ellard (2000) Diabetologia 43, 250	Yes
BDD0377	*HNF4A*	c.47dup	p.(Tyr16Ter)	Nonsense	0/15464	Pathogenic	Novel	Yes
BDD0387	*GCK*	c.1016A>G	p.(Glu339Gly)	Missense	0/118808	Pathogenic	Sagen (2006) Diabetes 55, 1713	Yes
BDD0422	*GCK*	c.766G>A	p.(Glu256Lys)	Missense	1/123047	Pathogenic	Gidh-Jain (1993) Proc Natl Acad Sci U S A 90, 1932	Yes
BDD0647	*GCK*	c.704T>C	p.(Met235Thr)	Missense	0/122988	Pathogenic	Gloyn (2003) Hum Mutat 22, 353	Yes
BDD0664	*HNF1A*	c.872dup	p.(Gly292fs)	Frameshift	0/132382	Pathogenic	Yamagata (1996) Nature 384, 455	Yes
BDD0665	*GCK*	c.675C>G	p.(Ile225Met)	Missense	0/123114	Likely Pathogenic	Massa (2001) Diabetologia 44, 898	Yes
BDD0717	*HNF1A*	c.872dup	p.(Gly292fs)	Frameshift	0/132382	Pathogenic	Yamagata (1996) Nature 384, 455	Yes
BDD0809	*HNF4A*	c.46_49+6delinsG	p.(?)	Aberrant splicing	0/15464	Pathogenic	Novel	Yes
BDD0840	*GCK*	c.766G>A	p.(Glu256Lys)	Missense	1/123047	Pathogenic	Gidh-Jain (1993) Proc Natl Acad Sci U S A 90, 1932	Yes
BDD0842	*GCK*	c.854G>A	p.(Gly285Asp)	Missense	0/120800	Likely Pathogenic	Novel (1 family in MODY DB)	Yes
BDD0911	*GCK*	c.766G>A	p.(Glu256Lys)	Missense	1/123047	Pathogenic	Gidh-Jain (1993) Proc Natl Acad Sci U S A 90, 1932	Yes
BDD1002	*HNF4A*	c.956_958dup	p.(Leu319dup)	In-frame amino acid deletion	0/122264	Pathogenic	Pearson (2005) Diabetologia 48, 878	Yes
BDD1107	*HNF1A*	c.814C>T	p.(Arg272Cys)	Missense	0/121947	Pathogenic	Yoshiuchi (1999) Diabetologia 42, 621	Yes
BDD1337	*GCK*	c.680-2A>G	p.(?)	Aberrant splicing	0/122599	Pathogenic	Osbak (2009) Hum Mutat 30, 1512	Yes
BDD1433	*GCK*	c.442T>A	p.(Phe148Ile)	Missense	0/123131	Likely Pathogenic	Osbak (2009) Hum Mutat 30, 1512	Yes
BDD1470	*GCK*	c.878T>G	p.(Ile293Arg)	Missense	0/122348	Pathogenic	Novel (3 families in MODY DB)	Yes
BDD1515	*HNF4A*	c.956_958dup	p.(Leu319dup)	In-frame amino acid deletion	0/122264	Pathogenic	Pearson (2005) Diabetologia 48, 878	Yes
BDD1526	*GCK*	c. 704T>C	p.(Met235Thr)	Missense	0/122988	Pathogenic	Gloyn (2003) Hum Mutat 22, 353	Yes
BDD1557	*HNF4A*	c.1A>G	p.(?)	Start-loss	0/122240	Pathogenic	Novel	Yes
BDD1586	*GCK*	c.623C>T	p.(Ala208Val)	Missense	1/123121	Pathogenic	Osbak (2009) Hum Mutat 30, 1512	Yes
BDD1930	*GCK*	c.490C>T	p.(Leu164Phe)	Missense	0/15478	Likely Pathogenic	Nam (2000) Diabetes Res Clin Pract 50, 169	Yes
BDD2002	*GCK*	c.766G>A	p.(Glu256Lys)	Missense	1/123047	Pathogenic	Gidh-Jain (1993) Proc Natl Acad Sci U S A 90, 1932	Yes
BDD2035	*GCK*	c.1144T>C	p.(Cys382Arg)	Missense	0/115895	Pathogenic	Osbak (2009) Hum Mutat 30, 1512	Yes
BDD2161	*GCK*	c.680-2A>G	p.(?)	Aberrant splicing	0/122599	Pathogenic	Osbak (2009) Hum Mutat 30, 1512	No
BDD2282	*HNF1A*	c.493T>C	p.(Trp165Arg)	Missense	0/138536	Pathogenic	Tatsi (2013) Pediatr Diabetes epub, epub	Yes

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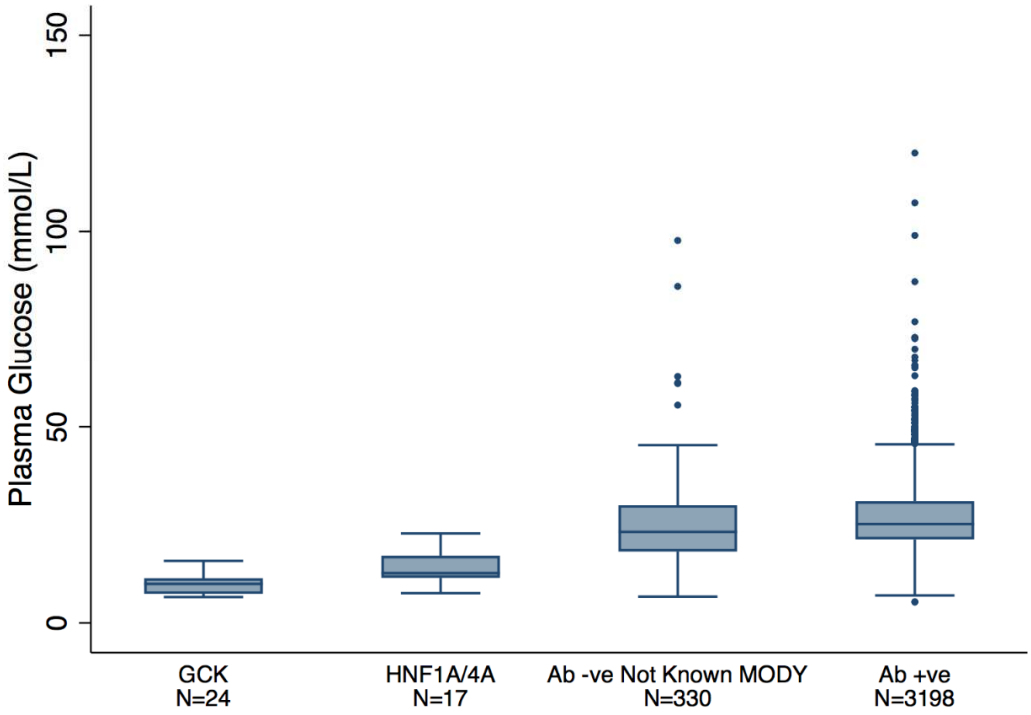
BDD2362	*GCK*	c.929T>G	p.(Val310Gly)	Missense	1/121775	Likely Pathogenic	Novel (2 families in MODY DB)	Yes
BDD2549	*HNF4A*	c.931C>T	p.(Arg311Cys)	Missense	0/121920	Pathogenic	Yorifuji (2012) Pediatr Diabetes 13, 26	No
BDD2655	*GCK*	c.869A>G	p.(Glu290Gly)	Missense	0/121651	Likely Pathogenic	Novel	No
BDD2788	*HNF1A*	c.1340C>T	p.(Pro447Leu)	Missense	0/15467	Pathogenic	Yamagata (1996) Nature 384, 455	No
BDD2801	*GCK*	c.1305dup	p.(Ile436fs)	Frameshift	0/120231	Pathogenic	Novel	No
BDD2844	*GCK*	c.1142T>C	p.(Met381Thr)	Missense	0/115895	Pathogenic	Osbak (2009) Hum Mutat 30, 1512	Yes
BDD2952	*GCK*	c.162T>G	p.(Ser54Arg)	Missense	3/123132	Likely Pathogenic	Novel (2 families in MODY DB)	Yes
BDD3040	*GCK*	c. 704T>C	p.(Met235Thr)	Missense	0/122988	Pathogenic	Gloyn (2003) Hum Mutat 22, 353	No
BDD3079	*GCK*	c.766G>A	p.(Glu256Lys)	Missense	1/123047	Pathogenic	Gidh-Jain (1993) Proc Natl Acad Sci U S A 90, 1932	Yes
BDD3233	*GCK*	c.571C>T	p.(Arg191Trp)	Missense	2/123005	Pathogenic	Ellard (2000) Diabetologia 43, 250	Yes
BDD3254	*GCK*	c. 704T>C	p.(Met235Thr)	Missense	0/122988	Pathogenic	Gloyn (2003) Hum Mutat 22, 353	Yes
BDD3490	*HNF4A*	c.47dup	p.(Tyr16Ter)	Nonsense	0/15464	Pathogenic	Novel	No
BDD3591	*HNF1A*	c.160C>T	p.(Arg54Ter)	Nonsense	0/116545	Pathogenic	Lambert (2003) Diabetes Care 26, 333	No
BDD3640	*GCK*	c.854G>A	p.(Gly285Asp)	Missense	0/120800	Likely Pathogenic	Novel (1 family in MODY DB)	No
BDD3791	*HNF1A*	c.25C>T	p.(Gln9Ter)	Nonsense	0/121466	Pathogenic	Novel	Yes
BDD3798	*HNF1A*	c.431T>C	p.(Leu144Pro)	Missense	0/123112	Pathogenic	Colclough (2013) Hum Mutat 34, 669	No
BDD3961	*HNF1A*	c.366C>G	p.(Tyr122Ter)	Nonsense	0/123098	Pathogenic	Novel	Yes
BDD3973	*GCK*	c.1167_1168dupCA	p.(Ile390fs)	Frameshift	0/112573	Pathogenic	Novel	Yes
BDD3980	*HNF1A*	c.872dup	p.(Gly292fs)	Frameshift	0/132382	Pathogenic	Yamagata (1996) Nature 384, 455	No

*Variants described according to Human Genome Variation Society (HGVS) nomenclature guidelines v15.11 and using the reference sequences NM_000162.3 for *GCK*, NM_000545.6 for *HNF1A*, NM_175914.4 for *HNF4A* and NM_000458.3 for *HNF1B*.
†GnomAD data is number of heterozygous individuals identified out of the total number of individuals with genotype quality (GQ) >= 20 and depth (DP) >= 10 over a 10bp window containing the variant. GnomAD data accessed on 03/11/2017.
‡Variants classified according to the ACGS and ACMG best practice guidelines for variant interpretation (http://www.acgs.uk.com/media/1092626/uk_practice_guidelines_for_variant_classification_2017.pdf and https://www.acmg.net/docs/Standards_Guidelines_for_the_Interpretation_of_Sequence_Variants.pdf).

SUPPLEMENTARY DATA

Supplementary Figure 2. Fasting plasma glucose in known MODY patients (both GCK and HNF1A/HNF4A) and those without known MODY (autoantibody negative and autoantibody positive).



SUPPLEMENTARY DATA

Supplementary Table 6. Differences in autoantibody negative patients with or without MODY. This table consist of only the 303 antibody negative patients who were sequenced for MODY. Plasma glucose and C peptide results based on log10 transformation.

	MODY		Not MODY		
Phenotype	N	mean (SD) or % (N)	N	mean (SD) or % (N)	P
Clinical features					
N	46		257		
Sex (% female)	46	54 (25)	257	38 (98)	0.05
Age at diagnosis (yrs)	46	12.1 (4.39)	257	12.0 (4.39)	0.84
Parental Diabetes (%)	46	63 (29)	257	27 (68)	$4x10^{-6}$
Polyuria (%)	38	34 (13)	215	79 (169)	$1x10^{-7}$
Polydipsia (%)	38	34 (13)	212	80 (169)	$6x10^{-8}$
Weight loss (%)	38	16 (6)	202	57 (115)	$2x10^{-6}$
BMI (SDS)	37	0.54 (1.21)	203	0.50 (1.92)	0.85
Acanthosis Nigricans (%)	37	0 (0.00)	202	9 (18)	0.08
Investigations- early					
Plasma glucose (mmol/L)	41	11.7 (4.13)	209	23.7 (10.0)	$7x10^{-18}$
HbA1c (%)	46	7.0 (3.7)	211	10.2 (5.0)	$4x10^{-19}$
DKA (%)	46	0 (0)	257	5 (14)	0.14
Investigations – delayed					
High risk HLA (%)	46	20 (9)	256	45 (116)	$1x10^{-3}$
C peptide (nmol/mol)	41	0.81 (0.63)	240	0.48 (0.99)	$1x10^{-4}$
C Peptide < 0.2 nmol/mol (%)	41	2 (1)	240	23 (54)	$1x10^{-3}$

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Supplementary Table 7. GCK-MODY only vs. not known-MODY. Plasma glucose and C peptide results based on log10 transformation

	GCK MODY		Not known MODY		
Phenotype	N	mean (SD) or % (N)	N	mean (SD) or % (N)	P
Clinical features					
N	29		3887		
Sex (% female)	29	41 (12)	3887	45 (1730)	0.85
Age at diagnosis (yrs)	29	11.0 (4.8)	3887	10.1 (4.4)	0.25
Parental Diabetes (%)	29	62 (18)	3887	12 (471)	$4x10^{-10}$
Polyuria (%)	23	26 (6)	3570	95 (3379)	$4x10^{-17}$
Polydipsia (%)	23	26 (6)	3559	94 (3350)	$2x10^{-16}$
Weight loss (%)	23	13 (3)	3449	76 (2619)	$4x10^{-10}$
BMI (SDS)	22	0.50 (1.23)	3341	-0.36 (1.55)	$4x10^{-3}$
Acanthosis Nigricans (%)	22	0 (0)	3453	1 (44)	1
Investigations- early					
Plasma glucose (mmol/L)	24	9.9 (2.5)	3528	26.7 (9.0)	$7x10^{-16}$
HbA1c (%)	29	6.3 (2.5)	3495	10.7 (4.5)	$2x10^{-47}$
DKA (%)	29	0 (0)	3887	15 (601)	0.02
Investigations – delayed					
4 Antibody negative (%)	29	100 (29)	3887	11 (416)	$2x10^{-28}$
High risk HLA (%)	29	14 (4)	3830	70 (2684)	$6x10^{-10}$
C peptide (nmol/mol)	26	0.92 (0.62)	3555	0.34 (0.43)	$3x10^{-8}$
C Peptide < 0.2 nmol/mol (%)	26	4 (1)	3555	40 (1433)	$1x10^{-4}$

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Supplementary Table 8. HNF1A/HNF4A MODY vs. Not known MODY.

	HNF1A/HNF4A MODY		Not known MODY		
Phenotype	N	mean (SD) or % (N)	N	mean (SD) or % (N)	P
Clinical features					
N	17		3887		
Sex (% female)	17	76 (13)	3887	45 (1730)	0.01
Age at diagnosis (yrs)	17	13.8 (3.2)	3887	10.1 (4.4)	$2x10^{-4}$
Parental Diabetes (%)	17	65 (11)	3887	12 (471)	$6x10^{-7}$
Polyuria (%)	15	47 (7)	3570	95 (3379)	$4x10^{-7}$
Polydipsia (%)	15	47 (7)	3559	94 (3350)	$7x10^{-7}$
Weight loss (%)	15	0.2 (3)	3449	76 (2619)	$9x10^{-6}$
BMI (SDS)	15	0.61 (1.2)	3341	-0.36 (1.6)	0.009
Acanthosis Nigricans (%)	15	0 (0)	3453	1 (44)	1
Investigations- early					
Plasma glucose (mmol/L)	17	14.2 (4.8)	3528	26.7 (9.0)	$7x10^{-7}$
HbA1c (%)	17	8.3 (2.4)	3495	10.7 (4.5)	$1x10^{-4}$
DKA (%)	17	0 (0)	3887	15 (601)	0.09
Investigations – delayed					
4 Antibody negative (%)	17	100 (17)	3887	11 (416)	$4x10^{-17}$
High risk HLA (%)	17	29 (5)	3830	70 (2684)	$7x10^{-4}$
C peptide (nmol/mol)	15	1.10 (0.63)	3555	0.34 (0.43)	$6x10^{-8}$
C Peptide < 0.2 nmol/mo) (%)	15	0 (0)	3555	40 (1433)	$7x10^{-4}$

Plasma glucose and C peptide results based on log10 transformation.

SUPPLEMENTARY DATA

Supplementary Table 9. HNF1A/HNF4A MODY vs. GCK MODY. Plasma glucose and C peptide results based on log10 transformation.

	GCK MODY		HNF1A/4A MODY		
Phenotype	N	mean (SD) or % (N)	N	mean (SD) or % (N)	P
Clinical features					
N	29		17		
Sex (% female)	29	41 (12)	17	76 (13)	0.03
Age at diagnosis (yrs)	29	11.0 (4.8)	17	13.8 (3.2)	0.04
Parental Diabetes (%)	29	62 (18)	17	65 (11)	1.00
Polyuria (%)	23	26 (6)	15	47 (7)	0.30
Polydipsia (%)	23	26 (6)	15	47 (7)	0.30
Weight loss (%)	23	13 (3)	15	20 (3)	0.66
BMI (SDS)	22	0.50 (1.23)	15	0.61 (1.2)	0.79
Acanthosis Nigricans (%)	22	0 (0)	15	0 (0)	1.00
Investigations- early					
Plasma glucose (mmol/L)	24	9.9 (2.5)	17	14.2 (4.8)	$6x10^{-4}$
HbA1c (%)	29	6.3 (2.5)	17	8.3 (2.4)	0.01
DKA (%)	29	0 (0)	17	0 (0)	1.00
Investigations – delayed#					
4 Antibody negative (%)	29	100 (29)	17	100 (17)	1.00
High risk HLA (%)	29	14 (4)	17	29 (5)	0.26
C peptide (nmol/mol)	26	0.92 (0.62)	15	1.10 (0.63)	0.38
C Peptide < 0.2 (nmol/mol) (%)	26	4 (1)	15	0 (0)	1.00

SUPPLEMENTARY DATA

Supplementary Table 10. Effectiveness of HbA1c and family history on identifying MODY in autoantibody negative individuals.

Criteria	Total number autoantibody negative	Total number of individuals tested for MODY	Number (%) of the 46 MODY patients detected
All	380	257	46 (100%)
HbA1c<7.5% (58mmol/mol)	100 (26%)	73 (28%)	36 (78%)
Parent affected	120 (32%)	96 (37%)	29 (63%)
HbA1c < 7.5% (58mmol/mol) or parent affected	174 (46%)	131 (51%)	44 (96%)
HbA1c < 7.5% (58mmol/mol) and parent affected	46 (12%)	38 (15%)	21 (46%)

*Note this table only includes the patients who had HbA1c at diagnosis data. This was available on 380 of 462 patients that were negative for all 4 autoantibodies and 257 of 303 patients that were negative for all 4 autoantibodies and were sequenced. Parental history was available on all subjects. The percentages shown are of the patients in whom HbA1c was available

SUPPLEMENTARY DATA

Supplementary Table 11. Initial and present treatment

No	Study Number	Sex	Age	Initial diagnosis	Initial treatment	Clinical / Research Diagnostic Test	Current Treatment	HbA1c mmol/mol	Follow up years
1	BDD0024	M	5.4	Unclassified	None	Clinical *GCK*	None	42	8
2	BDD0068	M	11.1	Unclassified	None	Clinical *GCK*	None	47	7.5
3	BDD0377	M	15	susp MODY	Insulin	Clinical *GCK*	None	40	3
4	BDD0387	F	15.6	Type 2	Diet	Clinical *GCK*	None	47	9.5
5	BDD0422	M	16.1	susp MODY	Diet	Clinical *GCK*	None	51	3
6	BDD0647	M	16.4	susp MODY	Diet	Clinical *GCK*	None	38	4.5
7	BDD0664	F	16	susp MODY	Diet	Clinical *GCK*	None	42	2
8	BDD0665	F	13.7	susp MODY	Diet	Clinical *GCK*	None	34	2
9	BDD0717	M	6.5	susp MODY	Diet	Clinical *GCK*	None	51	4
10	BDD0809	F	16.2	susp MODY	Diet	Clinical *GCK*	None	42	2
11	BDD0840	F	5.8	susp MODY	Diet	Clinical *GCK*	None	47	10
12	BDD0842	F	6.6	Type 1	Diet	Clinical *GCK*	None	46	8
13	BDD0911	M	9.9	susp MODY	Insulin	Clinical *GCK*	None	46	10
14	BDD1002	F	17	Type 2	Metformin	Clinical *GCK*	None	51	1.5
15	BDD1107	M	7.8	susp MODY	Diet	Clinical *GCK*	None	47	8.5
16	BDD1337	M	5.5	susp MODY	Diet	Clinical *GCK*	None	41	9
17	BDD1433	F	14.4	susp MODY	Insulin	Clinical *GCK*	None	40	8
18	BDD1470	F	11.8	susp MODY	Diet	Clinical *GCK*	None	42	6
19	BDD1515	M	16.9	susp MODY	None	Clinical *GCK*	None	47	0

SUPPLEMENTARY DATA

20	BDD1526	M	15	susp MODY	Diet	Clinical *GCK*	None	48	0
21	BDD1557	M	13.9	Type 1	Insulin	Clinical *GCK*	None	44	2
22	BDD1586	F	3.7	susp MODY	None	Clinical *GCK*	None	44	6.5
23	BDD1930	M	4.9	Type 1	Insulin	Clinical *GCK*	None	48	1
24	BDD2002	F	11.5	Type 1	Insulin	Clinical *HNF1A*	Sulphonylurea+Insulin*	47	6.5
25	BDD2035	F	15.5	Type 2	Metformin	Clinical *HNF1A*	Sulphonylurea	36	5
26	BDD2161	F	15.5	susp MODY	Insulin	Clinical *HNF1A*	None	45	8
27	BDD2282	F	11	Type 2	Diet	Clinical *HNF1A*	Sulphonylurea	59	9.5
28	BDD2362	M	13.9	susp MODY	Insulin	Clinical *HNF1A*	None	40	11
29	BDD2549	M	7.9	susp MODY	None	Clinical *HNF1A*	Sulphonylurea	68	10
30	BDD2655	F	15.1	Type 1	Insulin	Clinical *HNF4A*	None	52	10
31	BDD2788	F	7.2	susp.MODY	Diet	Clinical *HNF4A*	Sulphonylurea	55	10
32	BDD2801	F	11.8	susp MODY	Insulin	Clinical *HNF4A*	Insulin**	72	4.5
33	BDD2844	F	15.4	Type 1	Insulin	Clinical *HNF4A*	Insulin***	60	9
34	BDD2952	M	16.5	Type 1	Insulin	Clinical *HNF4A*	Insulin****	67	7.5
35	BDD3040	M	11	unclass.	Diet	Research *GCK*	None	46	7
36	BDD3079	M	15.5	Type 1	Diet	Research *GCK*	None	36	2.5
37	BDD3233	F	2.8	Type 1	Insulin	Research *GCK*	None	46	7
38	BDD3254	F	4	Type 1	Insulin	Research *GCK*	None	53	7
39	BDD3490	M	13.2	Type 2	Metformin	Research *GCK*	None	43	5
40	BDD3591	M	9.7	susp MODY	None	Research *GCK*	None	42	11

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41	BDD3640	F	10.8	susp MODY	None	Research *HNF1A*	None	49	6.5
42	BDD3791	F	15.8	Type 1	Insulin.	Research *HNF1A*	Sulphonylurea+Januvia	40	9
43	BDD3798	F	17.1	Type 2	Insulin+Metformin	Research *HNF1A*	Sulphonylurea	56	1
44	BDD3961	M	15.7	Type 1	Insulin	Research *HNF1A*	Sulphonylurea	69	2.5
45	BDD3973	F	16.9	Type 2	Diet	Research *HNF4A*	None	33	1
46	BDD3980	F	17	Type 1	Insulin	Research *HNF4A*	Sulphonylurea	50	6.5

Age = age at diagnosis of diabetes, susp = suspected, HbA1c after molecular genetic diagnosis
*Patient chose to stay on insulin in addition to sulphonylurea, **reported worse control on sulphonylurea so recommended insulin, *** has not tried Sulphonylurea, ****tried glibenclamide, but chose to continue Insulin

SUPPLEMENTARY DATA

Supplementary Table 12. Characteristics of the patients referred for genetic testing and autoantibody negative patients not referred for genetic testing by clinicians. Plasma glucose and C peptide results based on log10 transformation.

	Antibody Negative Patients Clinically Tested		Antibody Negative Patients Not Clinically Tested		
Phenotype	N	mean (SD) or % (N)	N	mean (SD) or % (N)	P
Clinical features					
N	76		386		
Sex (% female)	76	50 (38)	386	39 (151)	0.10
Age at diagnosis (yrs)	76	11.7 (4.1)	386	11.6 (4.6)	0.75
Parental Diabetes (%)	76	54 (41)	386	21 (80)	$2x10^{-8}$
Polyuria (%)	64	50 (32)	311	82 (256)	$2x10^{-7}$
Polydipsia (%)	64	52 (33)	308	82 (253)	$9x10^{-7}$
Weight loss (%)	62	27 (17)	296	63 (185)	$5x10^{-7}$
BMI SDS	62	0.75 (1.38)	296	0.37 (1.91)	0.07
Acanthosis Nigricans (%)	61	3 (2)	293	9 (25)	0.19
Investigations - early					
Plasma glucose (mmol/L)	64	16.3 (8.5)	307	24.6 (10.7)	$1x10^{-9}$
HbA1c (%)	71	8.1 (4.8)	309	10.3 (5.0)	$1x10^{-8}$
DKA (%)	76	1 (1)	386	7 (26)	0.10
Investigations – delayed					
High risk HLA (%)	76	29 (22)	381	45 (185)	0.002
C peptide (nmol/mol)	68	0.89 (0.69)	344	0.85 (1.03)	0.02
C Peptide < 0.2 (nmol/mol)	68	12 (8)	344	26 (89)	0.012