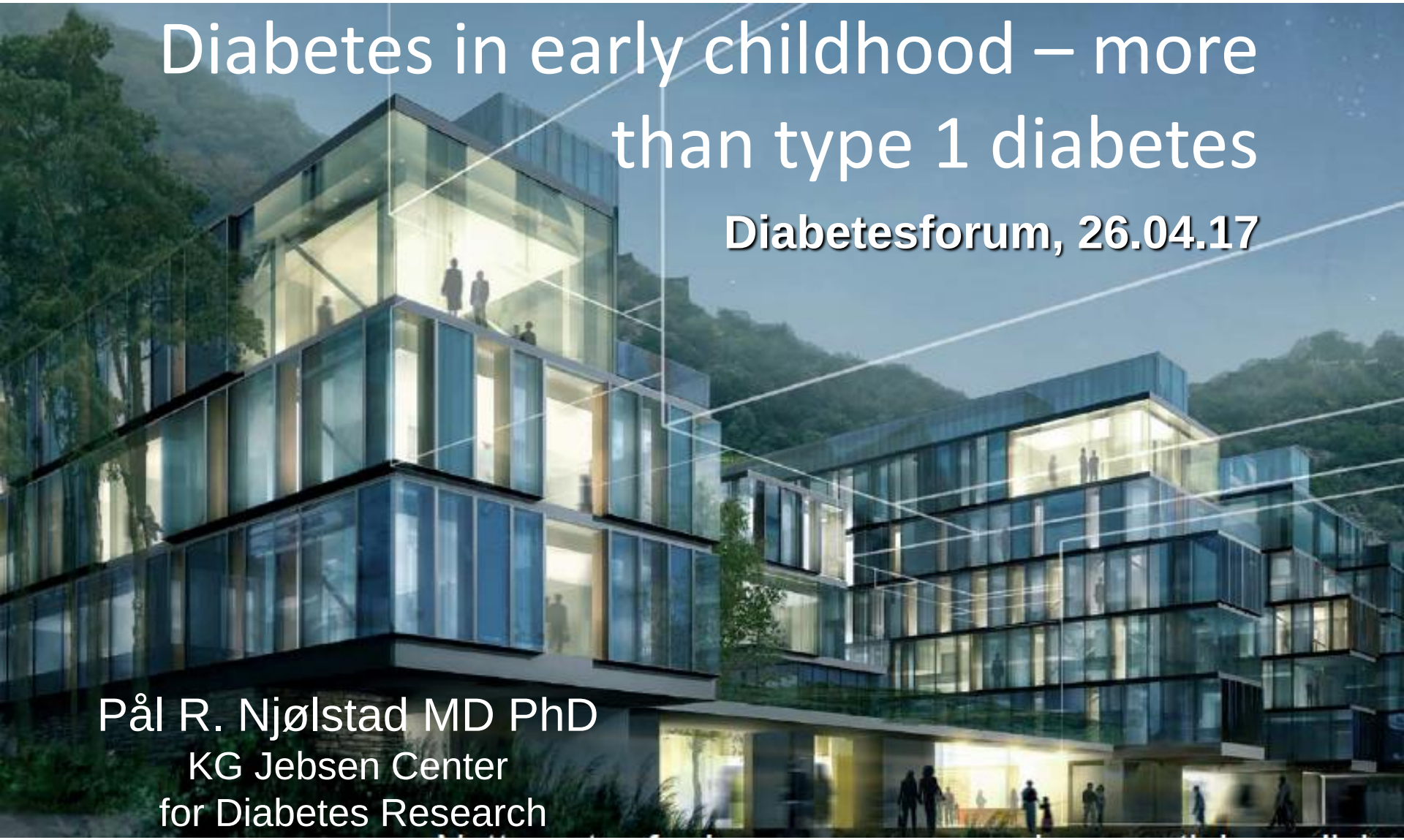
Diabetes in early childhood – more than type 1 diabetes

Diabetesforum, 26.04.17



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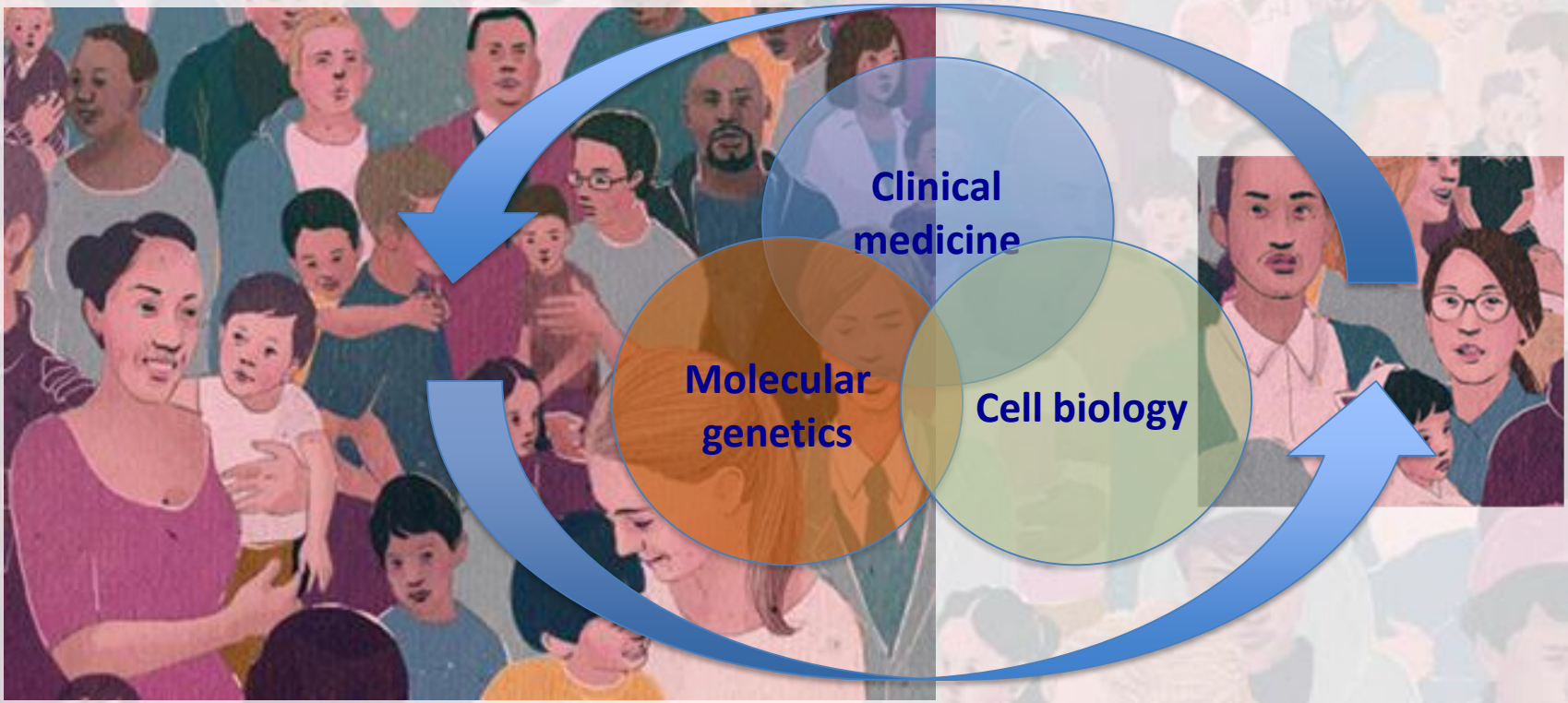
Precision medicine in diabetes



- Approach for disease prevention, diagnosis and treatment
- Individual variability in environment, lifestyle and biology

The Norwegian MODY Registry

Julia Yellow

Monogenic diabetes 2017 - many genes!

6q24
EIF2AK3
FOXP3
GATA6
GLIS3
IER3IP1
IL2RA
NEUROG3
NKX2.2
MNX1
PAX6
PTF1A
RFX6
SLC2A2
SLC19A2
WFS1
ZFP57

NDM
- Age of onset <6 months
- Autosomal dominant or recessive
- β-cell failure

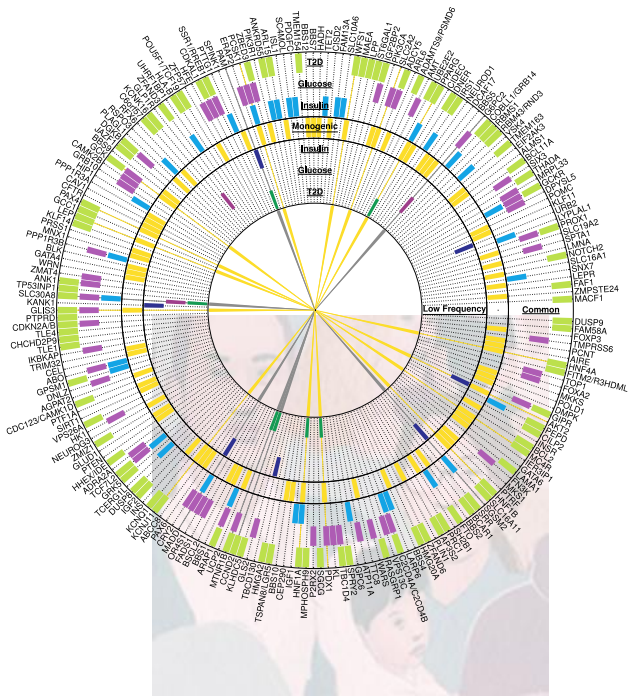
NDM plus organ dysfunction
- Bone
- Blood
- Cardiovascular system
- Central nervous system
- Endocrine system
- Exocrine pancreas
- Eye
- Gastrointestinal system
- Genitalia
- Kidney
- Skin

INS
ABCC8
KCNJ11
GCK
NEUROD1
PDX1

MODY
- Age of onset 6 months – 35 years
- Autosomal dominant
- β-cell failure

MODY plus organ dysfunction
- Adipose tissue
- Blood
- Cardiovascular system
- Central nervous system
- Exocrine pancreas
- Gastrointestinal system
- Genitalia
- Kidney
- Lung

APPL1
BLK
HNF1A
HNF4A
KLF11
PAX4
CFTR
HFE
LMNA
PPARG
TRMT10A
CEL
HNF1B



MT-TE
MT-TK
MT-TL1

Mitochondrial diabetes mellitus
- Deafness
- Mitochondrial inheritance

Flannick, Johansson, Njølstad, Nature Rev Endocrinol, 2016

A simpler picture….

Monogenic diabetes

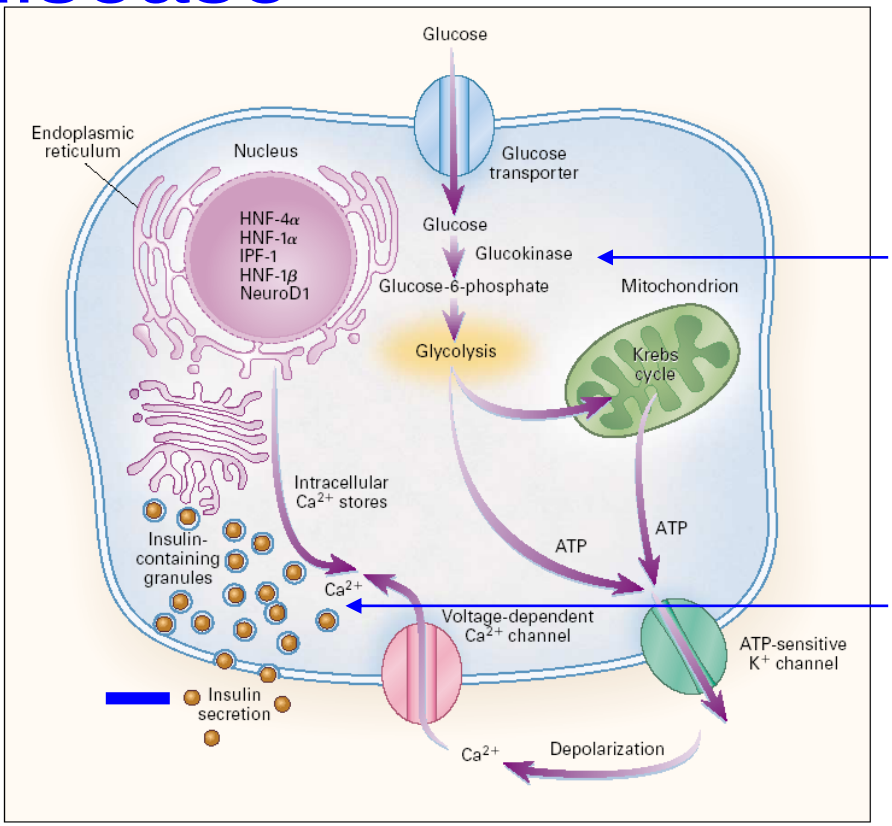
Neonatal diabetes
<6 months

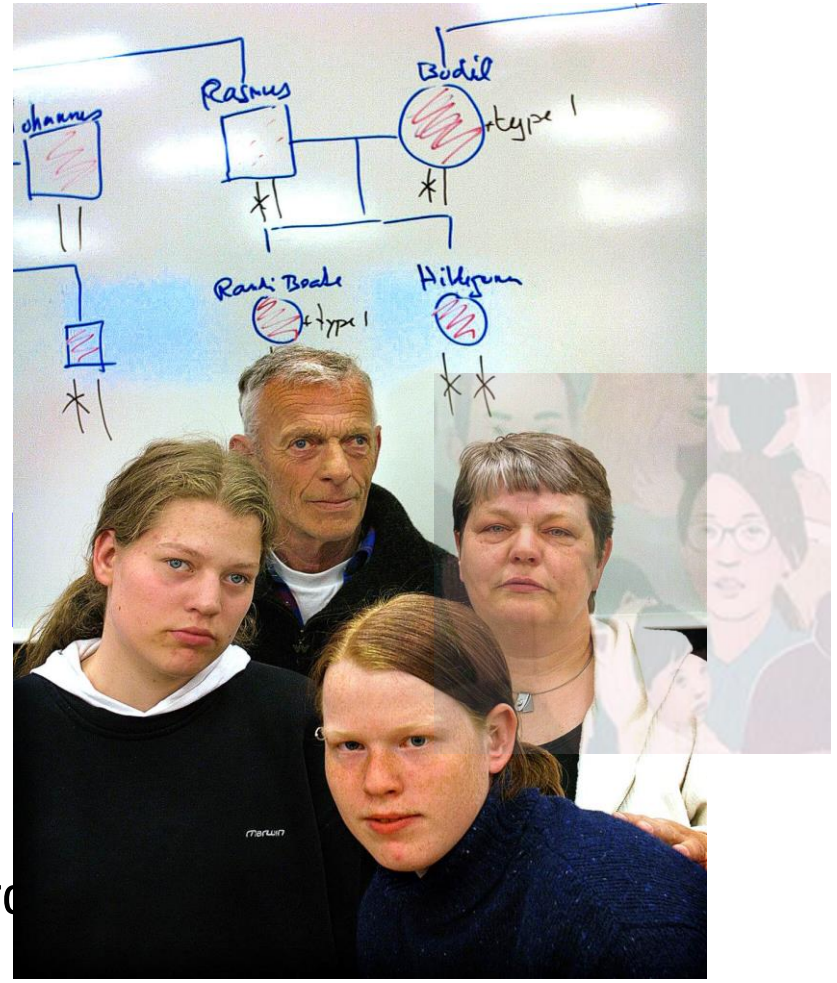
GCK KCNJ11 ABCC8 Other

MODY diabetes
6 months – 35 years

HNF1A GCK HNF1B Other

GCK: Neonatal diabetes is a genetic disease



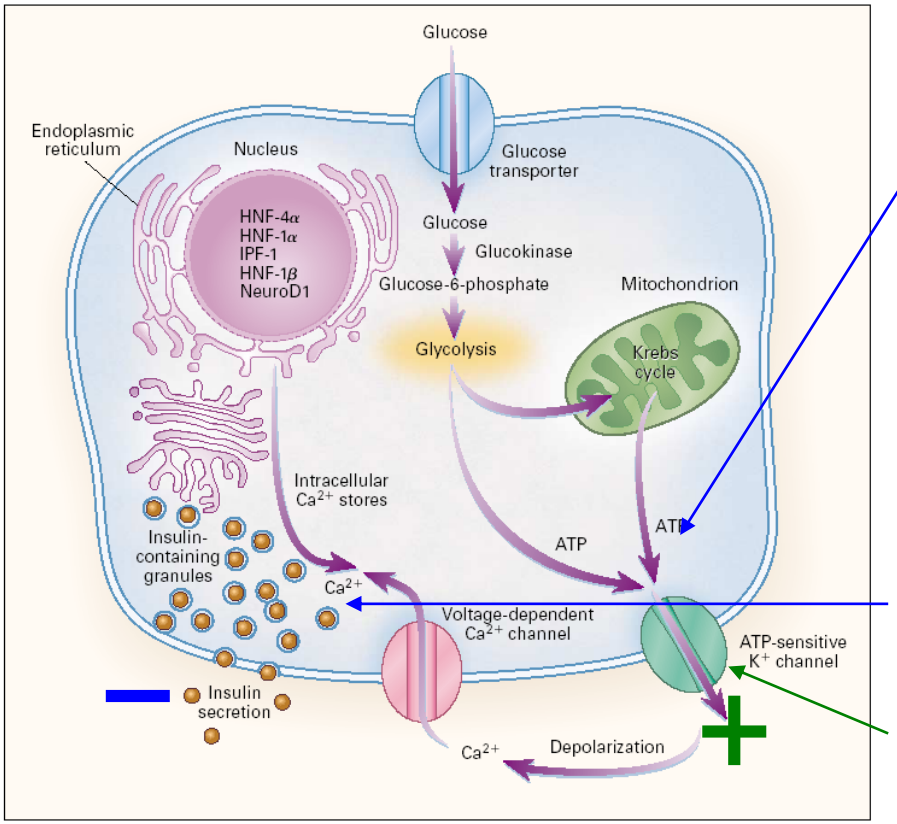


- Neonatal diabetes is a genetic disorc
- Affects insulin-producing beta cells
- Patients need insulin for life

Photo: Jan M. Lillebø, Bergens Tidende

Njølstad et al, NEJM 2001; Aukrust et al, JBC, 2014

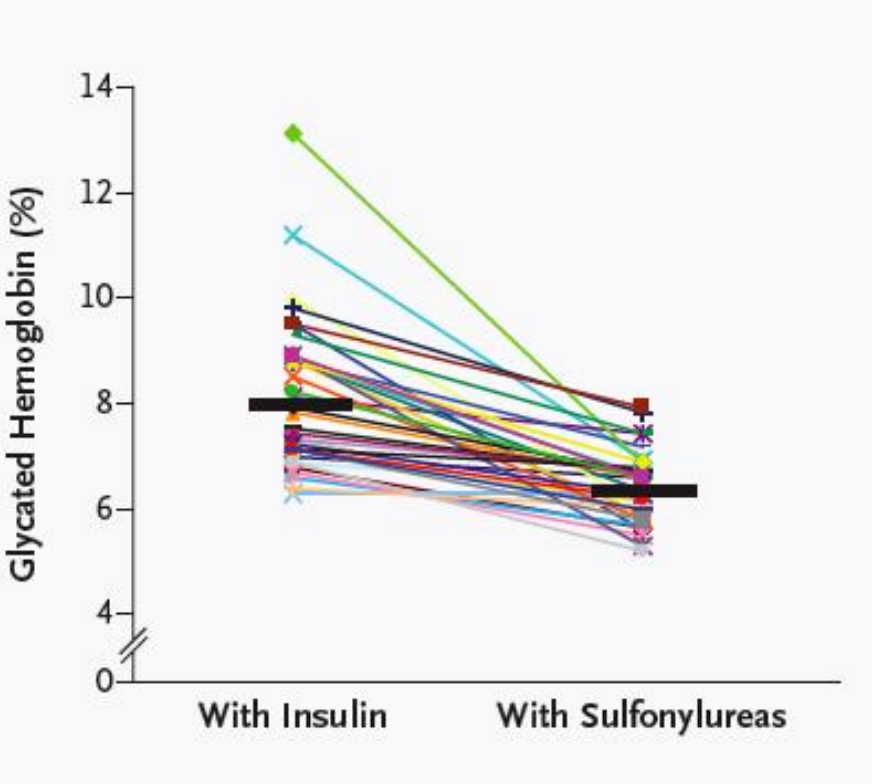
Neonatal diabetes can be due to *KCNJ11* mutations



- Mutations in *KCNJ11* can cause neonatal diabetes
- Can the oral drug sulfonylurea replace insulin?

Sagen et al, Diabetes 2004; Gloyn et al, NEJM, 2004

Changing medical practice

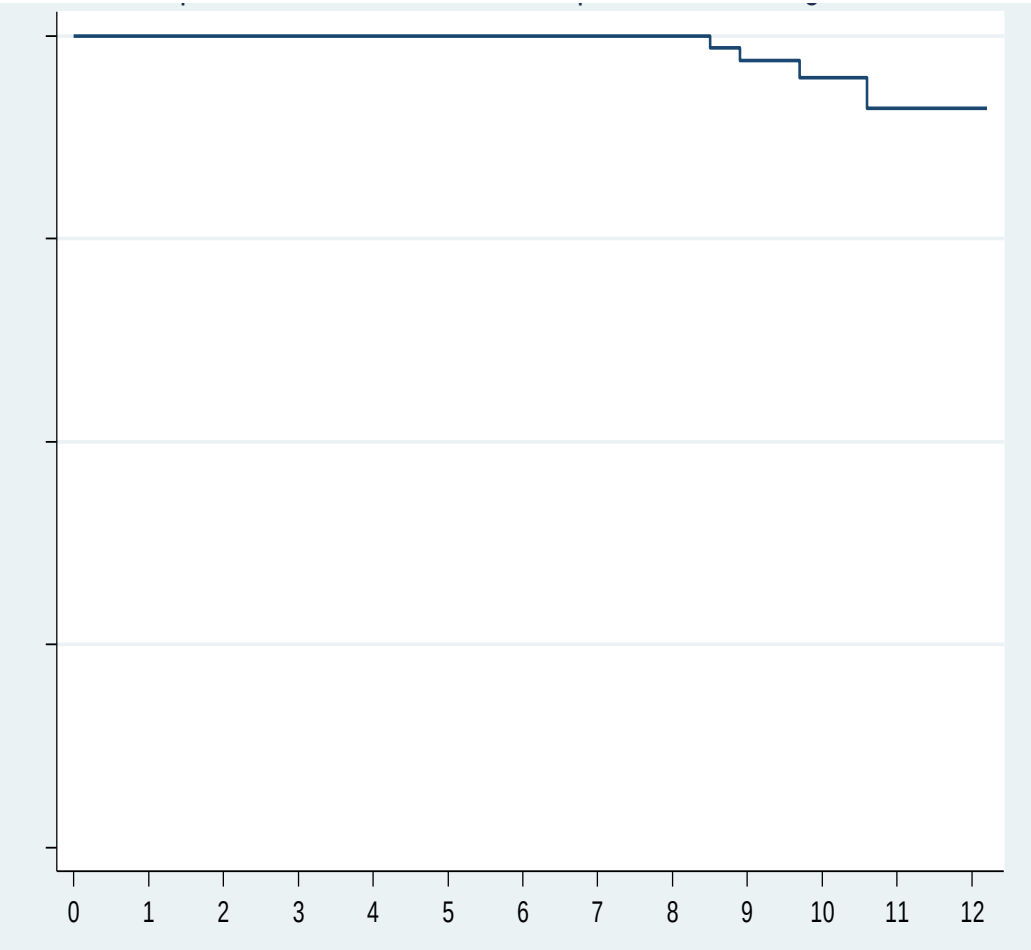


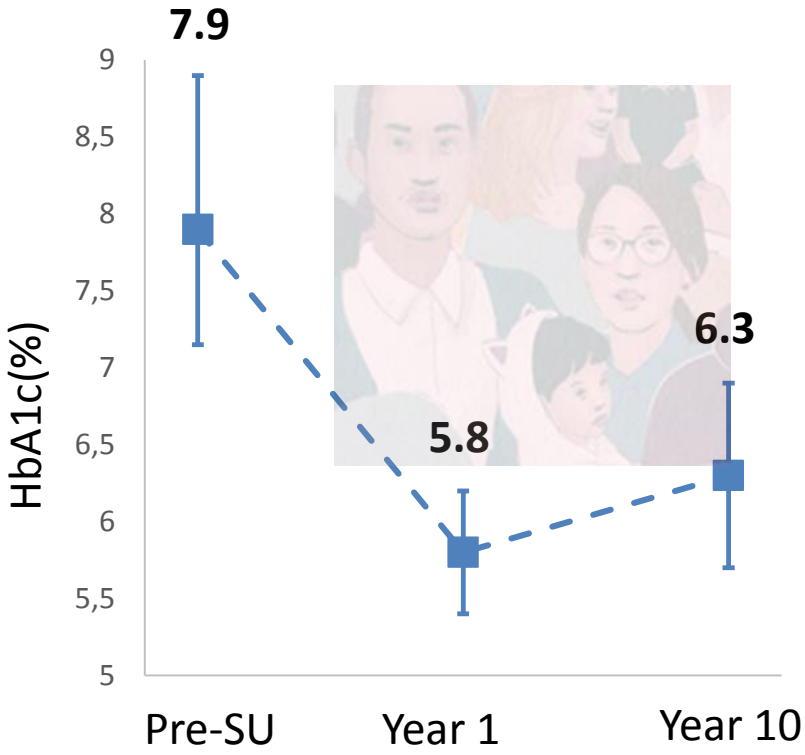
TV2, 2006

Children can avoid painful injections
Metabolic control is improved (HbA_{1c} 2%-points lower)
Reduced risk for long-term complications

Sagen et al, Diabetes 2004; Pearson, Flechtner, Njølstad et al, NEJM 2006

10 y sulfonylurea treatment is efficient and safe

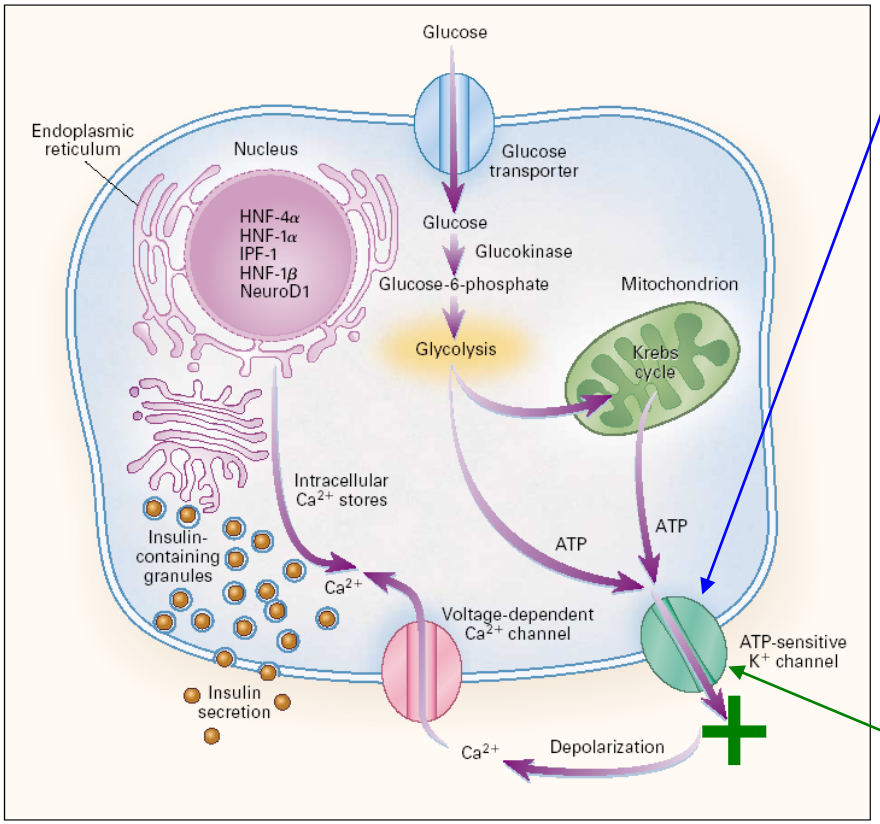




Kaplan-Meier survival estimate – 94% remaining on SU only

Sulen, Bowman, Polak, Barbetti, Skrivarhaug, Hattersley, Njølstad; unpublished

Neonatal diabetes due to *ABCC8* mutations



K_{ATP} channel (*ABCC8*)

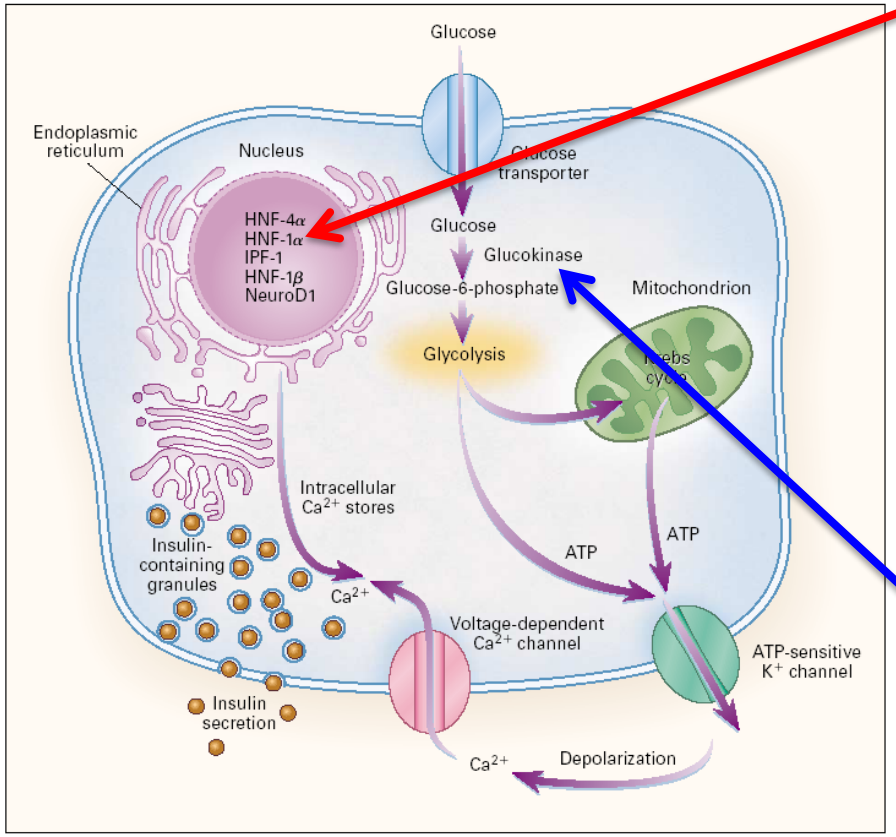
Sulfonylurea

- Adopted from Columbia, ”T1D”, discovered at yearly control
- Very small doses of sulfonylurea needed to replace insulin

Åsta Saulen, Grete Vigemyr et al, unpublished; Diabetes, 2015

HNF1A and *GCK* MODY have different clinical course

HNF1A



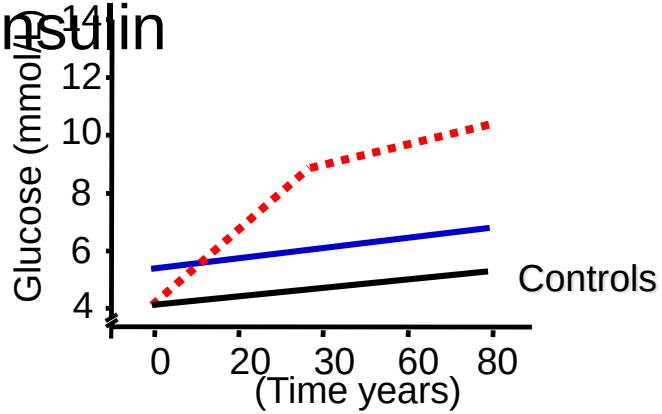
GCK

Sagen et al, Ped Diabetes 2008; Bjørkhaug et al, JCEM 2003

HNF1A and *GCK* MODY have different clinical course

HNF1A

- Progressive diabetes
- High risk for diabetes complications
- Sulfonylurea tablets and/or insulin



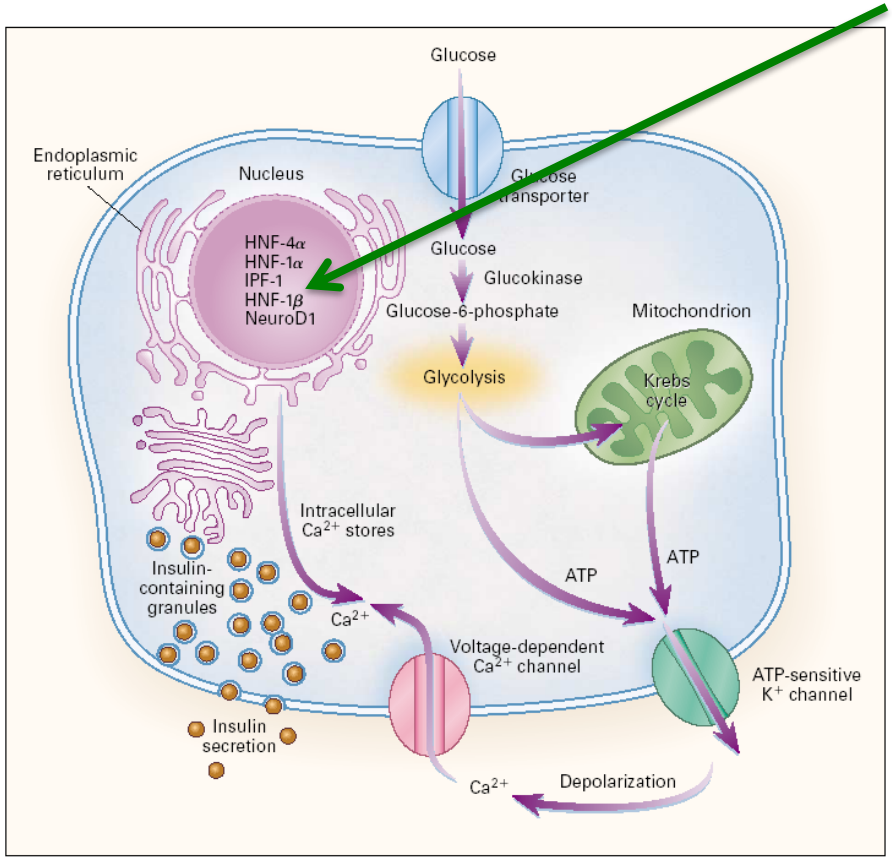
- Stable diabetes
- No risk for diabetes complications
- No treatment

GCK

Diabetikeren 1997; Unpublished

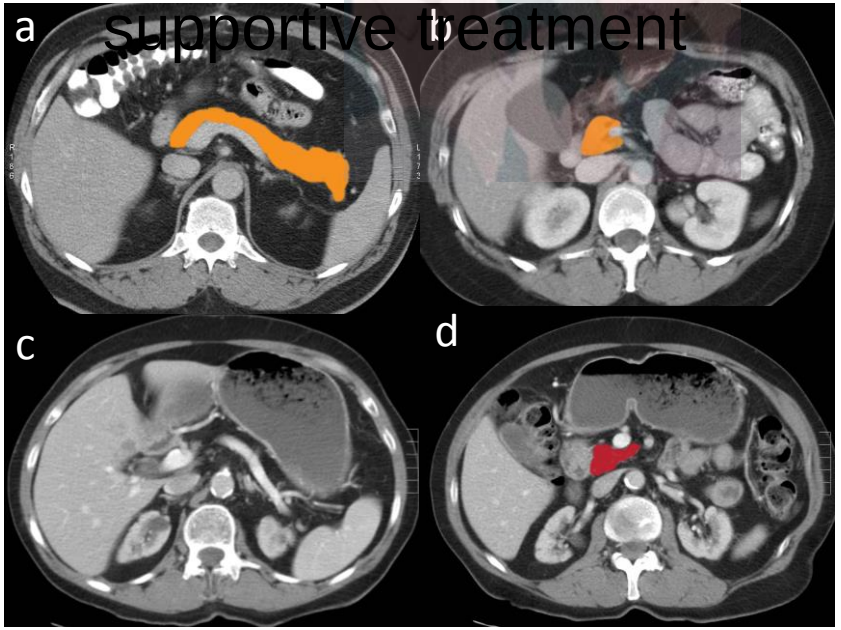
HNF1B MODY and early preventive treatment

HNF1B



- Progressive kidney failure
- Pancreas aplasia
- Diabetes +/-
- Insulin

- Early preventive and supportive treatment



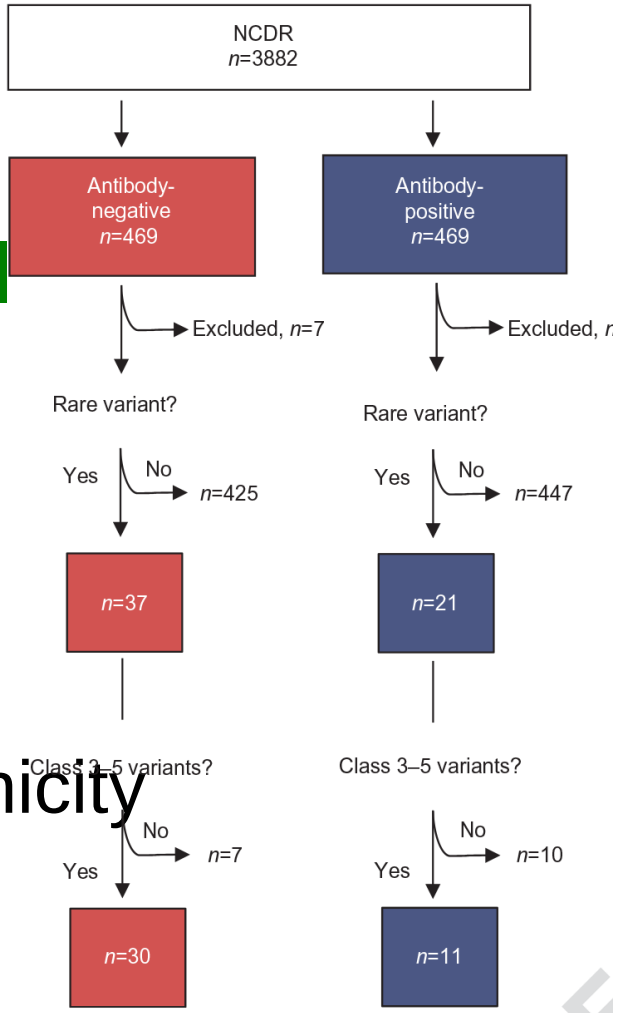
Tjora et al, Diabet Med 2013; Haldorsen et al, Nature Rev Endocrinol 2012

The Norwegian Childhood Diabetes Registry

Monogenic screen in childhood diabetes

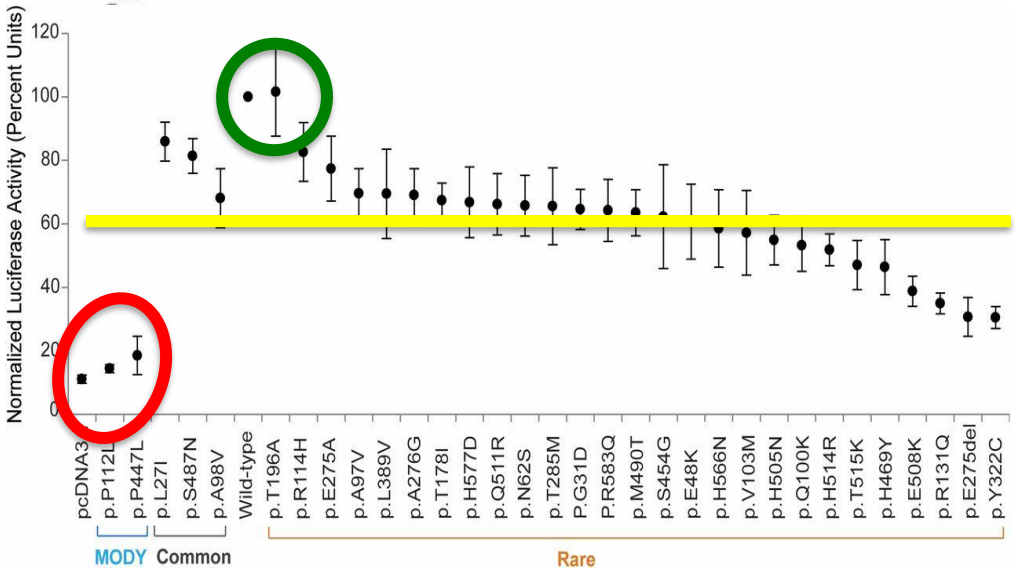
Exome sequencing of gene panel

- Monogenic diabetes genes
- 938 children with diabetes
  - 469 antibody negative
  - 469 antibody positive
- Bioinformatics score for pathogenicity



B Johansson et al, Diabetologia 2017

Childhood ”type 1 diabetes” can be monogenic diabetes



Implication for diagnosis and treatment?

- 6.5% mutation in a monogenic gene – most *HNF1A*
- Are these sensitive to sulfonylurea tablets?
- Functional studies and treatment trial under

Naimi et al. Diabetes 2017; B Johansson et al. Diabetologia 2017; Thor Bentzen, Åsta Sulen, unpublished

When to think monogenic diabetes?

Neonatal diabetes

- Less than 6 months: Neonatal diabetes!
- 80% genetic dx

MODY

- Age of diagnosis 6 months – 35 years
- Parent with diabetes of any kind, (BMI)
- Negative GAD/IA-2, elevated C-peptides
- 40% genetic dx

Genetic testing

- Haukeland University Hospital
- Next-generation panel sequencing, 2 weeks

KG JEBSEN CENTER FOR DIABETES RESEARCH

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