Imperial College London

Understanding metabolic disease with modern genomics

Shedding light on the dark side of the human genome

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Academy of Medical Sciences Springboard Fellow

14th September 2020, Parliamentary & Scientific Committee

The human genome, genes are just the tip of the iceberg!

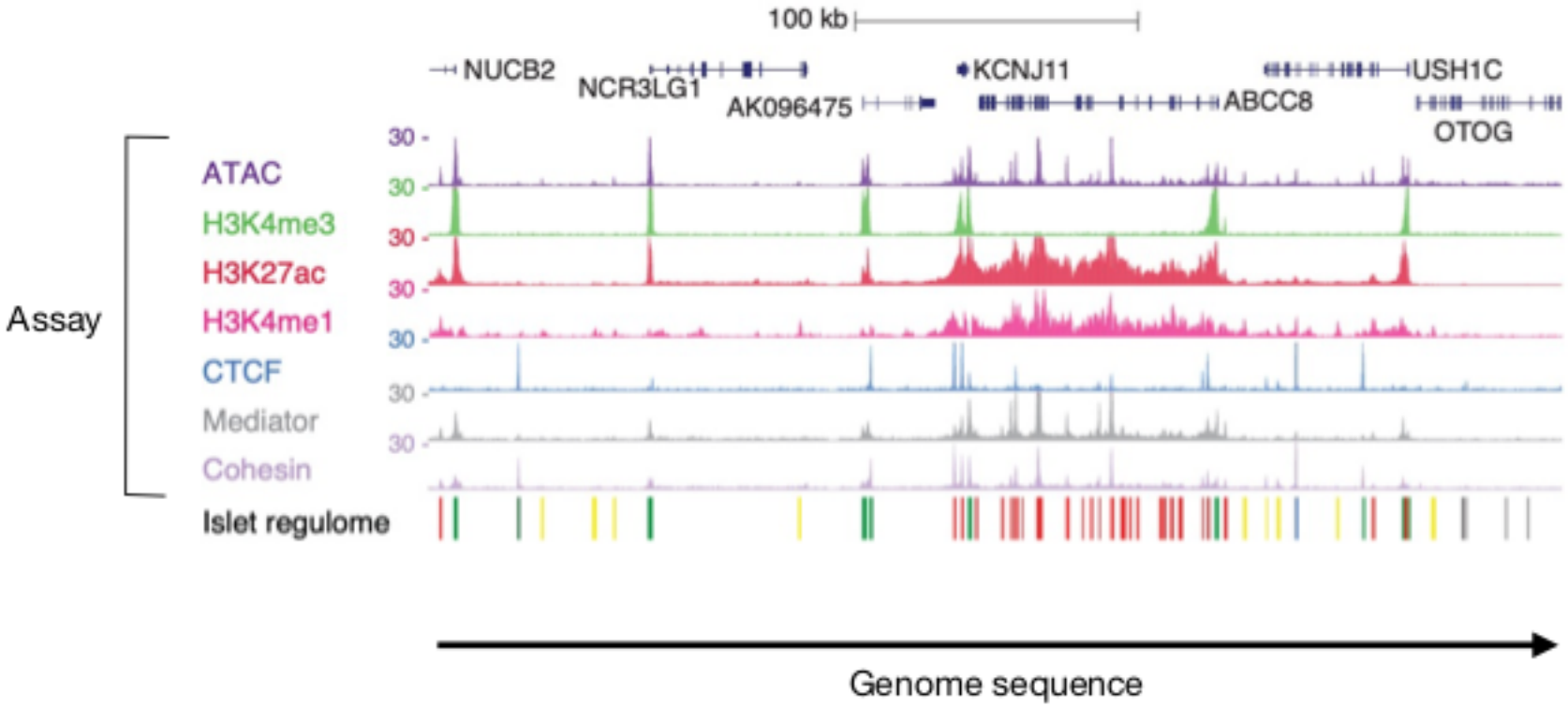
Coding sequence (<2%)

Non-coding sequence (>98%)

Transcriptional enhancers act as molecular switches to **fine tune** the expression of genes.

Coupling of biochemical assays with DNA sequencing

allows the identification of active enhancers at genome scale



Miguel-Escalada*, Bonas-Guarch*, Cebola* et al. *Nature Genetics* 2019

Sequence variation in enhancers contributes to a wide range of **human diseases**

Searching for causal mutations of regenerative capacity

Searching for causal mutations of pancreatic agenesis

Non-syndromic pancreatic agenesis

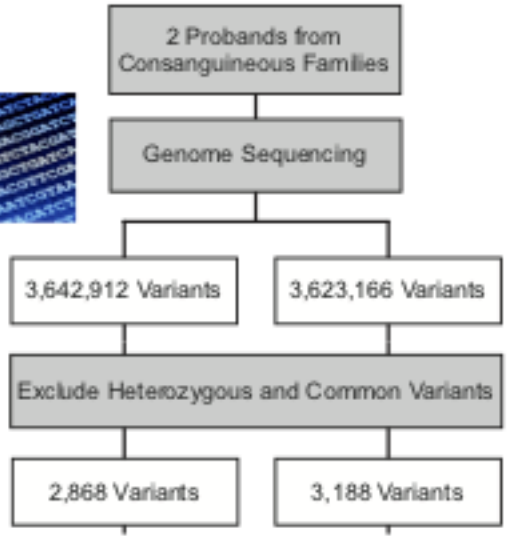
- Extremely rare condition resulting from impaired formation of the pancreas during embryonic development
- Insulin dependent neonatal diabetes
- Lack of extra-pancreatic features

- Sequencing of all coding genes in the genome did not reveal any pathogenic mutations

From whole genome sequencing to causal mutations

UNIVERSITY OF EXETER

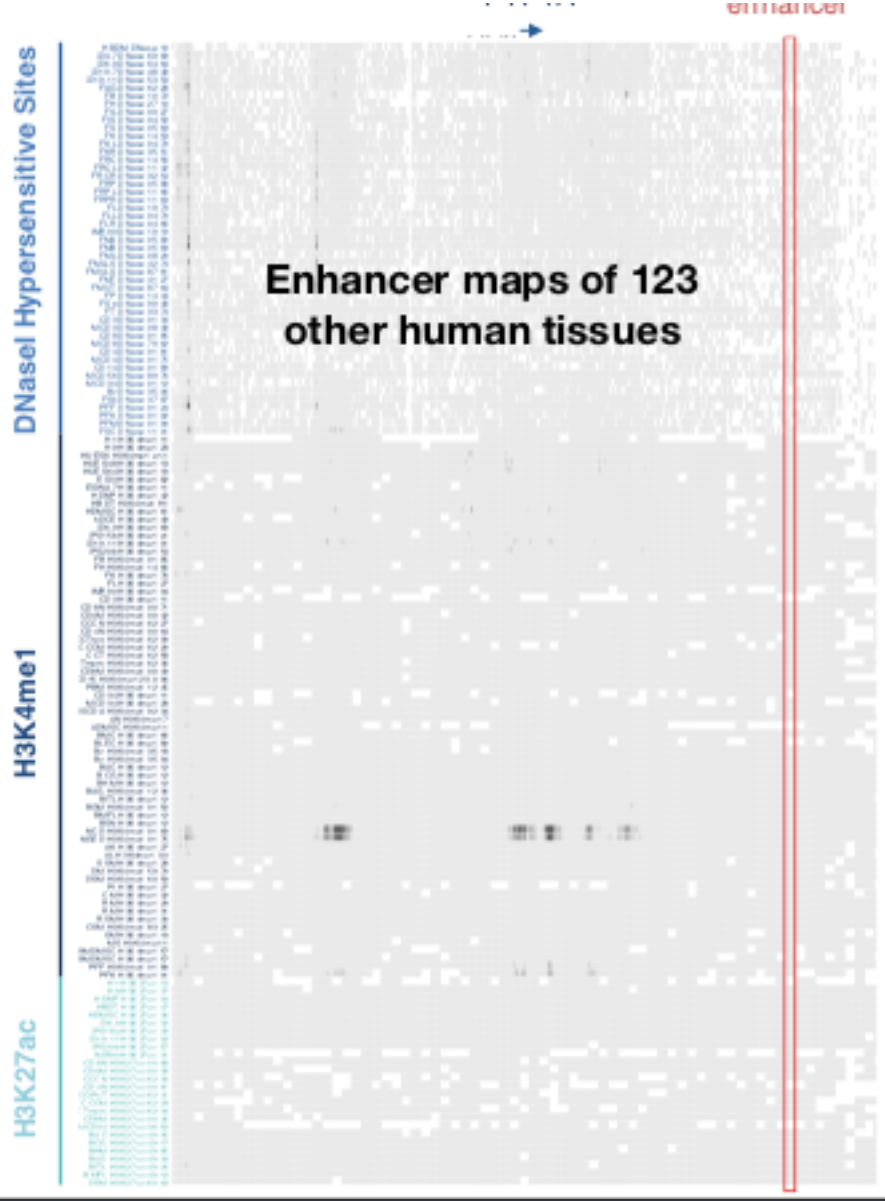
Prof Andrew Hattersley
Prof Sian Ellard
Dr Mike Weedon
Dr Sarah Flanagan



Weedon*, Cebola* et al. *Nature Genetics* 2014

PTF1A

PTF1A enhancer



Regulatory element maps in **disease-relevant** tissues are essential for appropriate interpretation of noncoding pathogenic variants.

Enhancer mutations are the most common cause of isolated pancreatic agenesis

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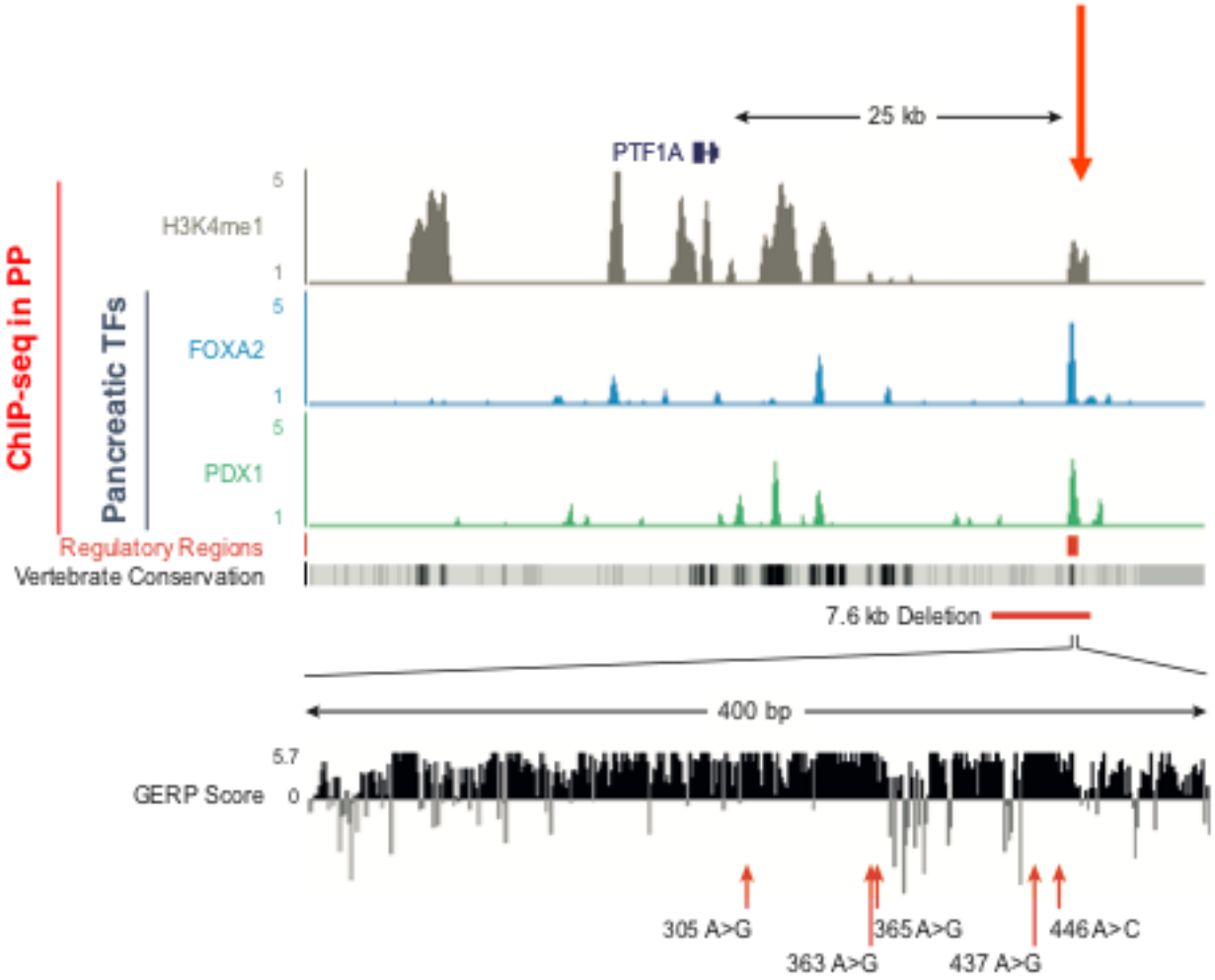
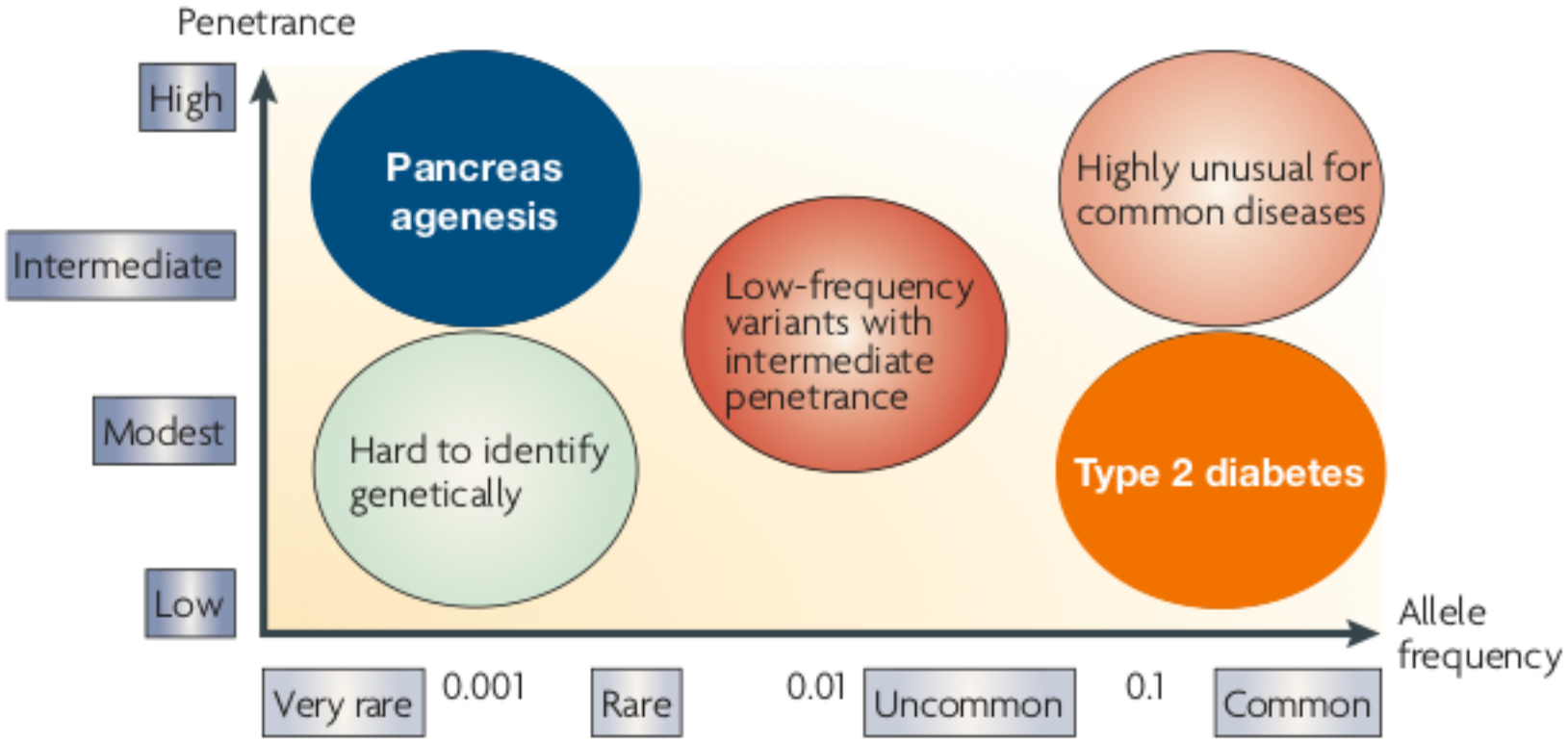


Weedon*, Cebola* et al. *Nature Genetics* 2014

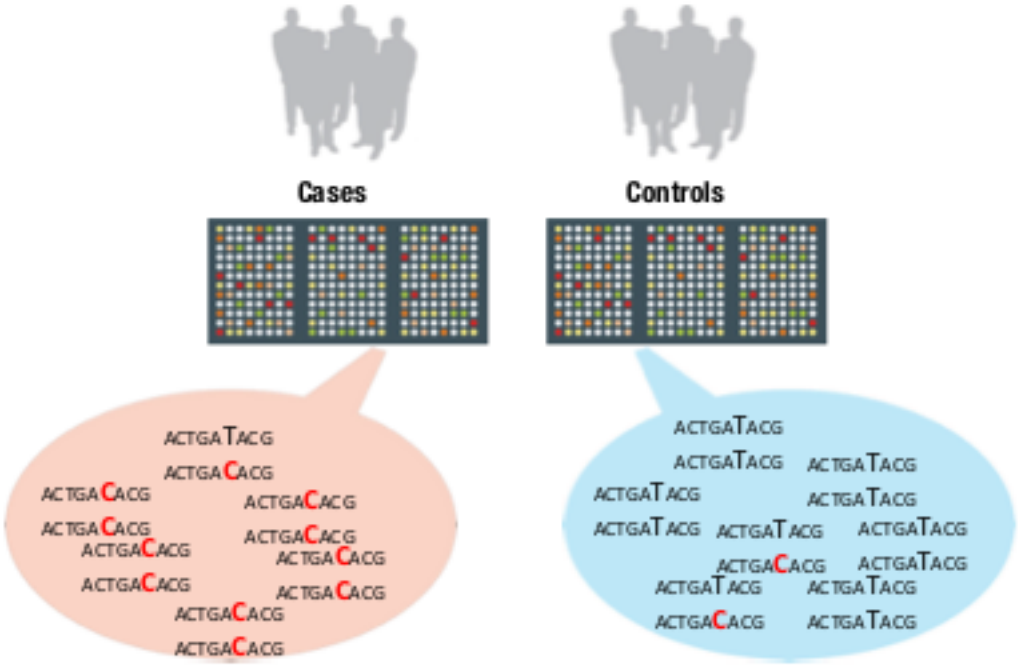
Not all DNA variants are the same for disease risk

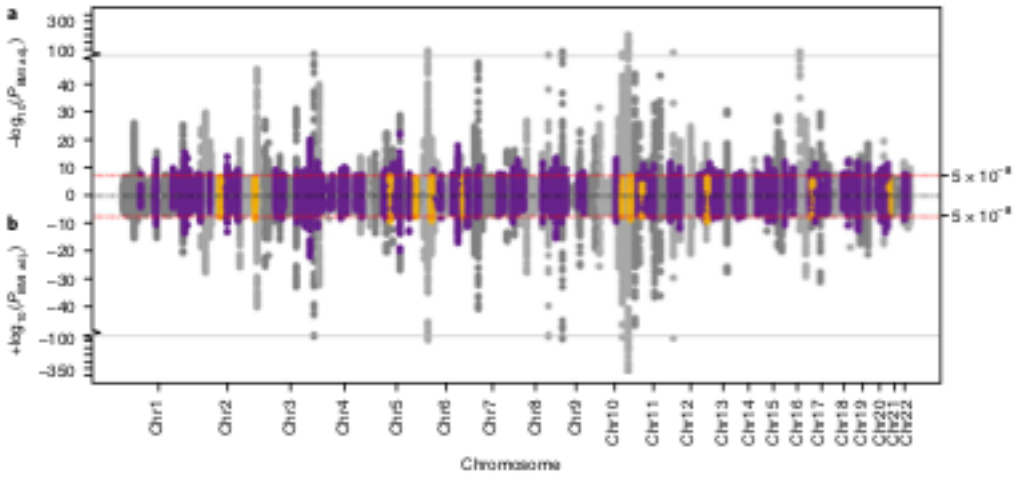


McCarthy et al. *Nature Reviews Genetics* 2008

Nearly 300 locations in the genome harbour DNA variants that alter

our risk of developing type 2 diabetes



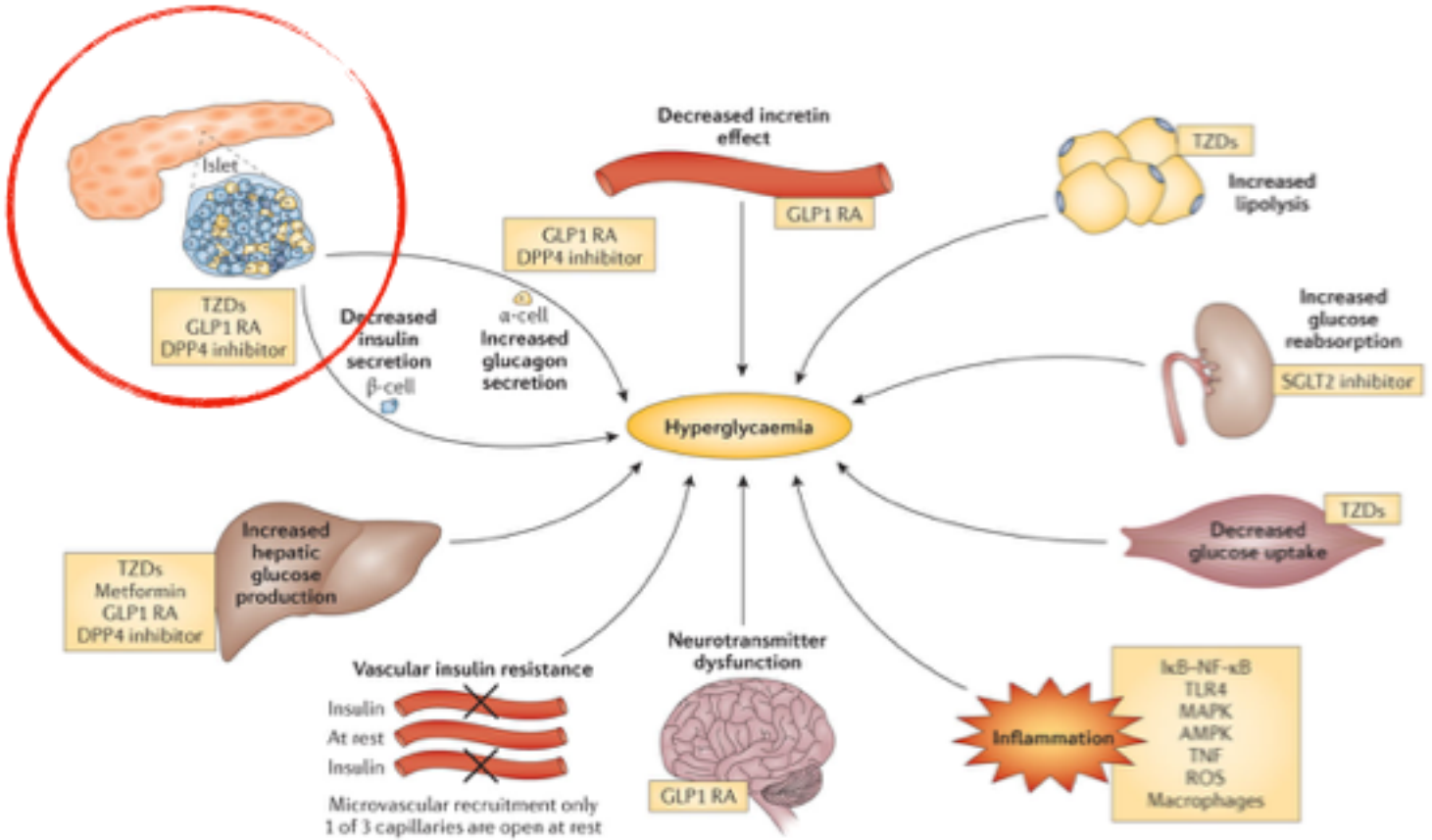


Mahajan et al. *Nature Genetics* 2018

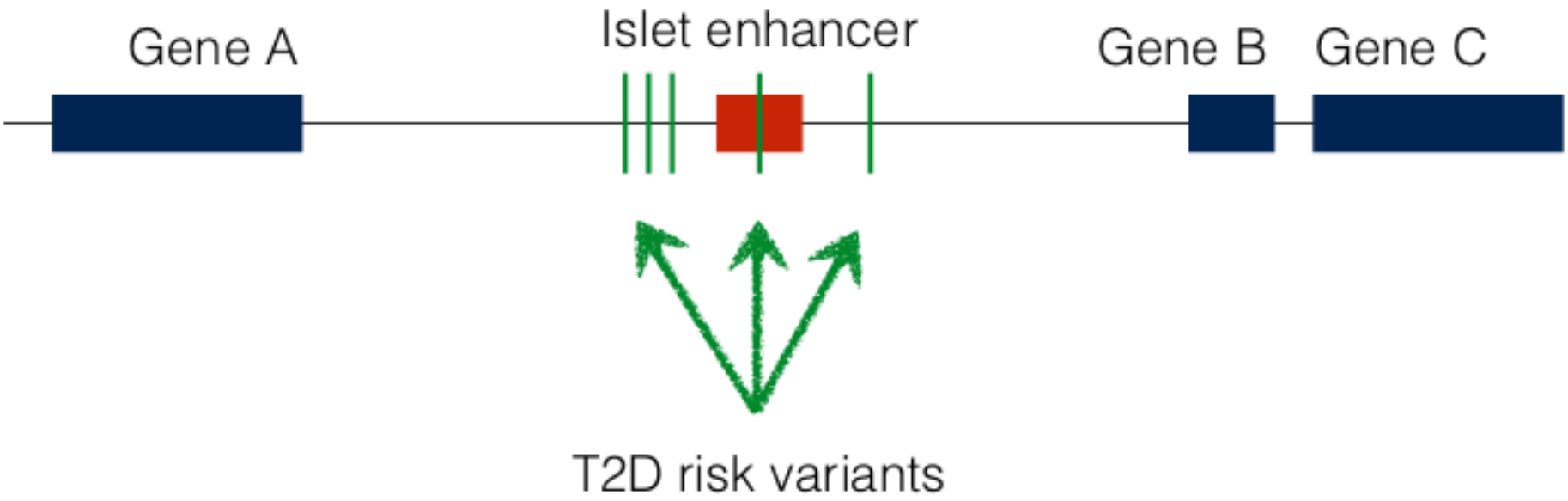
Type 2 diabetes results from alterations in multiple cell types and organs

Type 2 diabetes results from alterations in multiple cell types and organs

Pancreatic islets:
where insulin production occurs



DeFronzo, et al. *Nature Reviews Disease Primers* 2015



The human genome in 3D

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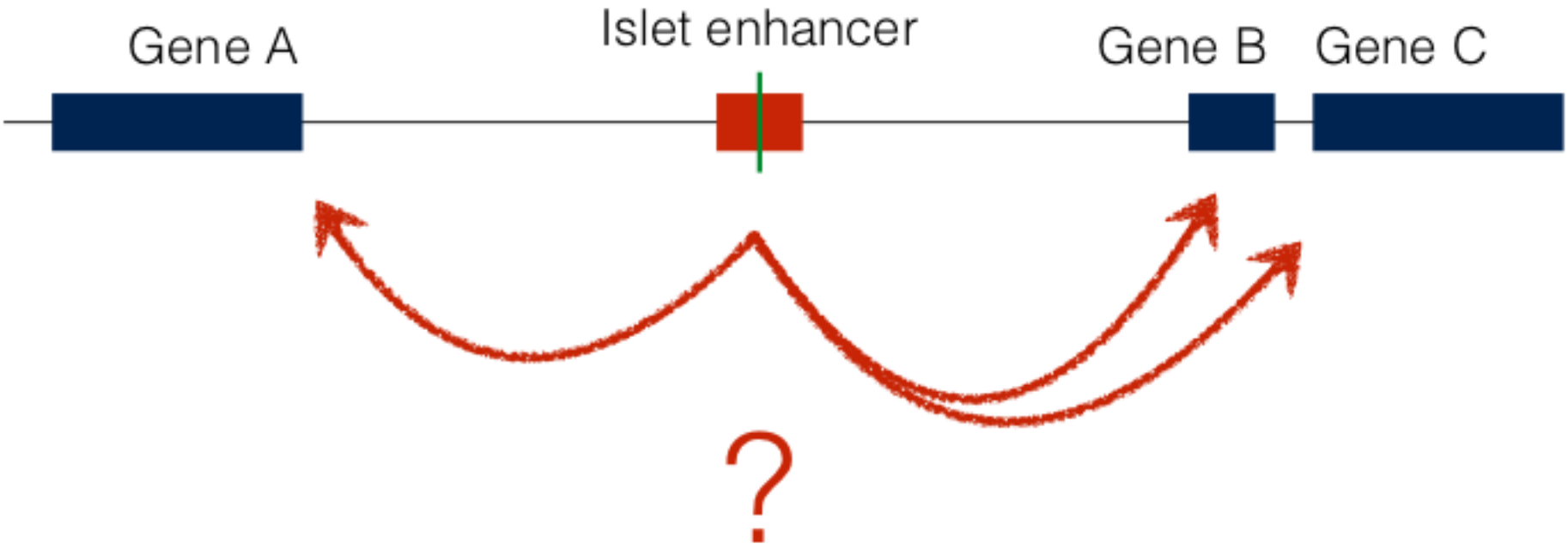
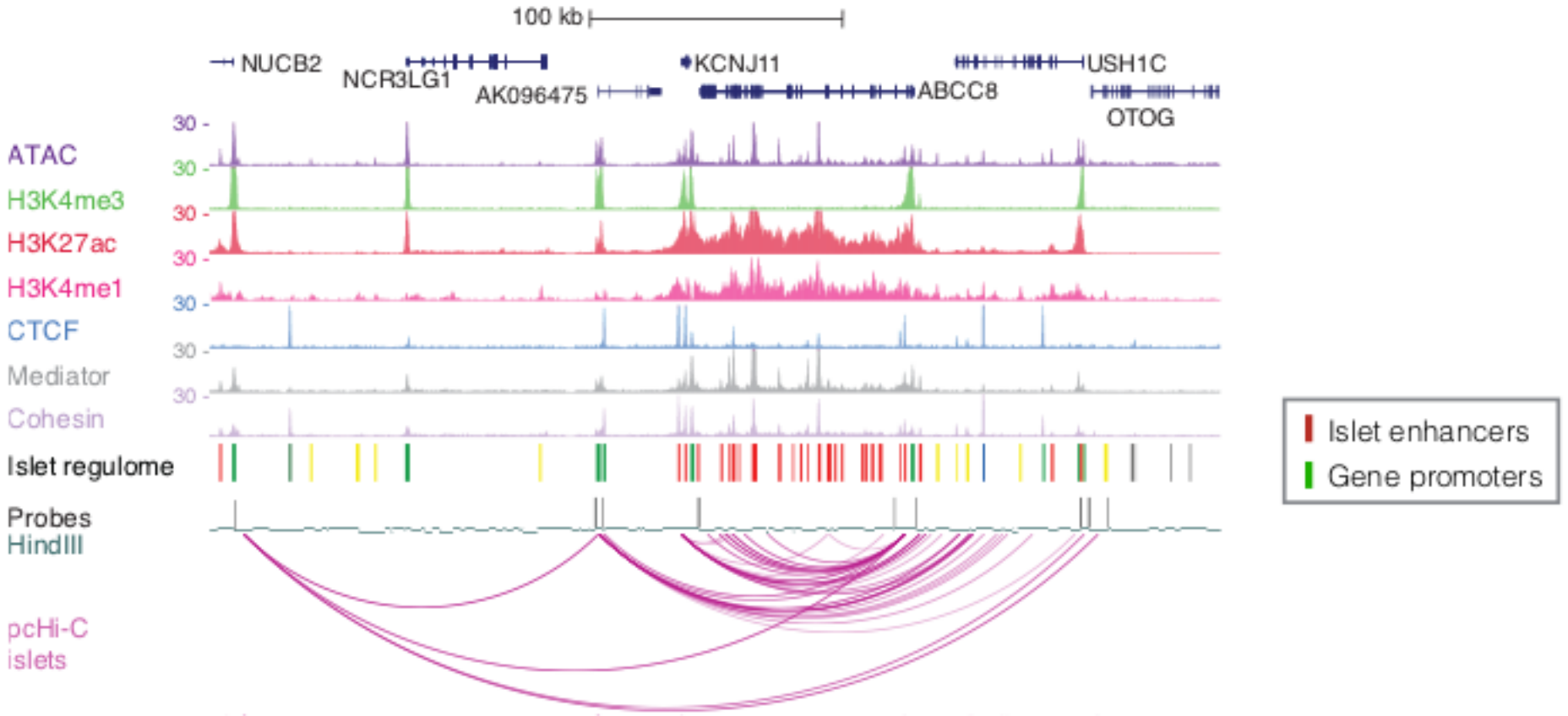
Yijun Ruan, Jackson Lab

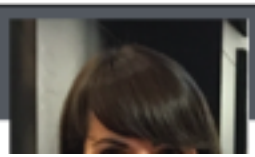


3D genome interactions in human pancreatic islets

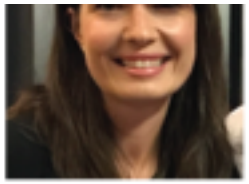


pcHi-C: Promoter capture Hi-C

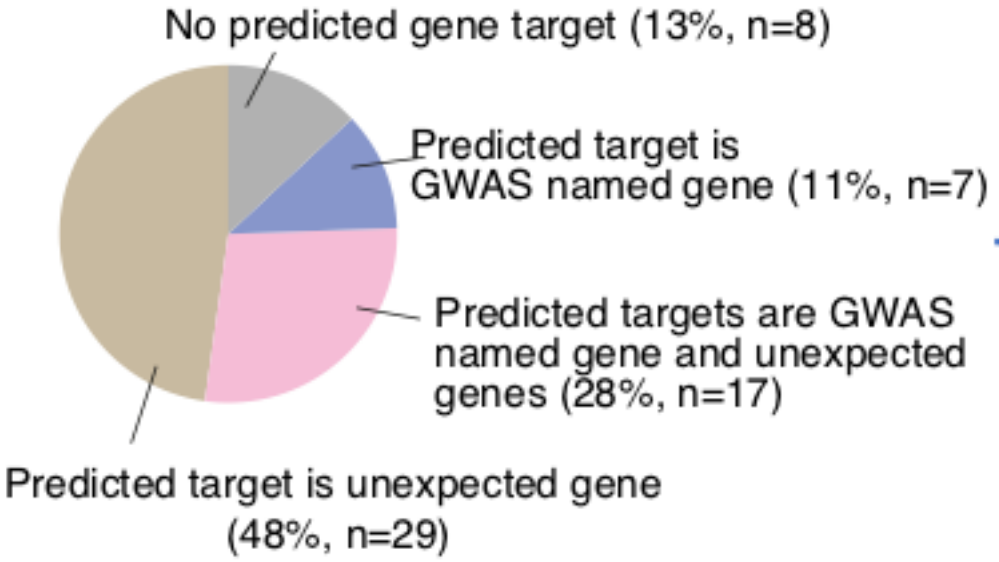
Collaboration with Peter Fraser's team (Babraham Institute, Cambridge)



Assignment of diabetes enhancers to target genes

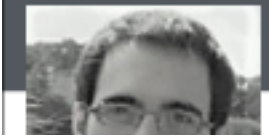


Dr Irene Miguel-Escalada



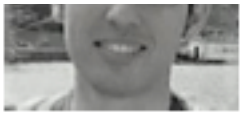
3D chromatin interactions reveal **new target genes** for >75% of islet T2D enhancers

Miguel-Escalada*, Bonas-Guarch*, Cebola* et al. *Nature Genetics* 2019



Enhancer hubs

Highly connected structures that regulate islet-specific expression

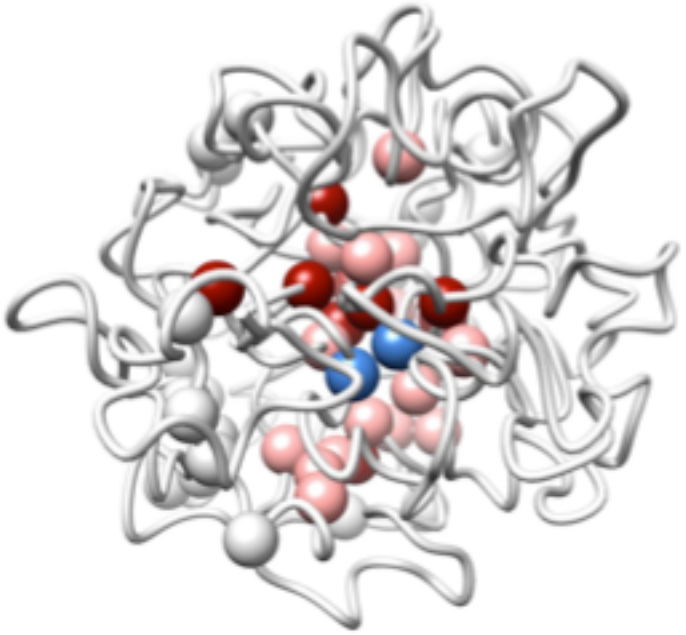


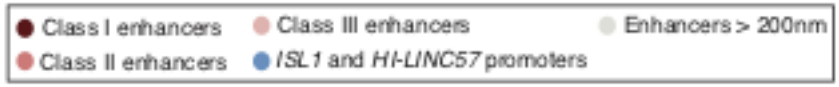
Joan Ponsa

Highly connected structures that regulate islet-specific expression

Enhancer hubs (n=1,318)

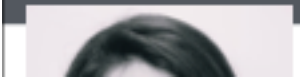
	Top functional annotations of hub genes	Adj. P-value	Examples
dbGaP	Diabetes Mellitus, type 2	6.1×10^{-7}	*JAZF1, GLIS3, PCSK1, ZFAND3*
KEGG	Insulin secretion	2.3×10^{-6}	*ABCC8, KCNJ11, STX1A, SNAP25*
	Circadian entrainment	2.8×10^{-5}	*RYR2, PER1, CACNA1D, CAMK2B*
	Maturity onset diabetes of the young	2.8×10^{-5}	*NEUROD1, PDX1, MAFA, NKX2-2*
Reactome	PDCL and TRiC in G-protein beta folding	3.8×10^{-4}	*RGS7, GNAZ, GNAI2*
	Regulation of insulin secretion	2.3×10^{-4}	*FFAR1, ADRA2A, STX1A, GCK*
Gene Ontology	Phosphorylation of RNA polymerase II	1.8×10^{-6}	*MNX1, HIPK2, CDK4, FOXO3*
	Negative regulation of transcription	1.2×10^{-5}	*INSM1, PAX6, DACH1*
	Positive regulation of transcription	3.2×10^{-5}	*RFX6, FOXO1, FOXA2, PDX1*
OMIM	Diabetes mellitus, type 2	0.35	*TCF7L2, SLC30A8, WFS1*



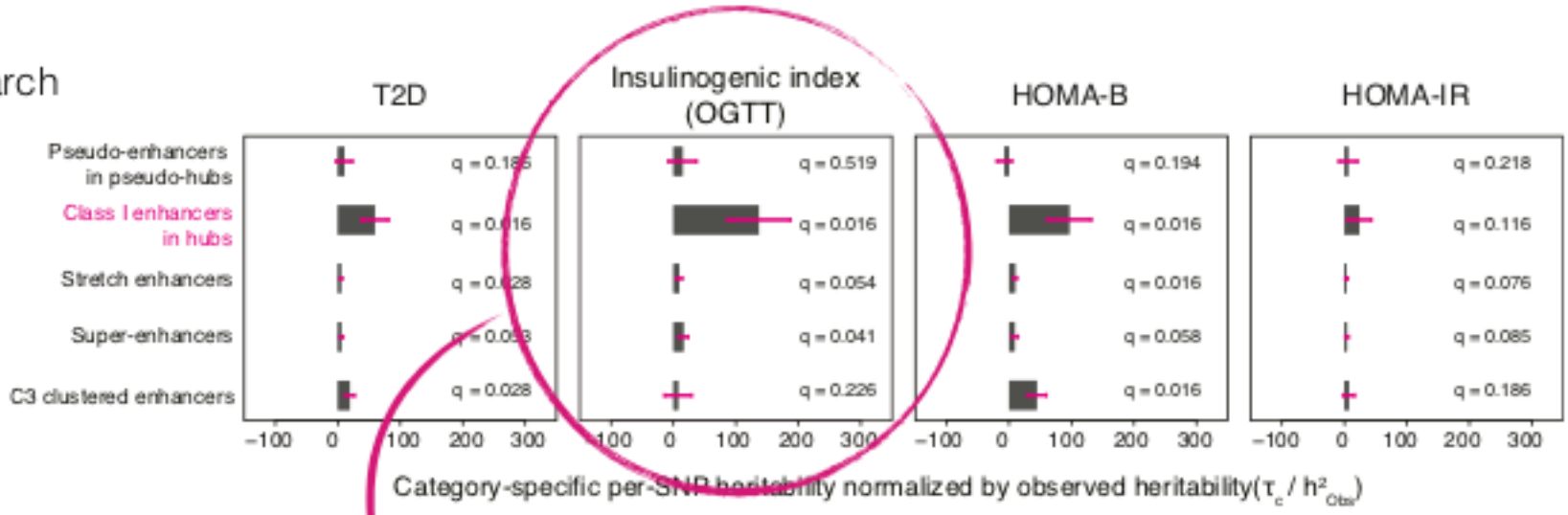


Collaboration with Marc Marti-Renom team (CRG, Barcelona)

Hubs contain common variants that affect islet function



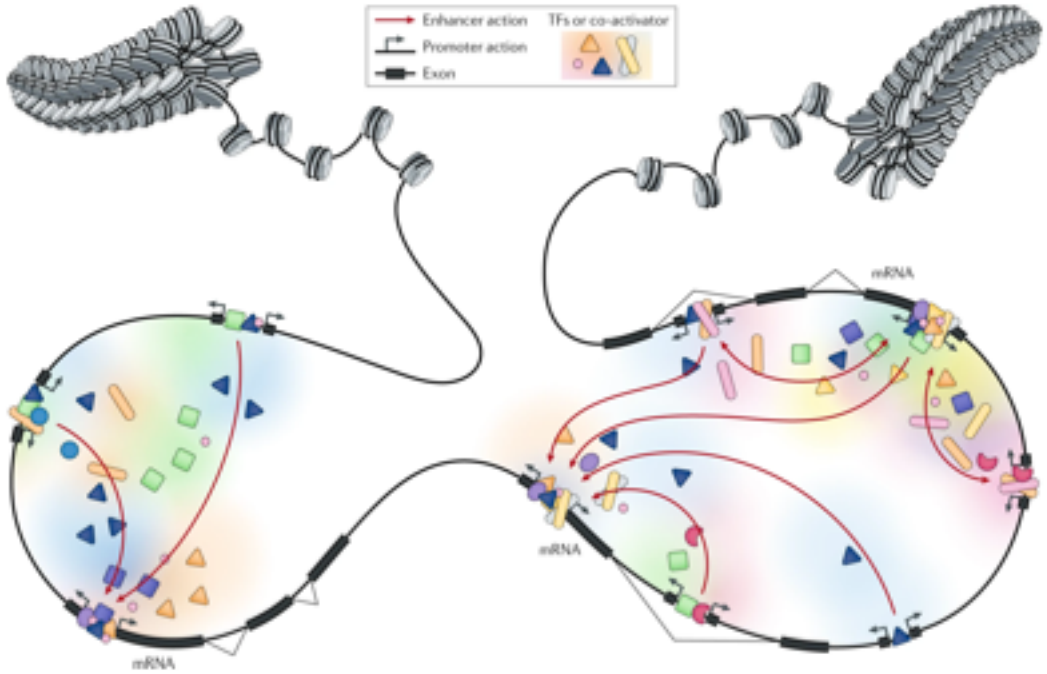
Dr Silvia Bonàs-Guarch



Insulin secretion variation in individuals without diabetes

Miguel-Escalada*, Bonas-Guarch*, Cebola* et al. *Nature Genetics* 2019

What looking the islet 3D genome has taught us



Anderson & Sandelin *Nat Rev Genet* 2019

- Genes important for **insulin production** in the pancreas are controlled by distinct 3D genomic domains ("enhancer hubs").
- DNA sequence variation in enhancer hubs affects insulin production, and plays a major role in the genetic risk of developing type 2 diabetes.
- Noncoding diabetes risk variants may alter the expression of multiple genes, this may imply multiple disease effector genes…

Moving forward

Biological insight

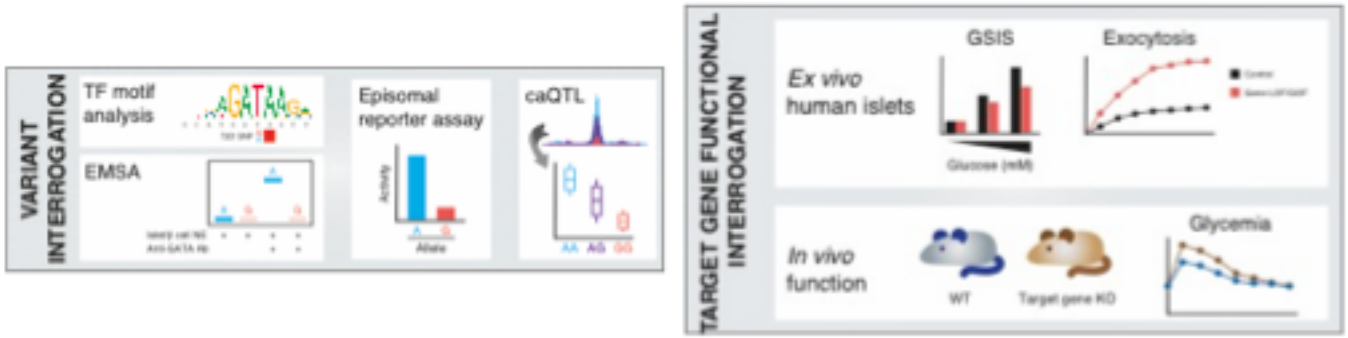
GWAS

Functional profiling
(enhancer maps)

Chromatin interactions

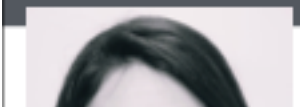
CRISPR/Cas9 perturbations

Candidate variants and
effector genes/transcripts



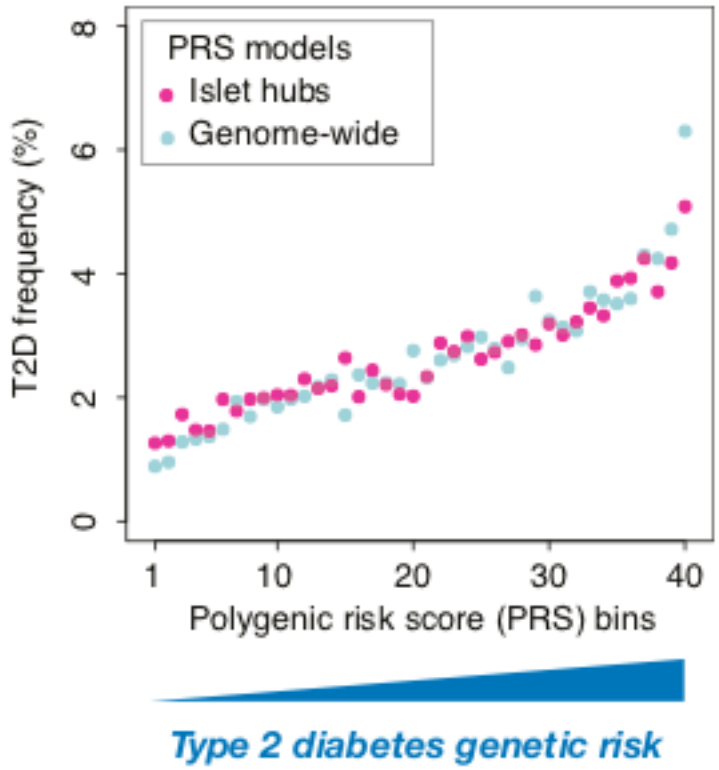
Cebola. *Current Diabetes Reports* 2020

Hubs variants are predictive of onset of diabetes



Dr Silvia Bonàs-Guarch

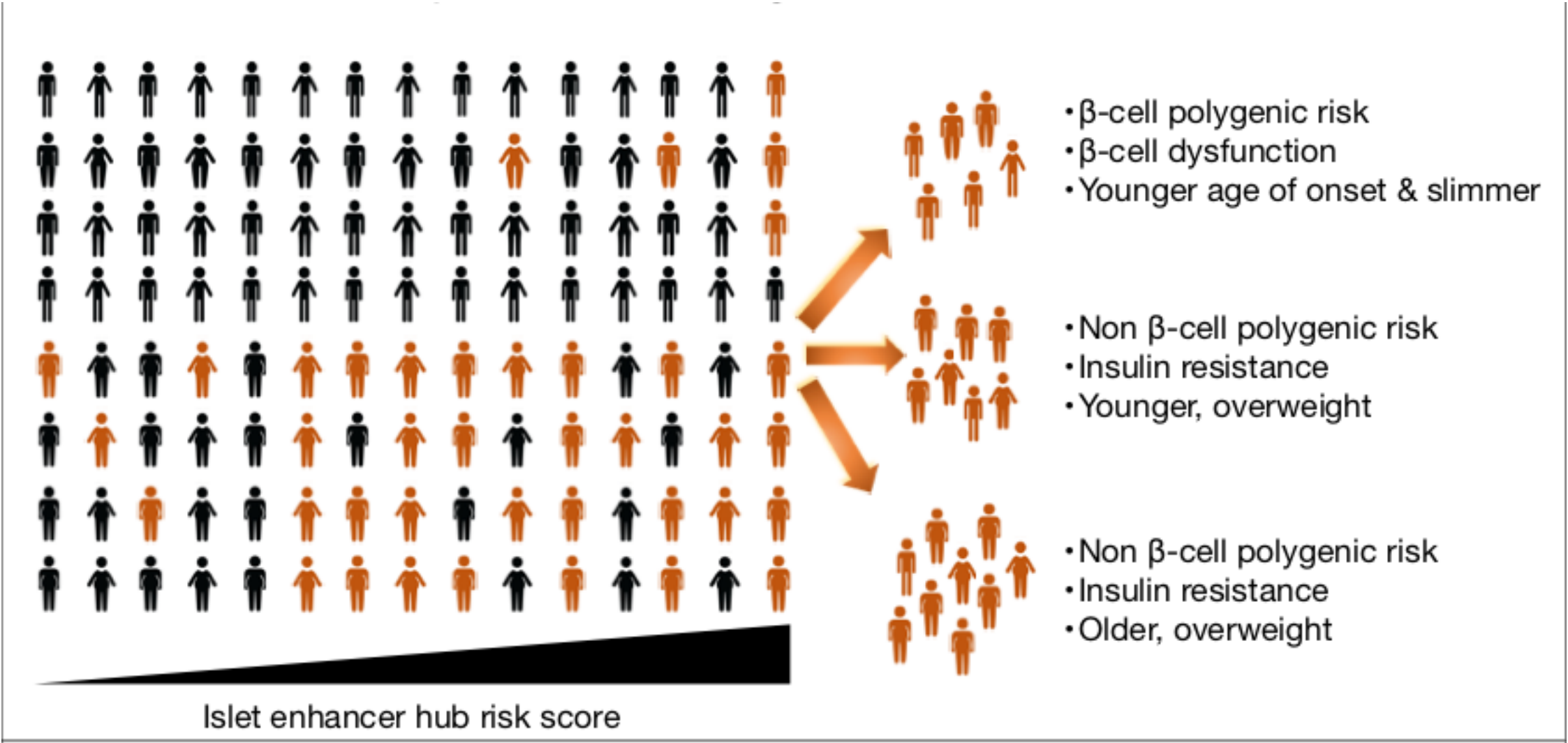
biobank uk



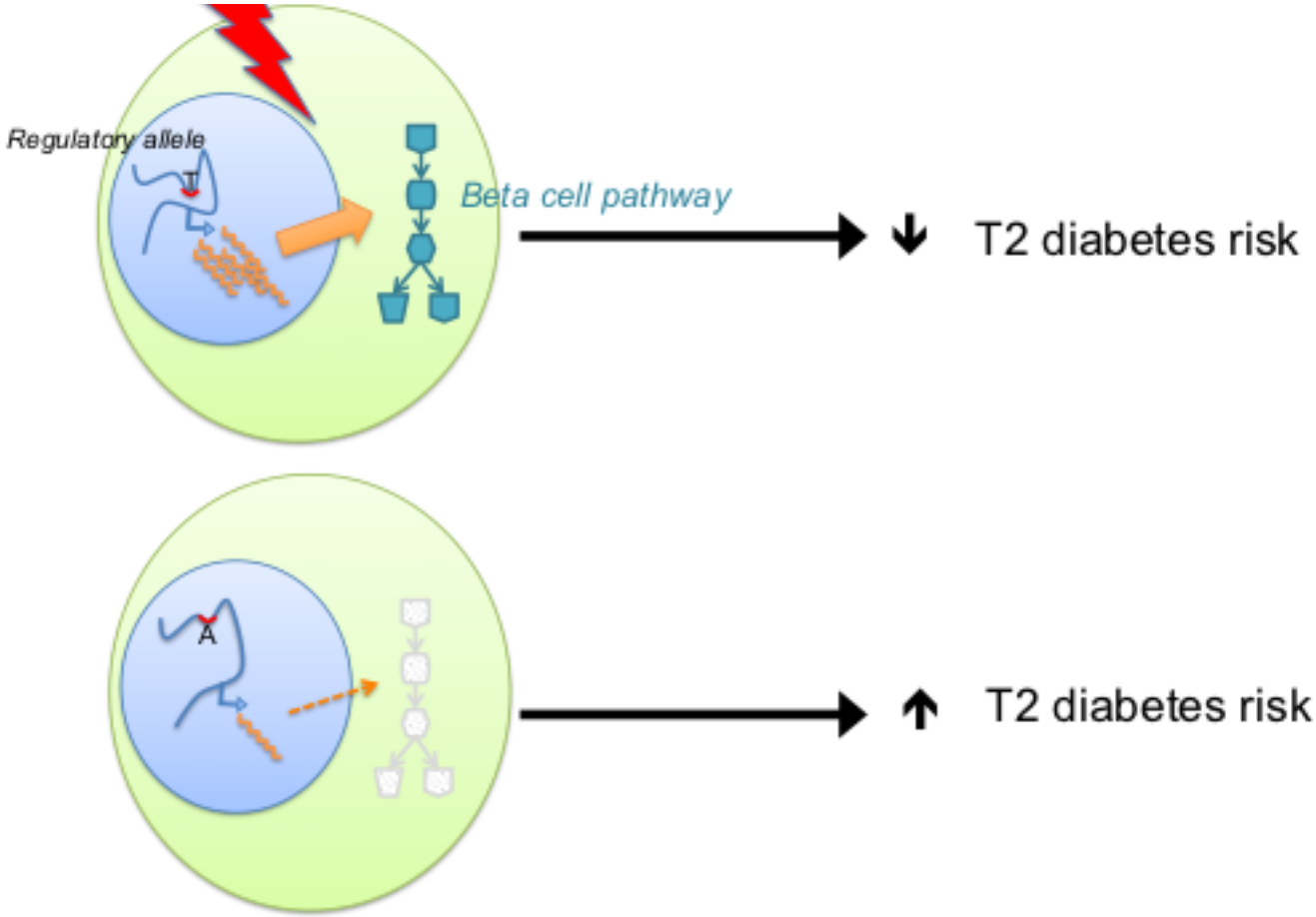
Only 1.6% of the genome

Miguel-Escalada*, Bonas-Guarch*, Cebola* et al. *Nature Genetics* 2019

Tissue-specific polygenic risk scores can help stratify patients who develop diabetes through different mechanisms



Therapeutic or preventive intervention



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Dr Ken Brayman