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**Systematic population screening, using biomarkers and genetic testing, identifies 2.5% of the U.K. pediatric diabetes population with monogenic diabetes**

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*Published in:*  
Diabetes Care

*DOI:*  
[10.2337/dc16-0645](https://doi.org/10.2337/dc16-0645)

*Publication date:*  
2016

*Document Version*  
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

*Citation for published version (APA):*

Shepherd, M., Shields, B., Hammersley, S., Hudson, M., McDonald, T. J., Colclough, K., Oram, R. A., Knight, B., Hyde, C., Cox, J., Mallam, K., Moudiotis, C., Smith, R., Fraser, B., Robertson, S., Greene, S., Ellard, S., Pearson, E. R., Hattersley, A. T., & on behalf of the UNITED Team (2016). Systematic population screening, using biomarkers and genetic testing, identifies 2.5% of the U.K. pediatric diabetes population with monogenic diabetes. *Diabetes Care*, 39(11), 1879-1888. <https://doi.org/10.2337/dc16-0645>

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**Table 1. Approaches used to identify monogenic diabetes in pediatric populations**

Type of study	Country	Area	Initial cohort (n)	Cohort characteristics	Testing strategy (subgroup tested)	Genes tested	Prevalence in genetically tested	Minimal prevalence of monogenic diabetes	Reference
<b>Systematic studies ordered by number in study</b>									
Multi-centre population based	USA	6 centres: California, Ohio, Hawaii, South Carolina, Washington	5963	1) Diagnosed <20yrs 2) Diagnosed<6mths	1) AB-ve (x2), fasting c-peptide $\geq 0.8$ ng/ml (n=586) 2) Diagnosed <6mths (n=7)	1) HNF1A, HNF4A, GCK, 2) KCNJ11, INS, ABCC8	1) 8.4% (47/586) 2) 71.4% (5/7)	1.2% 0.2% (Total 1.4%)	Pihoker 2013 Shankar2013
Nationwide population based	Norway	Nationwide	2756	Newly diagnosed aged 0-14 yrs	1) AB-ve (x2) and affected parent (n=46) 2) AB-ve, HbA1c <7.5% (58mmol/mol) and not on insulin (n=10) 3) diagnosed <12 mths (n=24)	1) HNF1A, HNF4A, MIDD 2)GCK, 3)KCNJ11, ABCC8, INS	1) 13.0% (6/46) 2) 30.0% (3/10) 3) 16.6% (4/24)	1.1%	Irgens 2013
Epidemiological data / nationwide genetic test results	Poland	3 centres: Lodz, Katowice, Gdansk	2568	Aged 0-18 yrs	1) AB-ve, affected parent, non insulin dependent 2) HbA1c<7.5% (58mmol/mol) 3) Diagnosed <6mths 4) Syndromic diabetes	1)HNF1A, HNF4A, HNF1B, 2)GCK 3)KCNJ11, ABCC8, INS, 4)WFS, Alstrom	32.1% (100/311)	3.1-4.2%	Fendler 2012
Single pediatric clinic population	USA	New York	939	Clinical diagnosis T1D Aged 6mths-20yrs	AB-ve (x3) plus either HbA1c $\leq 7\%$ (53mmol/mol) and $\leq 0.5$ u insulin /kg/day / > 1yr post diagnosis c-peptide+ or 3 gen. FH (n=58)	GCK HNF1A	8.6% (5/58)	0.5%*	Gandica 2015
Pediatric clinics in single city	Australia	Sydney	497	1) Clinical diagnosis T1D 2) Diagnosed 6mths – 16 yrs	AB-ve (x4- on 2 occasions (n=19)	1) HNF1A, HNF4A, 2) INS, KCNJ11	5% (1/19)	1.2%*	Hameed 2010
Single pediatric clinic population	Spain	Madrid	252	1) Clinical diagnosis T1D 2) Diagnosed 6mths-17yrs of age	AB-ve (x5) (n=25)	1)HNF1A, HNF4A, 2)KCNJ11, INS	8.0% (2/25)	0.8%*	Rubio-Cabezas 2009
Pediatric clinic: Case Histories	New Zealand	South Island	160	Pediatric diabetes <18yrs	AB-ve ( x2?) (n=4)	GCK, HNF1B, HNF1A	2.5% (4/160)	2.5%	Wheeler 2013
Nationwide	Japan	Centres throughout Japan	N/K	Aged 6mths -20yrs	1) AB-ve (x 2), BMI<25, dominant family history or 2) renal cysts (n=80)	1) HNF1A, GCK, HNF4A, MIDD, 2) HNF1B	47.5% (38/80)	-	Yorifuji 2012
Single pediatric clinic population	USA	Colorado	N/K	Diabetes <25 yrs	c-peptide $\geq 0.1$ ng/ml, AB-ve (x3) (n=97)	HNF1A, HNF4A, GCK, PDX1, HNF1B	22.7% (22/97)	N/K	Chambers 2015

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<b>Non systematic studies relying on clinical recognition and clinical testing</b>								
<b>Type of study</b>	<b>Country</b>	<b>Area</b>	<b>Initial cohort of subject with diabetes and the population taken from (n)</b>	<b>Cohort characteristics</b>	<b>How monogenic diabetes was defined</b>	<b>Number with monogenic diagnosis (% all diabetes)</b>	<b>Prevalence per 100,000 population</b>	<b>Reference</b>
Postal questionnaire survey	UK	Nationwide	15,255 (59M pop )	Diabetes <16 yrs 'non T1'	Confirmed by genetic test	20 (0.13%)	0.17	Ehtisham 2004
Questionnaire and telephone survey	Germany	State of Baden-Württemberg	2640 (2.6M) pop	0-20yrs	Clinician diagnosis (45% genetically confirmed)	58 (2.1%)	2.3	Neu 2009
Assessment of Childhood Diabetes registry	Germany	Saxony (34 paed clinics)	865 new cases Prevalence cases not stated (4.8M pop)	Newly diagnosed aged 0-15yrs	Confirmed by genetic test	21 (2.4%) prevalence in incident cases	Cannot be calculated	Galler 2009
Surveillance questionnaire (Physician reporting)	Canada	National	Not stated (35M pop Canada)	Newly diagnosed non-type 1 diabetes <18yrs	Clinical diagnosis genetically confirmed in ~50%	31 (% cannot be calculated)	0.32	Amed 2010#
Observational investigation of database	Austria / Germany	262 Pediatric clinics	40,567 Population	Age <20yrs , Diagnosed <18 yrs	Clinician diagnosis MODY usually confirmed by genetic test (polymorphisms not excluded#)	339 all cases (0.8%) 263 (0.65%) genetic positive#	Cannot be calculated	Schober 2009

N/K: Not known

\* only patients with a clinical diagnosis of Type 1 diabetes were included so the prevalence is likely to be underestimated

# subsequent study (Awa 2011 ) indicated 38% of reported HNF1A cases were polymorphisms not mutations.

**Table 2. Characteristics of the 20 patients identified with monogenic diabetes**

Study ID	Gene	Mutation	Protein effect	Gender	Age at diagnosis (yrs)	Diabetes duration (yrs)*	Initial treatment	Current treatment	BMI centile	Affected parent	UCPCR nmol/mmol	GAD	IA-2	Notes
211	<i>GCK</i>	c.97_117dup	p.(Val33_Lys39dup)	M	3	13	Insulin	None	99th	Mother	3.57	N/A	N/A	Known MODY
537	<i>GCK</i>	c.683C>T	p.(Thr228Met)	M	11	2	Diet	None	N/A	Mother	1.94	N/A	N/A	Known MODY Sibling of 538
538	<i>GCK</i>	c.683C>T	p.(Thr228Met)	M	9	1	Diet	None	N/A	Mother	1.73	N/A	N/A	Known MODY Sibling of 537
543	<i>GCK</i>	c.184G>A	p.(Val62Met)	M	4	0.2	Diet	None	N/A	Mother	N/A	N/A	N/A	Known MODY Sibling of 544
544	<i>GCK</i>	c.184G>A	p.(Val62Met)	M	3	2	Diet	None	N/A	Mother	N/A	N/A	N/A	Known MODY Sibling of 543
1396	<i>GCK</i>	c.1209del	p.(Ile404fs)	M	14	0.3	Diet	None	71st	Mother	N/A	N/A	N/A	Known MODY
8002095	<i>GCK</i>	c.1019G>T	p.(Ser340Ile)	M	9	5	Diet	None	88th	Father	0.79	Neg	N/A	Known MODY
8002372	<i>GCK</i>	c.1340G>A	p.(Arg447Gln)	M	18	0.6	Diet	None	90th	Neither	Not tested	Neg	Not tested	Newly identified MODY
599	<i>HNF1A</i>	c.608G>A	p.(Arg203His)	F	14	0.5	OHA	OHA	99th	Both parents	3.08	Neg	Neg	Known MODY
1012	<i>HNF1A</i>	c.872del	p.(Pro291fs)	F	10	0.7	Diet	Diet	99 <sup>th</sup>	Mother	5.6	Neg	Neg	Known MODY Sibling of 395
395	<i>HNF1A</i>	c.872del	p.(Pro291fs)	F	14	0.1	OHA	OHA	95th	Mother	5.8	Neg	Neg	Known MODY Sibling of 1012
455	<i>HNF1A</i>	c.872dup	p.(Gly292fs)	F	12	3	OHA	OHA	57th	Father	0.86	Neg	Neg	Known MODY
567	<i>HNF1A</i>	c.872dup	p.(Gly292fs)	M	8	2	Diet	OHA	94th	Mother	1.73	Neg	Neg	Known MODY
686	<i>HNF4A</i>	c.749T>C	p.(Leu250Pro)	M	16	0.7	Diet	Diet	99th	Father	4.74	N/A	N/A	Known MODY
1348	<i>HNF4A</i>	c.340C>T	p.(Arg114Trp)	F	15	0.2	Insulin	OHA	86th	Father	3.00	Neg	Neg	Newly identified MODY
1203	<i>HNF4A</i>	c.340C>T	p.(Arg114Trp)	M	7	2	Insulin	Insulin	39th	Neither	0.21	Neg*	Neg	Dual diagnosis: Newly identified HNF4A / known Type 1
377	<i>HNF4A</i>	c.-12G>A	p.(?)	F	11	2	Insulin	Insulin	99th	Mother	0.28	Neg	Neg	Newly identified MODY
854	<i>HNF1B</i>	c.1- ?_*151+?del	p.(0?) (whole gene deletion)	M	11	2	Insulin	Insulin	9th	Father	0.71	Neg	Neg	Newly identified MODY
555	<i>ABCC8</i>	c.4139G>A	p.(Arg1380His)	F	11	8	OHA	OHA	4 <sup>th</sup>	Father	3.00	Neg	Neg	Known MODY
758	<i>INSR</i>	c.3706C>G	p.(Pro1236Ala)	F	12	3	OHA	Diet	55th	Mother	9.07	N/A	N/A	Known MODY

\*Diabetes duration at time of study

\*GAD negative as defined in this study as <99<sup>th</sup> centile, but GAD 25.9 (97.5<sup>th</sup> centile)

N/A : Not applicable, genetic diagnosis made prior to study

Mutations described using the Human Genome Variation Society (HGVS) nomenclature guidelines according to the following reference sequences: *GCK* NM\_000162.3; *HNF1A* NM\_000545.6; *HNF4A* NM\_175914.4; *ABCC8* NM\_001287174.1; *INSR* NM\_000208.2