

19TH ANNUAL  
**WORLD CONGRESS  
INSULIN RESISTANCE DIABETES  
& CARDIOVASCULAR DISEASE**

CME Conference | December 2-4, 2021

Hilton Universal Hotel, Los Angeles, CA

Also Available Live Online Interactive & On-Demand

Exploring New Frontiers in Metabolism - Tomorrow's Clinical Science Today



# Has the Beta Cell Been Forgotten? 2 December 2021

## Gene Mutations Play a Dominant Role in $\beta$ -cell Failure in Type 2 Diabetes

Steven E. Kahn

VA Puget Sound Health Care System

University of Washington

Seattle, WA

# Dualities of Interest

Advisory Board, Consulting and Lectures

Bayer

Merck

Boehringer Ingelheim

Novo Nordisk

Casma Therapeutics

Pfizer

Eli Lilly

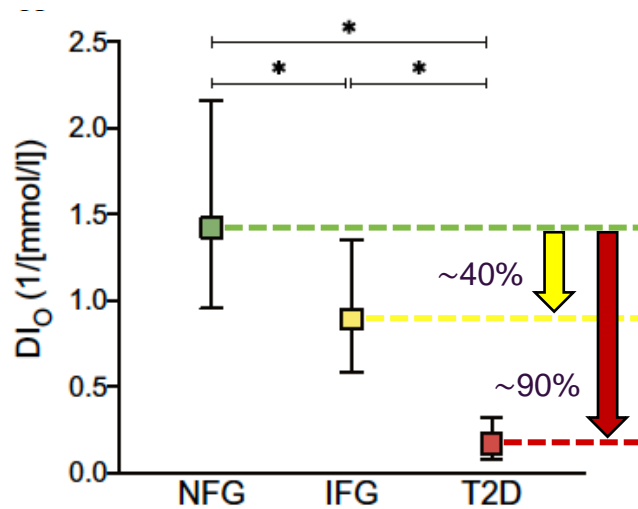
Third Rock Ventures

Intarcia

# Outline

1. Phenotypic characteristics and genetics of type 2 diabetes in adults.
2. Genetics of type 2 diabetes in youth.

# Relationship of Glucose Tolerance and Fasting Glucose with $\beta$ -cell Function



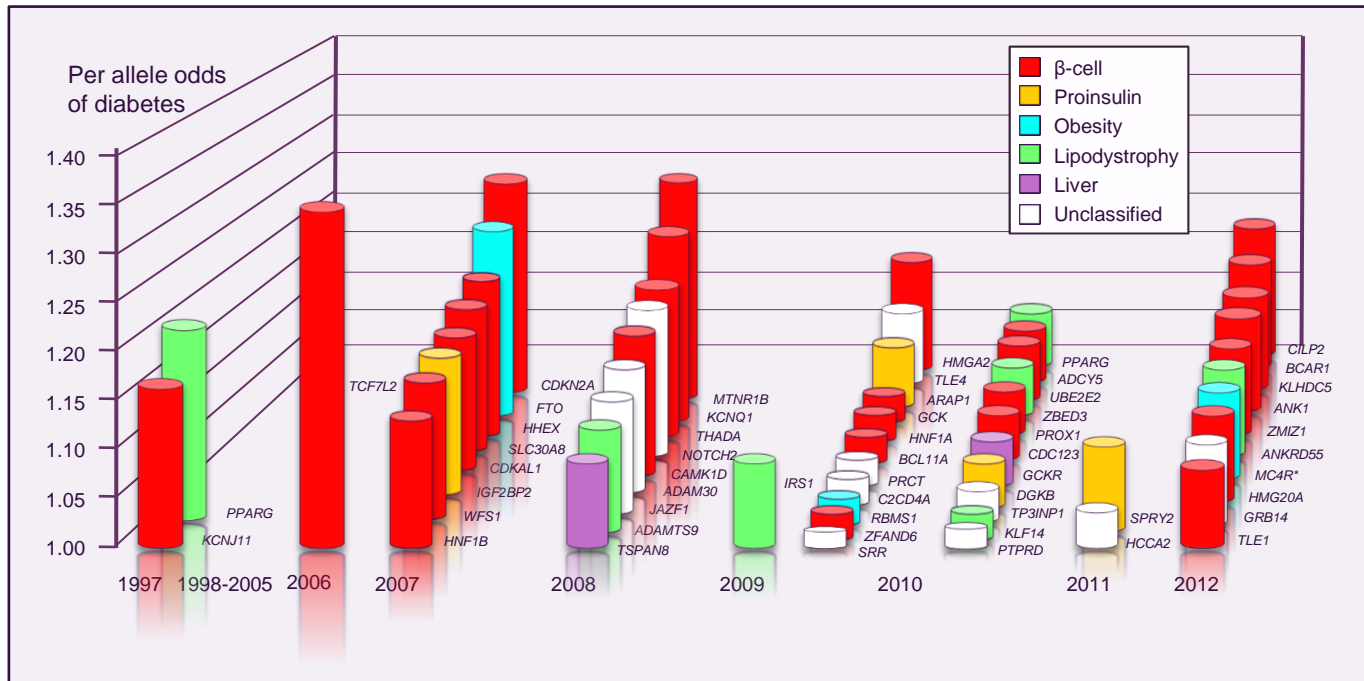
Number of individuals:

374

168

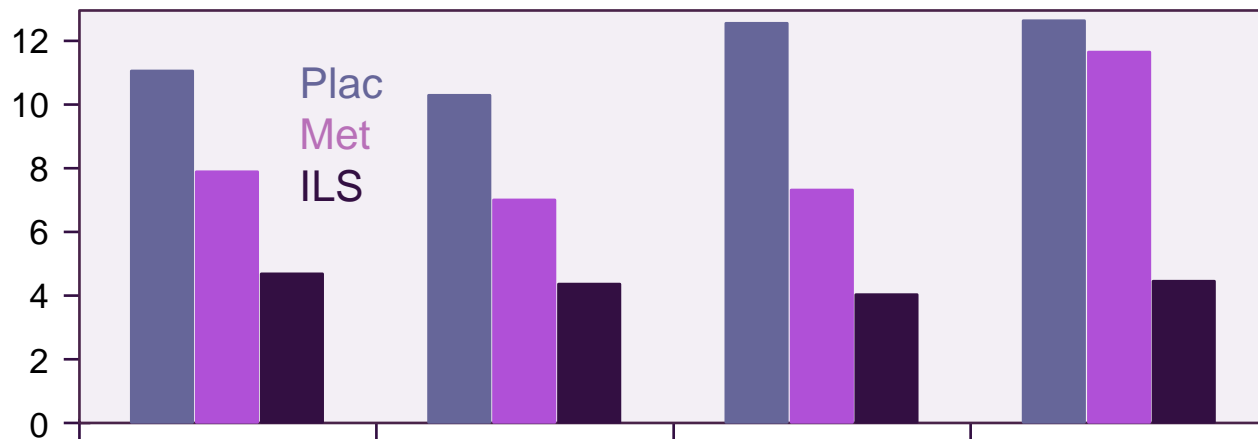
71

# Type 2 Diabetes Genes Associate Most Commonly with $\beta$ -cell Dysfunction



Adapted from Franks PW et al: Diabetes Care 36:1413-1421; 2013, Simons-Bik 59:293-301; 2010, Dimas AS et al: Diabetes 63:2158-2171; 2014, Thomsen SK et al: Diabetes 65:3805-3811; 2016 and Udler MS et al: PLoS Med 2018 Sep 21;15(9):e1002654

# DPP: Diabetes Incidence Rate by Weighted Genetic Risk Score of 34 T2D Gene Loci



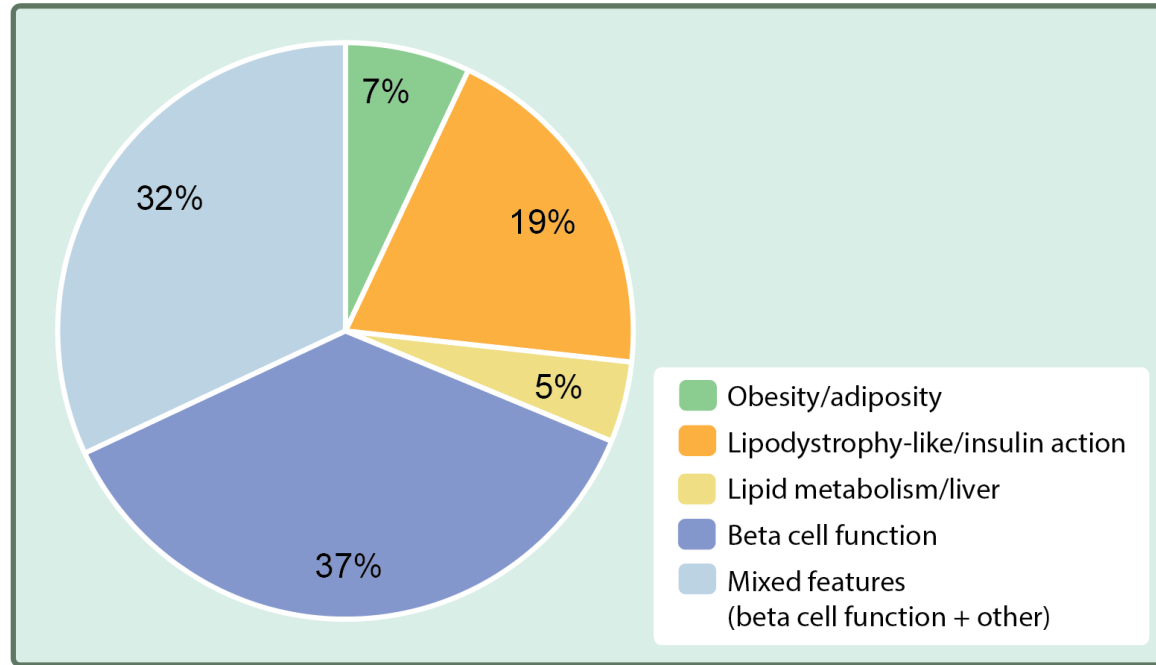
GRS Quartile	1	2	3	4
Weighted GRS	32 (24-34)	36 (34-37)	38 (37-40)	42 (40-51)
Fasting plasma glucose	105 (89-136)	105 (89-139)	106 (82-139)	106 (90-138)
2-h plasma glucose	162 (140-199)	165 (140-199)	162 (140-199)	162 (140-199)
Insulinogenic index	1.24 (1.17-1.32)	1.25 (1.18-1.33)	1.25 (1.17-1.32)	1.12 (1.05-1.20)
1 / HOMA-IR	0.157 (0.150-0.164)	0.157 (0.150-0.164)	0.159 (0.152-0.166)	0.161 (0.154-0.169)

# Partitioned Polygenic Score Clusters Capturing Etiological Heterogeneity in T2D

Physiological Impact		Phenotypic Features	Cluster Name		
			Udler <i>et al.</i> , 2018 (38)	Mahajan <i>et al.</i> , 2018 (20)	Examples of T2D Loci
Adverse impact on $\beta$ -cell function	High proinsulin	Low fasting insulin (+ high proinsulin)	$\beta$ -Cell	Insulin secretion 1	<i>ABO</i> , <i>ADCY5</i> , <i>HNH1A</i> , <i>HNH1B</i> , <i>MTNR1B</i> , <i>SLC30A8</i> , <i>TCF7L2</i>
	Low proinsulin	Low fasting insulin (+ low proinsulin)	Proinsulin	Insulin secretion 2	<i>IGF2BP2</i> , <i>CENTD2</i> / <i>ARAP1</i> , <i>CCND2</i>
Reduced insulin sensitivity	Mediation with fat distribution	High fasting insulin + low BMI + low WC + high TG	Lipodystrophy	Insulin action	<i>MACF1</i> , <i>GRB14</i> , <i>IRS1</i> , <i>PPARG</i> , <i>ANKRD55</i> , <i>KLF14</i> , <i>LPL</i> , <i>CMIP</i>
	Mediation via obesity	High fasting insulin + high BMI + high WC	Obesity	Adiposity	<i>NRXN3</i> , <i>FTO</i> , <i>MC4R</i>
	Mediation via lipid metabolism	Low TG	Liver/lipid	Dyslipidemia	<i>GCKR</i> , <i>TM6SF2</i>
Undetermined		No striking phenotype association	No assignment	Mixed features	<i>BCL11A</i> , <i>TLE1</i> , <i>PLEKHA1</i> , <i>HMGGA2</i> , <i>MTMR3</i>

Comparison of pPS clusters identified by Mahajan *et al.* (20) and Udler *et al.* (38).  
Abbreviations: TG, triglyceride; WHR, waist/hip ratio.

# Phenotypes Associated with 128 Gene Variants Linked to Type 2 Diabetes

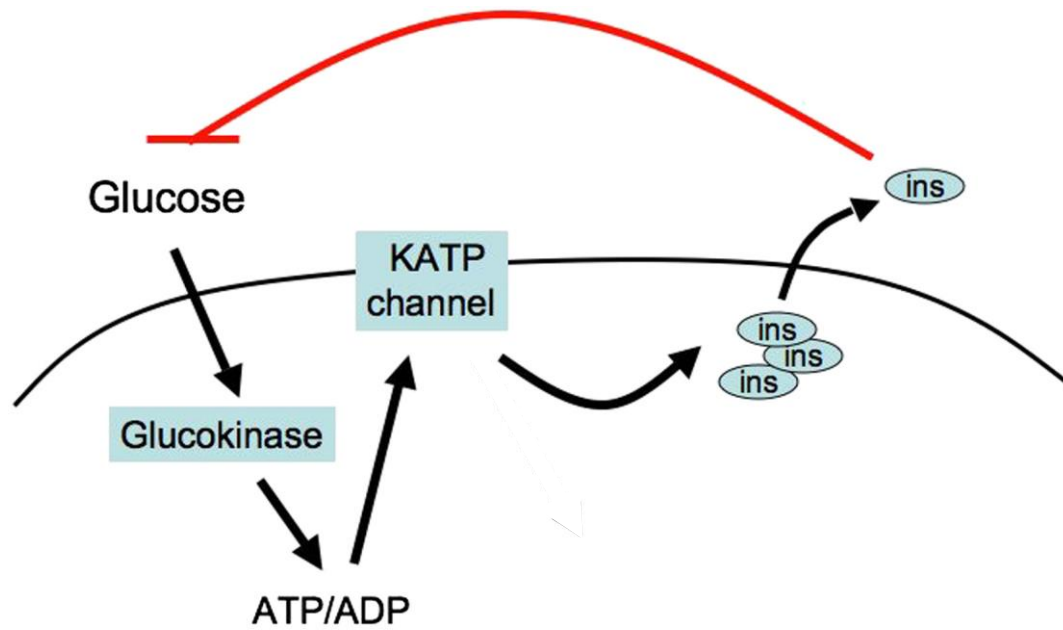




# Function of Select Gene Products Linked to the $\beta$ -cell in Type 2 Diabetes and MODY

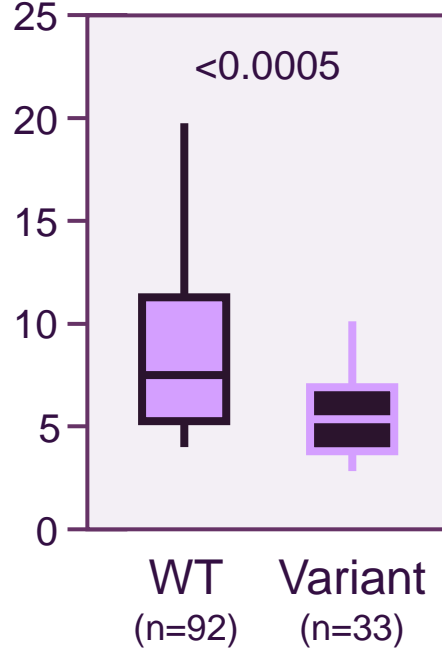
Function	Gene Product	Function	Gene Product
Growth and development	CDKAL1, GLIS3, HHEX, <i>HNF1A</i> , <i>HNF1B</i> , <i>HNF4A</i> , IGF2BP2	Transcription factor	<i>PAX4</i> , PROX1, RREB1, <b>TCF7L2</b> , ZBED3
Insulin production	INS	Peptide processing	SLC30A8
Insulin secretion	<i>ABCC8</i> , <i>KCNJ11</i> , KCNQ1	Potential of insulin secretion	GIPR
Glucose metabolism	G6PC2, <i>GCK</i>	Peptide degradation	IDE
Golgi vesicles and structure	AP3S2, ARAP1	Cell cycle regulation	CCND2, CDC123, CDKN2A
Cell adhesion and migration	BCAR1	Steroid hormone metabolism	HSD17B12

# Glucokinase is Critical In Glucose-stimulated Insulin Secretion by the $\beta$ -cell



# -30 (G>A) $\beta$ -cell GCK Promoter Variant is Associated with Reduced $\beta$ -cell Function

$(\Delta I_{30-0} / \Delta G_{30-0}) / F. Ins.$



NGT / IGT	Wild Type 55 / 37	Variant 10 / 23	p
Fasting Insulin (pM)	60 (45-78)	60 (47-104)	NS
Fasting Glucose (mM)	5.5 (5.3-5.9)	5.7 (5.4-6.1)	0.02
2-h Glucose (mM)	7.4 (6.4-8.5)	8.6 (7.4-9.5)	0.001

Data are medians (interquartile range)

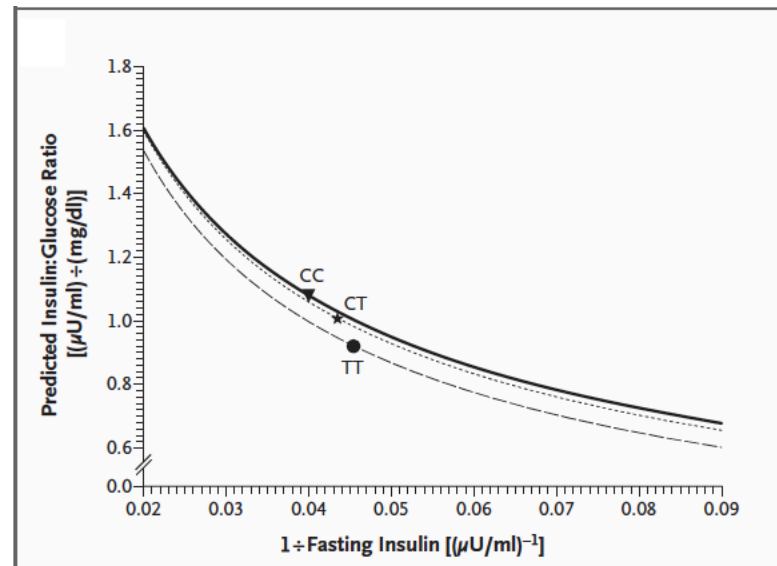
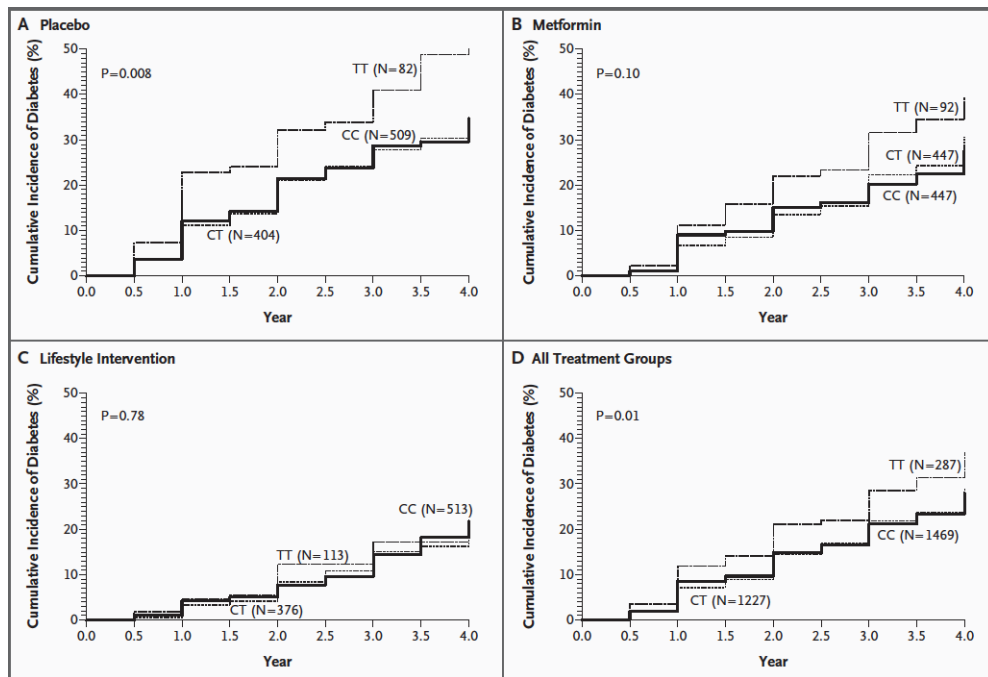
# TCF7L2:

## Transcription Factor 7 Like 2

UniProtKB/Swiss-Prot:

Participates in the Wnt signaling pathway and modulates MYC expression by binding to its promoter in a sequence-specific manner. Acts as repressor in the absence of CTNNB1, and as activator in its presence.

# TT Genotype at rs7903146 of TCF7L2 Increases the Risk of Developing Diabetes



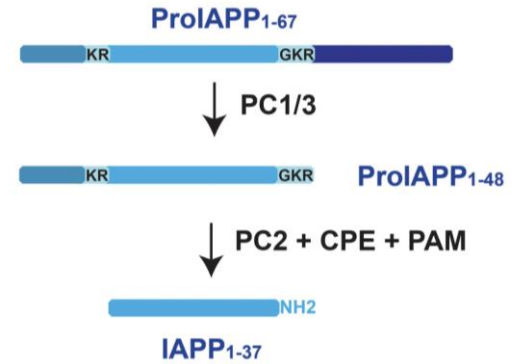
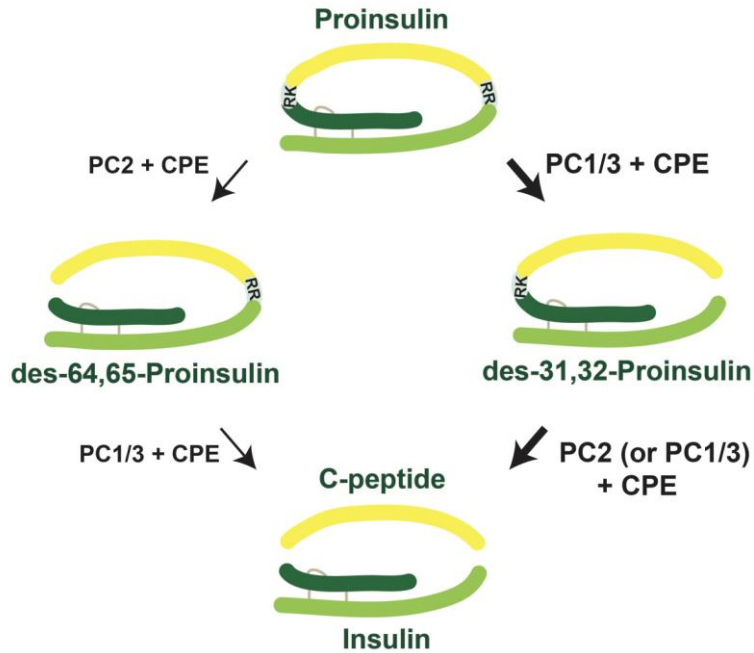
# SLC30A8:

## Solute Carrier Family 30 Member 8

UniProtKB/Swiss-Prot:

Facilitates the accumulation of zinc from the cytoplasm into intracellular vesicles, being a zinc-efflux transporter. May be a major component for providing zinc to insulin maturation and/or storage processes in insulin-secreting pancreatic  $\beta$ -cells.

# Pathways for Processing Proinsulin and ProIAPP in the $\beta$ -cell

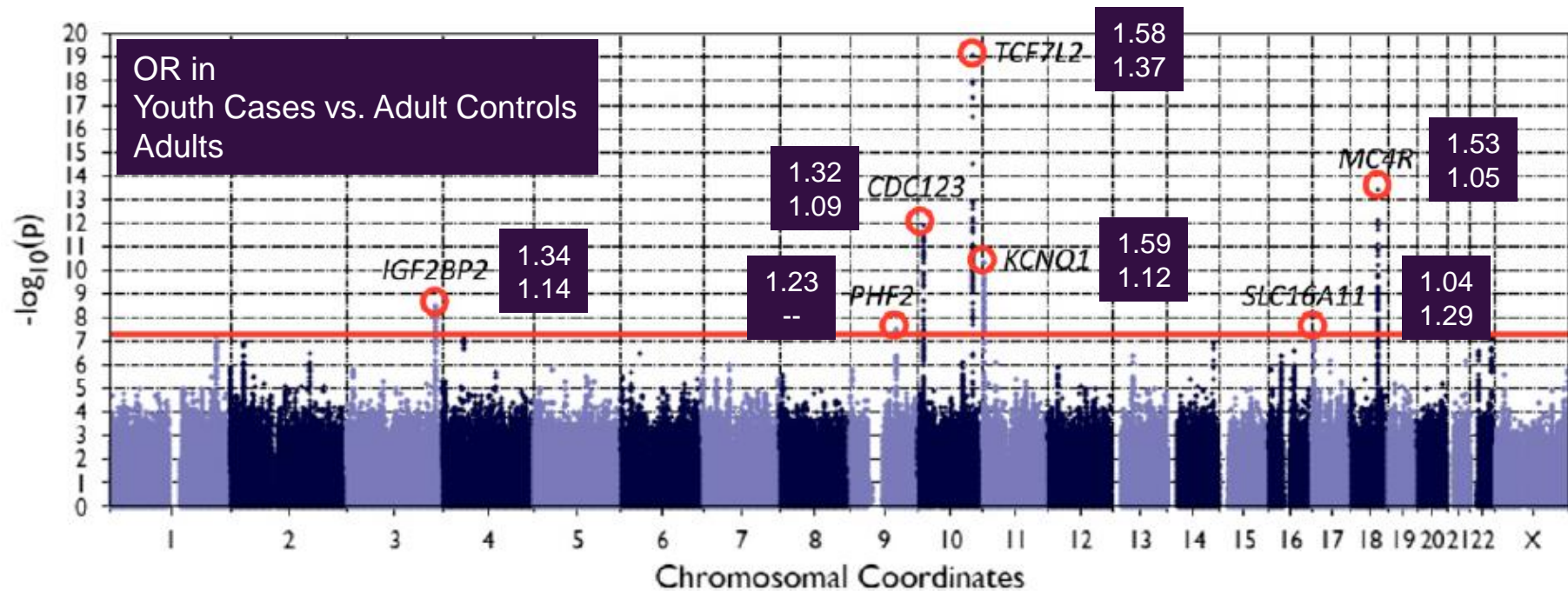


# Outline

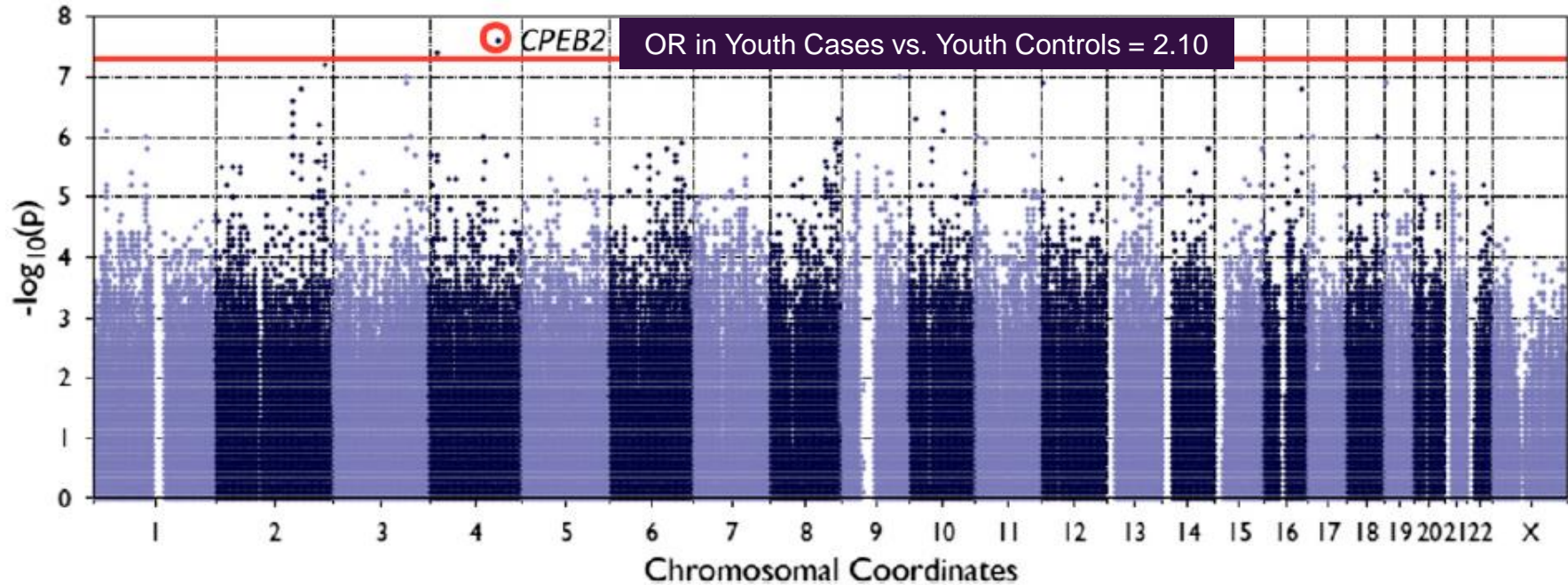
1. Phenotypic characteristics and genetics of type 2 diabetes in adults.
2. Genetics of type 2 diabetes in youth.



# Manhattan Plot for 3,006 Youth Cases With T2D vs. 6,061 Adult Controls Without Diabetes



# Manhattan Plot for 3,006 Youth Cases With T2D vs. 856 Youth Controls Without Diabetes



# Summary: Gene Mutations and the $\beta$ -cell

$\beta$ -cell dysfunction is a key component of the pathogenesis of type 2 diabetes and can be demonstrated in individuals who still have normal fasting glucose or normal glucose tolerance.

$\beta$ -cell dysfunction is the predominant phenotype associated with gene variants linked to type 2 diabetes. These genotypes affect different components of the  $\beta$ -cell's function.

Genes linked to type 2 diabetes in youth are similar to those in adults.

# Epigenetic Modifications Occurring in the $\beta$ -cell in Diabetes

