
بسم الله الرحمن الرحیم

ژمیران

ژنوم مرجع ایرانیان

From Genes to Diagnosis: Examining the Clinical and Genetic Spectrum of Maturity-Onset Diabetes of the Young (MODY) in Iran

Sara Asgarian, M.D

Topics

- ***MODY***
- *Population Characteristics*
- *Identifying previously-known MODY-Causing variants*
- *Identifying novel MODY-causing variants*
- *MODY Variants Pattern in Families*
- *Future Perspective*

Diabetes classification

Diabetes

- **Type 1**
- **Type 2**
- **Other specific types**
- **GDM**

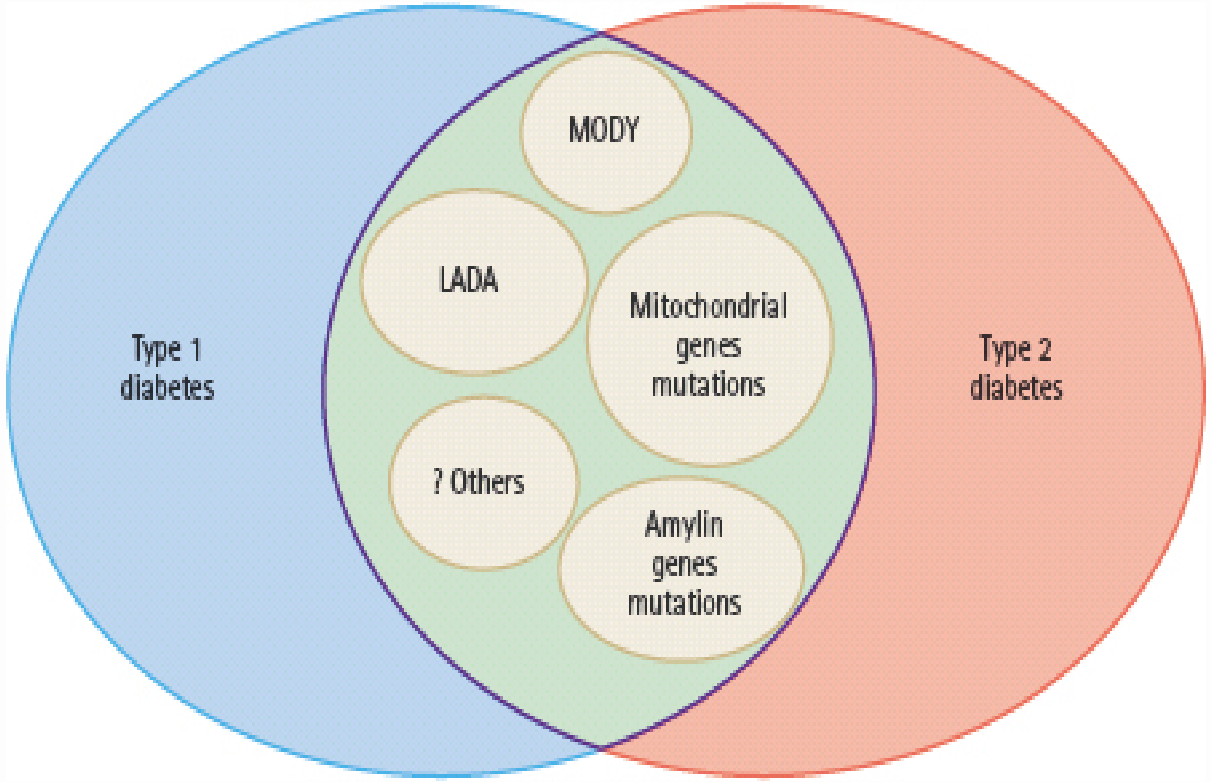
- **Monogenic diabetes syndromes**
- Diseases of the exocrine pancreas
- Chemical-induced diabetes

Monogenic Diabetes

- Up to 5% of all cases of diabetes mellitus

- Two main clinical phenotypes
  - Neonatal Diabetes
  - MODY

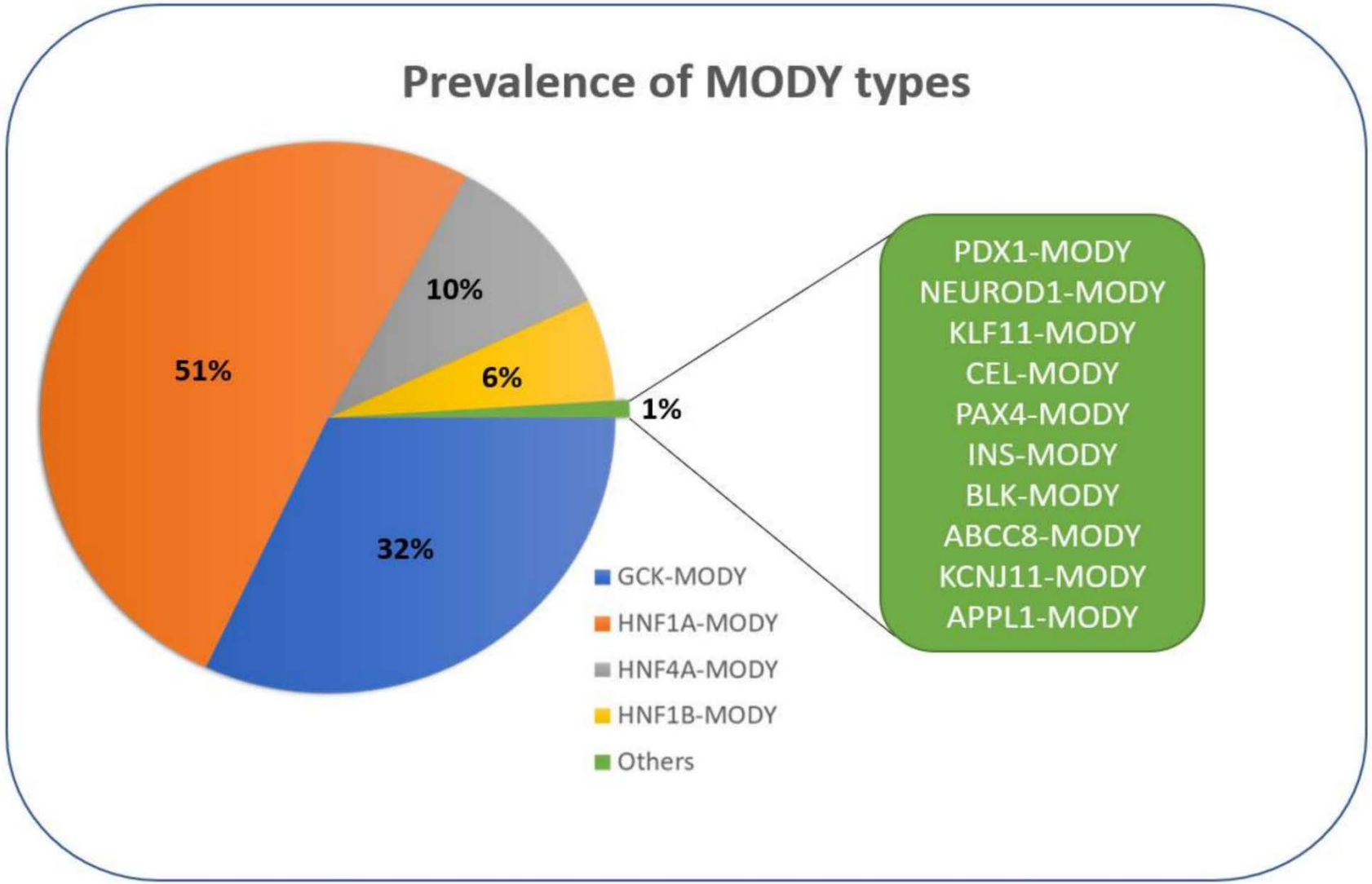
Maturity-Onset Diabetes of the Young



Etiology

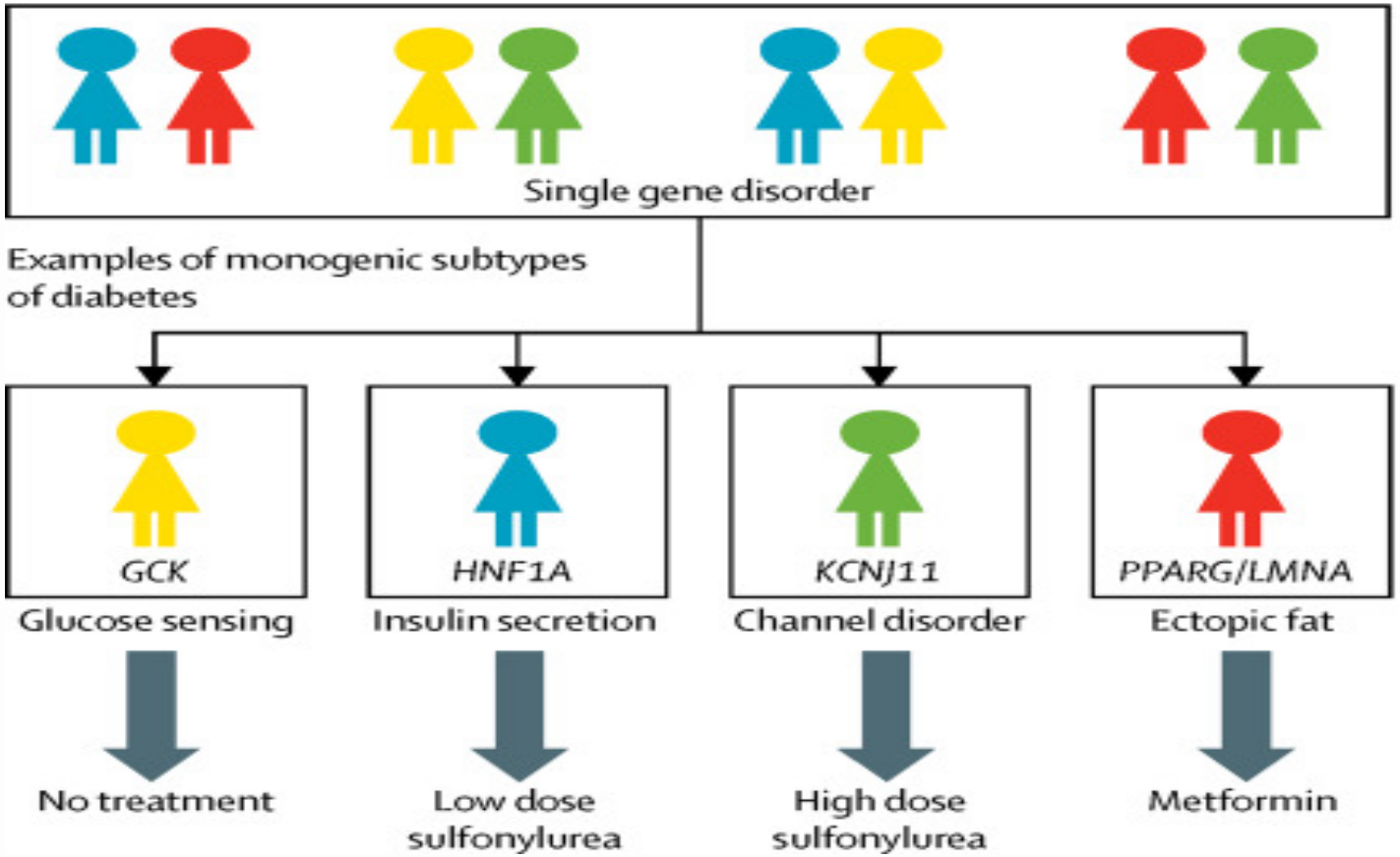
MODY type	Gene	Chromosomal locus	Frequency (%)	Year of recognition
MODY1	HNF4α	20q13	5	1991
MODY2	GCK	7p13	15–25	1993
MODY3	HNF1α	12q24	30–50	1996
MODY4	PDX/IPF1	13q12.2	<1	1997
MODY5	HNF-1β	17q12	5	1997
MODY6	NEUROD1	2q31	<1	1999
MODY7	KLF11	2p25	<1	2005
MODY8	CEL	9q34	<1	2006
MODY9	PAX4	7q32	<1	2007
MODY10	INS	11p15	<1	2008
MODY11	BLK	8p23.1	<1	2009
MODY12	ABCC8	11p15	<1	2012
MODY13	KCNJ11	11p15.1	<1	2012
MODY14	APPL1	3p14.3	<1	2015
MODYX	**RFX6**	**6q22.1**	**<1**	**2017**
MODYX	**NKX6-1**	**4q21.23**	**<1**	**2018**

MODY 1-14


Prevalence of MODY types
51%
10%
6%
1%
32%
GCK-MODY
HNF1A-MODY
HNF4A-MODY
HNF1B-MODY
Others
PDX1-MODY
NEUROD1-MODY
KLF11-MODY
CEL-MODY
PAX4-MODY
INS-MODY
BLK-MODY
ABCC8-MODY
KCNJ11-MODY
APPL1-MODY

Why diagnose MODY?

Changes treatment!



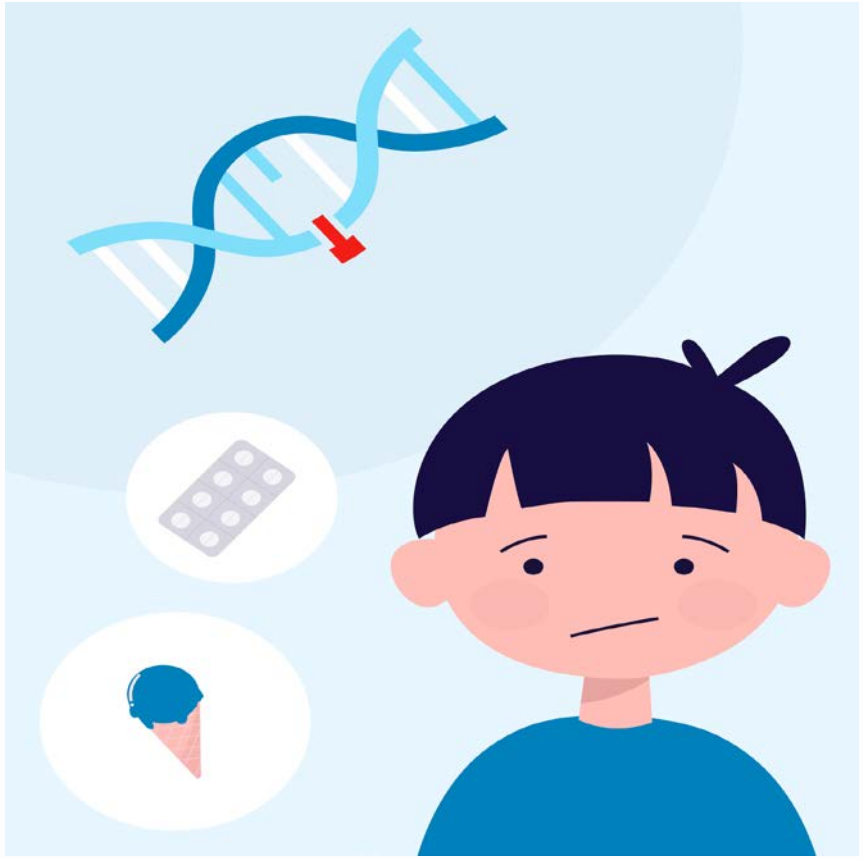
Early detecting for MODY is a essential for:

- Precise diagnosis
- Personalized treatment decision
- Long-term management
- Genetic counseling
- Family screening
- Reduced complication
- Missed research opportunities
- Psychological distress

MODY

Patients with MODY are characterized by:

- Young age of onset (<30 years)
- Non-obesity
- Absence of islet-autoantibodies
- Detectable C-peptide
- Positive family history for diabetes



How many cases are we missing?

- **80% of MODY cases are misdiagnosed as T1 or T2!**
- **Nature-2023**

  The second international consensus report on precision diabetes medicine 2023

  Highlighted the MODY **knowledge gap** to healthcare providers in the **Middle East region** to rectify this niche

Precision medicine for MODY

- MODY calculator: www.diabetesgenes.org/mody-probability-calculator/

- Test individuals with pediatric diabetes when at least three islet autoantibodies are antibody negative

Precision Medicine in Diabetes: A Consensus Report From the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

EXETER DIABETES

MODY Probability Calculator

Age at diagnosis (years)

Sex
- Male
- Female

Currently treated with insulin **or** tablets
- Yes
- No

Time to insulin treatment (if currently treated with insulin)
- Not currently treated with insulin
- Within 6 months of diagnosis
- Over 6 months after diagnosis

BMI (kg/m²)

HbA1c (%) or

HbA1c mmol/mol

Current Age (years)

Parent affected with diabetes
- Yes
- No

Ethnicity
- White
- Non-white

Other
- Renal cysts
- Deafness
- Partial lipodystrophy
- Severe Insulin Resistance in absence of obesity
- Severe obesity with other syndromic features

Topics

- *MODY*
- ***Population Characteristics***
- *Identifying previously-known MODY-Causing variants*
- *Identifying novel MODY-causing variants*
- *MODY Variants Pattern in Families*
- *Future Perspective*

Translation into practice

Diabetics	• FPG ≥ 126 mg/dl • OGTT ≥ 200 mg/dl • Use of glucose-lowering agents
Pre-diabetics	• FPG of 100–125 mg/dl • OGTT of 140–199 mg/dl
Non-diabetics	• FPG < 100mg/dl • OGTT < 140 mg/dl.

Based on American Diabetes Association (ADA) standards

Population characteristics

	All	Diabetics	Pre-Diabetics	Non-Diabetics
Number of subjects	27884	3043 (15.1%)	5835 (29.0%)	11184 (55.7%)
Age (mean ± SD)	46.0±20.3	65.4±14.7	51.5±19.1	38.4±17.5
Female %	14297 (51.2%)	1707 (56.0%)	2888 (49.5%)	6315 (56.4%)
BMI (kg/m2)	**27.4 ± 5.3**	29.8±5.3	28.4±5.1	25.9±5.0
Underweight	3.7%	0.6%	2.0%	5.9%
Normal weight	28.6%	15.6%	21.5%	38.2%
Overweight	38.8%	40.3%	41.3%	36.6%
Obese	28.7%	43.3%	35.1%	19.1%

Topics

- *MODY*
- *Population Characteristics*
- ***Identifying previously-known MODY-Causing variants***
- *Identifying novel MODY-causing variants*
- *MODY Variants Pattern in Families*
- *Future Perspective*

ClinVar database

National Library of Medicine
National Center for Biotechnology Information

Log in

ClinVar | ClinVar | Maturity-Onset Diabetes of the Young | Search
Create alert | Advanced | Help

Home | About | Access | Help | Submit | Statistics | FTP

Clinical significance
Conflicting interpretations (932)
Benign (369)
Likely benign (401)
Uncertain significance (876)
Likely pathogenic (344)
Pathogenic (445)

Types of conflicts
P/LP vs LB/B (21)
P/LP vs VUS (371)
VUS vs LB/B (562)

Molecular consequence
Frameshift (218)
Missense (1,248)
Nonsense (132)
Splice site (132)
ncRNA (364)
Near gene (0)
UTR (484)

Variation type
Deletion (255)
Duplication (100)
Indel (24)
Insertion (142)
Single nucleotide (2,621)

Variation size
Short variant (< 50 bps) (3,003)
Structural variant (>= 50 bps) (11)

Search results

Display options | Sort by Location | Download

Items: 1 to 100 of 3045

<< First | < Prev | Page 1 of 31 | Next > | Last >>

	Variation *Location*	Gene(s)	Protein change	Condition(s)	Clinical significance (Last reviewed)	Review status
1.	NM_007262.5(PARK7):c.293G>A (p.Arg98Gln) *GRCh37:* Chr1:8030994 *GRCh38:* Chr1:7970934	PARK7	R98Q	Renal cysts and **diabetes** syndrome, Autosomal recessive early-onset Parkinson disease 7, not provided	Benign/Likely benign (Oct 24, 2022)	criteria provided, multiple submitters, no conflicts
2.	NM_170707.4(LMNA):c.-88G>T *GRCh37:* Chr1:156084622 *GRCh38:* Chr1:156114831	LMNA		not provided, Charcot-Marie-Tooth disease type 2B1, Mandibuloacral dysplasia with type A lipodystrophy, Familial partial lipodystrophy, Dunnigan type, **Maturity onset diabetes** mellitus in **young**, Dilated cardiomyopathy 1A, Lethal tight skin contracture syndrome, Emery-Dreifuss muscular dystrophy, Congenital muscular dystrophy due to LMNA mutation,	Benign/Likely benign (Jan 12, 2018)	criteria provided, multiple submitters, no conflicts

Feedback

Clinvar results for 3045 variants

Clinical significance	n.	%
Conflicting interpretations	932	27.68
Benign	369	10.96
Likely benign	401	11.91
Uncertain significance	876	26.02
Likely pathogenic	344	10.22
Pathogenic	445	13.22

Molecular consequence	n.	%
Frameshift	218	8.46
Missense	1248	48.41
Nonsense	132	5.12
Split site	132	5.12
ncRNA	364	14.12
UTR	484	18.77

MODY pathogenic variants

NIH National Library of Medicine
National Center for Biotechnology Information

Log in

ClinVar | ClinVar | maturity onset diabetes of young | Search
Create alert | Advanced | Help

Home | About | Access | Help | Submit | Statistics | FTP

Clinical significance clear
Conflicting interpretations (0)
Benign (0)
Likely benign (0)
Uncertain significance (0)
✓ **Likely pathogenic** (115)
✓ **Pathogenic** (138)

Molecular consequence
Frameshift (0)
Missense (91)
Nonsense (59)
Splice site (25)
ncRNA (2)
Near gene (0)
UTR (5)

Variation type clear
Deletion (0)
Duplication (0)
Indel (0)
Insertion (0)
✓ **Single nucleotide** (176)

Variation size
Short variant (< 50 bps) (176)
Structural variant (>= 50 bps) (0)

Variant length
< 1kb, single gene (169)
> 1kb, single gene (0)
> 1kb, multiple genes (0)

Review status clear
Practice guideline (0)
Expert panel (0)

Search results

Display options | Sort by Gene | Download — Items: 1 to 100 of 176 — << First | < Prev | Page 1 of 2 | Next > | Last >>

Filters activated: Pathogenic, Likely pathogenic, Single nucleotide, Multiple submitters. Clear all to show 3045 items.

The following term was not found in ClinVar: clinsig established risk allele[Properties].

	Variation *Location*	Gene(s)	Protein change	Condition(s)	Clinical significance (Last reviewed)	Review status
1.	NM_000352.6(ABCC8):c.4136G>A (p.Arg1379His) *GRCh37:* Chr11:17417461 *GRCh38:* Chr11:17395914	ABCC8	R1379H, R1380H, R1378H, R1401H	**Maturity onset diabetes** mellitus in **young**, Monogenic **diabetes**, not provided	Pathogenic/Likely pathogenic (Oct 19, 2022)	**criteria provided, multiple submitters, no conflicts**
2.	NM_001807.6(CEL):c.337C>T (p.Gln113Ter) *GRCh37:* Chr9:135940146 *GRCh38:* Chr9:133064759	CEL	Q113*	not provided, **Maturity-onset diabetes** of the **young** type 8	Pathogenic/Likely pathogenic (Dec 17, 2022)	**criteria provided, multiple submitters, no conflicts**
3.	NM_000162.5(GCK):c.1072C>T (p.Arg358Ter) *GRCh37:* Chr7:44185277 *GRCh38:* Chr7:44145678	GCK	R21*, R357*, R358*, R359*, R36*	not provided	Pathogenic (Jun 21, 2022)	**criteria provided, multiple submitters, no conflicts**
4.	NM_000162.5(GCK):c.982G>T (p.Gly328Ter) *GRCh37:* Chr7:44186099 *GRCh38:* Chr7:44146500	GCK	G327*, G329*, G328*	Monogenic **diabetes**, **Maturity onset diabetes** mellitus in **young**	Pathogenic (May 9, 2023)	**criteria provided, multiple submitters, no conflicts**
5.	NM_000162.5(GCK):c.766G>T (p.Glu256Ter) *GRCh37:* Chr7:44187346 *GRCh38:* Chr7:44147747	GCK	E257*, E255*, E256*	**Maturity onset diabetes** mellitus in **young**, not provided	Pathogenic (Jul 14, 2022)	**criteria provided, multiple submitters, no conflicts**
	NM_000162.5(GCK):c.209-1G	GCK		**Maturity-onset**	Pathogenic/Likely	**criteria provided, multiple**

Identifying previously-known MODY-Causing variants

3045 Variants

- ClinVar database's search results for ”MODY"

- Genes known to be associated with MODY

- Clinical significance for Pathogenic/likely pathogenic

410 variants

- Available variants in TCGS data

MAF < 0.001% & mean sequencing depth > 20×

6 variants

About six previously-known variants

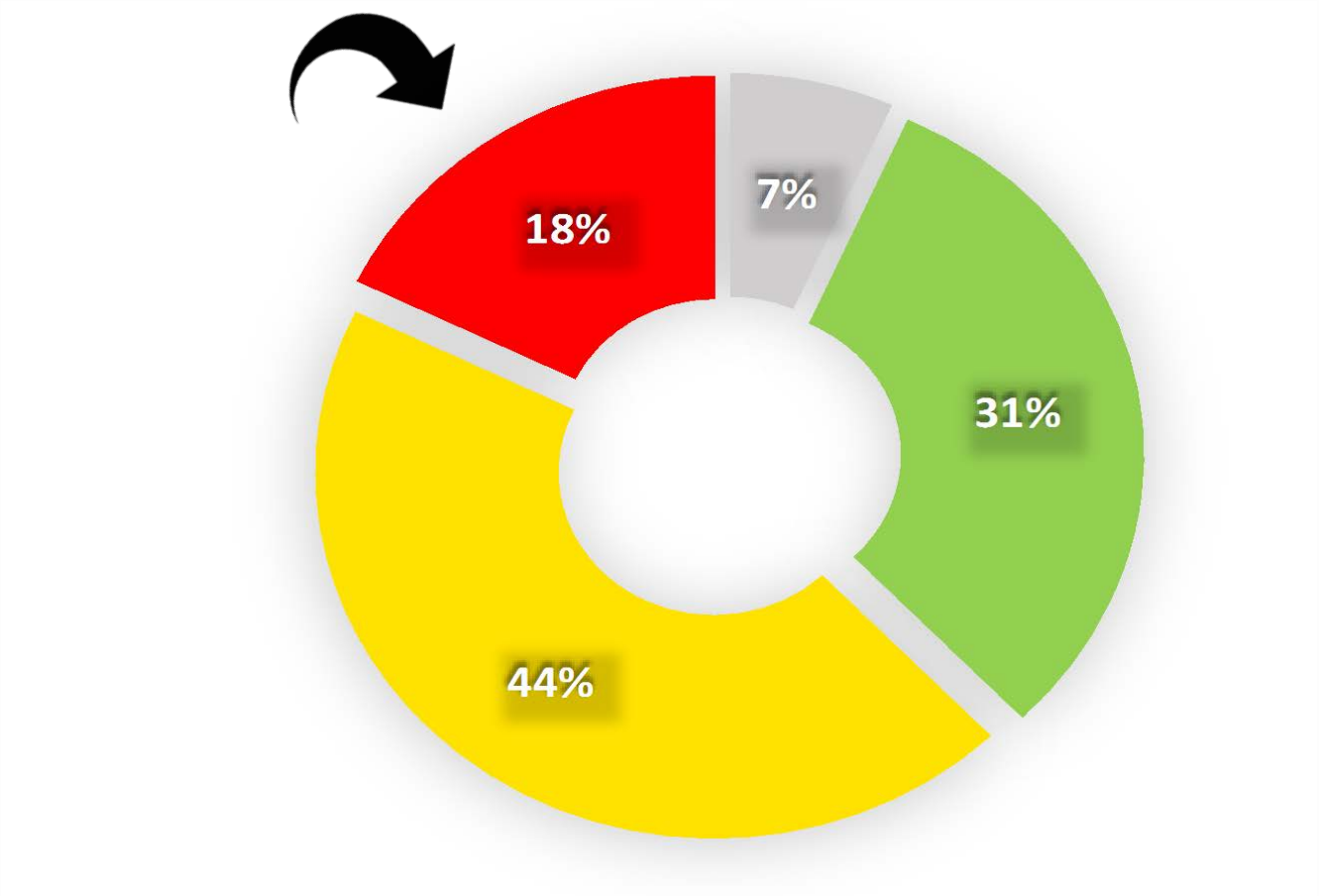
Diabetic carriers/All carriers

n.	Gene	MODY	Case/ family n.	Penetrance (%)	Diagnosis (n)	Clinical significance
1	HNF4A	1	1 / 1	100	DM	P/LP
2	INS	10	21 / 11	38	DM (8) Pre DM (8) N.D (3)	P
3	GCK	2	13 / 7	61.5	DM (3) Pre DM (5) N.D (4)	P
4	CEL	8	1 / 1	0	Pre DM	LP
5	HNF1A	3	1 / 1	100	DM	P
6	HNF1B	5	8 / 3	12.5	DM (1) Pre DM (5) N.D (2)	P

previously-known MODY variants

MODY type	Gene	Chromosomal locus	Frequency (%)	Year of recognition
MODY1	HNF4α	20q13	5	1991
MODY2	GCK	7p13	15–25	1993
MODY3	HNF1α	12q24	30–50	1996
MODY4	PDX/IPF1	13q12.2	<1	1997
MODY5	HNF-1β	17q12	5	1997
MODY6	NEUROD1	2q31	<1	1999
MODY7	KLF11	2p25	<1	2005
MODY8	CEL	9q34	<1	2006
MODY9	PAX4	7q32	<1	2007
MODY10	INS	11p15	<1	2008
MODY11	BLK	8p23.1	<1	2009
MODY12	ABCC8	11p15	<1	2012
MODY13	KCNJ11	11p15.1	<1	2012
MODY14	APPL1	3p14.3	<1	2015
MODYX	**RFX6**	**6q22.1**	**<1**	**2017**
MODYX	**NKX6-1**	**4q21.23**	**<1**	**2018**

Phenotype frequency of known MODY variants



MODY phenotype

Based on the International Society of Pediatric and Adolescent Diabetes (ISPAD) 2022 clinical criteria

MODY

- Age of DM onset < 25 years
- Positive family history of diabetes
- Absence of evidence for T1DM/T2DM

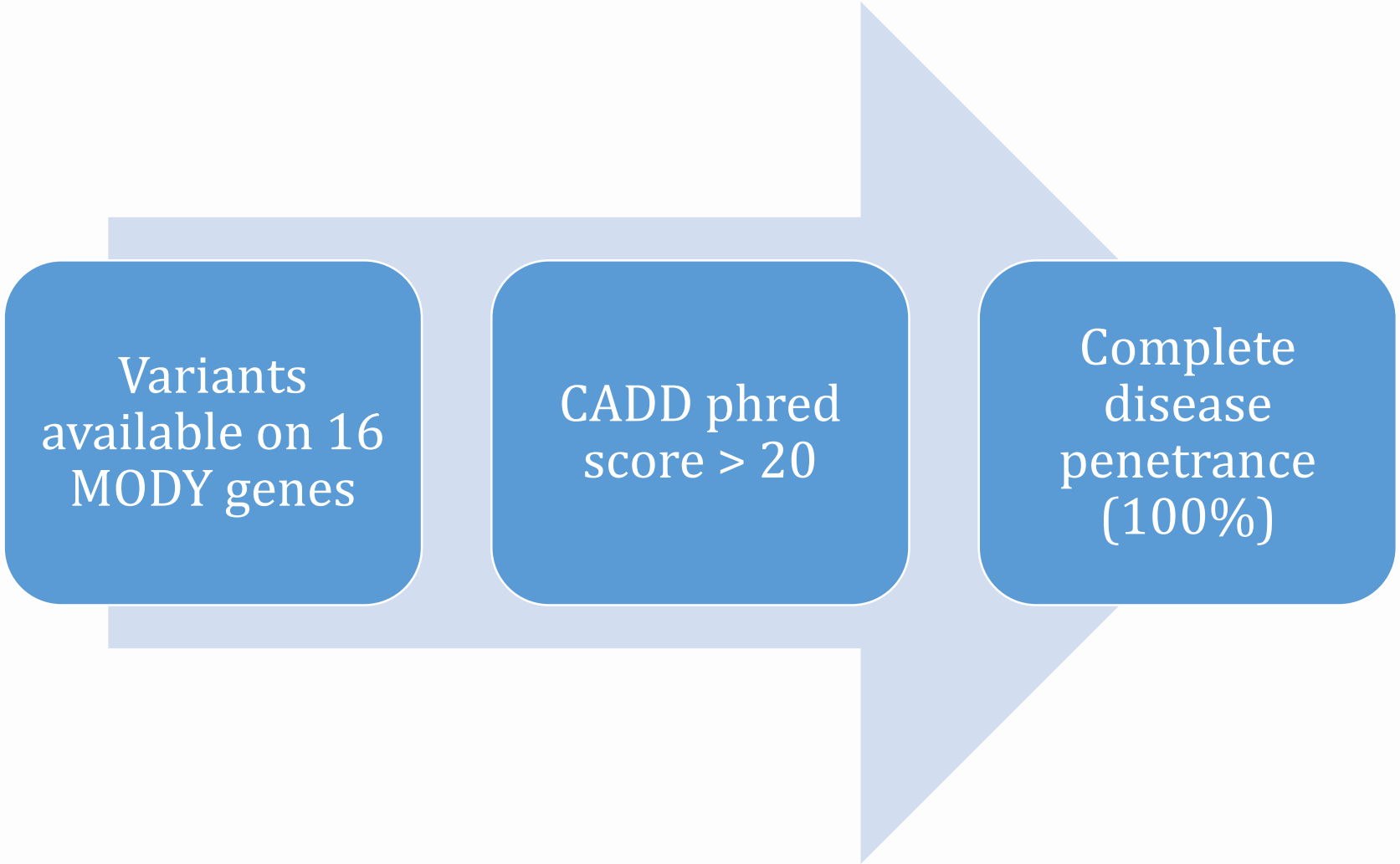
Phenotype mapping

n.	Gene	MODY	DM status	DM onset age	DM Family History
1	GCK	2	Pre DM - DM	51.5	
2	GCK	2	Pre DM - DM	51	+
3	HNF1A	3	NL - DM	13	+
4	HNF1B	5	Baseline DM	37	
5	HNF4A	1	NL - DM	20	+
6	INS	10	Baseline DM	59	
7	INS	10	Baseline DM	61	+
8	INS	10	Pre DM - DM	44	+

Topics

- *MODY*
- *Population Characteristics*
- *Identifying previously-known MODY-Causing variants*
- ***Identifying novel MODY-causing variants***
- *MODY Variants Pattern in Families*
- *Future Perspective*

Criteria for novel variants



Identifying novel MODY-causing variants

647,705 variants
- Variants available in TCGS data on 16 MODY genes

116 variants
- MAF <0.001% & mean sequencing depth > 20×

3 variants
- CADD Phred score > 20 & disease penetrance 100%

3 variants

MODY type	Gene	Chromosomal locus	Frequency (%)	Year of recognition
MODY1	HNF4α	20q13	5	1991
MODY2	GCK	7p13	15–25	1993
MODY3	HNF1α	12q24	30–50	1996
MODY4	PDX/IPF1	13q12.2	<1	1997
MODY5	HNF-1β	17q12	5	1997
MODY6	NEUROD1	2q31	<1	1999
MODY7	KLF11	2p25	<1	2005
MODY8	CEL	9q34	<1	2006
MODY9	PAX4	7q32	<1	2007
MODY10	INS	11p15	<1	2008
MODY11	BLK	8p23.1	<1	2009
MODY12	ABCC8	11p15	<1	2012
MODY13	KCNJ11	11p15.1	<1	2012
MODY14	APPL1	3p14.3	<1	2015
MODYX	**RFX6**	**6q22.1**	**<1**	**2017**
MODYX	**NKX6-1**	**4q21.23**	**<1**	**2018**

About three novel variants

Gene	MODY	case/ family n.	Penetrance (%)	Diagnosis (n)	Clinical significance
HNF1B	5	4 / 1	**100**	DM	Not Reported
PAX4	9	1 / 1	**100**	DM	Not Reported
KLF11	7	5 / 3	**100**	DM	Not Reported

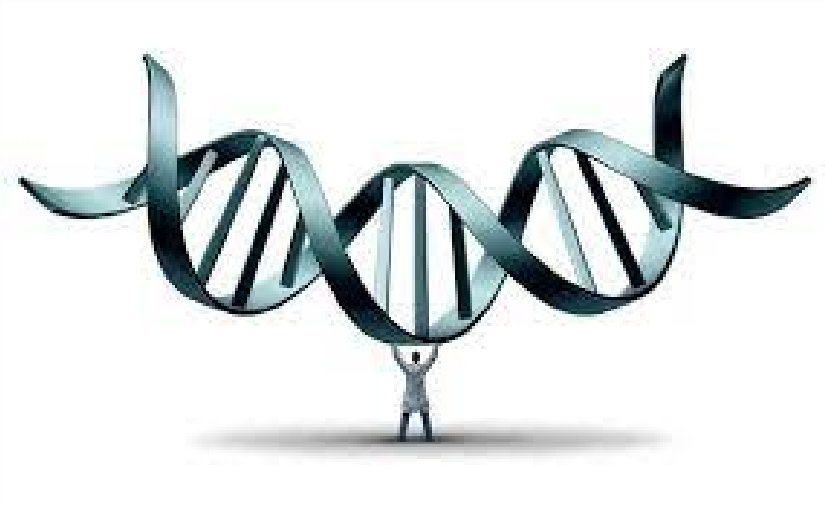
MODY variants summary

Gene	MODY	Novel	case/ family n	Penetrance (%)	Diagnosis (n)	Consequence	Clinical significance
HNF4A	1		1 / 1	**100**	DM	missense	P/LP
INS	10		21 / 11	38	DM (8) Pre DM (8) N.D (3)	missense	P
GCK	2		13 / 7	61.5	DM (3) Pre DM (5) N.D (4)	missense	P
CEL	8		1 / 1	0	Pre DM	frameshift	LP
HNF1A	3		1 / 1	**100**	DM	frameshift	P
HNF1B	5		8 / 3	12.5	DM (1) Pre DM (5) N.D (2)	synonymous	P
		*	4 / 1	**100**	DM	missense	Not Reported
PAX4	9	*	1 / 1	**100**	DM	missense	Not Reported
KLF11	7	*	5 / 3	**100**	DM	missense	Not Reported

Topics

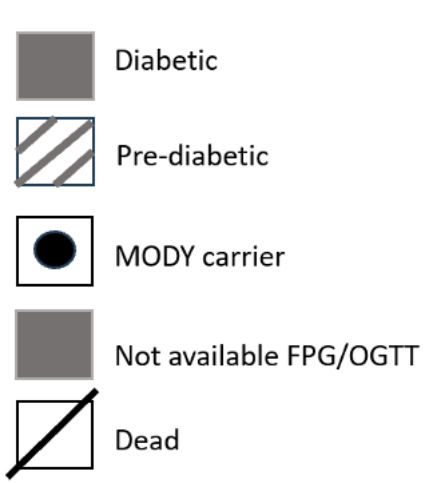
- *MODY*
- *Population Characteristics*
- *Identifying previously-known MODY-Causing variants*
- *Identifying novel MODY-causing variants*
- ***MODY Variants Pattern in Families***
- *Future Perspective*

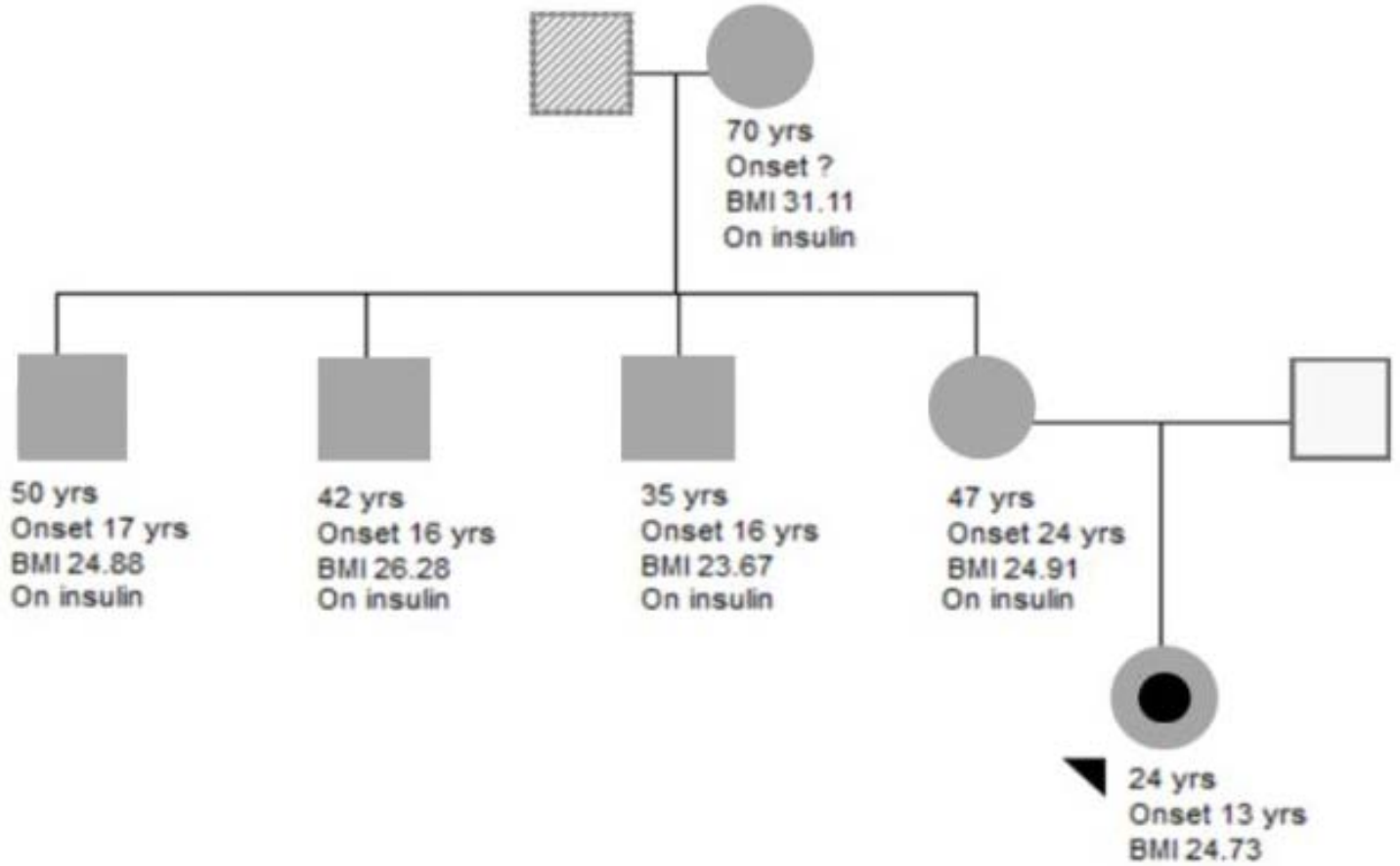
Final MODY candidates



MODY 3

- HNF1A
- Pathogenic variant
- Frameshift mutation
- Insertion p.Pro289fs
- One proband





EXETER DIABETES

MODY Probability Calculator

Age at diagnosis (years)	13
Sex	○ Male ● Female
Currently treated with insulin **or** tablets	○ Yes ● No
Time to insulin treatment (if currently treated with insulin)	● Not currently treated with insulin ○ Within 6 months of diagnosis ○ Over 6 months after diagnosis
BMI (kg/m²)	24.73
HbA1c (%) or	6.5
HbA1c mmol/mol	
Current Age (years)	20
Parent affected with diabetes	● Yes ○ No
Ethnicity	● White ○ Non-white
Other	☐ Renal cysts ☐ Deafness ☐ Partial lipodystrophy ☐ Severe Insulin Resistance in absence of obesity ☐ Severe obesity with other syndromic features

EXETER DIABETES

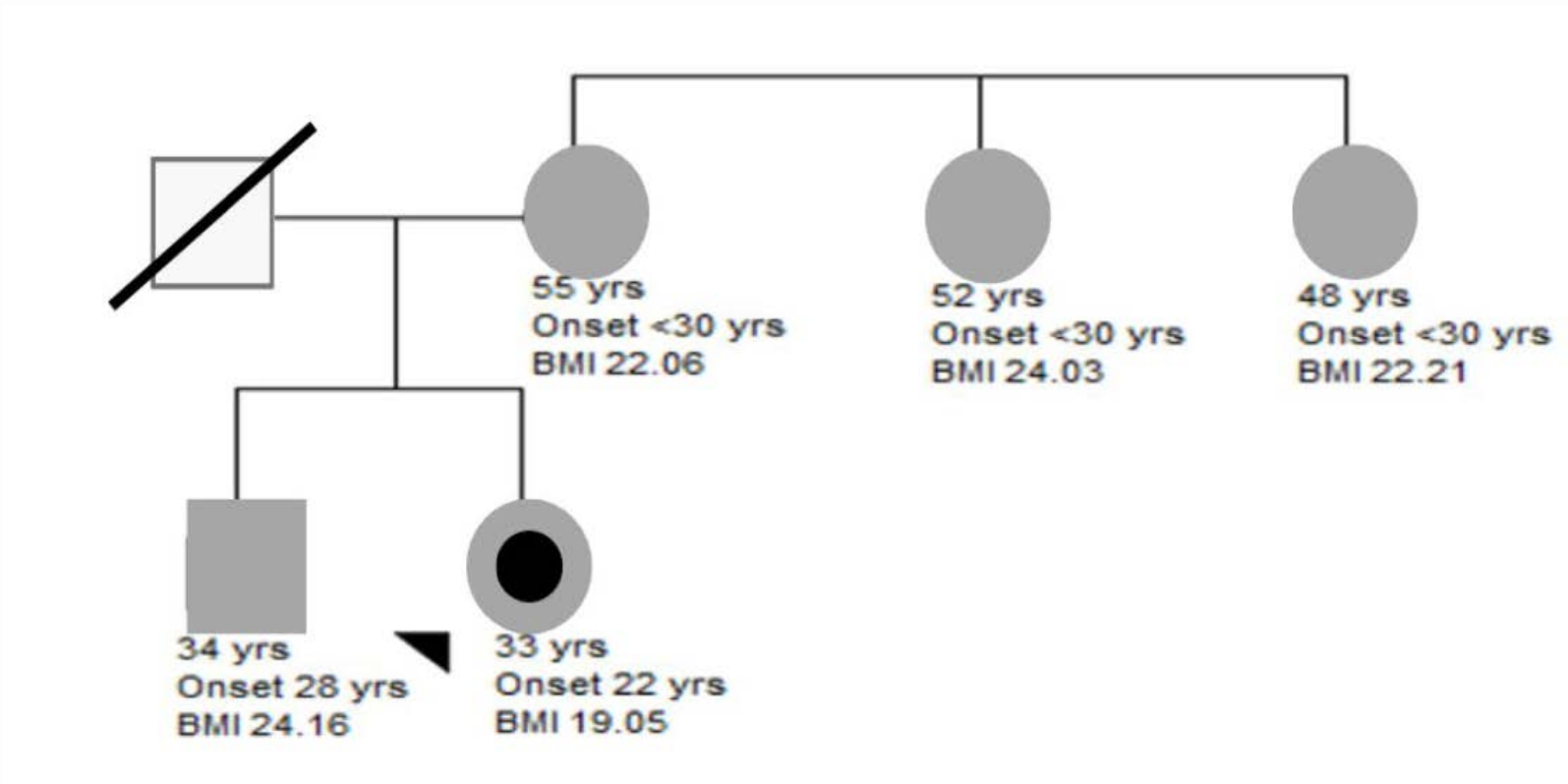
MODY Results

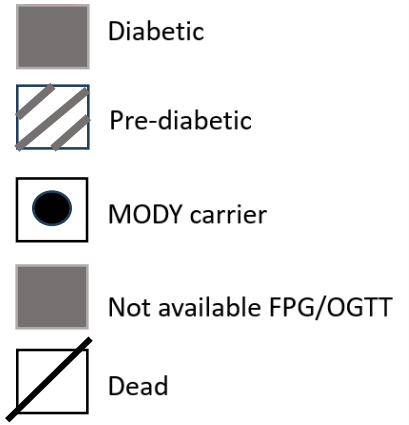
Based on the clinical features entered into the calculator, the probability of your patient having MODY is

75.5% (a 1 in 1.3 chance of having MODY)

MODY 1

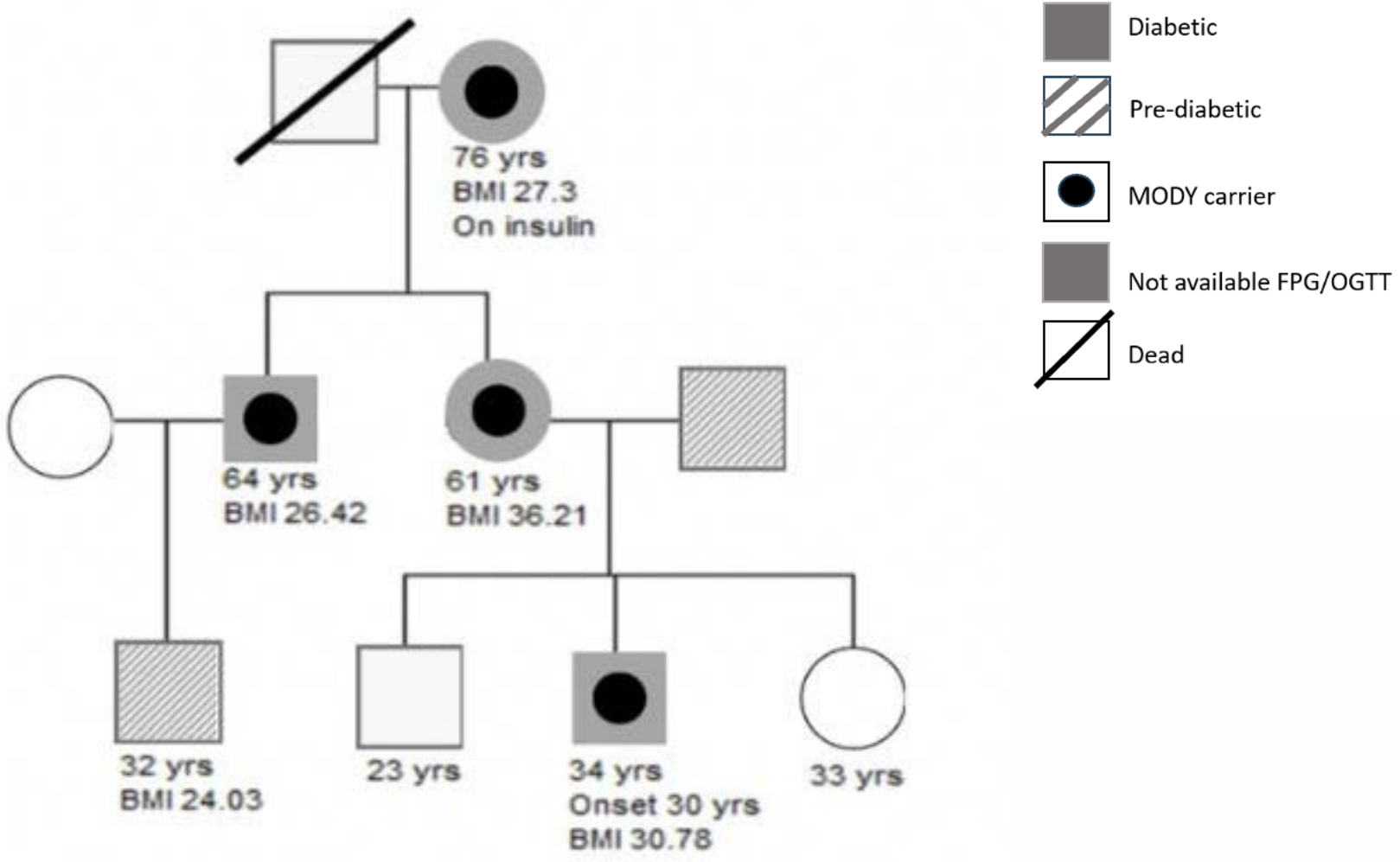
- HNF4A
- Pathogenic variant
- Missense mutation
- p.Val108Ile
- One proband





MODY 5 - novel

- A novel variant
- HNF1B
- Not reported in ClinVar
- Missense mutation
- Four cases from 1 family



Topics

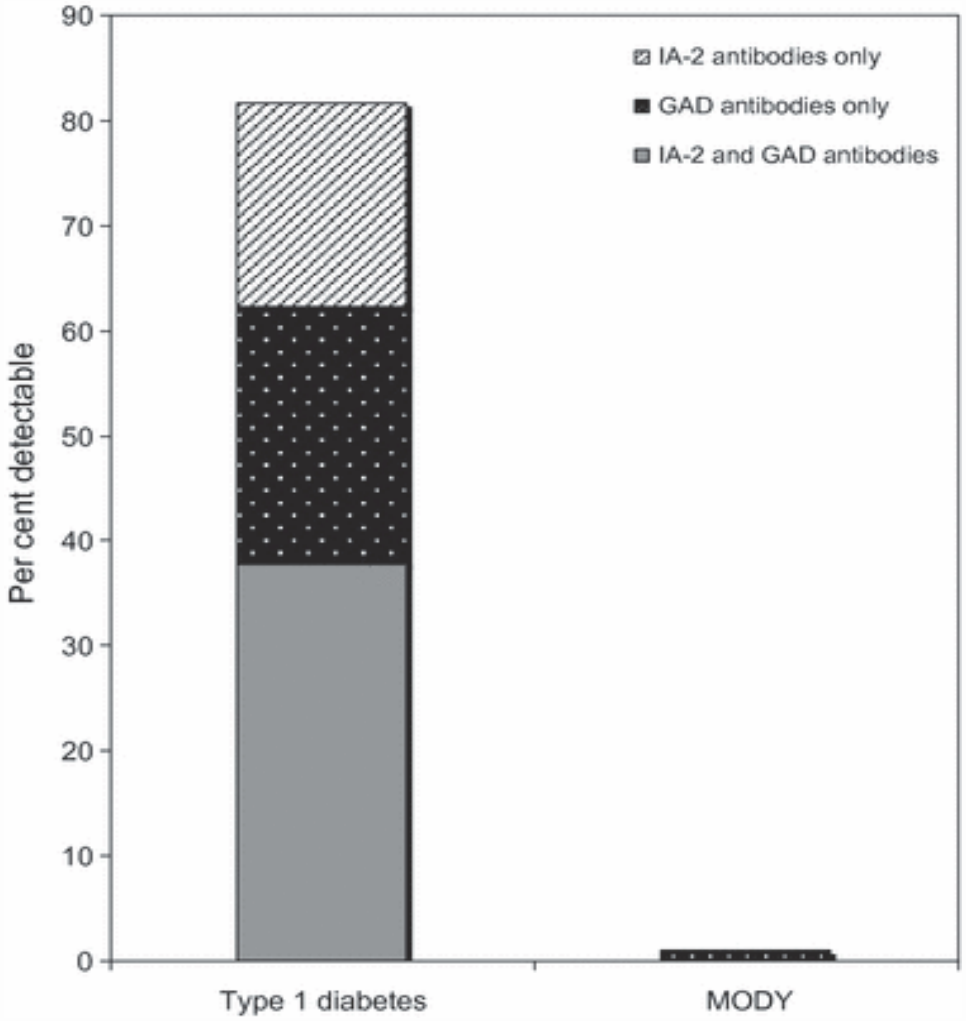
- *MODY*
- *Population Characteristics*
- *Identifying previously-known MODY-Causing variants*
- *Identifying novel MODY-causing variants*
- *MODY Variants Pattern in Families*
- ***Future Perspective***

What we need?

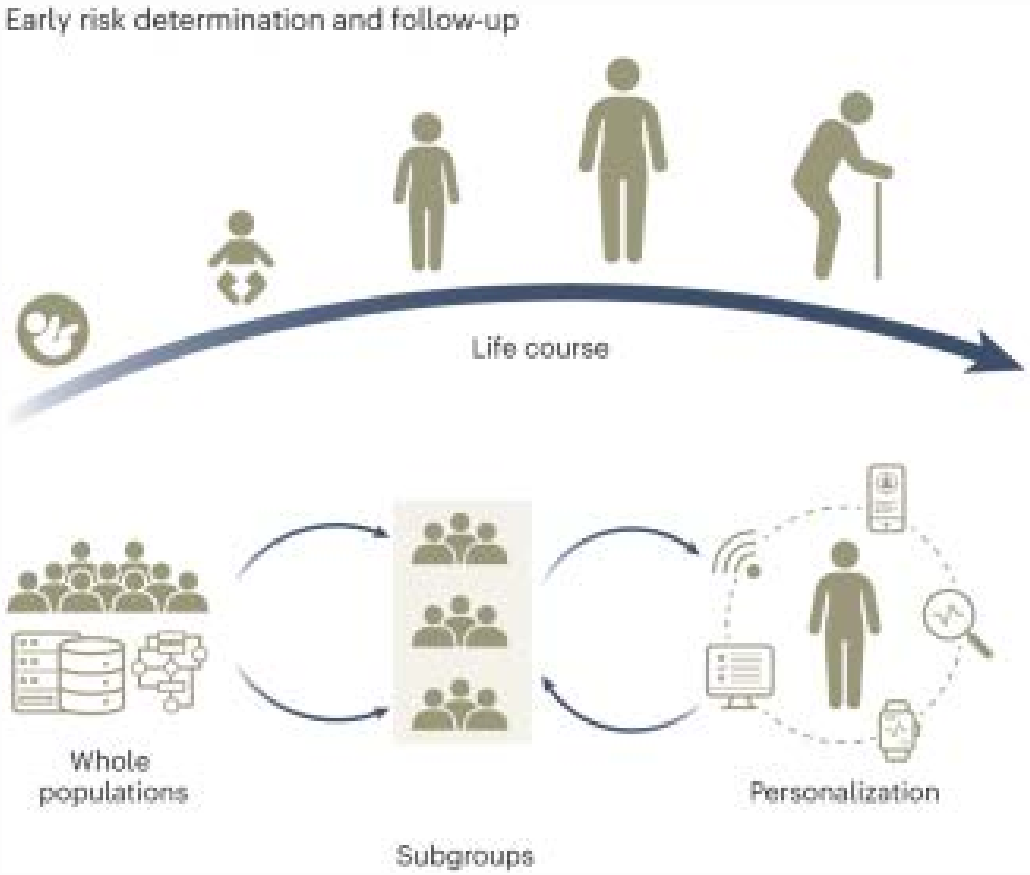
- C-peptide
- Auto antibody

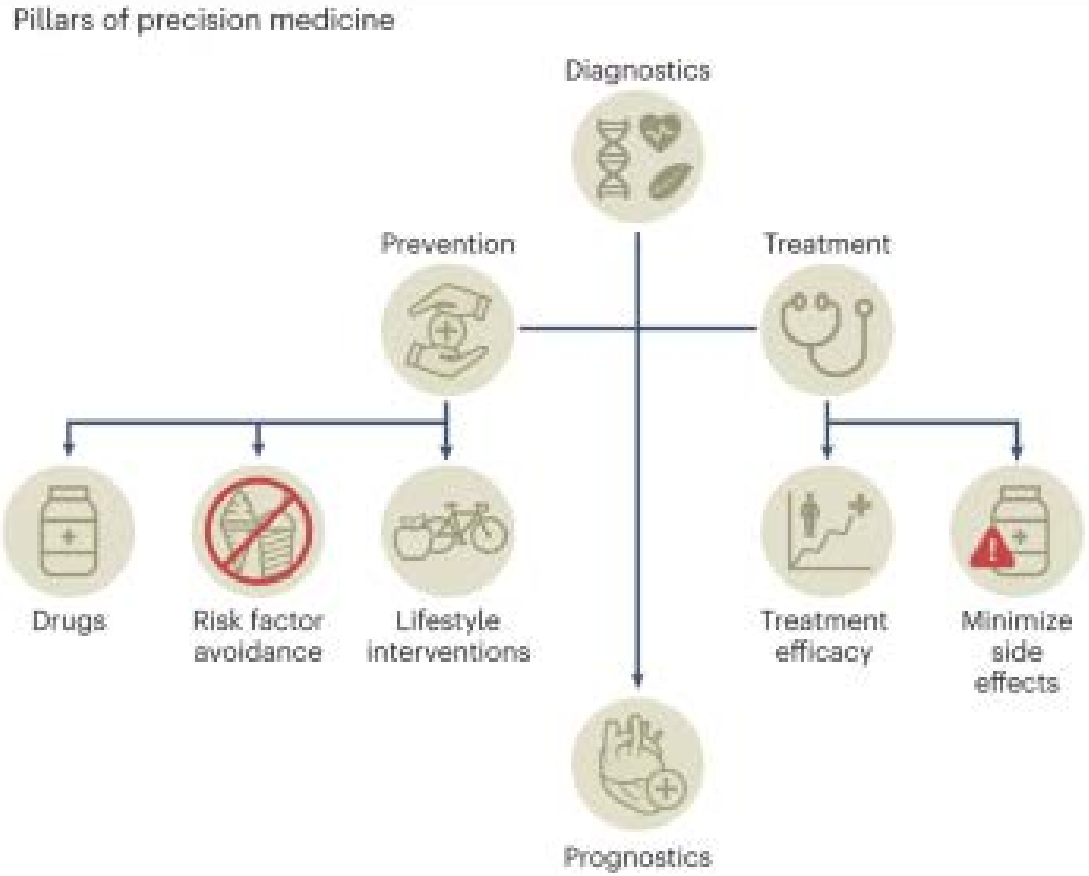
  islet cell antibodies

  antibodies to glutamic acid decarboxylase (GAD)
- HBA1C
- Any glucose lowering agent?



Precision medicine across the life





THANKS FOR YOUR ATTENTION

MODY 7 - novel

- in 5 probands from 3 families.
- except one individual who was a child (12 year old boy), all of them were diabetic indicating complete disease penetrance of this variation in our population.
- the AD inheritance for diabetic phenotype were not confirmed.

MODY 9 - novel

- in one proband
- diagnosed with diabetes giving this variant a complete penetrance.
- The variant transmission was unreachable as the only family member of the carrier in our cohort, was his 8 years old child whose glycemic status was not available in our data.

MODY 5

- One HNF1B
- Pathogenic variant
- Synonymous mutation
- p.Tyr172_Val173=
- Eight proband from three family
- There were no reported special clinical manifestation for Renal cysts and diabetes syndrome (RCAD) (malformation of the pancreas, exocrine pancreatic dysfunction, urogenital abnormalities, impaired renal function, renal cysts, hypomagnesaemia elevated liver enzymes, and neurocognitive defects) in any of our carriers for this variation

MODY 8

- CEL
- Likely pathogenic variant
- Frameshift mutation
- Duplication p.Val593fs
- One proband
- A 38-year-old Iranian man, was the only carrier of this mutation. He was normoglycemic in all follow up sections. Although genetic sequencing data for his other family members were not available, as no one in this pedigree were diabetic, it seems that this variant hasn't causative impact for MODY presentation in our population.

MODY 10

- GCK
- pathogenic variant
- Missense mutation
- p.Ile225Met
- 13 proband from seven families

- INS
- Pathogenic
- Missense mutation
- p.Arg6Cys
- 21 proband from 11 families

The AD inheritance for diabetic phenotype were not seen, and the disease penetrance was 38%, it seems that this variant hasn't causative impact for MODY presentation.

MODY 3

PABYACN	PHASE 1	PHASE 2	PHASE 3	PHASE 4	PHASE 5	PHASE 6
AGE	6	11	15	16	20	24
STATUS	missing	Normal	Diabetes	missing	Diabetes	missing
FBS	-	87	128	-	171	-
OGTT	-	-	-	-	-	-
BMI	-	24.73	25	-	25	-

Int J Mol Sci. 2023 Jan; 24(1): 130.
Published online 2022 Dec 21. doi: 10.3390/ijms24010130
PMCID: PMC9820507
PMID: 36613572

The Genetic Spectrum of Maturity-Onset Diabetes of the Young (MODY) in Qatar, a Population-Based Study

Asma A. Elashi,[1] Salman M. Toor,[1] Ilhame Diboun, Methodology, Investigation,[1,2] Yasser Al-Sarraj, Methodology, Investigation,[3] Shahrad Taheri, Resources, Writing – review & editing, Funding acquisition,[4] Karsten Suhre, Resources, Writing – review & editing, Funding acquisition,[5,6] Abdul Badi Abou-Samra, Resources, Writing – review & editing, Funding acquisition,[4] and Omar M. E. Albagha[1,7,*]

Nat Commun. 2017; 8: 888.
Published online 2017 Oct 12. doi: 10.1038/s41467-017-00895-9
PMCID: PMC5638866
PMID: 29026101

Heterozygous *RFX6* protein truncating variants are associated with MODY with reduced penetrance

Kashyap A. Patel,[#1] Jarno Kettunen,[#2,3,4] Markku Laakso,[5,6] Alena Stančáková,[6] Thomas W. Laver,[1] Kevin Colclough,[7] Matthew B. Johnson,[1] Marc Abramowicz,[8] Leif Groop,[9,10] Päivi J. Miettinen,[11,12] Maggie H. Shepherd,[1] Sarah E. Flanagan,[1] Sian Ellard,[1] Nobuya Inagaki,[13] Andrew T. Hattersley,[1] Tiinamaija Tuomi,[2,3,4,10] Miriam Cnop,[✉14,15] and Michael N. Weedon[✉1]

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

> BMC Med Genet. 2018 Feb 13;19(1):22. doi: 10.1186/s12881-018-0528-6.

Comprehensive genomic analysis identifies pathogenic variants in maturity-onset diabetes of the young (MODY) patients in South India

Viswanathan Mohan [1], Venkatesan Radha [2], Thong T Nguyen [3], Eric W Stawiski [3 4], Kanika Bajaj Pahuja [3], Leonard D Goldstein [3 4], Jennifer Tom [4], Ranjit Mohan Anjana [2],