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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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
Systematic studies ordered by number in study									
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 ≥0.8ng/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≤7% (53mmol/mol) and ≤0.5u 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 ≥0.1ng/ml, AB-ve (x3) (n=97)	HNF1A, HNF4A, GCK, PDX1, HNF1B	22.7% (22/97)	N/K	Chambers 2015

Non systematic studies relying on clinical recognition and clinical testing								
Type of study	**Country**	**Area**	**Initial cohort of subject with diabetes and the population taken from (n)**	**Cohort characteristics**	**How monogenic diabetes was defined**	**Number with monogenic diagnosis (% all diabetes)**	**Prevalence per 100,000 population**	**Reference**
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-Württenberg	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	*GCK*	c.97_117dup	p.(Val33_Lys39dup)	M	3	13	Insulin	None	99th	Mother	3.57	N/A	N/A	Known MODY
537	*GCK*	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	*GCK*	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	*GCK*	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	*GCK*	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	*GCK*	c.1209del	p.(Ile404fs)	M	14	0.3	Diet	None	71st	Mother	N/A	N/A	N/A	Known MODY
8002095	*GCK*	c.1019G>T	p.(Ser340Ile)	M	9	5	Diet	None	88th	Father	0.79	Neg	N/A	Known MODY
8002372	*GCK*	c.1340G>A	p.(Arg447Gln)	M	18	0.6	Diet	None	90th	Neither	Not tested	Neg	Not tested	Newly identified MODY
599	*HNF1A*	c.608G>A	p.(Arg203His)	F	14	0.5	OHA	OHA	99th	Both parents	3.08	Neg	Neg	Known MODY
1012	*HNF1A*	c.872del	p.(Pro291fs)	F	10	0.7	Diet	Diet	99th	Mother	5.6	Neg	Neg	Known MODY Sibling of 395
395	*HNF1A*	c.872del	p.(Pro291fs)	F	14	0.1	OHA	OHA	95th	Mother	5.8	Neg	Neg	Known MODY Sibling of 1012
455	*HNF1A*	c.872dup	p.(Gly292fs)	F	12	3	OHA	OHA	57th	Father	0.86	Neg	Neg	Known MODY
567	*HNF1A*	c.872dup	p.(Gly292fs)	M	8	2	Diet	OHA	94th	Mother	1.73	Neg	Neg	Known MODY
686	*HNF4A*	c.749T>C	p.(Leu250Pro)	M	16	0.7	Diet	Diet	99th	Father	4.74	N/A	N/A	Known MODY
1348	*HNF4A*	c.340C>T	p.(Arg114Trp)	F	15	0.2	Insulin	OHA	86th	Father	3.00	Neg	Neg	Newly identified MODY
1203	*HNF4A*	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	*HNF4A*	c.-12G>A	p.(?)	F	11	2	Insulin	Insulin	99th	Mother	0.28	Neg	Neg	Newly identified MODY
854	*HNF1B*	c.1-?_*151+?del	p.(0?) (whole gene deletion)	M	11	2	Insulin	Insulin	9th	Father	0.71	Neg	Neg	Newly identified MODY
555	*ABCC8*	c.4139G>A	p.(Arg1380His)	F	11	8	OHA	OHA	4th	Father	3.00	Neg	Neg	Known MODY
758	*INSR*	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 <99th centile, but GAD 25.9 (97.5th 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