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Title: Population-based assessment of a biomarker-based screening pathway to aid diagnosis of diabetes subtypes in young-onset patients

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Supplementary Materials

Targeted next generation sequencing was performed using a custom Agilent SureSelect exon-capture assay (Agilent Technologies, Santa Clara, CA, USA). The assay was designed to target exons from the 35 genes shown in Table S1.

The design and optimisation of the custom assay, library preparation, sequencing and data analysis were performed as described in Ellard *et al* 2013 Diabetologia 56: 1958-1963.

The assay included 13 known/putative MODY genes (*GCK*, *HNF1A*, *HNF4A*, *HNF1B*, *NEUROD1*, *INS*, *CEL*, *PDX1*, *TRMT10A*, *PAX4*, *PAX6*, *KCNJ11* and *ABCC8*), three genes where mutations cause diabetes through severe insulin resistance (*INSR*, *LMNA* and *PPARG*), the m.3243 region of the mitochondrial genome (where the m.3243A>G mutation causes MIDD) and 24 neonatal diabetes genes (*GCK*, *KCNJ11*, *ABCC8*, *INS*, *PDX1*, *PTF1A*, *HNF1B*,*NEUROD1*, *NEUROG3*, *MNX1*, *NKX2-2, RFX6*, *EIF2AK3*, *FOXP3*, *GLIS3*, *SLC19A2*, *SLC2A2*,*IER3IP1*, *IL2RA*, *ZFP57*, *WFS1*, *CISD2*, *GATA6* and *GATA4*).

Data were processed as described previously (Lango Allen *et al* 2011 Nat Genet 1:20-22) to identify potential pathogenic mutations located within 50 bp upstream and 10 bp downstream of each exon. 98% of nucleotides located within 50 bp upstream and 10 bp downstream of each exon were sequenced with a minimum read depth of x30, achieving a sensitivity and specificity of variant detection of 100%. Deletions/duplications >30 bp were identified by relative read depth coverage. All newly identified mutations were confirmed by Sanger sequencing.

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Supplementary Table S1. 35 genes tested in the Agilent SureSelect exon-capture assay

Gene (OMIM)	Genbank Reference Sequence	Phenotype	OMIM	Inheritance	References
ABCC8 600509	NM_001287174	Permanent neonatal diabetes	606176	Dominant (often *de novo*) or recessive	Proks *et al* 2006 Hum Mol Genet 15: 1793-1800[1] Babenko *et al* 2006 N Engl J Med 355: 456-466[2] Ellard *et al* 2007 Am J Hum Genet 81: 375-382[3]
		Transient neonatal diabetes	610374	Dominant (often *de novo*) or recessive	Babenko *et al* 2006 N Engl J Med 355: 456-466[2]
		MODY	610374	Dominant	Bowman *et al* 2012 Diabetologia 55: 123-127[4] Riveline *et al* 2012 Diabetes Care 35: 248-251[5]
BSCL2 606158	NM_032667	Congenital generalised lipodystrophy, severe insulin resistance and diabetes	269700	Recessive	Magre *et al* Nat Genet 2001 28: 365-370[6]
CEL 114840	NM_001807	MODY	609812	Dominant	Raeder *et al* 2006 Nat Genet 38: 54-62[7] Torsvik *et al* 2010 Hum Genet 127: 55-64[8] Raeder *et al* 2013 PLoS One 8: e60229[9]
CISD2 611507	NM_001008388	Wolfram Syndrome 2 (diabetes mellitus, hearing loss, optic atrophy and defective platelet aggregation).	604928	Recessive	Amr *et al* 2007 Amr J Hum Genet 81: 673-683[10]
EIF2AK3	NM_004836	Wolcott-Rallison syndrome	226980	Recessive	Delephine *et al* 2000 Nat Genet 25: 406-409[11]

604032					
FOXP3 300292	NM_014009	Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked syndrome (IPEX)	304790	X-Linked Recessive	Wildin *et al* 2001 Nat Genet 1: 18-20[12] Bennett *et al* 2001 Nat Genet 27: 20-21[13]
GATA4 600576	NM_002052	Permanent neonatal diabetes with pancreatic agenesis and congenital heart defects	Not assigned	Dominant (often *de novo*)	D'Amato *et al* 2010 Diabet Med 27: 1195-1200[14]
GATA6 601656	NM_005257	Permanent neonatal diabetes with pancreatic agenesis and congenital heart defects	600001	Dominant (often *de novo*)	Lango Allen *et al* 2011 Nat Genet 44: 20-22[15] De Franco *et al* 2013 Diabetes 62: 993-997[16]
GCK 138079	NM_000162	Permanent neonatal diabetes	606176	Recessive	Njolstad *et al* 2001 N Engl J Med 344: 1588-1592[17] Gloyn *et al* 2002 Diabetologia 45: 290[18] Osbak *et al* 2009 Hum Mutat 30: 1512-1526[19]
GCK 138079		MODY	125851	Dominant	Vionnet *et al* 1992 Nature 356: 721-722 Velho *et al* 1997 Diabetologia 40: 217-224 Osbak *et al* 2009 Hum Mutat 30: 1512-1526
GLIS3 610192	NM_001042413	Permanent neonatal diabetes with congenital hypothyroidism	610199	Recessive	Senee *et al* 2006 Nat Genet 38: 682-687[20] Dimitri *et al* 2011 Eur J Endocrinol 164: 437-443[21]
HNF1A 142410	NM_000545	MODY	600496	Dominant	Yamagata *et al* 1996 Nature 384: 455-458[22] Frayling *et al* 1997 Diabetes 46: 720-725[23] Colclough *et al* 2013 Hum Mutat 34: 669-685[24]

HNF1B 189907	NM_000458	Renal Cysts and Diabetes syndrome (RCAD)	137920	Dominant (often *de novo*)	Horikawa *et al* 1997 Nat Genet 17: 384-385[25] Yorifuji *et al* 2004 J Clin Endocrinol Metab 89: 2905-2908[26] Edghill *et al* 2006 J Med Genet 43: 84-90[27] Bellanne-Chantelot *et al* 2005 Diabetes 54: 3126-3132[28]
HNF4A 600281	NM_175914	MODY	125850	Dominant	Yamagata *et al* 1996 Nature 384: 458-460[29] Bulman *et al* 1997 Diabetologia 40: 859-862[30] Colclough *et al* 2013 Hum Mutat 34: 669-685[24]
IER3IP1 609382	NM_016097	microcephaly, epilepsy, and diabetes syndrome (MEDS)	614231	Recessive	Poulton et al 2011 Am J Hum Genet 89: 265-276[31] Abdel-Salam *et al* 2012 Am J Med Genet A 158A: 2788-96[32]
IL2RA 147730	NM_000417	Immunodysregulation, polyendocrinopathy, and enteropathy, X-linked syndrome (IPEX)	606367	Recessive	Caudy *et al* 2007 J Allergy Clin Immunol 119: 482-487[33]
INS 176730	NM_001185098	Permanent neonatal diabetes	606176	Dominant (often *de novo*) or recessive	Stoy *et al* 2007 Proc Natl Acad Sci USA 18: 15040-4[34] Edghill *et al* 2008 Diabetes 57: 1034-1042 [35]
		Transient neonatal diabetes	Not assigned	Dominant (often *de novo*) or recessive	Garin *et al* 2010 Proc Natl Acad Sci 107: 3105-3110[36]
		MODY	613370	Dominant	Edghill *et al* 2008 Diabetes 57: 1034-1042[35]

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					Molven *et al* 2008 Diabetes 57: 1131-1135[37]
INSR 147670	NM_000208	Severe insulin resistance	610549	Dominant	Odawara *et al* 1989 Science 245: 66-68[38]
KCNJ11 600937	NM_000525	Permanent neonatal diabetes	606176	Dominant (often *de novo*)	Gloyn *et al* 2004 N Engl J Med 350: 1838-1849[39]
		Transient neonatal diabetes	610582	Dominant (often *de novo*)	Yorifuji *et al* 2005 J Clin Endocrinol Metab 90: 3174-3178[40] Gloyn *et al* 2005 Hum Mol Genet 14: 925-934[41] Suzuki *et al* 2007 J Clin Endocrinol Metab 92: 3979-3985[42]
		MODY	Not assigned	Dominant	Yorifuji *et al* 2005 J Clin Endocrinol Metab 90: 3174-3178[40] Bonnefond *et al* 2012 PLoS One 7: e37423[43]
LMNA 150330	NM_170707	Familial Partial Lipodystropy (FPLD2)	151660	Dominant	Cao *et al* 2000 Hum Mol Genet 1: 109-112[44] Shackleton *et al* 2000 Nat Genet 24: 153-156[45] Speckman *et al* 2000 Am J Hum Genet 66: 1192-1198[46]
MNX1 142994	NM_005515	Neonatal diabetes & IUGR	Not assigned	Recessive	Flanagan *et al* 2014 Cell Metab 19: 146-154[47]
MTTL1 **m.3243A>G**	NC_012920	Maternally inherited diabetes and deafness (MIDD)	520000	Mitochondrial	Van den Ouweland *et al* 1992 Nat Genet 1: 368-371[48]

590050					Murphy *et al* 2008 Diabet Med 25: 383-399[49]
NEUROD1 601724	NM_002500	Permanent neonatal diabetes and neurological abnormalities	Not assigned	Recessive	Rubio-Cabezas *et al* 2010 Diabetes 162: 987-992[50]
		MODY	606394	Dominant	Malecki *et al* 1999 Nat Genet 23: 323-328[51]
NEUROG3 604882	NM_020999	Permanent neonatal diabetes with congenital malabsorptive diarrhoea	610370	Recessive	Rubio-Cabezas *et al* 2011 Diabetes 60: 1349-1353[52]
NKX2-2 604612	NM_002509	Neonatal diabetes and developmental delay	Not assigned	Recessive	Flanagan *et al* 2014 Cell Metab 19: 146-154[47]
PAX6 607108	NM_001604	Aniridia and impaired glucose tolerance	106210	Dominant	Yasuda *et al* 2002 Diabetes 51: 224-230[53] Nishi *et al* 2005 Diabet Med 22: 641-644[54] Osawa *et al* 2015 J Diabetes Investig 6: 105-106[55]
PDX1 600733	NM_000209	Permanent neonatal diabetes +/- pancreatic agenesis	260370	Recessive	Stoffers *et al* 1997 Nat Genet 15: 106-110[56] Thomas *et al* 2009 Pediatr Diabetes 10: 492-496[57] De Franco *et al* 2013 Diabet Med 30: e197-200[58]
		MODY	606392	Dominant	Stoffers *et al* 1997 Nat Genet 17: 138-139[59]
PPARG 601487	NM_015869	Familial Partial Lipodystropy (FPLD3)	604367	Dominant	Agarwal *et al* 2002 J Clin Endocrinol Metab 1: 408-411[60] Barroso *et al* 1999 Nature 402: 880-883[61]
PTF1A 607194	NM_178161	Permanent neonatal diabetes with cerebellar and pancreatic agenesis	609069	Recessive	Sellick *et al* 2004 Nat Genet 36: 1301-1305[62]

RFX6 612659	NM_173560	Permanent neonatal diabetes with pancreatic hypoplasia, intestinal atresia, and gallbladder aplasia or hypoplasia	601346	Recessive	Smith *et al* 2010 Nature 463: 775-780[63]
SLC2A2 138160	NM_000340	Fanconi-Bickel syndrome	227810	Recessive	Santer *et al* 1997 Nat Genet 17: 324-326[64]
SLC19A2 603941	NM_006996	Thiamine responsive megaloblastic anaemia, diabetes and deafness (TRMA) syndrome	249270	Recessive	Labay *et al* 1999 Nat Genet 22: 300-304[65]
TRMT10A 616013	NM_001134665	Diabetes, microcephaly and short stature	616033	Recessive	Igoillo-Esteve *et al* PLoS Genet 9: e1003888[66]
WFS1 606201	NM_006005	Wolfram syndrome (Diabetes insipidus, diabetes mellitus, optic atrophy and deafness, DIDMOAD)	222300	Recessive	Inoue *et al* 1998 Nat Genet 20: 143-148[67] Strom *et al* 1998 Hum Mol Genet 7: 2021-2028[68]
ZFP57 612192	NM_001109809	Transient neonatal diabetes	601410	Recessive	Mackay *et al* 2008 Nat Genet 40: 949-951[69]

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Supplementary Table S2 . Baseline characteristics of the 1365 patients who completed the biomarker screening pathway with no existing known cause for their diabetes: Data shown as median (IQR) unless otherwise specified

Male (n (%))	706 (52%)
Age at diagnosis (y)	13 (8,21)
Age at recruitment (y)	29 (19,40)
Duration of diabetes (y)	13.6 (5.6, 22.7)
BMI* (kg/m^2)	25.7 (23.2, 29.0)
HbA1c (mmol/mol)	72 (62, 85)
Current treatment (n (%)): Diet OHA Insulin +/- OHA	 15 (1%) 69 (5%) 1281 (94%)
White Caucasian (n(%))	1389 (98%)
Pediatric (<20years) (n(%))	351 (26%)

*child values adjusted to adult equivalent using the Child Growth Foundation Reference Standards[70]

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Supplementary Table S3. Additional details of the mutations identified in patients in the UNITED study

ID	Gene	Method found	Zygosity	Location	DNA level description	Protein level description	Mutation effect	Ref
211	*GCK*	Sanger Sequencing	Heterozygous	Exon 2	c.97_117dup	p.(Val33_Lys39dup)	In-frame deletion	[71]
523	*GCK*	Sanger Sequencing	Heterozygous	Exon 2	c.97_117dup	p.(Val33_Lys39dup)	In-frame deletion	[71]
537	*GCK*	Sanger Sequencing	Heterozygous	Exon 7	c.683C>T	p.(Thr228Met)	Missense	[72]
538	*GCK*	Sanger Sequencing	Heterozygous	Exon 7	c.683C>T	p.(Thr228Met)	Missense	[72]
542	*GCK*	Sanger Sequencing	Heterozygous	Exon 2	c.184G>A	p.Val62Met)	Missense	[73]
543	*GCK*	Sanger Sequencing	Heterozygous	Exon 2	c.184G>A	p.Val62Met)	Missense	[73]
544	*GCK*	Sanger Sequencing	Heterozygous	Exon 2	c.184G>A	p.Val62Met)	Missense	[73]
1155	*GCK*	Sanger Sequencing	Heterozygous	Exon 10	c.1343G>T	p.(Gly448Val)	Missense	[74]
82095	*GCK*	Sanger Sequencing	Heterozygous	Exon 8	c.1019G>T	p.(Ser340Ile)	Missense	[19]
535	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 2	c.379_381del	p.(Asn127del)	In-frame deletion	[75]
547	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 9	c.1748G>A	p.(Arg583Gln)	Missense	
554	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 4	c.872dup	p.(Gly292fs)	Frameshift	[22]
566	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 4	c.872dup	p.(Gly292fs)	Frameshift	[22]
603	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 7	c.1420C>T	p.(Gln474Ter)	Nonsense	[76]
617	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 4	c.779C>T	p.(Thr260Met)	Missense	[77]
892	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 2	c.476G>A	p.(Arg159Gln)	Missense	[78]

1370	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 4	c.872dup	p.(Gly292fs)	Frameshift	22
1409	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 4	c.872dup	p.(Gly292fs)	Frameshift	22
80480	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 5 & Intron 5	c.1093_1107+6del	p.(?)	Aberrant splicing	24
82261	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 1	c.185del	p.(Asn62fs)	Frameshift	24
82276	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 2	c.434C>T	p.(Ser145Phe)	Missense	75
82301	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 7	c.1340C>T	p.(Pro447Leu)	Missense	22
82310	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 1	c.185del	p.(Asn62fs)	Frameshift	24
82374	*HNF1A*	Sanger Sequencing	Heterozygous	Exon 5 & Intron 5	c.1093_1107+6del	p.(?)	Aberrant splicing	24
82258	*HNF4A*	Sanger Sequencing	Heterozygous	Exon 4	c.322G>A	p.(Val108Ile)	Missense	79
600	*HNF1B*	Sanger Sequencing	Heterozygous	Exon 4	c.982_986del	p.(Pro328fs)	Frameshift	80
82033	*HNF1B*	Sanger Sequencing	Heterozygous	Exon 2	c.466A>G	p.(Lys156Glu)	Missense	27
82006	*KCNJ11*	Sanger Sequencing	Heterozygous	Exon 1	c.601C>T	p.(Arg201Cys)	Missense	39
539	*LMNA*	Sanger Sequencing	Heterozygous	Exon 11	c.1930C>T	p.(Arg644Cys)	Missense	81
595	*LMNA*	Sanger Sequencing	Heterozygous	Exon 8	c.1444C>T	p.(Arg482Trp)	Missense	45
604	*3243*		Heteroplasmic	-	m.3243A>G	-	-	48
80541	*3243*		Heteroplasmic	-	m.3243A>G	-	-	48
82399	*3243*		Heteroplasmic	-	m.3243A>G	-	-	48
540	*NEUROD1*	Sanger Sequencing	Heterozygous	Exon 2	c.616dup	p.(His206fs)	Frameshift	51

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82372	*GCK*	Sanger sequencing	Heterozygous	Exon 10	c.1340G>A	p.(Arg447Gln)	Missense	[82]
82316	*HNF4A*	Sanger sequencing	Heterozygous	Intron 8 & Exon 9	c.1064-5_1070del	p.(?)	Aberrant splicing	-
377	*HNF4A*	Sanger sequencing	Heterozygous	5' UTR	c.-12G>A	p.(=)	Not known	-
80089	*HNF1A*	Sanger sequencing	Heterozygous	Exon 7	c.1349dup	p.(Asn450fs)	Frameshift	[24]
80170	*HNF1A*	Sanger sequencing	Heterozygous	Exon 2	c.391C>T	p.(Arg131Trp)	Missense	[23]
80173	*HNF1A*	Sanger sequencing	Heterozygous	Exon 2	c.495G>C	p.(Trp165Cys)	Missense	-
82003	*HNF1A*	Sanger sequencing	Heterozygous	Exon 1	c.28A>C	p.(Thr10Pro)	Missense	-
82352	*HNF1A*	Sanger sequencing	Heterozygous	Exon 4	c.814C>T	p.(Arg272Cys)	Missense	[83]
82013	*HNF1A*	Targeted capture	Heterozygous	Promoter	c.-258A>G	p.(0?)	Aberrant gene expression	[24]
307	*HNF1B*	Targeted capture	Heterozygous	Exons 1 to 9	c.1-?_1674+?del	p.(0)	Whole gene deletion	[28]
82014	*NEUROD1*	Targeted capture	Heterozygous	Exon 2	c.616dup	p.(His206fs)	Frameshift	[51]
183	*NEUROD1*	Targeted capture	Heterozygous	Exon 2	c.616dup	p.(His206fs)	Frameshift	[51]
82010	*MT-TL1*	Targeted capture	Heteroplasmic	-	m.3243A>G	-	-	[48]
82038	*PPARG*	Targeted capture	Heterozygous	Exon 6	c.1154G>A	p.(Arg385Gln)	Missense	-
80925	*TRMT10A*	Targeted capture	Homozygous	Exon 2	c.79G>T	p.(Glu27Ter)	Nonsense	-
17	*WFS1*	Targeted capture	Compound Heterozygous	Exon 8	c.874C>T & c.877del	p.(Pro292Ser) & (p.Leu293fs)	Missense & Frameshift	[84,85]

175	*POLD1*	Exome Sequencing	Heterozygous	Exon 15	c.1812-1814del	p.(Ser605del)	In-frame deletion	[86]

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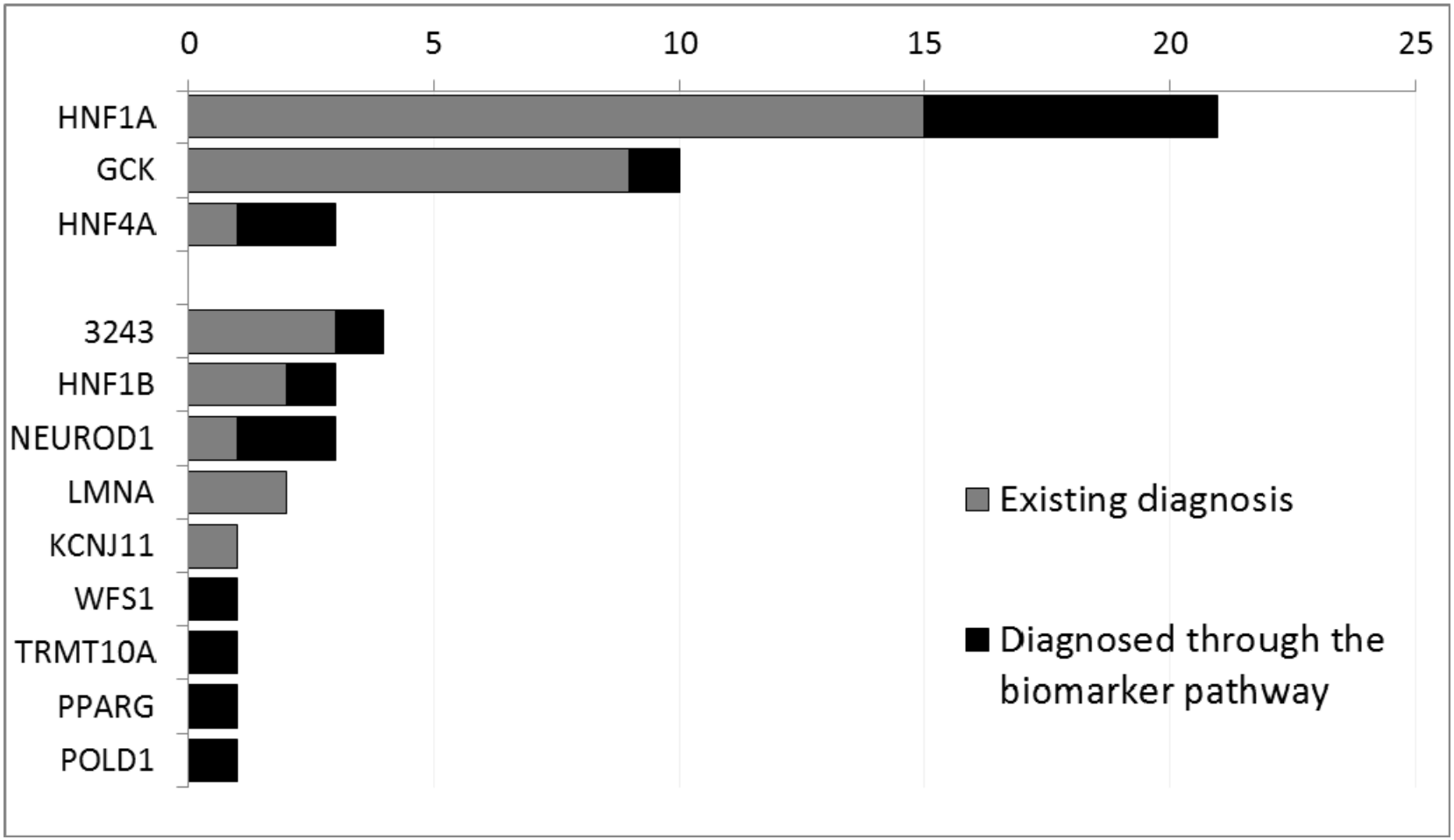
Supplementary Figure S1. Distribution of genetic causes of 54 confirmed cases of monogenic diabetes in Exeter and Dundee. Data presented as number of cases caused by mutations in each gene - grey bars indicate cases where the diagnosis was made prior to this study, black bars are those diagnosed as a result of the biomarker pathway.



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