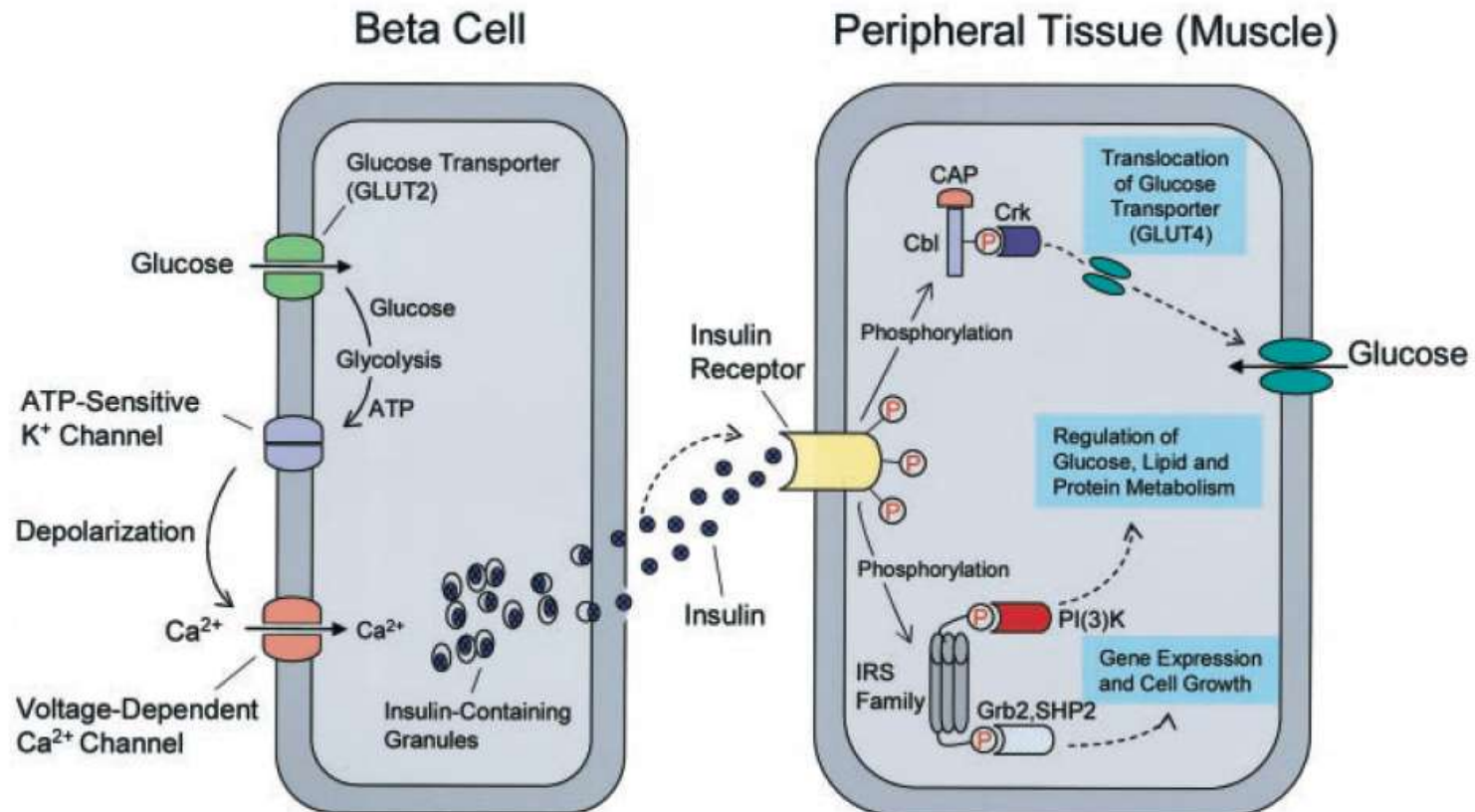


Etiology and genetics of type 2 diabetes

Kyong Soo Park
Seoul National University

Definition of Diabetes Mellitus

- a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both.

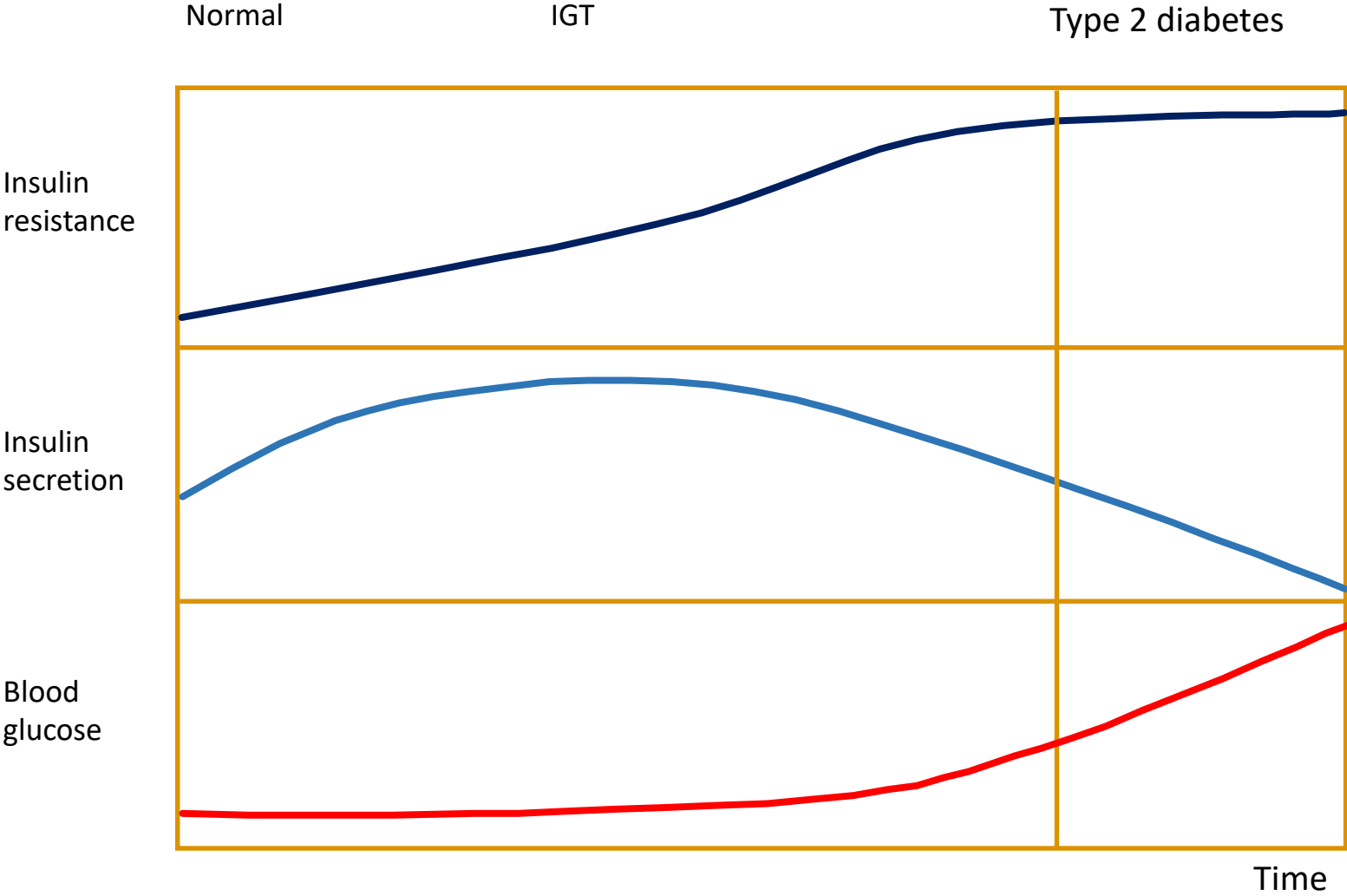


Type 2 Diabetes – due to a progressive loss of β -cell insulin secretion frequently on the background of insulin resistance

- may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance

Type 1 Diabetes – due to autoimmune β -cell destruction, usually leading to absolute insulin deficiency

Natural History of Type 2 Diabetes



Adapted from: Edelman SV, In *Advances in Internal Medicine* 1998; 43:449–500.

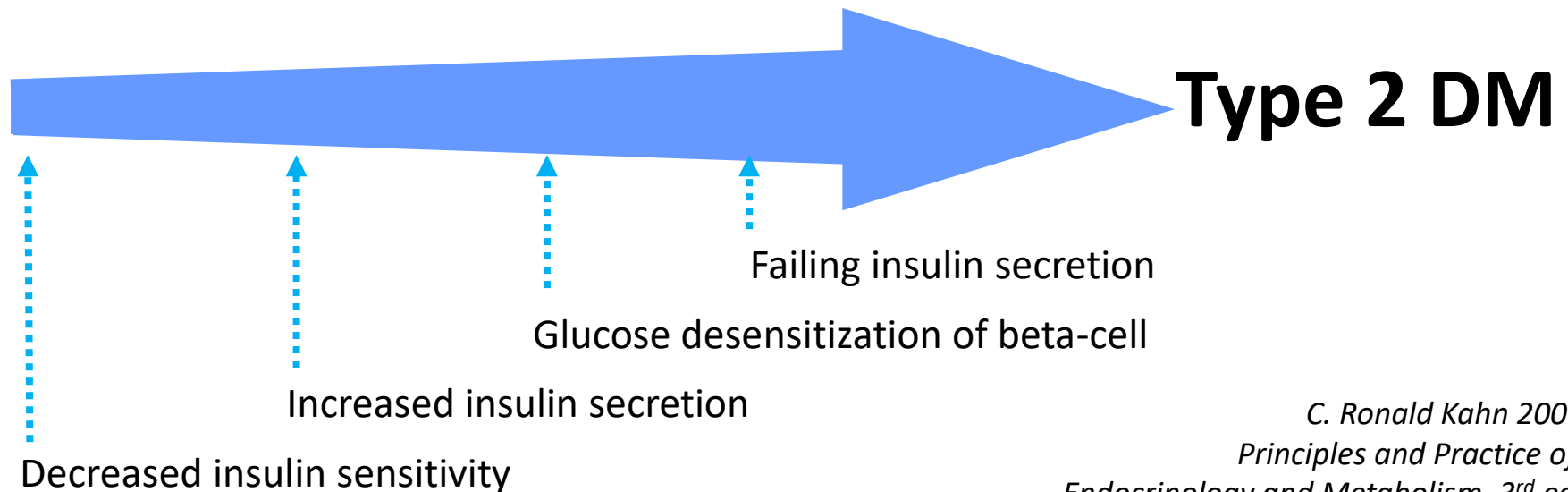
Pathogenesis of Type 2 diabetes

Genetic Factors

- Insulin secretion genes
- Beta-cell capacity genes
- Insulin resistance genes
- Obesity genes etc.

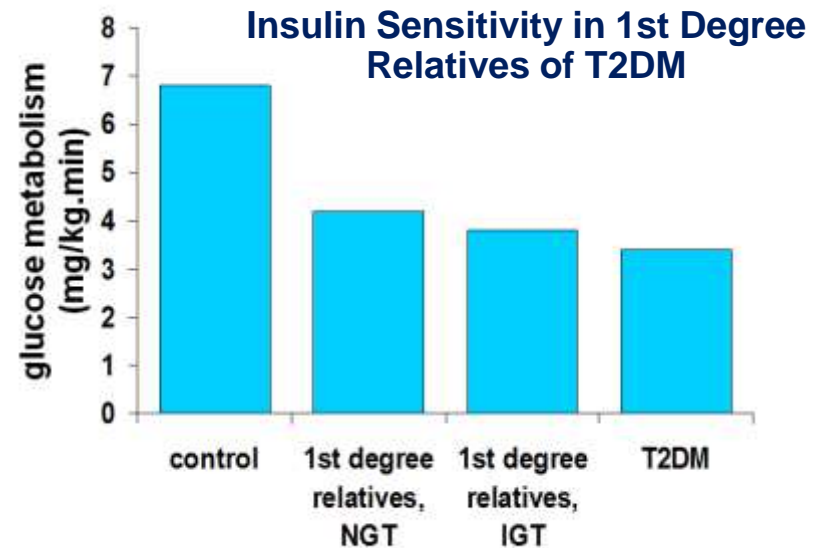
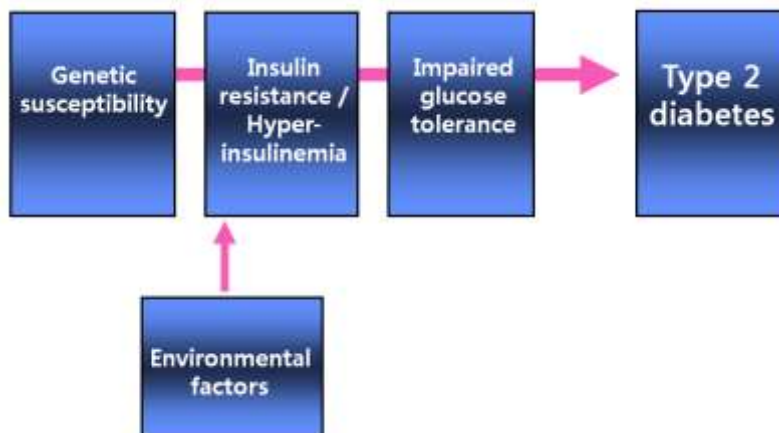
Environmental Factors

- Obesity
- Physical inactivity/ Age
- Diet
- Environmental toxin? etc



Type 2 Diabetes: Genetic Disease

- Concordance rate in identical twins : 70 - 90%.
- Individuals with a parent with type 2 DM have an increased risk of diabetes: If both parents have type 2 DM, the risk in offspring may reach 40%.
- Ethnic differences in the prevalence of T2D
- Polygenic and multifactorial
 - Environmental factors such as obesity, nutrition or physical inactivity modulate phenotype.



Searching Genes for Type 2 Diabetes

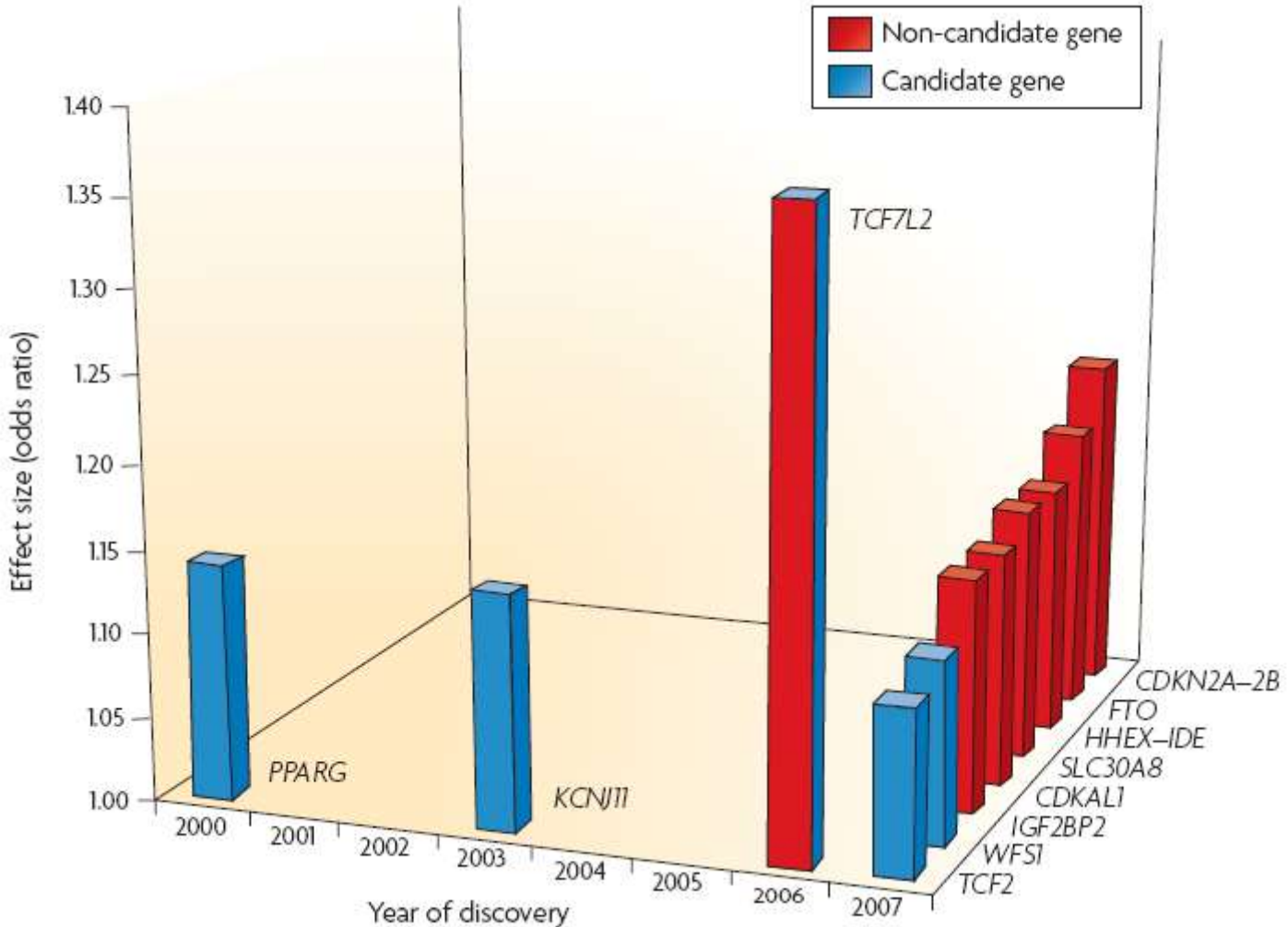
- Began over 4 decades ago with cloning of human insulin
- Candidate gene studies for insulin action and insulin secretion and family linkage studies
- **“Diabetes Mellitus — A Geneticist’s Nightmare”**



Type 2 diabetes

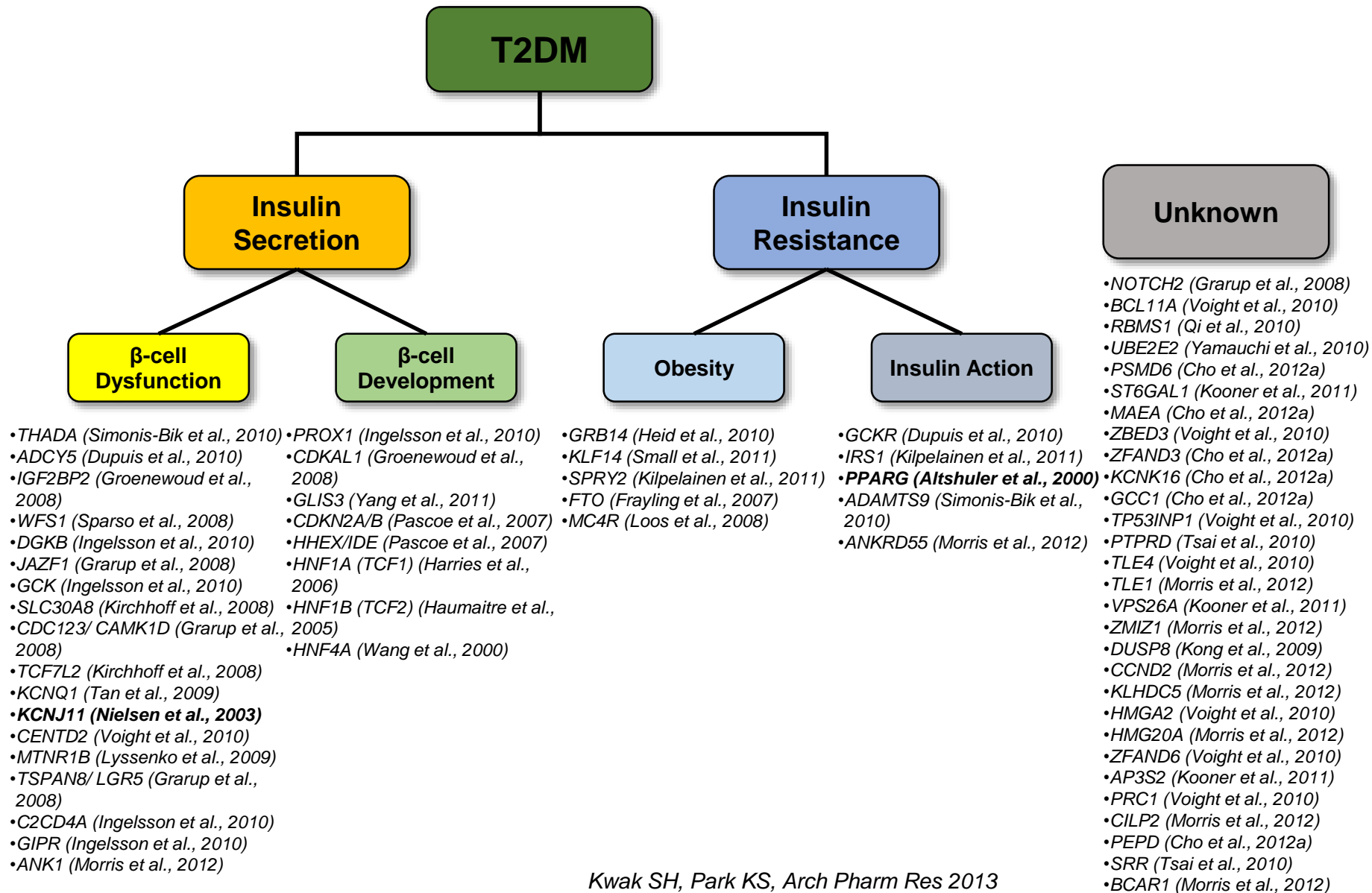
- Is genetically heterogenous
- Is almost certainly polygenic
- Strong gene/gene and gene/environmental interactions play important roles in development of type 2 diabetes

Genes confirmed to be involved in T2D risk



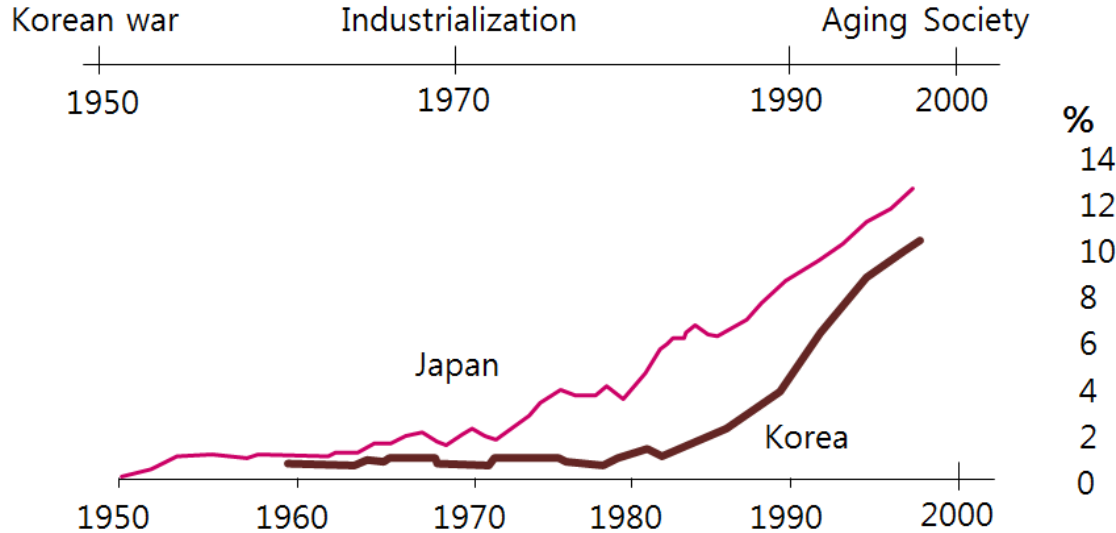
Genomewide association study

Common Genetic Variants of T2DM and Their Suggested Function



It's Not Just the Genes

Increased prevalence of diabetes



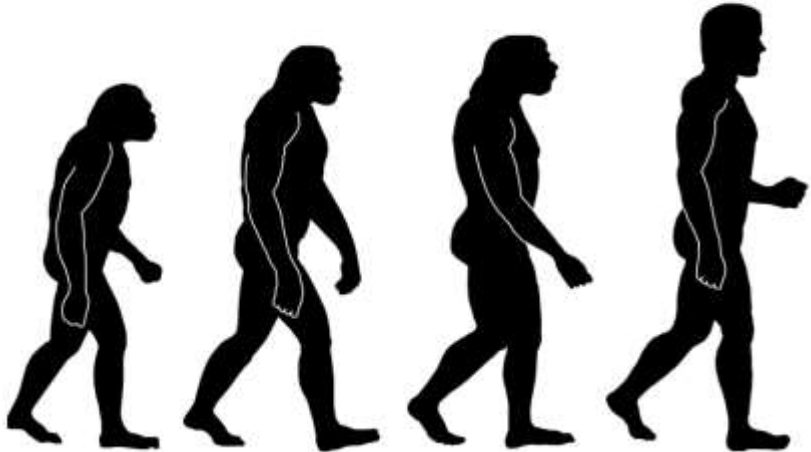
Integration of
Environmental Factors
with Genetic
Informations...

- Has potential to clarify the roles of both environment and genotype in disease causation

Environmental factors

- Westernized diet
- Physical inactivity
- Obesity
- Environmental pollutants
- Drugs etc.

Obesity and Diabetes/Insulin Resistance



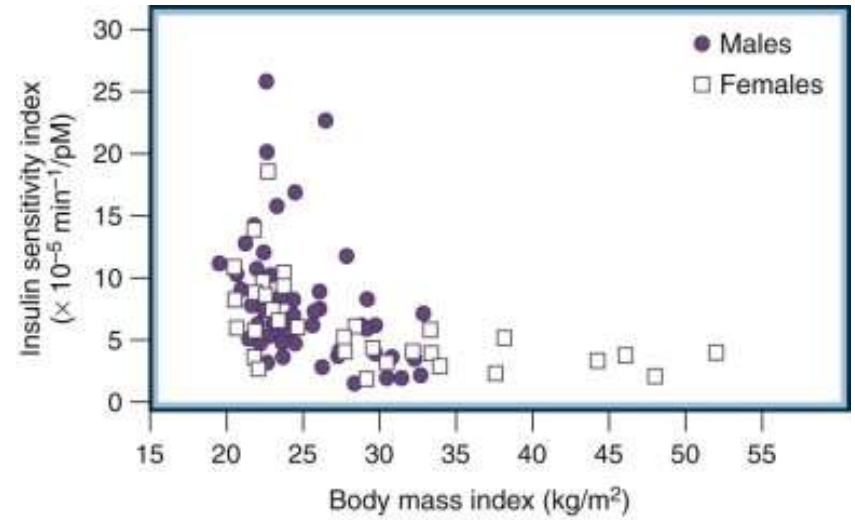
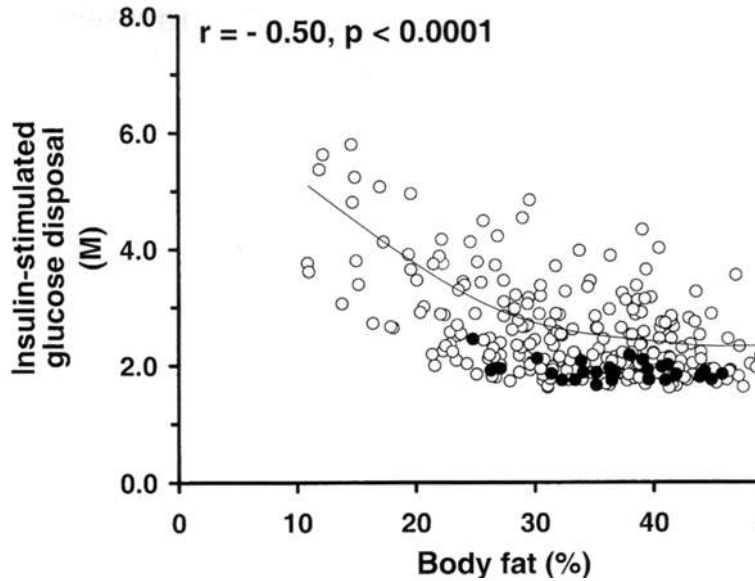
← 2.5 million years →



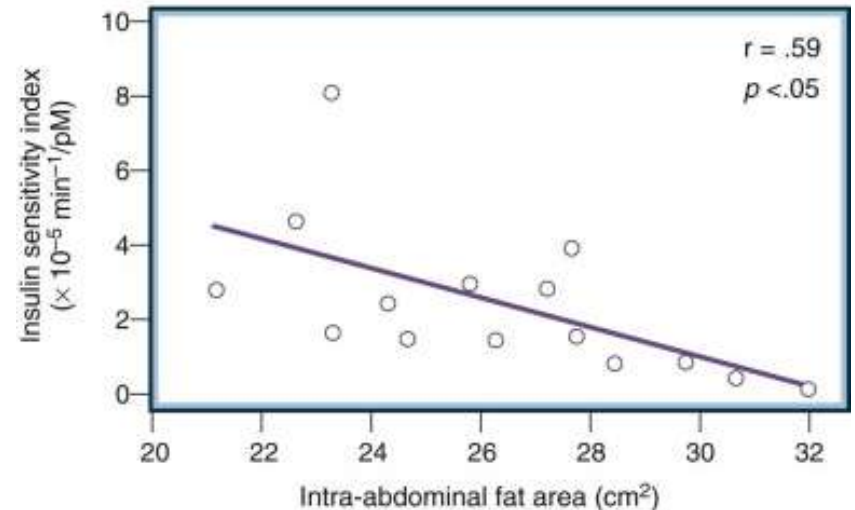
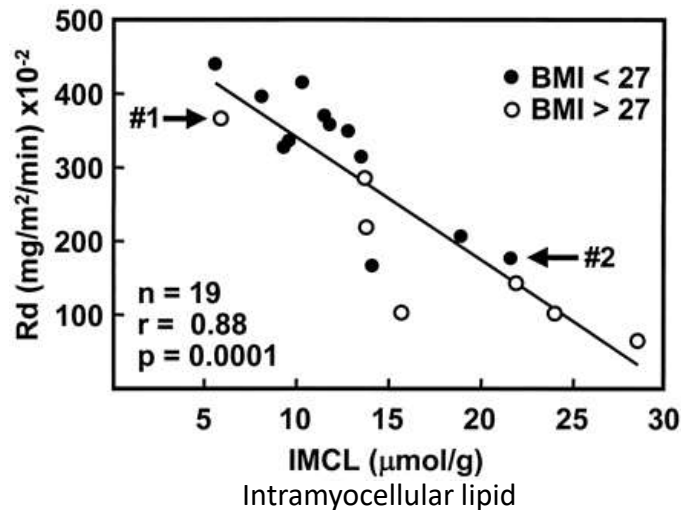
← 50 years →

Body fat and insulin resistance

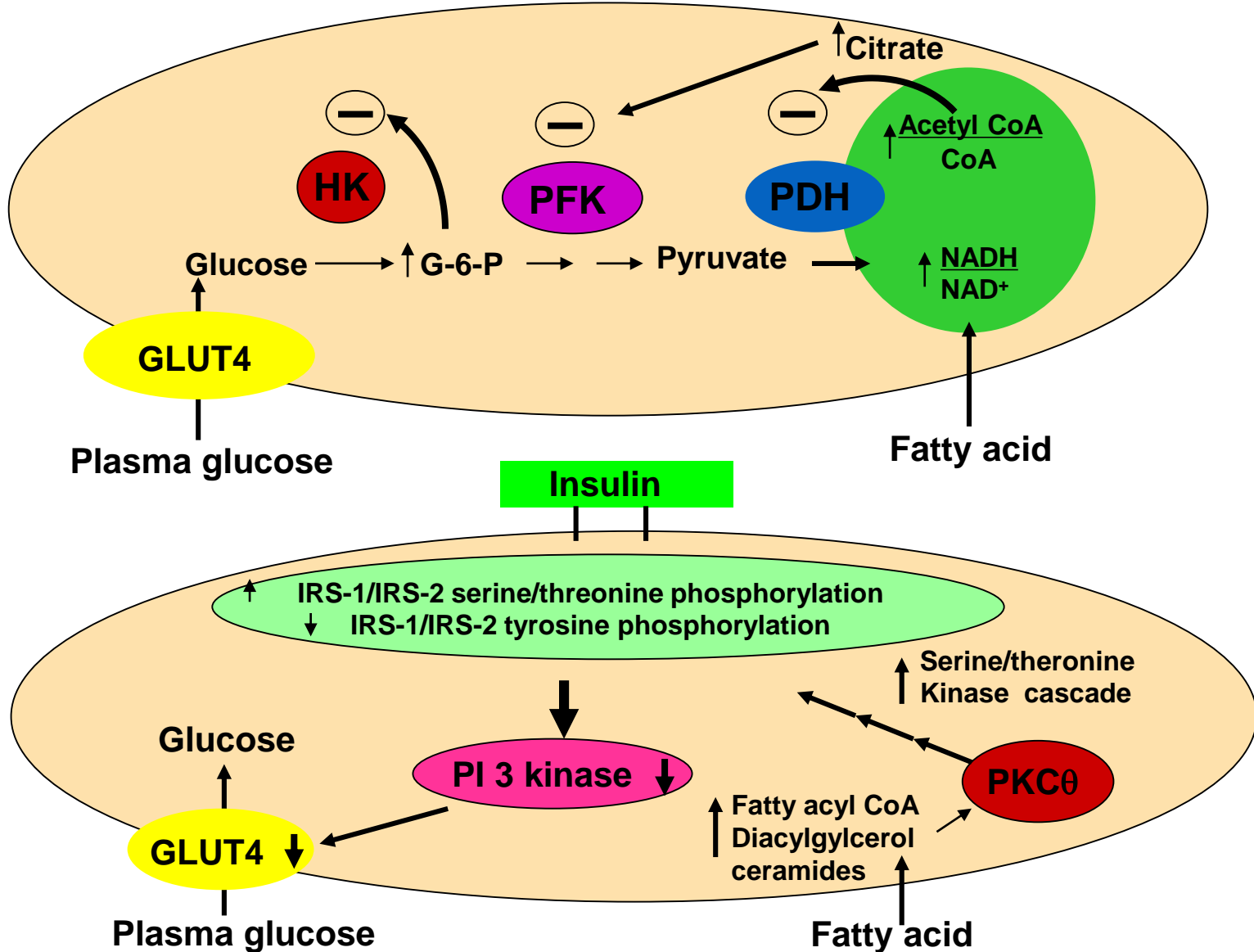
Insulin sensitivity



Insulin sensitivity



Increased FFA availability and Insulin Resistance



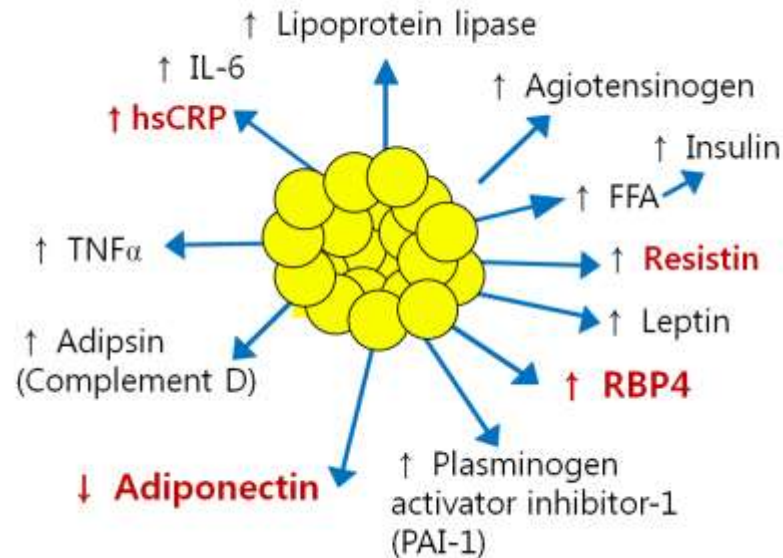
Adipokines for diabetes, metabolic syndrome and atherosclerosis

Genetic factors
Variations of adipokine genes

Environmental factors
Causing obesity

Adipocyte differentiation
ROS
Mitochondrial dysfunction
ER stress

Alterations in
Adipokines expression



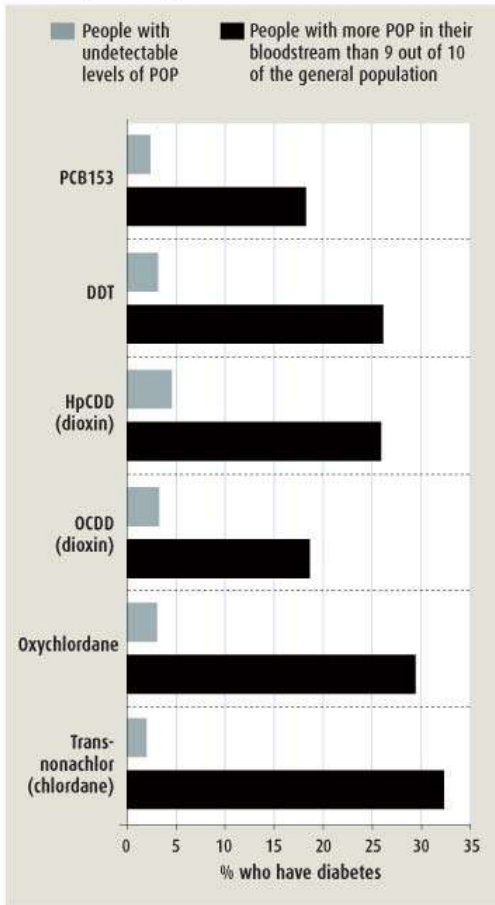
Insulin resistance
Diabetes mellitus

Atherosclerosis

Persistent organic pollutants(POPs) and diabetes

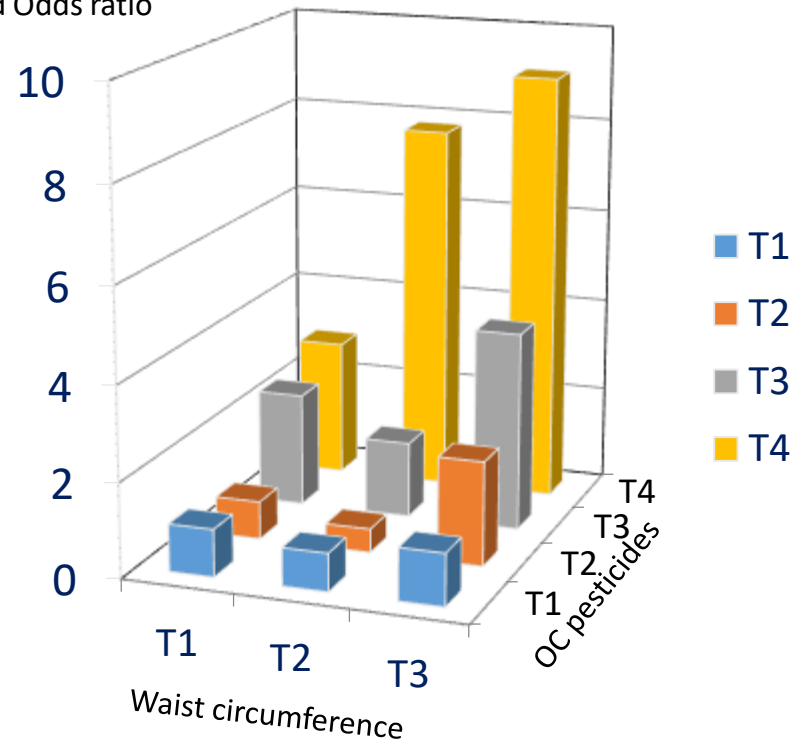
THE POPS PROBLEM

People with high levels of POPs in their bloodstream are much more likely to have type 2 diabetes than those with none



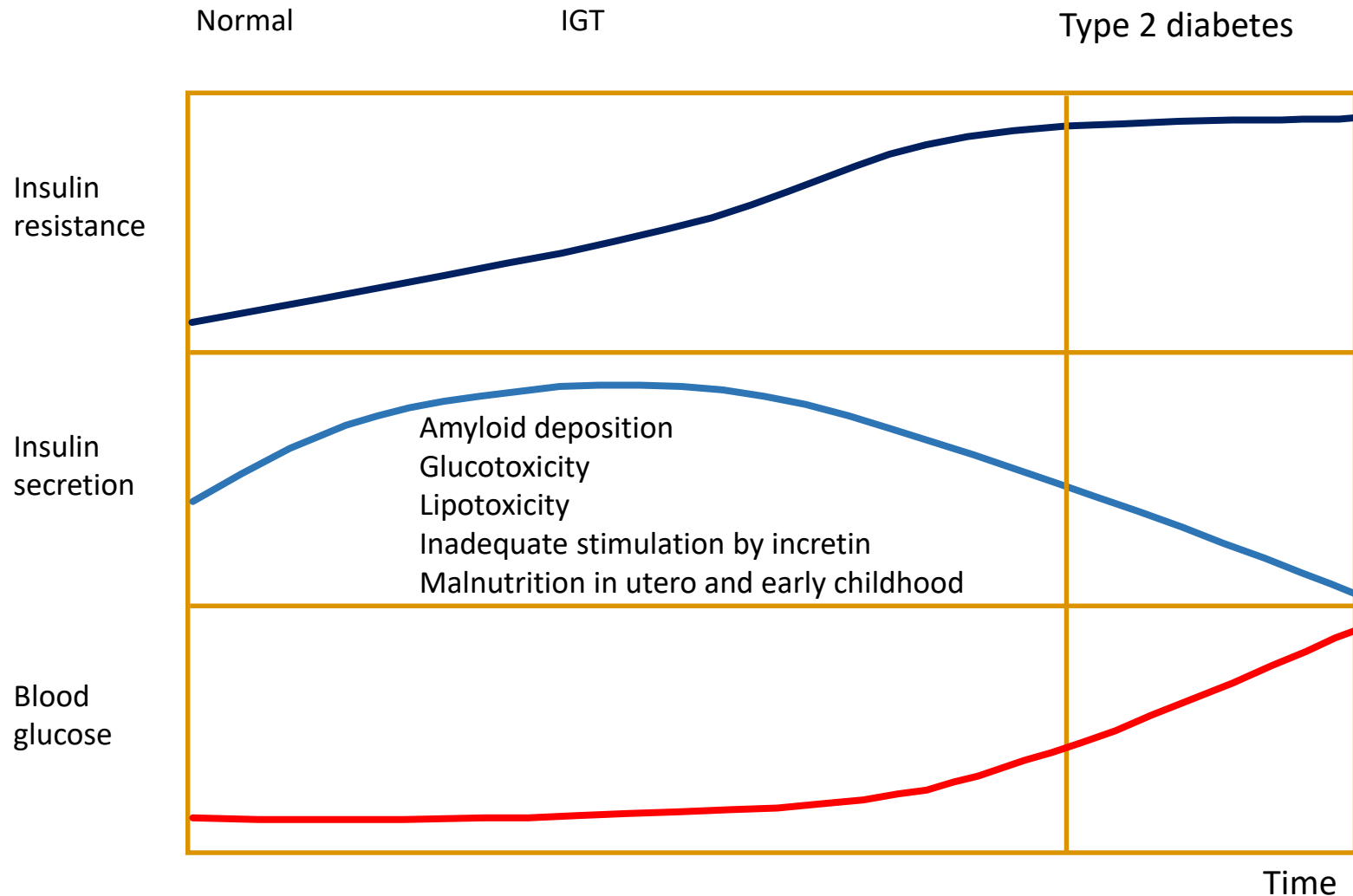
Interaction between waist circumference and serum concentrations of OC pesticides on the prevalence of insulin resistance

Adjusted Odds ratio



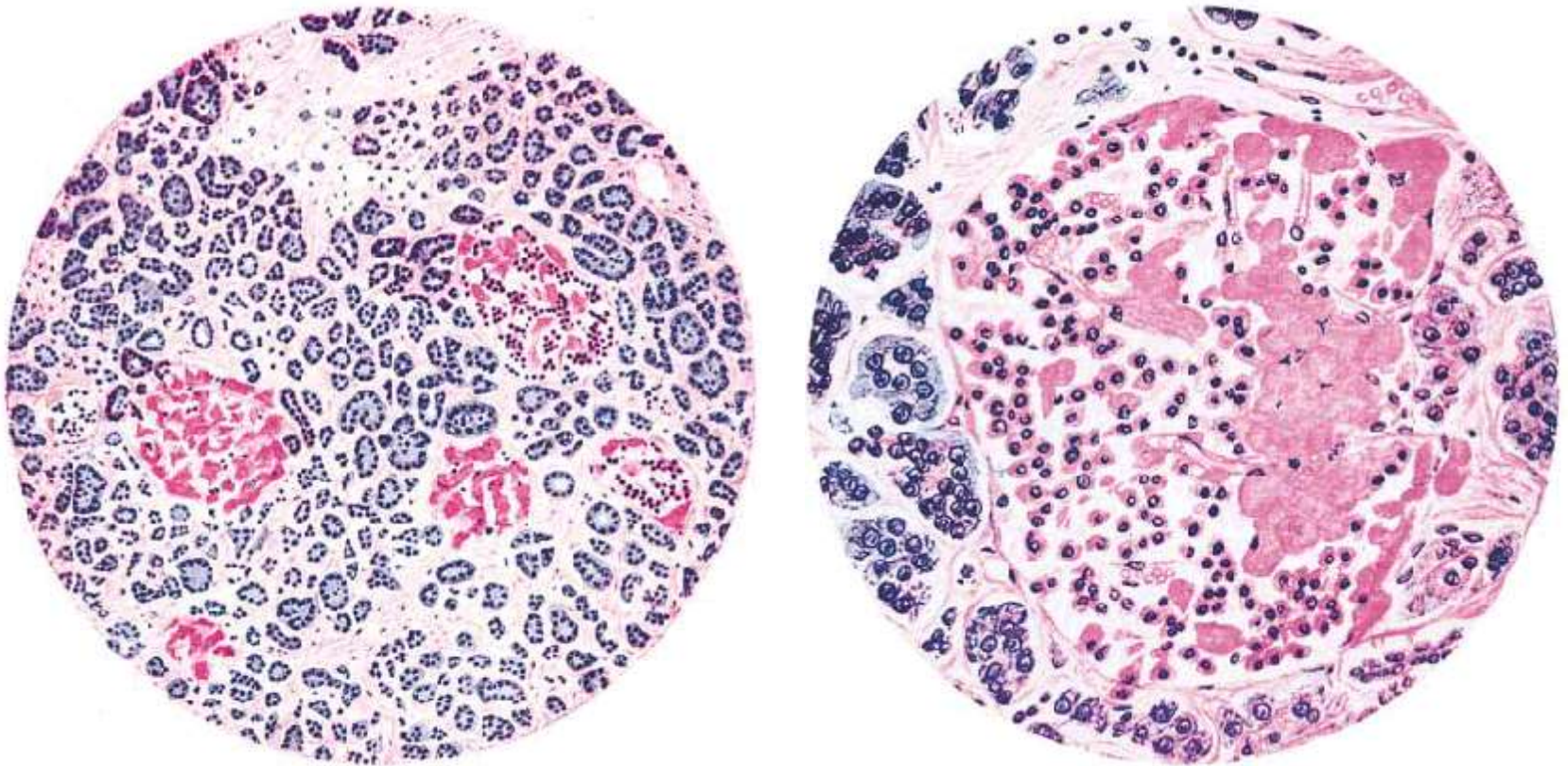
Lee DH et al. Diabetes Care 2007

Environmental factors for beta cell dysfunction



Islet pathology of type 2 diabetic patients

Amyloid deposition

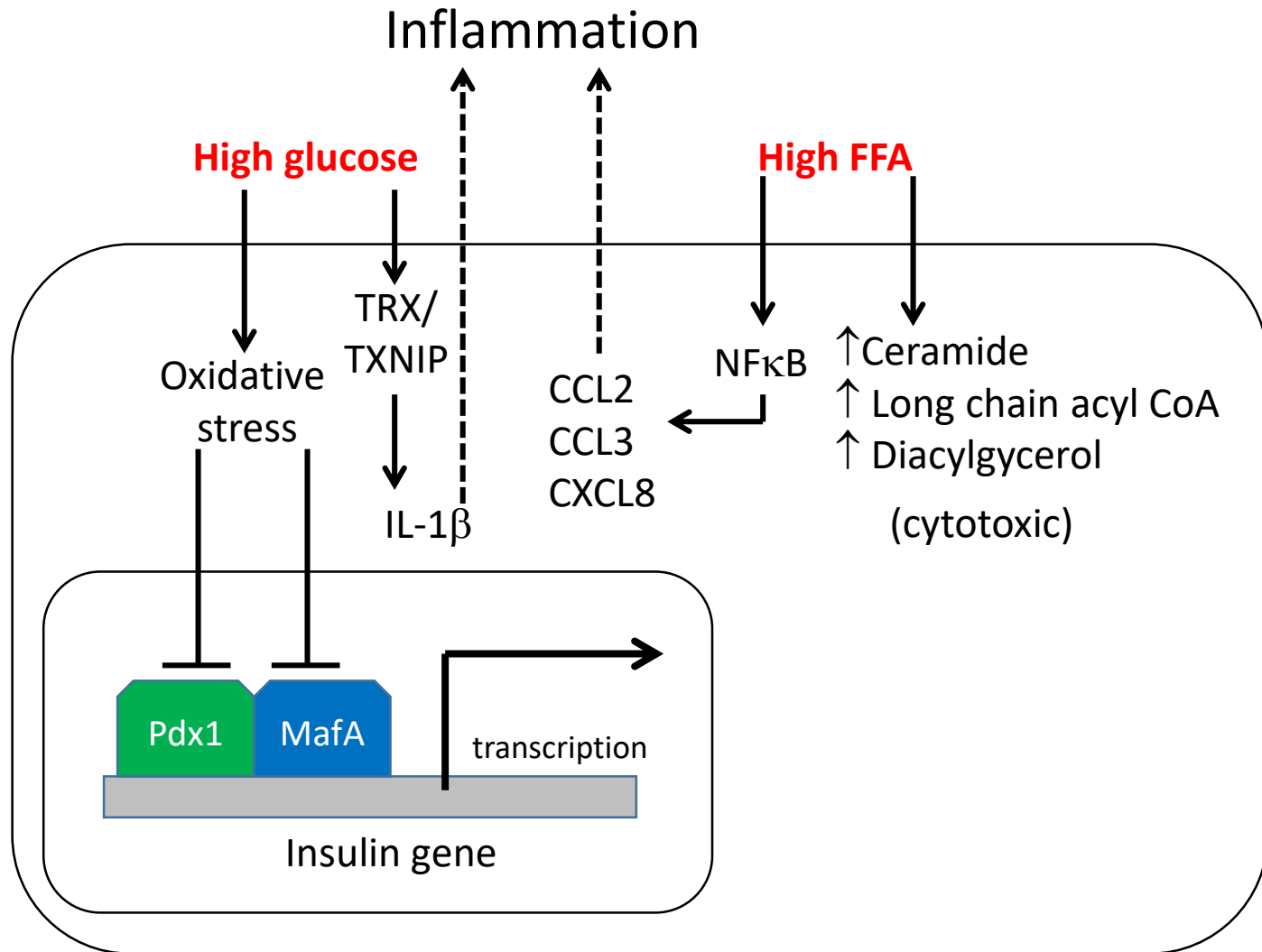


Hyaline degeneration of the islands of Langerhans

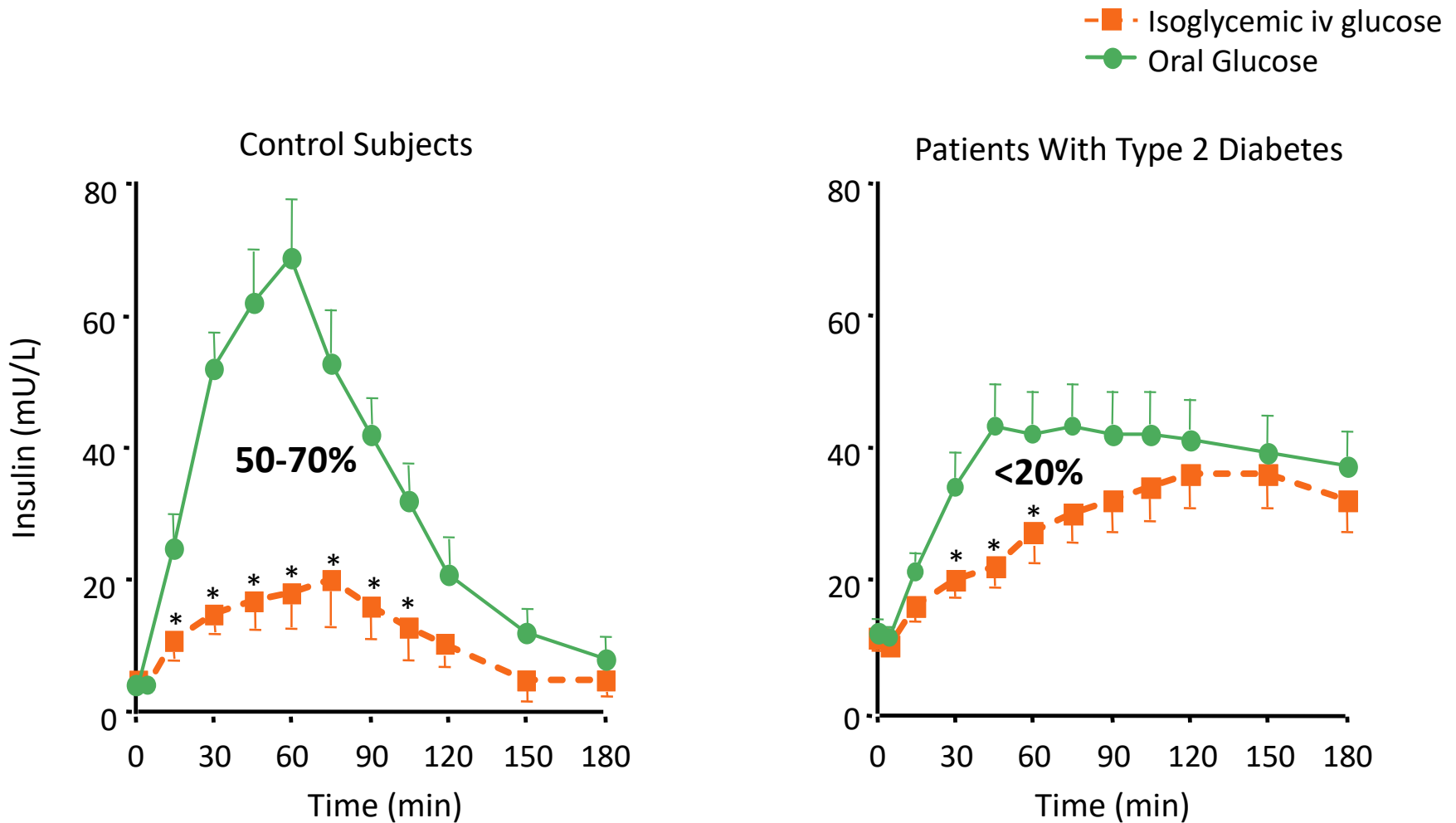
Opie E.L. J Exp Med 1901; 5: 527-40

Pictures are from N Engl J Med 2000; 343: 411-419

Gluco-/lipotoxicity and inflammation of beta cells



The incretin effect is reduced in Type 2 Diabetes



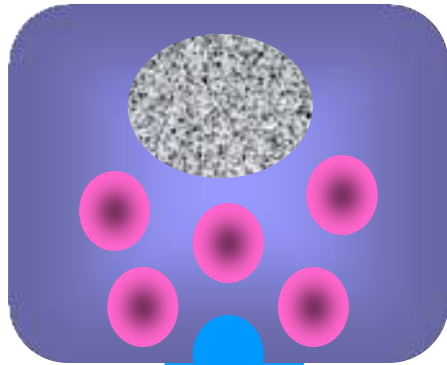
*p<.05 compared with respective value after oral load.

Nauck MA, et al. *Diabetologia*. 1986;29:46-52. Reprinted with permission from Springer-Verlag © 1986.

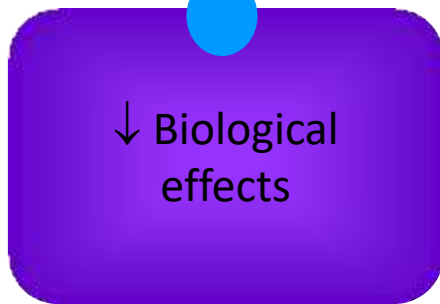
mitochondrial dysfunction in the pathogenesis of diabetes mellitus

Impaired insulin secretion

β cell

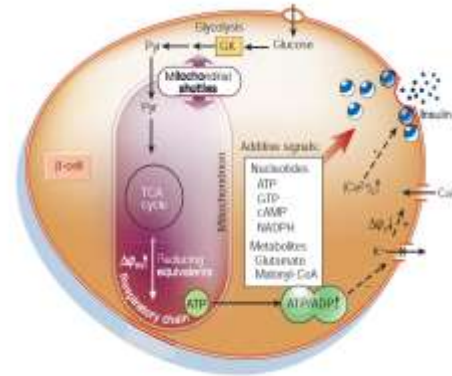


Target tissue

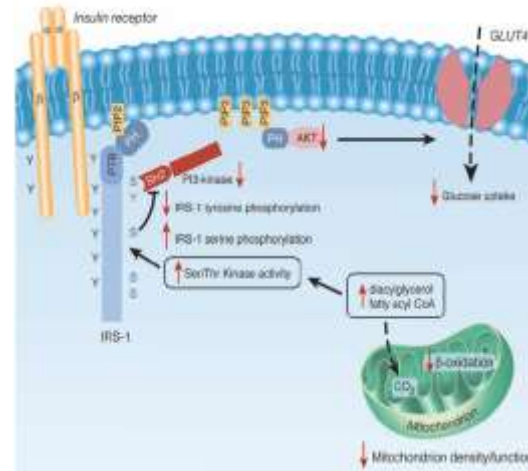


Insulin resistance

Maechler P and Wolheim CB. Nature 2001

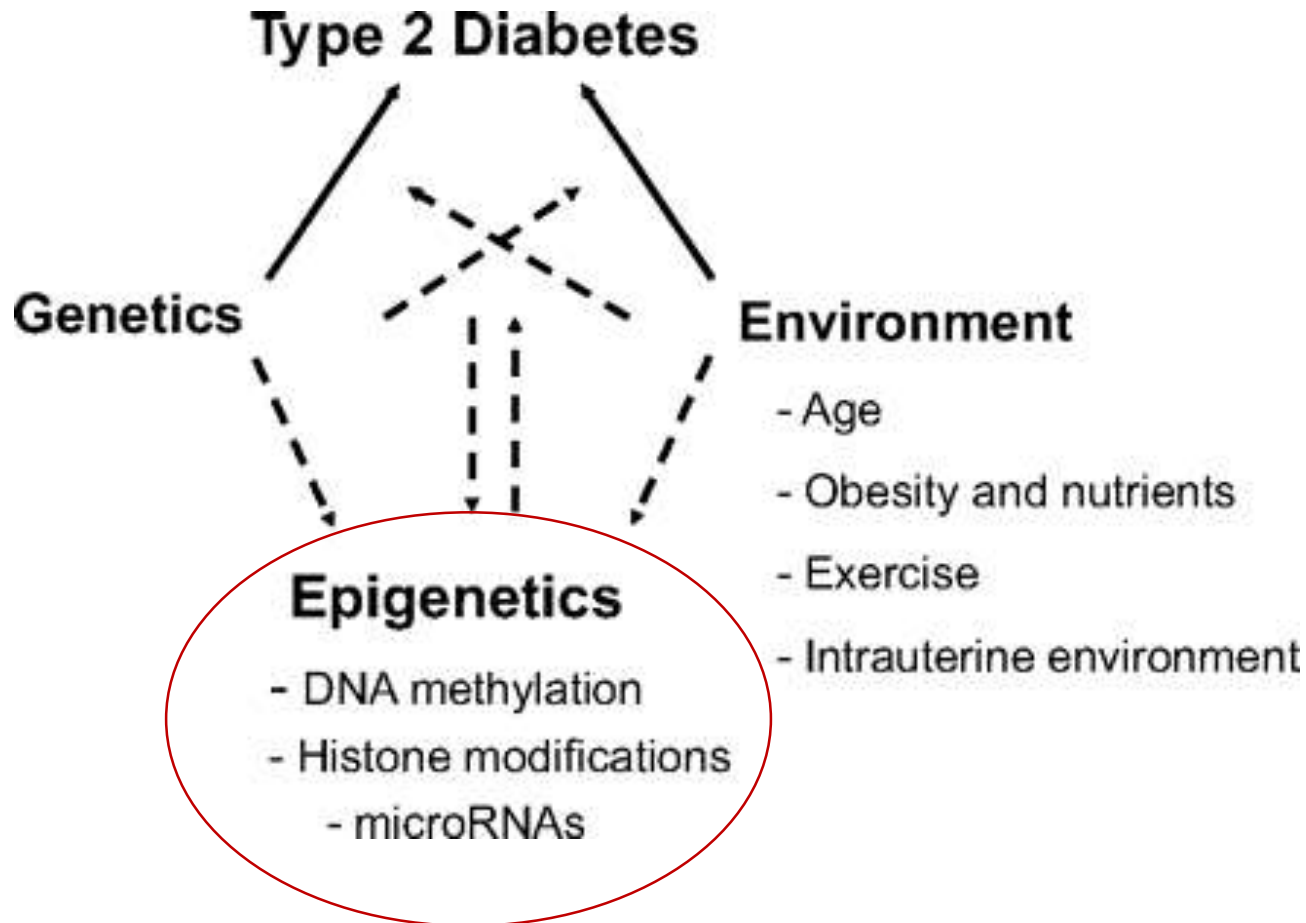


Mitochondrial dysfunction
As a unifying pathophysiological defect

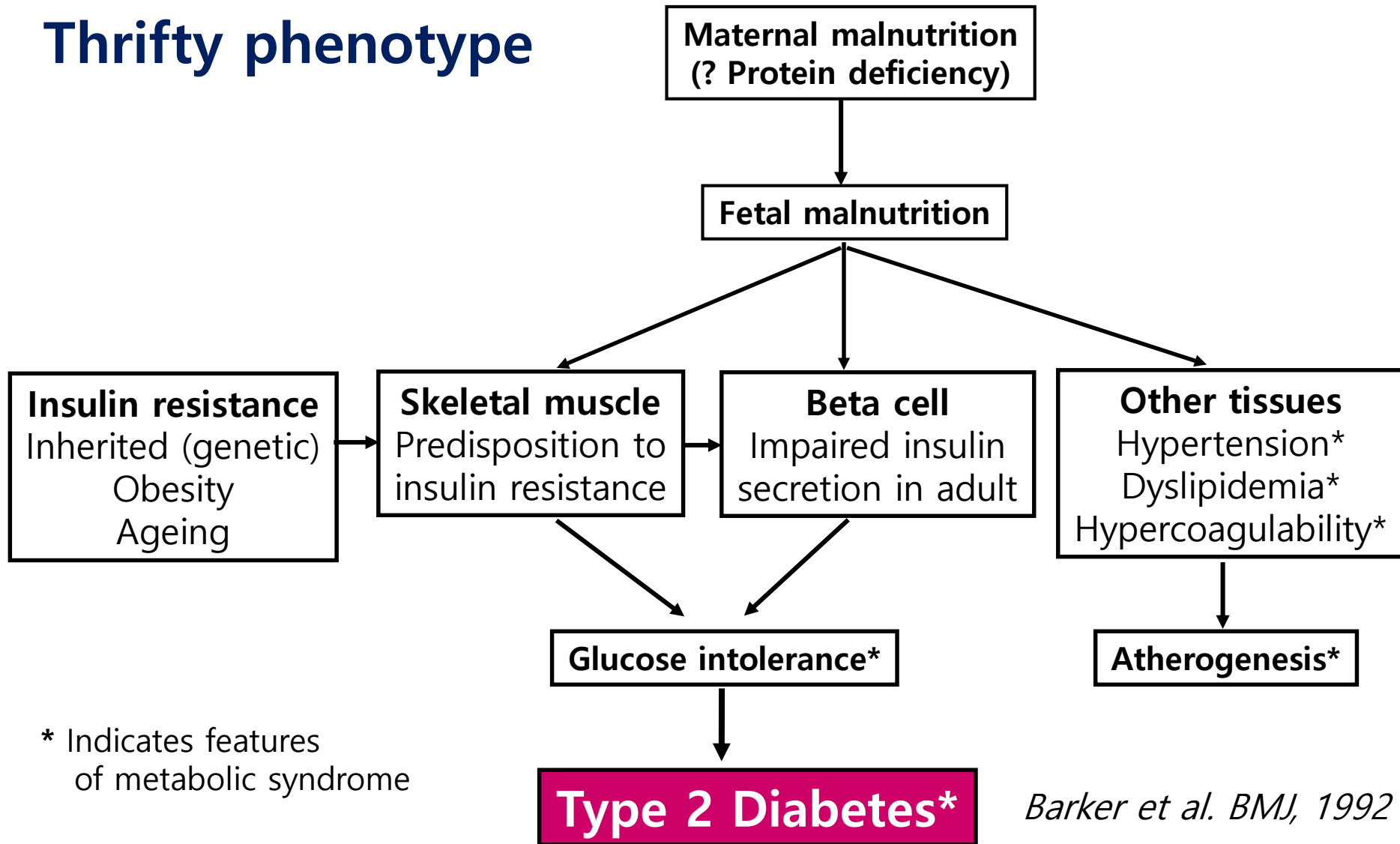


Lowell BB and Shulman GI: Science 2005

Gene to environment interaction



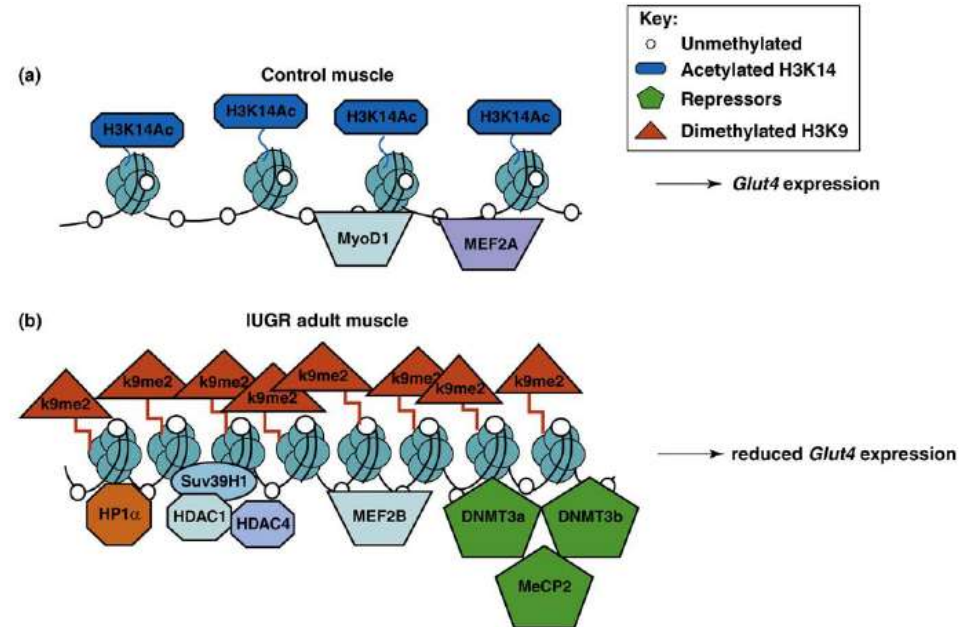
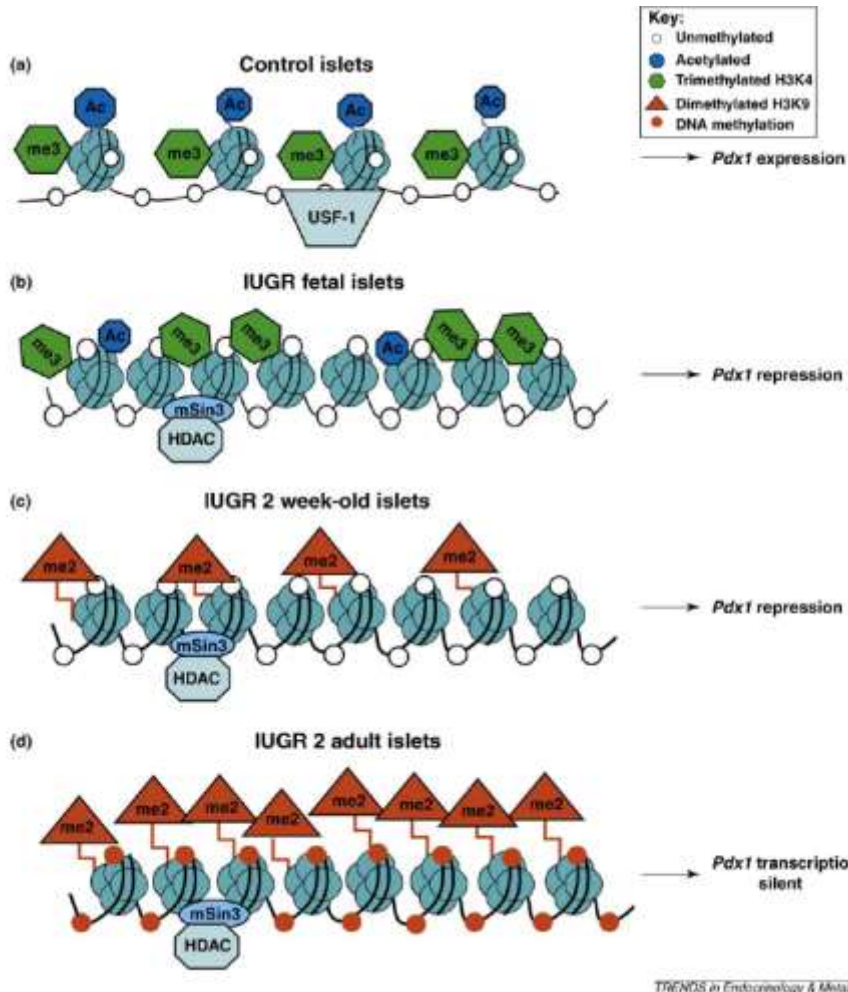
Thrifty phenotype



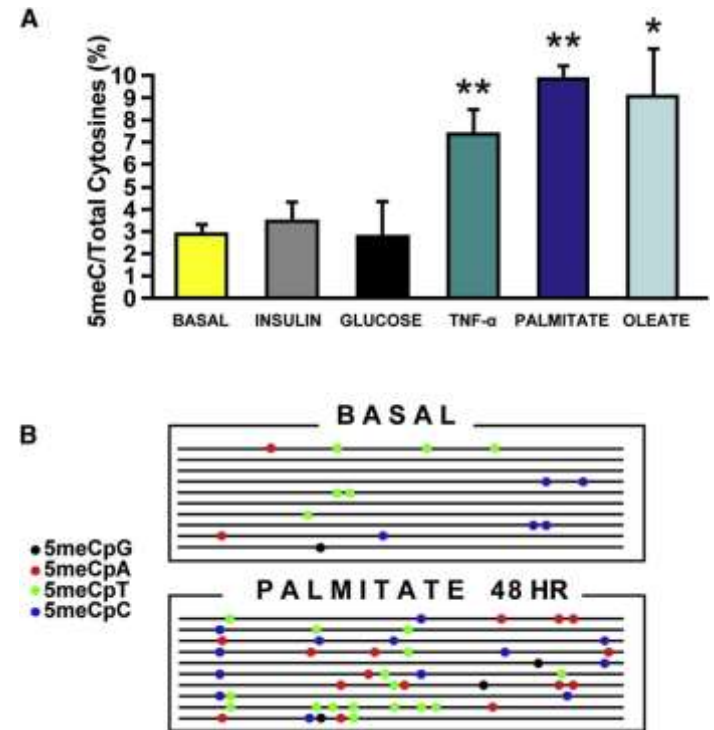
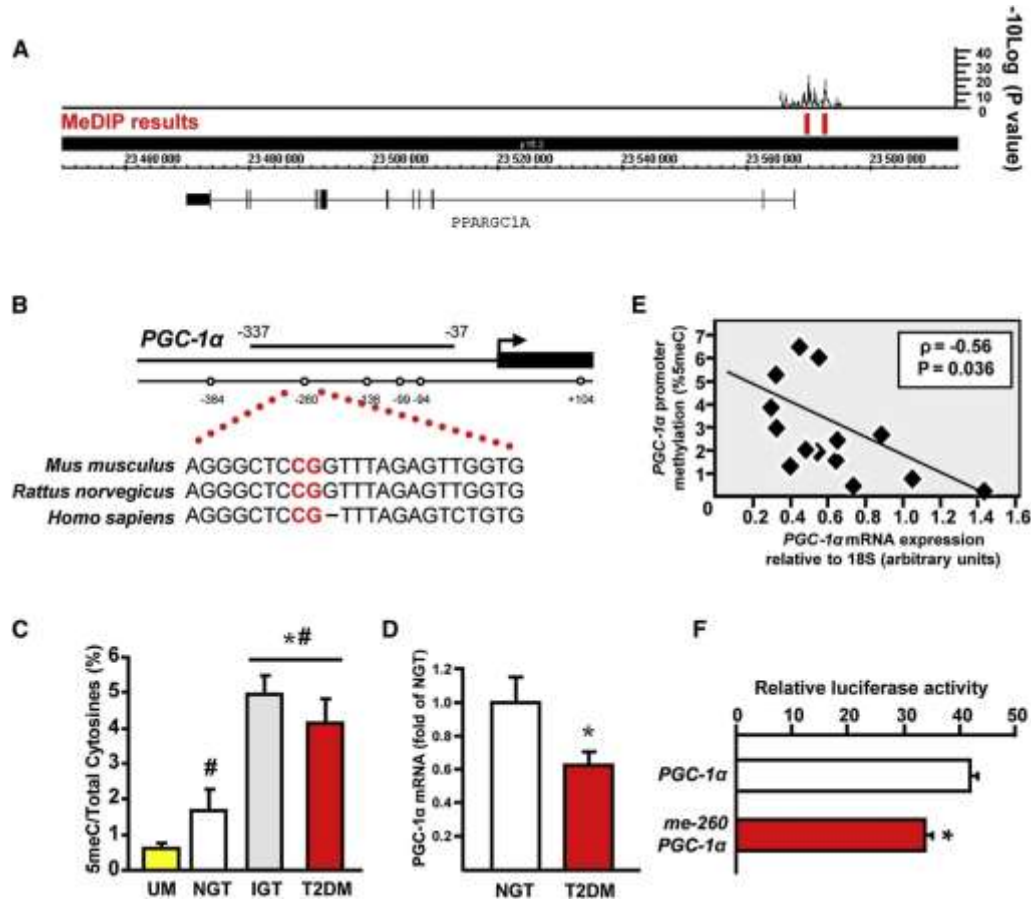
* Indicates features of metabolic syndrome

Barker et al. BMJ, 1992

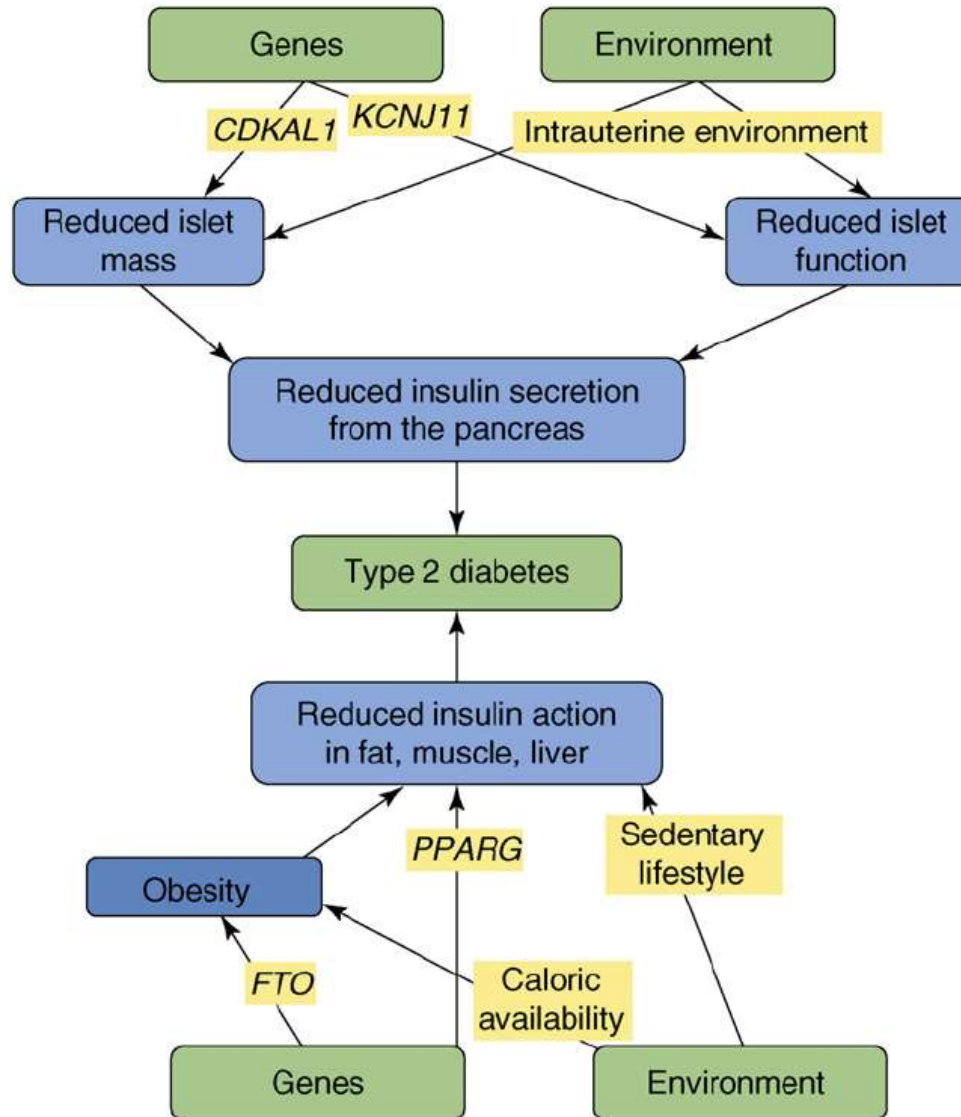
Epigenetic changes during development of T2DM



PGC-1 α promoter is hypermethylated in T2DM patients



Scheme of pathogenesis of T2DM

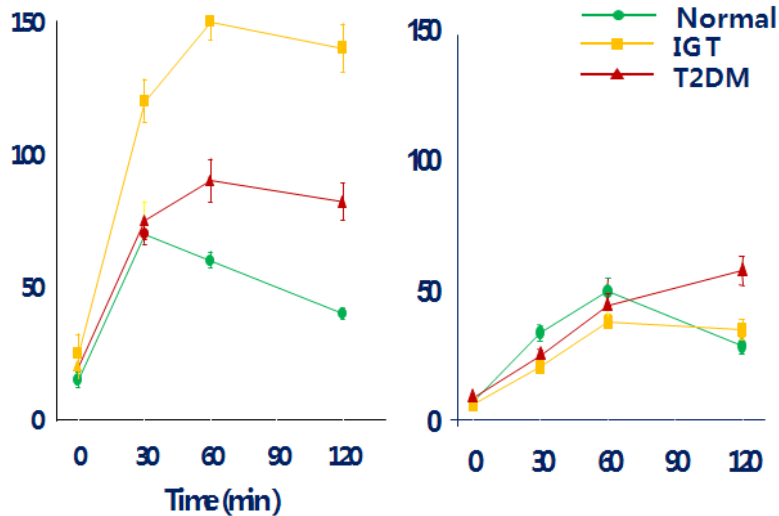


TRENDS in Genetics

Metabolic characteristics of Type 2 Diabetes in Korean

- Nonobese
- Lower insulin secretory capacity
- Less insulin resistance

Comparison of plasma insulin response to oGTT between Caucasian and Korean



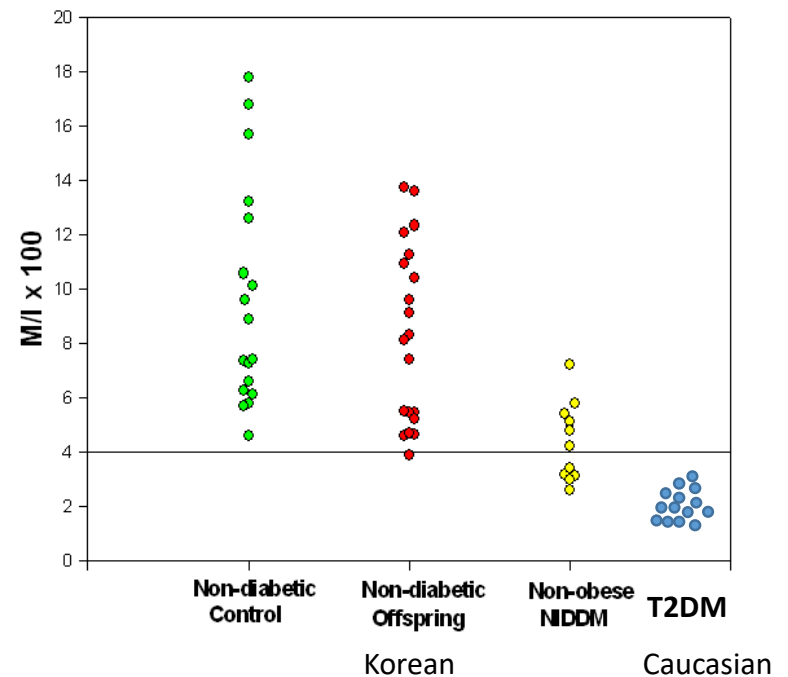
(Reaven, Diabetologia 1989)

Caucasian

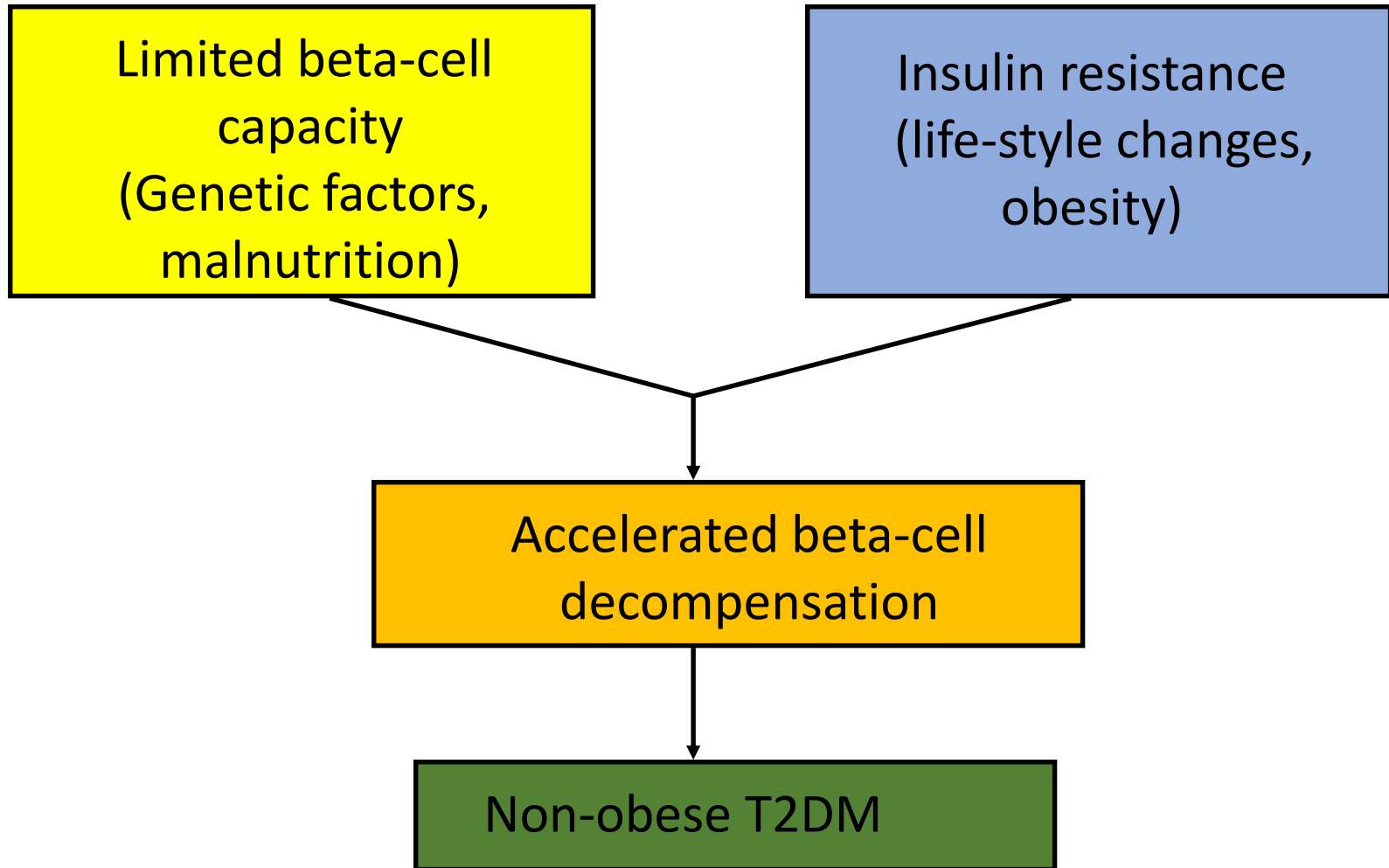
(K-U Lee et al, 1994)

Korean

Insulin sensitivity of T2 DM in Korea



Natural history of T2DM in Korean



Longitudinal changes in β -cell function and insulin sensitivity in development of T2DM in Korean



- Ansong(rural)
 - Population: 135,000
 - Age: 40-69 yr
 - Subject: 5,024
- Ansan(Urban)
 - Population: 550,000
 - Age: 40-69 yr
 - Subject: 5,014

Biennial FU with Detailed Clinical and Biochemical Information

Genetic
Information

Anthropometric
parameters

Demographic
parameters

Biochemical
parameters

Baseline
(2001)

1st FU
(2003)

2nd FU
(2005)

3rd FU
(2007)

4th FU
(2009)

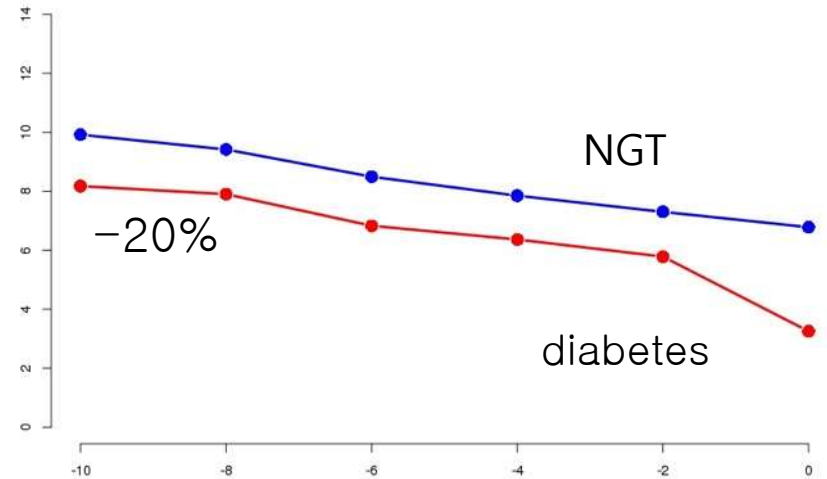
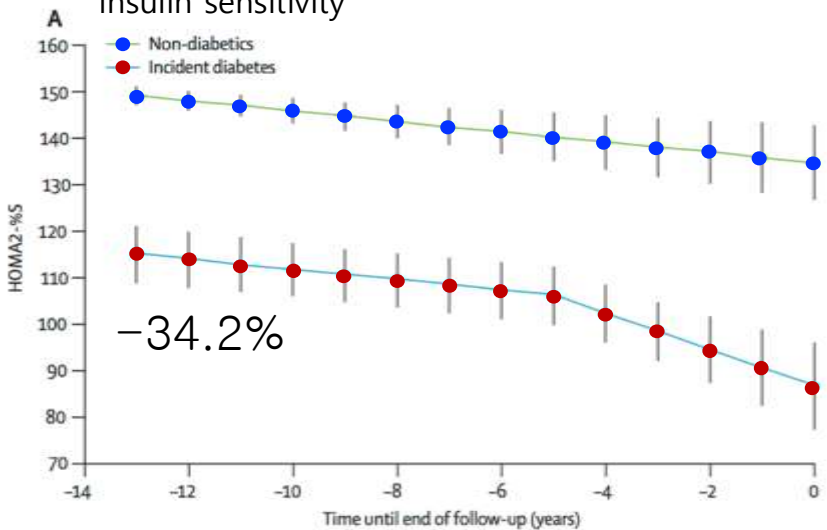
5th FU
(2011)

UK :Whitehall II study
Lancet 2009

Korean :Ansung-Ansan study
Lancet Diabetes Endocrinology 2016

Insulin sensitivity

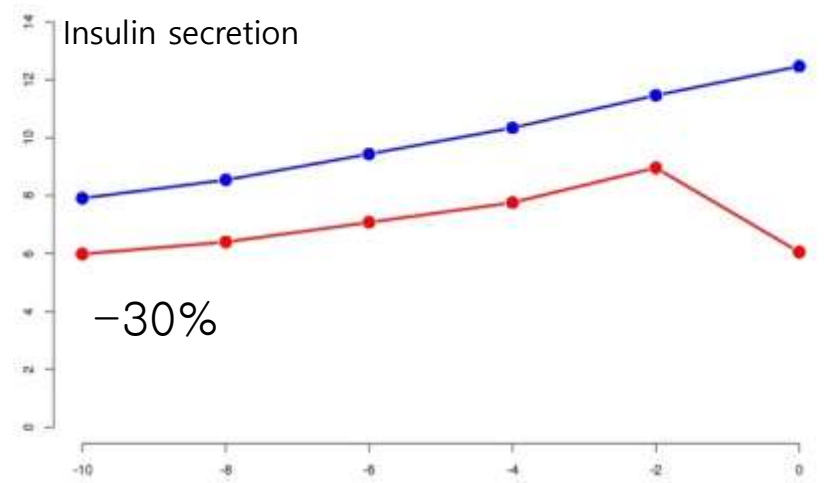
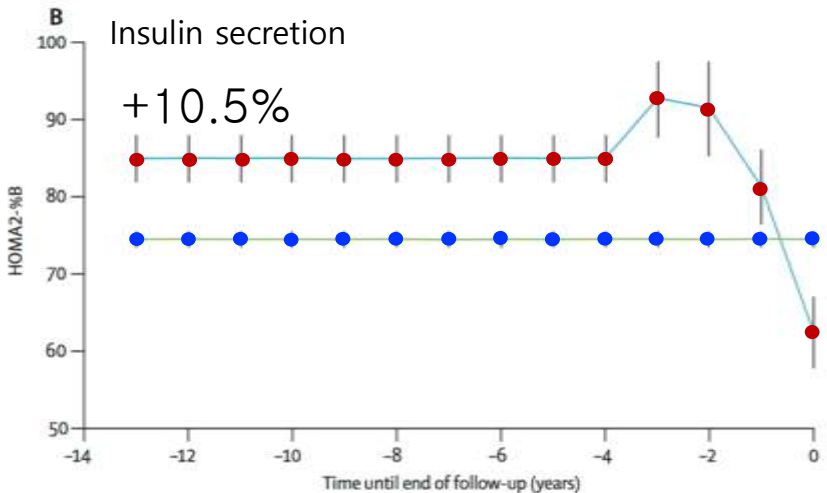
Insulin sensitivity



Non-diabetics	2927	65	84	25	1472	2115	50	143	90	138	3366	274	1	239
Incident diabetes	42	43	59	41	10	18	60	120	94	43	6	60	41	164

Insulin secretion

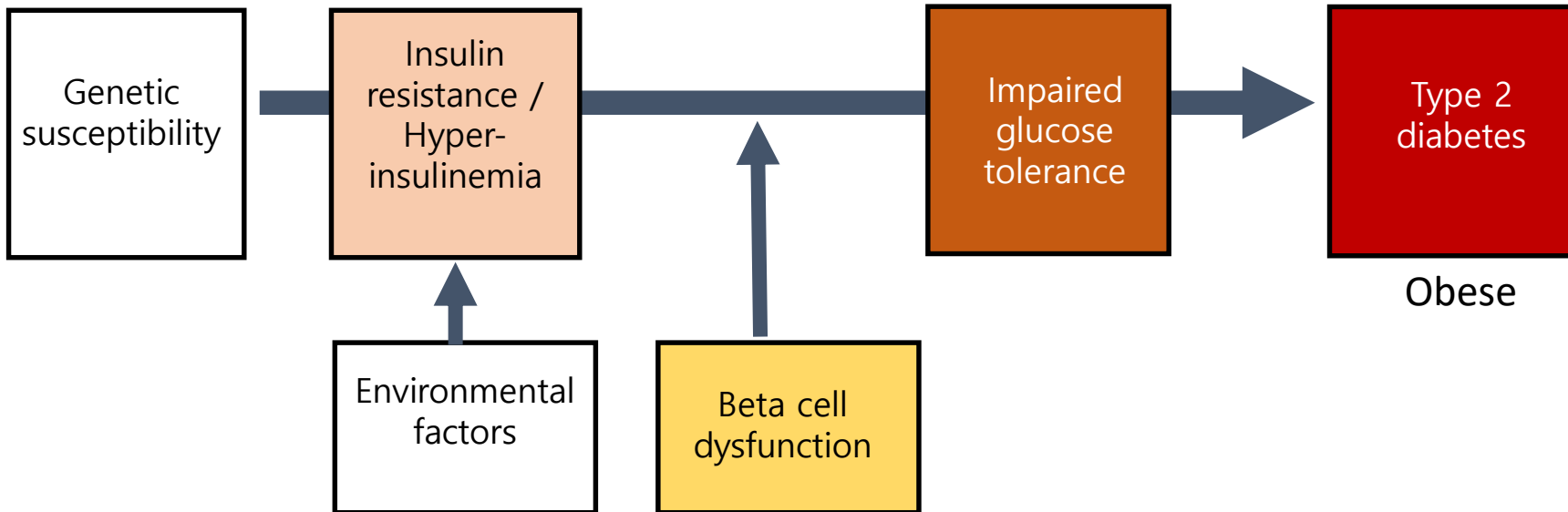
Insulin secretion



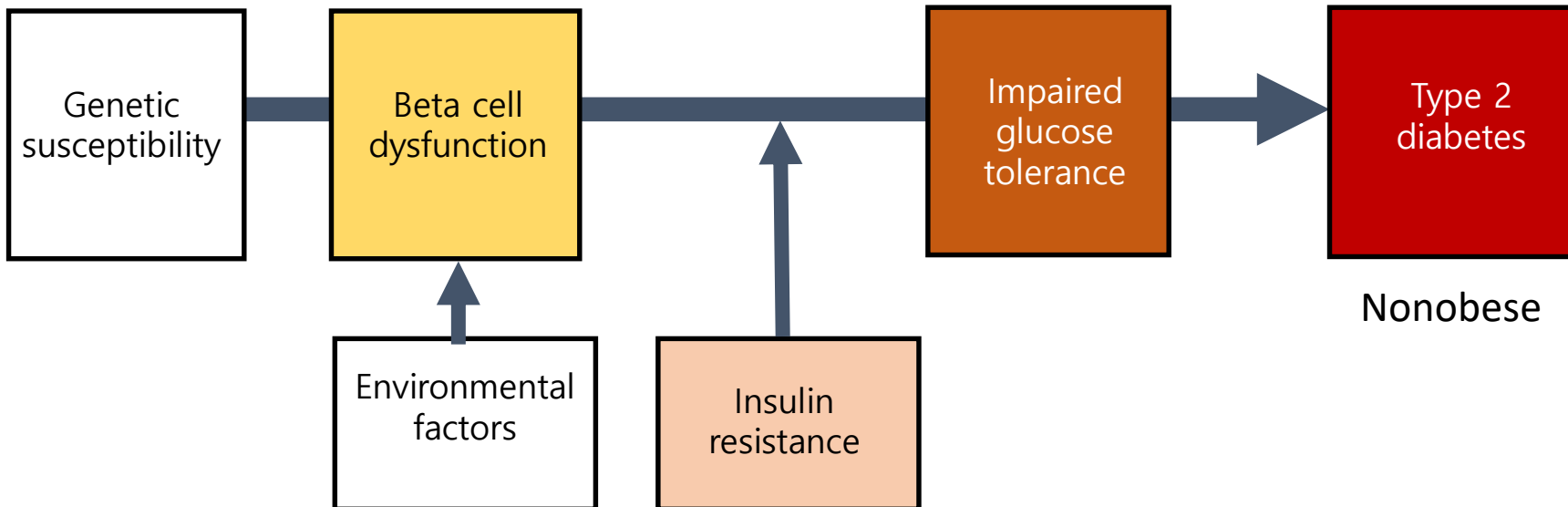
Non-diabetics	2927	65	84	25	1472	2115	50	143	90	138	3366	274	1	239
Incident diabetes	42	43	59	41	10	18	60	120	94	43	6	60	41	164

years before diabetes onset

Caucasian

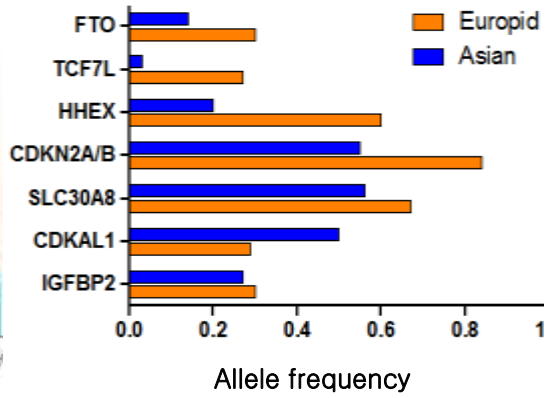
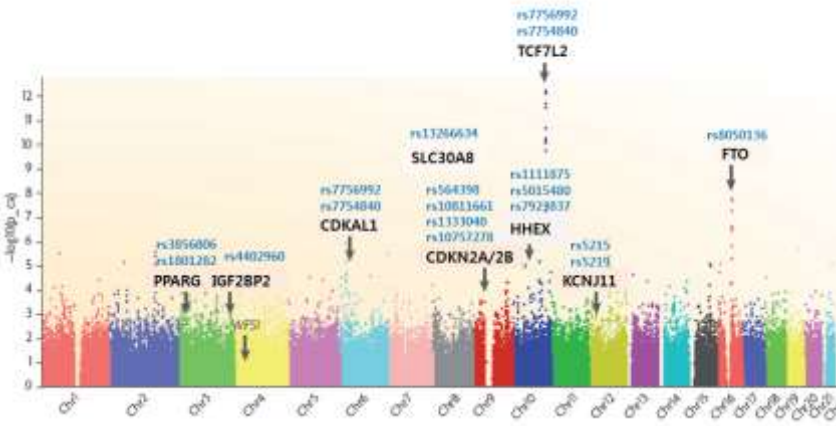


Korean

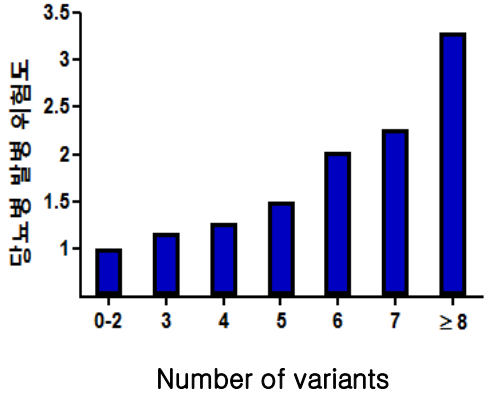


Genetic susceptibility of type 2 diabetes in Korean (common variants)

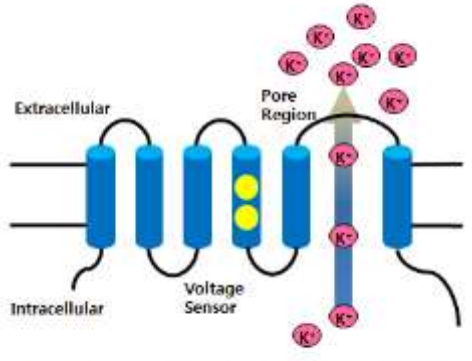
Trans-ethnic common genes



Diabetes 2008



Korean(Asian) specific genes

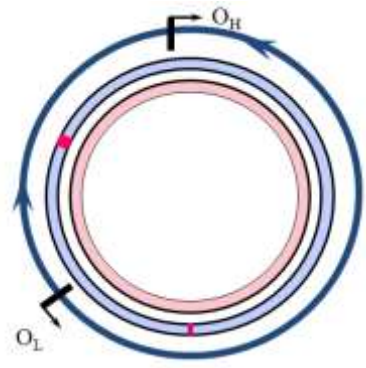


Voltage gated potassium channel **KCNQ1**
Nature Genetics 2008

UBE2E, C2CD4A-C2CD4B Nature Genetics 2010

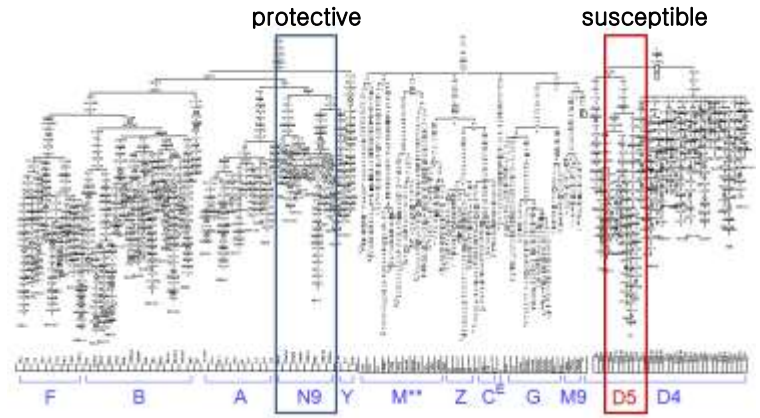
GLIS3, PEPD, FITM2-R3HDML-HNF4A, CNKN16, MAEA, GCC1-PAX4, PSMD6 and ZFAND3. GLIS3

Nature Genetics 2011



16189 T>C variant

Diabetologia 2008



mtDNA haplogroup

Am J Hum Genet 2007

Pathophysiology of type 2 diabetes mellitus – balanced view

