The Oxford Centre
for Diabetes, Endocrinology and Metabolism

How I assess a newly diagnosed young adult with diabetes

Katharine Owen

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“John” age 27

- Attends GP
- 2 month history thirst, polyuria, blurred vision
- Wt loss 3kg
- Mother has type 2 diabetes
- GP checks random glucose – 15.3mmol/l
- Diagnosis “Diabetes”

So John has diabetes....

But what kind of diabetes is it?

- Type 1?
- Type 2?
- Something else?

Does it matter?

What diagnostic tests can we use to help?

What do you want to know?

- Presentation: acute/non-acute/incidental
- Examination: BMI, comorbidities
- Investigations:
  - Immediate: BG, ketones, routine biochem, lipids
  - Back in 1-2 weeks: Beta-cell antibodies
  - Back in 6-8 weeks: Genetic testing if indicated
- Decision: does he need insulin today?
- Question: Do I need more information to decide the aetiology?

Treatment in newly diagnosed diabetes ….depends on aetiology

Type 1	Type 2	"Something else"
Insulin	Lifestyle ± Metformin	*Maybe* not Insulin or Metformin

What kind of diabetes?

- BMI 36, taxi driver
- ↑ BP, TG 4 mmol/l, ALT 80
- Lifestyle advice and metformin
- Took up triathalon, lost weight
- HbA1c 6.3%

- BMI 22, keen cyclist
- Normal BP and lipids
- Lifestyle advice and metformin
- 1 year: increasing BG
- HbA1c 9.4%
- Beta-cell Ab +ve

Jenni aged 18

- Urgent referral to young adult service with newly diagnosed diabetes
- 2kg weight loss – Mum checked CBG – 14mmol/l
- GP fasting glucose x 2: 8 and 12, HbA1c 9%
- Beta-cell antibodies pending
- Mild thirst but well otherwise. No ketones
- Mum type 1 diabetes since age 15
  - Good HbA1c (6-7%), no DKA, no complications

Jenni aged 18

- Patient seen 1 week later (in email contact, checking ketones)
- Lean with no signs of insulin resistance
- Antibodies (GADA, ICA) came back negative

So what kind of diabetes does she have?

Slim, young, Ab-ve, non acute presentation

→ not clearly type 1 or type 2

→ MODY?

Maturity-onset diabetes of the young (MODY)

- Group of monogenic causes of beta-cell dysfunction
- Approx 5% of young-onset diabetes in the UK
- Causes diabetes characterised by:
  - Young age of onset (classically<25, most by 45)
  - Parental history of diabetes
  - Absence of autoimmunity
  - Persistent insulin secretion
  - Absence of obesity and insulin resistance

Maturity-onset diabetes of the young (MODY)

Genetic causes

Glucokinase (*GCK*)
~ 30%

Hepatocyte Nuclear Factor 1-alpha (*HNF1A*)
Hepatocyte nuclear factor 4-alpha (*HNF4A*)
~60%

Rare: *HNF1B*
ABCC8
KCNJ11
INS
IPF1
NEUROD1
CEL

Unknown

Maturity-onset diabetes of the young (MODY)

Genetic causes

HNF1A-MODY

- Commonest cause of MODY in adults (50-60%)
- Multigenerational families
- Progressive β-cell dysfunction and treatment requirement
- Severe complications if poor control
- HNF4A has similar phenotype

Maturity-onset diabetes of the young (MODY)

Genetic causes

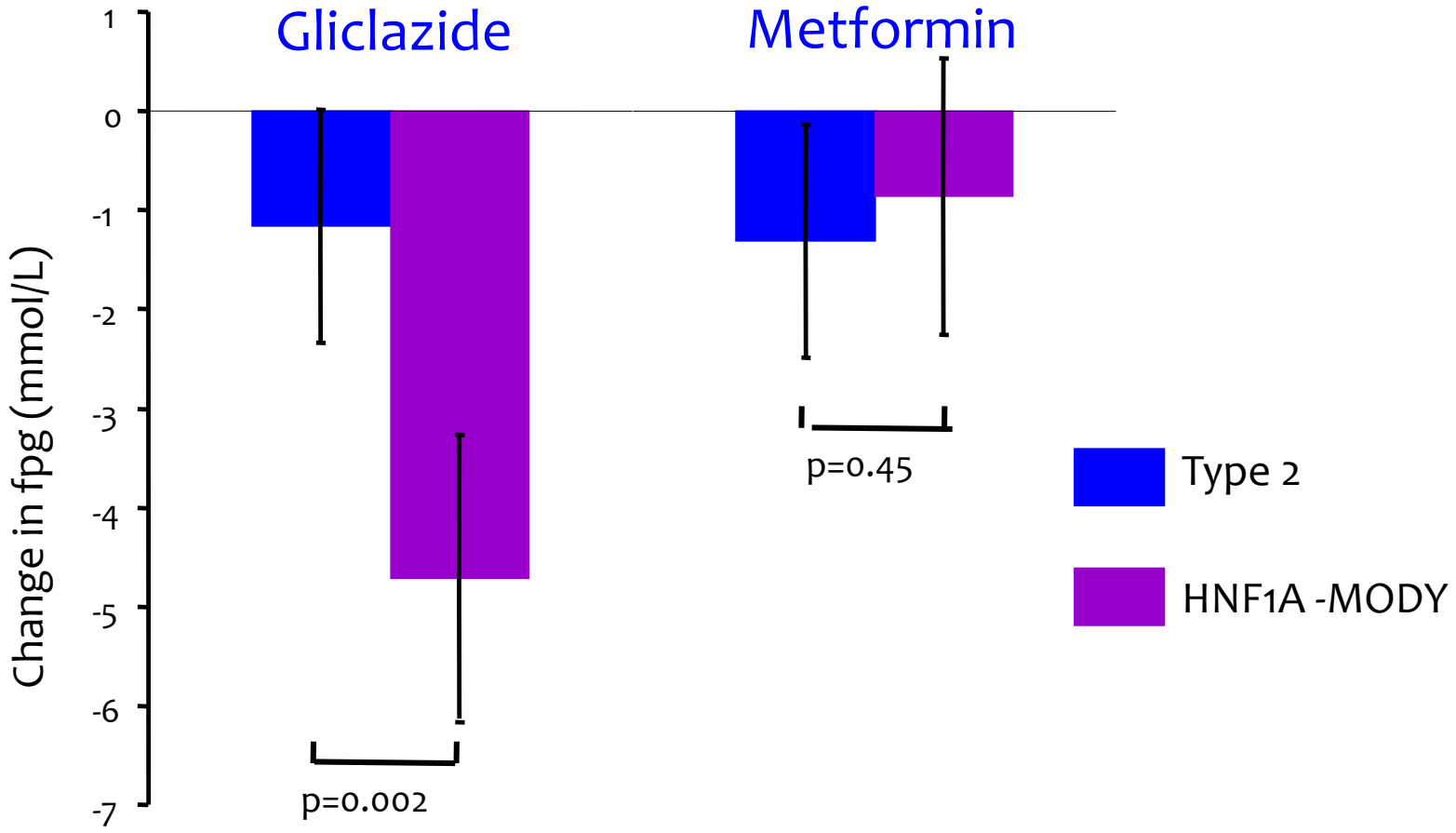
GCK-MODY

- Commonest cause of MODY in children
- Mild, lifelong, fasting hyperglycaemia - regulated
- Drug treatment does not alter HbA1c
- Microvascular complications not observed
- ~50% of asymptomatic hyperglycaemia in children

Why diagnose MODY ?

Changes treatment

Sulphonylurea sensitivity in HNF1A-MODY



Pearson *et al* (2003) Lancet

Before molecular diagnosis:

80 units/day insulin with HbA1c 8.6%

7 years later - after molecular diagnosis:

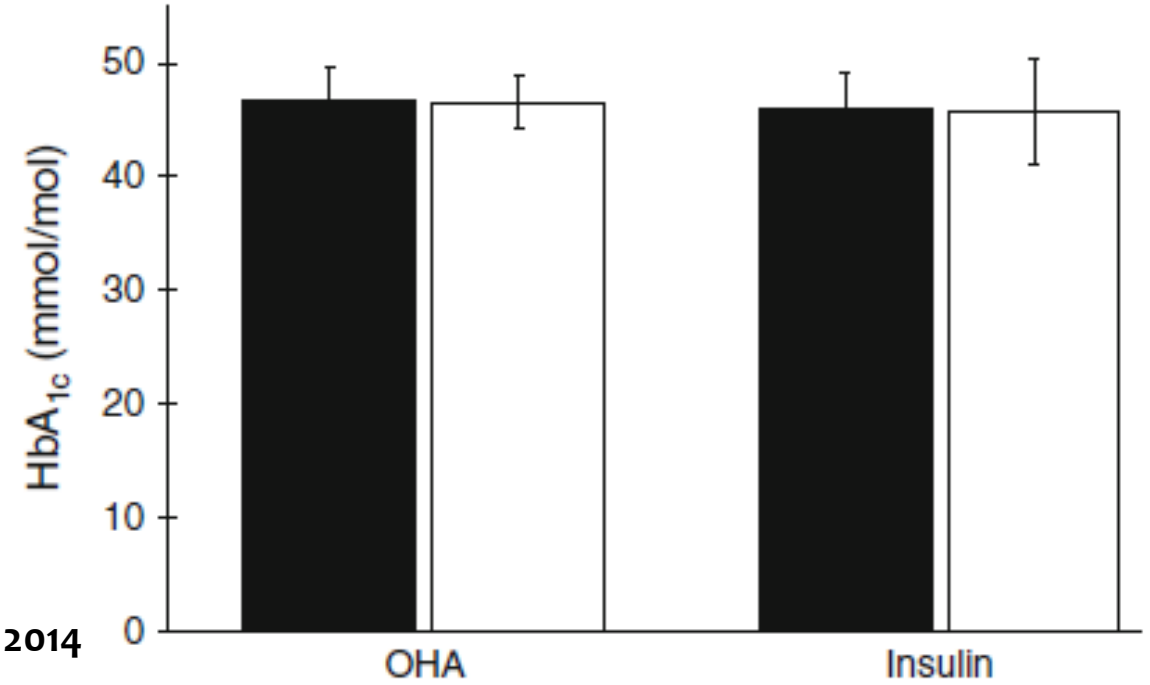
½ tablet gliclazide with HbA1c 5.8%

Treatment in GCK-MODY

No difference observed in HbA1c on different treatments

No change in HbA1c after stopping OHA or Insulin after GCK-MODY diagnosis

Treatment can be withdrawn when diagnosis confirmed



Stride et al Diabetologia 2014

Why diagnose MODY ?

Changes treatment

Jenni– what happened next

- Raised post-prandial BG and HbA1c
  - Commenced on gliclazide 40mg
- DNA sent for HNF1A/HNF4A sequencing
- Weekly contact – BG <10, no ketones, no hypos
- 6 weeks later: **Result *HNF4A* mutation**

- 3 years later remains well controlled HbA1c 6%

Following up a family.... Jenni

- Jenni's Mum: Type 1 DM since age 15
- But.....C-peptide is undetectable!!
- No mutation found in Mum – she has T1D
- Jenni's sister - asymptomatic but has HbA1c 6.4%, FPG 5.4mmol/l
- Has same *HNF4A* mutation
- Dad: 52, fit and well, marathon runner BMI 20
- FPG 5.4mmol/l, HbA1c 5.9%
- Is also a mutation carrier

Jack age 24

- Chemistry PhD student
- Presented with lethargy. No wt loss/osmotic sx
- FPG= 6.7 mmol, HbA1c = 6.6% , no ketones
- Dad recently diagnosed with “borderline DM”
- BMI 22, no signs insulin resistance
- GAD & ICA negative
- Glucokinase mutation suspected.....

  – and confirmed on test
- 6 week turnaround from initial visit

Outcomes in GCK-MODY

- 99 *GCK* mutation carriers (med age 49)
- 83 with T2D dx <45y (med age 55, 17 yrs of DM)
- 91 nondiabetic controls (median age 52)

Examined for clinically significant complications

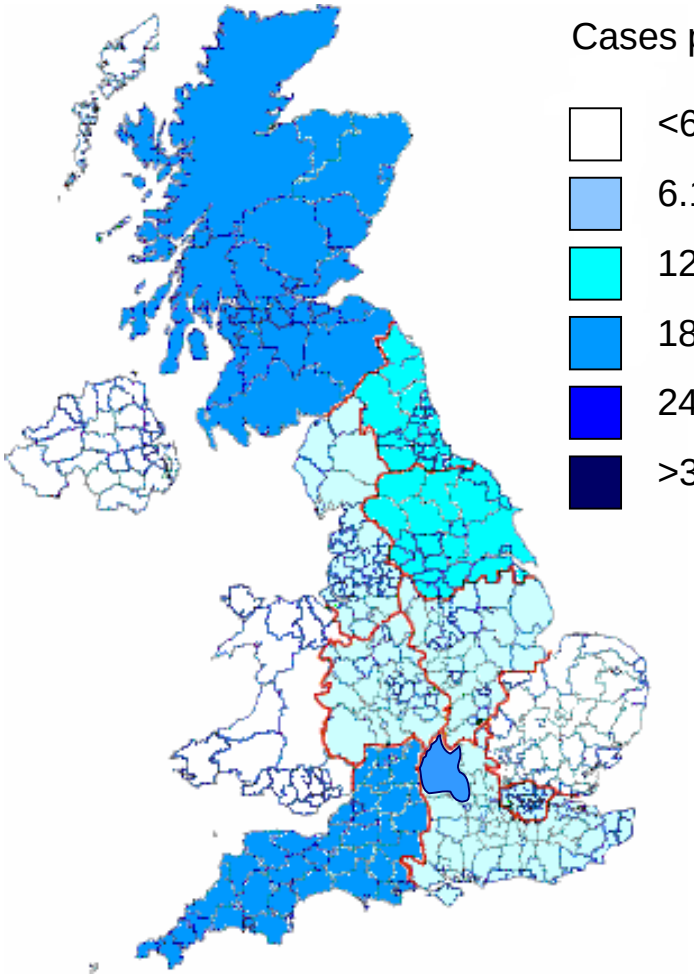
	GCK	T2	Control
Sig microvasc	**1%**	36%	2%
Laser for DR	**0%**	28%	0%
Macrovasc	**4%**	30%	11%
HbA1c	**6.9**	7.8	5.8

Steele et al JAMA 2014

Lessons from these cases

- Most patients like Jenni go on insulin and stay on insulin for 10-20 years or forever
- Jack might get labelled as Type 2
- Ask yourself - is this an atypical presentation for T1/T2?
- Use available tests (e.g. antibodies)
- Refer to monogenic diabetes clinic for a genetic test!

Missed Diagnosis……



- >80% UK MODY subjects remain unidentified
- 10-15 yr delay from diabetes diagnosis to MODY diagnosis

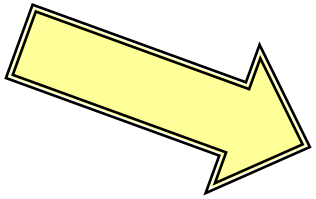
Prevalence of Monogenic Diabetes by region

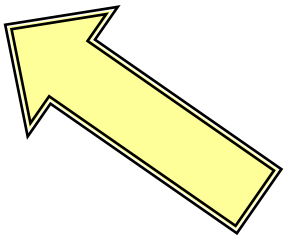
Shields *et al* (2010) Diabetologia

…..and Misdiagnosis

- Diagnosis is challenging due to overlap in clinical features with both Type 1 and Type 2 diabetes
- Clinicians have a reluctance to question original diagnostic label

“Type 2” diabetes diagnosed >30yrs





“Type 1” diabetes – no obvious reason to suspect MODY

Which patients with apparent T1D should have MODY testing?

- Endogenous insulin post honeymoon

  Clues: Low insulin dose <0.5 u/kg

  " Insulin holidays" with no ketosis

  There may not be a clue - measure c peptide!

C-peptide

A marker for endogenous insulin secretion

Negative post-honeymoon in T1D

Which patients with apparent T1D should have MODY testing?

- Endogenous insulin post honeymoon

  Clues: Low insulin dose <0.5 u/kg

  " Insulin holidays" with no ketosis

  There may not be a clue - measure c peptide!
- Antibody negative
- Family history of young-onset DM ~ mixed types
- In those close to diagnosis it can be very hard to tell the difference. If in doubt be safe.
- Please revisit the diagnosis
- About 1% of T1D, or 10% of those with positive C-peptide have MODY[1]

1. Thanabalasingham et al Diabetes Care 2012

Which patients with apparent T2D should have MODY testing?

- Young-onset (95% of MODY dx <45yrs)
- Lean, absence of insulin resistance
- β-cell antibody negative
- Hypoglycaemia on low dose SU
- Family history of young-onset DM (NB parental DM is as common in young T2 as in MODY[1,2])
- About 4% of T2D dx<45yrs and 15% of young T2D without Met Syn have MODY[3]

1. Owen et al Diabetic Med 2003, 2.Pihoker et al JCEM 2013 3.Thanabalasingham et al Diabetes Care 2012

When to use C-peptide

- To find out whether someone on insulin, particularly from diagnosis is insulin deficient

(generally means type 1 diabetes)

- Always send blood with a paired glucose
- Serial measurements track progress
- Fasting, random or post-meal urinary
- Also can help judge insulin resistance

When to use Beta-cell antibodies

- At diagnosis of diabetes in children and young adults
- Identifies those who *might not* have T1D
- Identifies the T2D who actually have LADA
- Use GAD and IA2 rather than ICA
- A one-off test costing ~£15 each

Other tools for diagnosis – Biomarkers

- HNF1A is a transcription factor controlling many genes in liver, kidney, gut
- Non-pancreatic features of *HNF1A* mutations could be used as diagnostic markers
- HNF1A regulates hepatic CRP secretion
- GWAS showed that common genetic variation near *HNF1A* was associated with alterations in CRP in healthy people
- Would there be larger differences in HNF1A-MODY?

CRP and HNF1A-MODY

Clinical Care/Education/Nutrition/Psychosocial Research
ORIGINAL ARTICLE

Assessment of High-Sensitivity C-Reactive Protein Levels as Diagnostic Discriminator of Maturity-Onset Diabetes of the Young Due to *HNF1A* Mutations

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GAYA THANABALASING
TIMOTHY J. JAMES, PH
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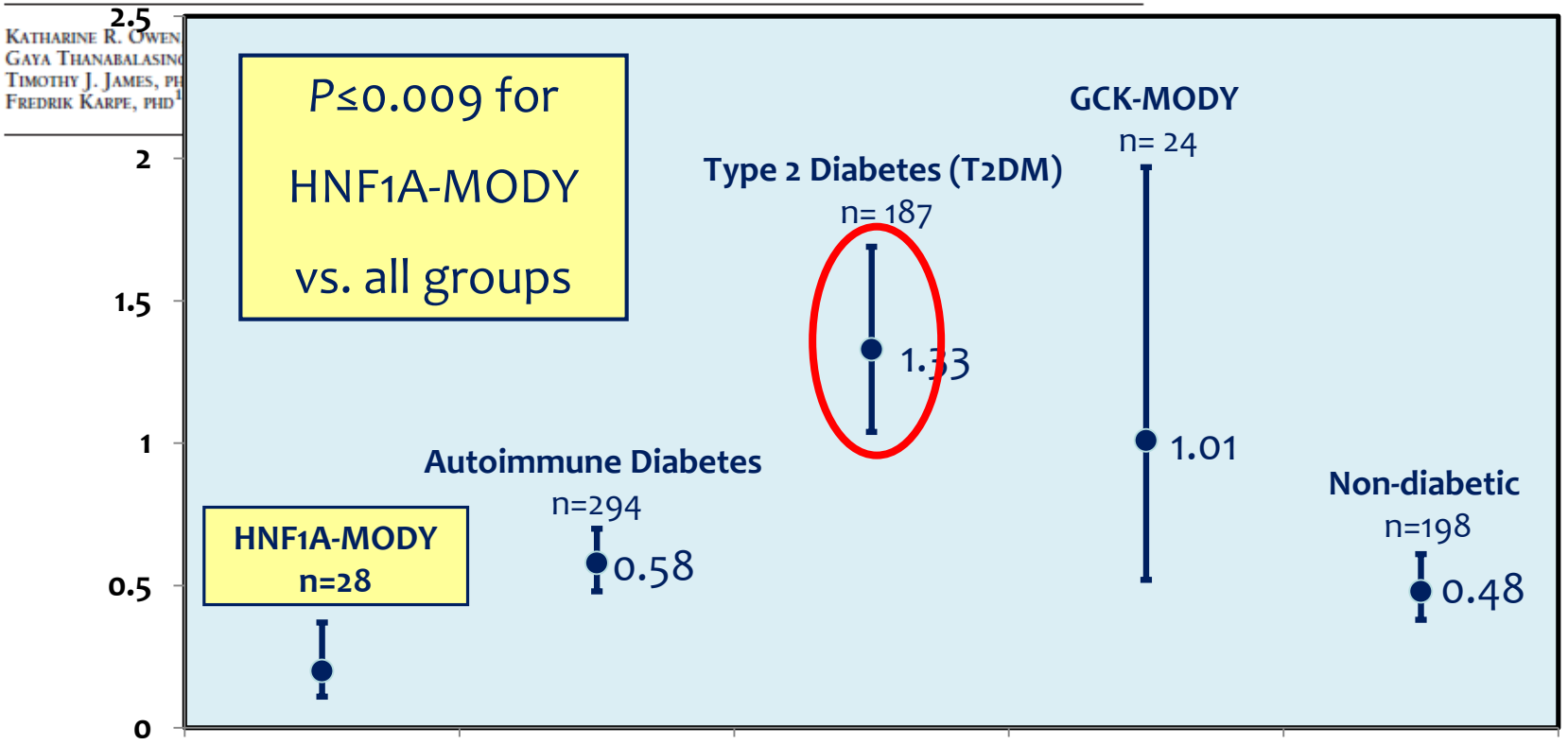
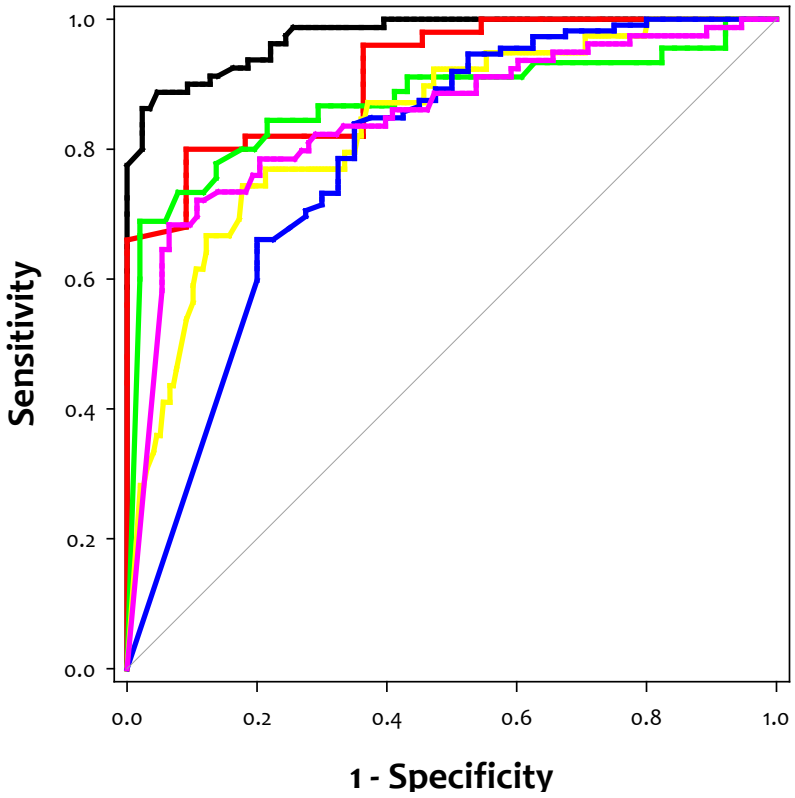


HsCRP levels can distinguish HNF1A-MODY from young adult-onset T2DM



Denmark AUC= 0.97
Norway AUC = 0.91
Poland AUC = 0.87
France AUC = 0.85
UK AUC = 0.83
Finland AUC = 0.79

~80% of HNF1A-MODY, but only 15-20% of T2D have a CRP<0.5mg/L

Thanabalasingham et al Diabetologia 2011

Other tools for diagnosis: 2. Exeter MODY calculator

Diabetologia (2012) 55:1265–1272
DOI 10.1007/s00125-011-2418-8

ARTICLE

The development and validation of a clinical prediction model to determine the probability of MODY in patients with young-onset diabetes

B. M. Shields · T. J. McDonald · S. Ellard · M. J. Campbell · C. Hyde · A. T. Hattersley

- Enter simple data (gender, dx age, BMI, HbA1c, parental history, time to insulin Rx)
- Gives probability of "MODY", based on pre-test prevalence and compared to previous UK cases
- Disadvantages: does not use biomarkers nor differentiate subtypes of MODY

http://www.diabetesgenes.org/content/mody-probability-calculator

Translation into practice – the Oxford MODY clinic

- Established ~2005
- Investigate uncertain aetiology and follow-up rare forms of diabetes (not severe IR)
- 300 patients through clinic
- 150 MODY tests sent to UK lab – 46% of tests positive
- 60% of tests were on probands, 37% positive
- Following up ~100 patients with rare diabetes

Investigation of New Diabetes diagnosed before 30 years

NB: For those presenting acutely treat as per usual practice with insulin. Check aetiology later

Check Beta-cell antibodies – GAD/IA2
Check C-peptide if insulin treated

Any positive antibody
C-peptide –ve

Probable Type 1 diabetes

Antibodies negative
C-peptide +ve

Clinical Features include:
BMI>30 kg/m^2 with additional features of insulin resistance (↑BP, ↑TG, ↑LFT, PCOS)

Yes

Probable Type 2 diabetes

No

Is this Diabetes plus other features ?

Mitochondrial diabetes?
Like MODY but with deafness, other neurology, maternal inheritance

Severe Insulin Resistance?
Young-onset metabolic syndrome, PCOS, acanthosis, BMI seems too low
Lipodystrophy (look at legs)

HNF1B- MODY?
Diabetes plus Cystic renal disease, GU anomalies

Is this classic MODY?
Lean, C-peptide +ve, Ab-ve
DKA unlikely
Often FH of diabetes dx ≤ 45 years

GCK-MODY?
Asymptomatic
FBG 5.5-8.0 mmol/l
HbA1c <58/7.5%
FH IGT, GDM

HNF1A/4A- MODY?
CRP<0.5 (HNF1A)
↑BW, neonatal hypos (HNF4A)

Rare causes

Paul age 42

Seen in MODY clinic Sept 2016

Diagnosed with diabetes in May 2016:

Presented with peripheral neuropathy

Tired, polyuria, weight loss - BMI 22

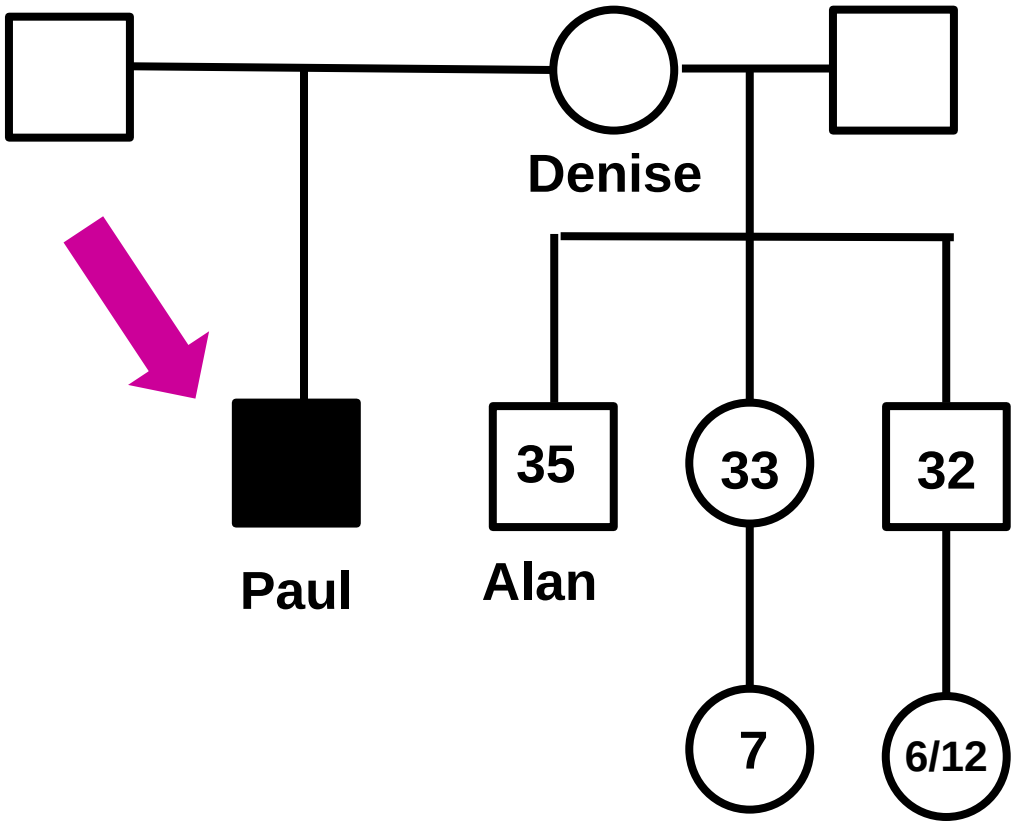
HbA1c 9.3%, No ketones, Chol 6.1 HDL 1.6

Placed on basal bolus insulin

GAD and ICA negative

C-peptide 708 pmol/l with glucose 14.2

Family History



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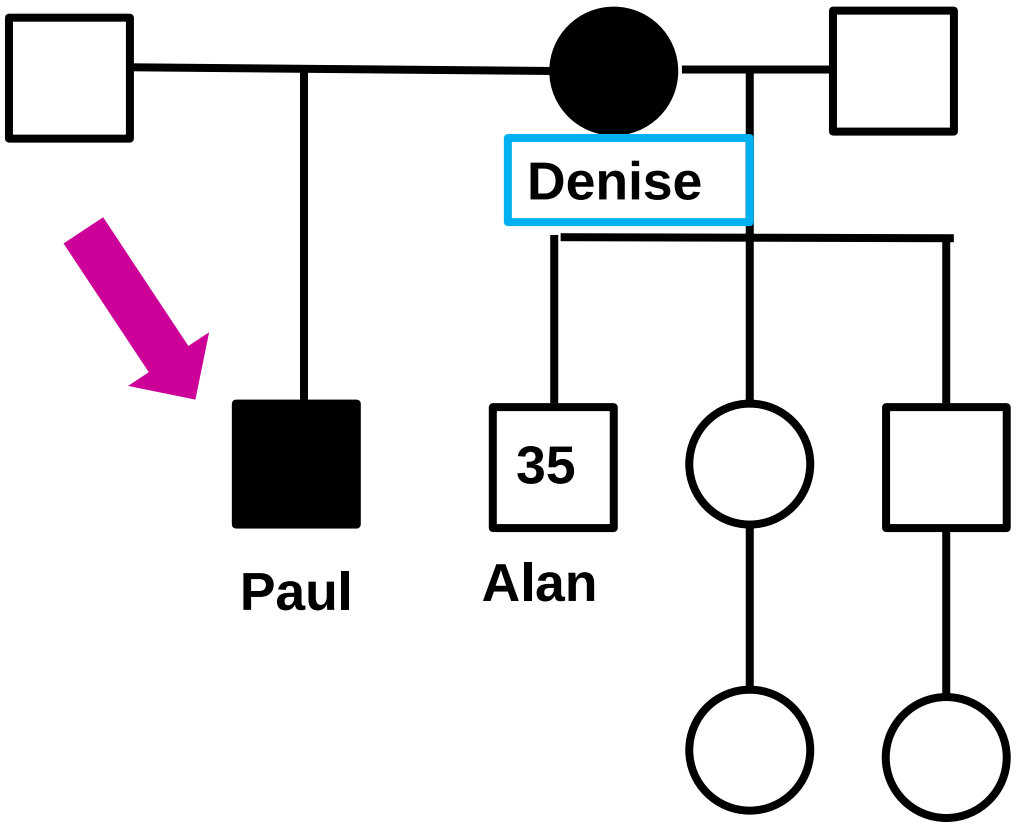
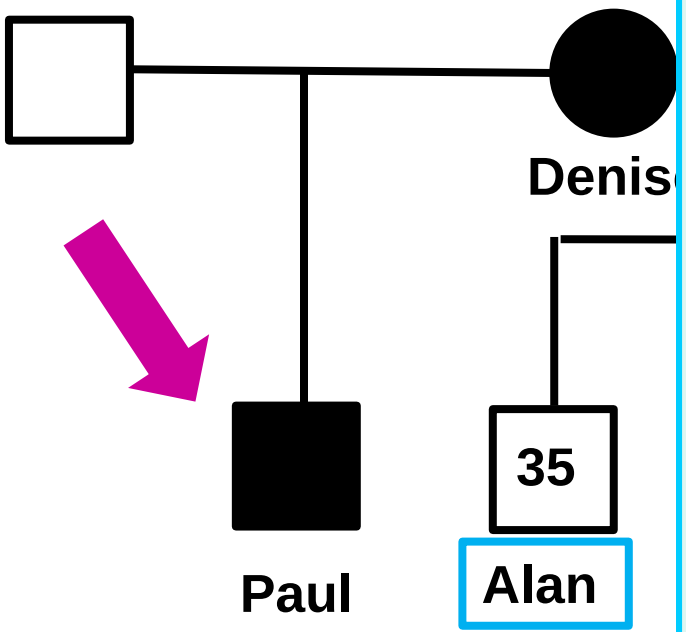


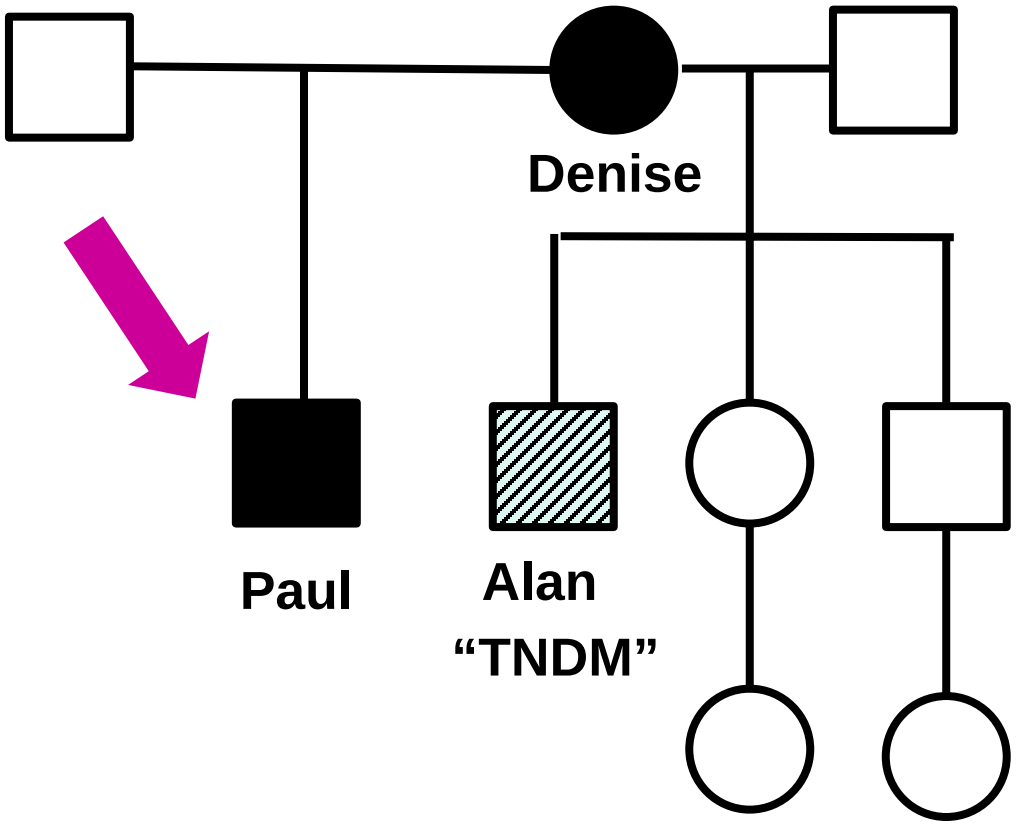
Denise age 59
Diagnosed 2010
Incidental finding, mild symptoms
BMI 25
Metformin ever since
HbA1c 6.5%

Family History



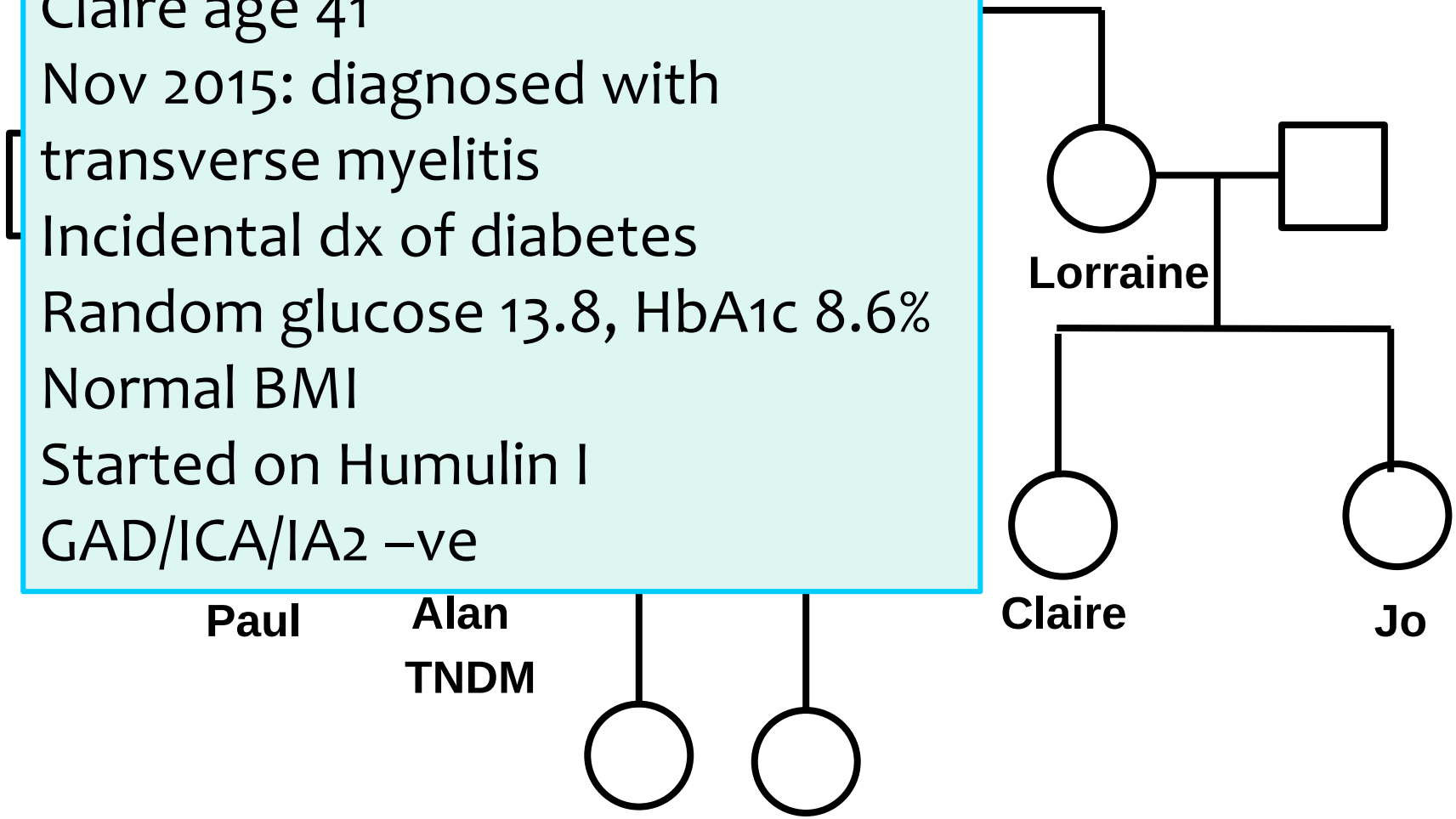
Alan, age 35
Diagnosed at 3 months old
Unwell, vomiting, failure to thrive
Presented in DKA
Improved once on insulin
Insulin dose gradually reduced until stopped at 16 months
Normal OGTT age 15
Well currently but no diabetes test since
Now lives on Vancouver Island

Family History

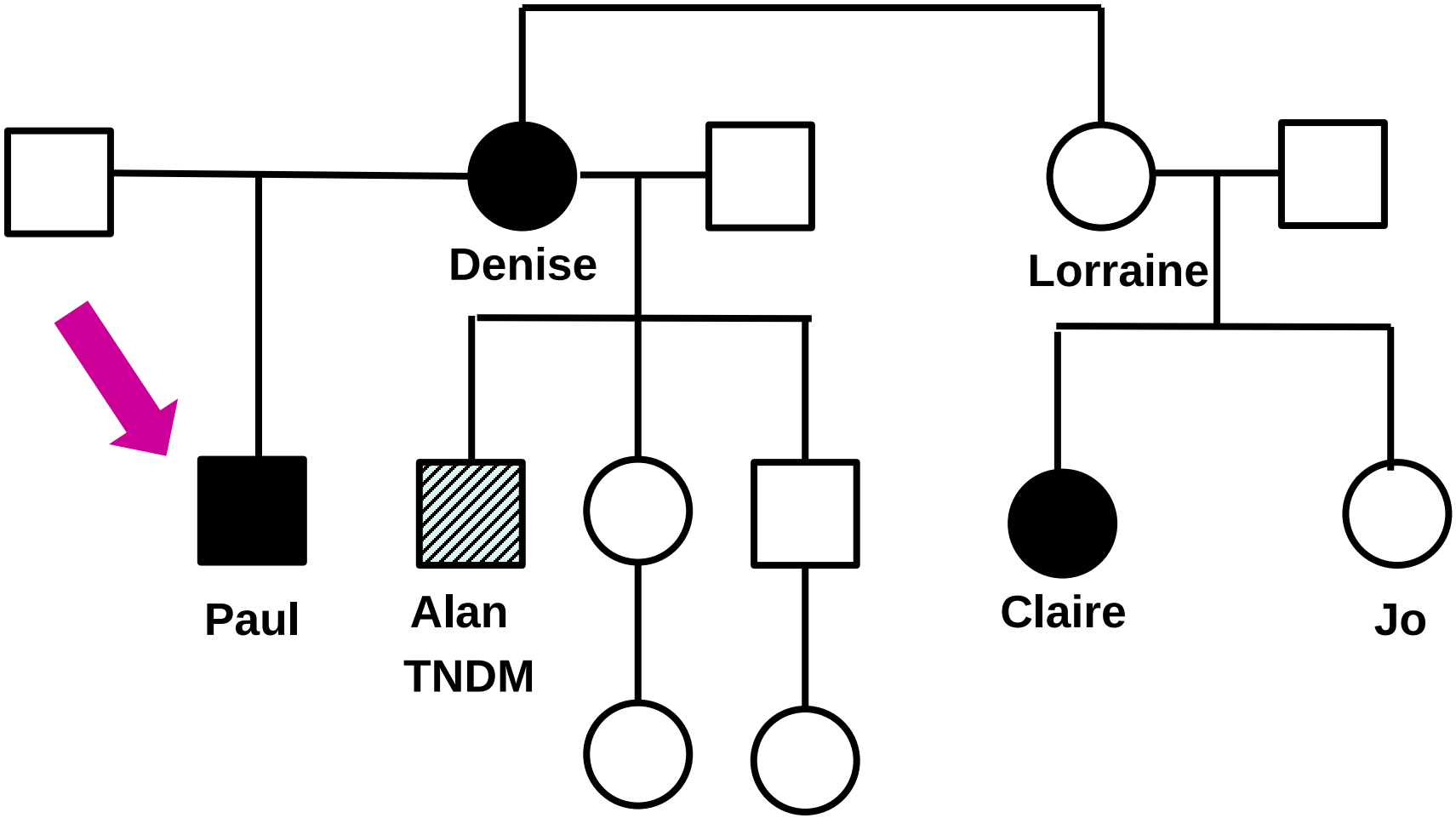


Family History

Claire age 41
Nov 2015: diagnosed with transverse myelitis
Incidental dx of diabetes
Random glucose 13.8, HbA1c 8.6%
Normal BMI
Started on Humulin I
GAD/ICA/IA2 –ve



Family History



Transient Neonatal Diabetes

- Defined as diabetes arising in first 6/12, which spontaneously remits
- May re-occur in adult life
- Genetic aetiology found in >90%

70% - Methylation defect at 6q24 (over expression of paternally expressed genes ZAC/HYMAI)

20% - mutation in beta-cell K-ATP channel genes (KCNJ11 or ABCC8)

More rarely: INS/HNF1B/SLCA2

Investigations

Genetic testing sent on Paul

FH of TNDM included in request

Next gen sequencing panel 25 genes

Missense mutation in ABCC8 (the SUR receptor)

Reported in a previous family with remitting-relapsing diabetes

Diabetes due to ABCC8 mutations sensitive to sulphonylurea drugs: high dose glibenclamide in Neonatal DM

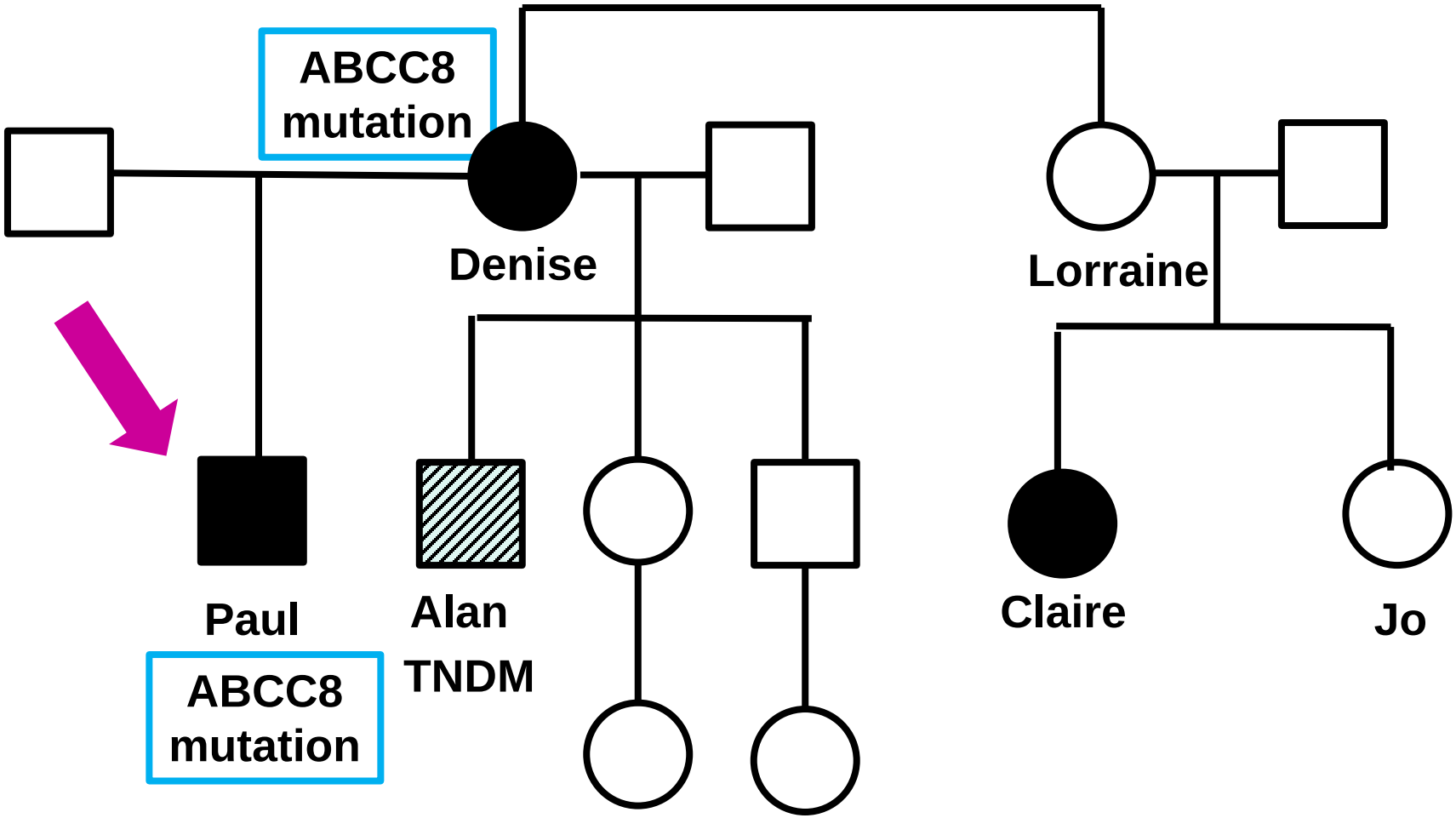
Possibly lower dose in "MODY-like"

Paul cont…..

- Stopped insulin Jan 2017, HbA1c 6.8%
- Gliclazide 40mg → 80mg daily
- July 2017 HbA1c 5.9% No hypos
- Microvascular complications

- Mother Denise has the same mutation

Family History



Claire and Lorraine

Claire tested and has same mutation

Lorraine reviewed age 63

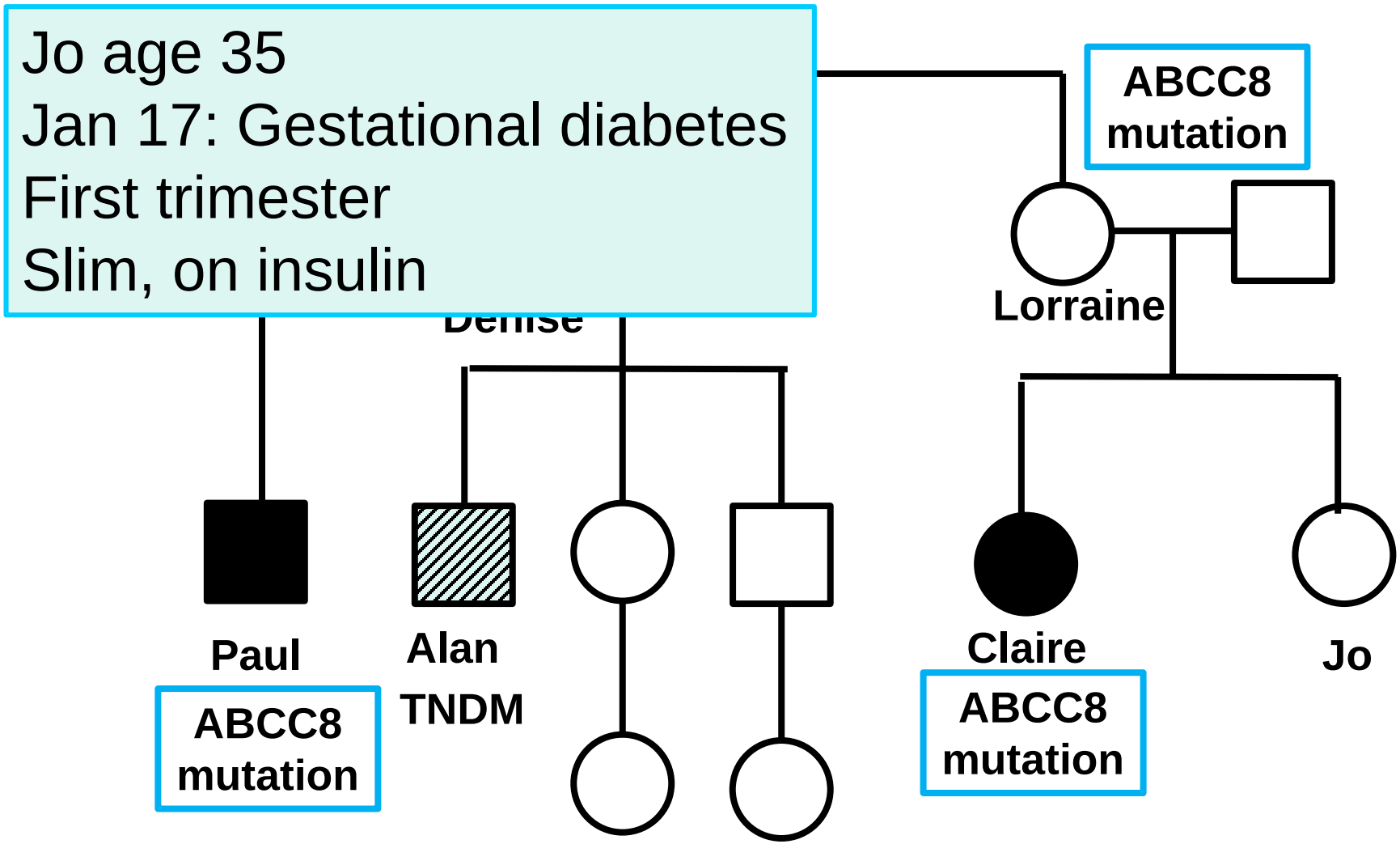
- Fit and well, no diabetes
- HbA1c 5.9%, fasting glucose 4.6 mmol/l
- Lorraine tested and has same mutation

May 2017: Claire came off insulin

Current treatment Gliclazide 20mg od

HbA1c 6.5%, no hypos

Family History



Jo

Jo tested in late pregnancy

Has same ABCC8 mutation

Baby delivered in July 2017 - well at birth

But - at risk of neonatal diabetes

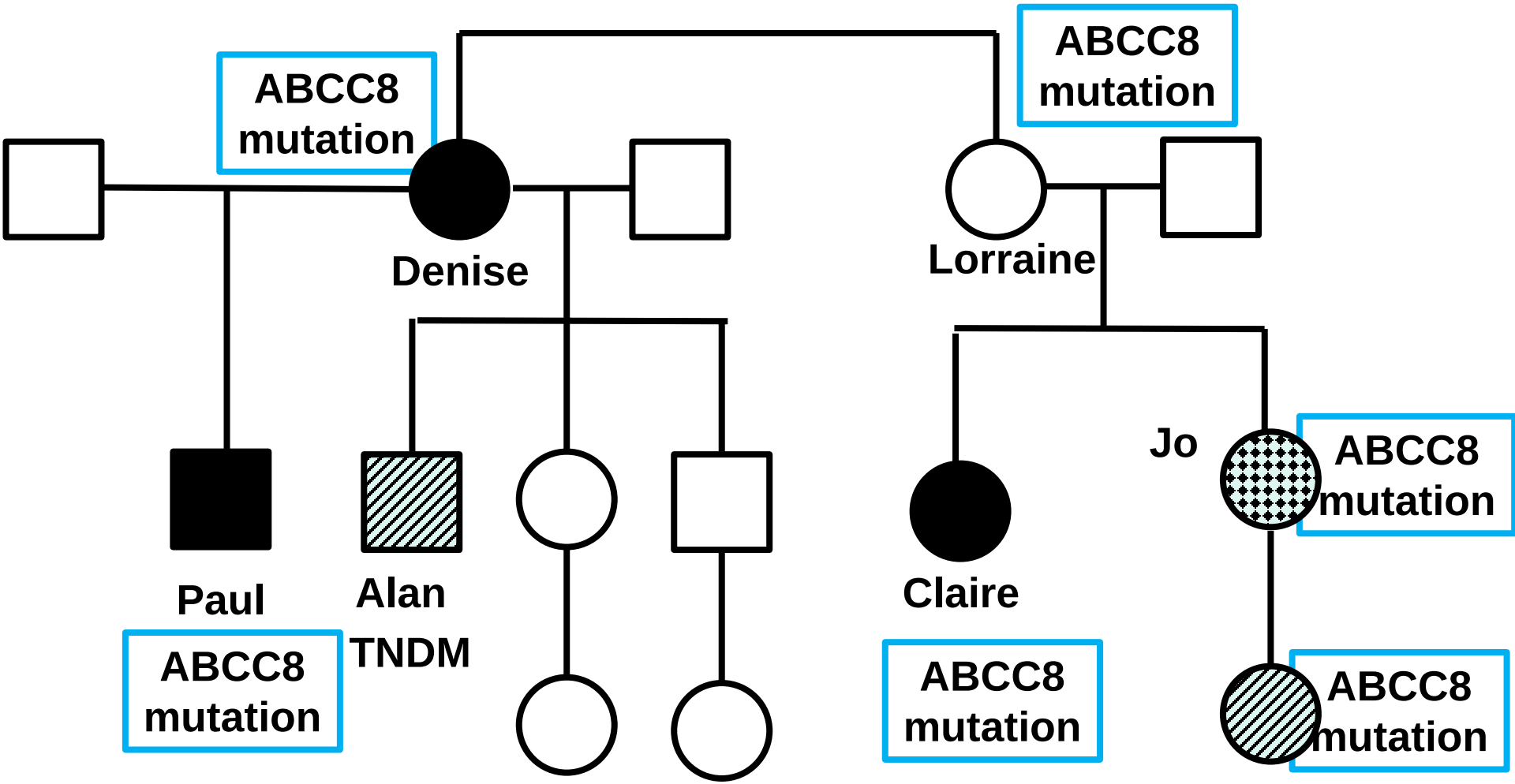
Cord blood genetic test shows same ABCC8 mutation

Research shows that glucose at 2/52 is already abnormal in those who will get neonatal diabetes

Normal BG so far

Jo normoglycaemic after delivery

Family History



Discussion points

- Emphasises very varied phenotype of ABCC8
  - PNDM, TNDM,MODY, T2D, GDM, normoglycaemia……
- A history of neonatal diabetes is ALWAYS important!
- Of 7 family members with mutation, only 1 known to have neonatal diabetes
  - Subclinical or absent in others
- Rare – take advice/collect data

Investigation of New Diabetes diagnosed before 30 years

NB: For those presenting acutely treat as per usual practice with insulin. Check aetiology later

Check Beta-cell antibodies – GAD/IA2
Check C-peptide if insulin treated

Any positive antibody
C-peptide –ve

Probable Type 1 diabetes

Antibodies negative
C-peptide +ve

Clinical Features include:
BMI>30 kg/m^2 with additional features of insulin resistance (↑BP, ↑TG, ↑LFT, PCOS)

Yes

Probable Type 2 diabetes

No

Is this Diabetes plus other features ?

Mitochondrial diabetes?
Like MODY but with deafness, other neurology, maternal inheritance

Severe Insulin Resistance?
Young-onset metabolic syndrome, PCOS, acanthosis, BMI seems too low
Lipodystrophy (look at legs)

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Diabetes plus Cystic renal disease, GU anomalies

Is this classic MODY?
Lean, C-peptide +ve, Ab-ve
DKA unlikely
Often FH of diabetes dx ≤ 45 years

GCK-MODY?
Asymptomatic
FBG 5.5-8.0 mmol/l
HbA1c <58/7.5%
FH IGT, GDM

HNF1A/4A- MODY?
CRP<0.5 (HNF1A)
↑BW, neonatal hypos (HNF4A)

Rare causes

The Team, Patients and Funders

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Christina Dudley
Beryl Barrow
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Julie Sutton
Vanessa Loach
Amanda Webster

Families from the Young Diabetes in Oxford Study and Oxford MODY Clinic

DIABETES UK
CARE. CONNECT. CAMPAIGN.

Oxford Biomedical Research Centre

NHS
National Institute for Health Research
Clinical Research Network
Thames Valley and South Midlands

Radcliffe Department of Medicine

UNIVERSITY OF OXFORD

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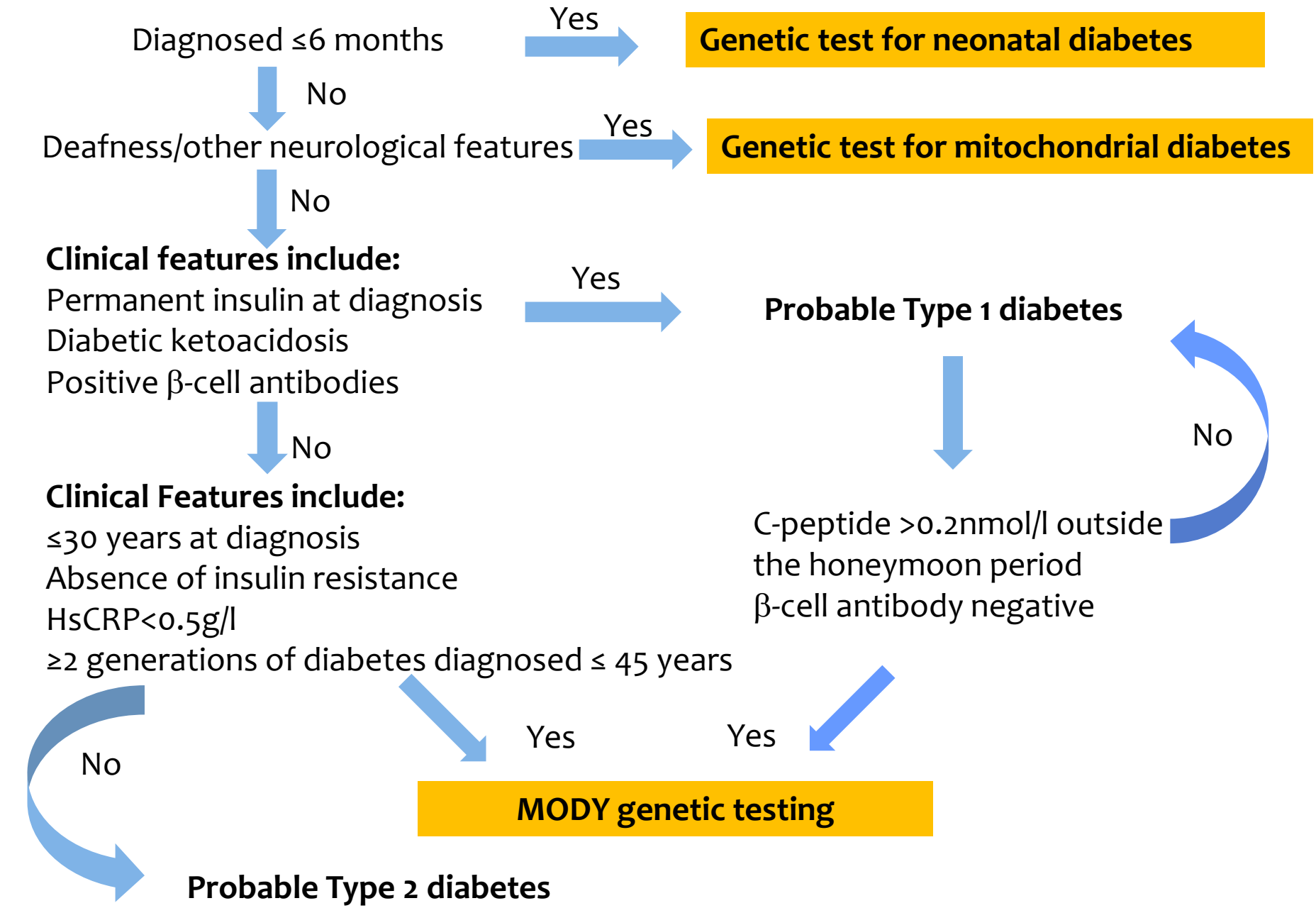
Investigation of Diabetes diagnosed ≤45 years



Roxanne age 22

- Recently diagnosed with T2 after attending GP c/o tinnitus - HbA1c 9.5%
- Lean, antibody negative, treated with OHA
- Mum has diabetes
- HNF1A/4A testing negative
- At 4 month review noted to have bilateral hearing aids!
- What is the diagnosis?

→ Maternally inherited diabetes and deafness

→Mitochondrial mutation found

Clinical characteristics of Mitochondrial Diabetes

- Mitochondria have separate DNA - inherited maternally
- Non-obese, β–cell defect, GADA –ve
- Fairly rapid progression to insulin
- Metformin relatively contraindicated
- Majority have sensorineural hearing loss +/- other neurological disorders
- Common mutation Mt3243 (also MELAS)

Lessons from this case

- Neurological features, particularly young-onset deafness, suggest mitochondrial diabetes

- Specialist referral indicated - multi-system disease

Nicola age 24

- Presented with incidental glycosuria.
- OGTT: fast 9.1 2hr 17.8 mmol/l
- Beta-cell Ab –ve
- Mother & Grandfather T2DM
- Hypertensive
- Fasting TG 4.6 mmol/l
- Acanthosis on neck/axilla
- BMI 24.9

A closer look….

Familial Partial Lipodystrophy (Kobberling-Dunnigan syndrome)

Clinical Features of Lipodystophy

- Lipodystrophy can be partial or generalised, genetic or acquired
- Genetic testing available
- Loss of sc fat from limbs/trunk after puberty
- Excess fat deposited in face and neck
- Muscular appearance of limbs
- Acanthosis, PCOS, dyslipidaemia
- Diabetes 2nd-5th decade
- Treat with insulin sensitisers, U500 insulin (toujeo now), leptin for generalised forms

Lessons from this case

Look at your patients!