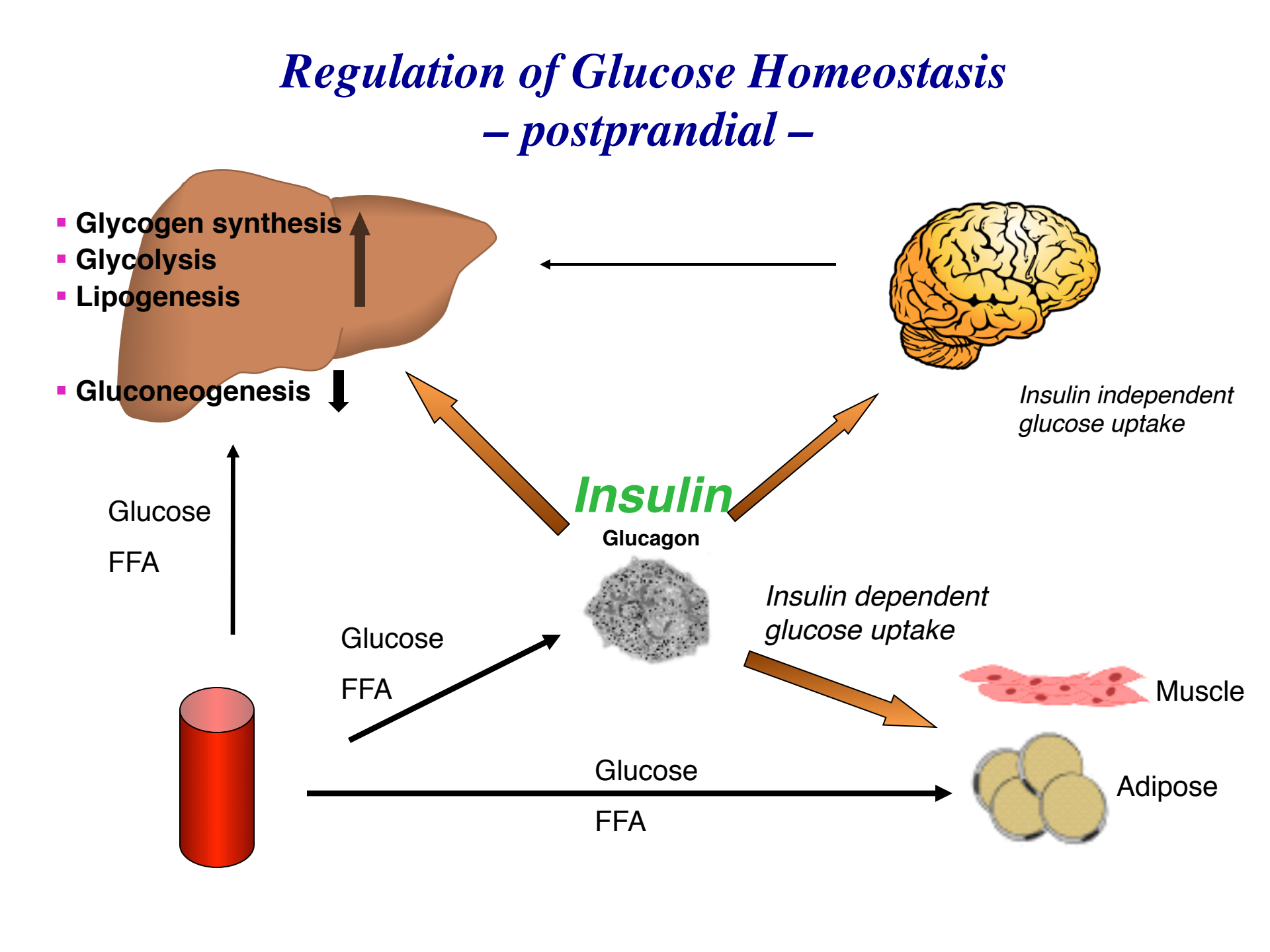
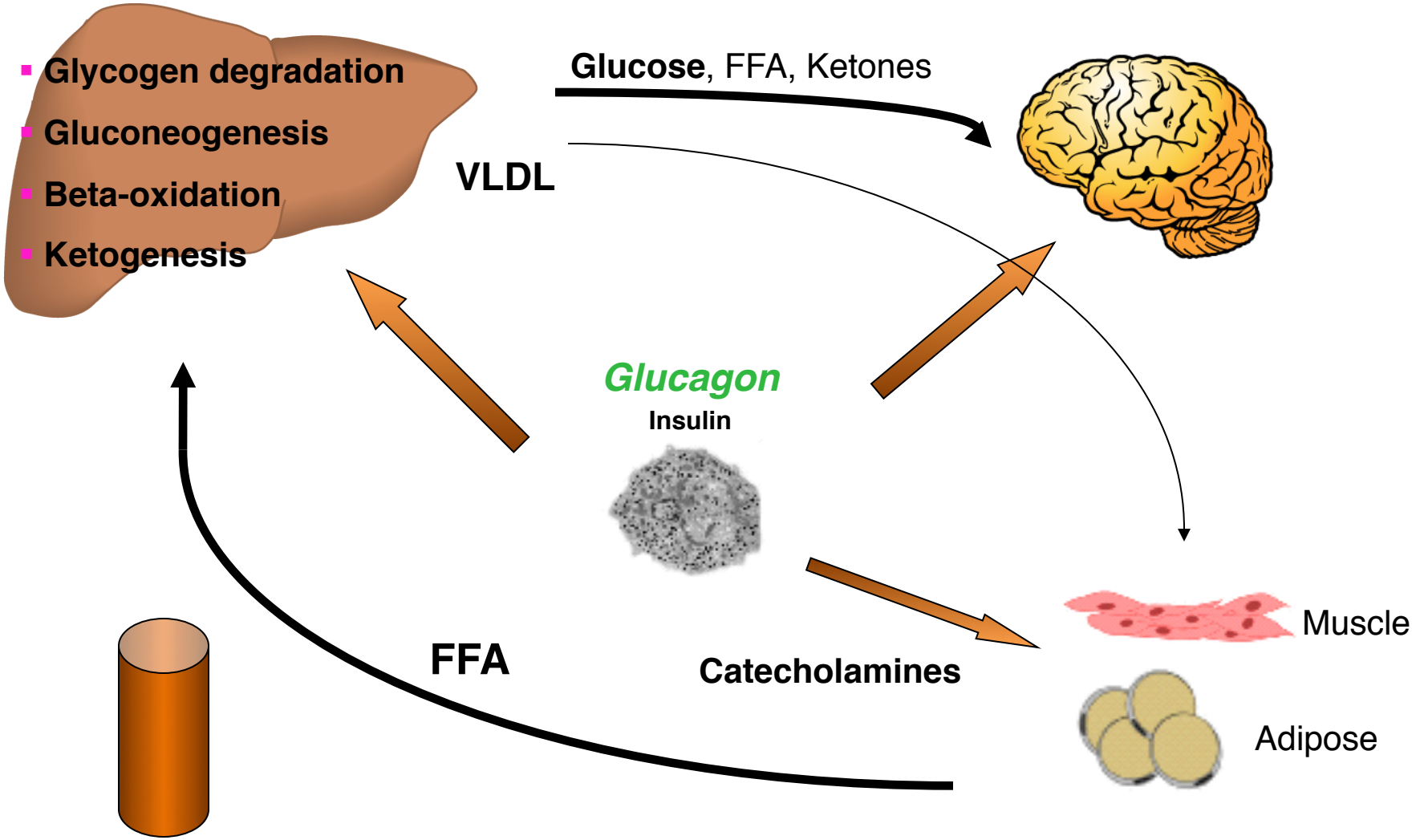
# Genetics of Type 2 Diabetes

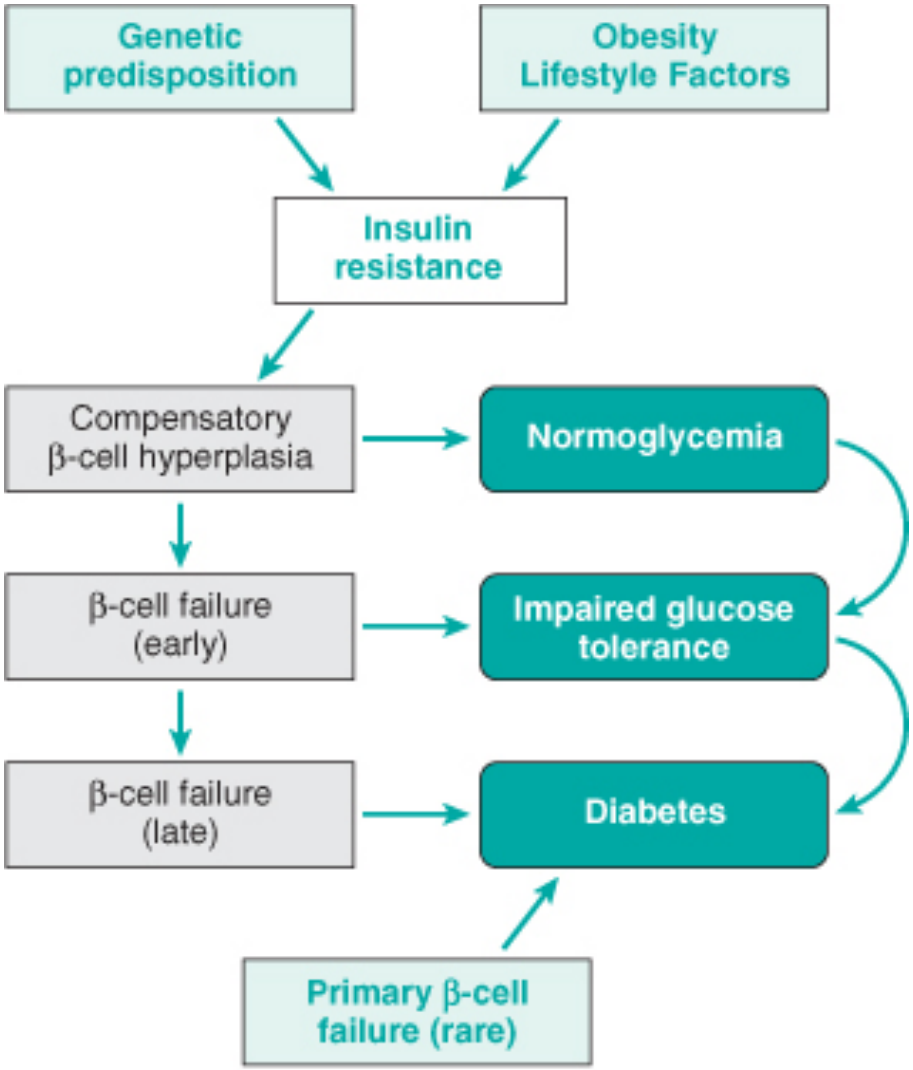
# *Regulation of Glucose Homeostasis – postprandial –*



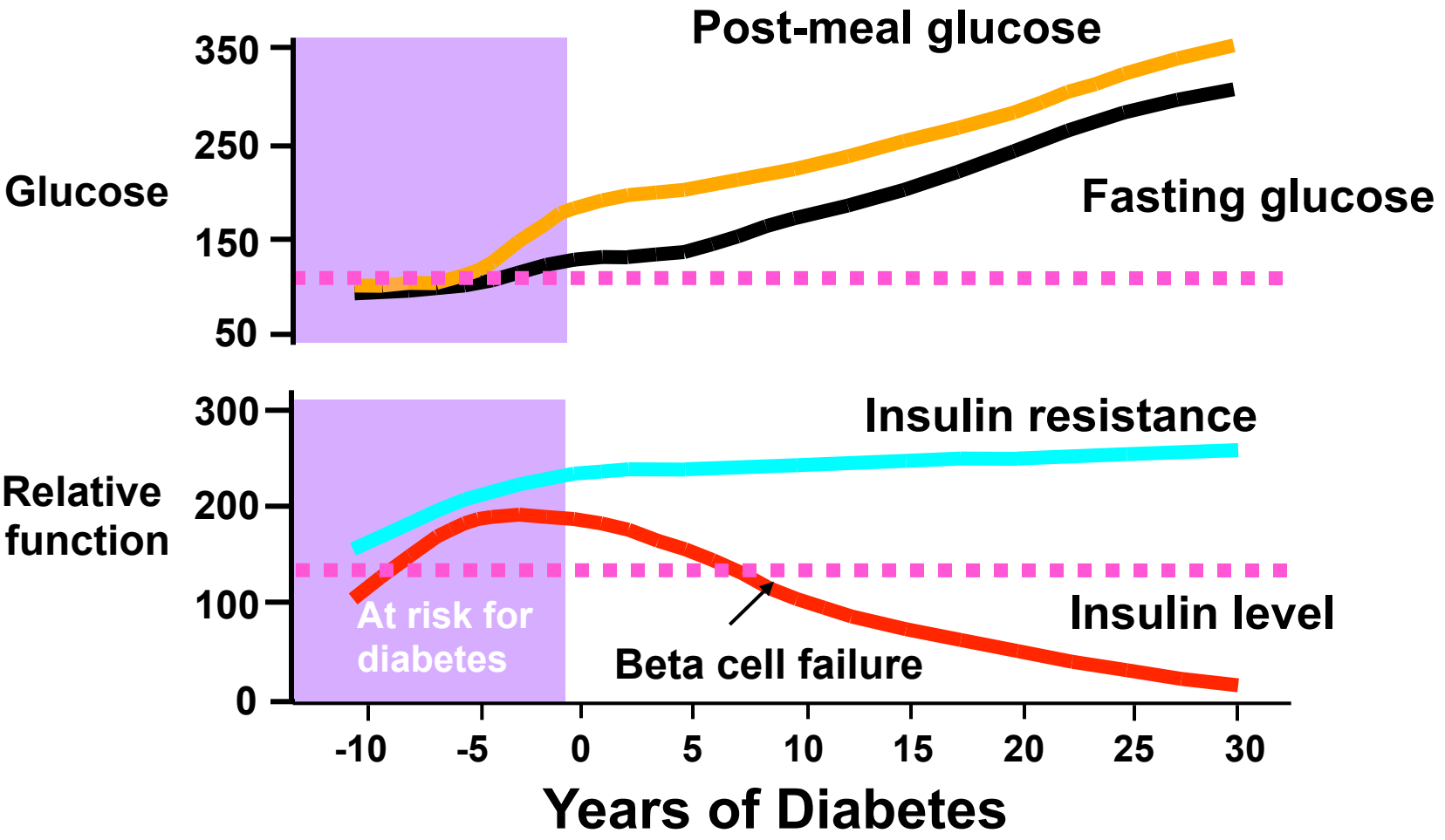
# *Regulation of Glucose Homeostasis – fasting –*



# Pathogenesis of type 2 diabetes

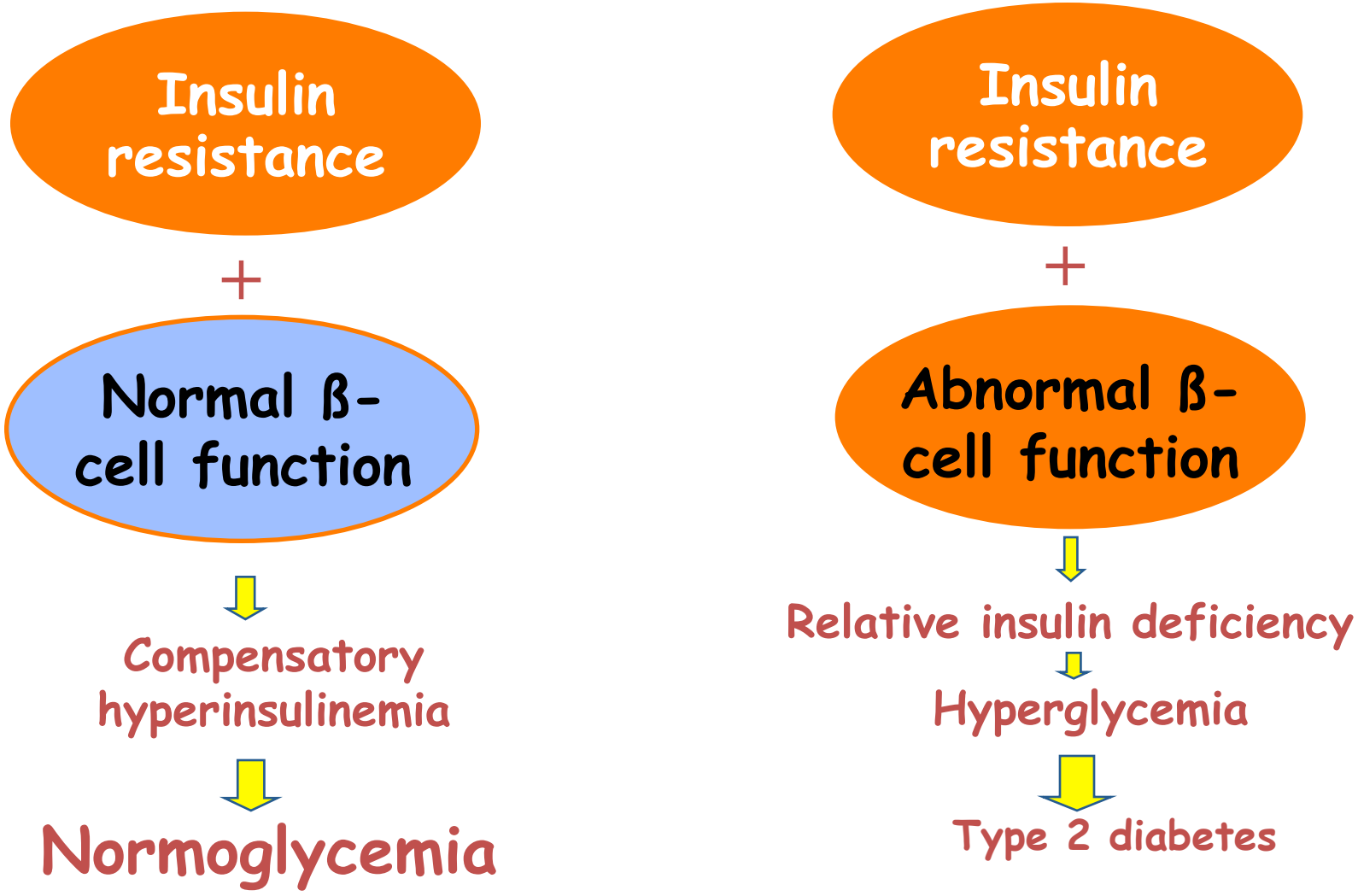


# Natural history of progression of hyperglycemia in type 2 diabetes

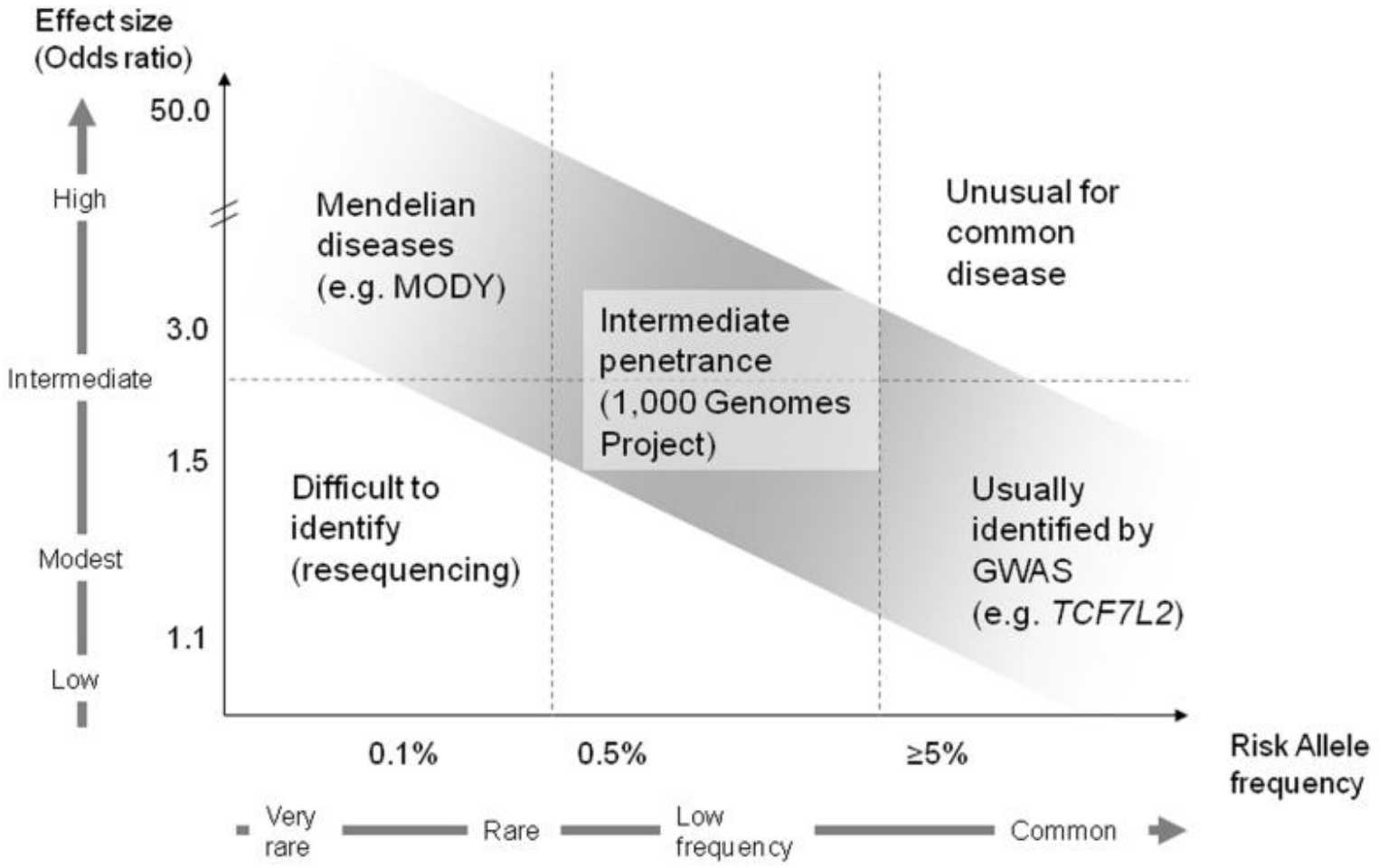


# Type 2 Diabetes

## Insulin Resistance & Impaired ß-Cell Function



# Frequency of genetic variation and disease susceptibility



# Genetics of Type 2 Diabetes

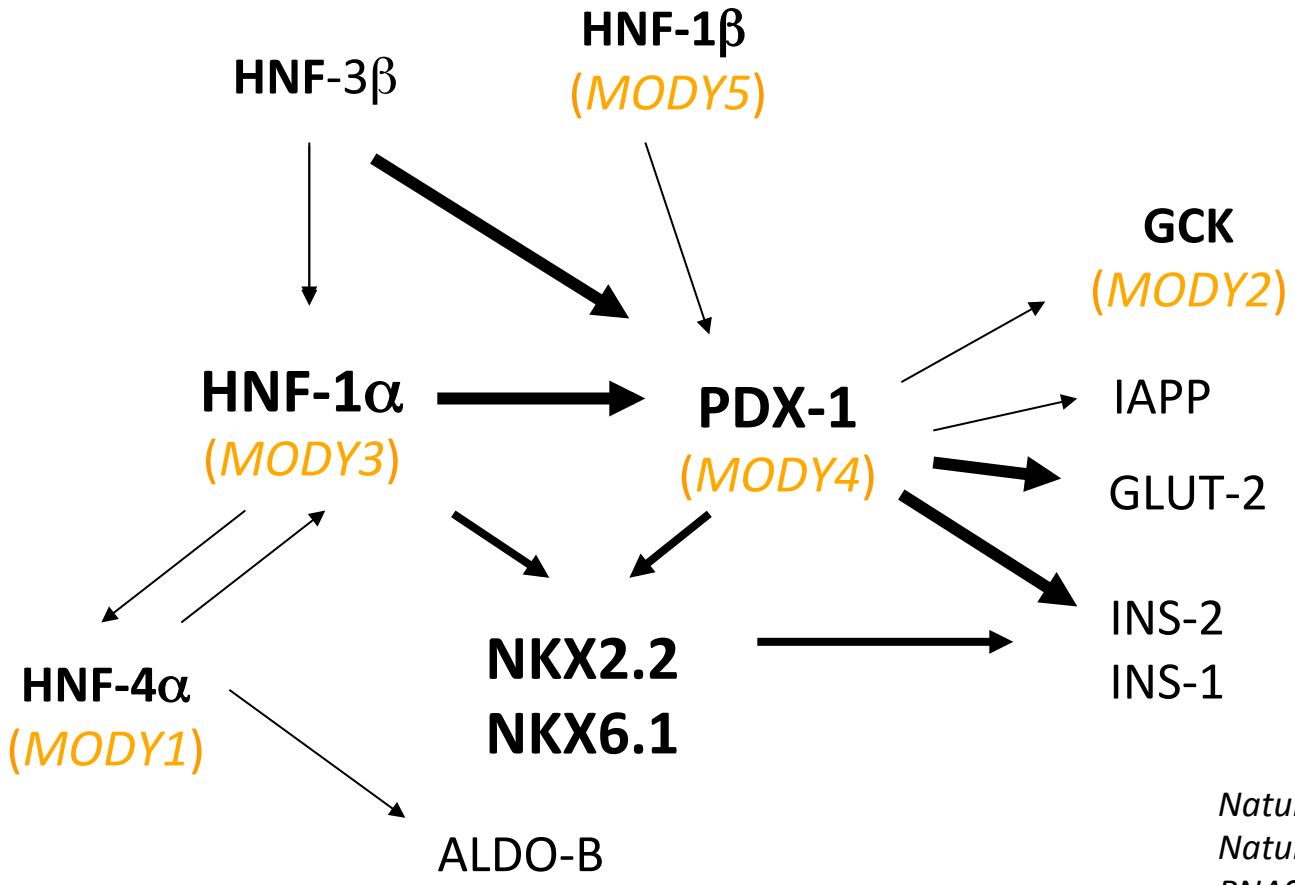
***Genetics of early-onset type 2 diabetes***

- Early-onset diabetes (< 25 years)
- Autosomal-dominant inheritance
- Defect in insulin secretion
- Absence of insulin resistance/obesity
- Phenotypically and genetically heterogeneous

# Genetic classification of early-onset type 2 diabetes (MODY)

| | | |
|---|---|---|
| **MODY1:** | Chromosome 20q12 | **HNF-4α** |
| **MODY2:** | Chromosome 7p15 | **GCK** |
| **MODY3:** | Chromosome 12q24 | **HNF-1α** |
| **MODY4:** | Chromosome 13q12 | **PDX-1** |
| **MODY5:** | Chromosome 17cen | **HNF-1β** |
| **MODY6:** | Chromosome 2q32 | **NEURO-D1** |

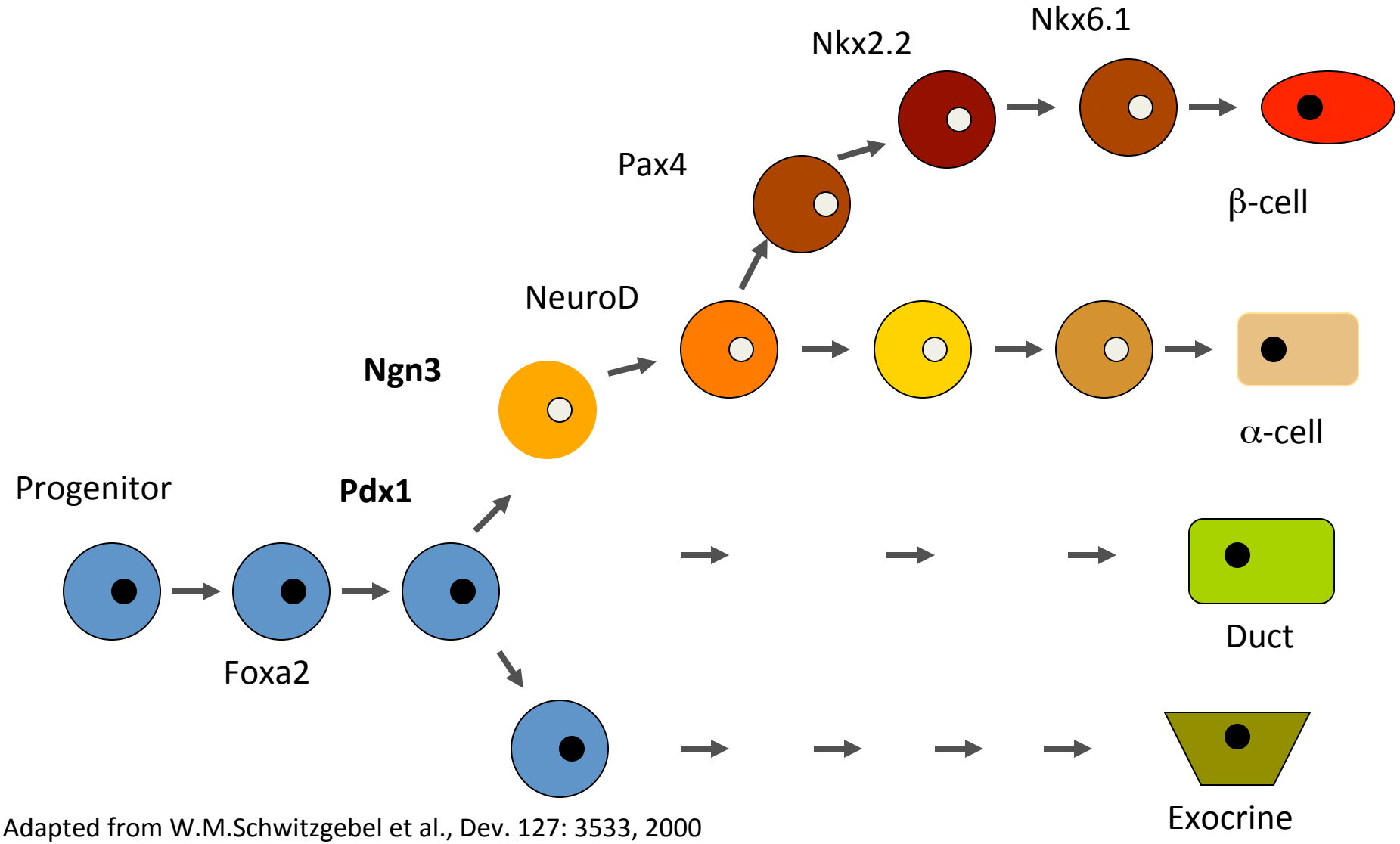
# The HNF-Transcriptional Network and its Regulation of Pancreatic β-Cell Genes





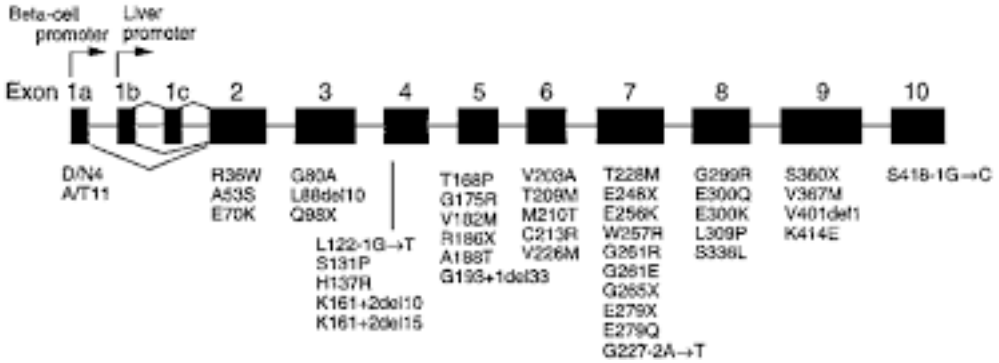
*Nature Genetics* **2**: 153-156, 1992
*Nature* **356**: 721-722, 1992
*PNAS USA* **89**: 7698-7702, 1992
*N Engl J Med* **328**: 697-702, 1993
*PNAS USA* **93**:3937-3941, 1996
*Nature* **384**:458-460, 1996

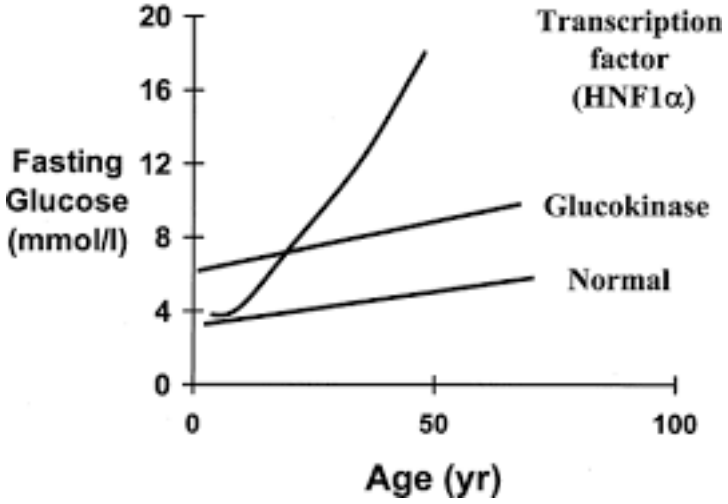
# Endocrine pancreas differentiation



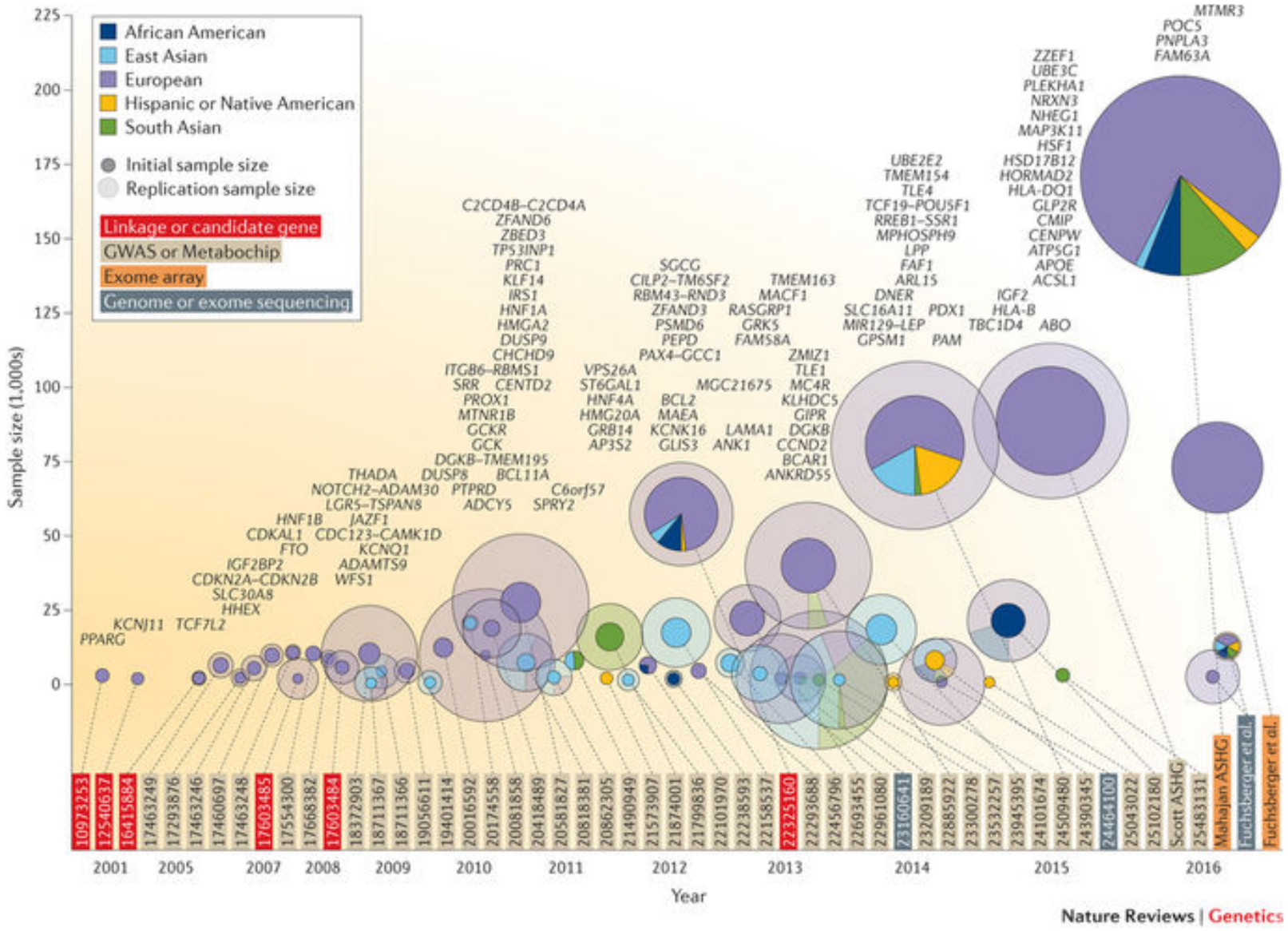

Adapted from W.M.Schwitzgebel et al., Dev. 127: 3533, 2000

# Glucokinase mutations

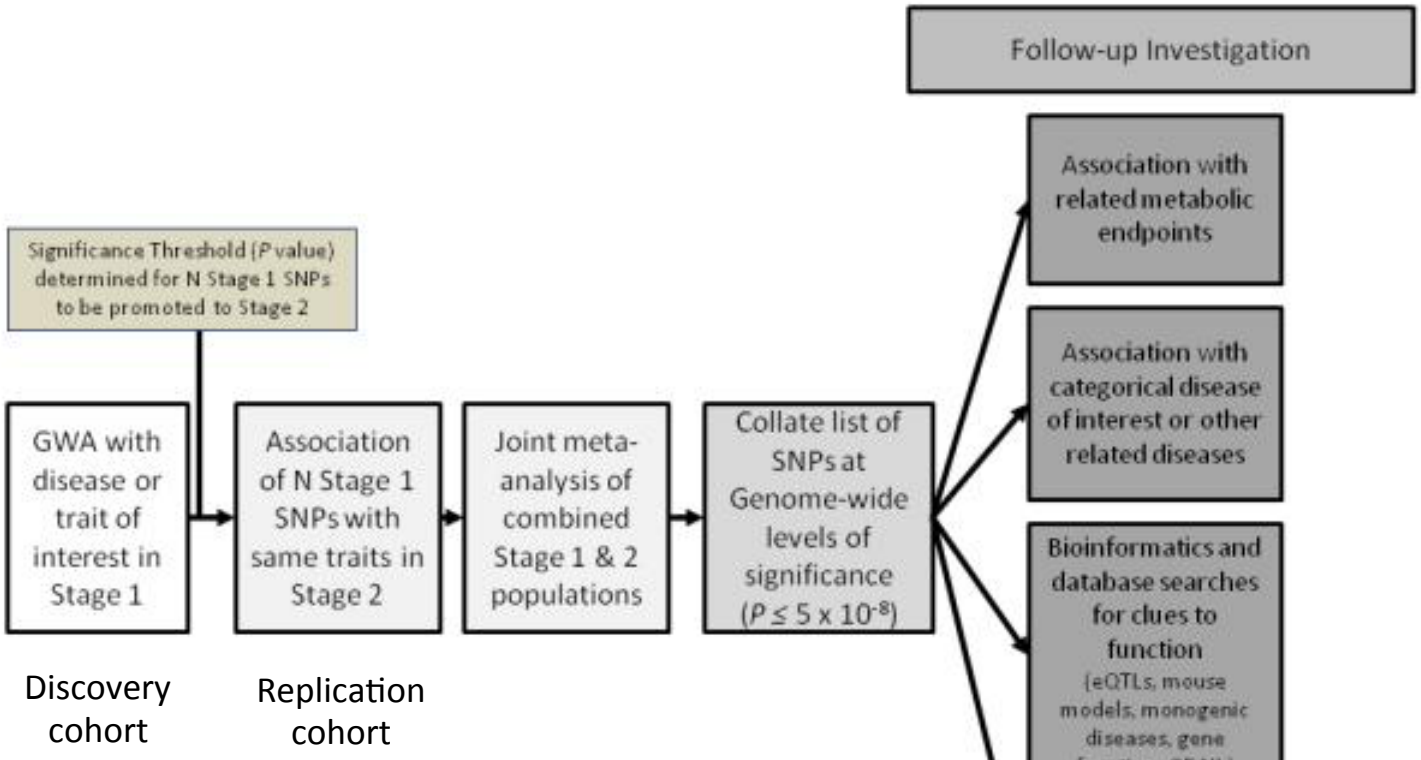


# History of T2D GWAS



# Schematic of a typical GWAS design




The top SNPs are promoted to stage 2 cohort based on:

1) A significance threshold that is usually dictated by pragmatic considerations,
2) whether there is prior knowledge of association between the disease the variant
3) whether an association is biologically plausible.
4) The SNPs that reach levels of genome-wide significance ($P$=5×10−8) are explored further using the functional analysis techniques listed.

# What have we learned from GWAS:

# GWAS has illustrated novel pathways

- The association of a missense mutation rs13266634 in *SLC30A8* (encoding Zn2+ Transporter, ZnT-8) with type 2 diabetes has highlighted the importance of Zn2+ transport in the β cell, the variant's influence on insulin packaging and secretion, and this pathway's potential relevance as a drug target.

# GWAS findings point to new fundamental biology

- The intronic SNP rs7903146 in *TCF7L2* is located in an open chromatin site in β cells; its risk T alllele is correlated with an increased transcription in human islets and with increased expression in cellular luciferase assays.

# Genetic discoveries support prior epidemiological observations

- The T allele of rs17550 in *FADS1* is associated with higher fasting glucose, lower HOMA-B, increased LDL and HDL cholesterol, and decreased triglycerides.
- Variants in *HNF1A* are associated with type 2 diabetes, C-reactive protein, coronary artery disease, and LDL cholesterol levels.
- *MTNR1B* and *CRY2* link T2D and circadian rhythms, in support of animal and human studies.
- *ADCY5* variants increase fasting and 2-hour glucose, as well as risk of type 2 diabetes; they are also associated with lower birth weight.

# Most GWAS loci point to the pancreatic β-cell

- The majority of loci associated with type 2 diabetes point to primary
- defects in the β cell. However,
- *IRS1* (encoding insulin receptor substrate-1) has been associated with T2D.
- Both *IGF1* and *GCKR* have been associated with measures of insulin resistance (HOMA-IR and fasting insulin) at genome-wide levels of significance.
- Increasing sample size and modifying study design have helped discover variants associated with insulin resistance.

# Genetic variability only explains 10% of T2D heritability

- GWAS have been limited to common variants and primarily
- populations of European descent.
- In order to find the “missing heritability” investigators are pursuing fine-mapping around the associated regions, leveraging the 1,000 Genomes project, applying next-generation sequencing, analyzing the Metabochip, using improved informatics for gene × gene and gene × environment interactions, expanding to non-white populations, and incorporating prior biological knowledge to interpret significance of variants.

# Common genetic variants are not yet useful in clinical prediction

- Although variants may be limited in their ability to predict type 2 diabetes, genetic information may sway a person to change lifestyle behavior that may reduce their risk of developing the disease.
- Genetic prediction may be more useful in younger age groups, before clinical risk factors develop.

# Common genetic variants provide an opportunity for therapeutic intervention and pharmacogenetic clinical trials

- Pharmacogenetic studies in polygenic diabetes have studied primarily *PPARG, KCNJ11, TCF7L2*.
- Two correlated variants at *KCNJ11* and *ABCC8* are associated with sulfonylurea failure and decreased mean fasting glucose on sulfonylurea therapy.
- Carriers of risk variants at *TCF7L2* are more likely to fail sulfonulyurea therapy than metformin and more likely to be on insulin therapy rather than diet alone.

# What's next?

- Using next-generation sequencing techniques to discover less common and rare variation.
- Fine-mapping and applying biological insight to the discovered associations to determine the causal variant.
- Exploiting genetic pleiotropy to understand how these genetic variants link common diseases.
- Continuing to develop informatics methods that examine epistasis and gene × environment interaction.
- Examining populations of non-European descent.
- Translating genetic knowledge to the clinician's bedside with targeted treatment algorithms and risk assessment tools that may influence patient's behavior based on risk.
- Leveraging the welcome collaborative spirit that has permeated the field to catalyze large international studies to enhance our understanding of the genetics of T2D.