Determinants of penetrance and variable expressivity in monogenic metabolic conditions across 77,184 exomes

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Extended Acknowledgements

Supplementary Tables

Supplementary Table 1: Summary characteristics of study populations.

	AMP-T2D-GENES T2D case	AMP-T2D-GENES control	UKB
Male (N)	9,231	9,239	17,732
Female (N)	9,508	10,640	20,834
age	58.20 (9.7)	57.345 (10.65)	58.272 (7.92)
BMI	29.27 (5.95)	27.49 (5.36)	27.36 (4.76)
ldl_mgdl	115.489 (38.26)	130.721 (36.24)	137.089 (33.06)
ldl (med corrected)	134.311 (45.79)	136.394 (39.79)	147.461 (33.06)
hdl_mgdl	46.601 (14.12)	51.775 (16.16)	57.266 (14.92)
tg_mgdl	180.644 (138.31)	139.618 (98.87)	150.605 (86.37)
tg (med corrected)	191.844 (148.60)	142.513 (100.98)	156.935 (92.94)
African American	2,480	2,626	NA
East Asian	2,666	2,533	NA
European	4,713	6,557	38,566
Hispanic	6,126	5,609	NA
Other	3	13	NA
South Asian	2,751	2,541	NA

Supplementary Table 2: Counts of clinically significant variants and carriers across conditions

		AMP T2D-GENES		UK Biobank	
Condition	**Genes**	**N_variants**	**N_carriers**	**N_variants**	**N_carriers**
High LDL	***LDLR***, and missense ***APOB***	53	126	37	90
Low LDL	***APOB***, ***PSCK9*** (restricted to LoF)	29	78	40	92
High HDL	***CETP***	15	26	13	23
High triglycerides	***APOA5***, ***LPL***	13	23	10	56
Monogenic obesity	***MC4R***	9	29	13	31
MODY	***GCK***, ***HNF1A***, ***HNF4A***, ***HNF1B***, ***PDX1***	17	22	14	16
MODY Extended	*AKT2*, *KLF11*, *APPL1*, ***ABCC8***, *KCNJ11*, *NEUROD1*, *CEL*, ***INS***	2	2	NA	NA
Lipodystrophy	*AKT2*, ***LMNA,*** *PLIN1*, ***PPARG***	8	8	3	7
Neonatal Diabetes*	***ABCC8***, *GATA4*, *GATA6*, ***INS***, *KCNJ11*, ***HNF1B***	3	3	NA	NA

Note: Bold genes indicate genes that have clinically significant variant carriers
*These variants are incorporated in categories above. The *INS* and *HNF1B* variants were LOF; the *ABCC8* variant has been seen in both neonatal and MODY patients

Supplementary Table 3: Comparison of Top 1% gePS with interquartile range and monogenic carries

	Top 1% of gePS vs Interquartile range (25-75%)		Monogenic carriers vs Top 1% gePS	
Condition	**Estimate**	**Pvalue***	**Estimate**	**Pvalue****
Low LDL cholesteol mg/dL (med adj)	-17.23	3.03E-10	-42.87	2.74E-17
Low LDL cholesterol mg/dL (no lipid meds)	-16.01	2.19E-09	-40.29	7.09E-14
High LDL cholesterol mg/dL (med adj)	16.47	2.43E-09	33.72	2.32E-05
High LDL cholesterol mg/dL (no lipid meds)	12.45	3.70E-06	33.28	2.47E-03
High HDL cholesterol mg/dL	6.46	6.82E-10	12.65	2.61E-03
High triglycerides mg/dL	49.57	8.61E-14	51.44	0.04
Obesity kg/m2	1.86	6.96E-09	0.14	0.90
Diabetes Odds Ratio	2.66	4.25E-07	9.95	1.46E-03

*Regression comparing the top 1% to the interquartile range (25-75%) of the gePS. Adjusted for age, sex and 10 PC's. Age in controls restricted to >=60.

**Regression comparing the top 1% of the gePS to carriers in UK Biobank. Adjusted for age, sex and 10 PC's. Age in controls restricted to >=60.

Pvalues two-sided

Supplementary Table 4: Mean serum LDL values based on ascertainment approach.

	Individuals ascertained on serum LDL cholesterol			Individuals not ascertained on LDL cholesterol			
Condition	**Total**	**Carriers**	**Carrier LDL***	**Total**	**Carriers**	**Carrier LDL***	**Pvalue****
	N	**N**	**Mean (95% CI)**	**N**	**N**	**Mean (95% CI)**	
"High LDL"	249	18	329 (284-375)	19,186	55	198 (178-219)	0.00041
"Low LDL"	253	15	49.2 (43.0-55.4)	19,186	35	77.0 (66.0-88.0)	0.055
Restricted to shared LDL variants							
Condition	**Total**	**Carriers**	**Carrier LDL***	**Total**	**Carriers**	**Carrier LDL***	**Pvalue*****
"High LDL"	NA	7	321 (235-407)	NA	7	183 (123-244)	0.0116
"Low LDL"	NA	5	54.8 (41.4-68.3)	NA	11	92.0 (64.9-119)	0.0491

*LDL values adjusted for lipid-lowering medication use per methods

**Regression comparing LDL values in carriers ascertained on serum LDL cholesterol to carriers not ascertained. Adjusted for age, sex and 10 PC's

***Regression comparing LDL values in carriers ascertained on serum LDL cholesterol to carriers not ascertained; restricted to shared LDL variants. Adjusted for age, sex and 5 PC's

Pvalues two-sided

Supplementary Table 5: Impact of polygenic score on trait expressivity in monogenic carriers.

A) Effect size of gePS on trait in monogenic variant carriers

Trait	N monogenic carriers	gePS beta*	Pvalue	Beta in direction of increasing expressivity
High LDL	83	-0.88	0.886	no
Low LDL	90	-3.89	0.227	yes
High HDL	20	17.52	0.012	yes
High triglycerides	54	80.57	0.014	yes
Obesity	31	1.48	0.137	yes

*per SD global polygenic risk score (gePS)

Model adjusted for age, sex, PC's; Pvalues two-sided

B) Assessment of interaction of carrier status and gePS

Trait	Variable	beta	Pvalue
Low LDL	CarrierStatus	-56.55	1.87E-52
Low LDL	gePS	-5.55	2.62E-197
Low LDL	CarrierStatus*gePS	2.17	0.54
Low LDL no lipid meds	CarrierStatus	-53.19	9.59E-61
Low LDL no lipid meds	gePS	-5.14	1.17E-185
Low LDL no lipid meds	CarrierStatus*gePS	1.67	0.58
High LDL	CarrierStatus	54.94	5.60E-46
High LDL	gePS	5.58	7.71E-199
High LDL	CarrierStatus*gePS	-4.63	0.2
High LDL no lipid meds	CarrierStatus	47.24	7.13E-15
High LDL no lipid meds	gePS	5.15	8.89E-186
High LDL no lipid meds	CarrierStatus*gePS	-15.39	0.037
High HDL	CarrierStatus	18.47	4.83E-10
High HDL	gePS	2.53	2.49E-270
High HDL	CarrierStatus*gePS	8.29	0.001
High triglycerides	CarrierStatus	135.58	6.13E-27
High triglycerides	gePS	15.34	8.76E-232
High triglycerides	CarrierStatus*gePS	34.36	0.01
Obesity	CarrierStatus	2.14	0.01
Obesity	gePS	0.78	6.74E-228
Obesity	CarrierStatus*gePS	0.61	0.50

*per SD global polygenic risk score (gePS)

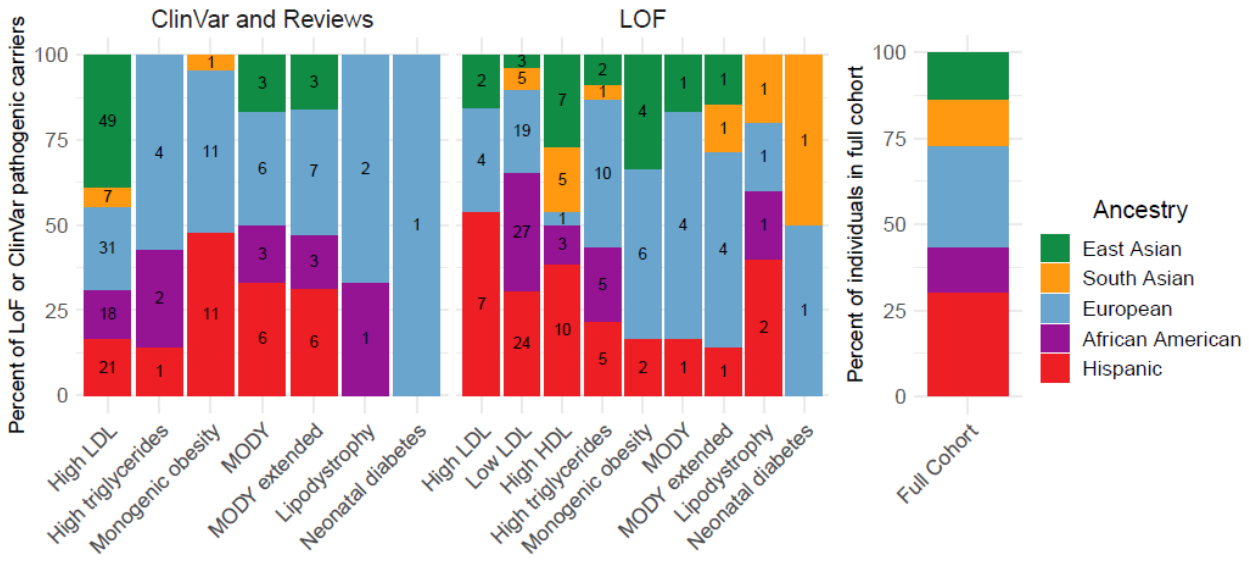
Model adjusted for age, sex, PC's; Pvalues two-sided

Supplementary Table 6: Frequency cut-offs used for ClinVar variant curation.

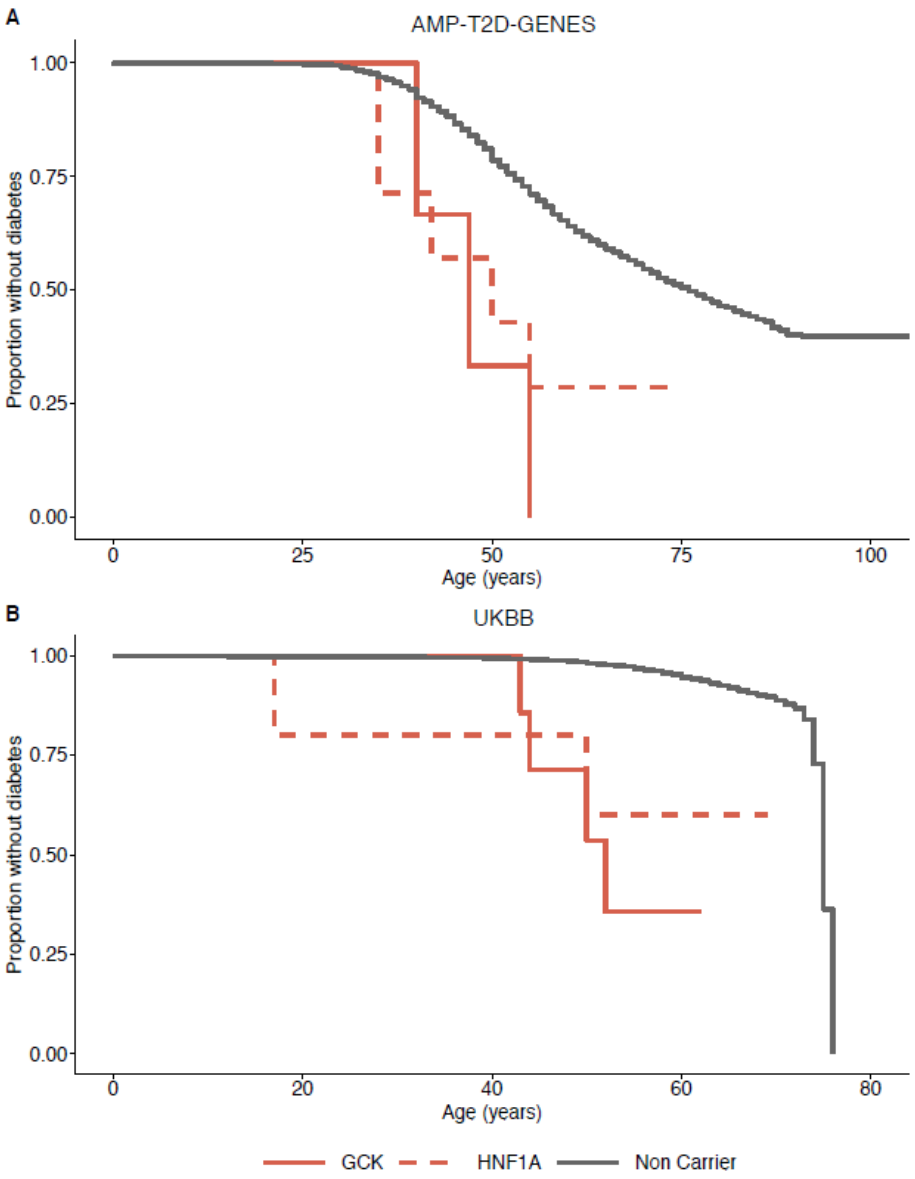
Phenotype (Genes - only genes with ClinVar P/LP clinical testing variants are listed)	GnomAD Frequency Cut-offs			
	PM2	PM2 supporting	BS1	BA1
High LDL (*APOB*, *LDLR*)	Absent/0.0%	N/A	0.5% - 5%	>5%
Obesity (*MC4R*)	Absent/0.0%	<0.02%	N/A	N/A
High Triglycerides (*APOA5*, *LPL*)	AC<=1	N/A	N/A	N/A
MODY (*GCK*, *HNF1A*, *HNF1B*, *HNF4A*, *PDX1*; Extended: *ABCC8*, *CEL*, *INS*, *KCNJ11*)	<0.002%	N/A	0.0033% - 0.01%	>0.01%
Neonatal Diabetes (*ABCC8*, *HNF1B, INS*, *KCNJ11*)	<0.002%	N/A	0.0033% - 0.01%	>0.01%
Lipodystrophy (*LMNA*, *PPARG*)	<0.002%	N/A	0.0033% - 0.01%	>0.01%

Note: Most AMP T2D participants are included in gnomAD, so we used an adjusted gnomAD allele frequency calculated by subtracting the number of AMP T2D carriers from the number of total gnomAD carriers

Supplementary Figures



Supplementary Figure 1. Distribution of clinically significant variants across ancestries. Percent of AMP-T2D-GENES carriers in each ancestry across conditions, broken down by ClinVar/review variants (left panel) and pLoF variants (middle panel), compared to the ancestry of the full cohort (right panel).



Supplementary Figure 2. Carriers of clinically significant variants in MODY genes show a younger age of diabetes diagnosis compared to the rest of the AMP-T2D-GENES cohorts and UK Biobank population.

Kaplan-Meier curves of the proportion of individuals without a diabetes diagnosis in AMP-T2D-GENES (**A**) and UK Biobank (**B**). We used age of diabetes diagnosis when reported, and for all others we used the most recent age recorded with no diabetes diagnosis. Lines are colored by clinically significant carrier status: carriers red and non-carriers grey. Line type for clinically significant carriers indicates the gene the variant falls within.

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