Genetic determinants of fetal growth in monogenic diabetes

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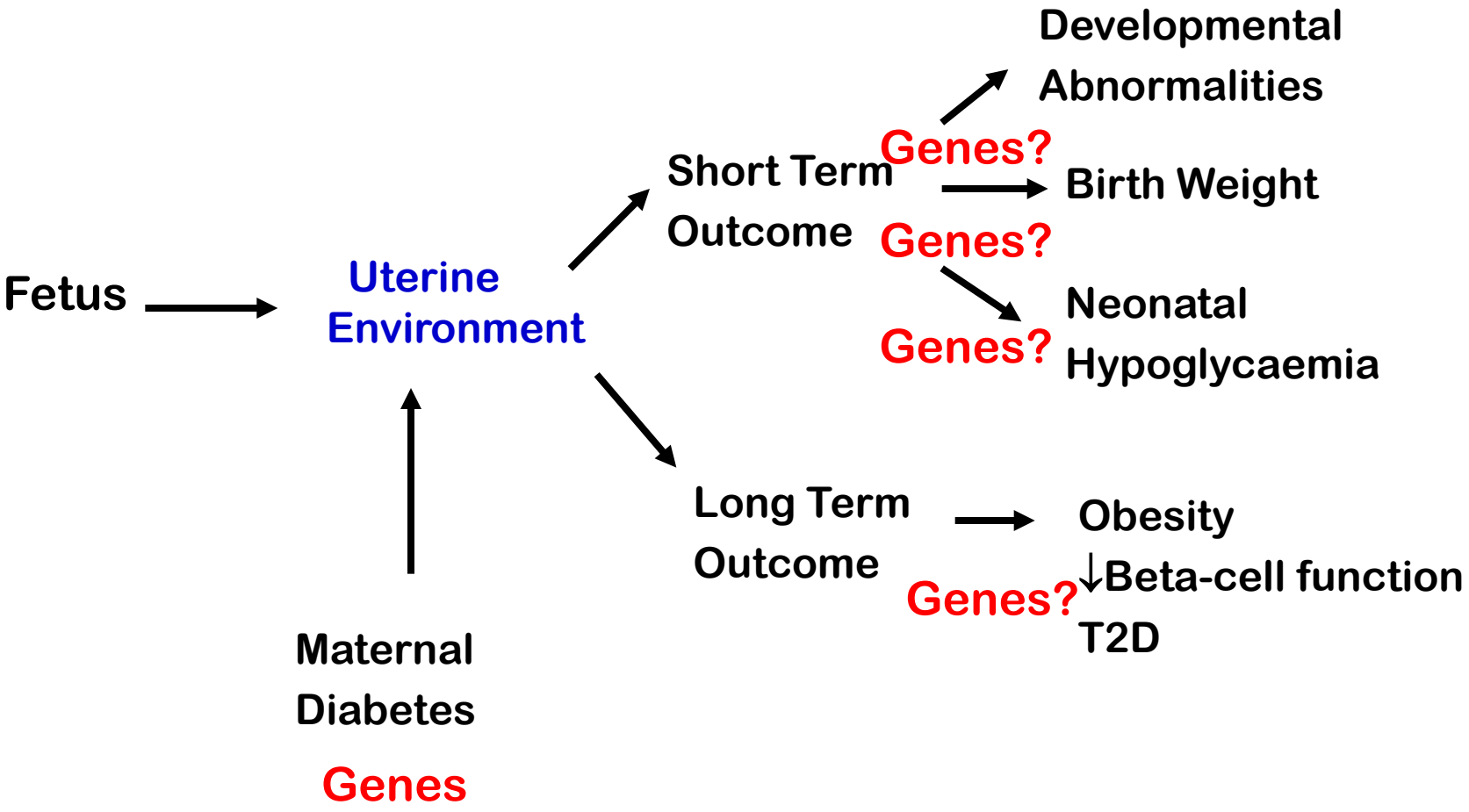
Fetal Outcomes



Maturity-onset diabetes of the young (MODY): in the pre genetic era

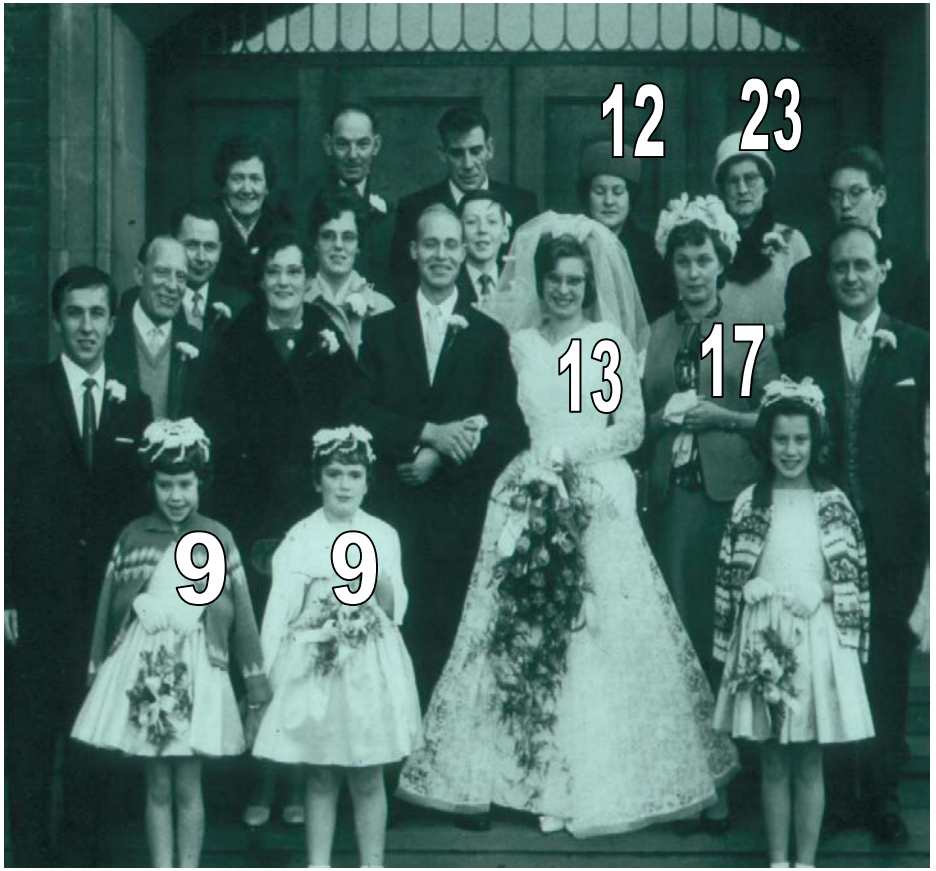
Early diagnosis of diabetes (<25)

Non insulin-dependent diabetes

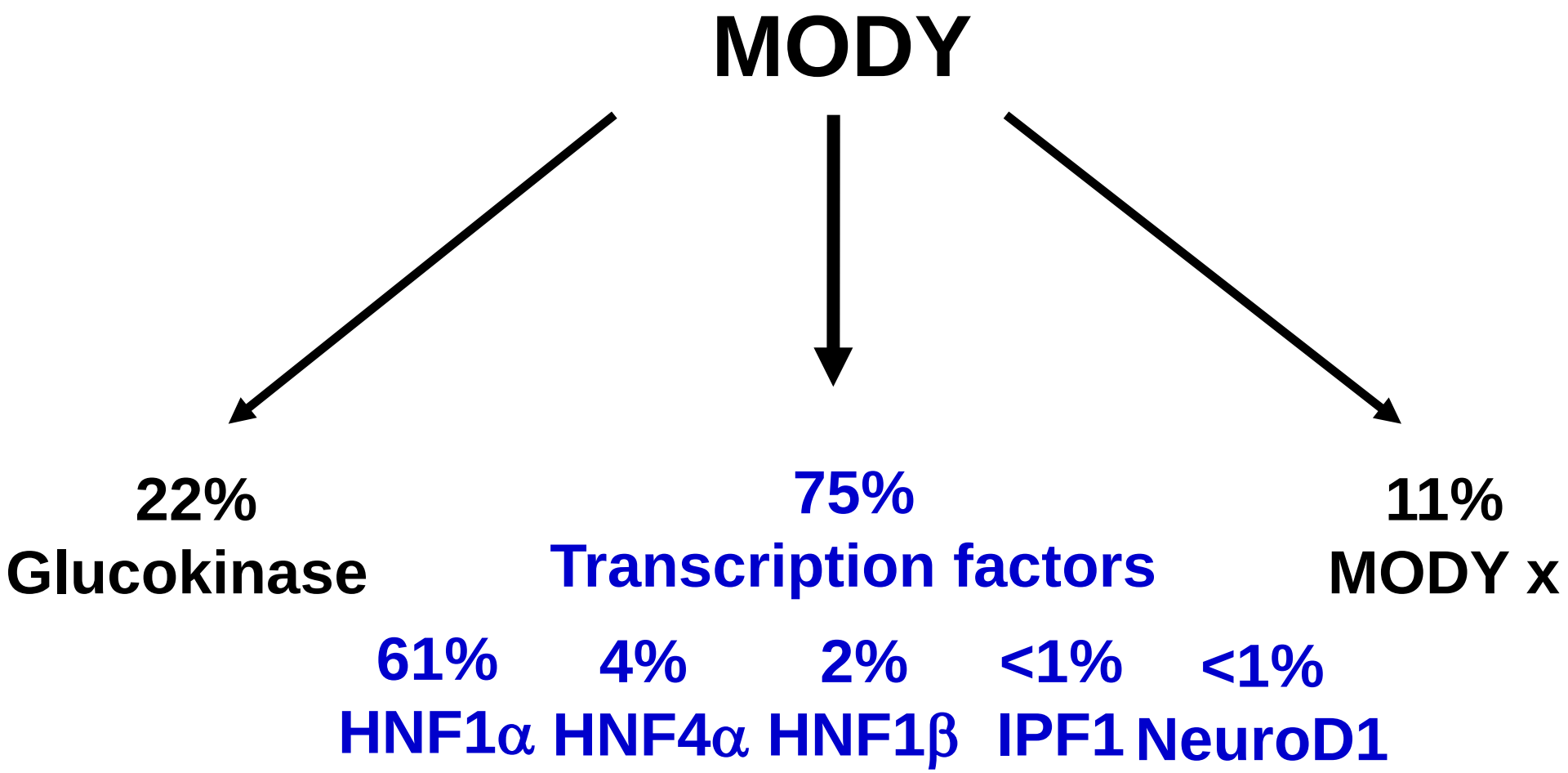
Autosomal dominant inheritance
Caused by a single gene defect

Defect in beta-cell function

Tattersall (QJM 1974)



MODY: in the post genetic era



Ellard unpublished, Frayling et al Diabetes 2001

Linda: Slim Gestational diabetes

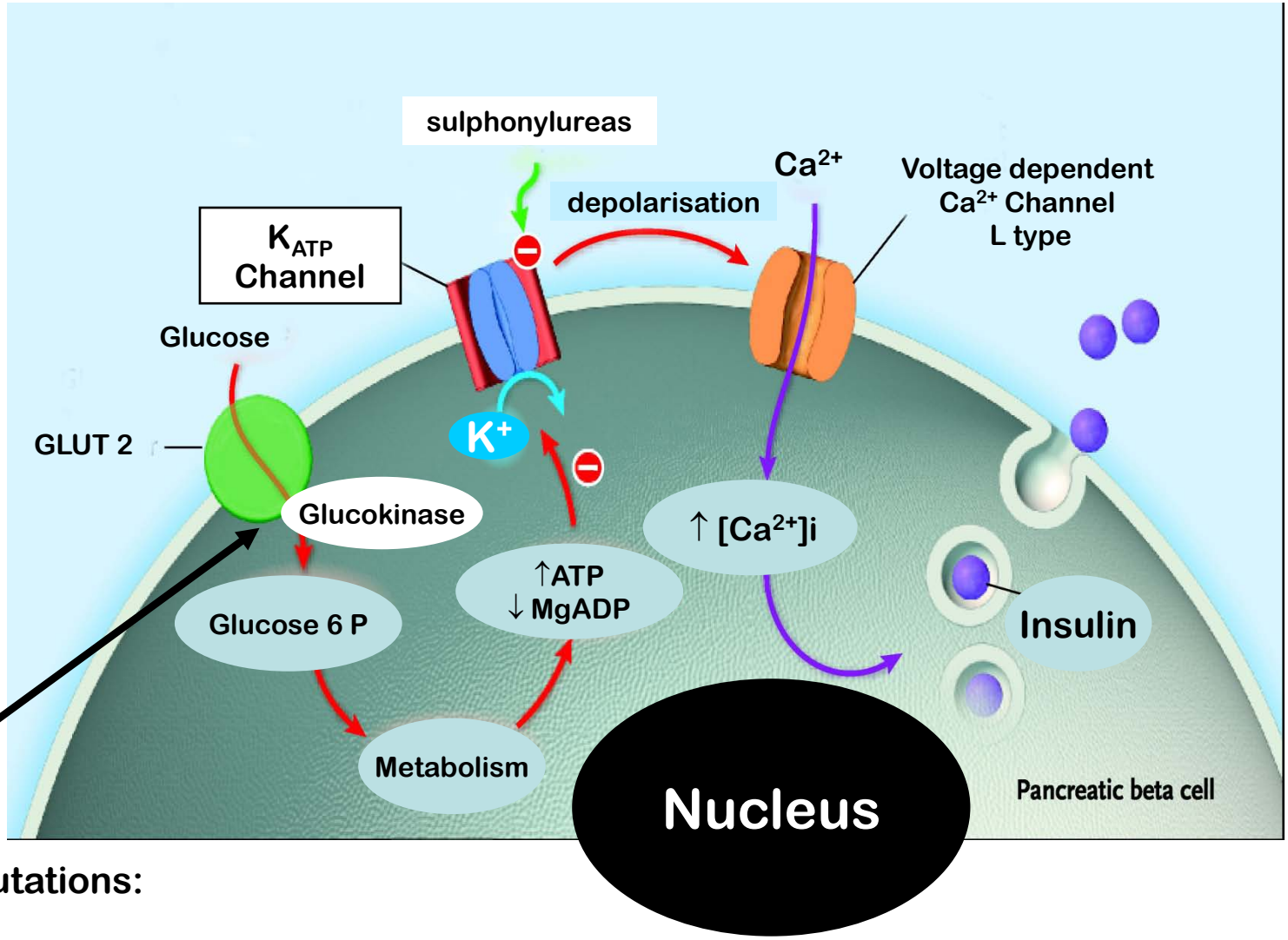
26 yr UK Caucasian woman,
BMI 24 pre –pregnancy
1st Pregnancy Rpg (screen) 10 mmol/l 17 wks

OGTT 28 wks fpg 6.5 mmol/l 2hr 8.0 mmol/l
Insulin treated 94U/day, good control HbA1c 5.8%
Baby 3200g 38 weeks Caesarean delivery

Post pregnancy stopped insulin
6 week OGTT fpg 7.3 mmol/l 2hr 9.2 mmol/l

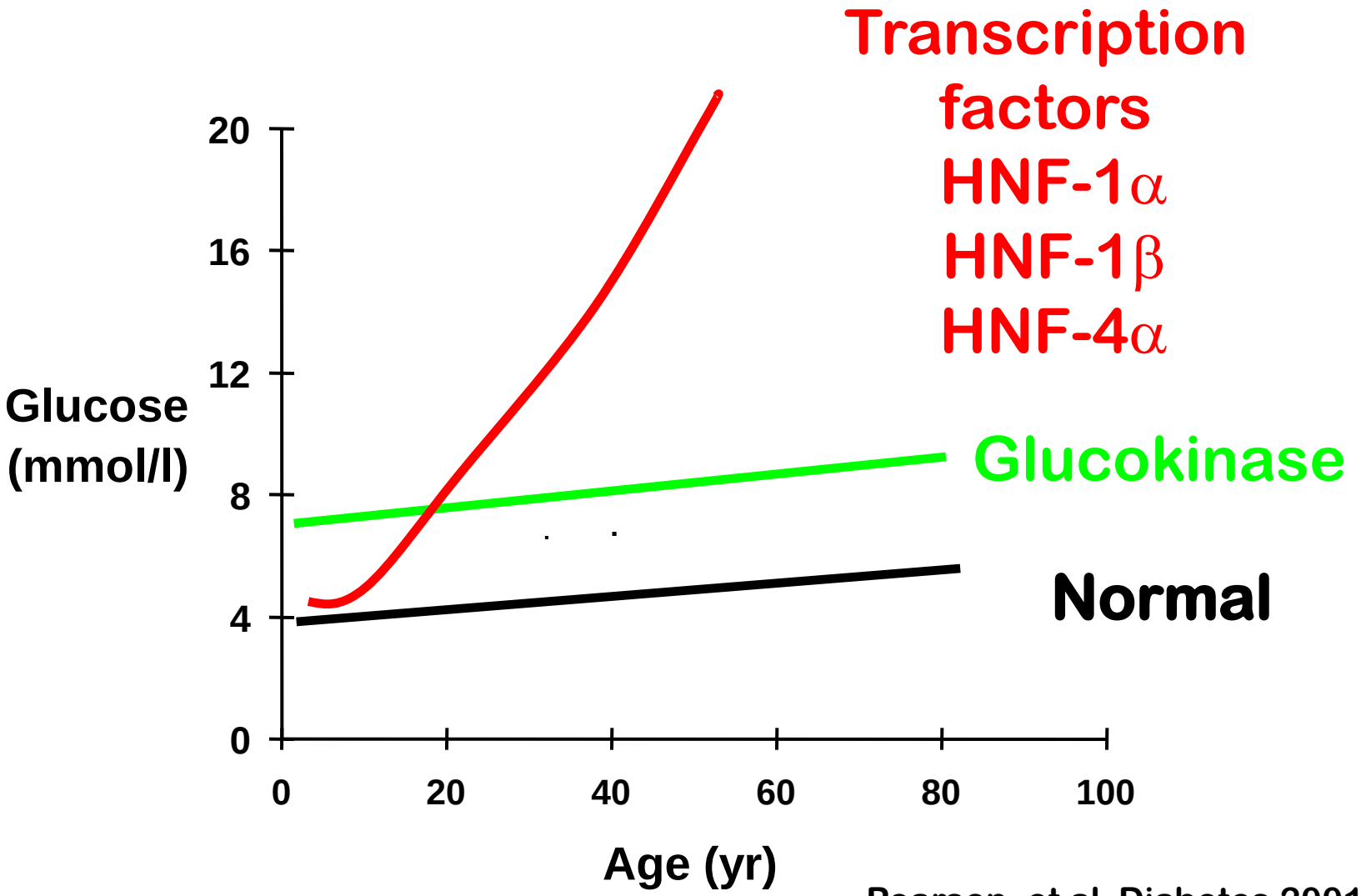
Glucokinase MODY

Glucokinase – the pancreatic glucose sensor



Heterozygous Glucokinase mutations: cause MODY

Mild fasting hyperglycaemia with Glucokinase Mutations



Pearson, et al Diabetes 2001

Glucokinase (MODY2) mutations in GDM

Prevalence

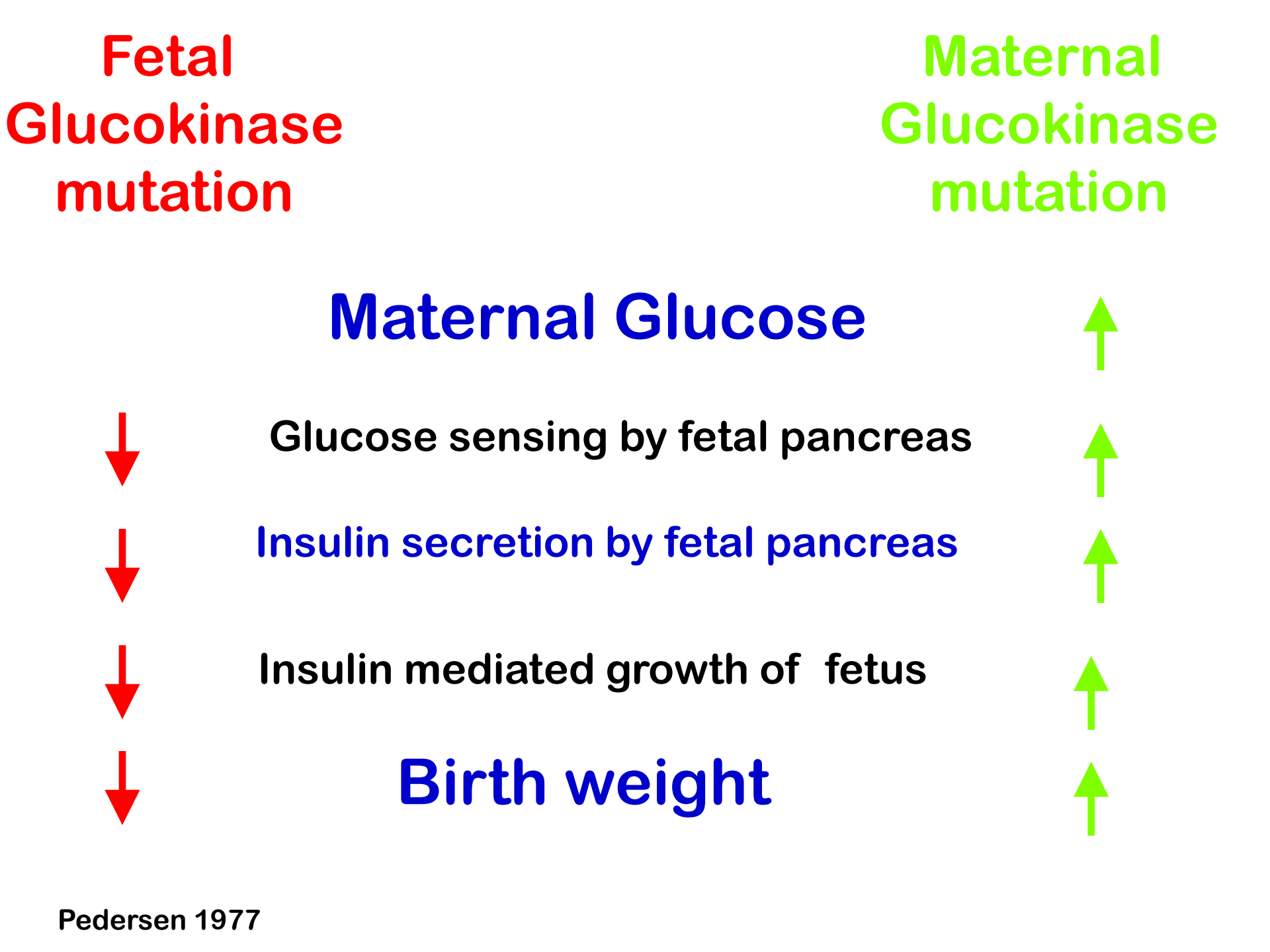
UK Caucasian clinic: 2-4%GDM patients have a GCK mutation (Ellard et al, Diabetelogia 2000)
I :10000 of the population

Glycaemia

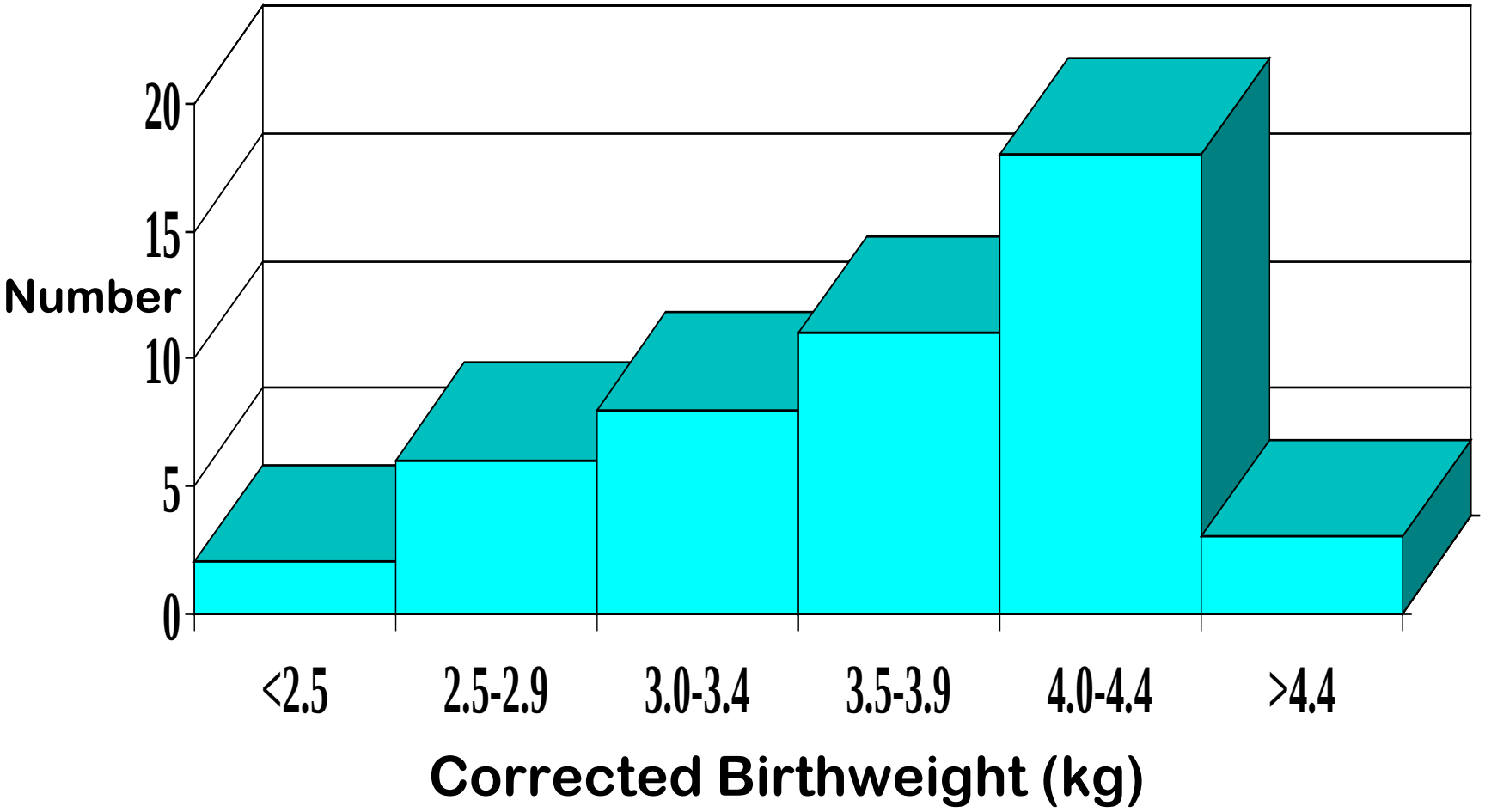
Persistent raised FPG(5.5-8.5 mmol/l)
Pregnancy and post natal
Little rise in OGTT (2.1(0.5 – 4.5)mmol/l)
HbA1c 6.2 (5.4-7.1%)

Genetically test if:

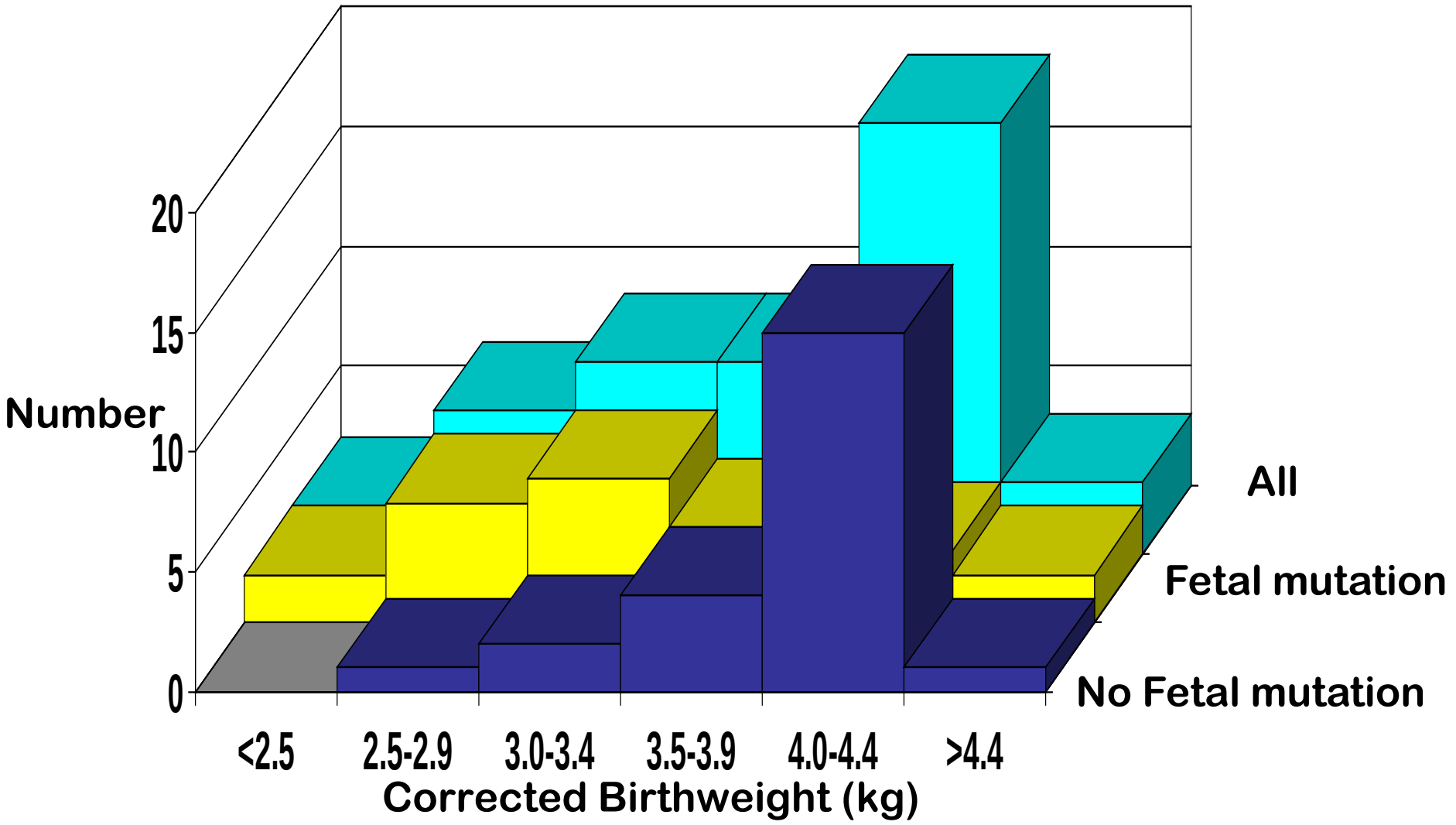
Consistent fpg > 5.5 mmol/l
especially if increment < 3mmol/l, slim, mild hyperglycaemia in family members


Fetal Glucokinase mutation
Maternal Glucokinase mutation
Maternal Glucose
Glucose sensing by fetal pancreas
Insulin secretion by fetal pancreas
Insulin mediated growth of fetus
Birth weight
Pedersen 1977

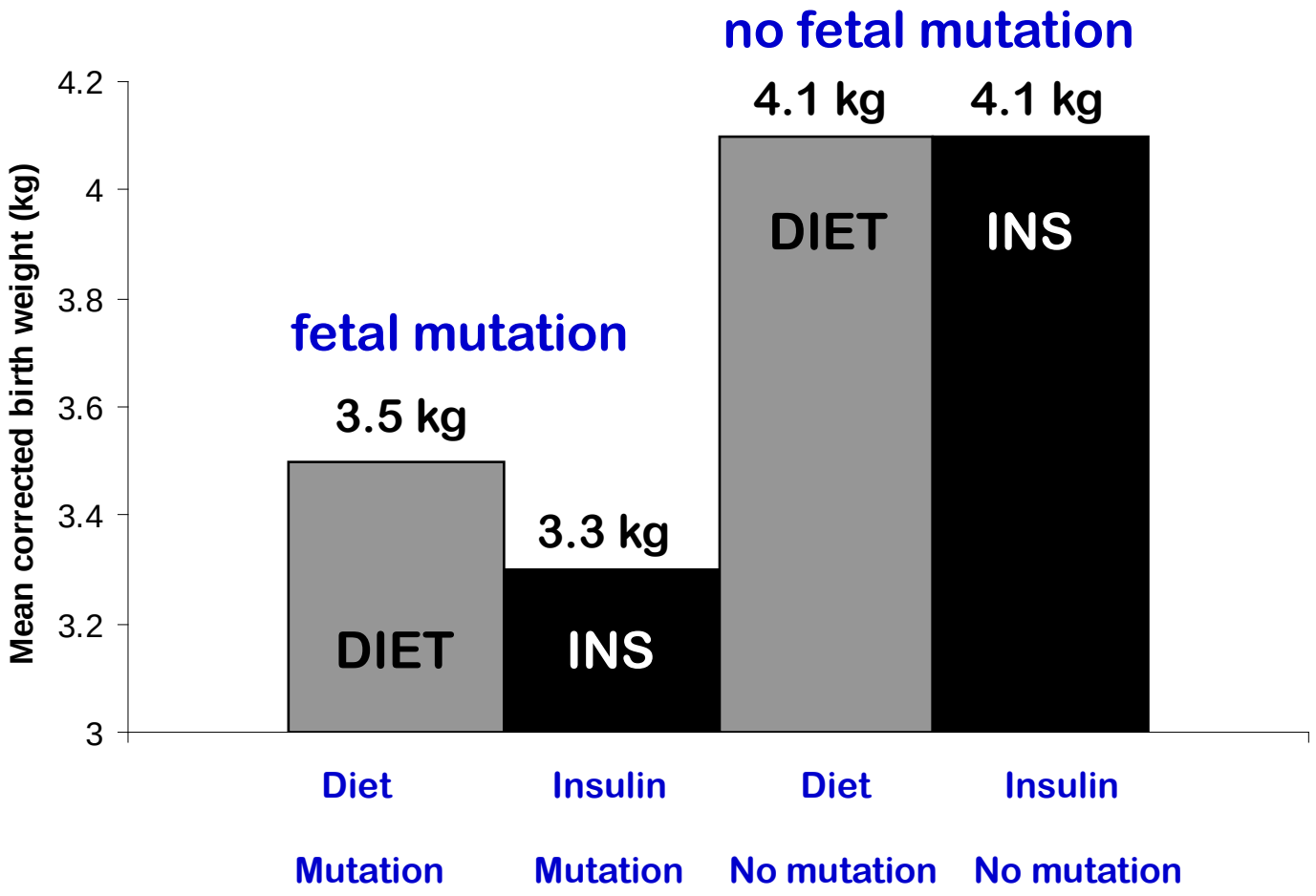
Fetal birth weight in offspring of mothers with glucokinase mutations



Fetal birth weight in offspring of mothers with glucokinase mutations

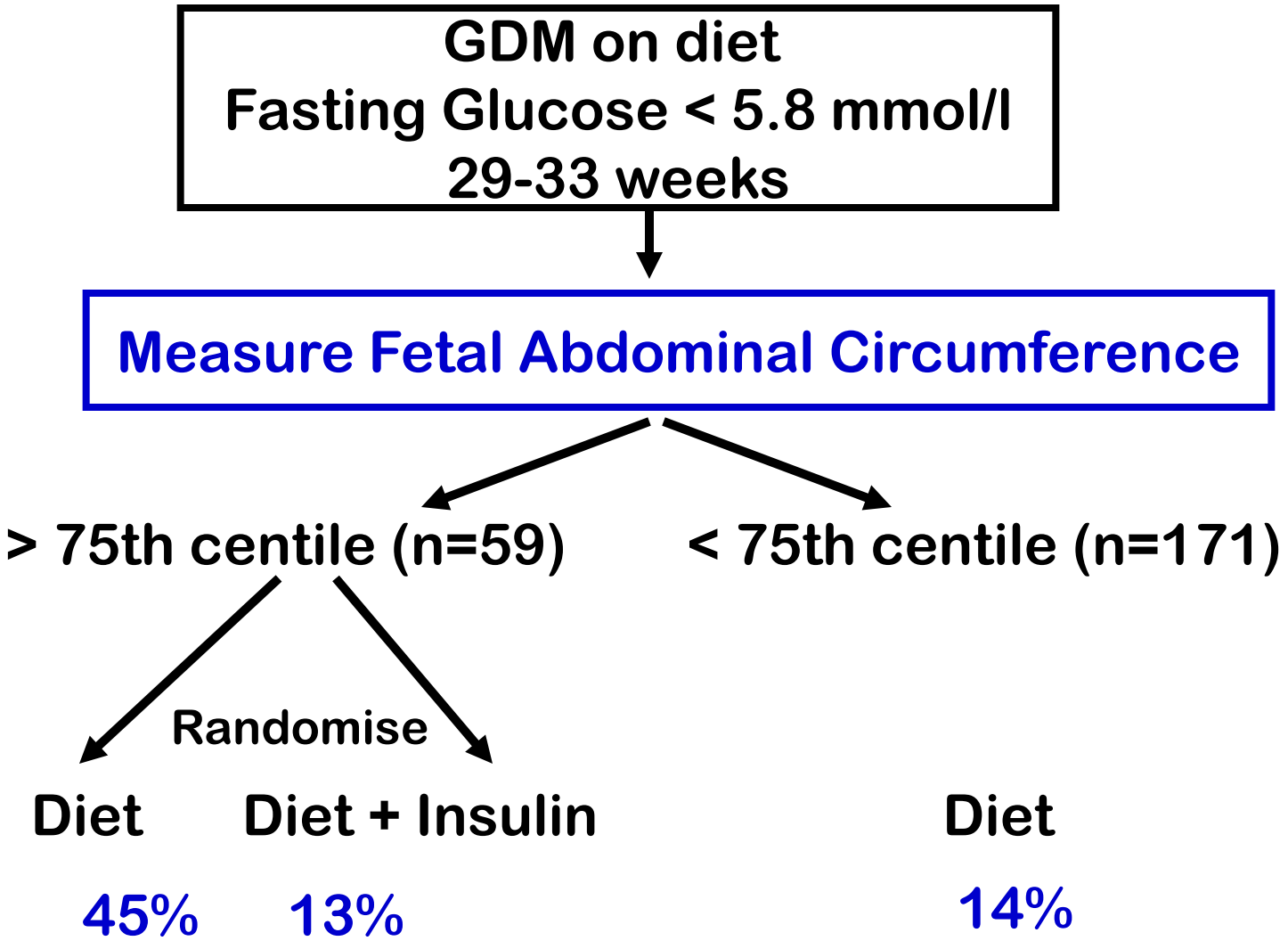


Fetal mutation not insulin treatment determines fetal outcome in GCK pregnancy



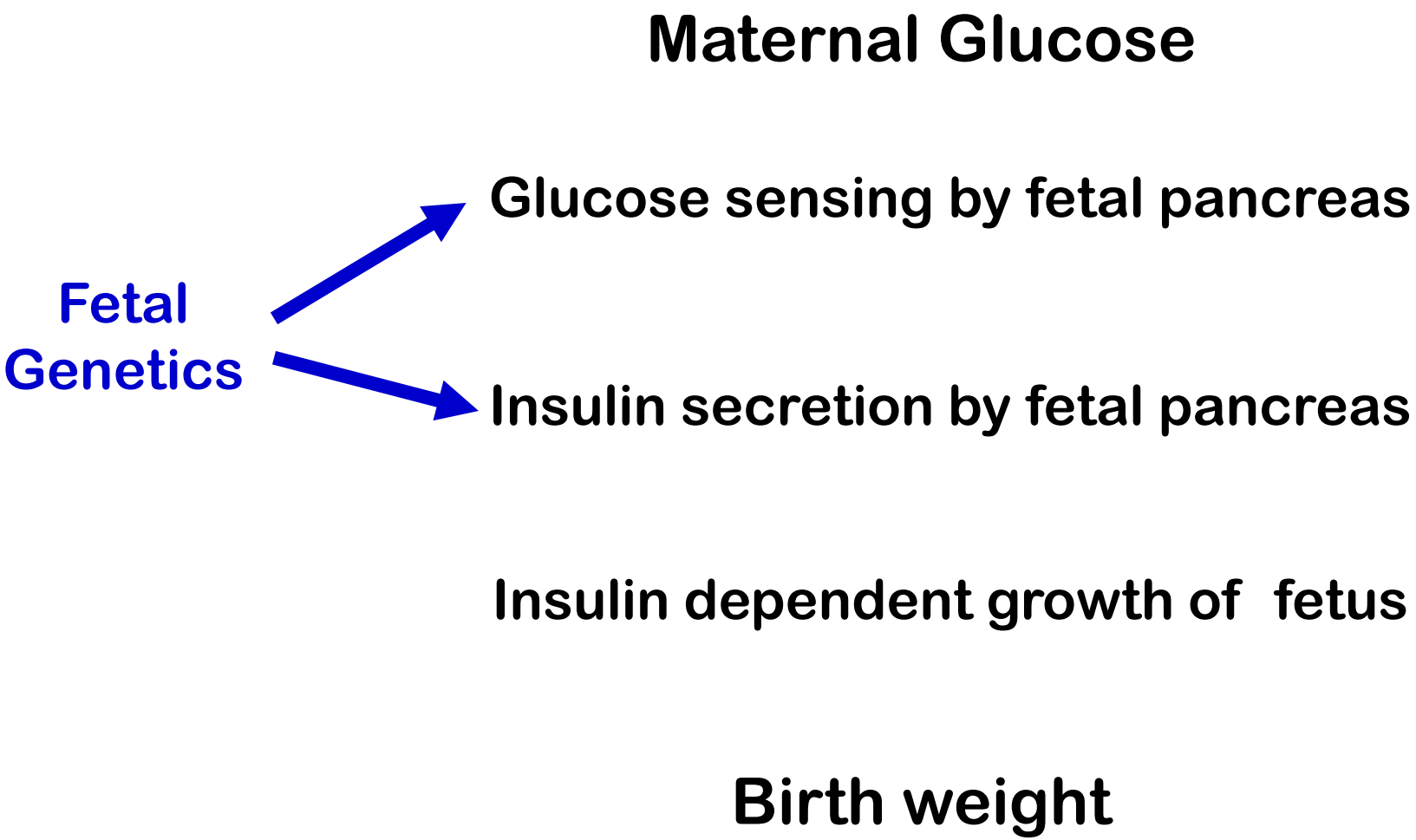
Spyer et at Diabetic Medicine, 2009

In Glucokinase Pregnancy Aggressive Treatment of Glycaemia may not be required



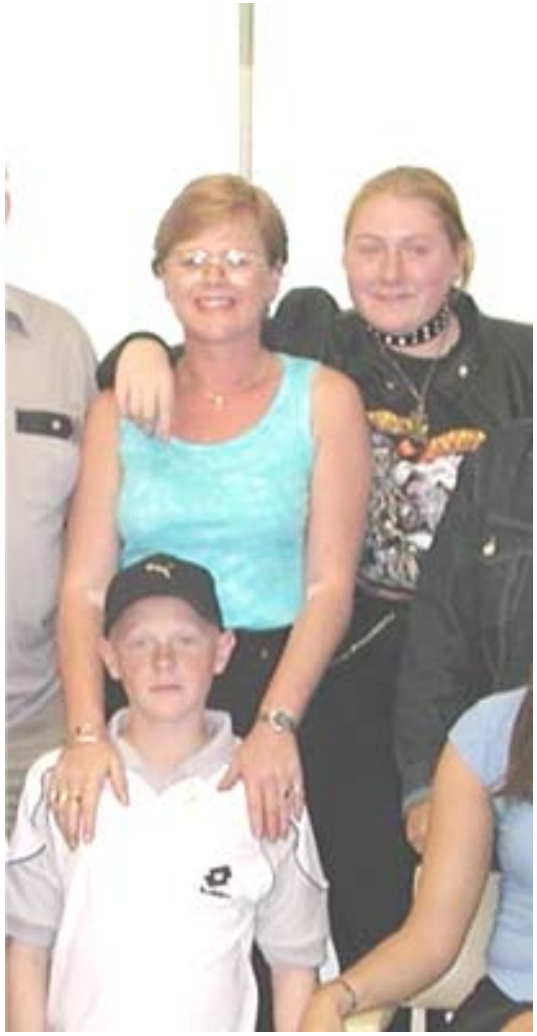
Buchanan et al (Diabetes Care 1994)

Fetal Insulin mediated growth depends on fetal insulin secretion as well as maternal glycaemia



Hattersley Lancet 1999

Claire



- Diagnosed diabetes aged 23 yr
- BMI 25 kg/m^2
- Treated with qds insulin initally
- HbA1c 8.3%

Attends pre-pregnancy counseling

Family history of diabetes

Autosomal dominant

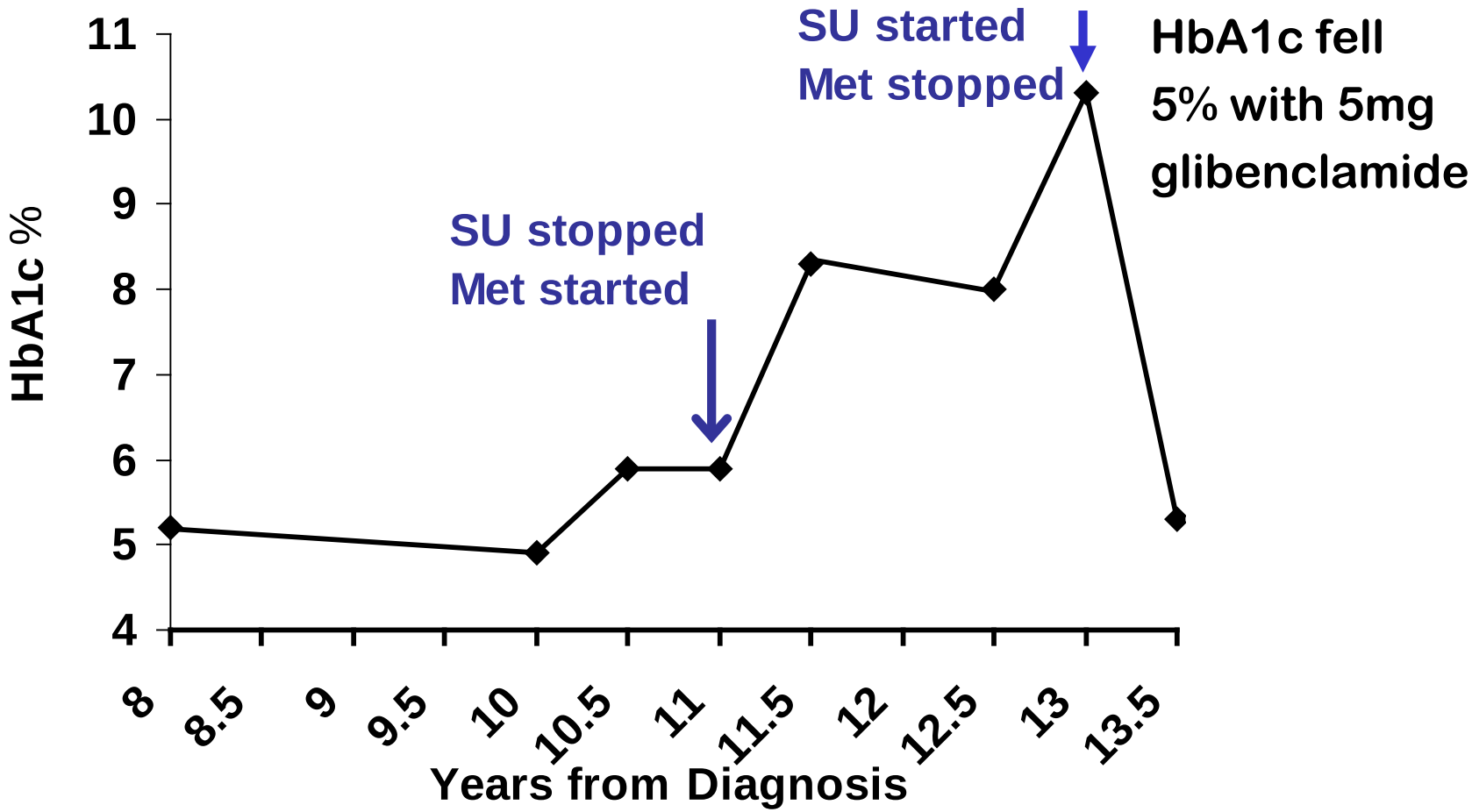
"Type 1 and Type 2"

Genetic testing

HNF1A mutation in all diabetic family members

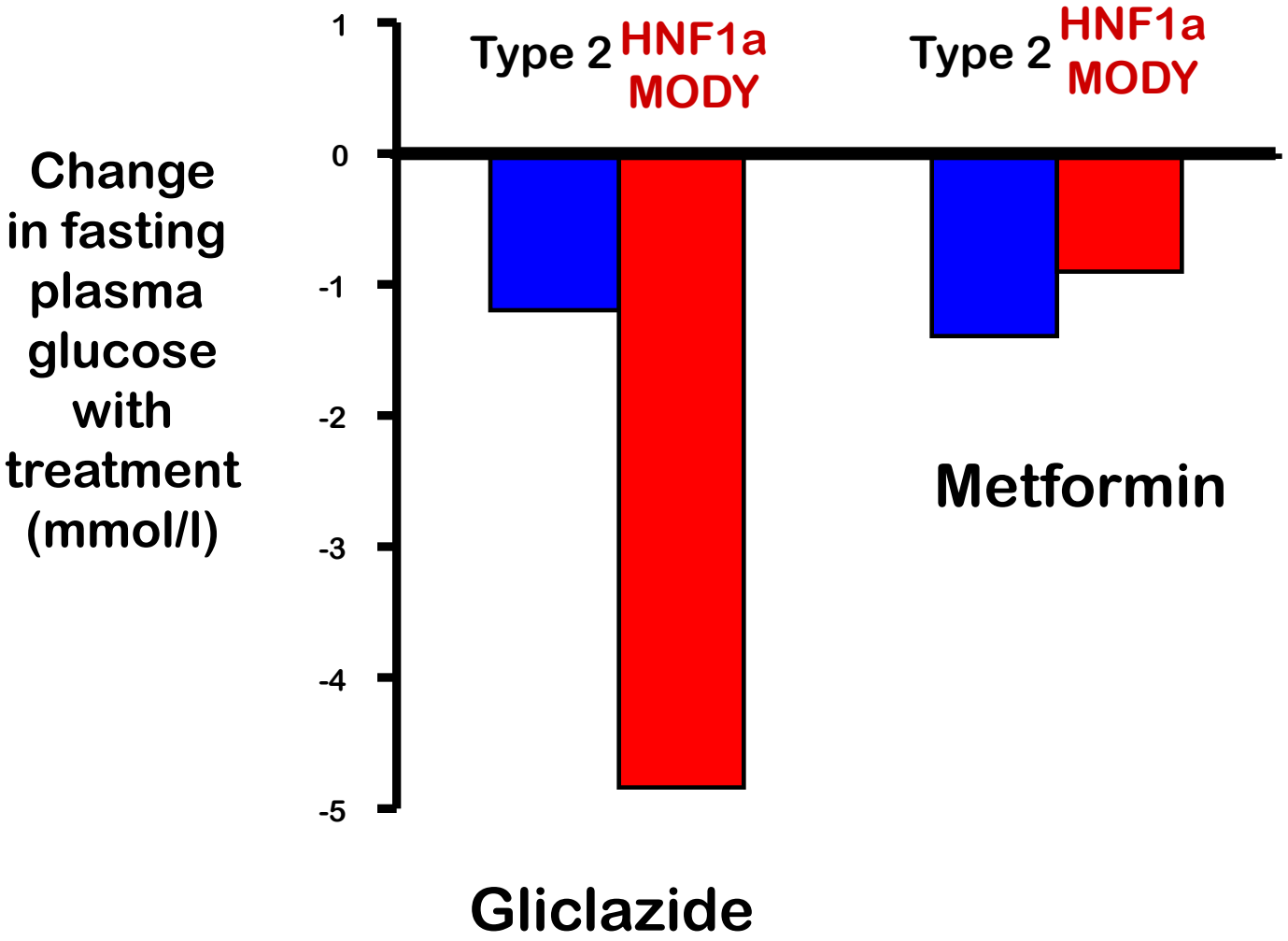
What treatment pre-pregnancy ?

Sulphonylurea sensitivity in a patient with an HNF1α mutation



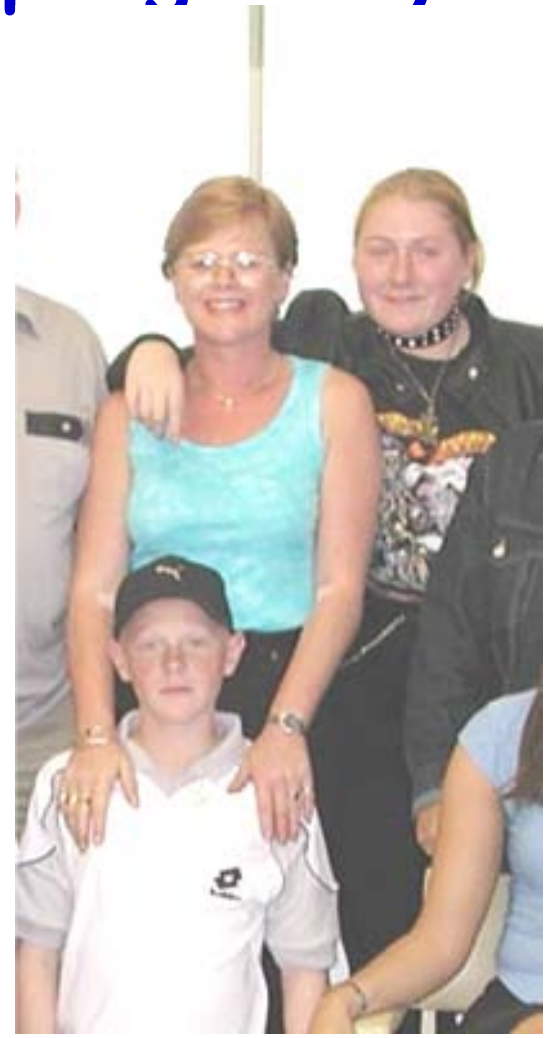
Pearson et al. Diab Med 2000

HNF1a patients respond better to Gliclazide than Type 2 patients



Pearson et al Lancet 2003

What treatment should Claire have in pregnancy as she has HNF1A MODY?



- Diagnosed diabetes aged 23 yr
- BMI 25 kg/m^2
- Treated with qds insulin initially
- HbA1c 8.3%

Control usually better with sulphonylureas in HNF1A

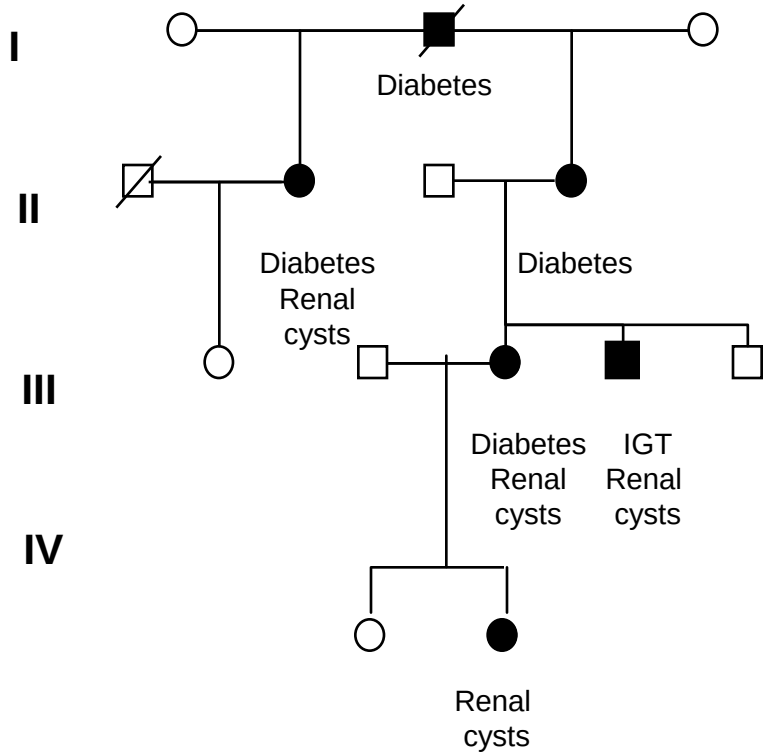
Glibenclamide does not cross placenta data that safe in T2D

Insulin more safety data but less good glycaemic control in HNF1A

Should be off insulin post pregnancy

No impact of fetal mutation

Susan



HNF-1B mutation
Renal cysts and diabetes

Second pregnancy
GDM glucose 13 mmol/l
First trimester
Insulin treated
US 17 weeks
– enlarged cystic kidneys
Birth weight 2.8kg 39 weeks
Family history of diabetes and renal cysts

HNF-1Beta mutations: result in a developmental syndrome Renal Cysts And Diabetes (RCAD)

Renal cysts – impaired renal development

- Often seen on anti-natal scanning - variable
- Renal function variable - mild impairment - endstage renal failure 40% require dialysis
- Different developmental renal disease including glomerulocystic kidney disease, unilateral kidneys, dysplastic kidneys etc
-

Diabetes -impaired pancreas development

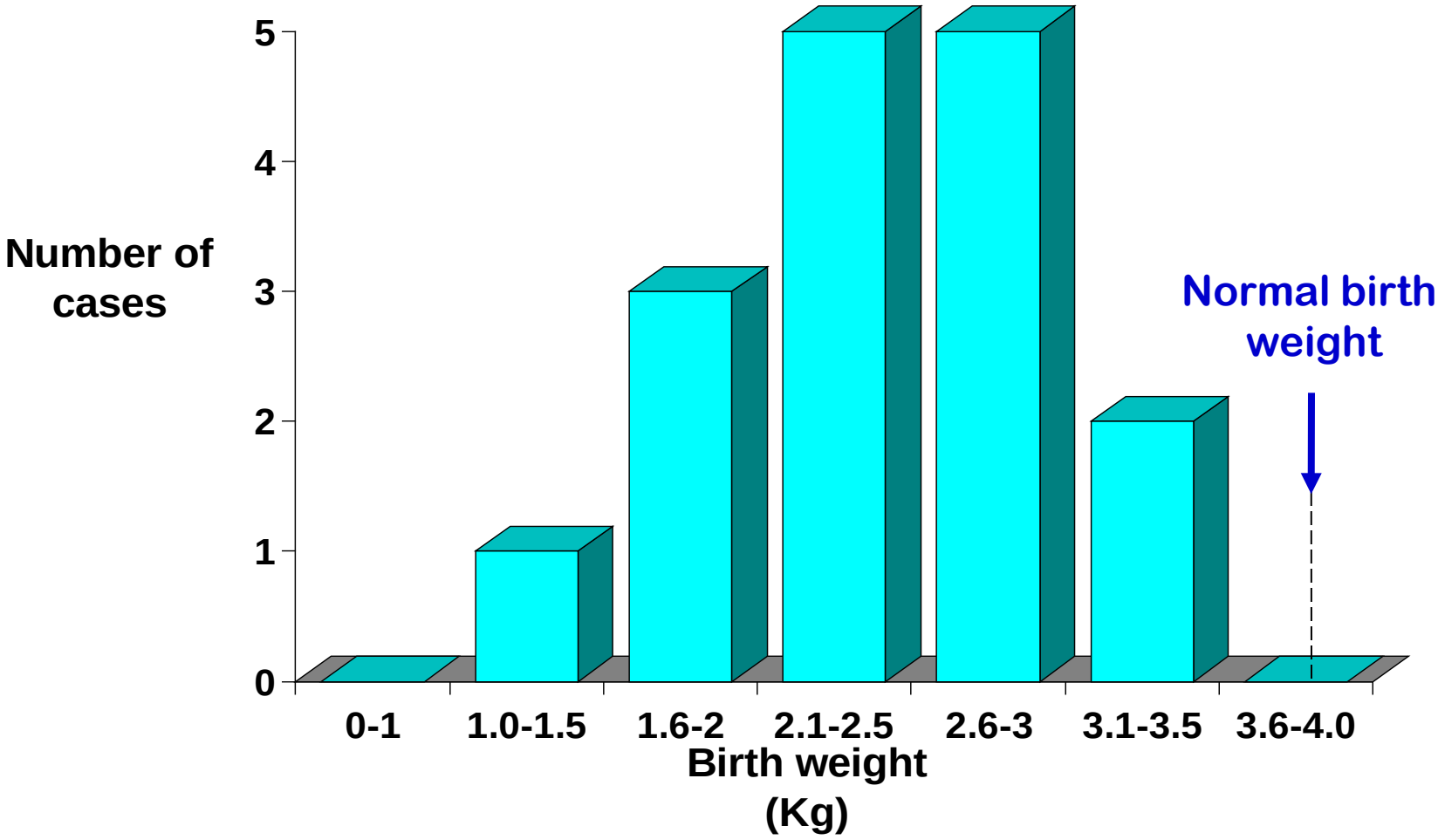
- Diagnosis 22 (10 - 47) yr, usually on insulin – reduced no. of beta-cells
- Exocrine pancreatic dysfunction (hypoplastic pancreas and reduced fecal elastase

Impaired fetal insulin secretion in utero would reduce birth weight

Review Bingham and Hattersley Nephrol Dial & Transplant 2004

HNF-1β fetal mutations result in low birth weight despite being normoglycaemic at birth

Low birth weight (median 2.6 kg)
50% Small Gestational Age



Edghill E et al Diabetic Medicine 2006

The Biggest Baby in Bradford


Big sleep: Five-day-old Reece with a two-week-old girl who is a third of his weight. Inset, mother Pauline

Pre-gestational diabetes
Diabetes – diet diag 25 yr
Father and 1 brother early-onset diabetes

Pregnancy
First pregnancy aged 26
Treated with insulin in pregnancy
HbA1c 6.5% last trimester

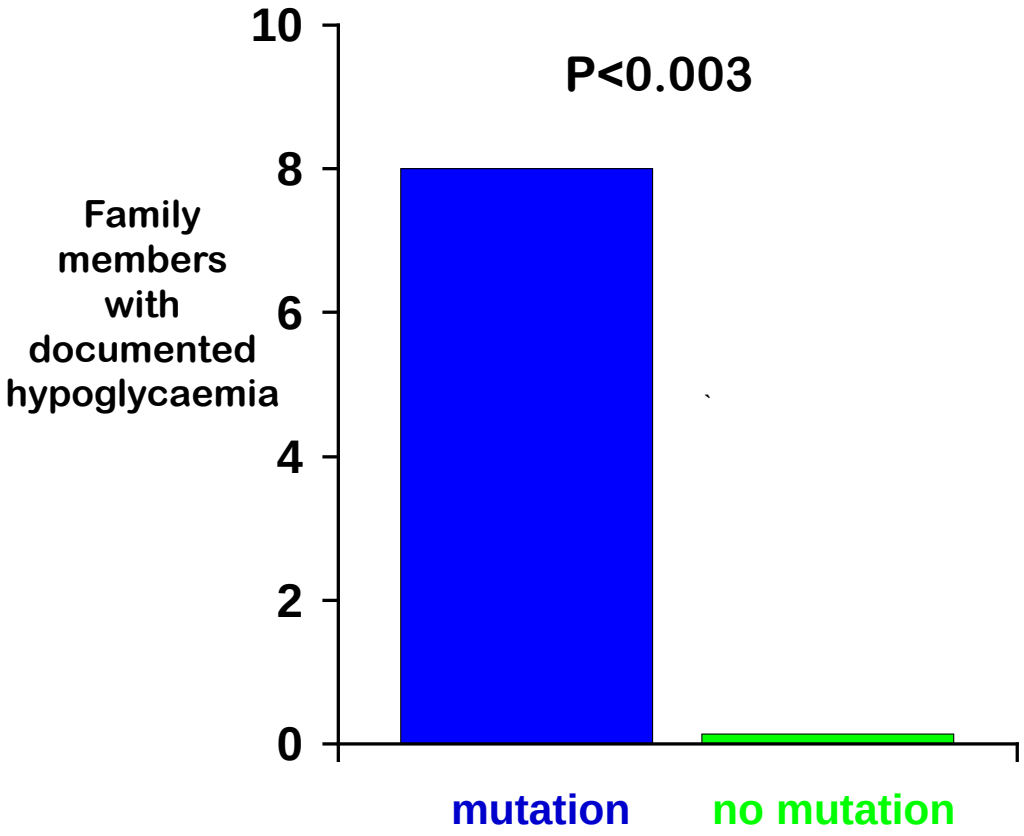
Son: Macrosomia Birth weight 5.9 kg
hypoglycaemia–glucose 1.2 mmol/l
persisted- treated Diazoxide 6/12

Patient, Father and Brother
All diabetes all macrosomic >4.3Kg

HNF4alpha mutation identified

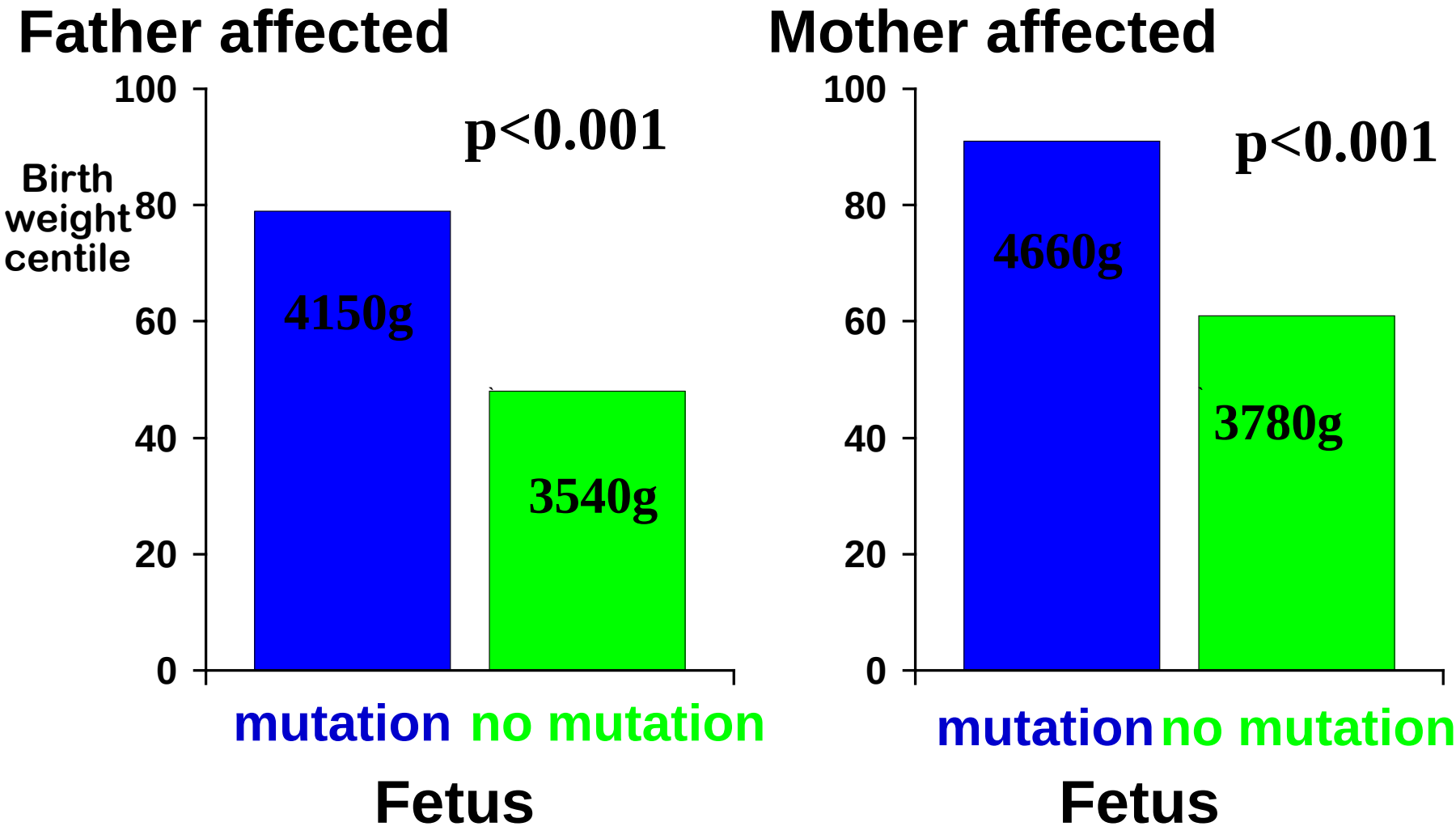
Neonatal Transient Hypoglycaemia in HNF4α mutation carriers

Neonatal Hypoglycaemia (<2.0 mmol/l >48 hrs) common in HNF4α mutation carriers



Pearson et al PLoS Medicine 2007

Birth weight is increased by 800g with fetal mutations in HNF4α



Pearson et al PLoS Medicine 2007

Managing HNF-4alpha in pregnancy

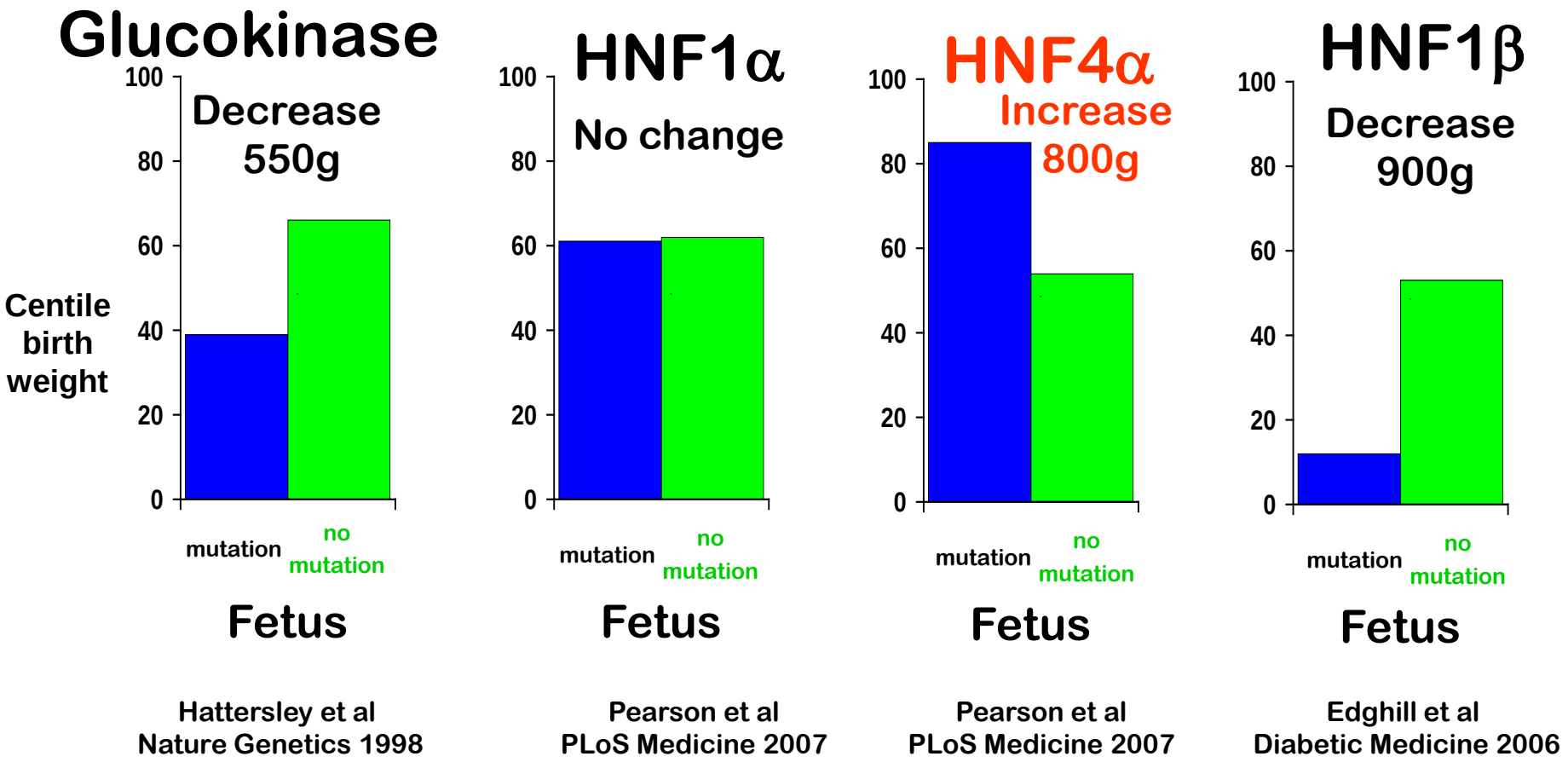
Hyperinsulinaemia in utero leading to macrosomia and n hypoglycaemia as neonate/infant

Need very strict control of maternal glycaemia ?Sulphonyureas
Even if normoglycaemic high risk of macrosomia. Fetal scanning and early delivery

Offspring will develop neonatal hypoglycaemia and then diabetes if inherit mutation

Pearson et al PLoS Medicine 2007

Birth weight in MODY subtypes reflects fetal beta cell function



Hattersley et al
Nature Genetics 1998

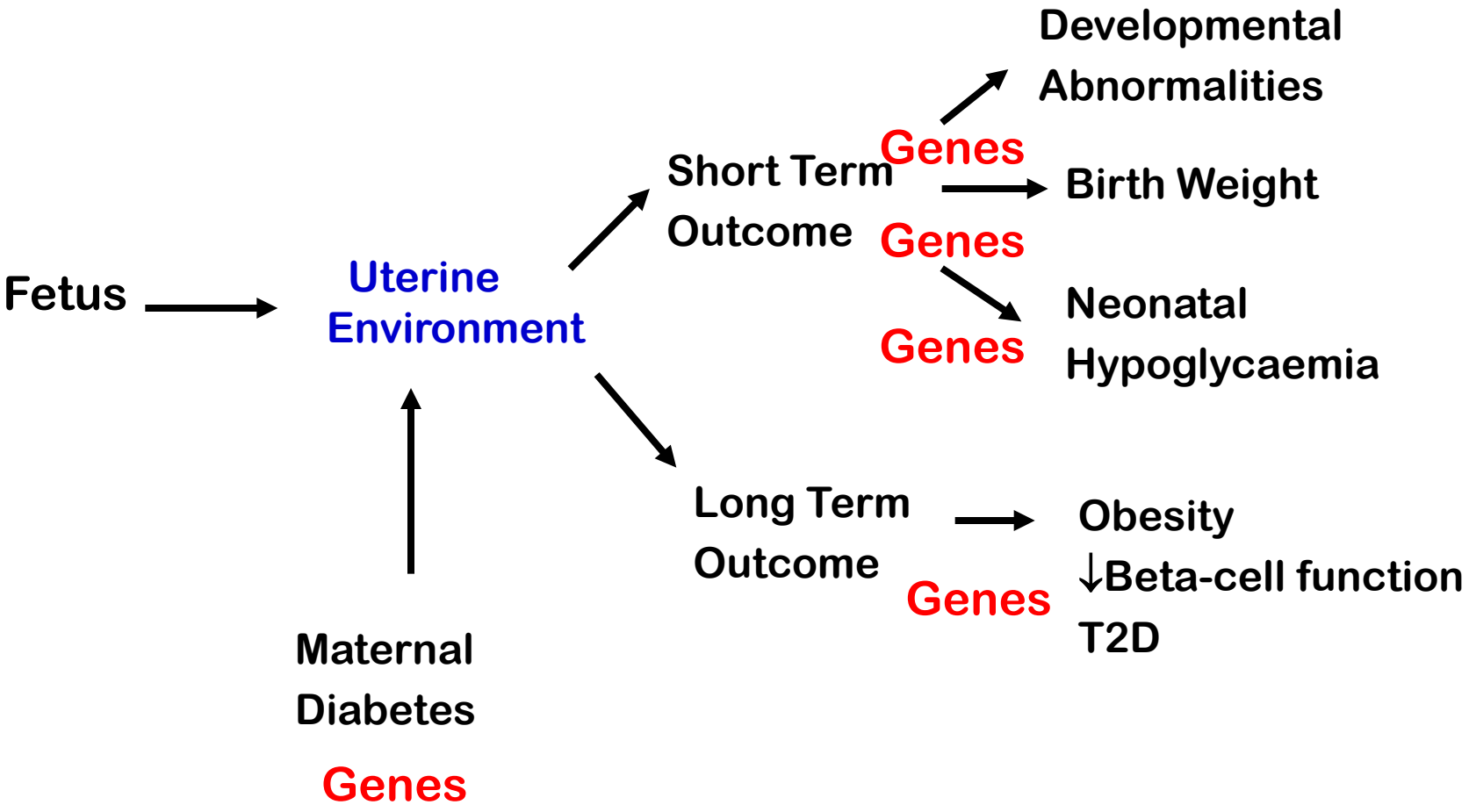
Pearson et al
PLoS Medicine 2007

Pearson et al
PLoS Medicine 2007

Edghill et al
Diabetic Medicine 2006

McCarthy & Hattersley Diabetes 2008

Fetal Outcomes



The future- knowing fetal genotype

Knowing fetal genotype alters management

– e.g. 2 cases of GCK pregnancy knowing fetus affected meant no treatment of maternal hyperglycaemia
(Chakera et al Diabetes Care in Press)

Non invasive testing of mother for fetal genotype being developed

using next generation sequencing from maternal blood.
Please inform us of any monogenic pregnancies for research study

Conclusion

Diagnosing monogenic diabetes is important to help appropriate treatment of maternal hyperglycaemia and understanding the fetal response to maternal hyperglycaemia.

See www.diabetesgenes.org

Acknowledgements

The Exeter team

Collaborators

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The Wellcome Trust

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