University of Nebraska Medicine:
2022 Diabetes Update
September 30, 2022

Monogenic Diabetes:
Precision Diabetes Medicine in practice

Louis H. Philipson MD, PhD

Director, Kovler Diabetes Center
James C. Tyree Professor of Diabetes Research and Care
Section of Adult and Pediatric Endocrinology,
Diabetes and Metabolism
University of Chicago Medicine

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Learning Objectives

At the end of this session, attendees will be able to:

1. Understand the biochemical and pathophysiologic characteristics of dominantly inherited monogenic diabetes and its various forms
2. Understand the impact a correct diagnosis of diabetes can have on treatment and management
3. Understand how specific diabetes strategies stemming from genetics can be used to optimize care and quality of life.

Grand Rounds

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Key Points

- Identify key conditions, diagnoses and syndromes related to monogenic diabetes
- Identify when oral therapies or no therapy at all can used to better care for patients with specific types of monogenic diabetes.

Grand Rounds

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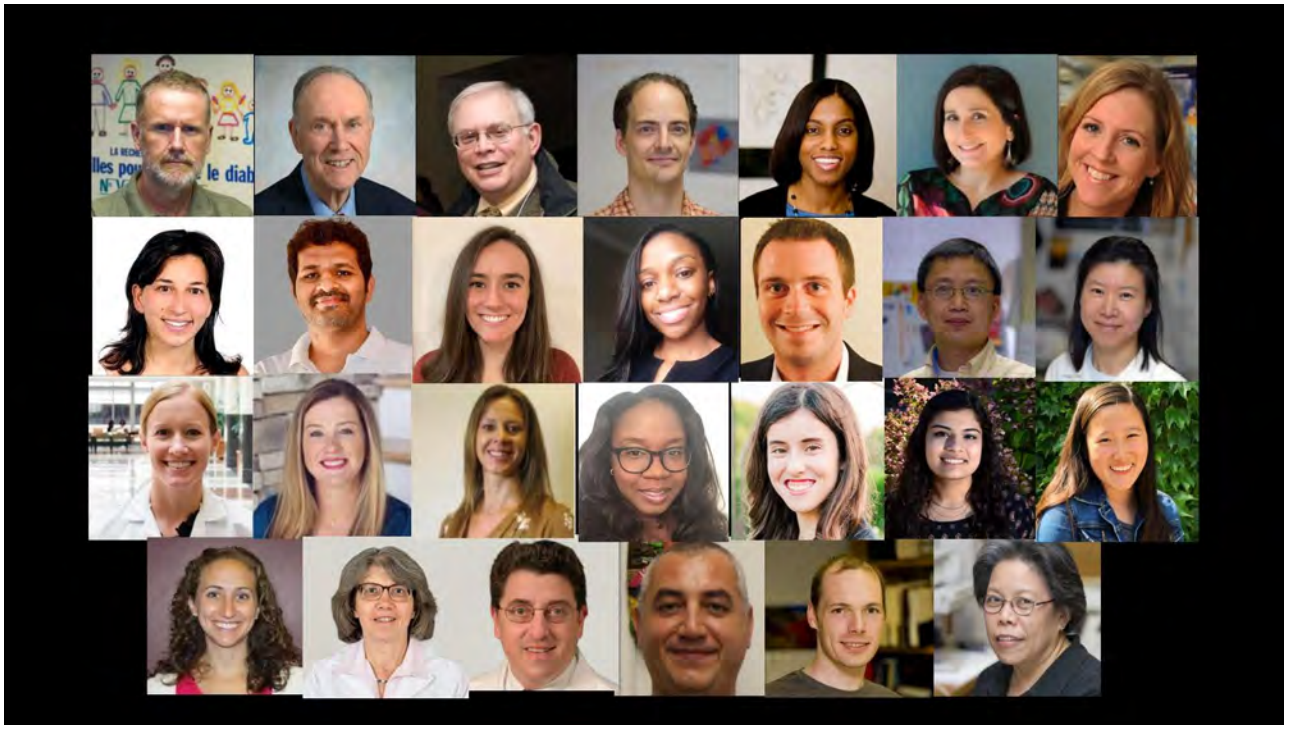

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Monogenic Diabetes timeline

1987 and earlier - Fajans, MODY

1993 - Froguel et al, GCK / MODY2

1993- Fajans, SUs can treat some MODY

1994 - Fajans, abnormal insulin secretion in the RW pedigree (M1)

1996 - Bell, HNF4A - MODY1

1996 - Bell, HNF1A - MODY3

1997 - Staffers, IPF1 MODY4 - RARE

1997-99 - Bell, HNF1b - MODY5, RCAD

1998 - Bell, SUs treat HNF1NHNF4A OM

1998-2000 - low renal threshold for glucose in HNF1A OM

2001 - Njolstad - GCK and NDM

1997-2001 - rare recessive NMD - PDX1, EIF2AK3, GCK

2004-6 - Hattersley, Ashcroft, Gloyn - KCNJ11, ABCC8, sulfonylureas

2007 - Insulin gene mutations and NDM

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Lilly Jaffe: our Chicago story

Diagnosed with type 1 diabetes at *one month of age*

Diabetes well controlled with intensive insulin management

Seen at 6.5 years of age

Genetic testing revealed a mutation in *KCNJ11* **R201C**

Results of genetic testing strongly suggested that Lilly's diabetes could be controlled with high doses of sulfonylureas

Lilly was switched from insulin to glyburide at 6 years of age

Lilly is now 20 years old - no insulin for 14 years

See: "Journey to a miracle - the movie"

C!rticagoil.Wribunc

NEWS

A Front Page News Sports Business Lifestyles Opinion A&E

Home > featuredArtic-les > Diabetes

One girl, one story living on

Chronicled in Tribune, LillyJaffe'• treatment has made13lives better --and perhaps many more one day

Septemberu, 2007 | ByJeremy Manier, Tribune staffreporter

This is a storyof13people with a rareform ofdiabetes, the doctors whochanged their lives and theTribune science writer whohelped them allbefore he died.

Thechain ofevents strutted last Sept.11, when theTribune published a sto,yabout LillyJaffe, a 6-year-old withTypei diabetes who had needed insulinshots herwhole life.Doctors at the University of Chicago weaned her frominsulinafter realizing she had a recentlydiscovered geneticdefect that theycouldcorrect withpilli.

TheJaffe familyconsidered her therapy a medical miracle.

LLlyls story brought hund,reds of inquiries to the U. of C.teamfrom families who hoped theirdiabetic children could be treated thesameway.Thatturned up 13patients withthe same raremutation that Lilly has, as well as others witha differentgenetic variant thescientistshad never seen before.

On Monday, the U. of C. doctors published a paper on that newgeneticcauseof diabetesin theonline edition of theProceedingsofthe National Academy of Sciences.Patients with that rare mutation still need insulin, though the team hopesthe condition could yield insights into more common forms o(diabetes.

For the 13 patientswhoshowed up \\Sibthe other, readily treatable mutation, lifewill neverbe the same. Theygive partof the credit to Peter Gomer, theaward-~'inning Tribunereporter who wrote Lilly\ story while battlingadvanced lung cancer.

Thetreatment for Lilly\ form ofdiabeteshas transformed Lauren Moore, 4, ofOrlando. Lauren's parents got the Tribunearticle from a Chicago relative and feltchills as they read it, hoping thatLauren wasone of the rarepatients like Lilly.

Theybegantarrangements forgenetic tests the nextday. Ane-mail from the U of C.a couple of weekslater relayed thegood news: Lauren had thesamet reatable problem as Lilly.

"I don't remember the last time I cried that hard," said Lauren's mother, Melissa.

After a five-day treatment in Chicago lastyear, Lauren's parentsput away herinsulin pumpforgood. They said they feela deepdebt to the U.of C. doctors andto Gomer, whodied in June.

"The factthathe wrotethatarticle had a profound effect on our entirefamily," said Lauren's mother. "I feel our goal nowis to find other people with the sameondition."

LIFE-CHANGING NEWS FOR LILLY

dhicAc CAMPAIGN

Building on pioneering achievements. UChicago Medicine works to better understand and treat a disease that affects nearly one in 10 Americans.

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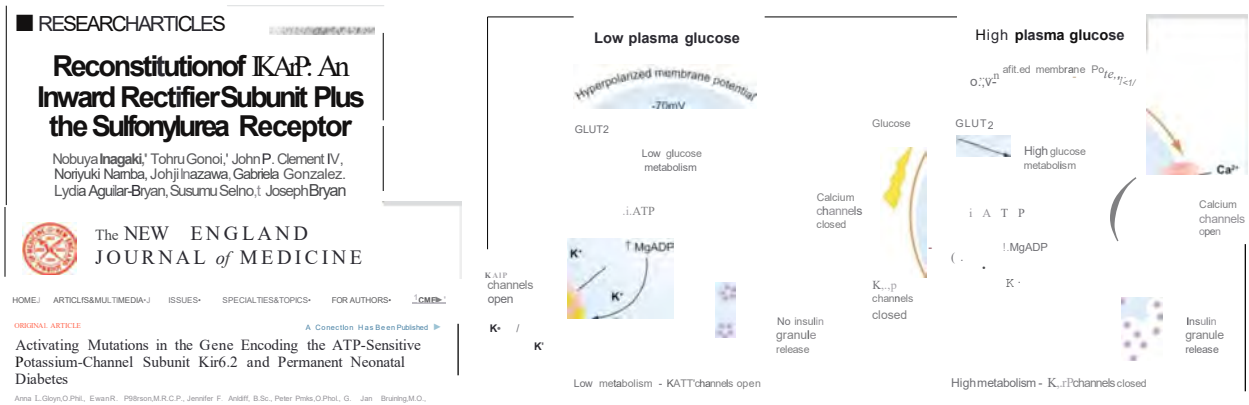
Lilly's medical miracle made possible by basic research



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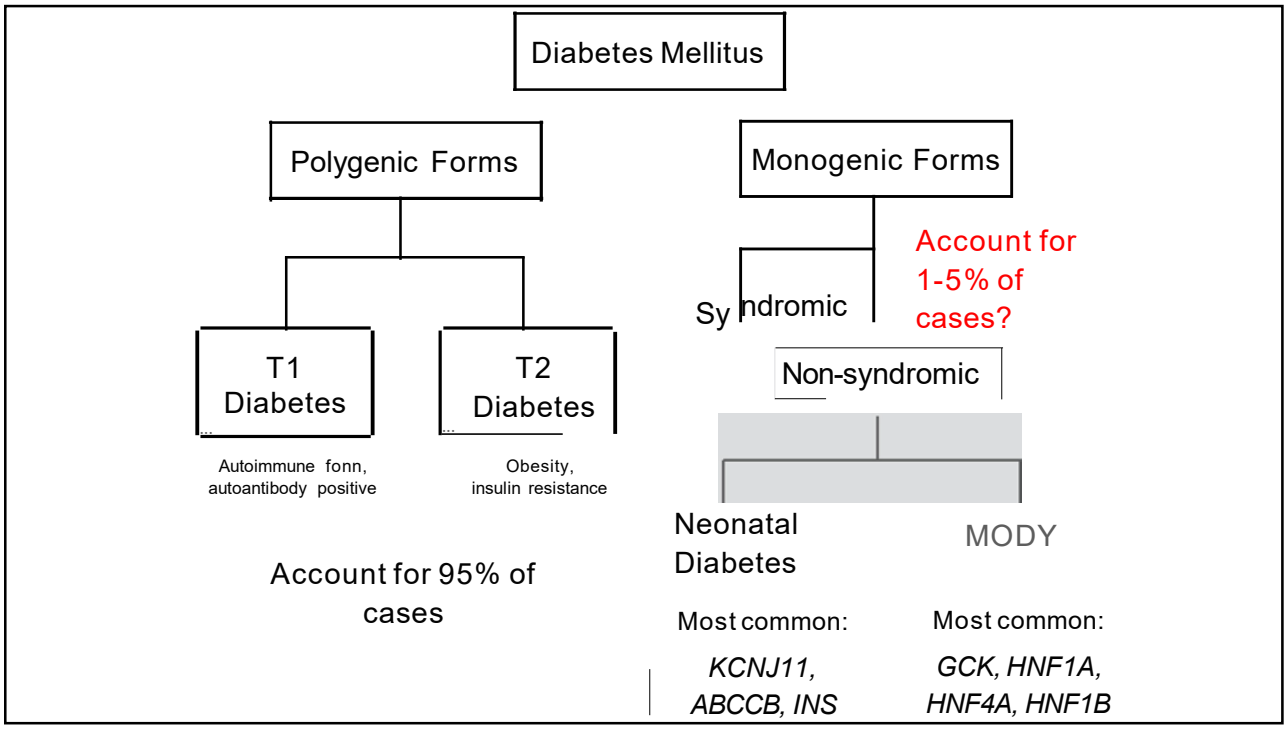

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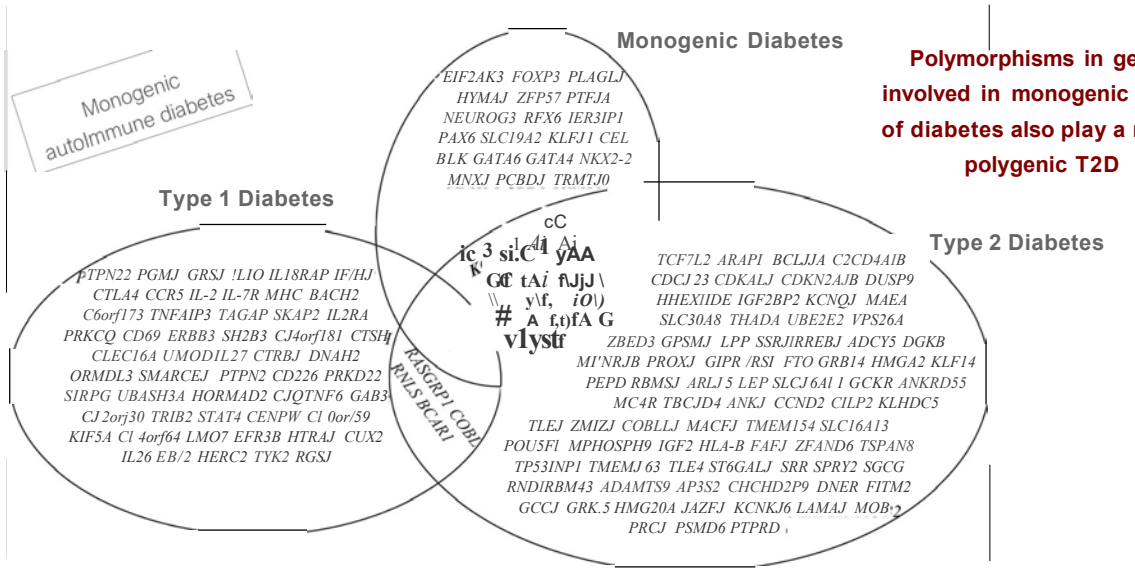
Monogenic Diabetes: What It Teaches Us about the Common Forms of Diabetes



Yang Y, Chan L. Monogenic Diabetes: What It Teaches Us on the Common Forms of Type 1 and Type 2 Diabetes. Endocr Rev. 2016 Jun;37(3):190-222.

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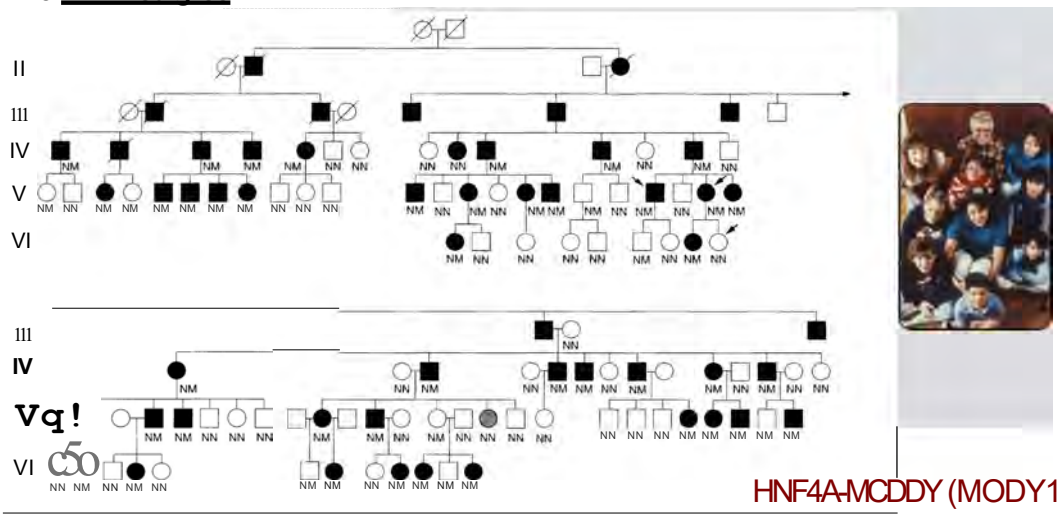
University of Chicago and University of Michigan Pioneered the Genetic Studies of Diabetes

Stefan S. Fajans

University of Michigan

1918-2014

The R-W Pedigree



HNF4A-MCDDY (MODY1)

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Case 2

- 58 year old female initially found to be hyperglycemic at age 19 with fasting blood glucose of 130 mg/dl .
- *BM/ was 19 kglm^2.*
- BG retested at age 23 during pregnancy, and was diagnosed as having gestational diabetes and then type 2 diabetes mellitus.
- Initially diet-controlled, but transitioned between oral agents (including metformin and troglitazone) and insulin due to fluctuating diagnoses of *gestational, type 1 and T2DM*
- Presented to a new endocrinologist's office at age 58. Mild-moderate insulin resistance: 0.87 units insulin/kg; using 90 units/day via insulin pump
- *Current weight 230 pounds and BM/ 40.7kglm^2*

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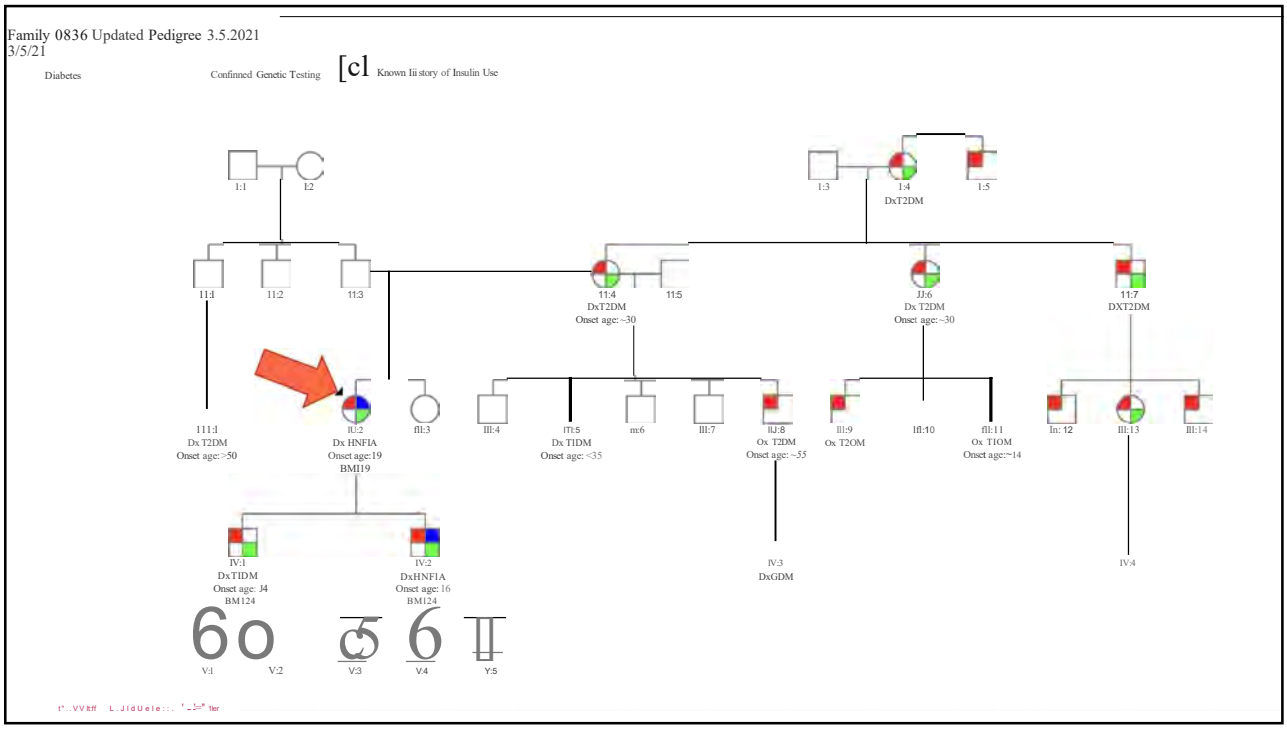

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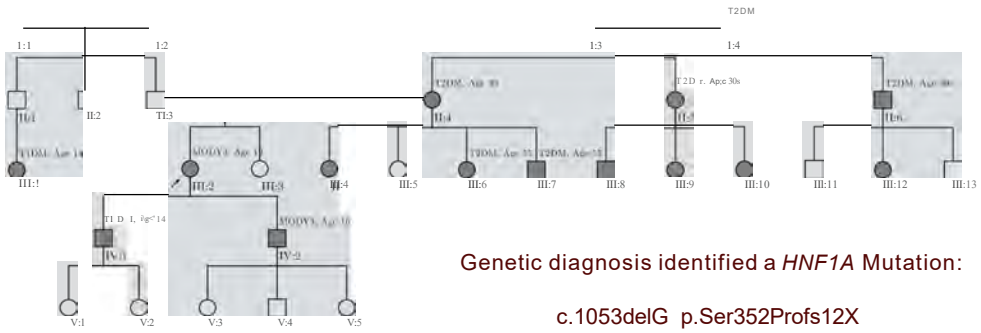

Genetic diagnosis identified a *HNF1A* Mutation:

c.1053delG p.Ser352Profs12X

1. Obesity doesn't always mean T2D
2. Inquire about your patient's family history
3. Genetic testing to confirm
4. HNFIA-MODY 3 usually responds to low dose sulfonylurea - even with hypoglycemia

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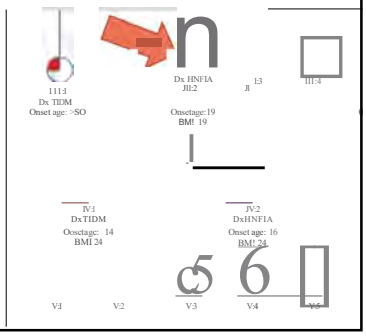
HNF1A - MODY3

- SUs were started; A1c improved to the 6% range
- Insulin was withdrawn as she lost weight She has lost over 70 lbs
- Her children were ambivalent about genetic testing
- Had euglycemic DKA after SGLT2i



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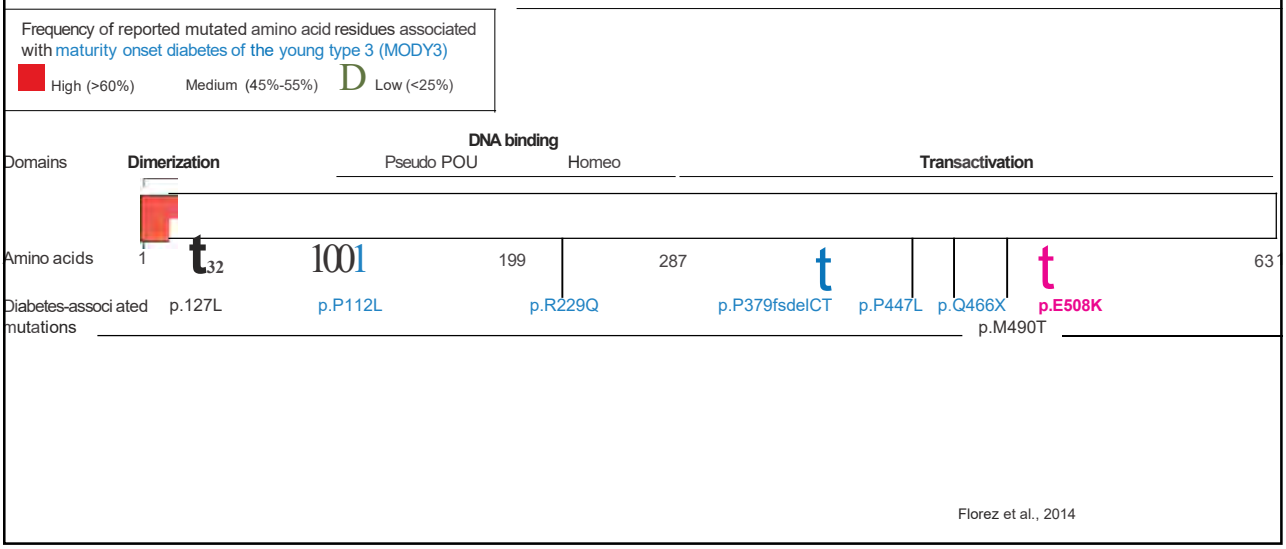
HNF1A - MODY3



Florez et al., 2014

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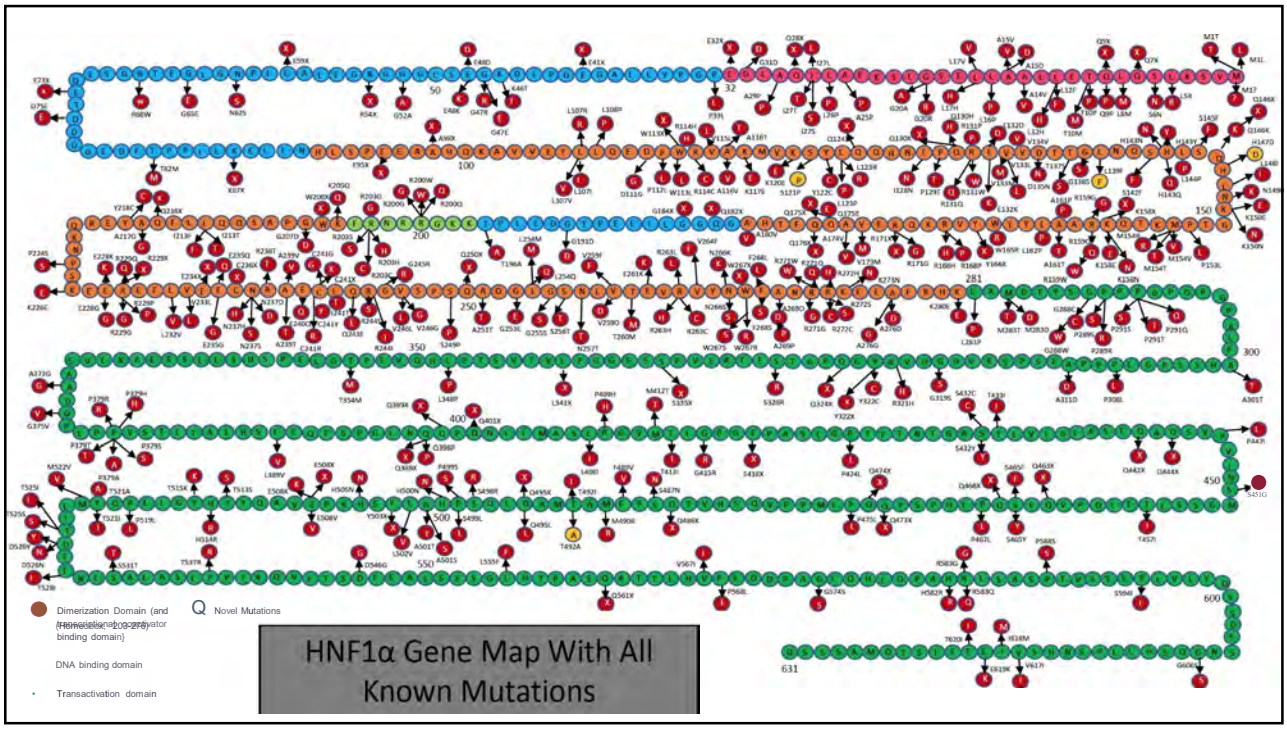

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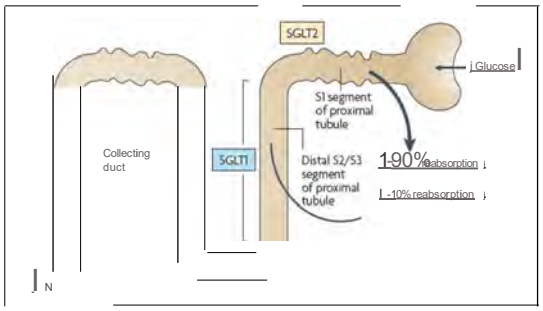
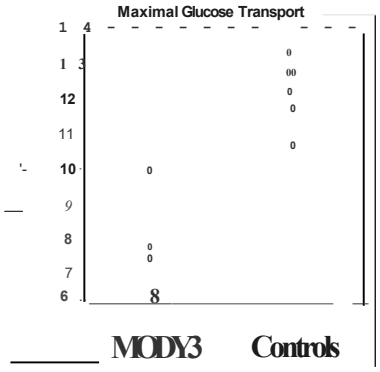
HNF1A and Renal Glucosuria





- MODY3 patients are characterized by reduced tubular reabsorption of glucose.
- The renal defect is due to reduced expression of the SGLT2 (2000)
- *HNF1A* directly controls SGLT2 gene expression.

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Pontoglio M. et al. 2000

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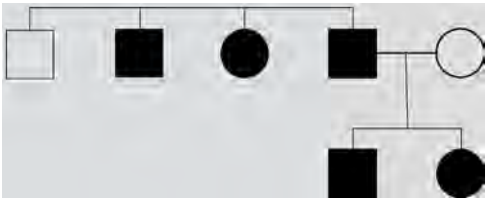
Case 3: Diabetes or hyperglycemia?

- Dx age 26
- FBG mildly elevated: 124 mg/dl during routine physical

  HbAIc ranges between **5.6% and 6.2%**
- BMI: **23.0 kg/m²**
- Diabetes autoantibody tests: negative
- ***On insulin for 13 years,*** -20 units per day (0.26 u/kg/day



Genetic testing revealed GCK MODY2: Thr168Asn

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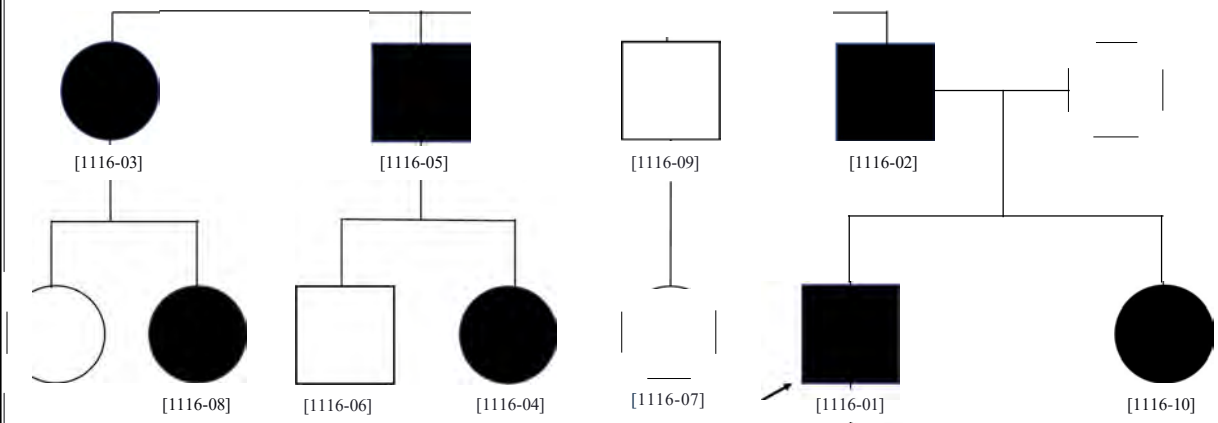
1116 Family Pedigree

Confirmed GCK c.503C>A (p.Thr168Asn)



- 1116-01 dx at 26 y/o, GCK confirmed at 36 y/o
- 1116-02 dx at 24 y/o GCK confirmed at 76 y/o
- 1116-03 dx prediabetic at 43 y/o, GCK confirmed at 62 y/o
- 1116-04 dx prediabetic at 33 y/o, GCK confirmed at 38 y/o
- 1116-05 dx at 26 y/o, GCK confirmed at 71 y/o
- 1116-08 elevated blood glucose ~21, GCK confirmed at 27 y/o
- 1116-10 dx pre-diabetic at unknown age, GCK confirmed at 38 y/o
- 1116-11 BG never tested, GCK confirmed at 9 months

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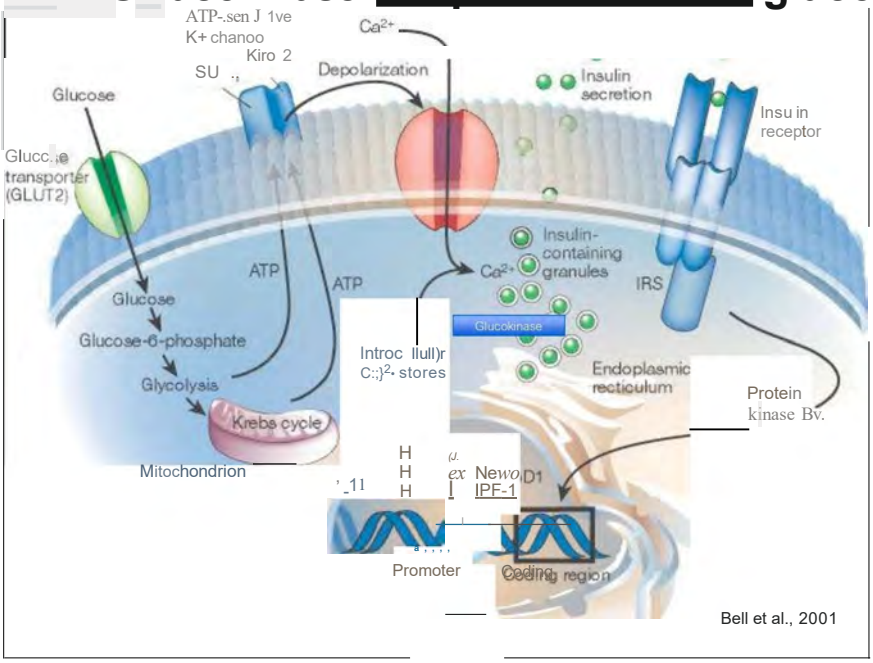
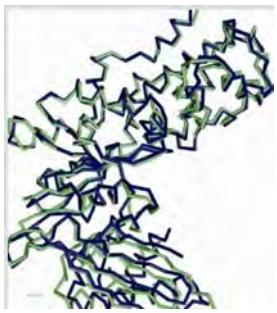
G lucokinase: the pancreatic/liver glucose sensor



Bell et al., 2001



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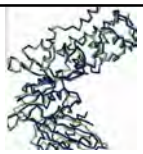
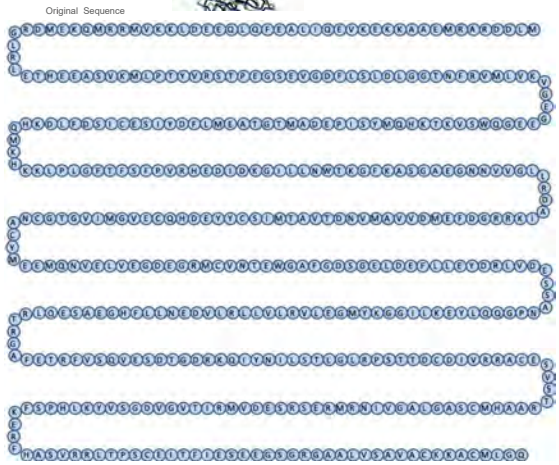
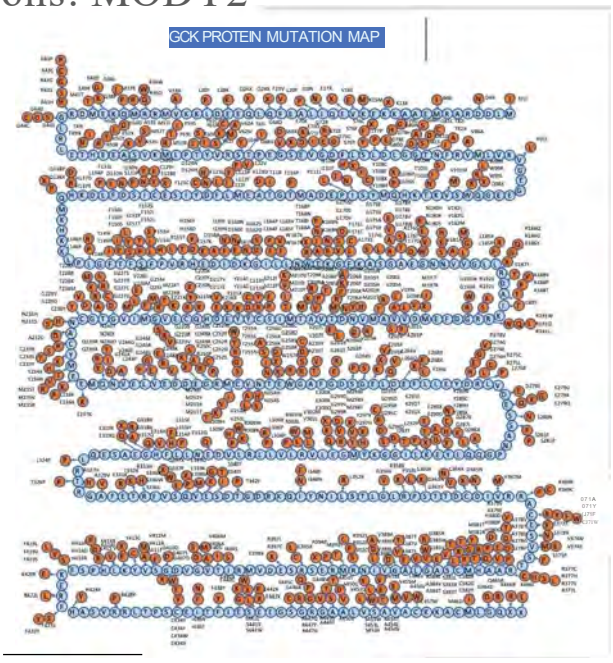


GCK Mutations: MODY2





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Case4

Proband

- Dx: age 21
- Polyuria, weight loss, fatigue
- (195#, 5'11 - **BMI:** 27.2 kg/m^2)
- Advancing deafness
- BG: 280 mg/di after 12-hrfast
- Ab negative
- Rx: Insulin, oral medications (metformin - nausea)
- 2-3 years A1c in 6% range

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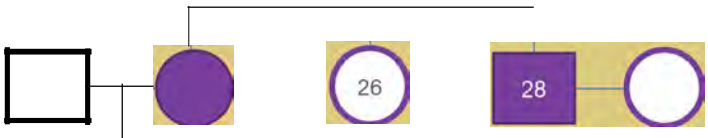

3rd Generation

- T1D

4th Generation

- T1D
- T1D
- Autism Spectrum

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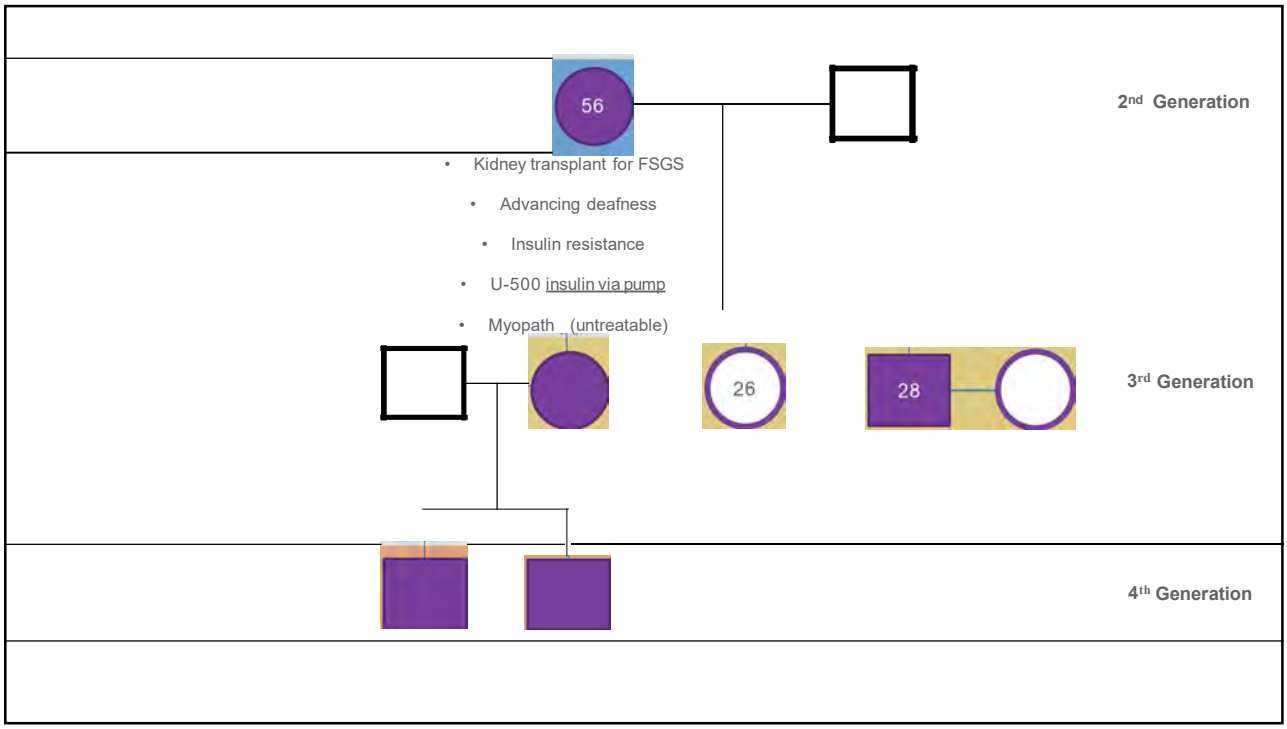
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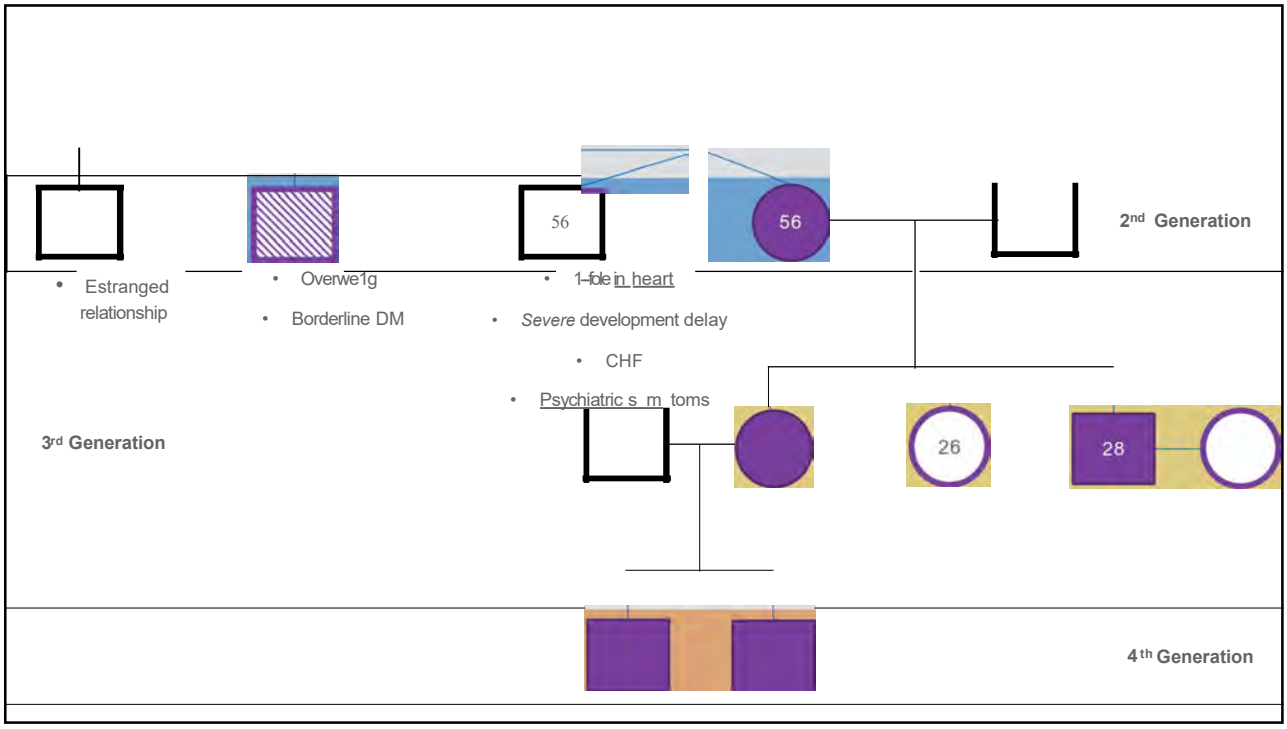
2nd Generation
• Kidney transplant for FSGS
• Advancing deafness
• Insulin resistance
• U-500 insulin via pump
• Myopath (untreatable)
26
28
3rd Generation
4th Generation

25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2nd Generation
• Estranged relationship
• Overwe1g
• Borderline DM
• 1-fde in heart
• Severe development delay
• CHF
• Psychiatric s m toms
3rd Generation
26
28
4th Generation

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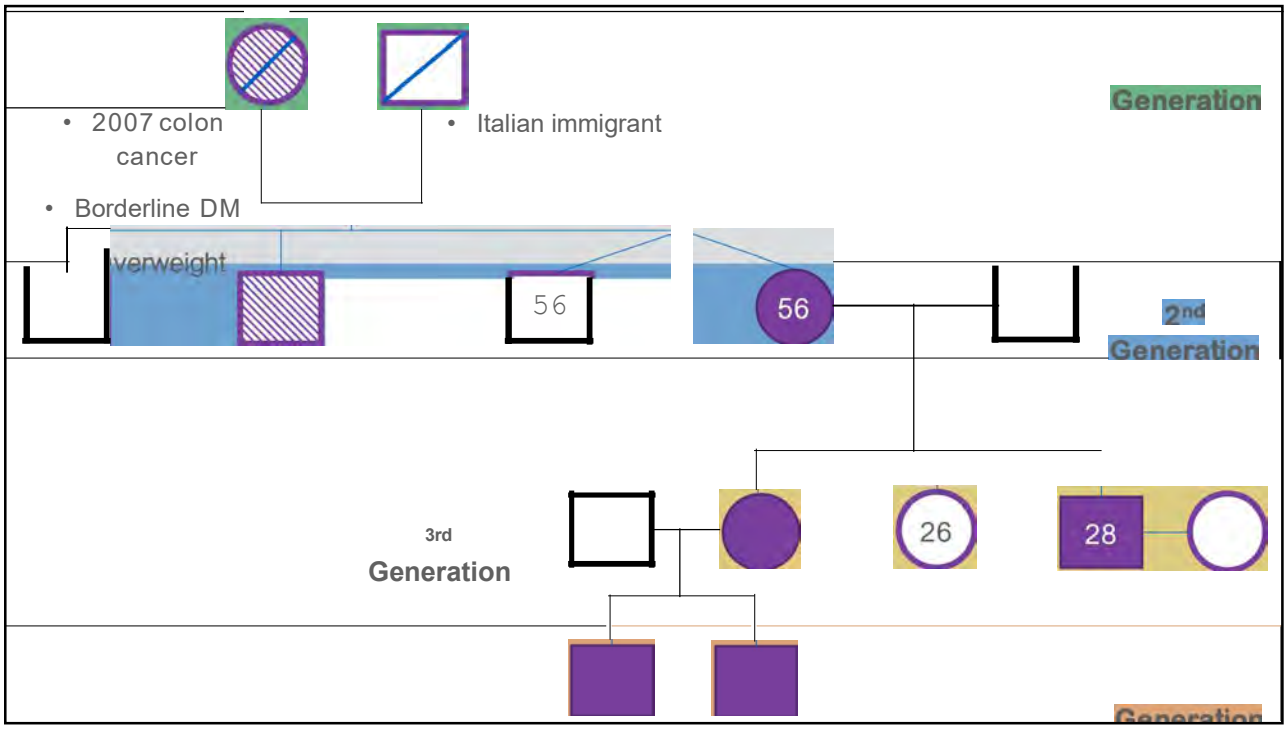

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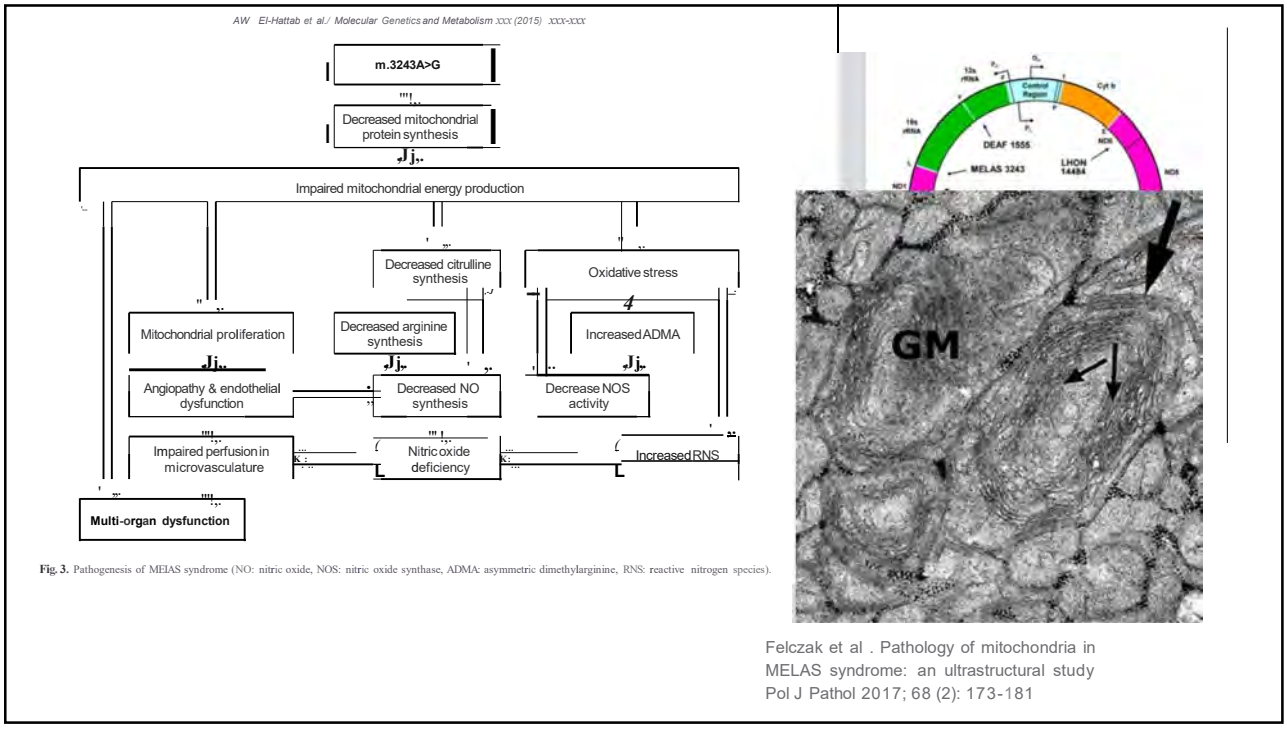

Felczak et al . Pathology of mitochondria in MELAS syndrome: an ultrastructural study Pol J Pathol 2017; 68 (2): 173-181

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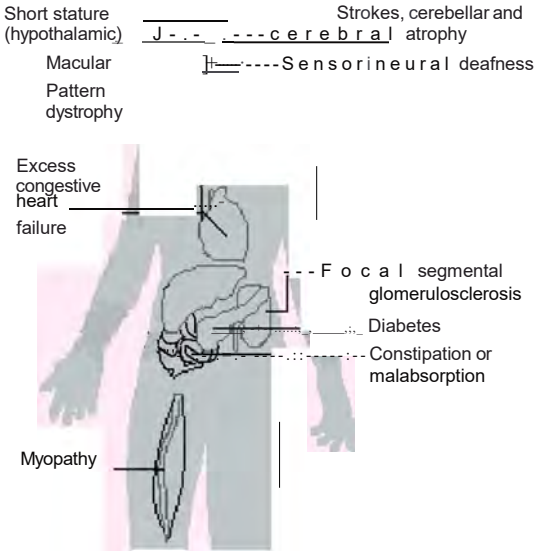
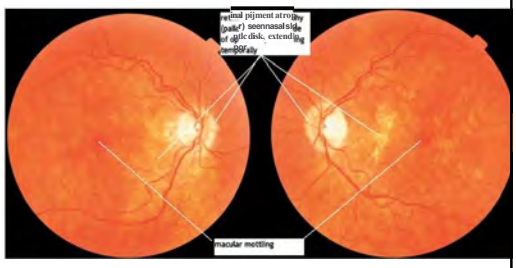


FIGURE 1 Organs potentially affected by m.3243A>G mutation. CHF, congestive heart failure; FSGS, focal segmental glomerular sclerosis.

Organs affected in MIDD

R. Murphy, D. M. Turnbull, M. Walker and A. T. Hattersley

Clinical features, diagnosis and management of maternally inherited diabetes and deafness (MIDD) associated with the 3243A>G mitochondrial point mutation. Diabetic Medicine 25, 383-399 2008



tE 2 Retinal change ;;sm in m.3243A>G mutation.

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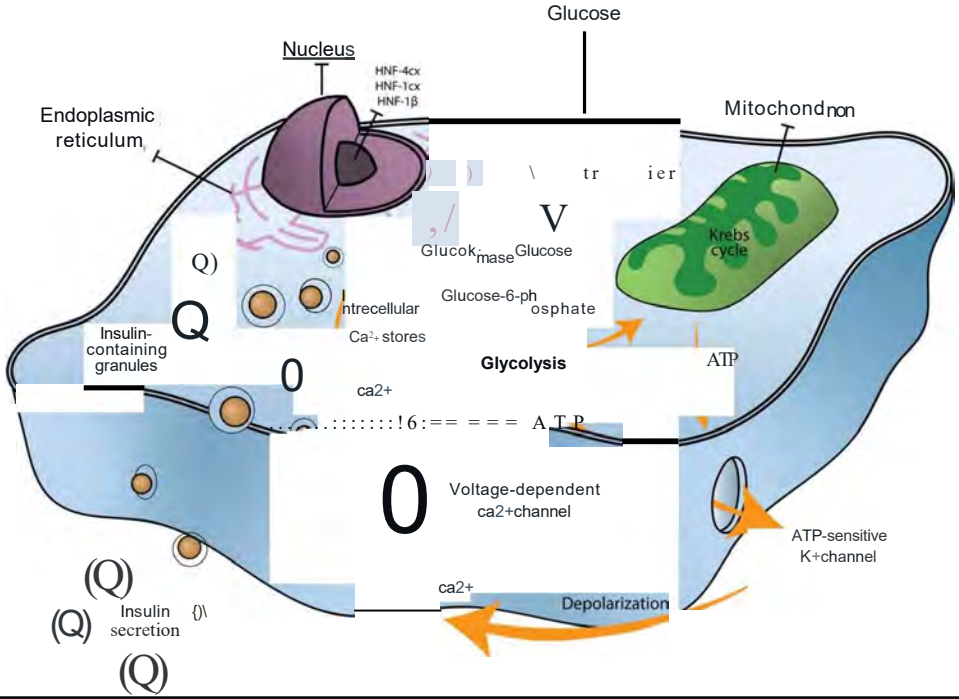

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Monogenic Diabetes: Mostly Beta-cell Dysfunction

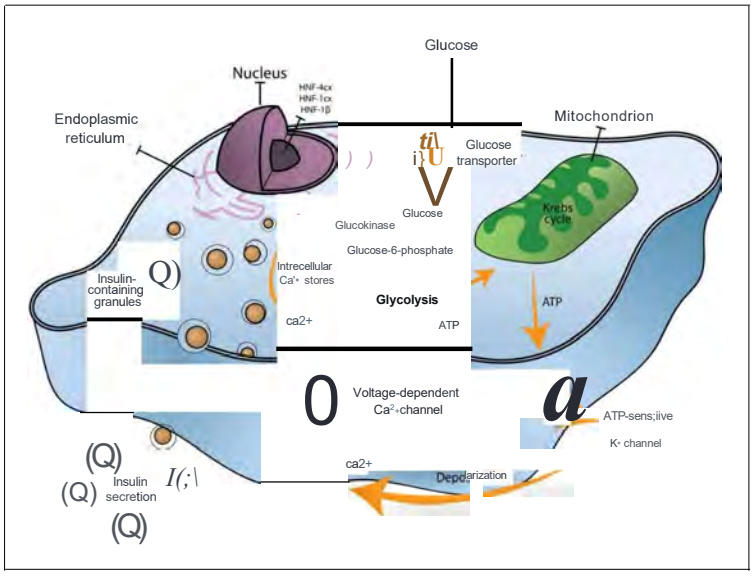
Gene expression
HNF1A, HNF18, HNF4A, PDX1,NEUROD1, GL/53 PAX4, PAX6, NEUROG3, PTF1A, RFX6, GATA6,MNX1, NKX2-2, GATA4, PCBD1

ER stress
EIF2AK3, WFS1, WFS2/ C/5D2, IER3/P1, DNAJC3

Insulin synthesis
INS

Epigenetic disorder of the beta cell
6q24,ZFP57

Glucose transport
SLC2AZ {GLUTZ}



Glucose metabolism
GCK

Disorder of autoimmunity
FOXP3,AIRE, STAT3, IL2RA

Exocrine pancreas
CEL, CFTR, HFE

Ion channel dysfunction
KCNJ11, ABCCB

Insulin secretion
SLC19A2 {Thiamine transporter-1)

tRNA methyl-transferase
TRMT10A

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Clinical features, diagnosis and management of maternally inherited diabetes and deafness (MIDD) associated with the3243A>G mitochondrial point mutation

R.Murphy•t, D. M. Turnbull*, M. Walker§ and A. T. Hattersley•

Neurologic phenotypes with m.3243A.G And other mito mutations

MELAS
MERRF
PEO
KSS
Leigh Syndome

Disease	Clinical features	Investigation
MELAS (MIM no. 540000) Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes	Stroke < 40 years (predominantly occipital and temporal cortical) leading to hemianopia or hemiparesis, encephalopathy (characterized byseizures or dementia or both), blood lactic acidosis or RRF in muscle Other common accompanying symptoms: headaches, recurrent vomiting, myopathy of facial, trunk and limb muscles with excessive fatigue, opthalmoparesis, ataxia, diabetes, and cardiomyopathy	Blood: m.3243A>G in 80% of cases [222,223] (other mutations in m.3250 and m.3253), elevated lactate Muscle biopsy: RRF, reduced complex 1 and 4 activity MRI: occipital strokes, bilateral basal ganglia calcification, cerebellar and cerebral atrophy CSF: elevated lactate
MERRF (MIM no. 545000) Myoclonicepilepsy associated with ragged red fibres	Myodonic epilepsy (commonly beginning in 20s or 30s) and ragged red fibres in muscle. Also may have myoclonus, dementia, cardiomyopathy, pyramidal tract signs, neuropathy, optic nerve atrophy, neurosensory hearing loss, cardiac dysrhythmias	Blood: lactate, creatine kinase elevated, m.8344 in 80% (rarely m.8356, m.8363 and m.3243) CSF: lactate elevated EEG: epileptiform activity CT and MRI: general cerebral atrophy Muscle biopsy: RRF, multiple biochemical deficiencies in COX, complex 1)
(C)PEO (MIM n. 609286) (Chronic) progressive external opthalmoplegia	Isolated external opthalmoplegia	Blood: 50% patients who do not have mtDNA deletions or duplications have m.3243A>G [224,225) Muscle biopsy: for genetic testing
KSS (MIM no. 530000) Kearns-Sayre syndrome	External opthalmoplegia < 20 years, retinopathy, proximal myopathy (facial, pharyngeal, trunk and shoulder), cardiac arrhythmia and cerebellar ataxia, but no stroke-like episodes If onset > 20 years or any of four symptoms missing then 'opthalmoplegia-plus syndrome' Other common features: short stature, deafness, dementia, diabetes, delayed puberty	Blood: increased lactate in 50% (rest/exercise), 80% havedeletionof mtDNA,others mostly m.3243A>G [225,226] Muscle biopsy: deficiency of COX particularly within RRF ECG: conduction defects CSF elevated protein, lactate
Leigh syndrome (MIM no. 256000)	Progressive neurodegenerative disease, which usually affects infants but rarely described in adults. Presents with failure to thrive, developmental delay, perinatal asphyxia, respiratory dysfunction, cranial nerve dysfunction, ataxia, dystonia, muscle weakness and lactic acidosis. Frequently fatal during first few years	Blood: lactate elevated, may be because of nuclear genes (X-linked recessive, autosomal recessive) and mitochondrial point mutations:> 90% at m.8993, rarely m.3243A>G [227) MRI: characteristic symmetric lesions of medulla oblongata, mesencephalon,aqueduct, cerebellum, basal ganglia Muscle: No RRF, but multiple deficiencies of respiratory chain

CK,creatine kinase; COX, cyclooxygenase; CSF, cerebrospinal fluid; CT, computerized tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging; RRF, ragged red fibres.

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Prevalence of mitochondrial diabetes

European populations	0.3 - 9%
Japanese populations	0-11%
Diabetes + deafness	**5-60%**

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Heteroplasmy

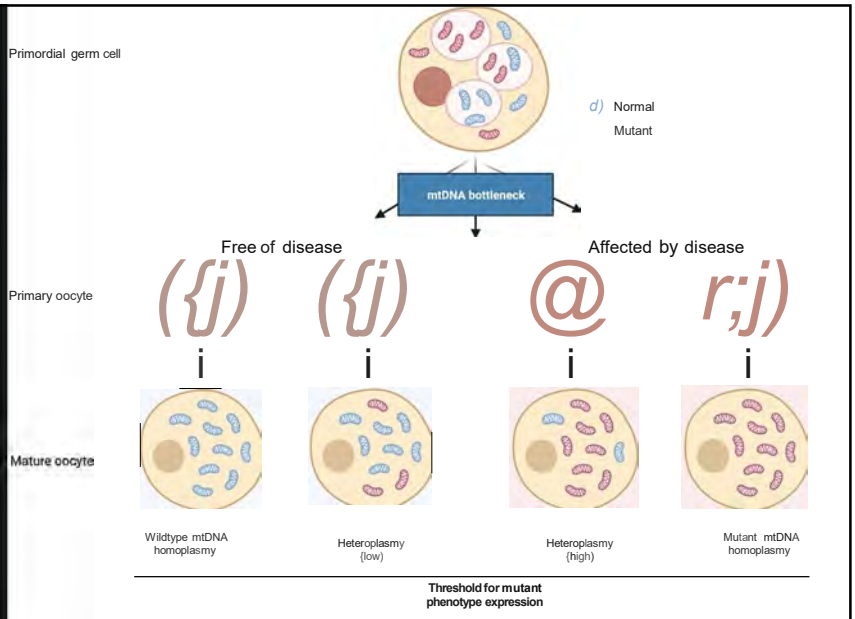

Figure 6. Mitochondrial DNA transmission. Homoplasmic variants are transmitted from mother to offspring. The mitochondrial bottleneck explains how there can be extreme divergence in the heteroplasmy between mother and offspring. There is a genetic bottleneck during development that results in different heteroplasmy in each individual oocyte. This is a major challenge when providing genetic counselling for mothers with heteroplasmic mtDNA variants because the level of heteroplasmy will determine the clinical outcome in the offspring. This figure is derived from a previous published work (1) and created with BioRender.com.

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MIDD: Drugs to avoid

such as tetracyclines and chloramphenicol;

such as valproate, phenytoin and phenobarbitone

used in the treatment of human immunodeficiency virus (HIV) and

(particularly in the context of other risk factors for lactic acidosis).

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MIDD: Possible therapies

Coenzyme 010 (CoQ) is thought to act as an electron carrier of the respiratory chain in mitochondria and may improve

the mutation-associated dysfunction in MIDD. Anecdotal case reports. Randomized, double-blind, control trials

are necessary in order to clarify the value of CoQ in **MIDD.**

Maintenance of adequate thiamine intake seems important to maintain optimal mitochondrial function [6].

Kidney, K-P and other organ transplants ??

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Ng YS, Lim AZ, Panagiotou G, Turnbull DM, Walker M. Endocrine Manifestations and New Developments in Mitochondrial Disease. Endocr Rev. 2022;43(3):583–609.

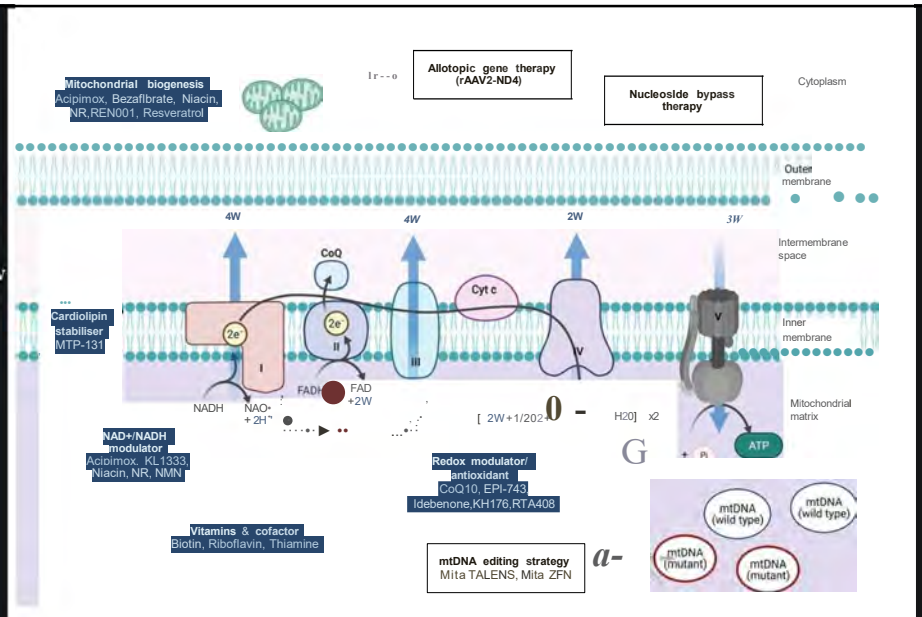

Figure 5. Emerging treatment strategies for mitochondrial diseases. Repurposed and novel small molecules targeting different mitochondrial path ways (mitochondrial biogenesis, cardiolipin stabilizer, NAD+/NADH modulator, redox modulator/antioxidant) are classified as generic treatment ap proaches that have the potential to translate across different types of mitochondrial disease. On the other hand, specific treatment approaches such as allotopic gene therapy for LHON, nucleoside bypass therapy for mtDNA depletion syndrome, and methods of eliminating pathogenic mtDNA variants are examples of precision medicine in the mitochondrial field. Created with BioRender.com.

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MODY type	Gene name (locus)	Protein (function)	Phenotypes/syndromes	OMIM[1]	Association with T2DM (low-frequency or common variants)[2]
MODY1	*HNF4A* (20q12)	HNF-4a (transcription factor)	Diabetes in adolescence or early adulthood (and neonatal hyperinsulinism)	125850, 600281	+
MODY2	GCK(7p13)	Glucokinase (glycolytic enzyme)	Mild hyperglycemia (onset in early childhood and life-long) (frequent)	138079, 125851	+
MODY3	*HNF1A* (12q24.2)	HNF-1a (transcription factor)	Diabetes in adolescence or early adulthood (frequent)	600496, 142410	+
MODY4	*PDX1* (13q12.1)	IPF1 (transcription factor)	Diabetes in early adulthood (similar to *HNF1A* but rare)	606392, 600733	+
MODY5	*HNF1B* (17q21)	HNF-1p (transcription factor)	Diabetes in early adulthood, renal cysts and diabetes (RCAD)	137920, 189907	+
MODY6	*NEUROD1* (2q31.3)	NeuroD1 or Beta2 (transcription factor)	Diabetes in early adulthood (similar to *HNF1A* but rare)	606394, 601724	
MODY7	*KLF11* (2p25)	Kruppel-like factor 11 (transcription factor)	Diabetes in childhood and early adulthood	603301, 610508	+
MODY8	*CEL* (9q34)	Carboxyl-ester lipase enzyme	Diabetes in early adulthood; pancreatic exocrine insufficiency, pancreatic atrophy and lipomatosis	114840, 609812	
MODY9	*PAX4* (7q32)	Paired box gene 4 (transcription factor)	Diabetes in early adulthood	167413, 612225	+
MODY10	*INS* (11p15.5)	Preproinsulin, insulin (hypoglycemic hormone, effect on anabolism)	Diabetes in childhood and early adulthood	613370, 176730	
MODY11	*BLK* (8p23)	B lymphocyte kinase (non-receptor tyrosine kinase)	Diabetes in early adulthood	191305, 613375	+
MODY12	*ABCC8* (11p15.1)	SUR1 (sulfonylurea receptor; KATP channel regulatory subunit)	Diabetes in childhood and early adulthood	600509	+
MODY13	*KCNJ11* (11p15.1)	Kir6.2 (KATP channel pore-forming subunit)	Diabetes in childhood and early adulthood	600937	+
MODY14	*WFS1* (4p16)	Wolfram syndrome 1 (Wolframin)	Diabetes in early adulthood	606201, 222100	Vaxillaire et al., 2016

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United States Monogenic Diabetes Programs

Bell, Greeley, Naylor, Philipson - University of Chicago

Liana Billings / North Shore - Find MODY with Rochelle Naylor

Toni Pollin, Maryland - and MDEP

Miriam Udler, MGH

Andrea Steck, BOC Denver

Sara Pinney and Diva Deleon, CHOP, Philadelphia

Fumi Urano (Wolfram) - Wash U, St Louis

Elif Oral (Lipodystrophies) Peter Arvan (INS) - UMich, Ann Arbor

Maria Redondo, Ashok Belasubramanyam and Colleagues - Baylor, Houston

Wendy Chung and Robin Goland - Berrie Center, Columbia, NYC

Mark Anderson and Mike German - UCSF, San Francisco

Anna Gloyn - Stanford

Kevin Pantalone and Colleagues - Cleveland Clinic, Cleveland

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MOM Sequencing Resources

University of Chicago Genetic Labs
Ambry (owned by Konica Minolta)
Quest / Athena
LabCorp
Invitae
Columbia University
Genewiz
Veritas Genetics
Macrogen
Helix
Psomagen
Akesogen
Illumina (WGS, CLIA)
HudsonAlpha
Tempus (WES)
Eurofins
ACGT

LMM (Harvard)
Natera
Myriad
Diagnomics
Fulgent Genetics
GeneDx
Blueprint Genetics
WashU Genomics and Pathology Services

<u>Patient-initiated clinical testing</u>
Genome Medical
InformedDNA
PWN Health

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Personalized Medicine:
Learning from Monogenic Forms of

1. Understand the phenotype-genotype connection

3. Identify those who should have cost-effective genetic testing
4. Decide how those genes should be evaluated
5. Realize that not all phenotypes will have a known genetic cause
6. Recognize that therapy may be directed by the specific mutation
7. Act on the implications for the other family members

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Goals of UChicago Monogenic Diabetes Registry

- Continue to identify new cases
- Educate Clinicians and people with MOM
- Study and Refine "Return of Genetic Results" and Cascade testing
- Continue to follow participants at least yearly
- Better define the natural history especially syndromes
- Better understand variable penetrance, age of onset
- Role of associated and modifying genes
- New studies into monogenic autoimmunity
- Build a Data Commons of participants for the investigator community

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Genetic Testing Should Be Considered:

Anyone diagnosed with diabetes at or under 12 months of age

A diabetes patient who is part of a family with 3 or more consecutive generations affected by diabetes

A diabetes patient with stable, mildly elevated blood sugars, often found incidentally during a routine check-up

A "type 1" diabetes patient who has negative blood testing for autoantibodies; typically done at the time of diabetes diagnosis (antibodies typically tested include 1 or more of the following: GAD65, islet cell or ICA,
IA-2, insulin, ZnT8)

A "type 1" diabetes patient who generates a significant amount of insulin years beyond diagnosis (detectable blood levels of C-peptide, proinsulin, and/or insulin)

A "type 2" diabetes patient who is normal in weight or not significantly overweight and shows no signs of insulin resistance

Diabetes paired with pancreatic insufficiency (the digestive role of the pancrea; $_3$is impaired, with s m toms such as diarrhea and as

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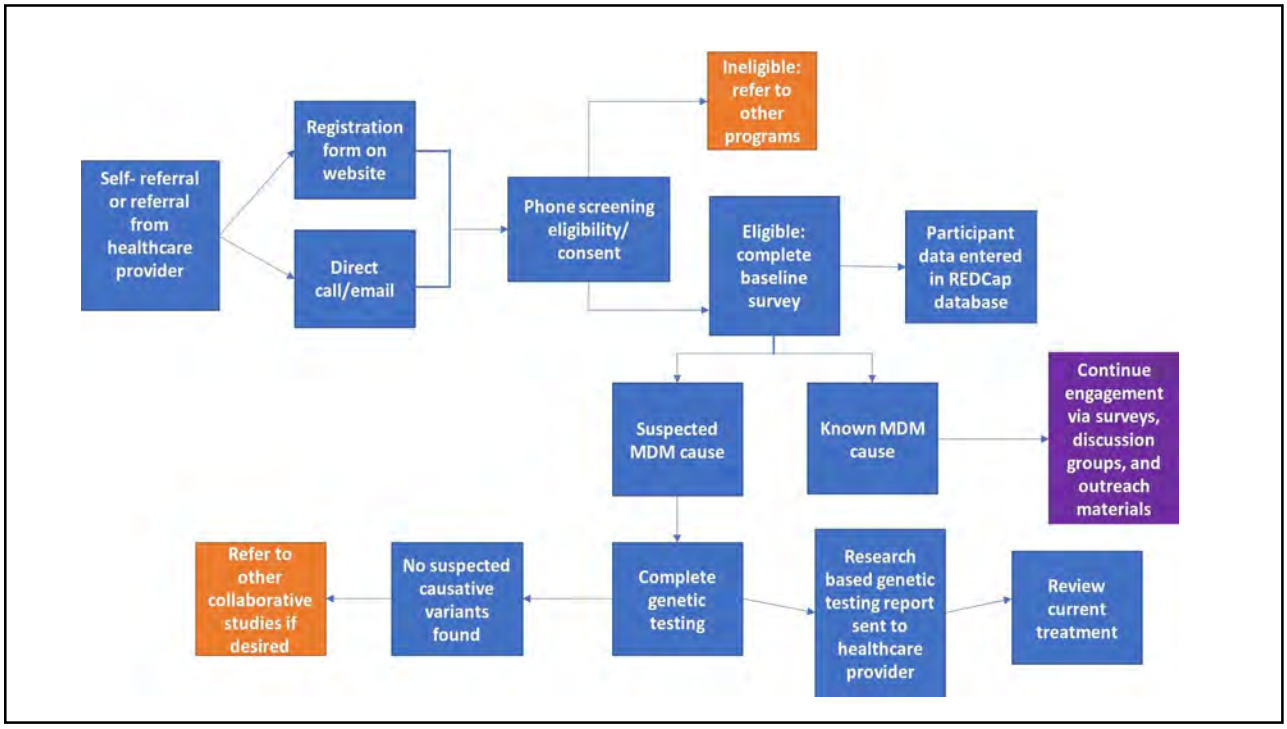

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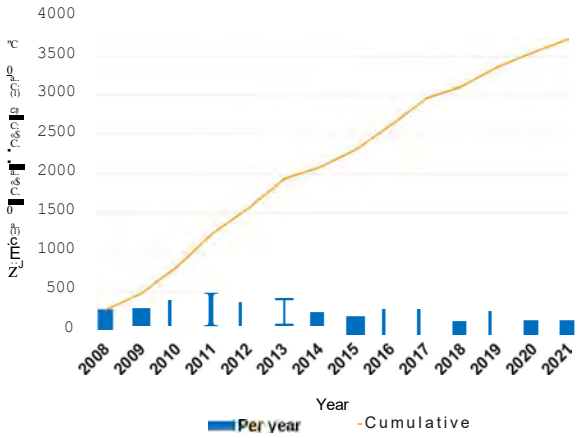
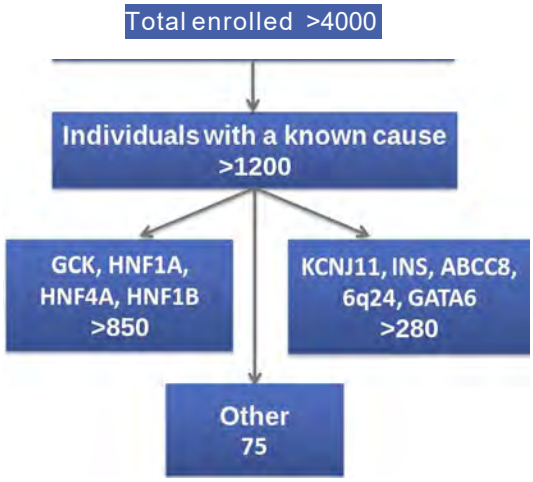
Monogenic Diabetes Registry - Steadily Increasing Enrollment





AT THE FOREFRONT OF MEDICINE
UChicago Medicine
Comer Children's

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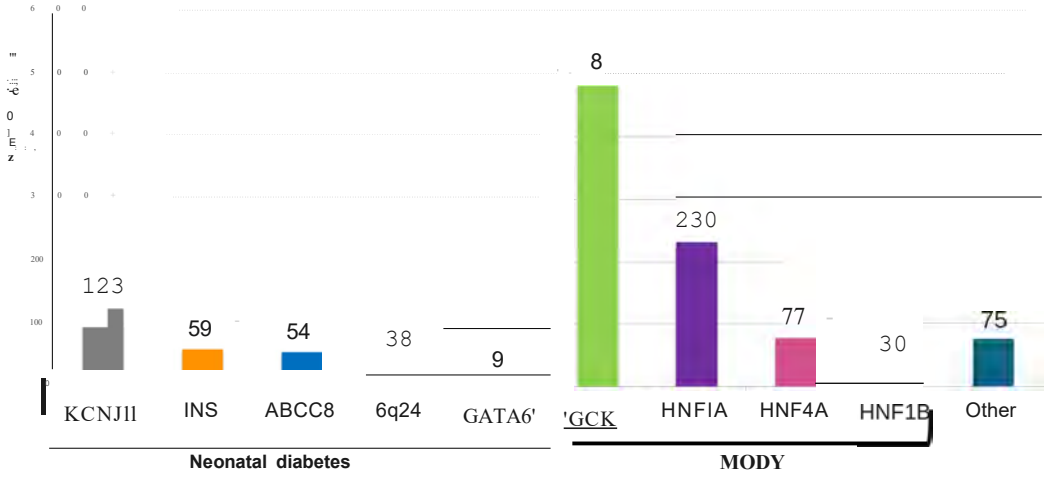
UChicago Monogenic Diabetes Registry



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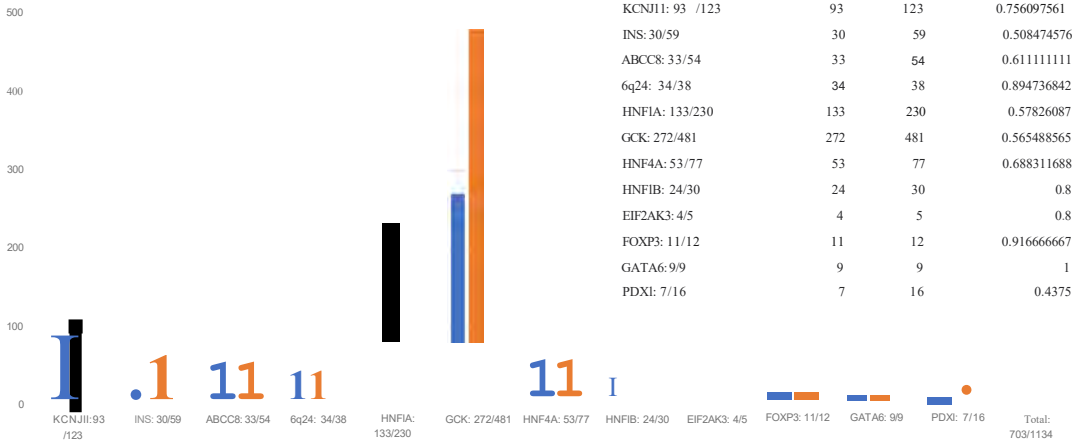
Proband vs total: results of cascade testing



KCNJ11: 93 /123	93	123	0.756097561
INS: 30/59	30	59	0.508474576
ABCC8: 33/54	33	54	0.611111111
6q24: 34/38	34	38	0.894736842
HNF1A: 133/230	133	230	0.57826087
GCK: 272/481	272	481	0.565488565
HNF4A: 53/77	53	77	0.688311688
HNF1B: 24/30	24	30	0.8
EIF2AK3: 4/5	4	5	0.8
FOXP3: 11/12	11	12	0.916666667
GATA6: 9/9	9	9	1
PDX1: 7/16	7	16	0.4375

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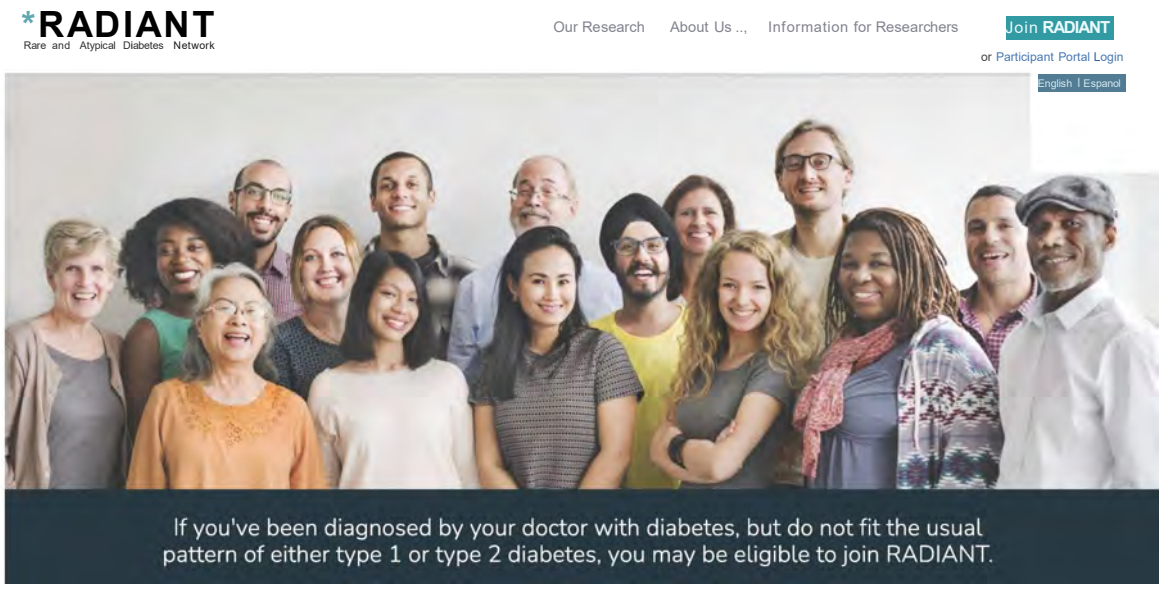

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- RADIANT opened 09/30/2020, projected end date 5/31/2024
- Funded by two U54 grants from NIDDK

- Pis: Lou Philipson (University of Chicago Medicine)+
- Ashok Balasubramanyam (Baylor College of Medicine)
- Jeff Krischer, Chair, University of South Florida
- Jose Florez, (MGH, Harvard)
- Christine Lee and Ellen Leschek PO NIDDK
- 14 RADIANT Clinical Centers across USA
- Genomic Cores at Baylor College of Medicine and the Broad Institute

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* RADIANT
Rare and Atypical Diabetes Network

RADIANT Inclusion/Exclusion Criteria

INCLUSION

- High likelihood of rare & atypical DM:
  - T2D dx preoubertal or non-obese
  - Mendelian pattern w/early onset (<18 YR)
  - Syndromic
  - Non-progressive or rapidly progressive
  - Low insulin requirements (<0.5 u/kg/day)
  - Cyclical, periods of remission
  - Lean PCOS or GDM
  - "A-8-" or "A-8+" subtypes of Ketosis-Prone Diabetes (unprovoked DKA at dx)

EXCLUSION

- High likelihood of **KNOWN DM:**
  - Typical T1D
  - Typical T2D
  - "Solved" genetic causes such as:
    - Known Monogenic Diabetes syndrome
    - Known Lipodystrophy syndrome
    - Known Wolfram Syndrome
- Pregnant women
- Refusal to consent for genetic testing

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RADIANT/ Atypical Diabetes Status

- >900 participants enrolled in Stage 1 as of August 2022
- Now getting the first genetic data - WGS and mito DNA
- About 20% so far are antibody positive- meaning type 1 diabetes
- Additional approaches are needed to better reach a diverse population to discover and characterize diabetes subtypes.
- The goal is to better understand the contributions of genetics and environment to the physiology of diabetes in a dataset that will provide a resource through the NIDDK to the diabetes research community.

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PDM: paradigm shift for Precision Medicine in Diabetes?

Can guide diagnosis, treatment, predict outcomes

The role of genetics in risk scores and atypical monogenic forms is likely to be helpful in specific circumstances

Hypothesis is that PDM is cost-effective but this remains to be shown by additional groups

T2D subtype analysis either as clusters or using simple clinical measures to guide strategy in new ways is emerging as way forward

There is still a need to have a simple diagnostic approach for Type 1 Diabetes

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Acknowledgements

Thanks to all the participants, patients and their families

Funding Sources

NIH/NIDDK

JDRF - Jaffe Family

Lewis - Sebring Foundation

Kovler Diabetes Center

American Diabetes Association

Helmsley Trust

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Thanks to all the participants

and t eir families.

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