Citation

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Supplementary Tables

Supplementary Table 1: Characteristics of MODY cohort

Characteristics	MODY cohort
N	1227
Age of diagnosis of diabetes, years	21 (14-30)
Female Sex	58%
Age at recruitment, years	30 (18-42)
BMI, kg/m^2	25.1 (21.6-29.5)
Parents with diabetes	72%
HbA1c, %	7.5 (6.5-9.3)
HbA1c, mmol/mol	58 (48-78)
On Insulin alone	41%
On Insulin and other hypoglycaemic agents	13%
On other hypoglycaemic agents alone	47%
European ancestry (self-reported)	84%

Supplementary Table 1: Population frequency of variants in *BLK, KLF11* and *PAX4* published as MODY causing

Table showing coding variants where they were associated with MODY-like diabetes. Allele frequency taken from gnomAD v2.1.1. The *HNF1A* and *HNF4A* variants included here for comparison are those from the original papers used in the LOD score calculations in Table 1.

Gene	Variant	Included in LOD score calculation	Allele count /total alleles in gnomAD v2.1.1	Allele frequency in gnomAD v2.1.1	Allele count in ancestry with maximum frequency/total alleles in the ancestry	Maximum Allele frequency in a single ancestry in gnomadv2.1.1 (ancestry)	Reference for variants
BLK	p.A71T	Yes	3281/282812	0.012	420/10368	0.041 (Ashkenazi Jewish)	[1]
KLF11	p.Q62R	No	25823/282778	0.091	1497/10370	0.144 (Ashkenazi Jewish)	[2]
	p.T220M	Yes	1207/282762	$4.27x10^{-03}$	1098/24958	0.044 (African/African American)	[2]
	p.A347S	Yes	36/282304	$1.28x10^{-04}$	17/35410	$4.80x10^{-04}$ (Latino/Admixed American)	[2]
PAX4	p.R19Q	No	4/251336	$1.59x10^{-05}$	1/ 34592	$2.89x10^{-05}$ (Latino/Admixed American)	[3]
	p.R31L	No	105/250972	$4.18x10^{-04}$	102/30616	0.003 (South Asian)	[4]
	p.R52C	No	5/251274	$1.99x10^{-05}$	1/18392	$5.44x10^{-05}$ (East Asian)	[3]
	p.A89V	No	14/251416	$5.57x10^{-05}$	11/113704	$9.67x10^{-05}$ (European non-Finnish)	[3]
	p.R97H	No	8/251406	$3.18x10^{-05}$	4/30616	$1.31x10^{-04}$ (South Asian)	[5]
	p.P142L	No	5/251402	$1.99x10^{-05}$	5/113720	$4.4x10^{-05}$(European non-Finnish)	[3]
	p.R164W	Yes	14/282800	$4.95x10^{-05}$	3/24948	$1.2x10^{-04}$ (African/African American)	[6]
	p.R192H	No	2214/282856	$7.83x10^{-03}$	2182/19946	0.109 (East Asian)	[6]
	p.R192S	No	783/282850	$2.77x10^{-03}$	770/19950	0.039 (East Asian)	[7]

	p.A198V	No	0	0	0	0	[8]
HNF1A	p.P447L	Yes	3/249186	$1.20x10^{-05}$	1/20812	$4.81x10^{-05}$ (European Finnish)	[9]
	p.V380Sfs*4	Yes	0	0	0	0	[9]
	p.E548Rfs*112	Yes	0	0	0	0	[9]
	p.R131Q	Yes	1/251390	$3.98x10^{-06}$	1/113698	$8.80x10^{-06}$ (European non-Finnish)	[9]
	c.1768+1G>A	Yes	0	0	0	0	[9]
	c.1108-2A>G	Yes	0	0	0	0	[9]
HNF4A	p.Q255*	Yes	0	0	0	0	[10]
	p.R141*	Yes	0	0	0	0	[11]

Supplementary Table 3: Bayesian false discovery probability at range of prior probability for enrichment of variant in MODY cohort versus UK Biobank

Variant type	Gene	BFDP at 0.5	BFDP at 0.2	BFDP at 0.1
Ultra-rare PTV	*BLK*	0.38	0.71	0.85
	KLF11	0.50	0.80	0.90
	PAX4	0.50	0.80	0.90
	HNF1A	3.00×10^{-10}	1.20×10^{-09}	2.70×10^{-09}
	HNF4A	0.01	0.03	0.06
Ultra-rare missense	*BLK*	0.54	0.82	0.91
	KLF11	0.46	0.78	0.89
	PAX4	0.37	0.70	0.84
	HNF1A	1.45×10^{-38}	5.80×10^{-38}	1.31×10^{-37}
	HNF4A	3.00×10^{-26}	1.20×10^{-25}	2.70×10^{-25}
Rare PTV	*BLK*	0.26	0.58	0.76
	KLF11	0.15	0.41	0.61
	PAX4	0.27	0.60	0.77
	HNF1A	1.82×10^{-30}	7.28×10^{-30}	1.64×10^{-29}
	HNF4A	7.94×10^{-05}	3.18×10^{-04}	7.14×10^{X04}
Rare missense	*BLK*	0.63	0.87	0.94
	KLF11	0.66	0.88	0.95
	PAX4	0.50	0.80	0.90
	HNF1A	2.61×10^{-34}	1.05×10^{-33}	2.35×10^{-33}
	HNF4A	4.45×10^{-22}	1.78×10^{-21}	4.01×10^{-21}
All PTV	*BLK*	0.26	0.58	0.76
	KLF11	0.15	0.41	0.61
	PAX4	0.41	0.74	0.86
	HNF1A	2.10×10^{-30}	8.41×10^{-30}	1.89×10^{-29}
	HNF4A	7.94×10^{-05}	3.18×10^{-04}	7.14×10^{-04}

Supplementary Table 4: Gene burden test for synonymous variants in MODY cohort and UK Biobank

The frequency of ultra-rare (allele count=1) synonymous variants in a MODY cohort n=1227 were compared to the frequency in the UK Biobank n=185,898.

*excluding two synonymous variants in *HNF1A* that were on a haplotype with a pathogenic PTV

Variant type	Gene	Allele count in MODY cohort	Allele frequency in MODY cohort	Allele count in Population cohort (UK biobank)	Allele frequency in Population cohort (UK Biobank)	Odds ratio (95%CI)	*P* value
Ultra-rare synonymous	*BLK*	0	0	61	$1.64x10^{-04}$	0 (0-9.5)	1
	KLF11	0	0	55	$1.48x10^{-04}$	0 (0-11)	1
	PAX4	0	0	38	$1.02x10^{-04}$	0 (0-15)	1
	HNF1A	3	$1.22x10^{-03}$	47	$1.26x10^{-04}$	9.7 (1.9-30)	0.004
	*HNF1A**	1	$4.07x10^{-04}$	47	$1.26x10^{-04}$	3.2 (0.08-19)	0.27
	HNF4A	0	0	38	$1.02x10^{-04}$	0 (0-15)	1

Supplementary Table 5: Gene burden test using gnomAD v2.1.1 as an alternative population control cohort

The frequency of ultra-rare (allele count=1) PTV, missense and synonymous variants in a MODY cohort n=1227 were compared to the frequency in the GnomAD v2.1.1 n=141,456.

*excluding two synonymous variants in *HNF1A* that were on a haplotype with a pathogenic PTV

Variant type	Gene	Allele count in MODY cohort	Allele frequency in MODY cohort	Allele count in Population cohort (GnomAD v2.1.1)	Allele frequency in Population cohort (GnomAD v2.1.1)	Odds ratio (95%CI)	*P* value	Prior Probability	Bayesian false discovery probability (BFDP)
Ultra-rare PTVs	*BLK*	1	$4.07x10^{-04}$	28	$1.12x10^{-04}$	3.7 (0.089-22)	0.2	0.2	0.78
	KLF11	0	0	29	$1.15x10^{-04}$	0 (0-14)	1	0.2	0.80
	PAX4	0	0	6	$2.40x10^{-05}$	0 (0-65)	1	0.2	0.80
	HNF1A	13	$5.30x10^{-03}$	3	$1.21x10^{-05}$	441 (121-2415)	$3.93x10^{-24}$	0.99	3.36E-03
	HNF4A	3	$1.22x10^{-03}$	6	$2.41x10^{-05}$	51 (8.2-238)	$1.00x10^{-04}$	0.99	0.07
Ultra-rare Missense	*BLK*	2	$8.15x10^{-04}$	187	$7.85x10^{-04}$	1 (0.12-3.8)	0.7	0.2	0.84
	KLF11	1	$4.07x10^{-04}$	191	$7.60x10^{-04}$	0.54 (0.013-3.0)	1	0.2	0.82
	PAX4	4	$1.63x10^{-03}$	118	$4.72x10^{-04}$	3.5 (0.93-9.1)	0.03	0.2	0.48
	HNF1A	18	$7.33x10^{-03}$	151	$6.07x10^{-04}$	12 (7-20)	$1.20x10^{-13}$	0.99	5.58E-16
	HNF4A	10	$4.07x10^{-03}$	105	$4.21x10^{-04}$	9.7 (4.5-19)	$2.25x10^{-07}$	0.99	8.97E-07
Ultra-rare Synonymous	*BLK*	0	0	90	$3.59x10^{-04}$	0(0-4.4)	1	NA	NA
	KLF11	1	$4.07x10^{-04}$	83	$3.30x10^{-04}$	1.2(0.031-7.1)	0.6	NA	NA

	PAX4	0	0	53	$2.12x10^{-04}$	0(0-7.4)	1	NA	NA
	HNF1A	4	$1.63x10^{-03}$	91	$3.66x10^{-04}$	4.5(1.2-12)	0.014	NA	NA
	*HNF1A**	2	$8.15x10^{-04}$	91	$3.66x10^{-04}$	2.2(0.27-8.3)	0.23	NA	NA
	HNF4A	0	0	66	$2.65x10^{-04}$	0(0-5.9)	1	NA	NA

Supplementary Table 6: Gene burden test using gnomAD v3 as an alternative population control cohort

The frequency of ultra-rare (allele count=1) PTV and missense variants in a MODY cohort n=1227 were compared to the frequency in the GnomAD v3 n=76,156.

*excluding two synonymous variants in *HNF1A* that were on a haplotype with a pathogenic PTV

Variant type	Gene	Allele count in MODY cohort	Allele frequency in MODY cohort	Allele count in Population cohort (GnomAD v3)	Allele frequency in Population cohort (GnomAD v3)	Odds ratio (95%CI)	*P* value	Prior Probability	Bayesian false discovery probability (BFDP)
Ultra-rare PTVs	*BLK*	1	0.00041	22	0.000154	2.7 (0.064-16)	0.3	0.2	0.80
	KLF11	2	0.00081	8	$5.58x10^{-05}$	15 (1.5-73)	0.012	0.2	0.44
	PAX4	1	0.00041	5	$3.49x10^{-05}$	12 (0.25-104)	0.1	0.2	0.73
	HNF1A	17	0.00693	1	$6.98x10^{-06}$	999 (156-41761)	$1.18x10^{-29}$	0.99	0.71
	HNF4A	3	0.00122	3	$2.09x10^{-05}$	58 (7.8-437)	$1.00x10^{-04}$	0.99	0.44
Ultra-rare Missense	*BLK*	2	$8.15x10^{-04}$	154	$1.07x10^{-03}$	0.76 (0.09-2.8)	1	0.2	0.83
	KLF11	3	$1.22x10^{-03}$	125	$8.72x10^{-04}$	1.4 (0.29-4.2)	0.5	0.2	0.84
	PAX4	2	$8.15x10^{-04}$	70	$4.89x10^{-04}$	1.7 (0.2-6.3)	0.3	0.2	0.81
	HNF1A	24	$9.78x10^{-03}$	97	$6.77x10^{-04}$	15 (8.9-23)	$6.87x10^{-19}$	0.99	9.16E-29
	HNF4A	15	$6.11x10^{-03}$	64	$4.47x10^{-04}$	14 (7.3-24)	$4.67x10^{-12}$	0.99	6.91E-16
Ultra-rare Synonymous	*BLK*	1	$4.07x10^{-04}$	44	$3.07x10^{-04}$	1.3 (0.33-7.8)	0.53	NA	NA

	KLF11	1	$4.07x10^{-04}$	68	$4.75x10^{-04}$	0.86 (0.021-4.9)	1	NA	NA
	PAX4	0	0	30	$2.09x10^{-04}$	0 (0-7.5)	1	NA	NA
	HNF1A	5	$2.04x10^{-03}$	60	$4.19x10^{-04}$	4.9 (1.5-12)	0.0048	NA	NA
	*HNF1A**	3	$1.22x10^{-03}$	60	$4.19x10^{-04}$	2.9 (0.59-9)	0.09	NA	NA
	HNF4A	0	0	52	$3.63x10^{-04}$	0 (0-4.3)	1	NA	NA

Supplementary Table 7: Gene burden test for rare variants (MAF<0.0001) in MODY cohort and UK Biobank. The frequency of rare (MAF<0.0001) PTV and missense variants in a MODY cohort n=1227 were compared to the frequency in the UK Biobank n=185,898.

*excluding two synonymous variants in *HNF1A* that were on a haplotype with a pathogenic PTV

Variant type	Gene	Allele count in MODY cohort	Allele frequency in MODY cohort	Allele count in Population cohort (UK biobank)	Allele frequency in Population cohort (UK Biobank)	Odds ratio (95%CI)	*P* value	Prior Probability	Bayesian false discovery probability (BFDP)
Rare PTVs	*BLK*	3	0.0012	124	0.0003335	3.7 (0.75-11)	0.05	0.2	0.58
	KLF11	2	0.0008	33	$8.876x10^{-05}$	9.2 (1.1-36)	0.02	0.2	0.41
	PAX4	2	0.0008	55	0.0001479	5.5 (0.65-21)	0.05	0.2	0.60
	HNF1A	22	0.009	8	$2.152x10^{-05}$	420 (180-1092)	$4.71x10^{-42}$	0.99	1.84×10^{-32}
	HNF4A	3	0.0012	4	$1.076x10^{-05}$	114 (17-673)	$9.66x10^{-06}$	0.99	8.02×10^{-07}
Rare Missense	*BLK*	7	0.0029	1245	0.0033	0.85 (0.34-1.8)	0.9	0.2	0.87
	KLF11	9	0.0037	1236	0.0033	1.1 (0.5-2.1)	0.7	0.2	0.88
	PAX4	8	0.0033	749	0.0020	1.6 (0.7-3.2)	0.2	0.2	0.80
	HNF1A	45	0.0183	1006	0.0027	6.9 (5-9.3)	$1.98x10^{-22}$	0.99	2.64×10^{-36}
	HNF4A	26	0.0106	583	0.0016	6.9 (4.4-10)	$1.42x10^{-13}$	0.99	4.50×10^{-24}
Rare Synonymous	*BLK*	6	$2.44x10^{-03}$	756	$2.03x10^{-03}$	1.2 (0.44-2.6)	0.65	NA	NA

	KLF11	1	4.07×10^{-04}	514	1.38×10^{-03}	0.29 (0.0074-1.6)	0.27	NA	NA
	PAX4	0	0	181	4.87×10^{-04}	0 (0-3.2)	0.64	NA	NA
	HNF1A	10	4.07×10^{-03}	1014	2.73×10^{-03}	1.5 (0.71-2.8)	0.24	NA	NA
	*HNF1A**	8	3.26×10^{-03}	1014	2.73×10^{-03}	1.2 (0.51-2.4)	0.56	NA	NA
	HNF4A	5	2.04×10^{-03}	581	1.56×10^{-03}	1.3 (0.42-3.1)	0.44	NA	NA

Supplementary Table 8: Gene burden test for all PTVs excluding last exon in MODY cohort and UK Biobank

The frequency of PTV variants in a MODY cohort n=1227 were compared to the frequency in the UK Biobank n=185,898.

Variant type	Gene	Allele count in MODY cohort	Allele frequency in MODY cohort	Allele count in Population cohort (UK biobank)	Allele frequency in Population cohort (UK Biobank)	Odds ratio (95%CI)	*P* value	Prior Probability	Bayesian false discovery probability (BFDP)
PTVs	*BLK*	3	0.00122	124	0.000334	3.7 (0.75-11)	0.052	0.2	0.58
	KLF11	2	0.00081	33	$8.88x10^{-05}$	9.2 (1.1-36)	0.02	0.2	0.41
	PAX4	2	0.00081	94	0.000253	3.2 (0.38-12)	0.1	0.2	0.74
	HNF1A	22	0.00896	8	$2.15x10^{-05}$	420 (180-1093)	$4.71x10^{-42}$	0.99	$2.12x10^{-32}$
	HNF4A	3	0.00122	4	$1.08x10^{-05}$	114 (17-673)	$9.66x10^{-06}$	0.99	$8.02x10^{-07}$

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