# Diagnosing and treating rare genetic diabetes:

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www.diabetesgenes.org

# MODY is found in 1-2% patients in paediatric clinics and young adults in Sweden, USA & UK

Can not rely on clinical surveys

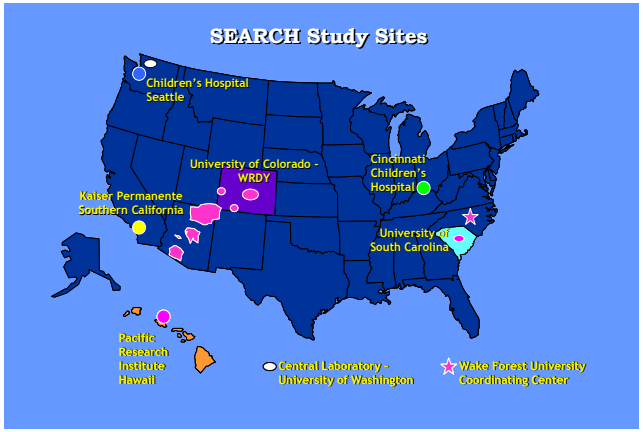
MODY 0.13% UK Clinicians Survey 15,255 patients (Ethisham 2004)

In Paediatric Clinics prevalence 1-2%

Large scale studies based on sequencing CP+ve Ab -ve

| Prevalence | Total | Population |
|---|---|---|
| 1.5% | 3966 | Sweden BDD |
| 1.2% | 3850 | USA multi-ethnic SEARCH |
| 1.6% | 908 | SW England - UNITED |

# 94% of MODY is not correctly diagnosed and 73% not correctly treated in the USA




## SEARCH

Population based study 5 USA paediatric diabetes centres diagnosed < 20 yrs

HNF1A/HNF4A/GCK mutations found in 8% (47/586) patients antibody negative, C peptide +ve diabetes

6% (3/47 )diagnosed as MODY (42%T1D 52%T2D)

1.2 % minimum prevalence In USA Paediatric clinic

24% on correct treatment (61% on insulin)

Gilliam, Pihoker, Ellard Hattersley for the SEARCH study group

Gilliam et al JCEM 2013

# MODY found in 15% Swedish antibody neg children: most are not correctly diagnosed or treated

3966 Swedish patients diagnosed < 18years 2005-10

10% antibody negative (IA2, GAD, Insulin, Zn transporter)

58/391 15% antiibody negative HNF1A/HNF4A/GCK mutations found
Minimum prevalence in diabetes 1.5%

<40% diagnosed as MODY

45% on correct treatment
(50% on insulin unnecessarily)

Lernmark, Marcus, Hattersley Ellard et al and the BDD study group

# Why is the diagnosis of MODY usually missed in the UK?

No problem of technical aspects (single UK lab)
Testing rapid and accurate (relatively cheap)
Problem in the clinical recognition (cant test all)

Diagnosis is difficult – multi-factorial not single dimension

Diagnostic classification is hardest at diagnosis of diabetes

## Clinical Training

Diabetes is a treatment speciality not a diagnostic speciality
Little expertise: Few senior consultants know they have seen a case
Rarely teaching sessions on diagnosis or genetics
MODY in genetics section not clinical section at conferences

# A practical approach to monogenic diabetes

Patients diagnosed as children or young adults

Type 1 diabetes diagnosed at 3 months
Incidental hyperglycaemia and GDM
“Type 1” with a diabetic parent
Atypical “Type 2” diabetes
Neonatal hypoglycaemia and macrosomia
Renal cysts and diabetes

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# Insulin-treated diabetes diag. 12 weeks

## Sophie

Presented 12 weeks

glucose 46 mmol/l
in diabetic ketoacidosis

Treated 4 insulin injections a day

HbA1c 7 - 10%
Problems with hypos

No insulin production
No Pancreatic autoantibodies

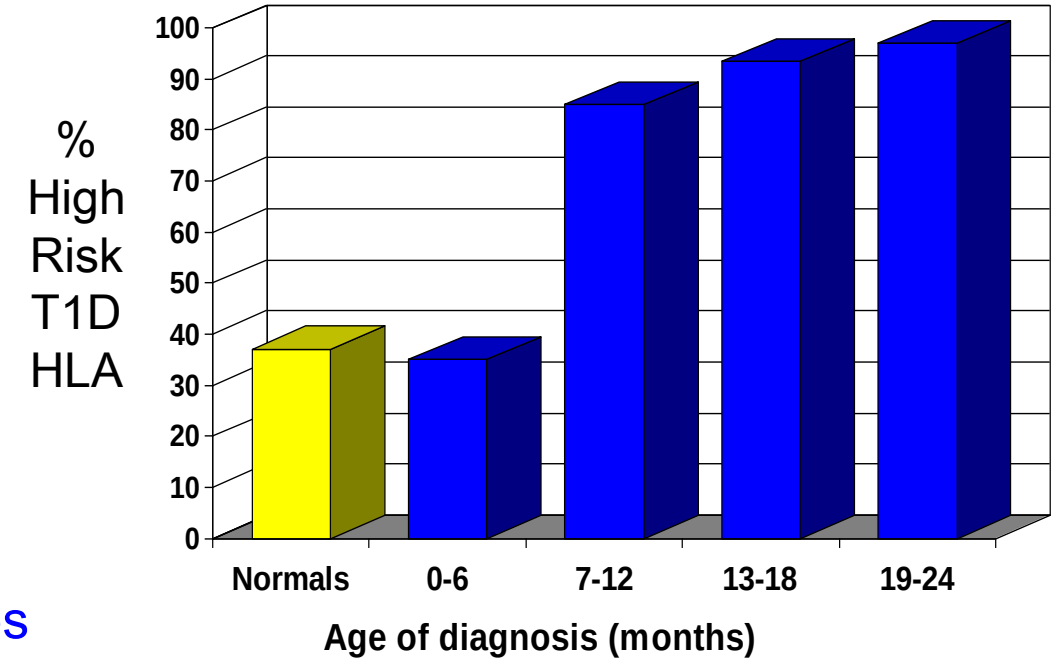
# Defecting the molecular defect

Not Type 1 although insulin dependent

Diagnosed at 3 months

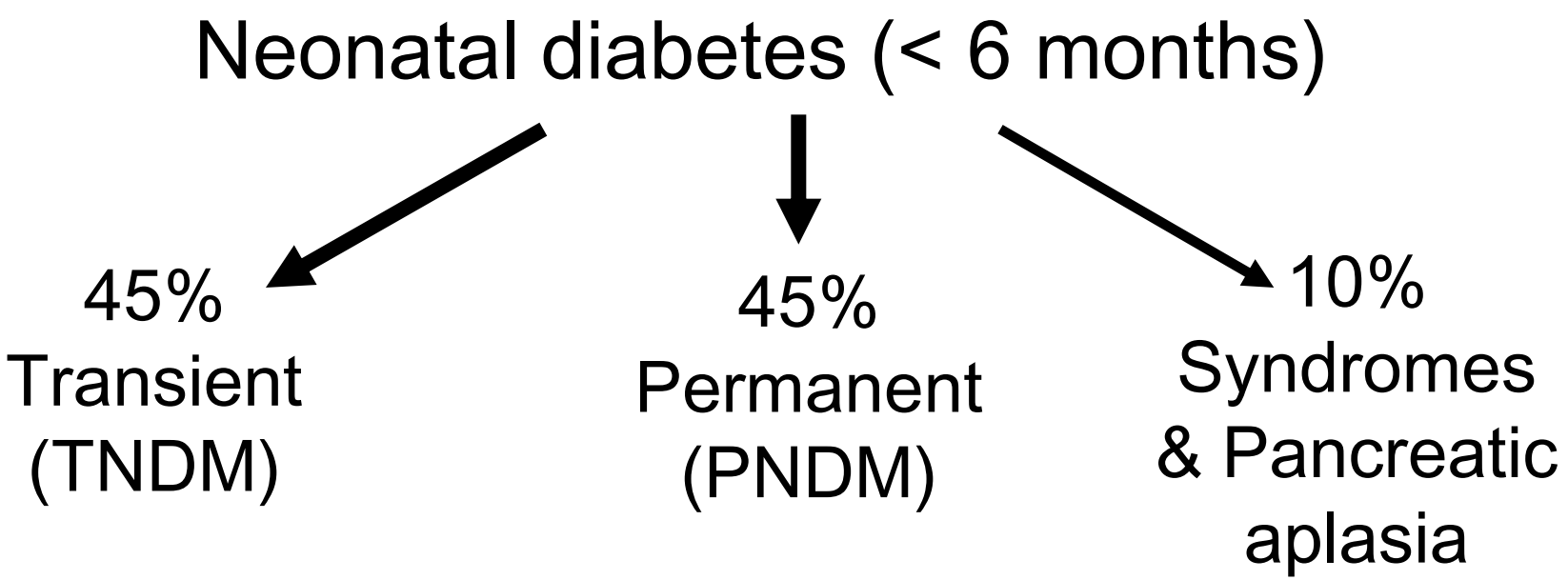
Diagnosis: Neonatal diabetes

Type 1 diabetes does not occur before 6 months

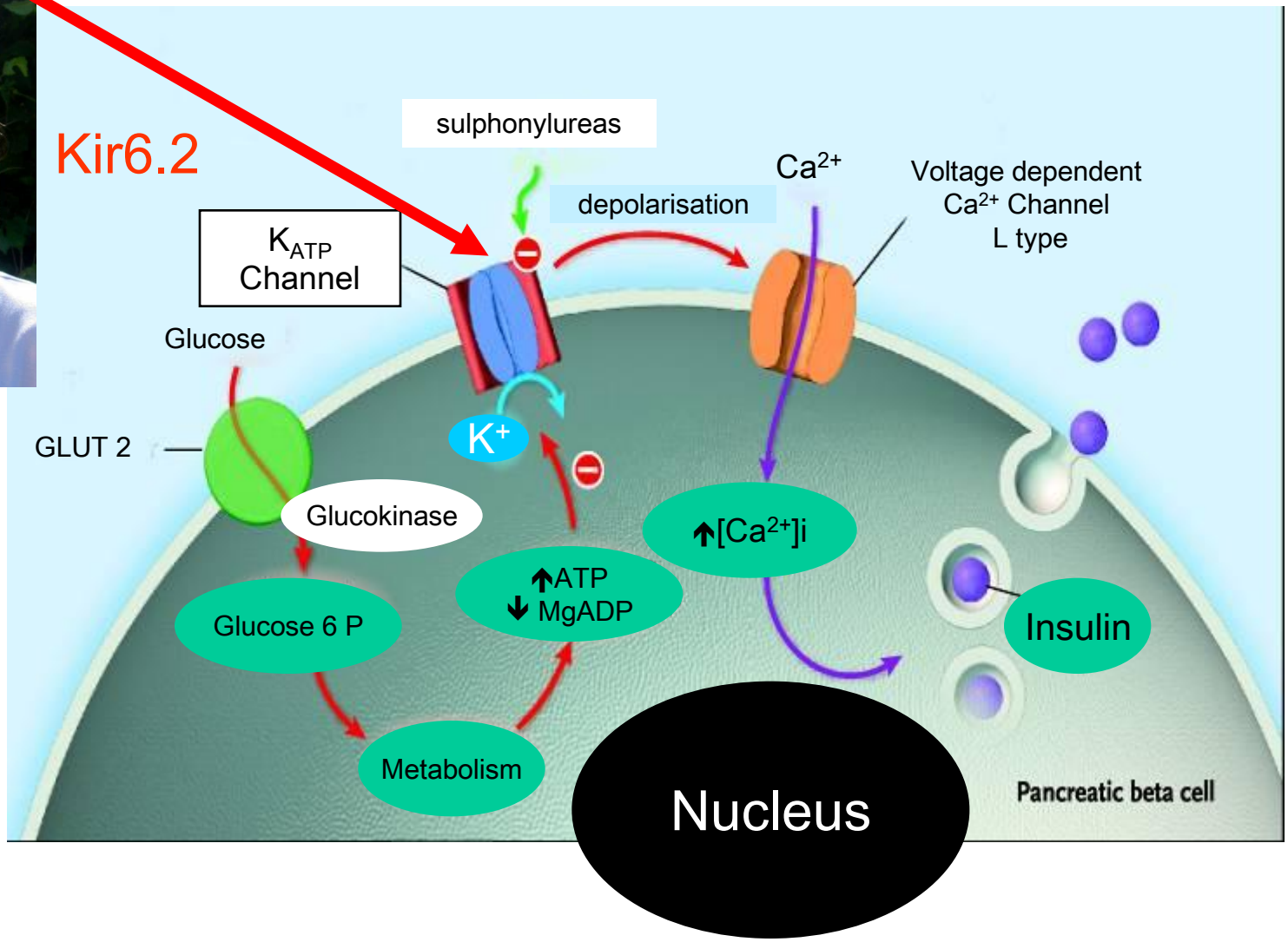



Edghill et al Diabetes 2006
Iafusco et al Diabetologia 2002

# Neonatal diabetes: in the pre-genetic era

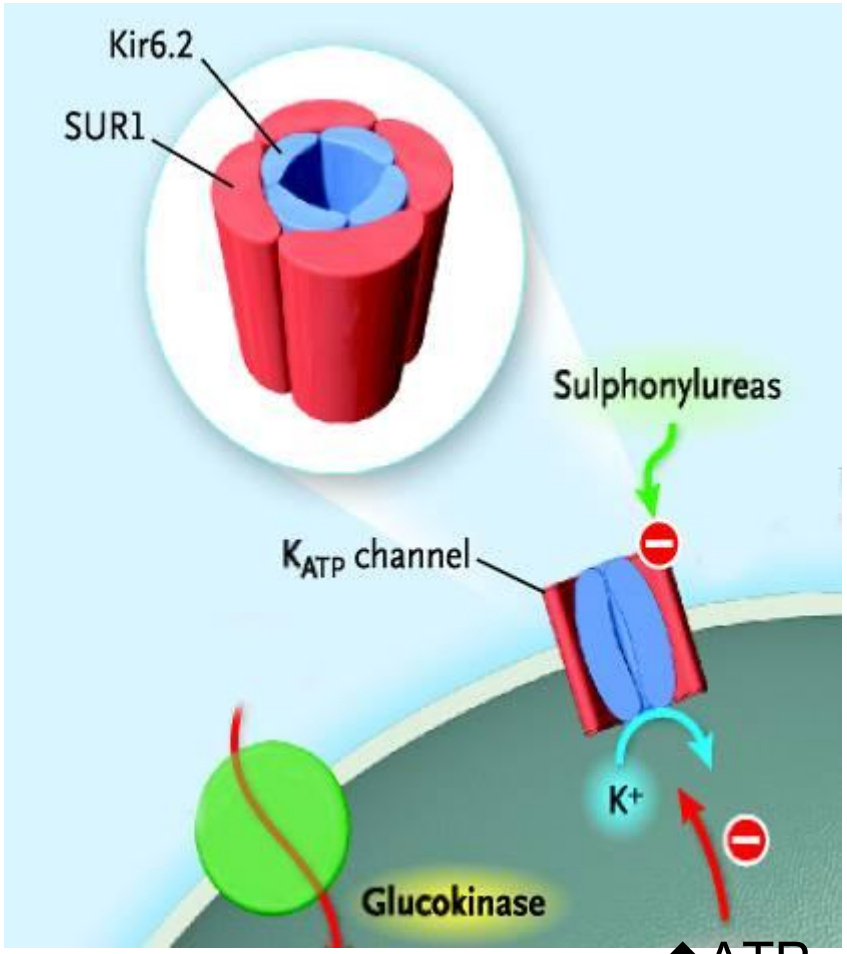


# Kir6.2 mutations – loss of communication between glucose sensing and insulin secretion



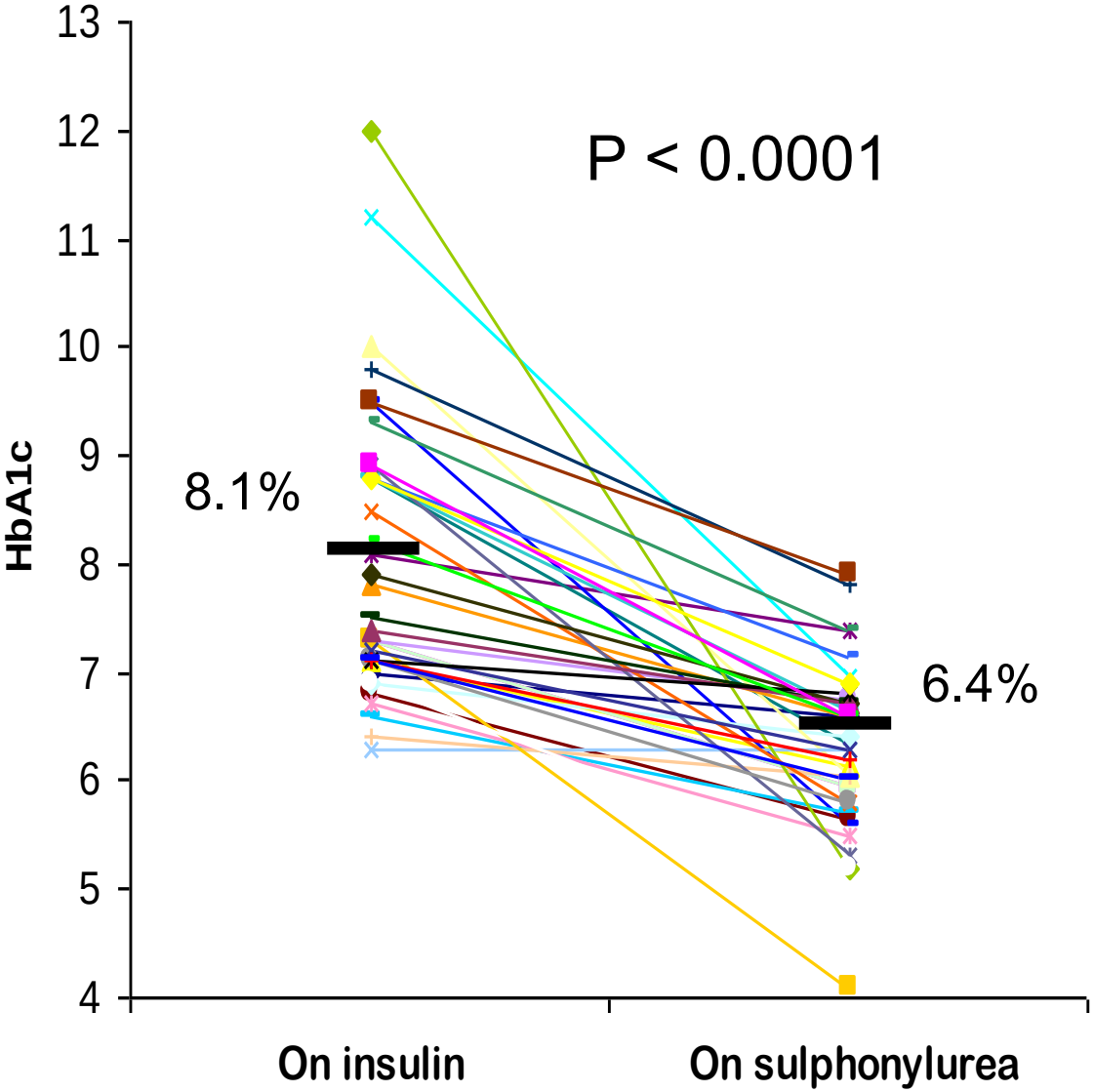

Adapted from Gloyn et al NEJM 04

# The mutated $K_{ATP}$ channel could close with sulphonylureas




| Glucose | Sulphonylurea |
| --- | --- |
| ATP does not close $K_{ATP}$ channel | Sulphonylureas close $K_{ATP}$ channel |
| ↓ | ↓ |
| Membrane Hyperpolarised | Membrane depolarised |
| ↓ | ↓ |
| No calcium influx | Calcium influx |
| ↓ | ↓ |
| No insulin secretion | Insulin secretion |

# 90% of Kir6.2 patients stop insulin
# Glycaemic control is improved in all patients

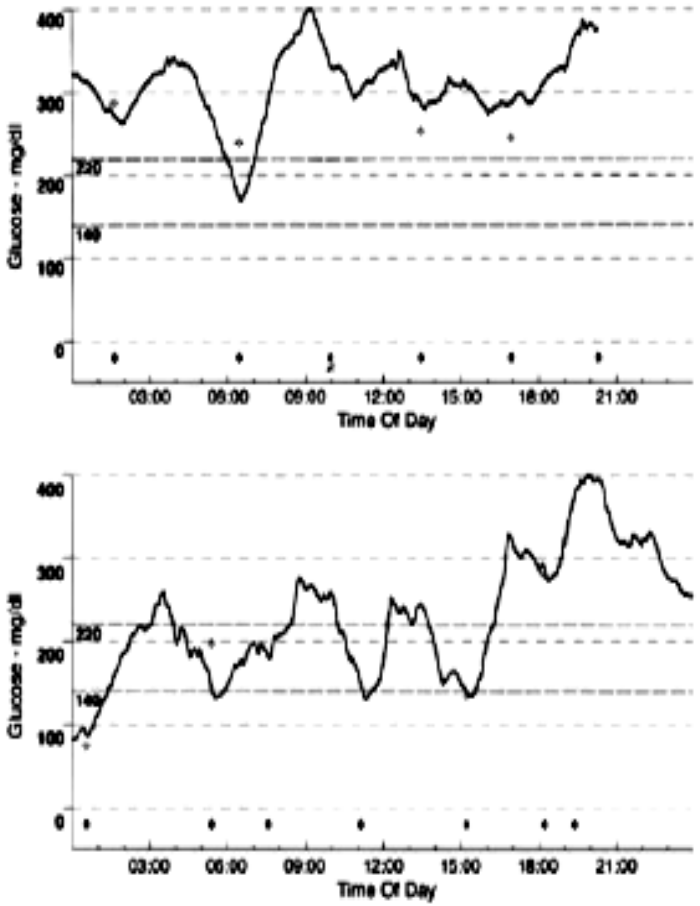



Ewan Pearson

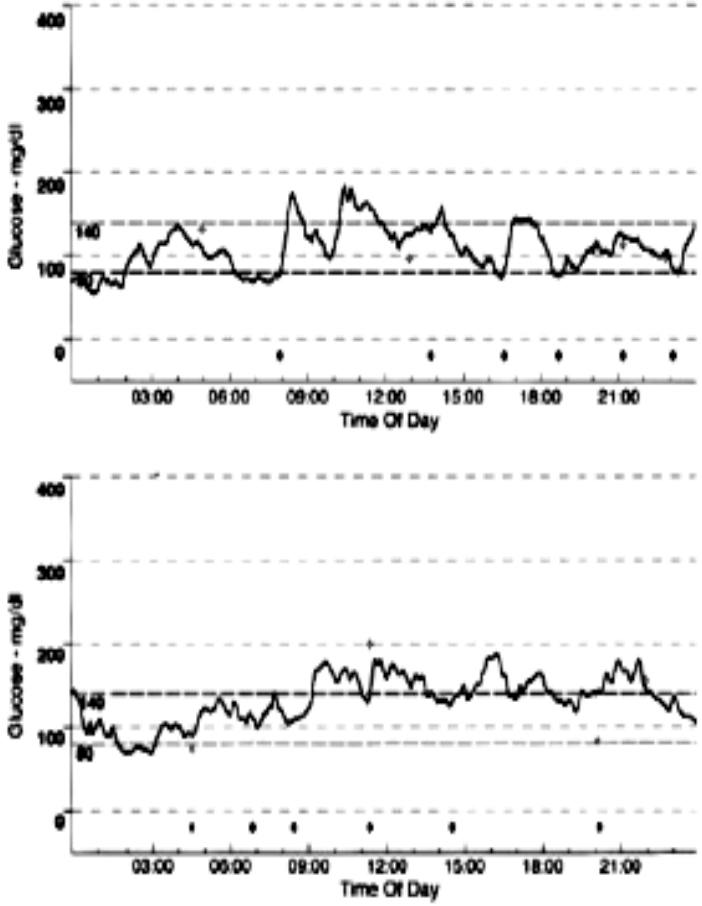
Pearson et al NEJM 2006

# Glucose values fluctuate less as well as being lower

Insulin pump

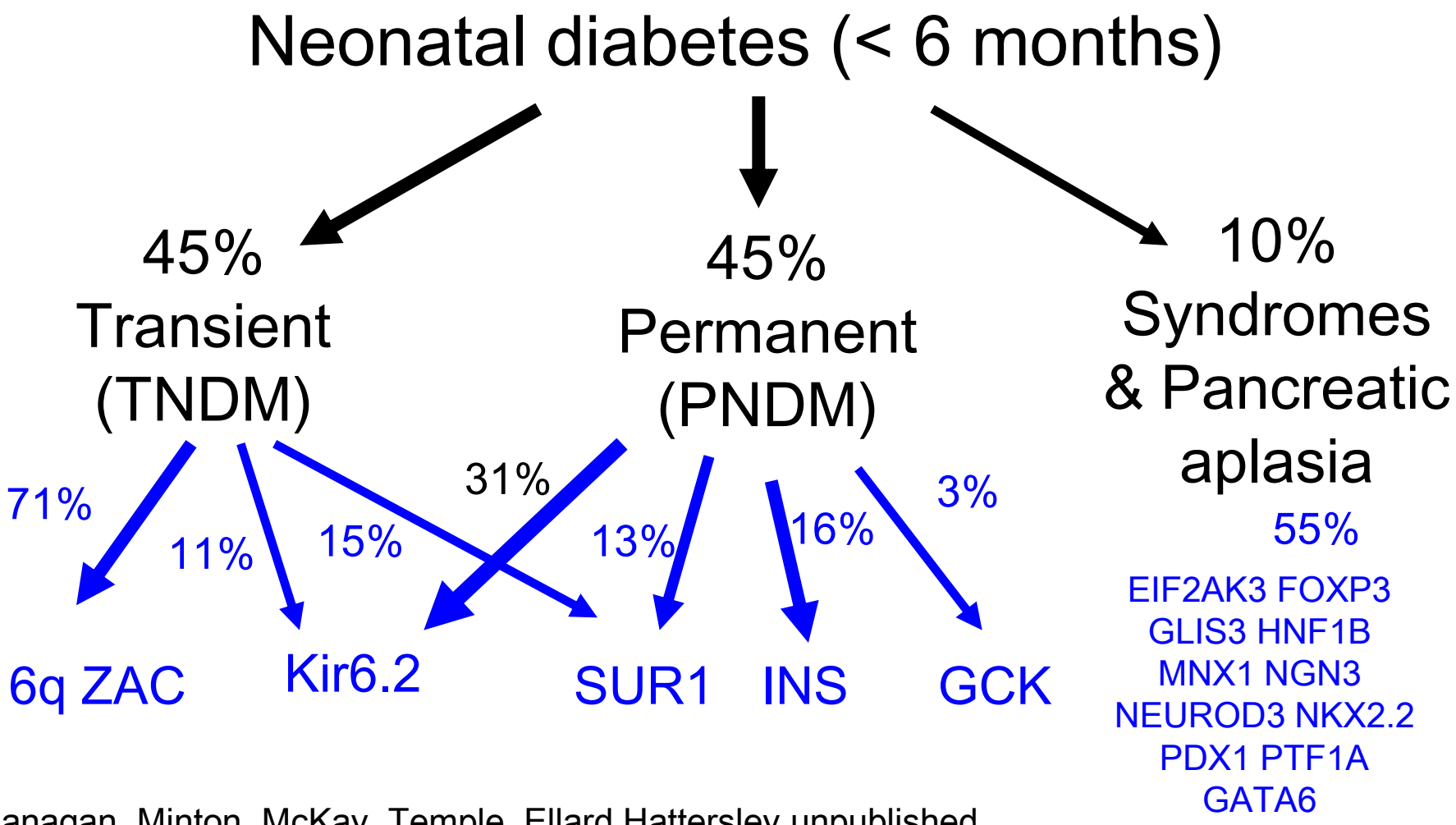



7.5 mg Glibenclamide




Zung et al JCEM 04

# Neonatal diabetes: in the post genetic era – more to come




Flanagan, Minton, McKay, Temple, Ellard Hattersley unpublished,

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# Slim Gestational diabetes and incidental paediatric hyperglycaemia

**Mother – Susan**

24 yr  UK Caucasian woman,

Gestational diabetes

Low dose Insulin treated in pregnancy only

“not diabetic” post pregnancy

6 week OGTT fpg 6.3 mmol/l  2hr 8.2 mmol/l

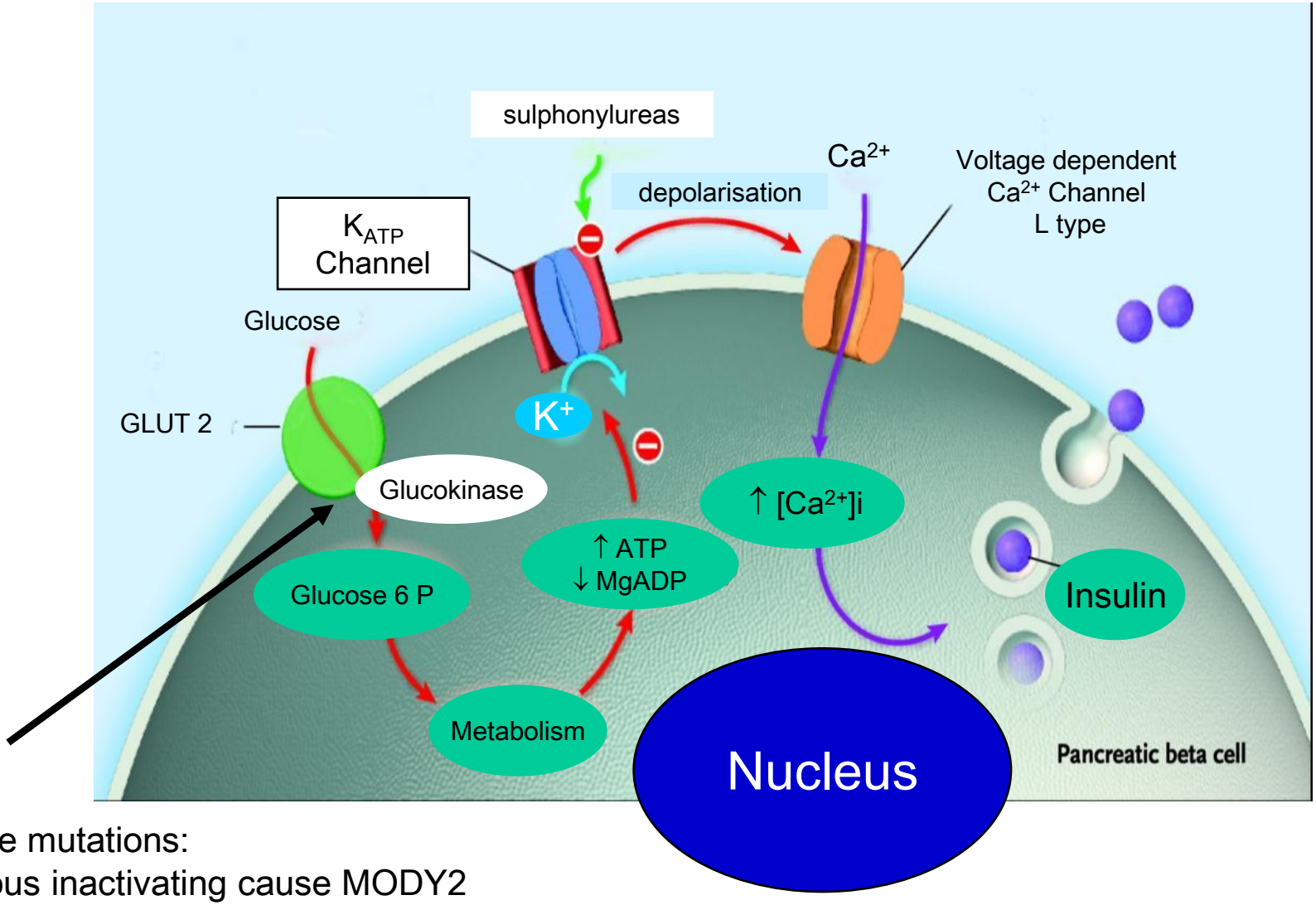
**Clare**

Baby 3200g 38 weeks Caesarean delivery

2 yr incidental hyperglycaemia RBG 10 mmol/l when admitted with Pneumonia.
Rpt. fasting when well
hyperglycaemia 6.6 mmol/l

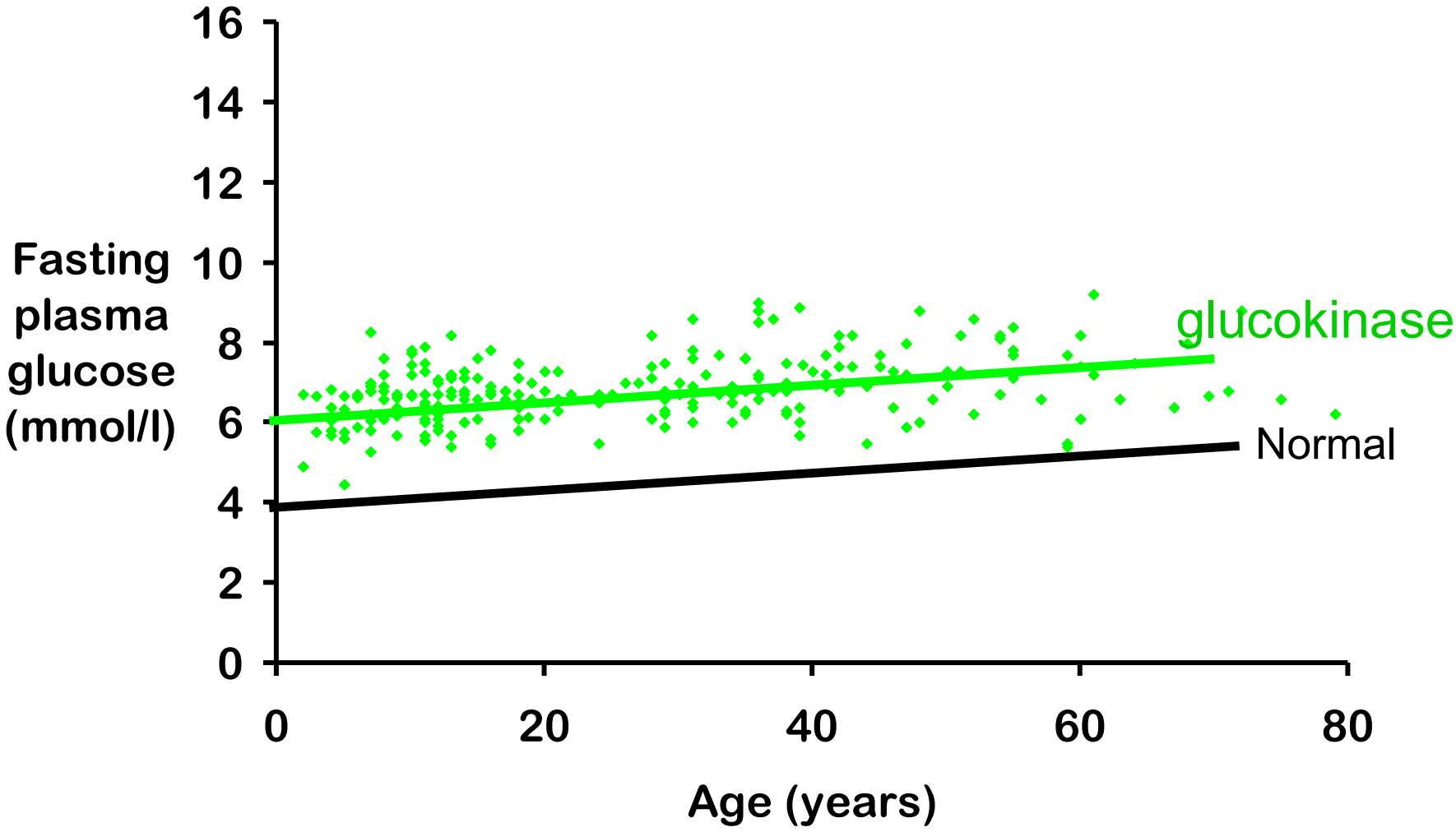
Glucokinase MODY

# Glucokinase – the pancreatic glucose sensor



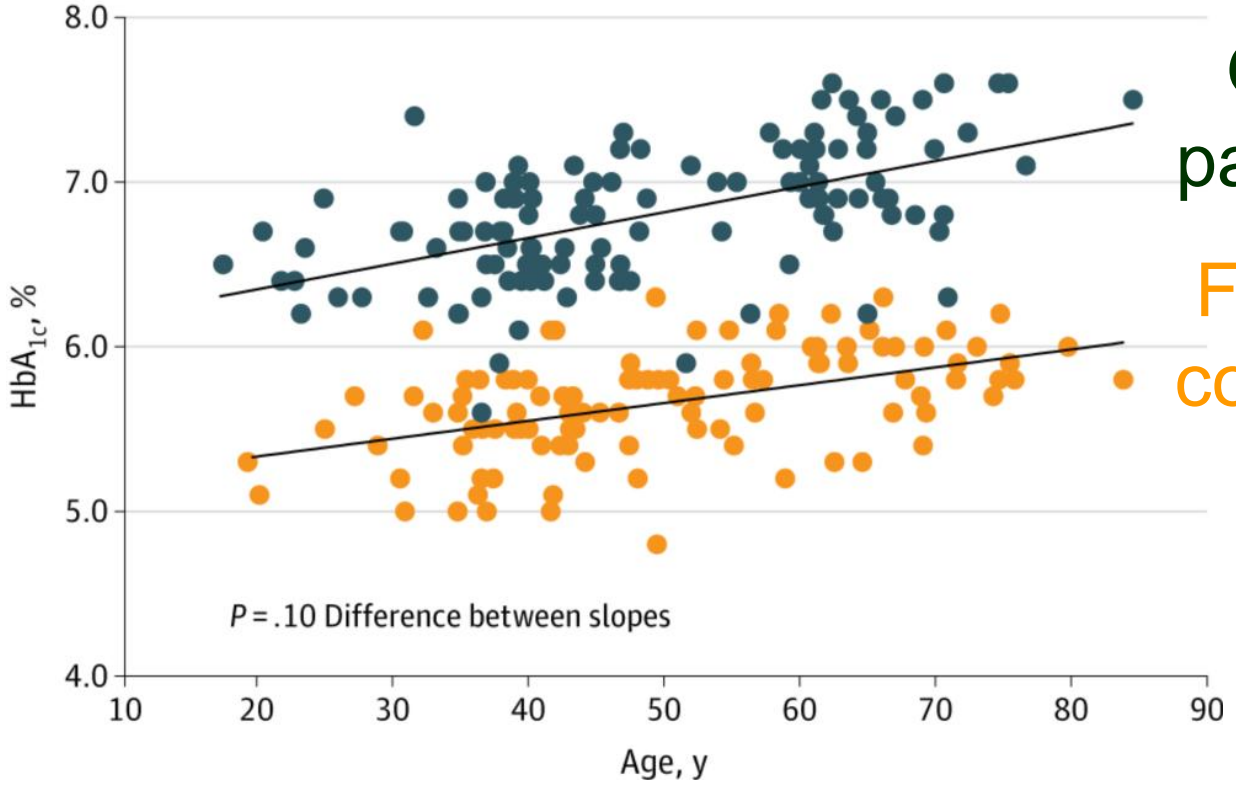

Glucokinase mutations:
Heterozygous inactivating cause MODY2

# Glucokinase - all patient have similar mildly raised fasting blood glucose values




European MODY Consortium (n =242) Stride et al Diabetologia 20

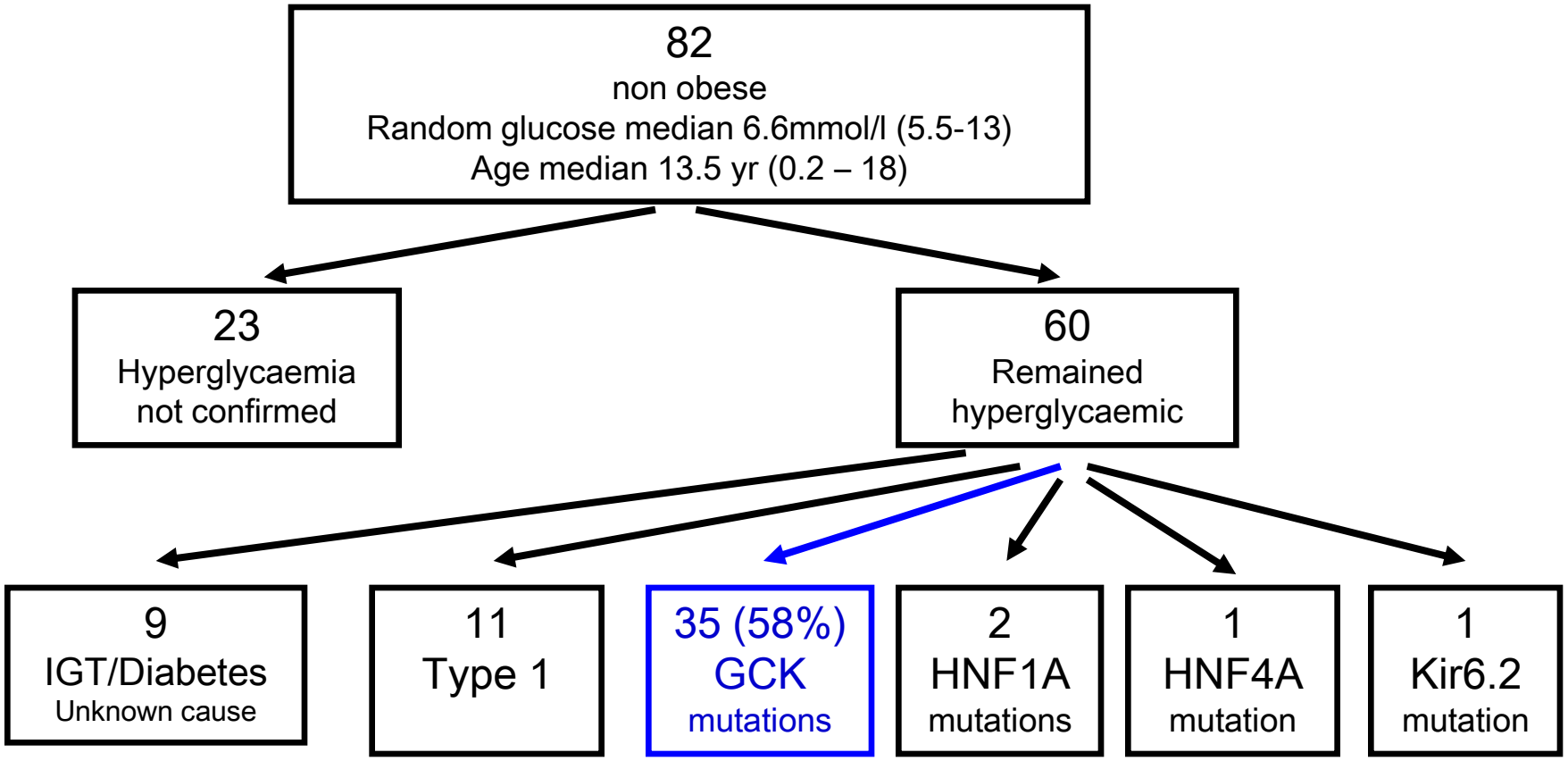
# Glucokinase - all patient have similar mildly raised fasting HbA1c




Steele et al JAMA 2014

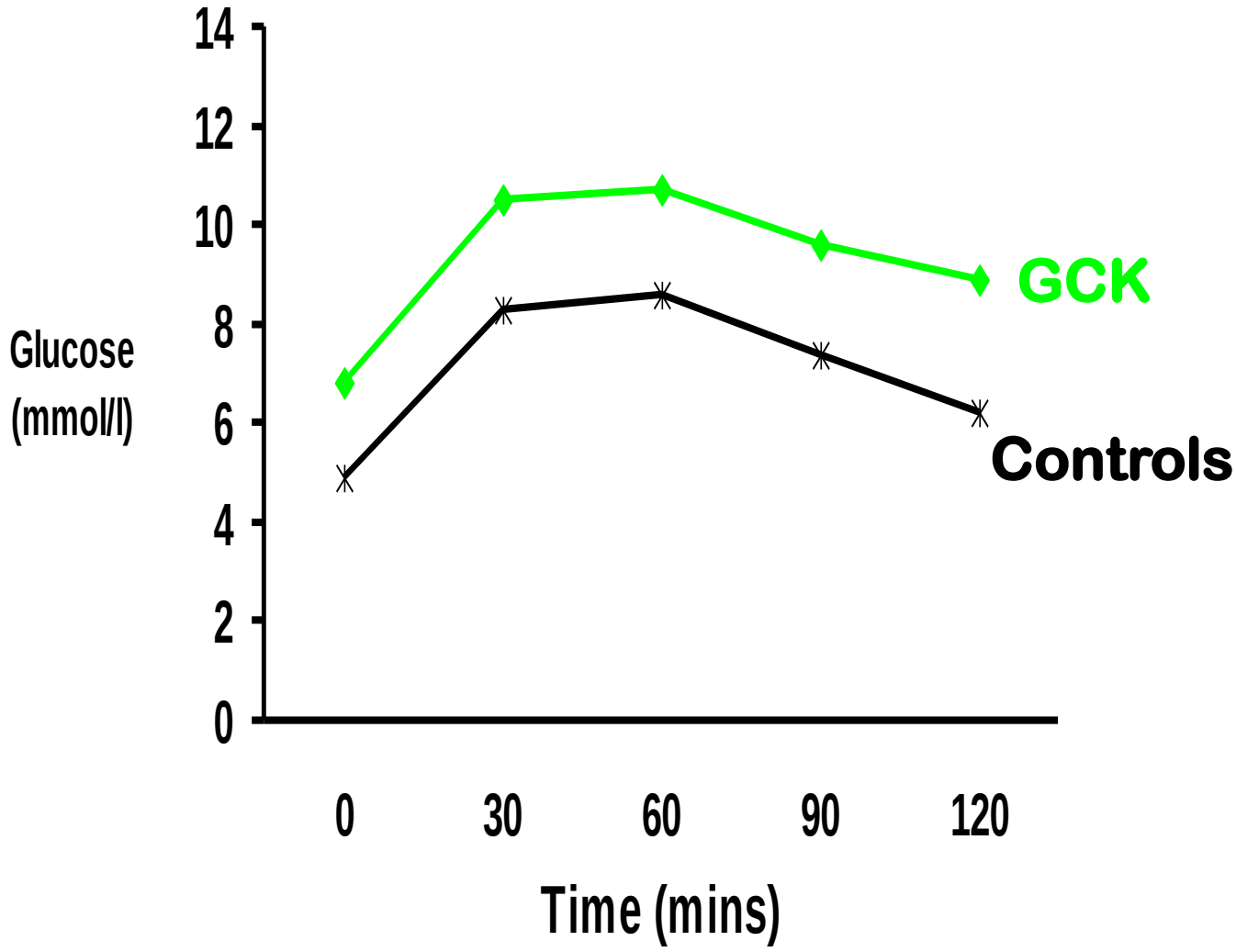
# Paediatric Incidental Hyperglycaemia

## Glucokinase mutations 1 in 1000 pop




Feigerlová et al Eur J of Paed 2006

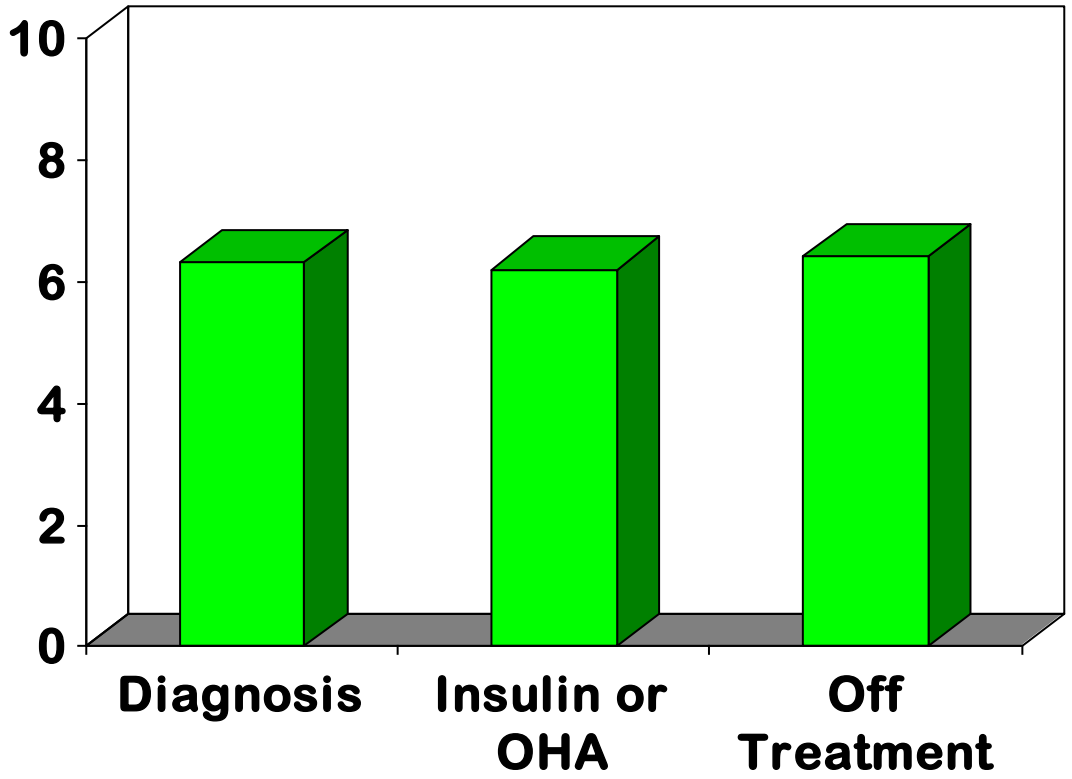
# Glucokinase patients regulate their glucose around a raised set point in OGTT




European MODY Consortium (n =245) Stride et al Diabetologia 2002

# GCK Patients do not need treatment 1

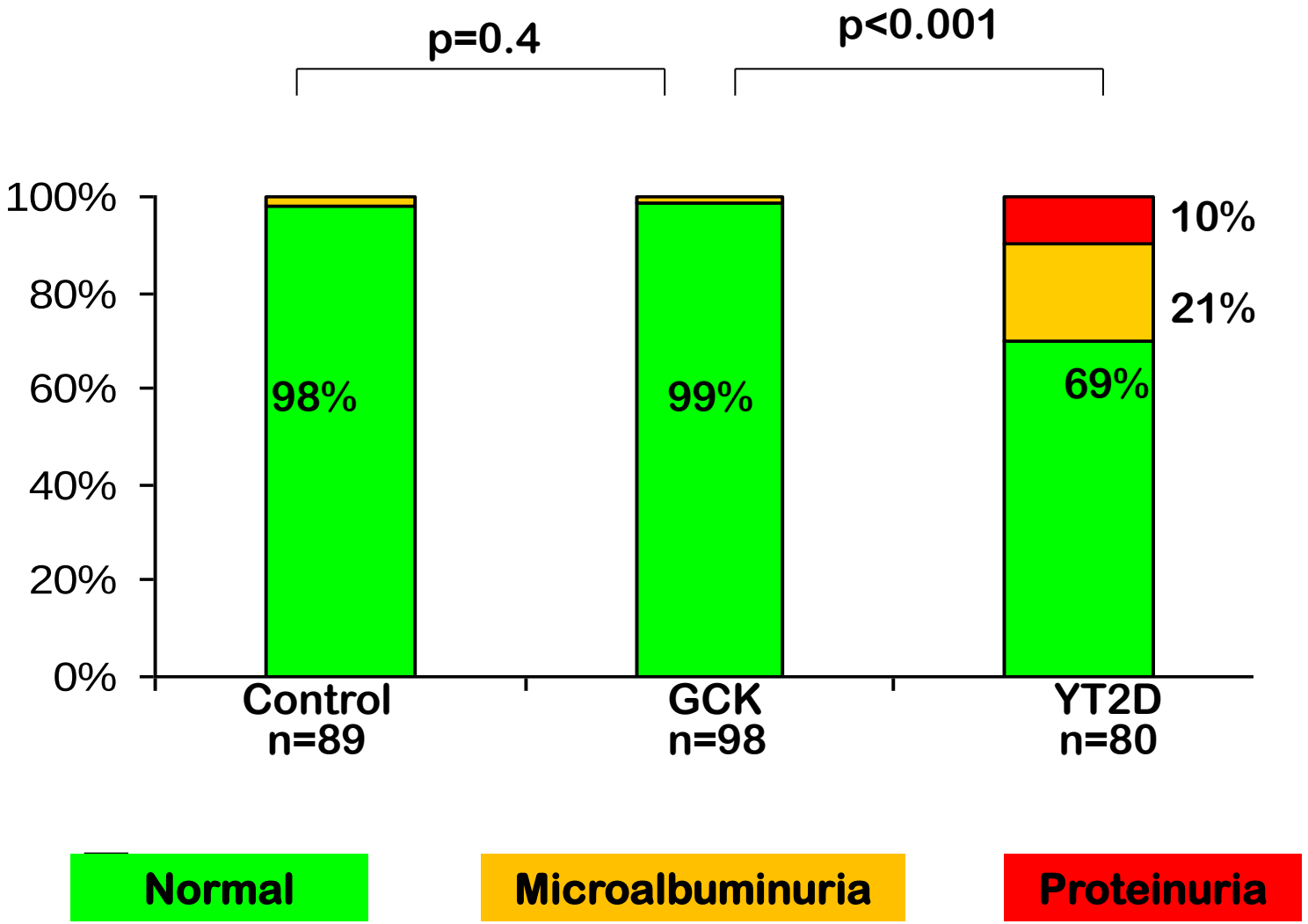
## HbA1c does not change on treatment in patients with GCK mutations (n=24)



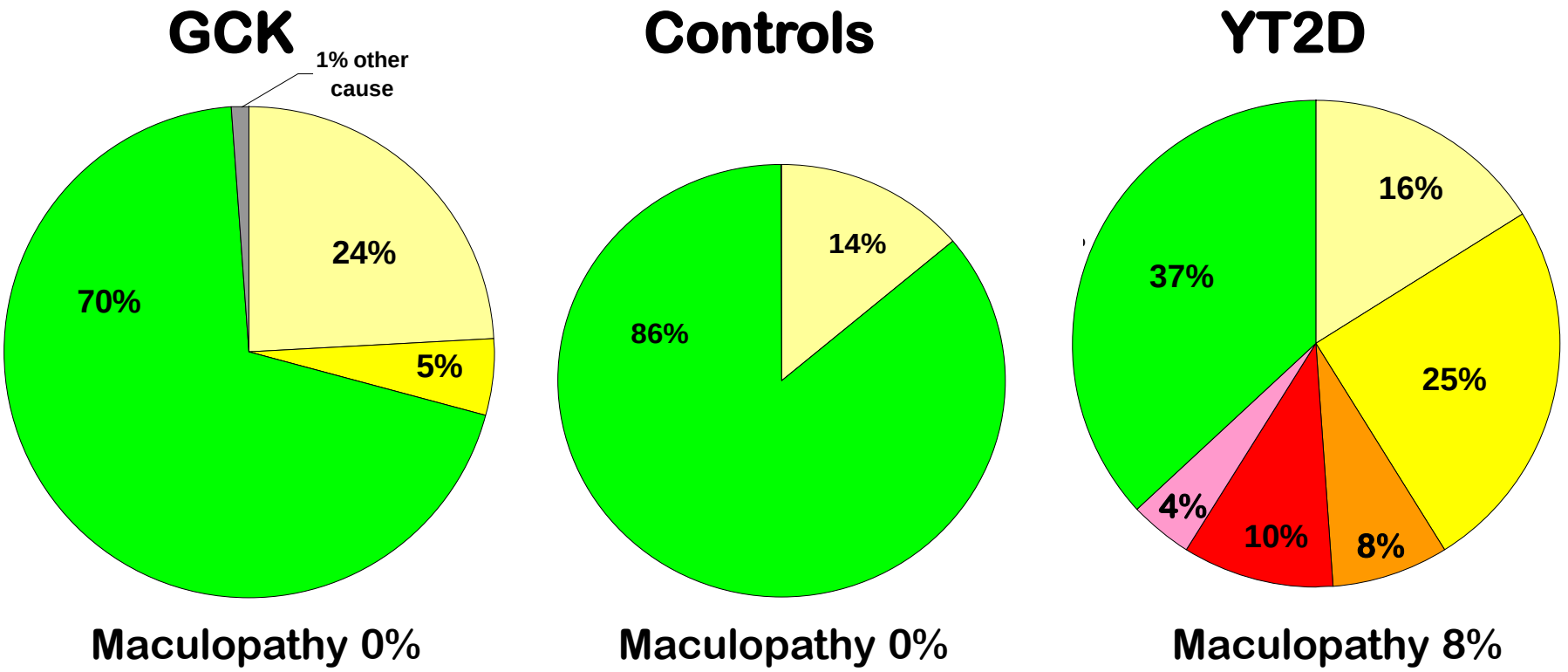

Stride Carey, Ellard & Hattersley unpublished

# GCK Patients do not need treatment 2

## GCK patients untreated for 50 yrs have no significant nephropathy



# GCK Patients do not need treatment 2:
## GCK patients untreated for 50 yrs have no significant retinopathy



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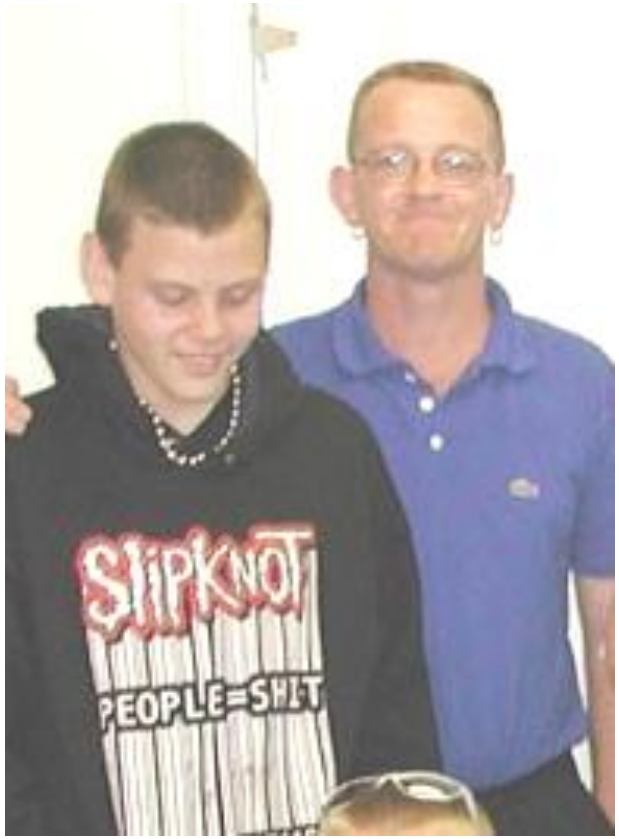
# Peter – Type 1 with diabetic parent




- 15 yr old boy
- Diagnosed with diabetes age 13
  rpg 21mmol/l
- BMI 19 kg/$m^2$
- Treated with basal bolus insulin 0.6U/kg
  HbA1c 8.2%
- Father T1D

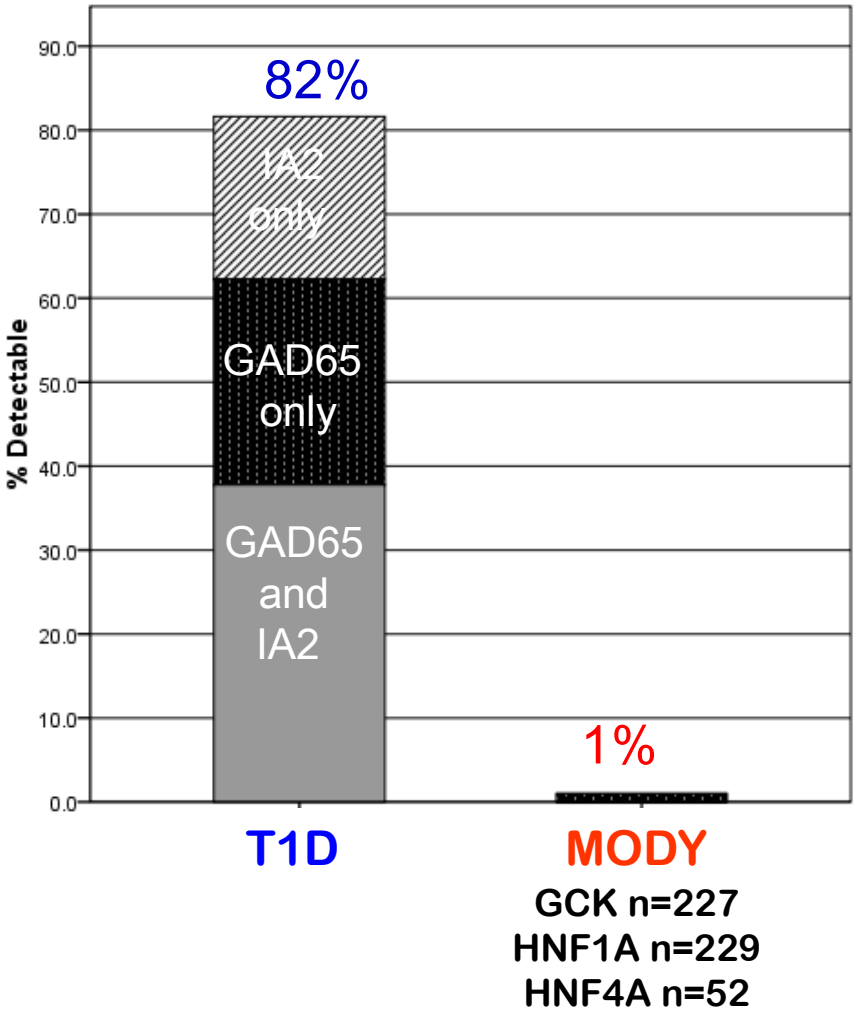
Familial Type 1 or HNF1A/4A MODY?

# Family history of diabetes


Autosomal dominant

“Type 1 and Type 2”

# GAD65 and IA2 antibody prevalence in recently diag. T1D (n=99) & MODY (n=508)

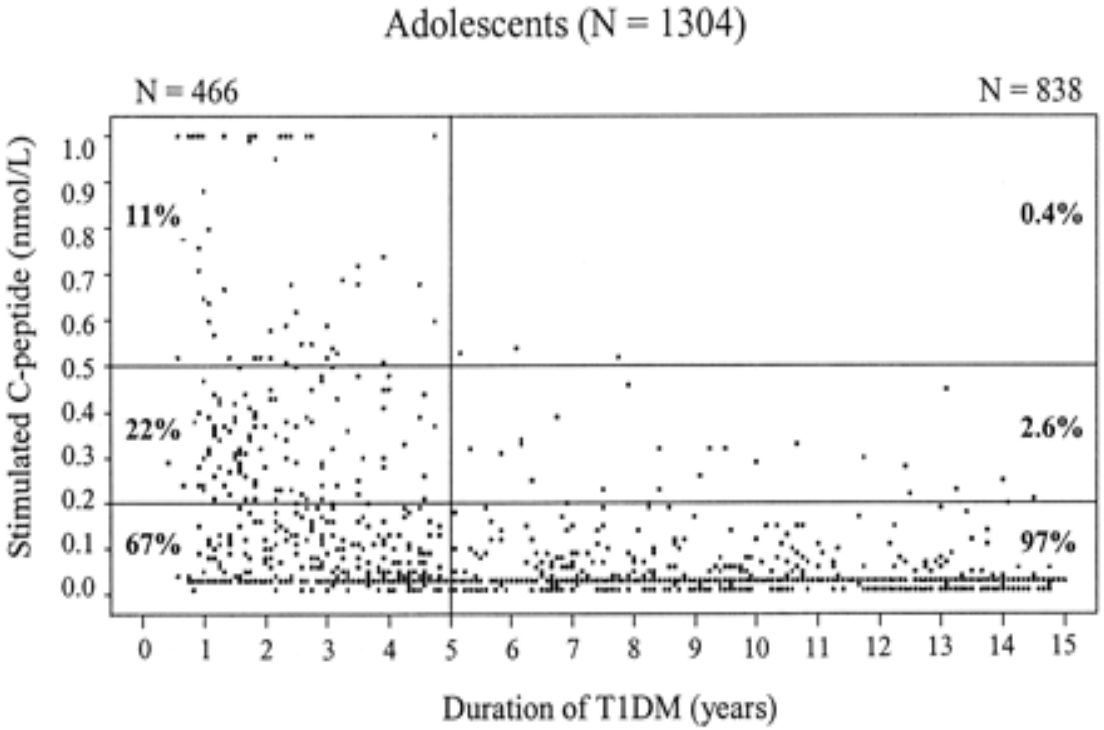



**Sensitivity 98%**
**Specificity 82%**

IA2 and/or GAD antibodies (99th cent > 50) make MODY very unlikely

McDonald Diabetic Med 2011

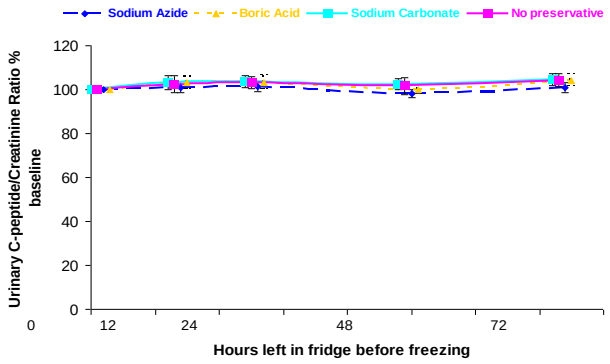
# Stimulated C-peptide response <0.2nmol/l helps to confirm diagnosis of Type 1 outside honeymoon



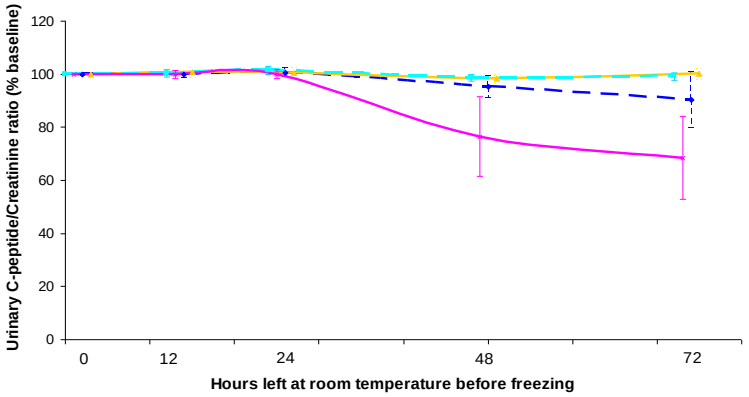

**However needs a Mixed Meal Tolerance Test (MMTT) so inpatient and blood test needing rapid spinning - rarely done**

# Urinary C peptide Creatinine ratio (UCPCrR) stable and reproducible alternative to blood

## at 4°C for ≥ 3 days



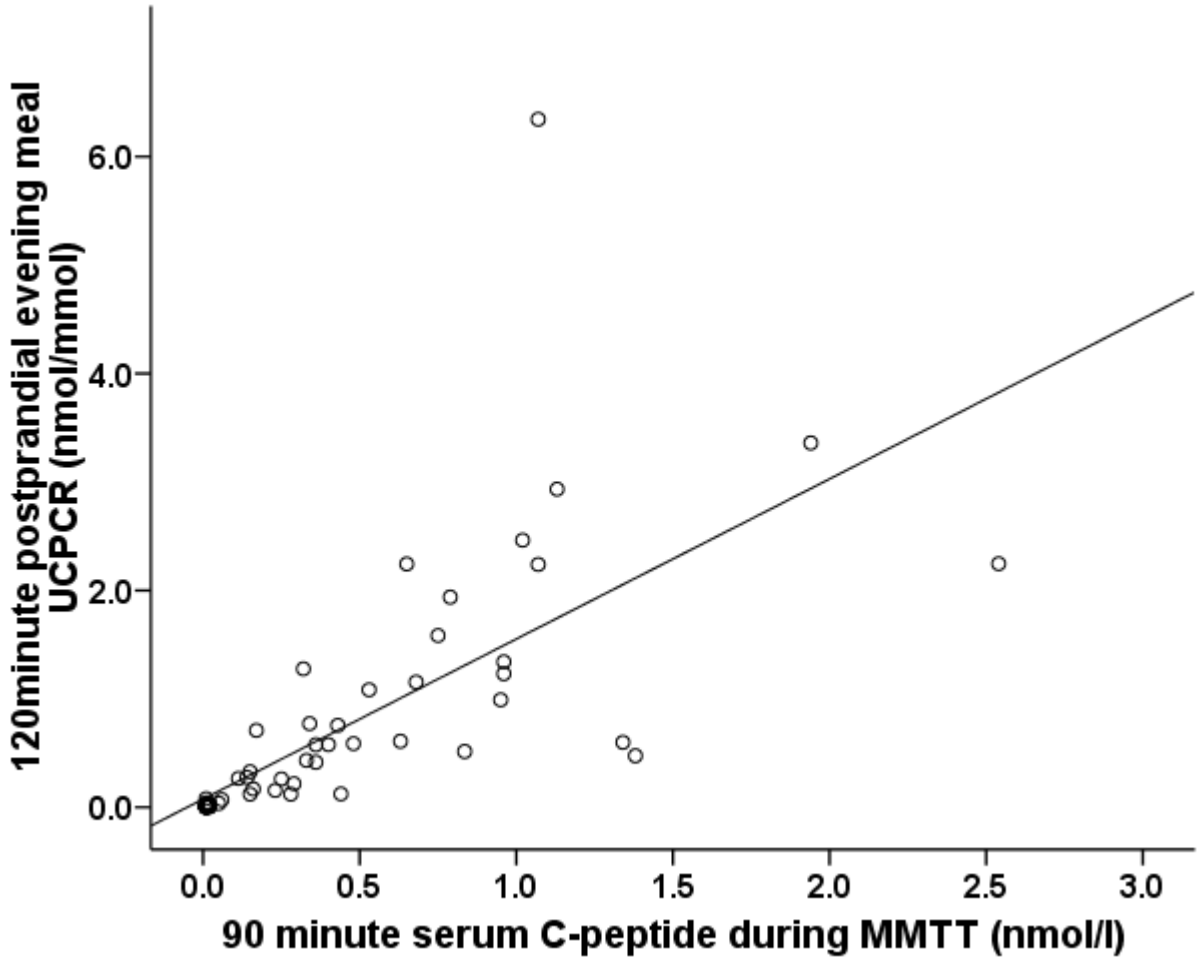

## at 20°C for ≥ 3 days in boric acid




Can get stimulated C-peptide value
by taking urine 2 hrs after a meal

McDonald Clinical Chemistry 2009

# A home postprandial UCPCR may be a non-invasive alternative in routine practice

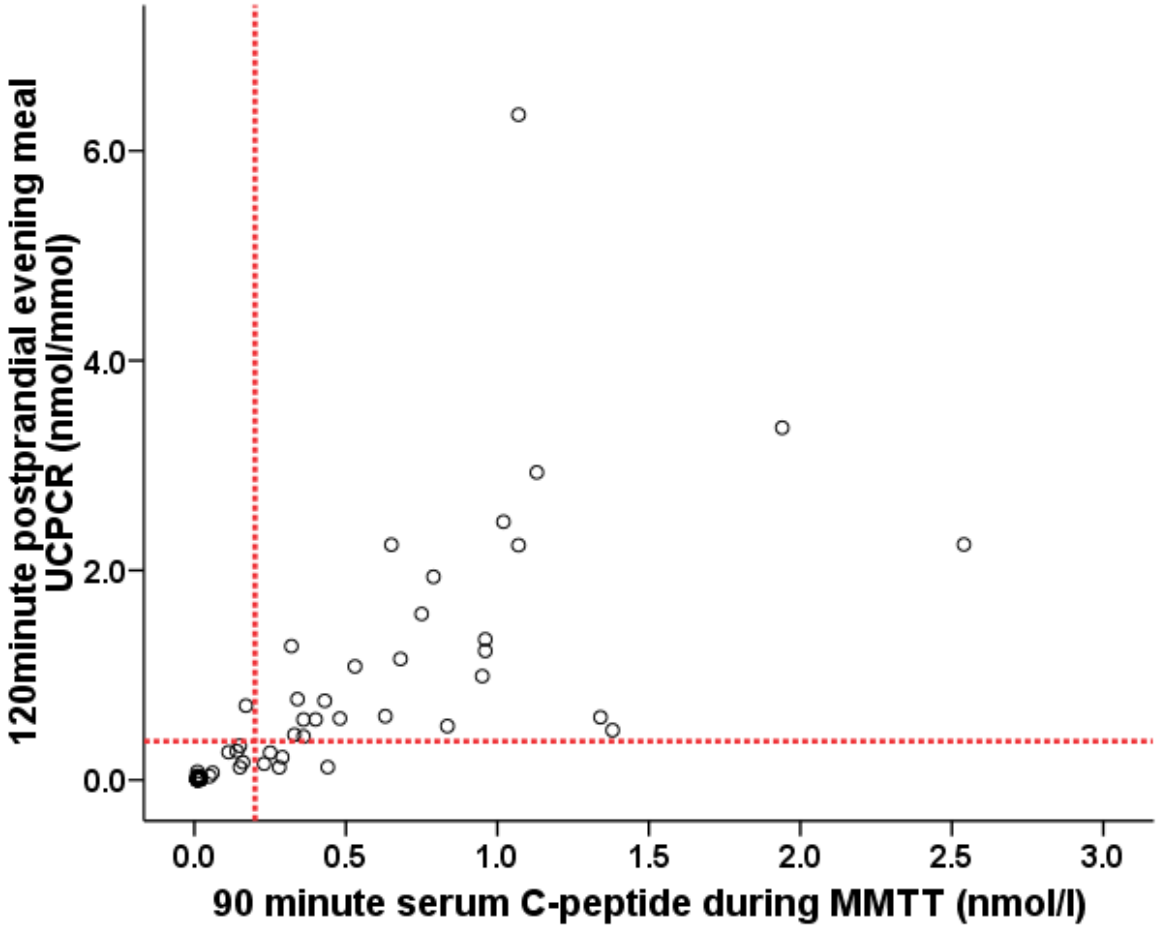



r= 0.91
p<0.0001

Besser et al Diabetes Care 2011

# Can define a cut off equivalent of serum C pep 0.2 nmol/l for UCPCR

0.20




ROC curve

AUC 0.97

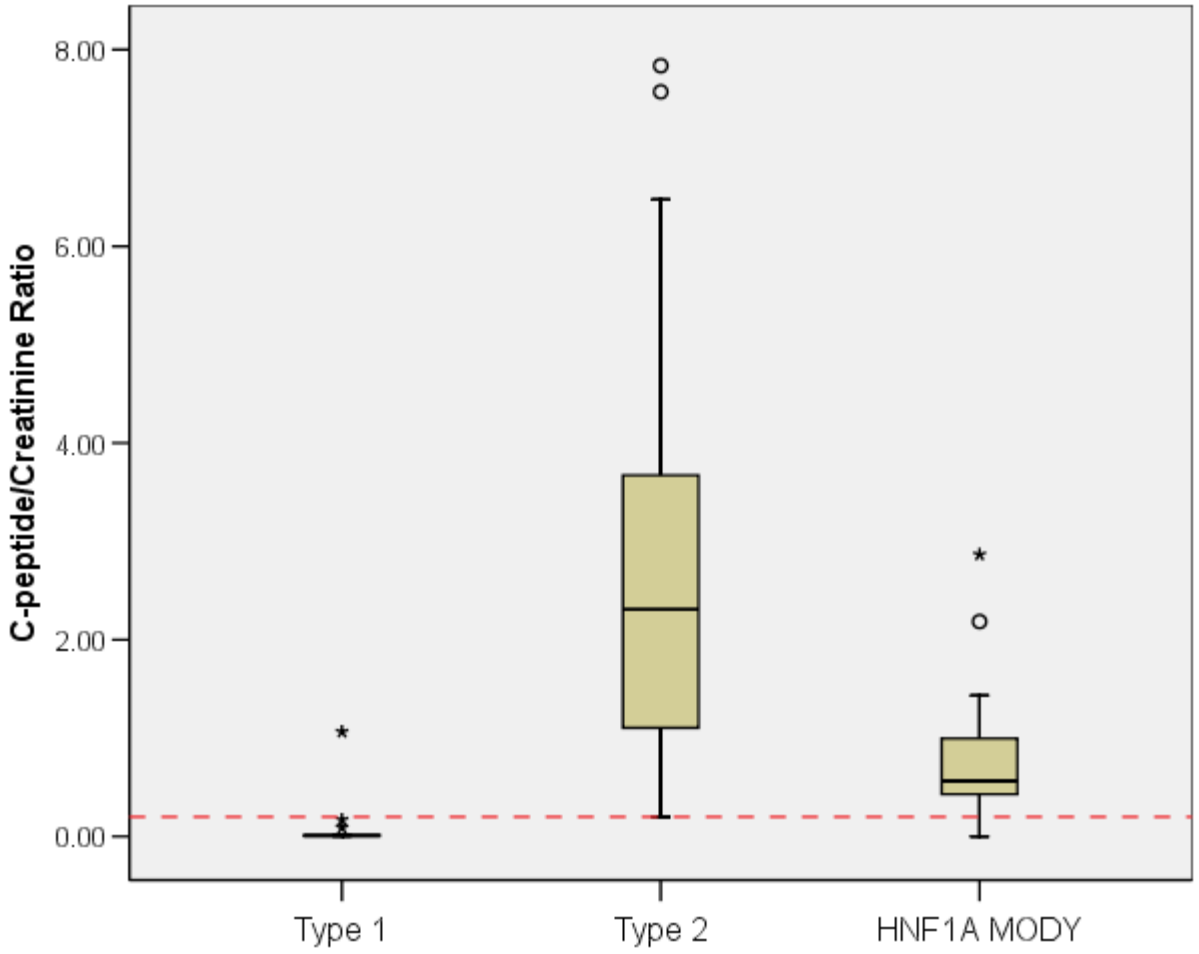
84% sensitive

97% specific

0.37

Besser et al Diabetes Care 2011

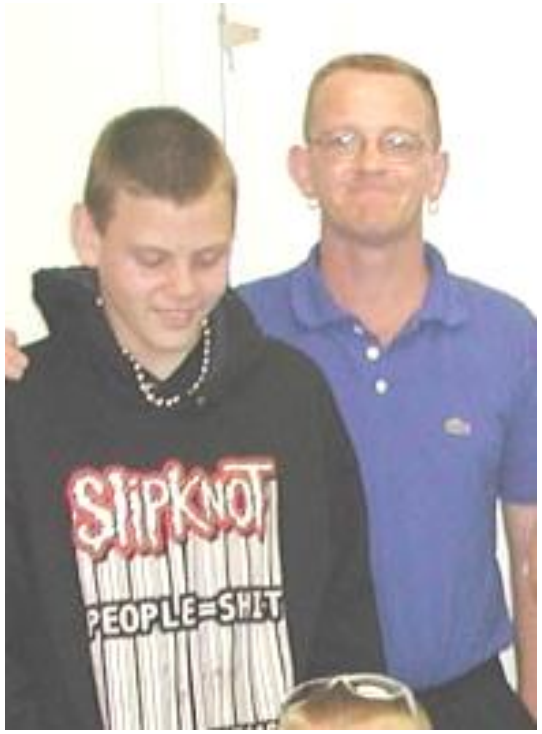
# UCPCr ratio allows differentiation of Type 1 from other subgroups > 5 years after diag.




UCP/Cr < 0.2
Sensitivity: 95%
Specificity: 95%

Besser et al Diabetes Care 2011

# Peter – Type 1 with diabetic parent



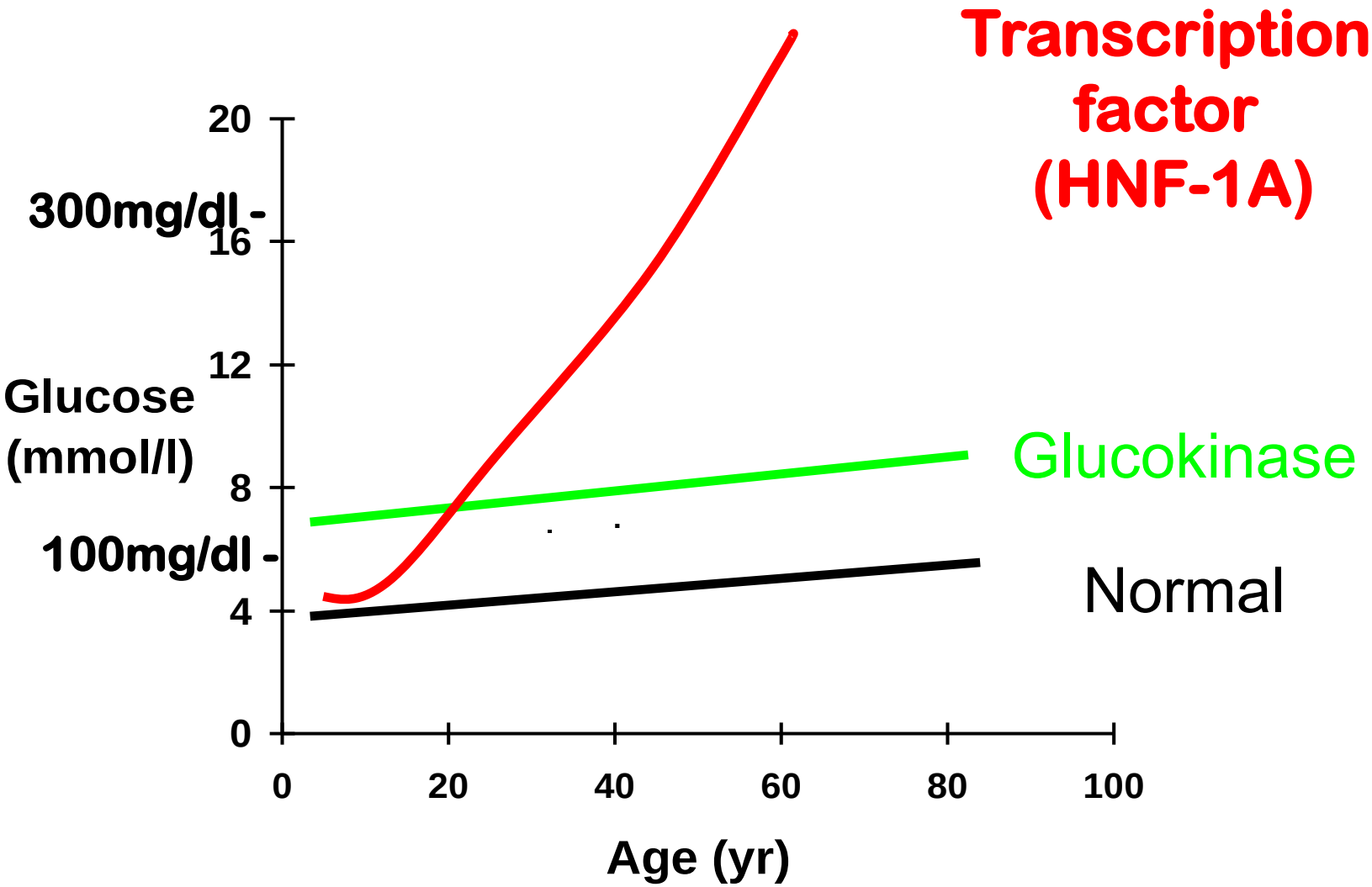

- 15 yr old boy
- Diagnosed with diabetes age 13
  rpg 21mmol/l
- BMI 19 kg/m$^2$
- Treated with basal bolus insulin 0.6U/kg
  HbA1c 8.2%
- Father diabetes 24 yrs insulin from diagnosis

GAD & IA2 Negative, UCPCR 1.7 (>0.2)

HNF1A mutation detected

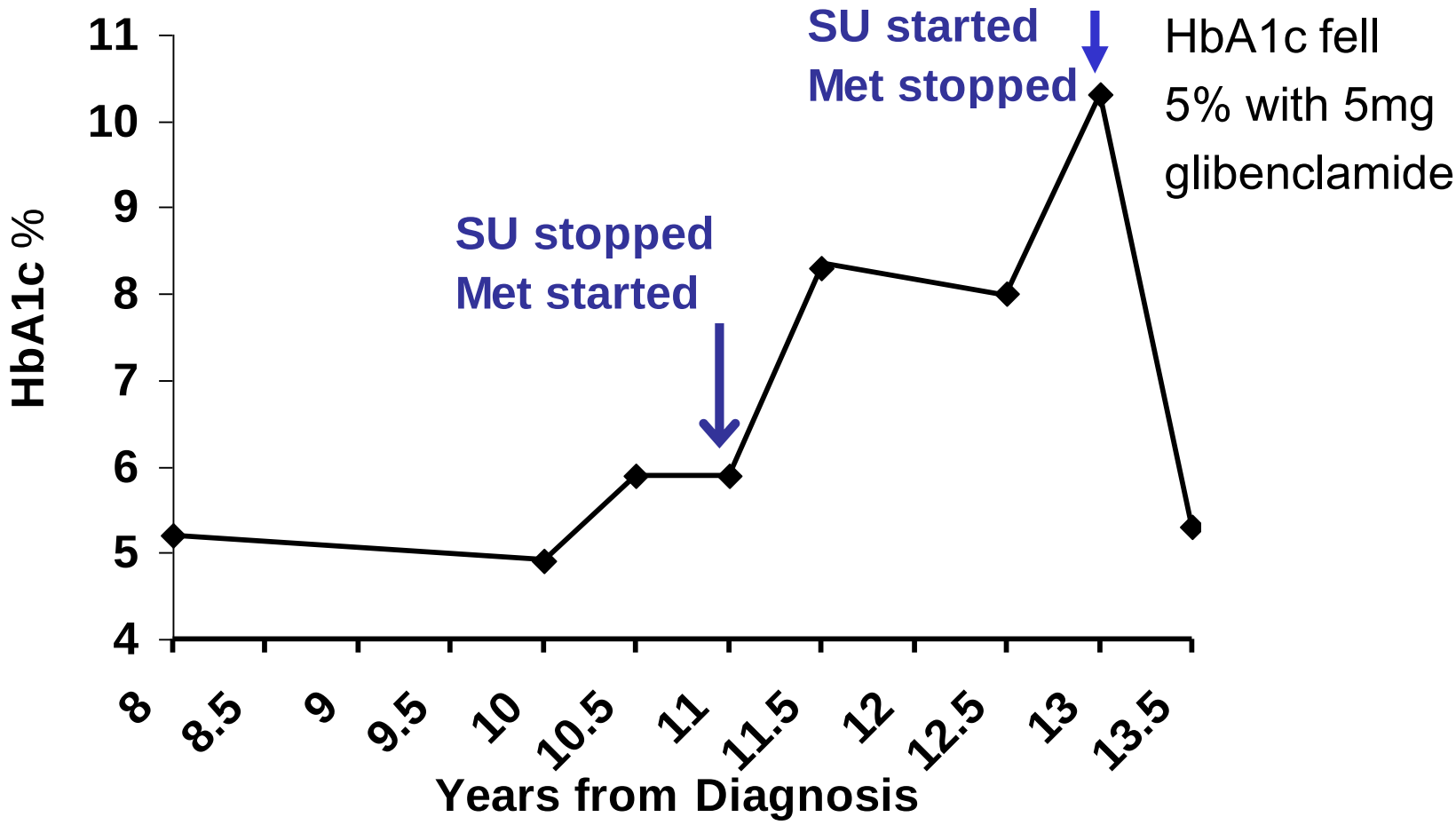
Treatment?

# Hepatic Nuclear factor 1-a diabetes deteriorating glycaemia with age



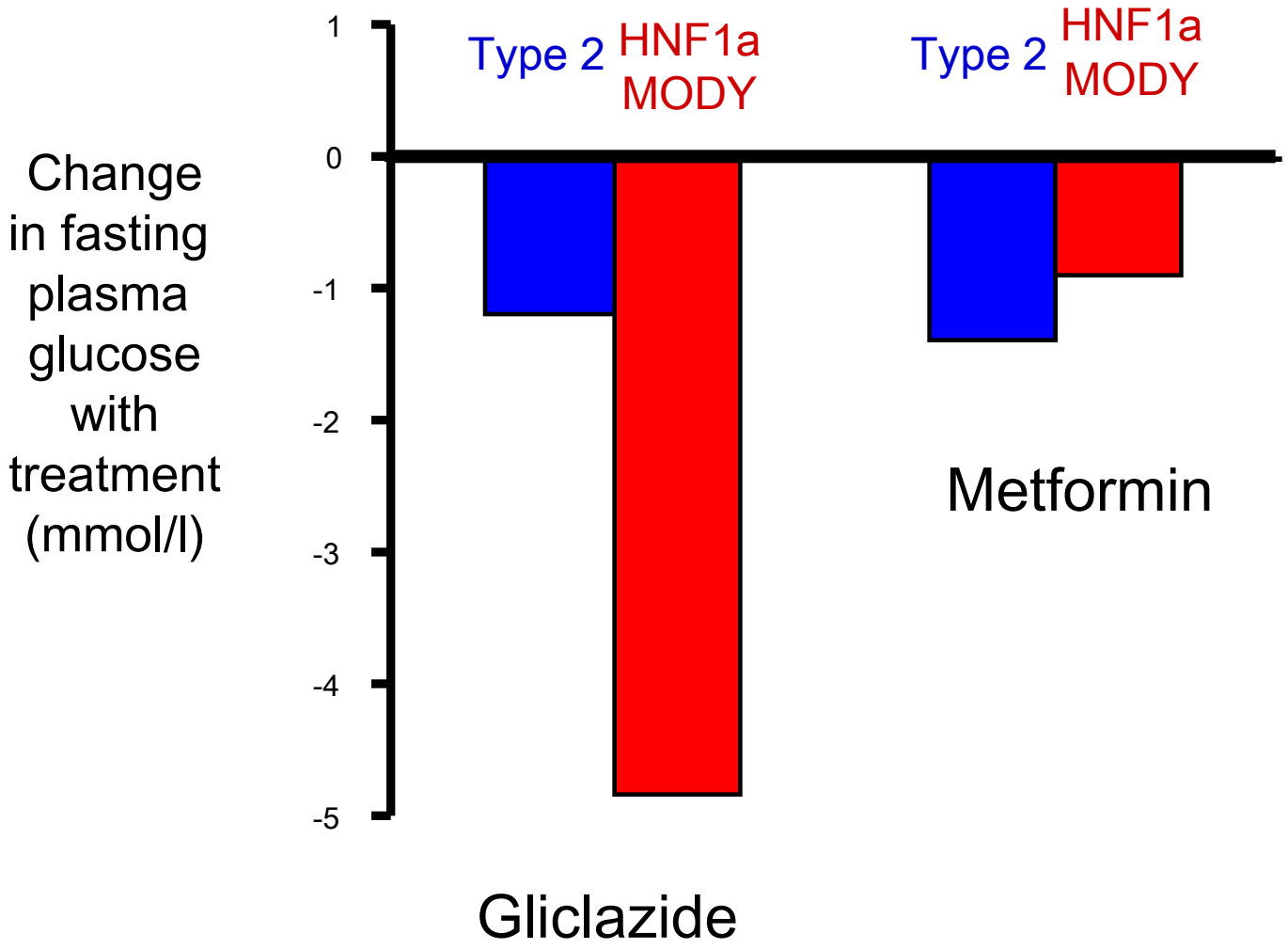

Stride & Hattersley Annals of Medicine 2002

# Sulphonylurea sensitivity in a patient with an HNF1A mutation



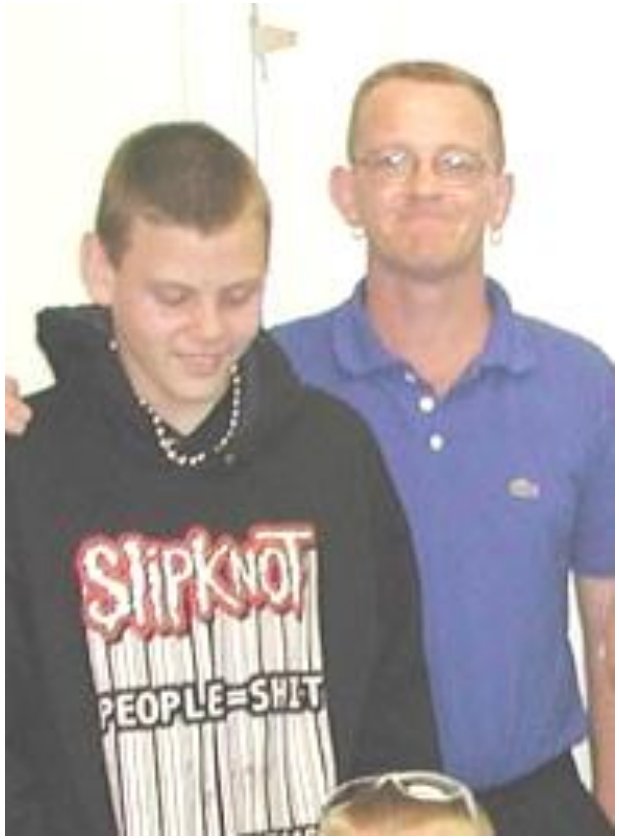

Pearson et al. Diab Med 2000

# HNF1A patients respond much better to Gliclazide than Type 2 patients




Pearson et al Lancet 2003

# Peter – antibody negative C peptide positive Type 1 with diabetic parent

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  rpg 21mmol/l
- BMI 19 kg/$m^2$
- Treated with basal bolus insulin 0.6U/kg
  HbA1c 8.2%

- HNF1A mutation diagnosed

HbA1c 6.8% 40 mg gliclazide

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# James: “Young T2D”

15 yr  UK Caucasian,

Diag Type 2

- random glucose 13 mmol/l
- mild symptoms
- picked up by mother
- BMI 27 kg/$m^2$
- HbA1c 7.8% on Metformin

- FH Mother (31yr), Maternal uncle (28yr), Mat grandfather Type 2
- IA2 and GAD negative

Is this Type 2 or MODY?

| | MODY | Type 2 | Type1 |
|---|---|---|---|
| Non insulin dependent | Yes | Yes | No |
| Parents affected | 1 | 1-2 | 0-1 |
| Age of onset < 25yr | Yes | Yes | Yes |

**MODY diagnostic criteria separate well from Type 1 but not from Type 2 in paediatric clinic**

| | MODY | Type 2 | Type1 |
|---|---|---|---|
| Non insulin dependent | Yes | Yes | No |
| Parents affected | 1 | 1-2 | 0-1 |
| Age of onset < 25yr | Yes | unusual | Yes |
| Obesity | +/- | + + + | +/- |
| Acanthosis Nigricans | - | + + | - |
| Racial groups (Type 2 prevalence) | low | high | low |

Obesity, Acanthosis and racial group help differentiate MODY from young adult/paed T2D
If in doubt TEST as major difference in treatment!

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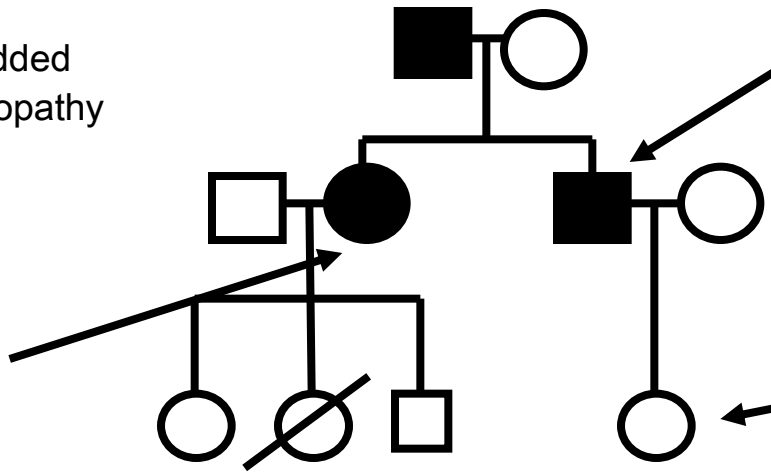
# Familial young-onset diabetes and hypoglycaemia

BMI 26.5
Δ 28yr now 58
OHA initially
recently insulin added
Background retinopathy

BMI 24
Δ 28yr Vasculitis,
Asymptomatic diabetes
Rx insulin, when on steroids
GAD and ICA negative
6/12 insulin stopped – fpg 5-7,
HbA1c 5.5%



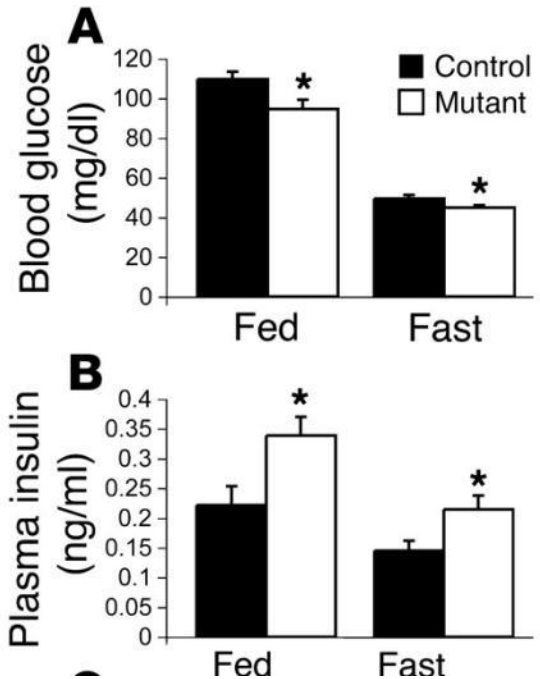
BMI 25
Δ 15yr now 33
Insulin from diagnosis
HbA1c 8.2%

HNF4A mutation in all 4 family members

Macrosomia - birth weight 4.9 kg
Hypoglycaemia - glucose 1.2 mmol/l
Hypoglycaemia persisted- 1.8 mmol/l
hyperinsulinaemia 117pmol/l
treated Diazoxide 6/12

# Neonatal Transient Hypoglycaemia in HNF4A mutation carriers

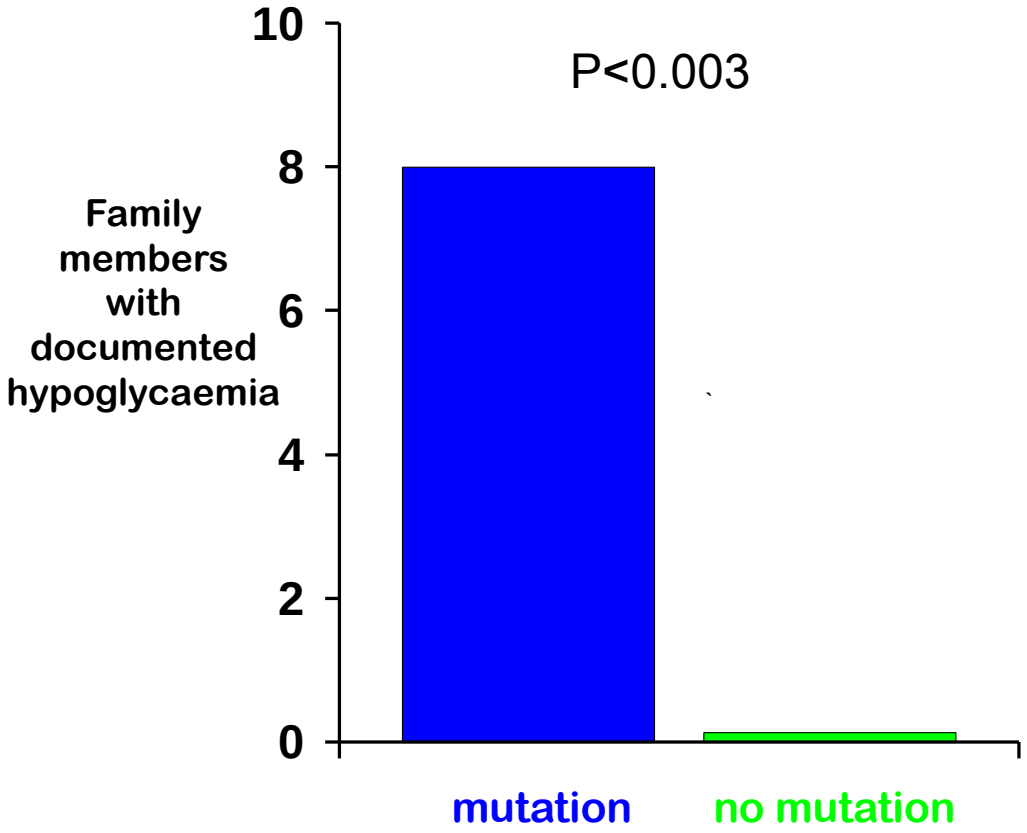
**beta-cell specific KO HNF-4a mice initial hyperinsulinaemia and latter IGT**




**Initial beta-cell defect increases insulin secretion**

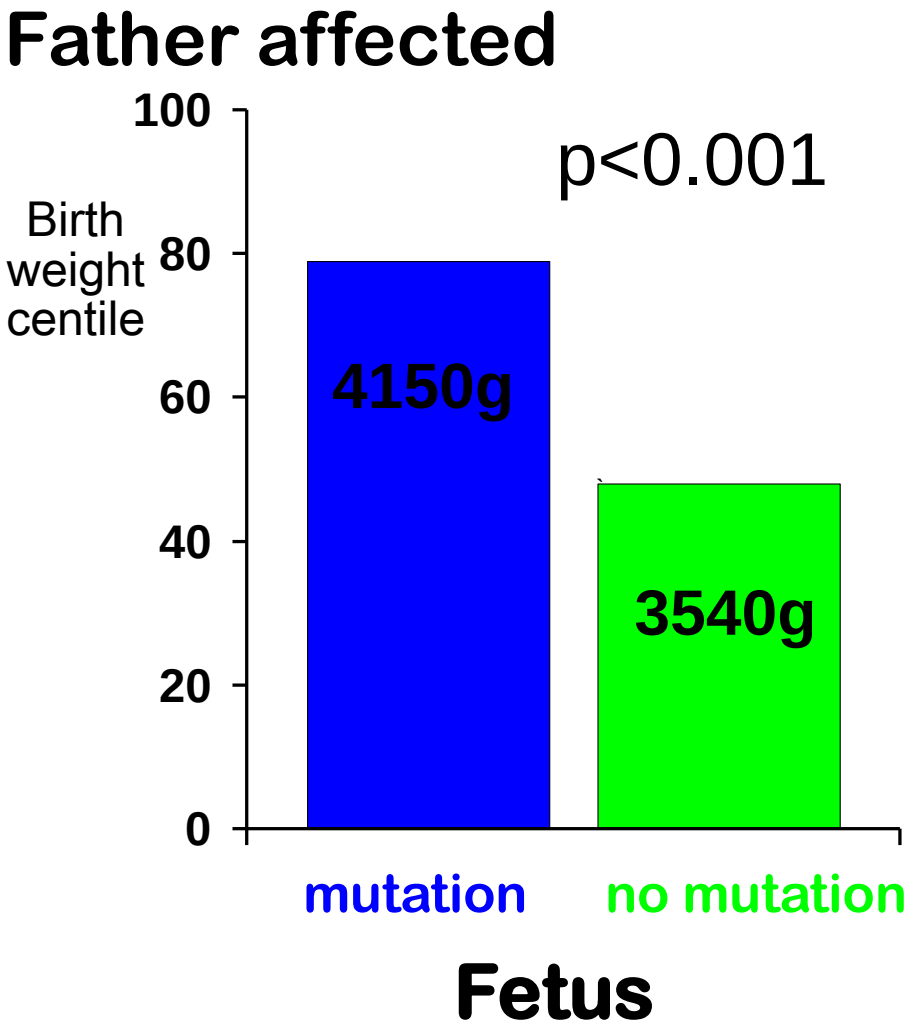
Gupta, R. K. et al. JCI.2005;115:1006-1015

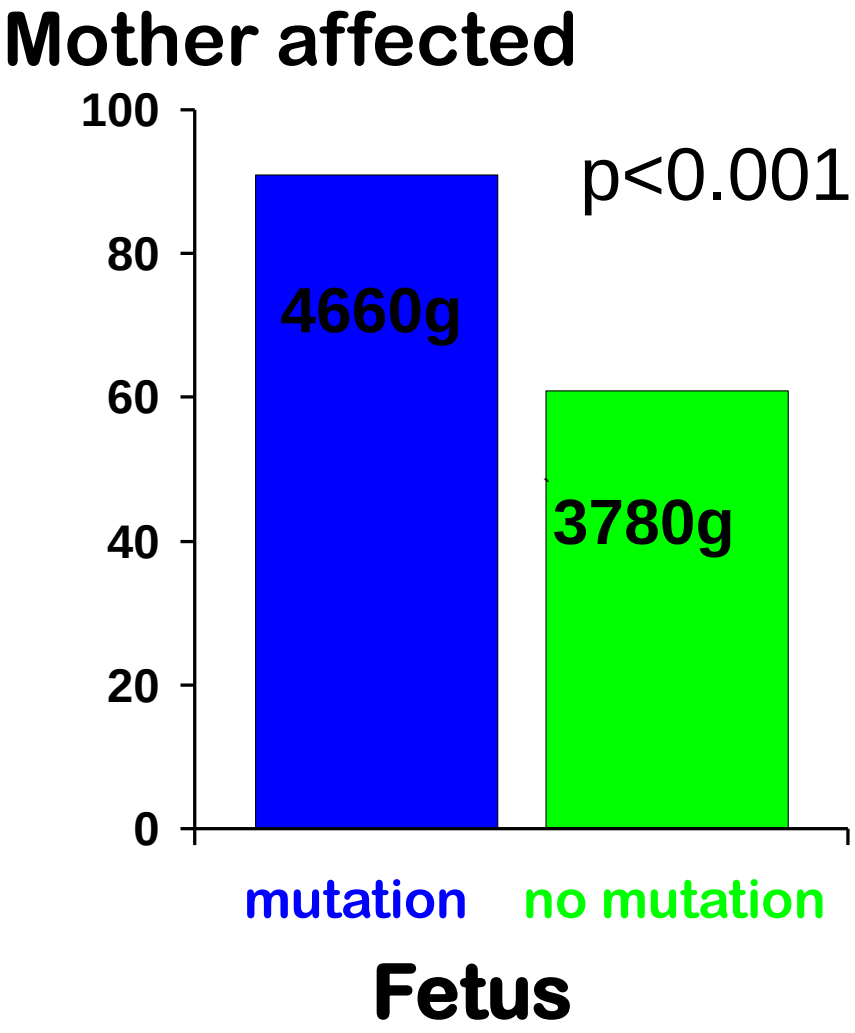
**Neonatal Hypoglycaemia (<2.0 mmol/l >48 hrs) common in HNF4A mutation carriers**




Pearson et al PLoS Medicine 2007

# Birth weight is increased by 800g with fetal mutations in HNF4A families




Pearson et al PLoS Medicine 2007

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# Paul: Renal cysts and diabetes

- 15 yr old boy
- Referred by renal team
  rpg 21mmol/l
  long standing renal impairment
  renal cysts  in utero
- BMI 19 kg/$m^2$
- Treated with basal bolus insulin
  0.6U/kg
  HbA1c 8.2%

Hepatic Nuclear Factor 1B mutation

# HNF-1B mutations/deletions: a new syndrome Renal Cysts And Diabetes (RCAD)

## Renal cysts

- Frequently seen on anti-natal scanning
- Renal function variable – 40% endstage renal failure
- Commonest known aetiology for developmental renal disease. Different renal histologies including glomerulocystic kidney disease.

## Diabetes

- Diagnosis 22 (10 - 47) yr, usually on insulin

## Other features

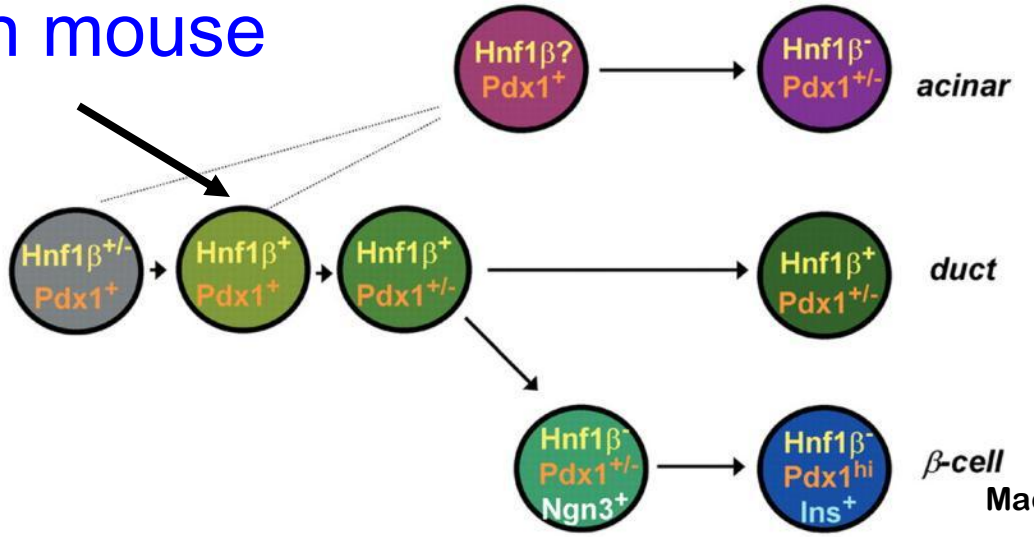
- Uterine and genital developmental abnormalities, abnormal LFTs, gout, low magnesium, insulin resistance

Horikawa Nature Genetics 1997, Nishigori et al Diabetes 1998, Lindner et al 1999 Hum Mol Gen, Bingham et al 2000 Kidney Int, Bingham et al 2001 AmJ Hum Gen, Bingham et al 2002 Kidney Int, Edghill Human Genetics 2005, Bellane-Chantelot 2005 Diabetes

# HNF-1B critical in early pancreatic development

## HNF1B in mouse

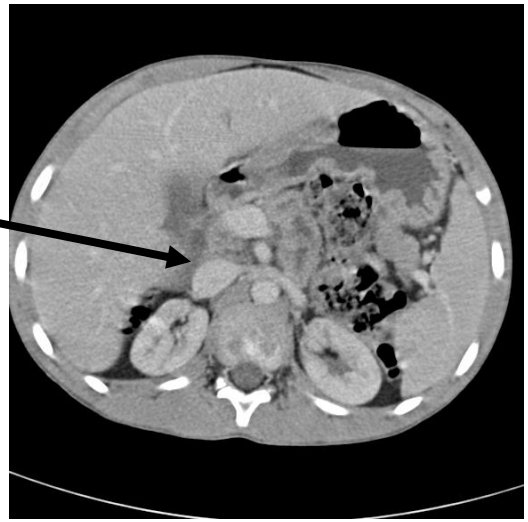
Pancreatic precursor cells



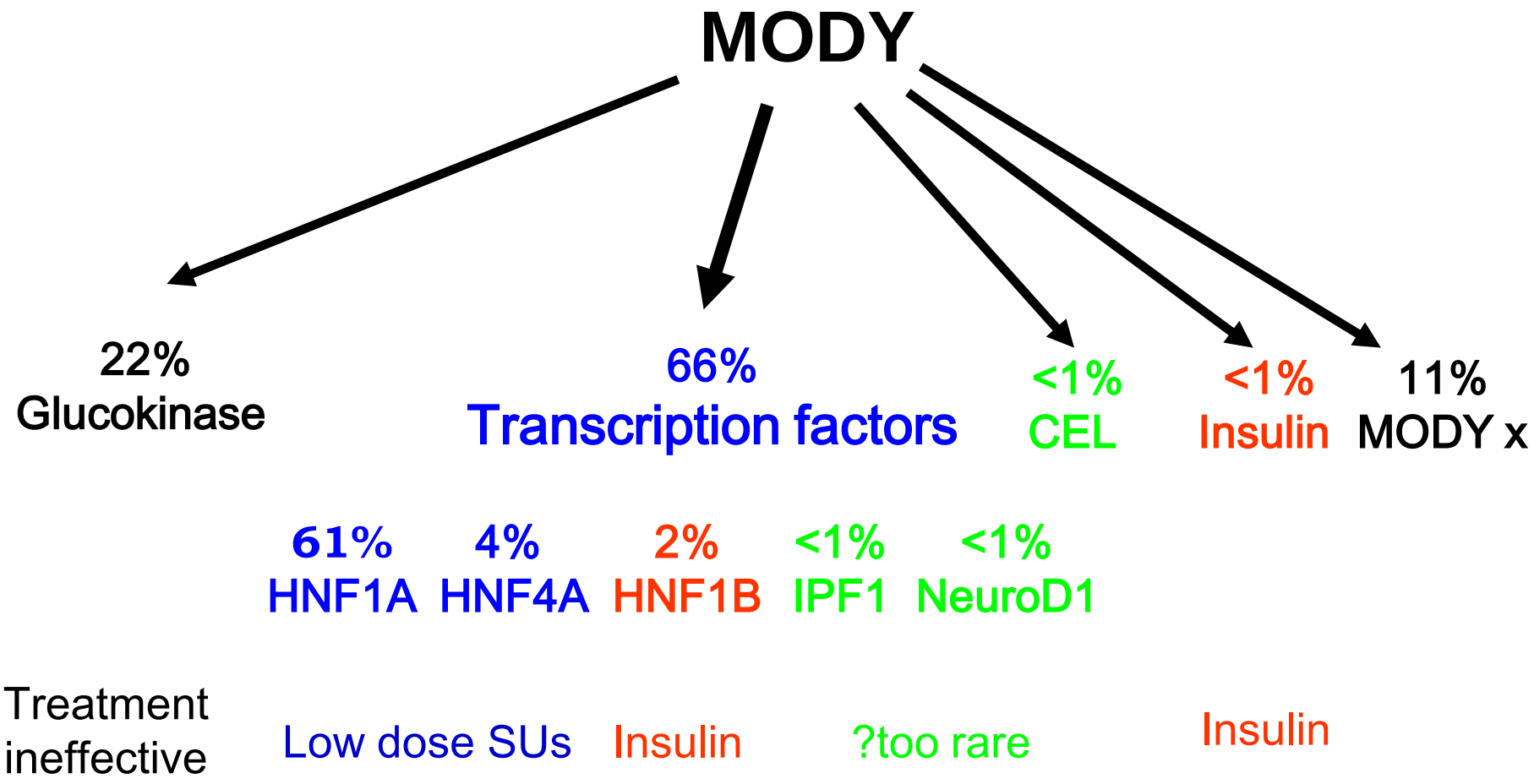

Maestro M *et al,* HMG 2004

## Explains Patient Features

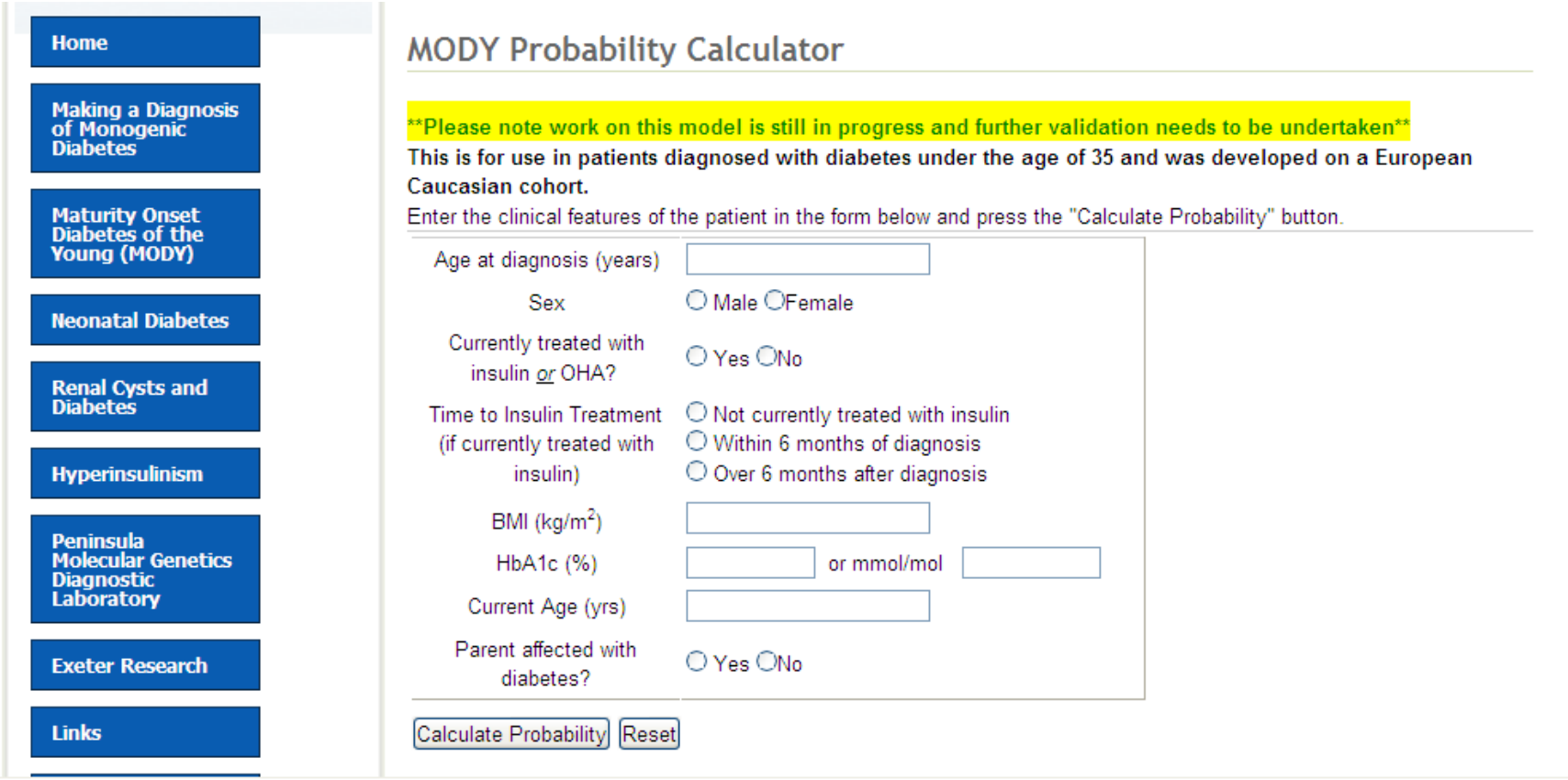
**Hypoplastic pancreas on CT**
**Diabetes**
**Pancreatic Exocrine dysfunction**
Bellane-Chantelot et al 2004 Ann Intern Med
**Low birth weight – decreased 900g**
Edghill et al Diabetic Medicine 2006



# In MODY the genetic subtype determines clinical picture and treatment response



# Web-based Probability Calculator for patients diagnosed < 35 years based on clinical criteria www.diabetesgenes.org




Shields B et al Diabetologia 2012

# A practical approach to monogenic diabetes

Probability model

One stop diagnostic stop
UCPCR, IA2 and GAD and genetic testing

Website www.diabetesgenes.org

Monogenic diabetes course
Exeter 10th/11th Feb 2014

# Acknowledgements

## The Exeter team

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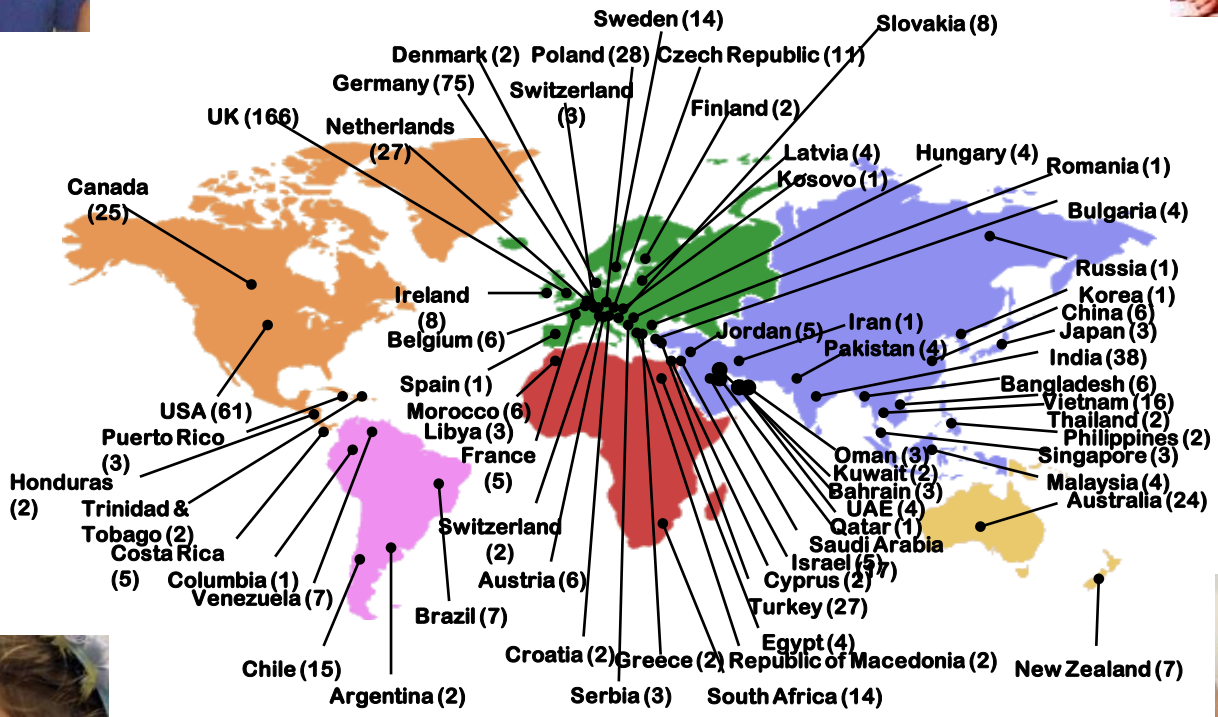
The Wellcome Trust

ISPAD

Diabetes UK

# The most important team of all!
# The patients and their families




## www.diabetesgenes.org