Type 1 diabetes 2007-2017

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Division of Endocrinology
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Endorama 2018

Duality of interest

- I own patents for diagnostic tests for some of the genes that will be discussed
- Research support from Eli Lilly
- I have received an Ipad and a T-shirt from *Illumina*

Has life improved for T1D patients in the past 10 years?

- Yes
- But mostly by KT (knowledge transfer)
- However, big breakthroughs in science
  - Highly promising for the next decade!

Most promising developments

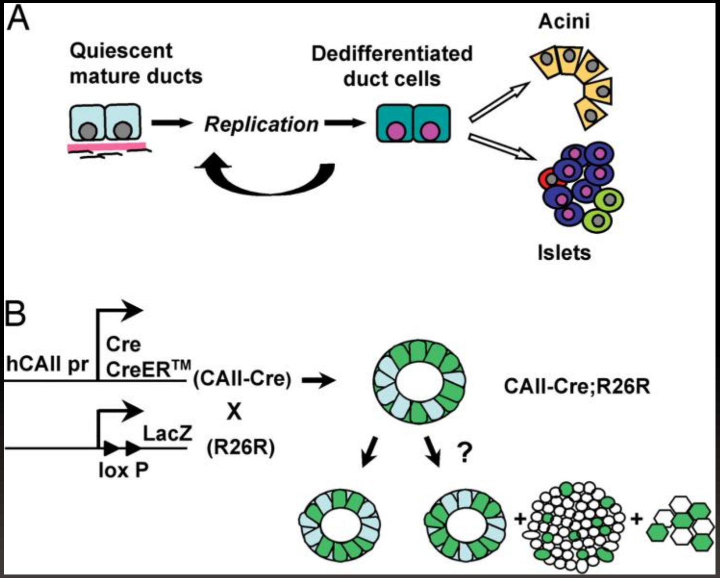
- Beta cell engineering
  - Regeneration
  - In vitro generation for transplant
- Closed-loop insulin delivery
- Advances in Genetics

β-cell engineering

- Regeneration of the patient's own β-cells
  - Science fiction?
- Intensive research as to how β-cells are formed.

Transdifferentiation

- What are the precursor cells?
  - Ductal cells (Inada et al., Proc Natl Acad Sci USA, 2008)
  - Acinar cells (Zhou et al. *Nature* 2008)
  - Existing β-cells (Dor et al., *Nature* 2005)
  - α-Cells (Thorel et al., *Nature* 2010)

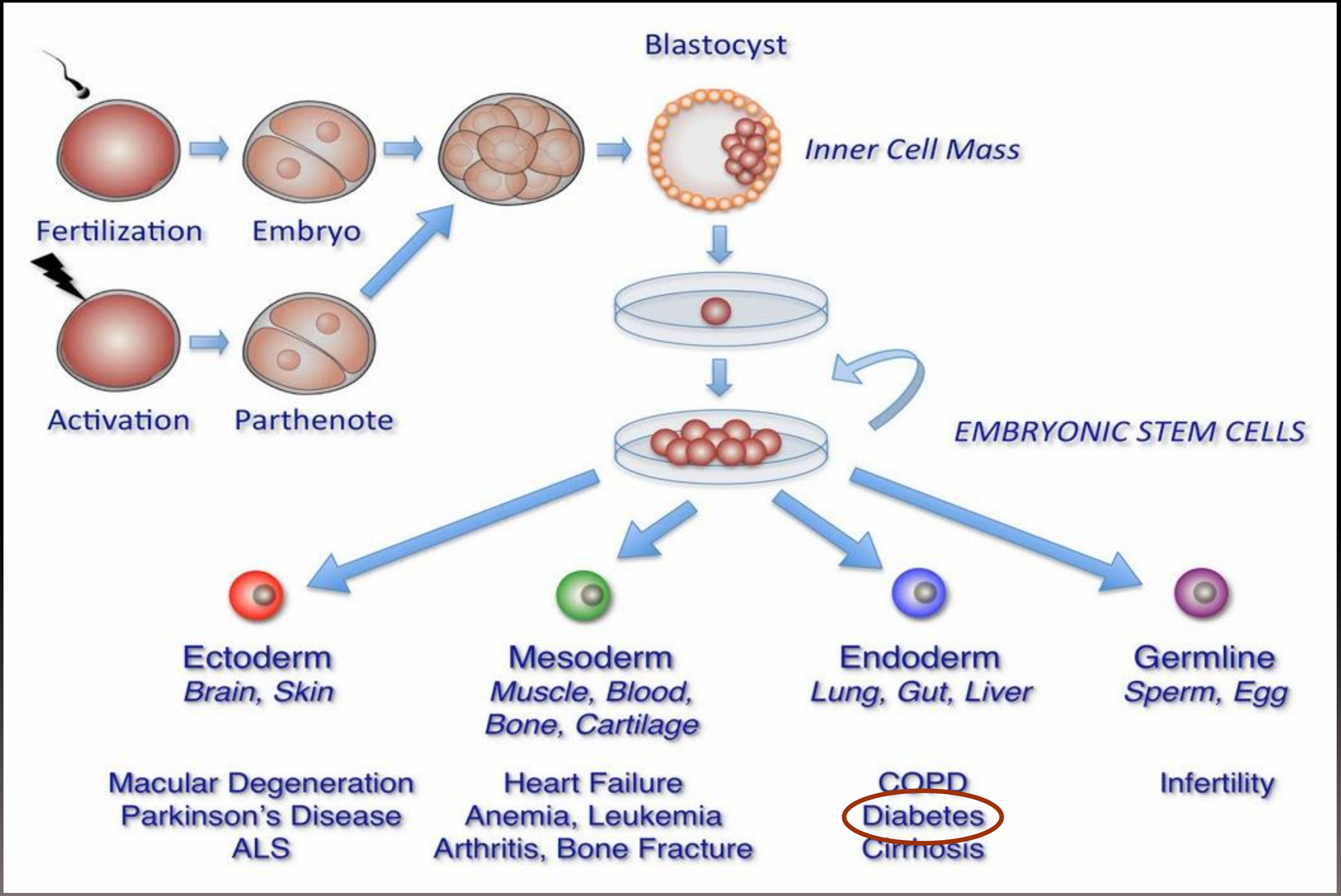


- What drives this transformation?

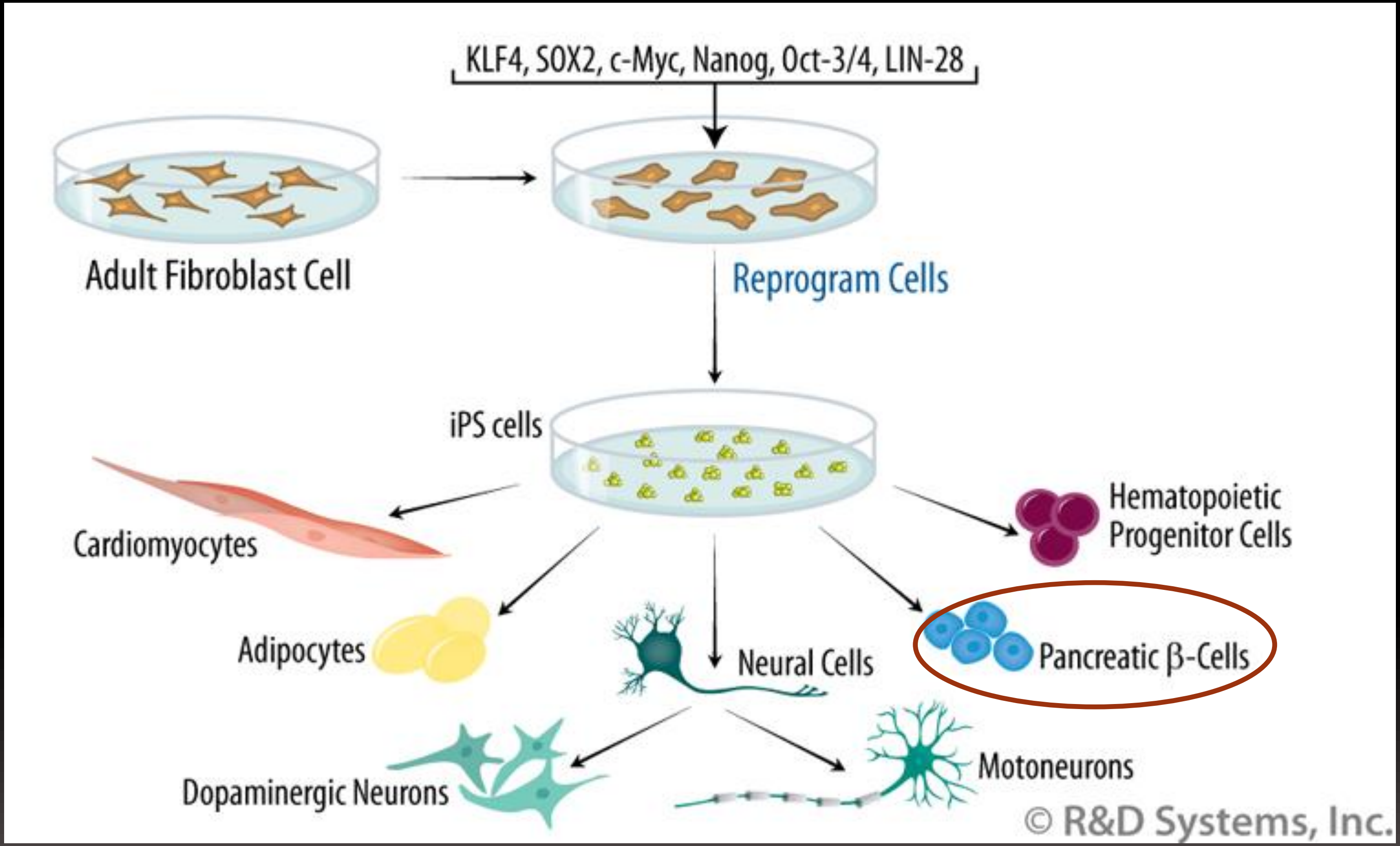
β-cells generated for transplantation

- Generated in *vitro*, from embryonic stem cells
- Allotransplantation
- Same rejection issues as for islet transplant
- Solves the problem of supply
- May make encapsulation more effective

β-cell generation from human pluripotent stem cells (hPSC)



Induced pluripotent stem cells



R&D systems website

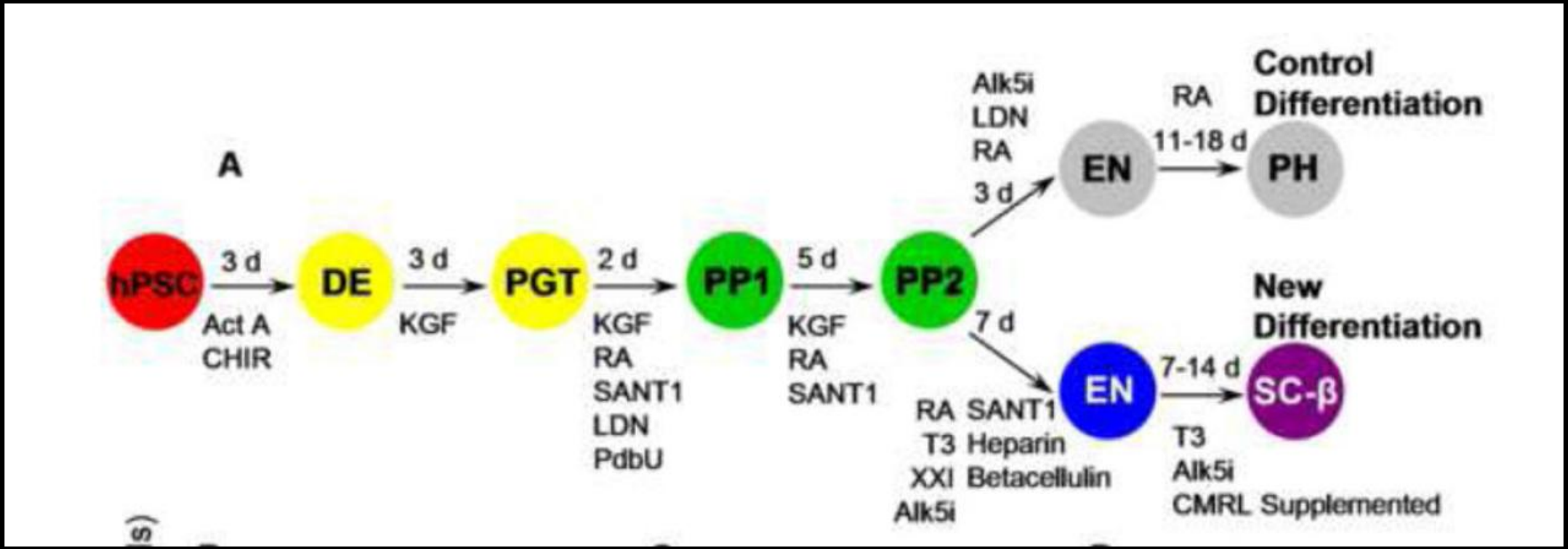
Cell

Resource

Generation of Functional Human Pancreatic β Cells In Vitro

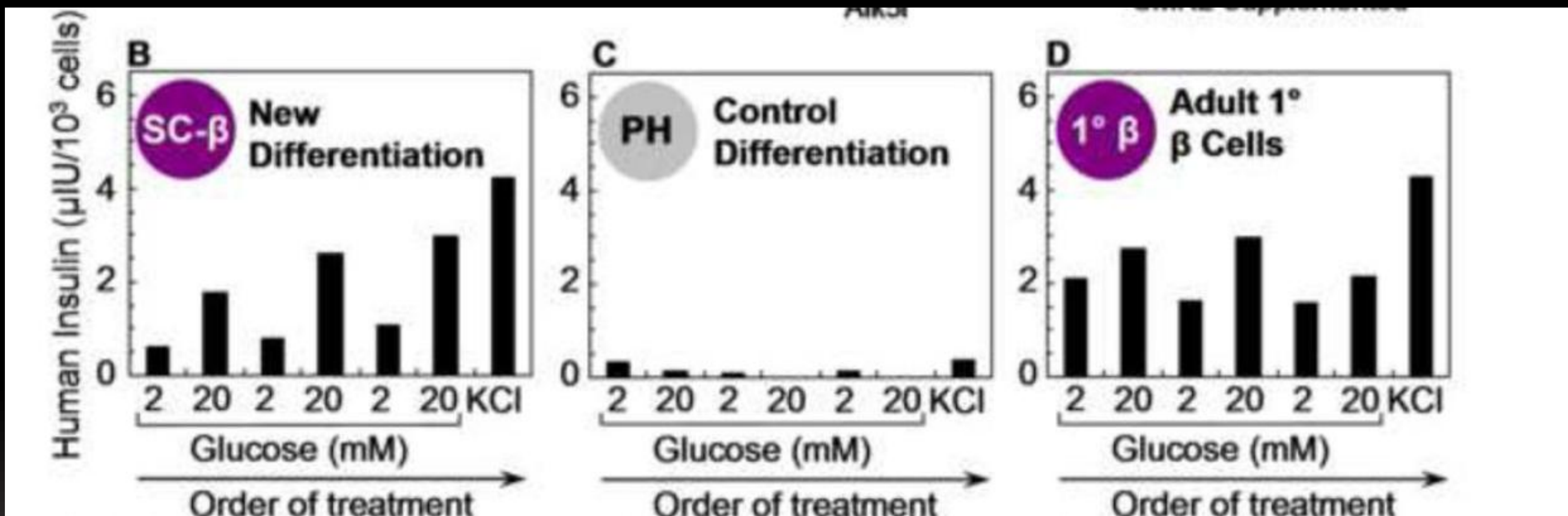
Felicia W. Pagliuca,[1,3] Jeffrey R. Millman,[1,3] Mads Gürtler,[1,3] Michael Segel,[1] Alana Van Dervort,[1] Jennifer Hyoje Ryu,[1] Quinn P. Peterson,[1] Dale Greiner,[2] and Douglas A. Melton[1,*]
[1]Department of Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Harvard University, 7 Divinity Avenue, Cambridge, MA 02138, USA
[2]Diabetes Center of Excellence, University of Massachusetts Medical School, 368 Plantation Street, AS7-2051, Worcester, MA 01605, USA
[3]Co-first author
*Correspondence: dmelton@harvard.edu
http://dx.doi.org/10.1016/j.cell.2014.09.040

Generation of β–cells from hPSC



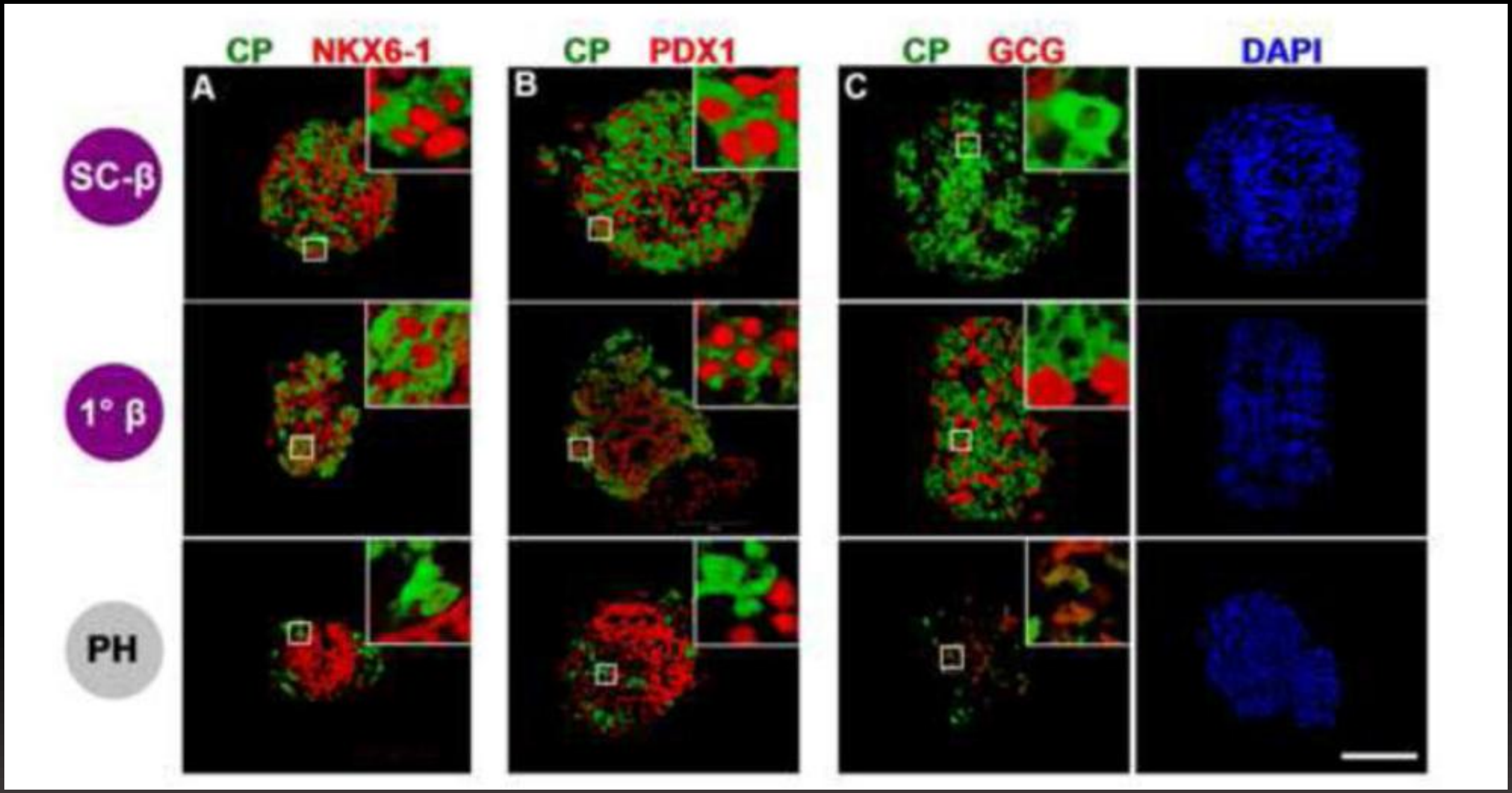
- Pagluca et al. *Cell* 2014

Glucose-stimulated insulin release



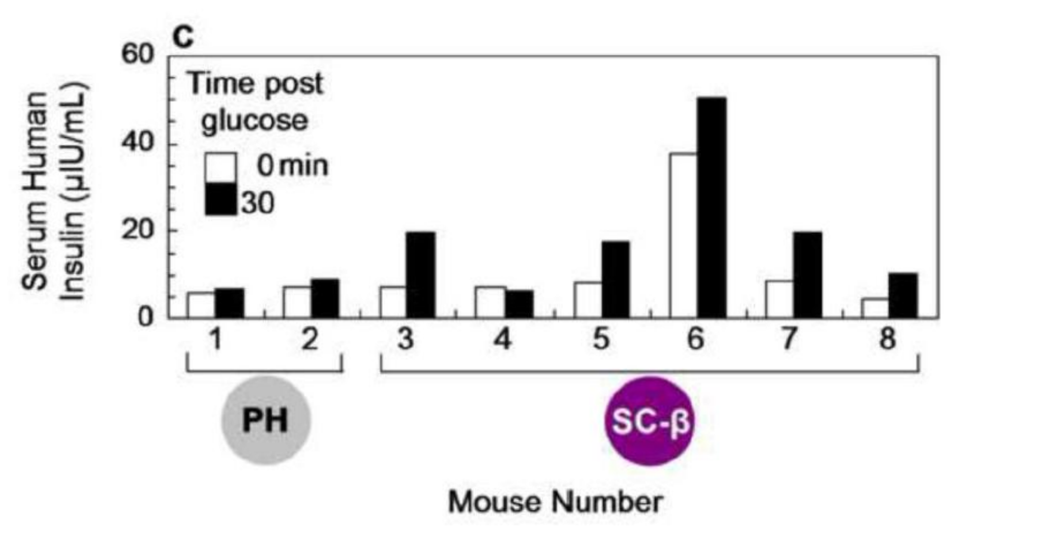
- Pagluca et al. *Cell* 2014

Correct β-cell phenotype

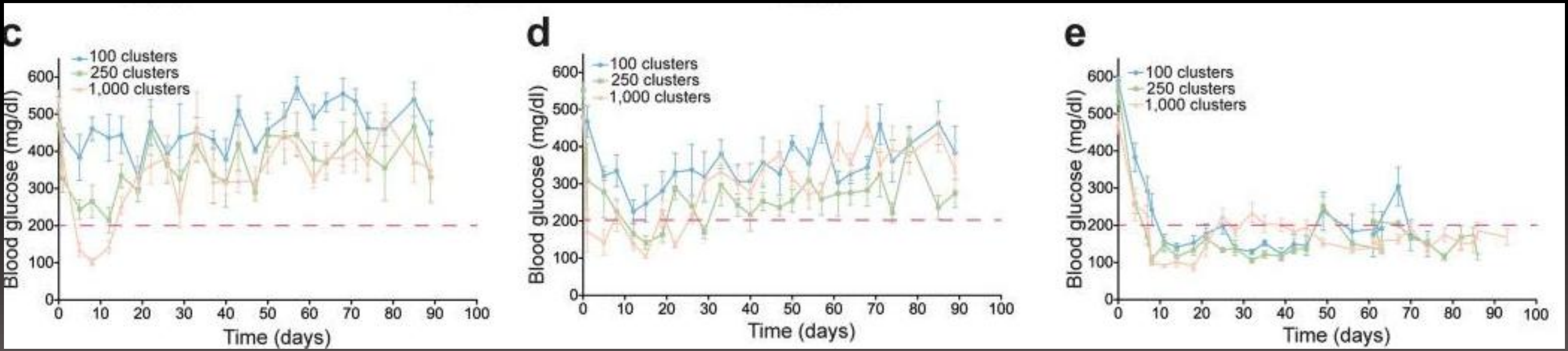


- Pagluca et al. *Cell* 2014

Transplanted to mice



- Pagluca et al. *Cell* 2014



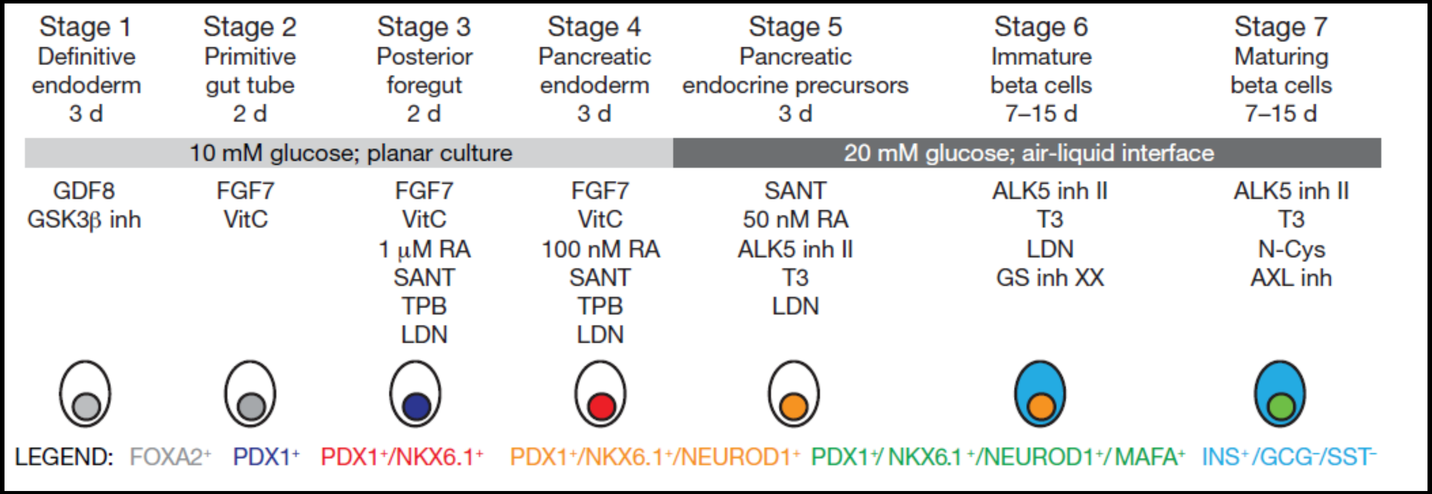
- Vegas et al. *Nature Medicine* 2016

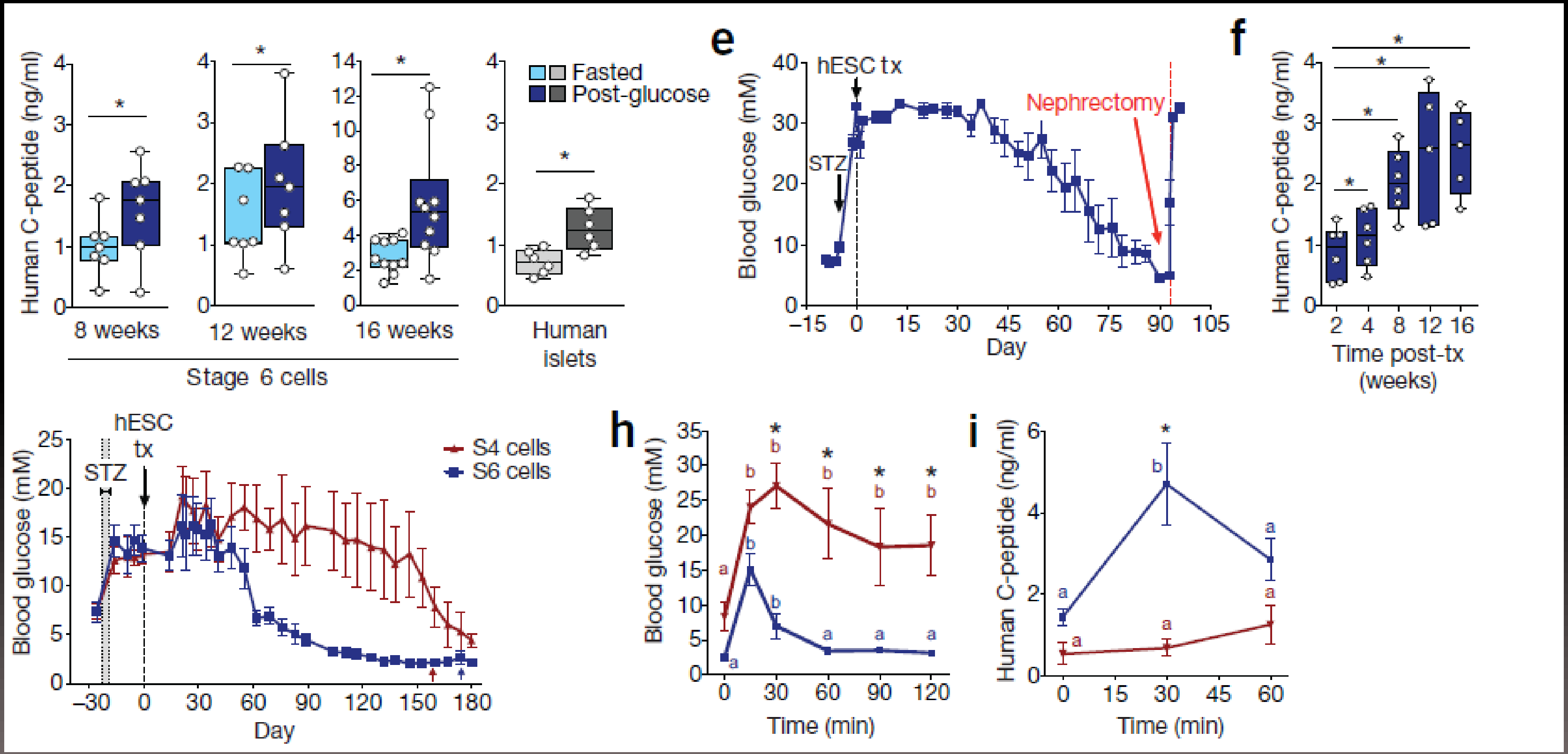
nature biotechnology

ARTICLES

Reversal of diabetes with insulin-producing cells derived *in vitro* from human pluripotent stem cells

Alireza Rezania[1], Jennifer E Bruin[2], Payal Arora[1], Allison Rubin[1], Irina Batushansky[1], Ali Asadi[2], Shannon O'Dwyer[2], Nina Quiskamp[2], Majid Mojibian[2], Tobias Albrecht[2], Yu Hsuan Carol Yang[2], James D Johnson[2,3] & Timothy J Kieffer[2,3]

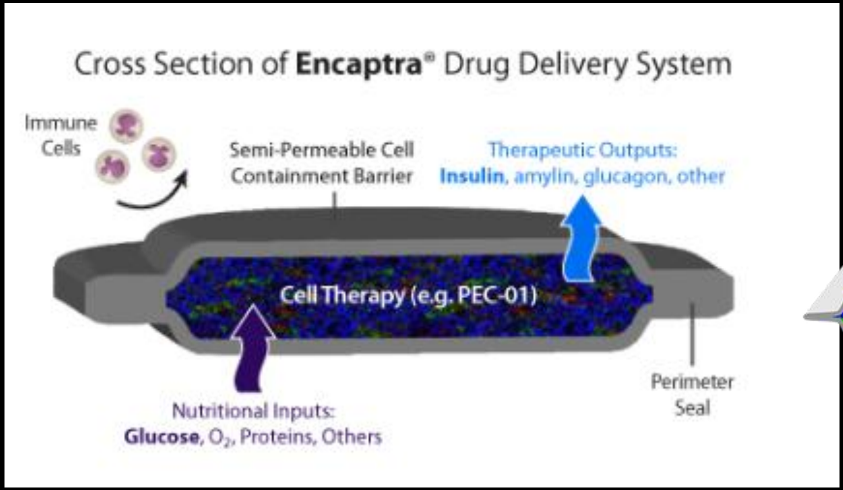


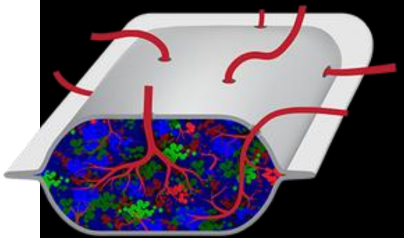


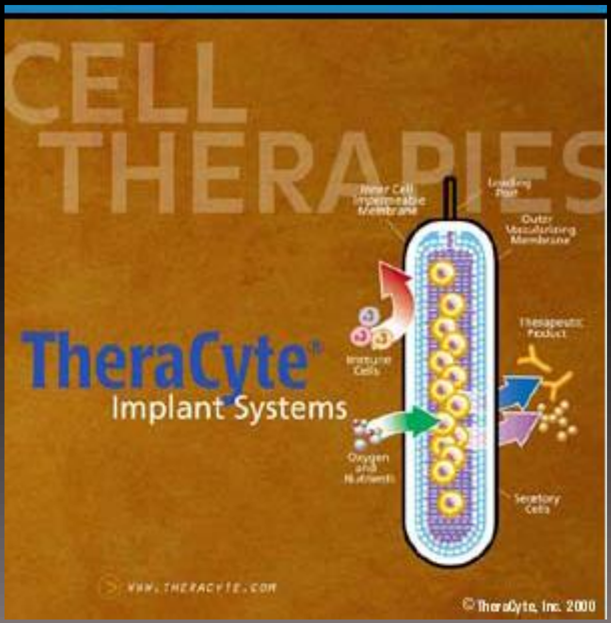
Rezania et al. *Nature Biotechnology* 2014

Encapsulation devices

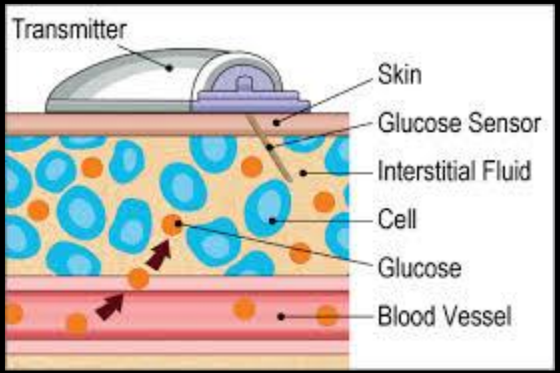
VIACYTE
Regenerating Health™



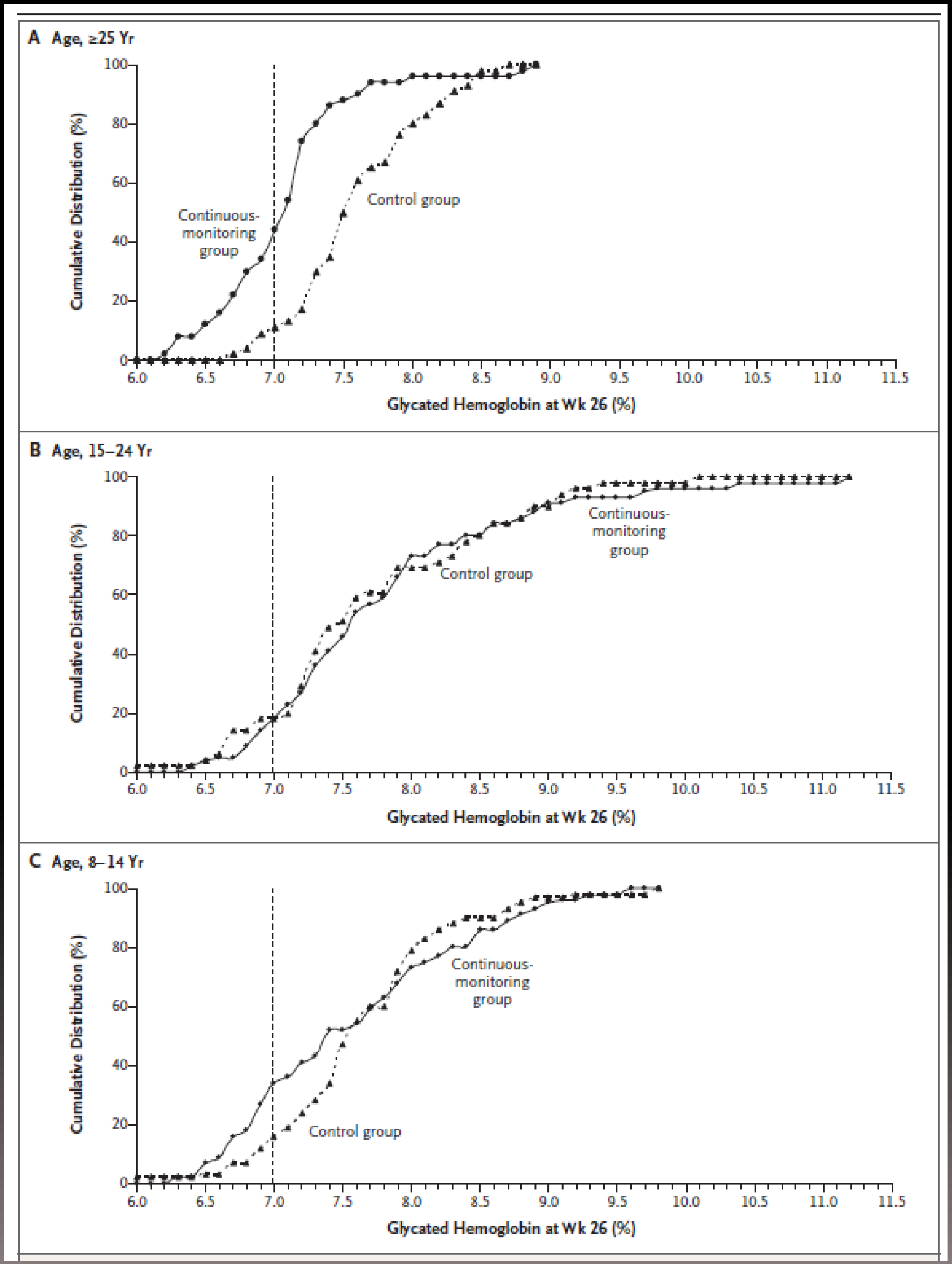




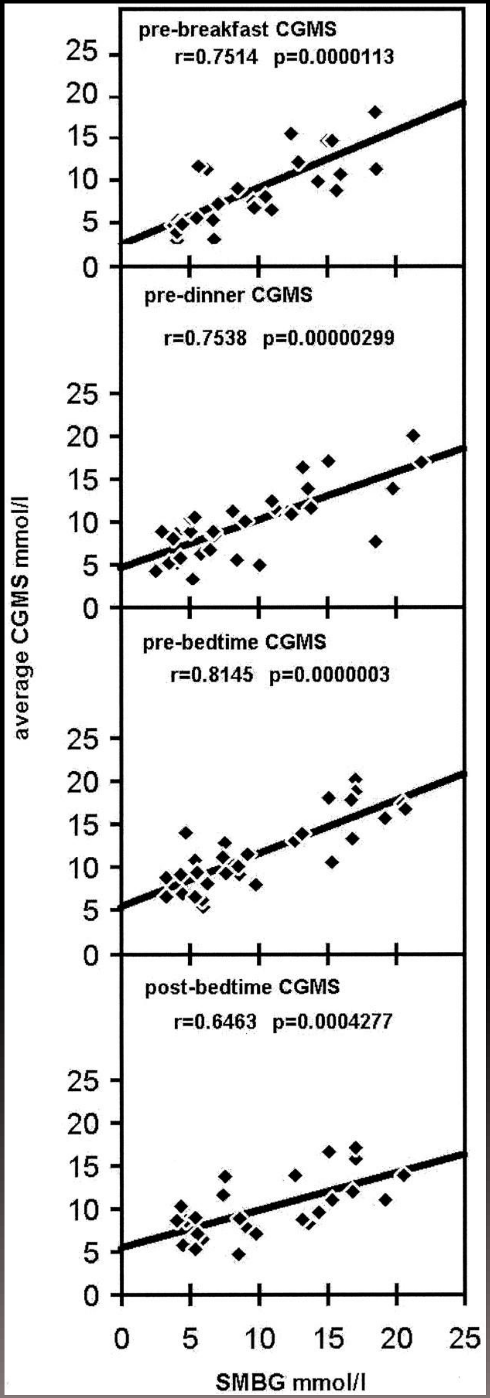
Glucose sensing and closing the loop



CGM: clinical effectiveness?



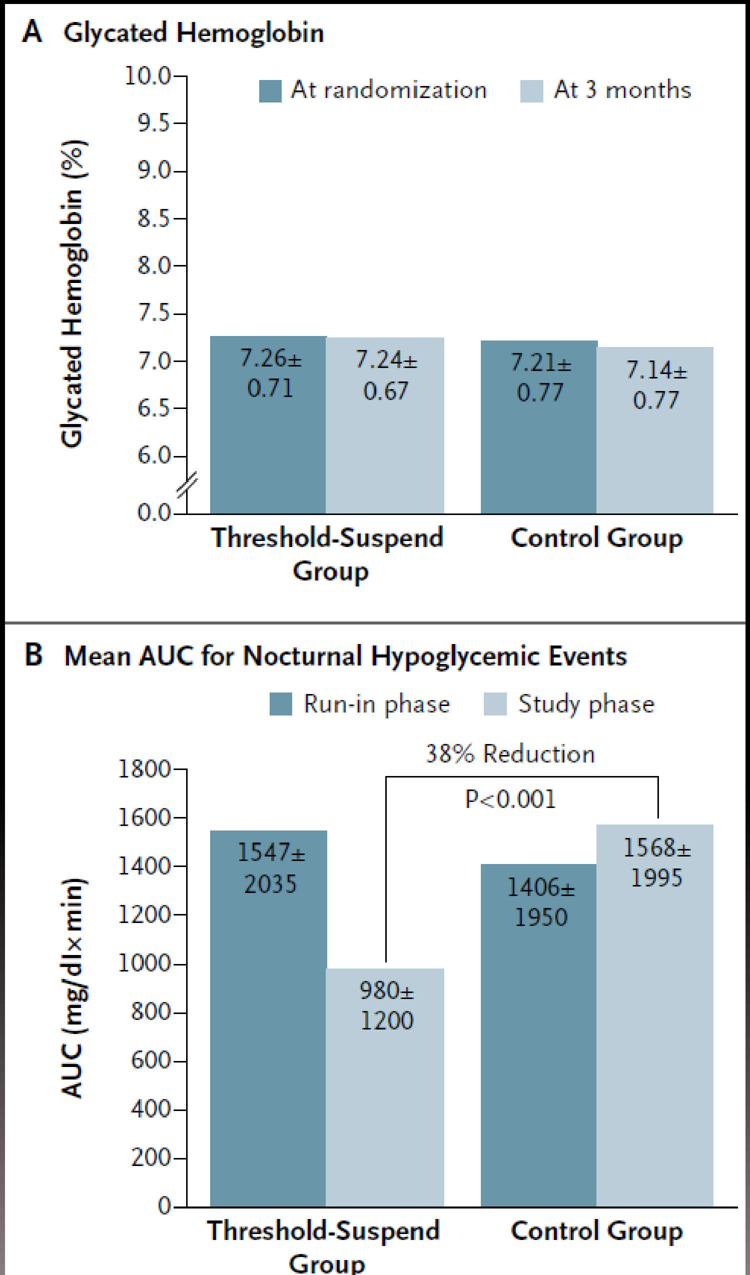
The JDRF study *New Engl J Med* 2008



- Fact
- Fingerprint testing is pretty goodif you do it regularly!

Zavalkoff &Polychronakos, 2003

Threshold pump interruption



- Bergenstal et al., *N Engl J Med* 2013

CLOSING THE LOOP !

Outpatient studies

Articles

2 month evening and night closed-loop glucose control in patients with type 1 diabetes under free-living conditions: a randomised crossover trial

Jort Kropff, Simone Del Favero*, Jerome Place*, Chiara Toffanin*, Roberto Visentin, Marco Monaro, Mirko Messori, Federico Di Palma, Giordano Lanzola, Anne Farret, Federico Boscari, Silvia Galasso, Paolo Magni, Angelo Avogaro, Patrick Keith-Hynes, Boris P Kovatchev, Daniela Bruttomesso, Claudio Cobelli*, J Hans DeVries*, Eric Renard*, Lalo Magni*, for the AP@home consortium*

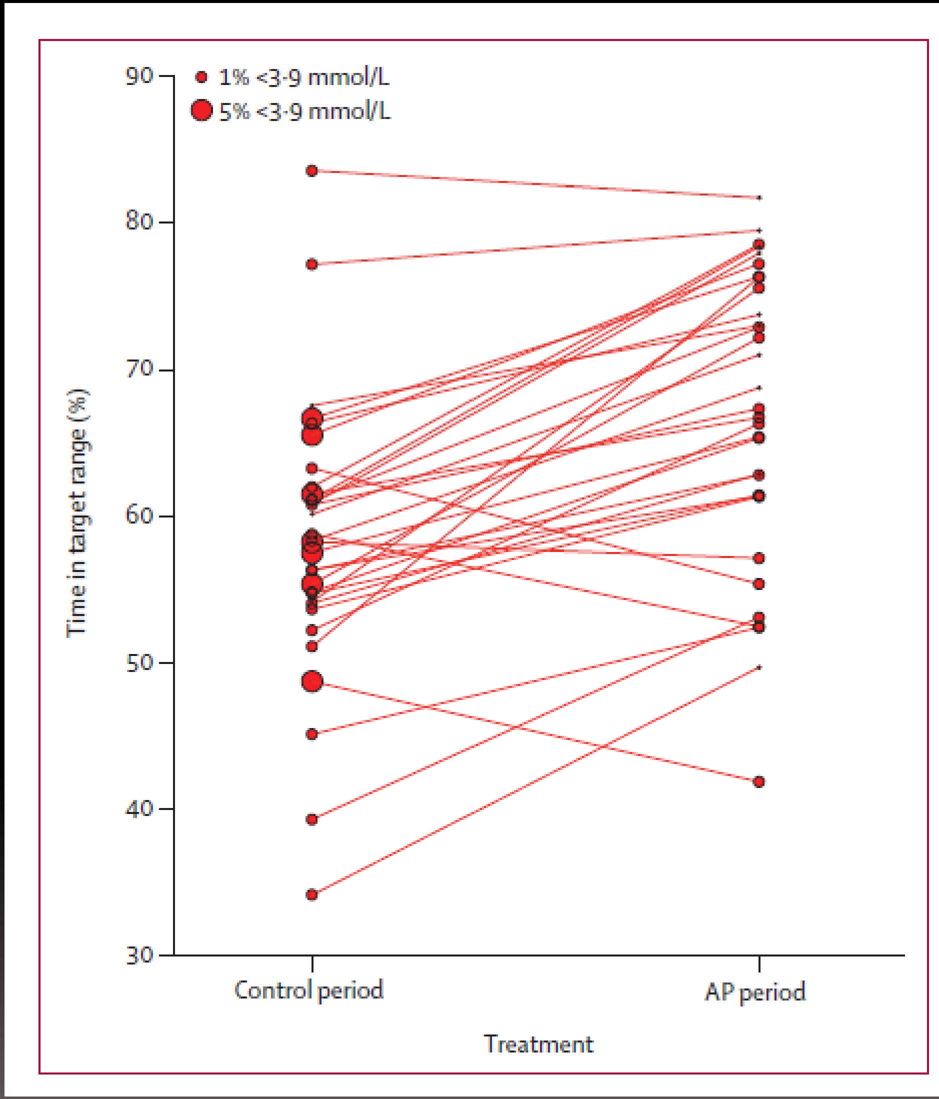
Evening and night closed loop

	Artificial pancreas period (n=32)	Control period (n=32)	Paired difference* (n=32)	p value
Evening and night (2000–0800 h)				
Glucose concentration (mmol/L)†	9·0 (0·8)	9·3 (0·8)	−0·3 (−0·6 to −0·1)	0·0053
SD of glucose concentration† (mmol/L)†	3·1 (0·6)	3·4 (0·6)	−0·3 (−0·4 to −0·2)	<0·0001
Time spent at glucose concentration				
4·4–7·8 mmol/L†	37·7% (9·1)	31·2% (6·0)	6·5% (3·8 to 9·2)	<0·0001
3·9–10 mmol/L†	66·7% (10·1)	58·1% (9·4)	8·6% (5·8 to 11·4)	<0·0001
>10 mmol/L†	31·6% (9·9)	38·5% (9·7)	−6·9% (−9·8 to −3·9)	<0·0001
<3·9 mmol/L‡	1·7% (0·8 to 2·5)	3·0% (1·6 to 4·9)	−1·6% (−2·3 to −1·0)	<0·0001
<2·8 mmol/L‡	0·1% (0·0 to 0·2)	0·3% (0·1 to 0·6)	−0·1% (−0·3 to −0·1)	0·00014
Number of hypoglycaemic events per week				
<3·9 mmol/L†	4·3 (1·9)	5·8 (2·9)	−1·5 (−2·5 to −0·4)	0·0068
<2·8 mmol/L†	1·1 (1·1)	2·2 (1·7)	−1·1 (−1·5 to −0·7)	<0·0001

- 32 adults
-

Kropff et al., *Lancet Diabetes* Endocrinol 2015

Individual evening-night values



Kropff et al., *Lancet Diabetes* Endocrinol 2015

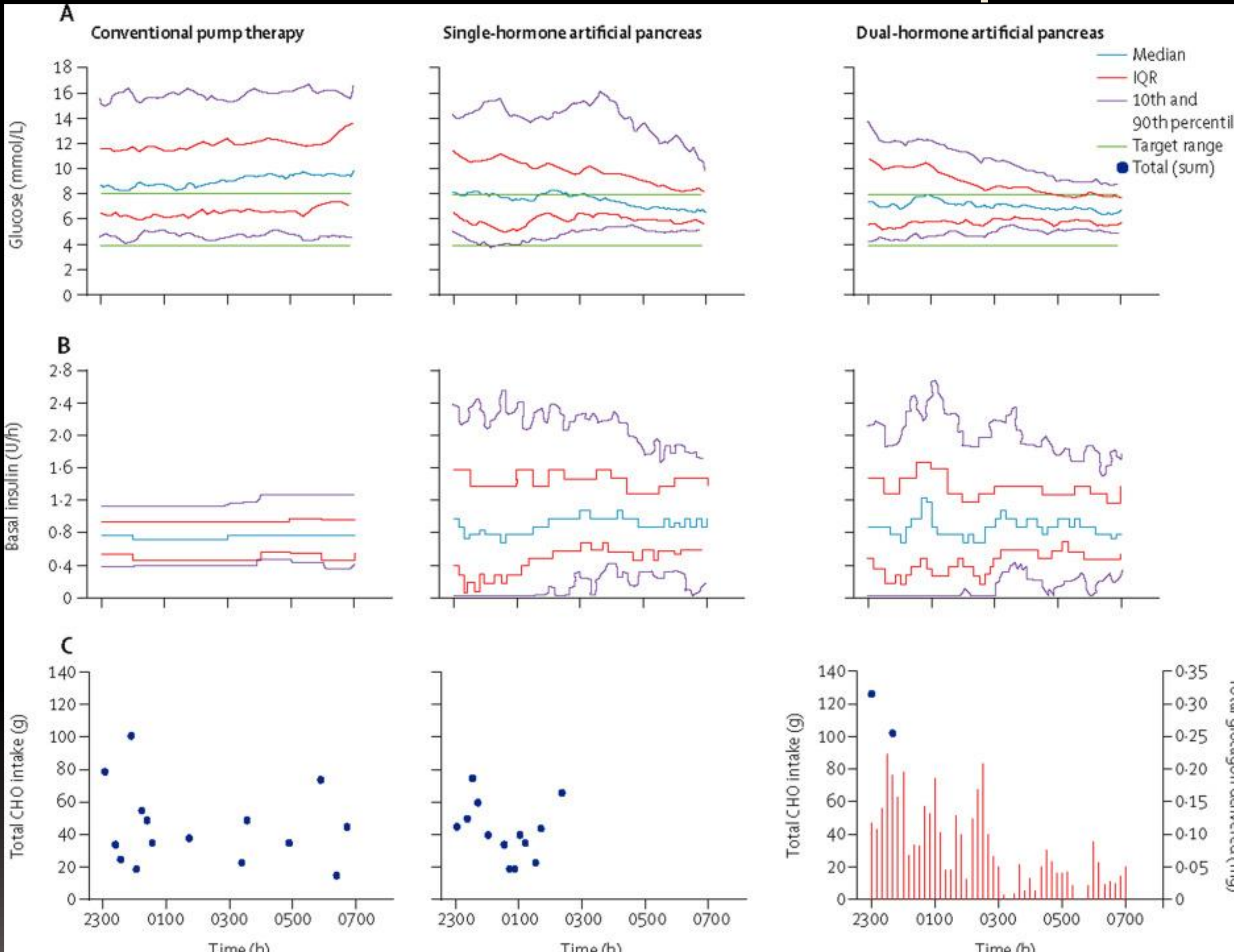
Dual hormone pump

Articles

Outpatient overnight glucose control with dual-hormone artificial pancreas, single-hormone artificial pancreas, or conventional insulin pump therapy in children and adolescents with type 1 diabetes: an open-label, randomised controlled trial

Ahmad Haidar, Laurent Legault, Laurence Matteau-Pelletier, Virginie Messier, Maryse Dallaire, Martin Ladouceur, Rémi Rabasa-Lhoret

Dual-hormone closed loop

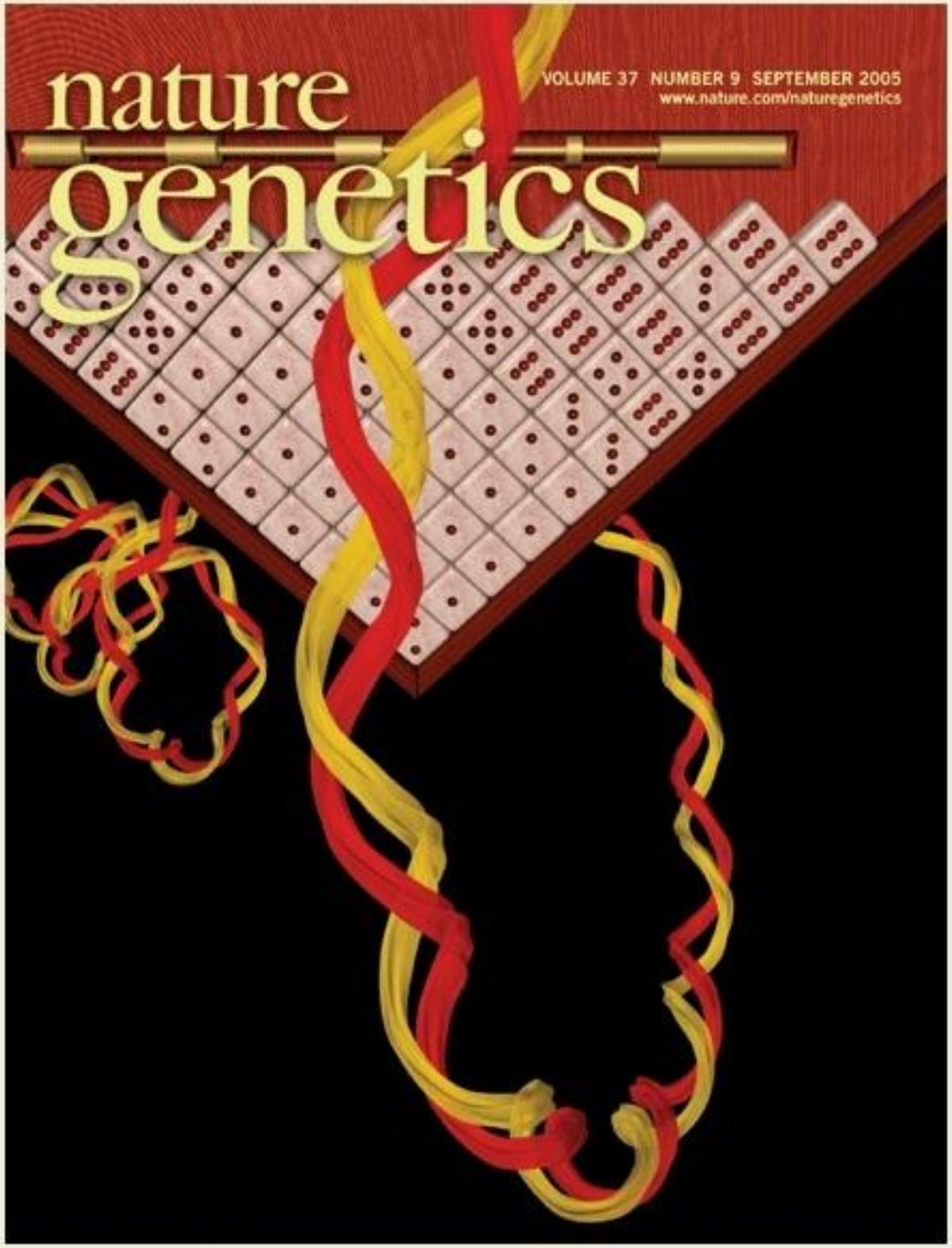


- Haider et al., *Lancet Diabetes Endocrinol* 2015

FDA approval!

Basal use only. Boluses need to be calculated

Genetics!!



Cover art: "Stochastic with Double Strand" Ray-tracing capture of virtual installation by Constantin Polychronakos http://virtualbeing.ca

I am ONLY a clinician.
Why do I need to care about the genome?

I am ONLY a
genome scientist.
Why do I need to care
about treating
diabetes ?

Genetics of type 1 diabetes

Multifactorial disorder fam

strong genetic component.

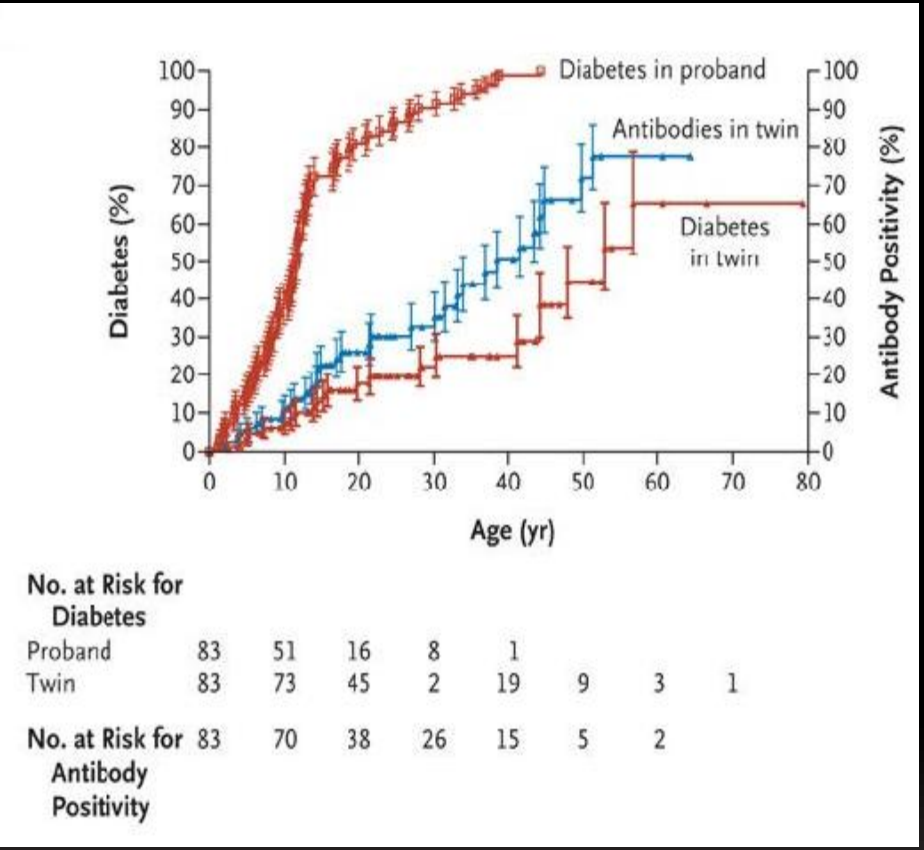
monozygotic twins

dizygotic twins ~5%

sibs

general population

polygentic tr



Genetic determination of complex traits

- Why are some individuals susceptible to disease and other are not?
- Subtle differences in DNA sequence
- Most are single-nucleotide polymorphisms

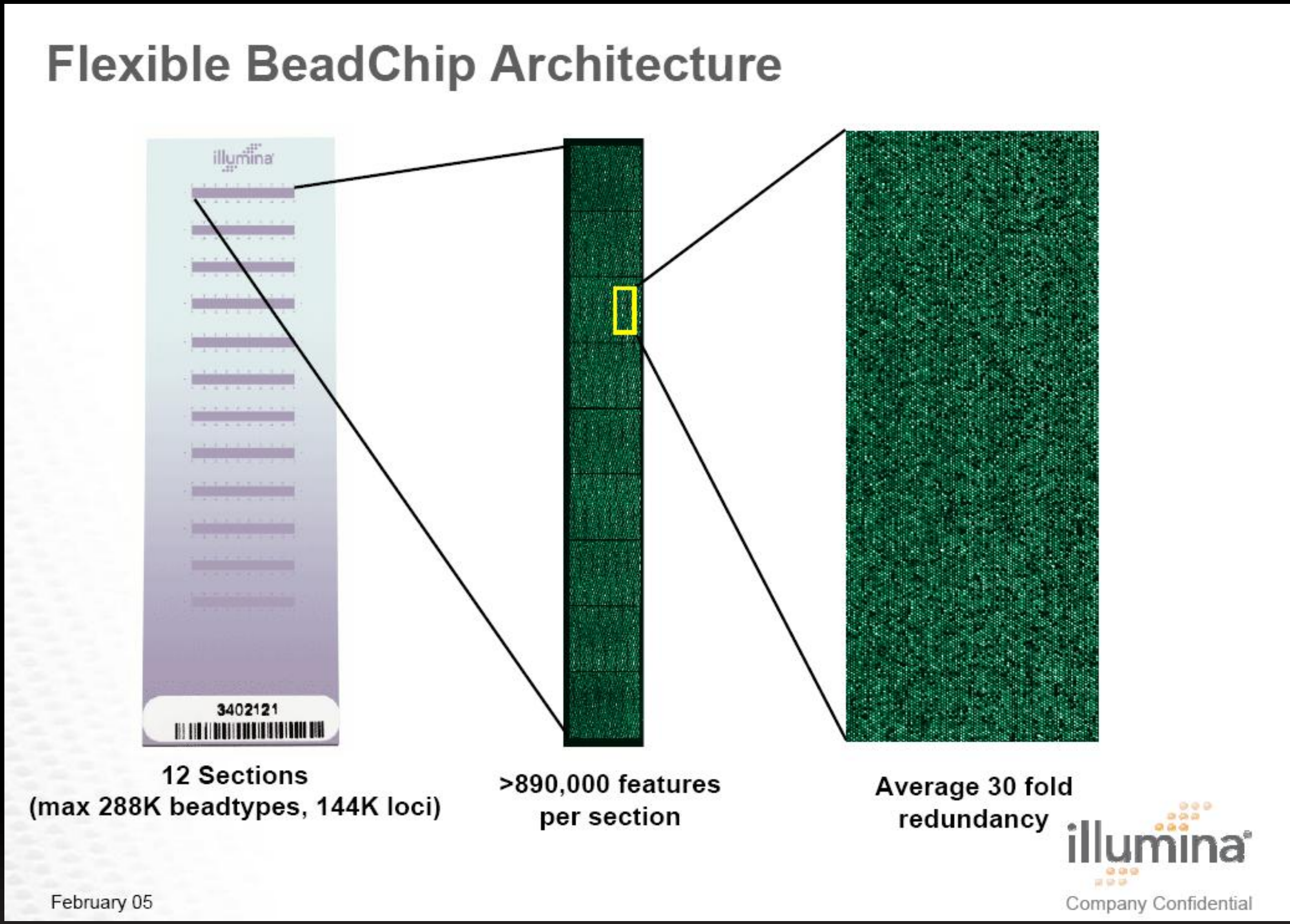
- DNA sequence identity between two unrelated individuals

99.9 %

- A kilobase-scale linkage disequilibrium map of the human genome

- Most (~80%) of genetic variation can be captured by genotyping ~500,000 SNPs

Illumina SNP microarray



- Microarray-based genotyping of 550,000 SNPs

doi:10.1038/nature06010

nature

LETTERS

A genome-wide association study identifies *KIAA0350* as a type 1 diabetes gene

Hakon Hakonarson[1,3*], Struan F. A. Grant[1,3*], Jonathan P. Bradfield[1*], Luc Marchand[5], Cecilia E. Kim[1], Joseph T. Glessner[1], Rosemarie Grabs[5], Tracy Casalunovo[1], Shayne P. Taback[6], Edward C. Frackelton[1], Margaret L. Lawson[7], Luke J. Robinson[1], Robert Skraban[1], Yang Lu[5], Rosetta M. Chiavacci[1], Charles A. Stanley[4], Susan E. Kirsch[8], Eric F. Rappaport[9], Jordan S. Orange[10], Dimitri S. Monos[2,10], Marcella Devoto[3,11], Hui-Qi Qu[5] & Constantin Polychronakos[5]

Vol 447|7 June 2007|**doi:10.1038/nature05911** nature

ARTICLES

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

The Wellcome Trust Case Control Consortium*

OPEN ACCESS Freely available online

PLoS GENETICS

A Genome-Wide Meta-Analysis of Six Type 1 Diabetes Cohorts Identifies Multiple Associated Loci

Jonathan P. Bradfield[1], Hui-Qi Qu[2¤], Kai Wang[1], Haitao Zhang[1], Patrick M. Sleiman[1], Cecilia E. Kim[1], Frank D. Mentch[1], Haijun Qiu[1], Joseph T. Glessner[1], Kelly A. Thomas[1], Edward C. Frackelton[1], Rosetta M. Chiavacci[1], Marcin Imielinski[1], Dimitri S. Monos[3,4], Rahul Pandey[1], Marina Bakay[1], Struan F. A. Grant[1,3,5], Constantin Polychronakos[2*], Hakon Hakonarson[1,3,5*]

1 The Center for Applied Genomics, The Children's Hospital Philadelphia, Philadelphia, Pennsylvania, United States of America, **2** Departments of Pediatrics and Human Genetics, McGill University, Montreal, Canada, **3** Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, United States of America, **4** Department of Pathology and Laboratory Medicine, Abramson Research Center, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States of America, **5** Division of Human Genetics, Abramson Research Center, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, United States of America

Known T1D loci to date

SNP[a]	Chr.	LD region (Mb)[b]	Gene of interest (#)[c]	P values GWA[d]	Replication	Combined	Risk allele	MAF[e]	OR (95% CI)[f] Case-control	Families
rs3024505	1q32.1	204.87–205.12	*IL10* (5)	2.2×10^{-6}	0.00015	1.9×10^{-9}	C	0.169	0.84 (0.77–0.91)	0.96 (0.88–1.04)
rs10517086	4p15.2	25.64–25.75	(0)	2.8×10^{-7}	0.00021	4.6×10^{-10}	A	0.299	1.09 (1.02–1.17)	1.09 (1.02–1.16)
rs9388489	6q22.32	126.48–127.46	*C6orf173* (1)	5.1×10^{-8}	1.4×10^{-6}	4.2×10^{-13}	G	0.452	1.17 (1.10–1.24)	1.05 (0.99–1.12)
rs7804356	7p15.2	26.62–27.17	(10)	3.3×10^{-8}	0.0051	5.3×10^{-9}	T	0.238	0.88 (0.82–0.94)	0.99 (0.92–1.06)
rs4948088	7p12.1	50.87–51.64	*COBL* (1)	2.7×10^{-6}	0.0019	4.4×10^{-8}	C	0.047	0.77 (0.67–0.90)	0.93 (0.79–1.10)
rs7020673	9p24.2	4.22–4.31	*GLIS3* (1)	1.9×10^{-9}	0.00013	5.4×10^{-12}	G	0.502	0.88 (0.83–0.93)	0.97 (0.91–1.03)
rs10509540	10q23.31	90.00–90.27	*C10orf59* (1)	6.9×10^{-9}	4.9×10^{-24}	1.3×10^{-28}	T	0.285	0.75 (0.70–0.80)	0.81 (0.76–0.87)
rs4763879	12p13.31	9.51–9.87	*CD69* (6)	2.8×10^{-7}	1.1×10^{-5}	1.9×10^{-11}	A	0.368	1.09 (1.02–1.16)	1.12 (1.05–1.19)
rs1465788	14q24.1	68.24–68.39	(2)	1.4×10^{-8}	1.5×10^{-5}	1.8×10^{-12}	G	0.287	0.86 (0.80–0.91)	0.95 (0.89–1.02)
rs4900384	14q32.2	97.43–97.60	(0)	1.1×10^{-6}	0.00042	3.7×10^{-9}	G	0.288	1.09 (1.02–1.16)	1.08 (1.01–1.16)
rs4788084	16p11.2	28.19–28.94	*IL27* (24)	5.2×10^{-8}	8.4×10^{-7}	2.6×10^{-13}	G	0.424	0.86 (0.81–0.91)	0.94 (0.88–1.00)
rs7202877	16q23.1	73.76–74.09	(7)	5.7×10^{-11}	1.2×10^{-6}	3.1×10^{-15}	G	0.096	1.28 (1.17–1.41)	1.09 (0.99–1.20)
rs2290400	17q12	34.63–35.51	*ORMDL3* (23)	1.3×10^{-7}	8.2×10^{-7}	5.5×10^{-13}	G	0.495	0.87 (0.82–0.93)	0.92 (0.87–0.98)
rs7221109	17q21.2	35.95–36.13	(3)	9.9×10^{-10}	0.0083	1.3×10^{-9}	C	0.353	0.95 (0.89–1.01)	0.94 (0.88–1.00)
rs425105	19q13.32	51.84–52.02	(5)	1.5×10^{-7}	2.6×10^{-5}	2.7×10^{-11}	A	0.162	0.86 (0.79–0.93)	0.90 (0.82–0.98)
rs2281808	20p13	1.44–1.71	(3)	5.0×10^{-7}	4.8×10^{-6}	1.2×10^{-11}	C	0.362	0.90 (0.84–0.95)	0.90 (0.85–0.96)
rs5753037	22q12.2	28.14–29.00	(14)	1.8×10^{-14}	5.8×10^{-5}	2.6×10^{-16}	T	0.391	1.10 (1.04–1.17)	1.08 (1.02–1.15)
rs2664170	Xq28	153.48–154.10	(16)	3.0×10^{-5}	5.8×10^{-5}	7.8×10^{-9}	G	0.316	1.16 (1.07–1.24)	1.06 (0.97–1.16)
rs2269241	1p31.3	63.87–63.94	*PGM1* (1)	5.9×10^{-6}	0.0069	4.2×10^{-7}	G	0.192	1.10 (1.02–1.18)	1.05 (0.98–1.14)
rs1534422	2p25.1	12.53–12.60	(0)	6.7×10^{-6}	0.025	2.1×10^{-6}	G	0.460	1.08 (1.02–1.15)	1.01 (0.95–1.08)
rs12444268	16p12.3	20.17–20.28	(2)	2.0×10^{-6}	0.0045	1.7×10^{-7}	A	0.295	1.10 (1.03–1.17)	1.04 (0.97–1.11)
rs16956936	17p13.1	7.56–7.66	(2)	3.2×10^{-6}	0.0097	5.3×10^{-7}	C	0.135	0.92 (0.84–1.00)	0.92 (0.83–1.01)

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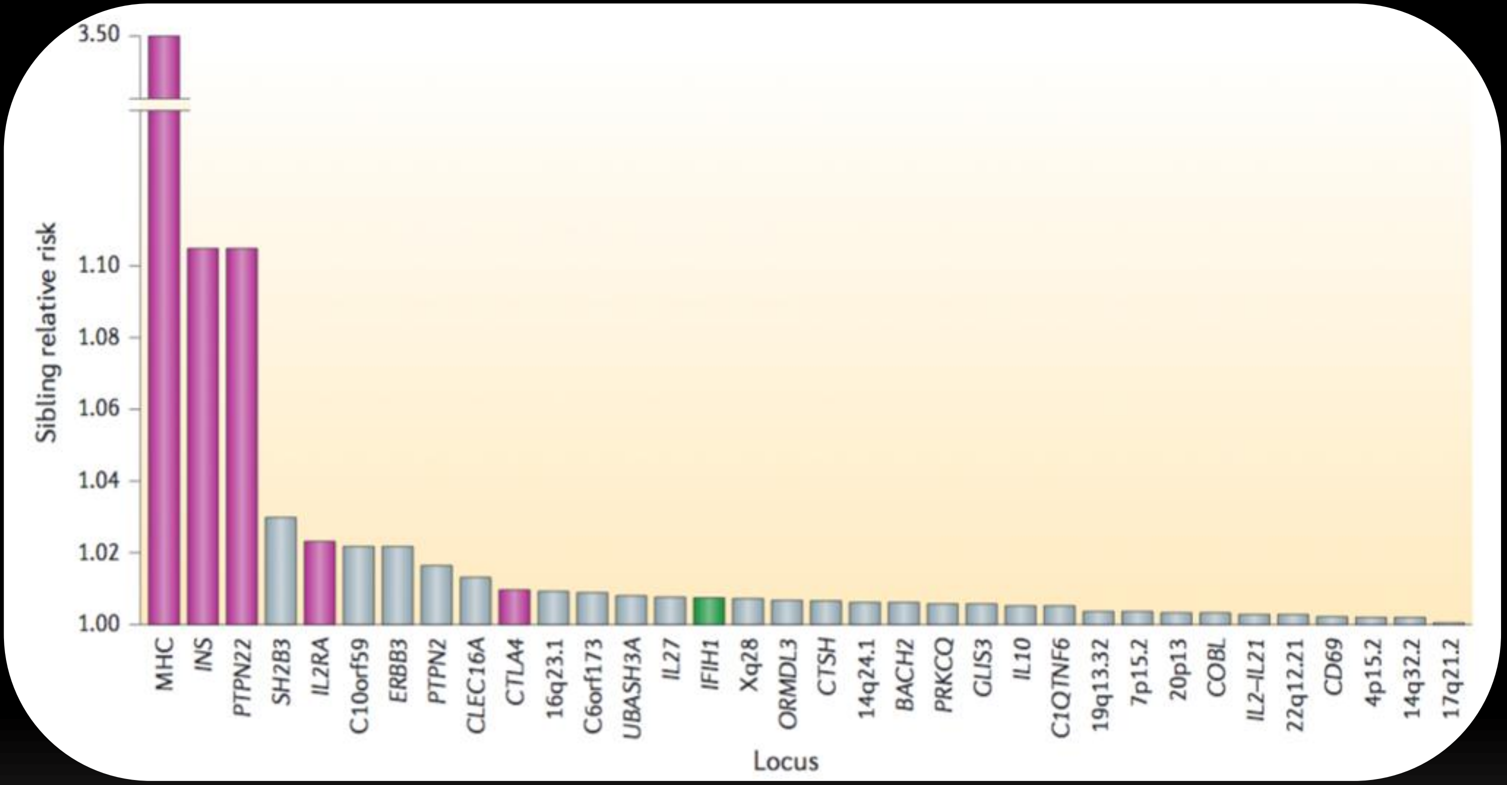
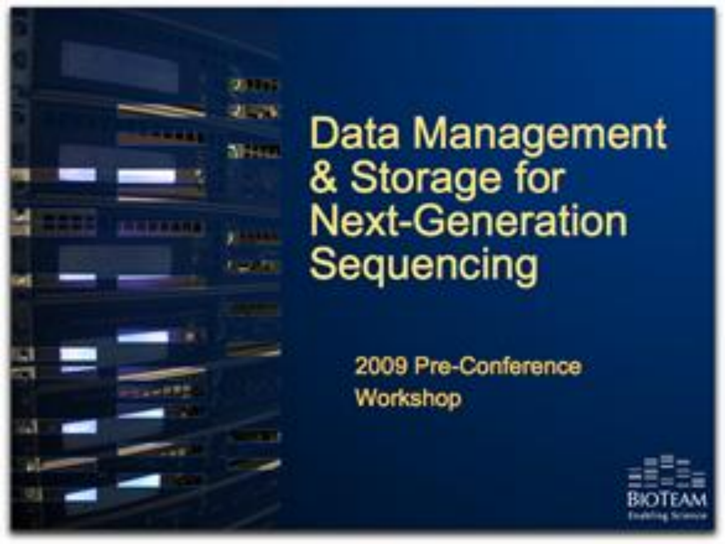
rs7202877	16q23.1	73.76–74.09	(7)	5.7×10^{-11}	1.2×10^{-6}	3.1×10^{-15}	G	0.096	1.28 (1.17–1.41)	1.09 (0.99–1.20)
rs2290400	17q12	34.63–35.51	*ORMDL3* (23)	1.3×10^{-7}	8.2×10^{-7}	5.5×10^{-13}	G	0.495	0.87 (0.82–0.93)	0.92 (0.87–0.98)
rs7221109	17q21.2	35.95–36.13	(3)	9.9×10^{-10}	0.0083	1.3×10^{-9}	C	0.353	0.95 (0.89–1.01)	0.94 (0.88–1.00)
rs425105	19q13.32	51.84–52.02	(5)	1.5×10^{-7}	2.6×10^{-5}	2.7×10^{-11}	A	0.162	0.86 (0.79–0.93)	0.90 (0.82–0.98)
rs2281808	20p13	1.44–1.71	(3)	5.0×10^{-7}	4.8×10^{-6}	1.2×10^{-11}	C	0.362	0.90 (0.84–0.95)	0.90 (0.85–0.96)
rs5753037	22q12.2	28.14–29.00	(14)	1.8×10^{-14}	5.8×10^{-5}	2.6×10^{-16}	T	0.391	1.10 (1.04–1.17)	1.08 (1.02–1.15)
rs2664170	Xq28	153.48–154.10	(16)	3.0×10^{-5}	5.8×10^{-5}	7.8×10^{-9}	G	0.316	1.16 (1.07–1.24)	1.06 (0.97–1.16)
rs2269241	1p31.3	63.87–63.94	*PGM1* (1)	5.9×10^{-6}	0.0069	4.2×10^{-7}	G	0.192	1.10 (1.02–1.18)	1.05 (0.98–1.14)
rs1534422	2p25.1	12.53–12.60	(0)	6.7×10^{-6}	0.025	2.1×10^{-6}	G	0.460	1.08 (1.02–1.15)	1.01 (0.95–1.08)
rs12444268	16p12.3	20.17–20.28	(2)	2.0×10^{-6}	0.0045	1.7×10^{-7}	A	0.295	1.10 (1.03–1.17)	1.04 (0.97–1.11)
rs16956936	17p13.1	7.56–7.66	(2)	3.2×10^{-6}	0.0097	5.3×10^{-7}	C	0.135	0.92 (0.84–1.00)	0.92 (0.83–1.01)



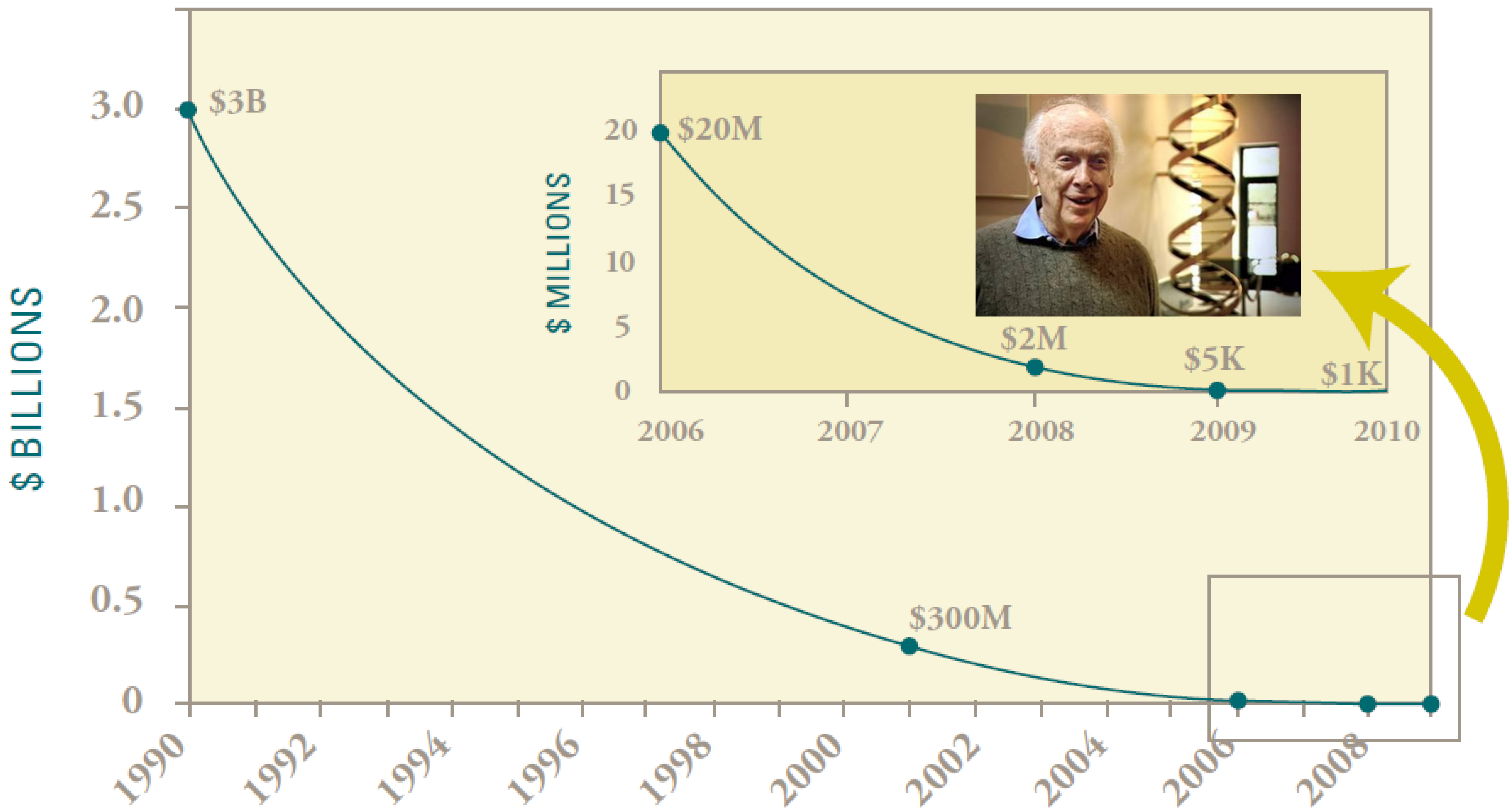
Constantin Polychronakos & Quan Li,
***Nature Reviews Genetics*, 2011**

Recent methodological breakthroughs

Massively parallel sequencing



Massively parallel sequencing



Sources: Wheeler DA et al., Nature 2008; 452:872-6; Mardis E. Genome Biology 2006; 7:112; Keim B. Wired Science October 06, 2008; The 2009 and 2010 values are projected. Current cost of complete genome sequencing (as of April 2009) is $60,000 (Applied Biosystems).

Massively parallel sequencing

Vol 463 | 11 February 2010 | doi:10.1038/nature08748 nature

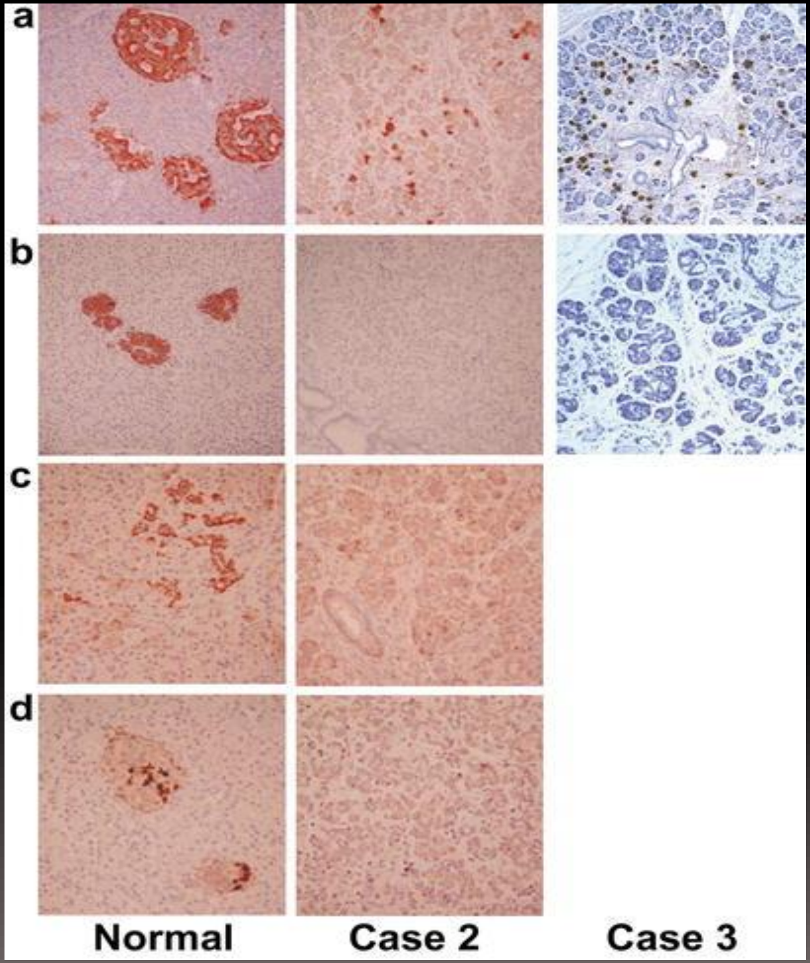
ARTICLES

Rfx6 directs islet formation and insulin production in mice and humans

Stuart B. Smith[1], Hui-Qi Qu[2]*, Nadine Taleb[2]*, Nina Y. Kishimoto[1], David W. Scheel[1], Yang Lu[2], Ann-Marie Patch[3], Rosemary Grabs[2], Juehu Wang[1], Francis C. Lynn[1]†, Takeshi Miyatsuka[1], John Mitchell[2], Rina Seerke[1], Julie Désir[4], Serge Vanden Eijnden[4], Marc Abramowicz[4], Nadine Kacet[5], Jacques Weill[5], Marie-Ève Renard[5], Mattia Gentile[6], Inger Hansen[7], Ken Dewar[8], Andrew T. Hattersley[3], Rennian Wang[9], Maria E. Wilson[10], Jeffrey D. Johnson[10], Constantin Polychronakos[2] & Michael S. German[1,11]

The Mitchell-Riley syndrome

Autosomal recessive NDM with intestinal atresia



Chromogranin

Insulin

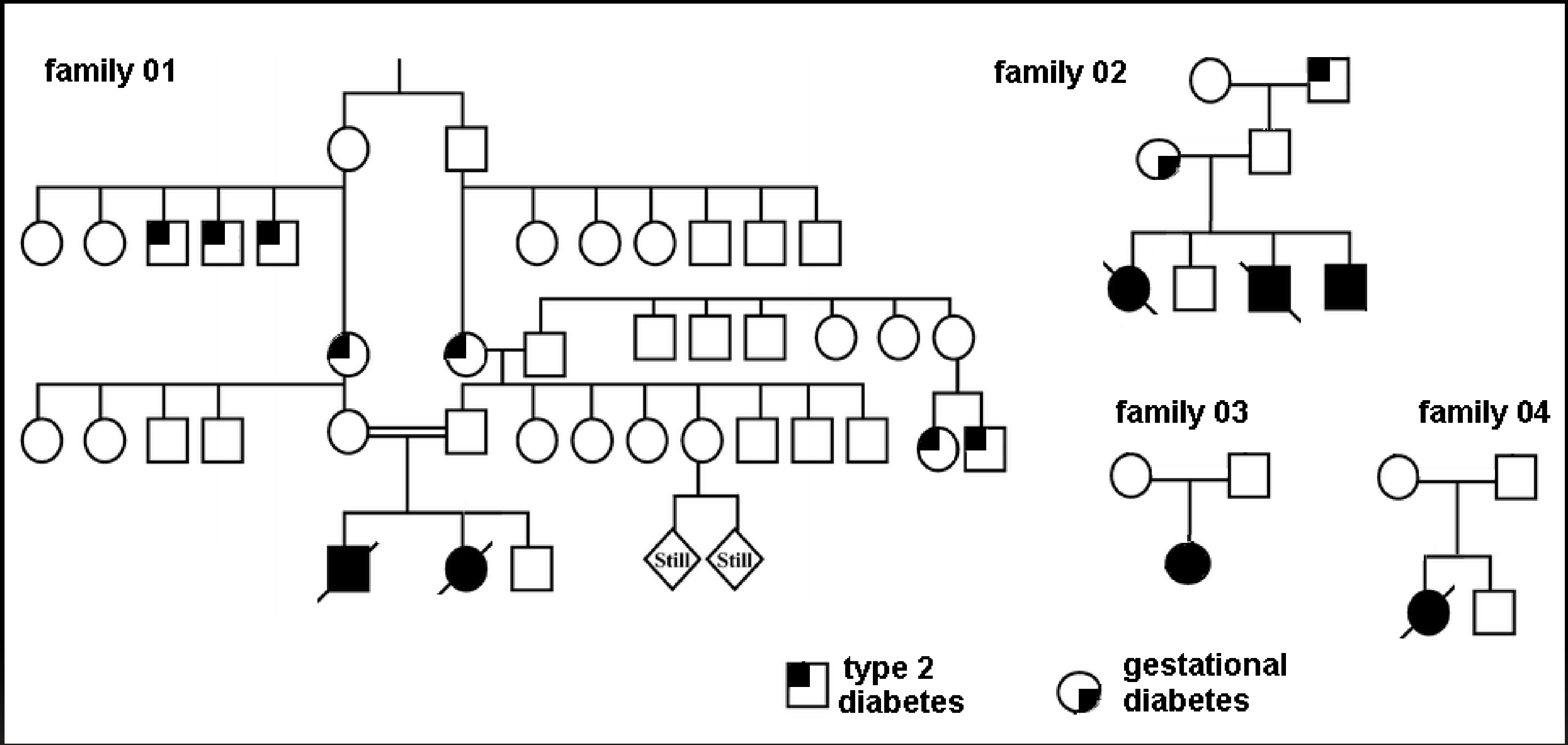
Glucagon

Somatostatin

Complete absence of islets

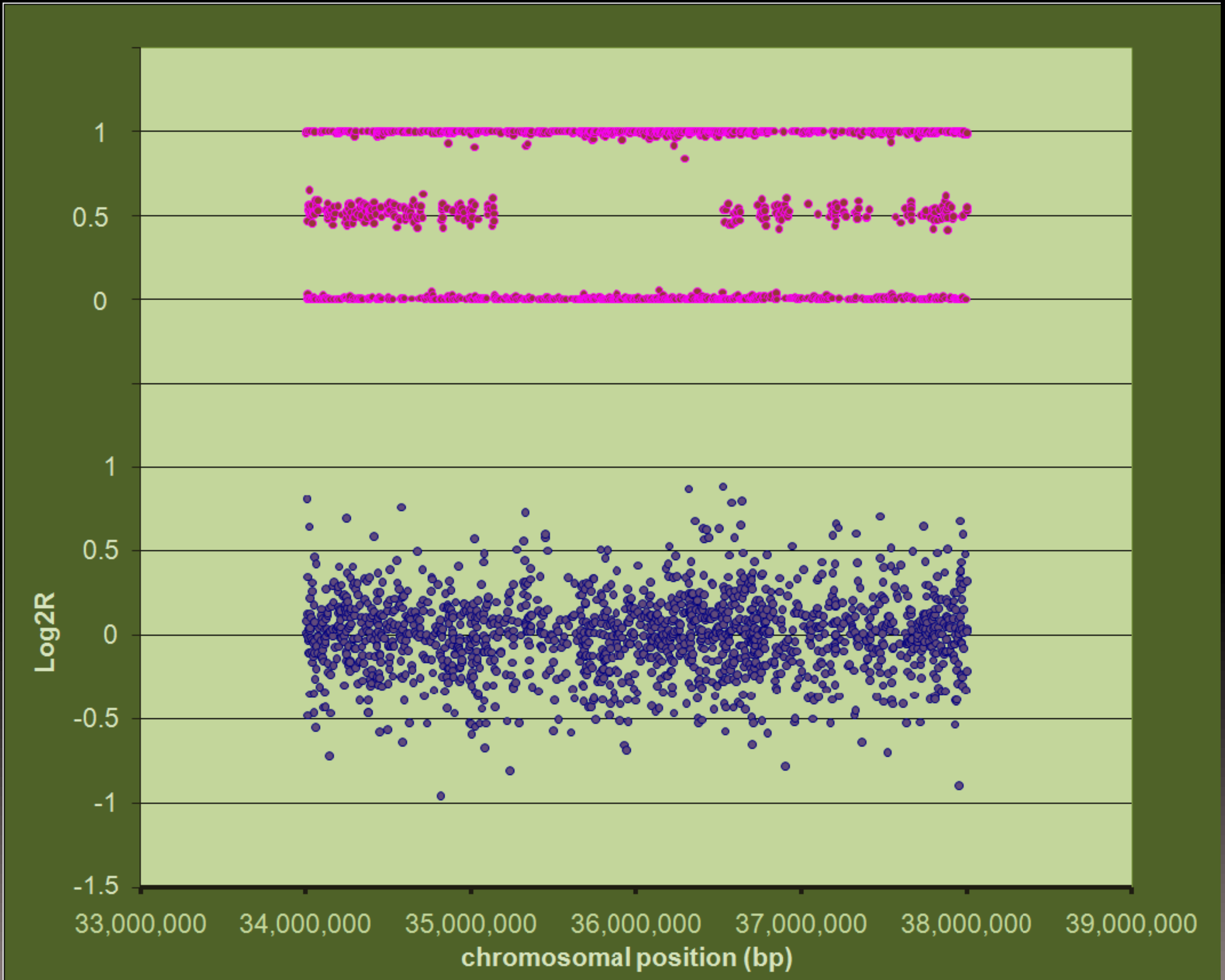
Mitchell et al., *Diabetologia* 2004

Autosomal recessive



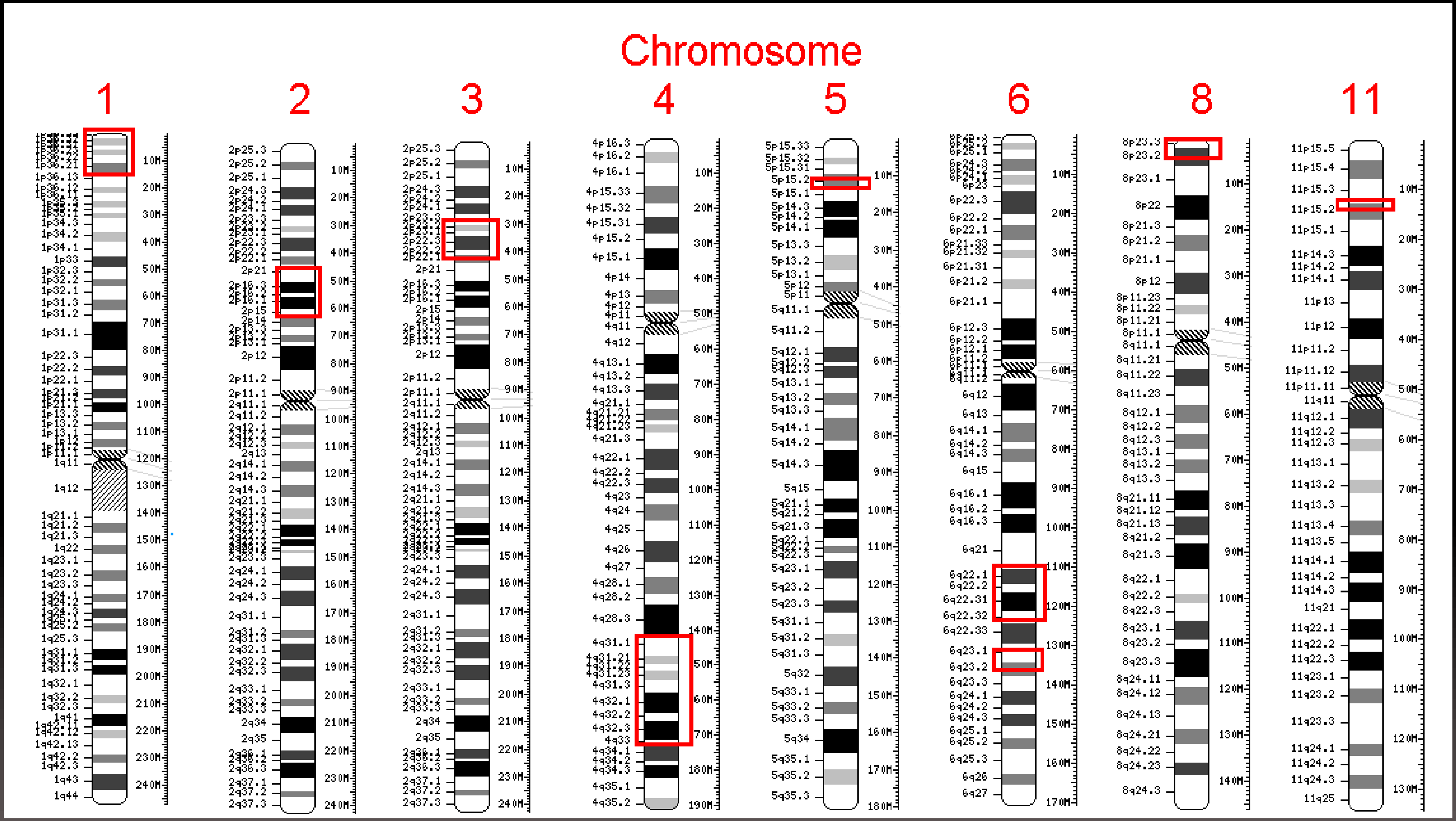
Two siblings of a consanguineous family

Detection of homozygosity by descent



Areas of homozygosity

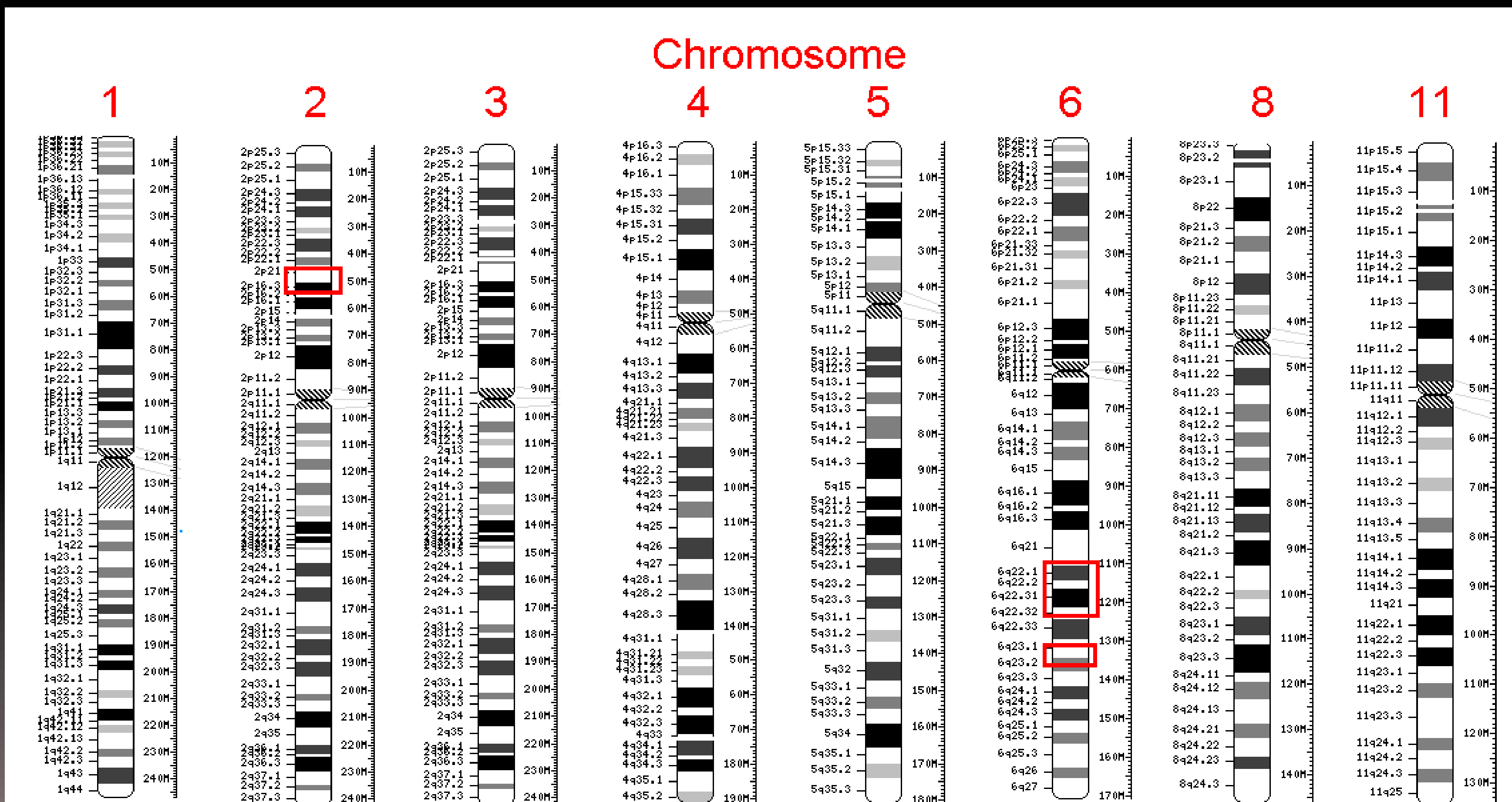
Offspring of second cousins



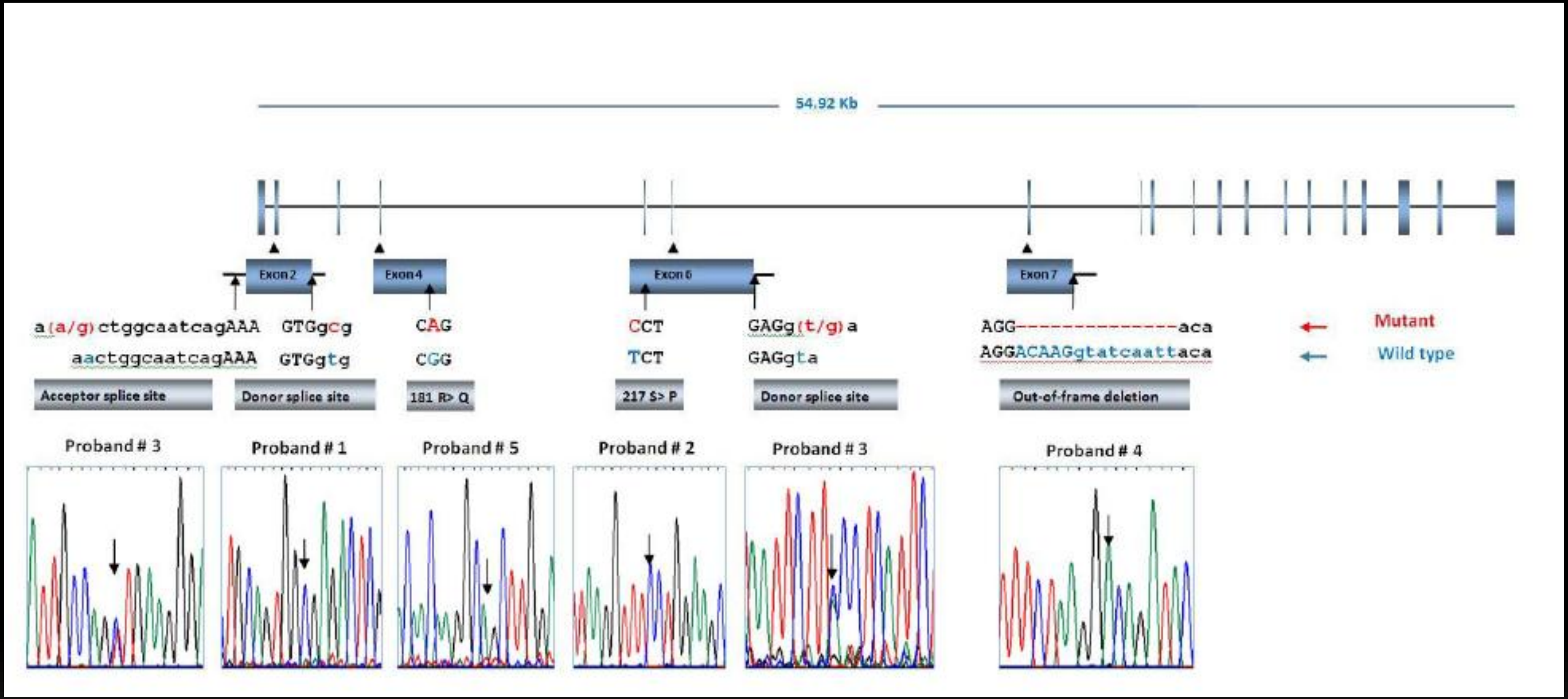
No known islet development gene in these regions

Overlap with a second consanguineous cas

Offspring of first cousins

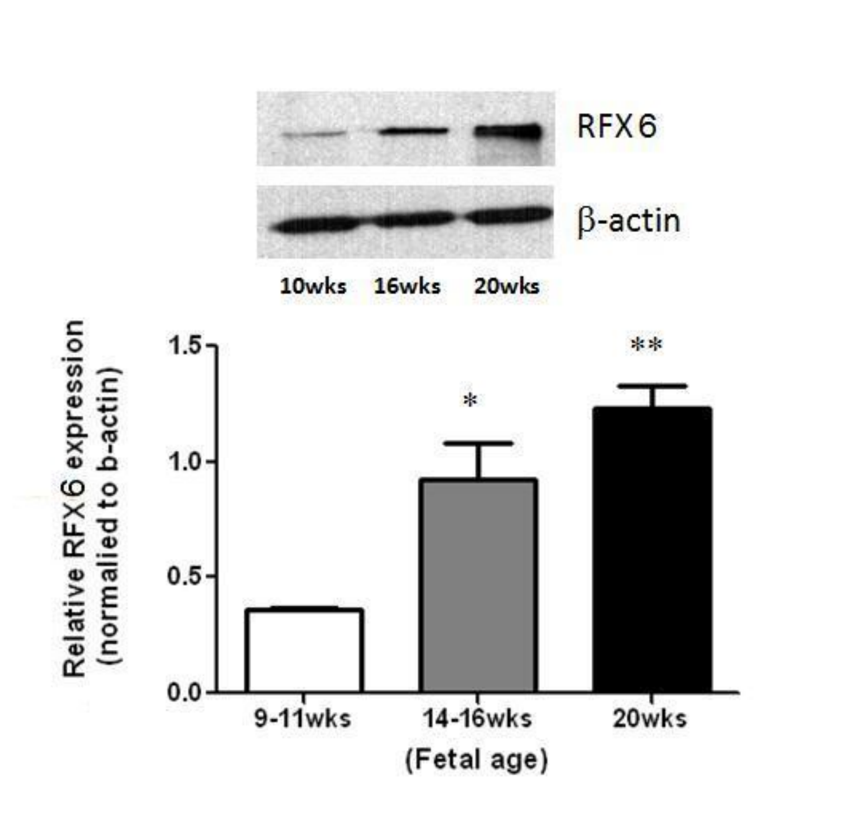


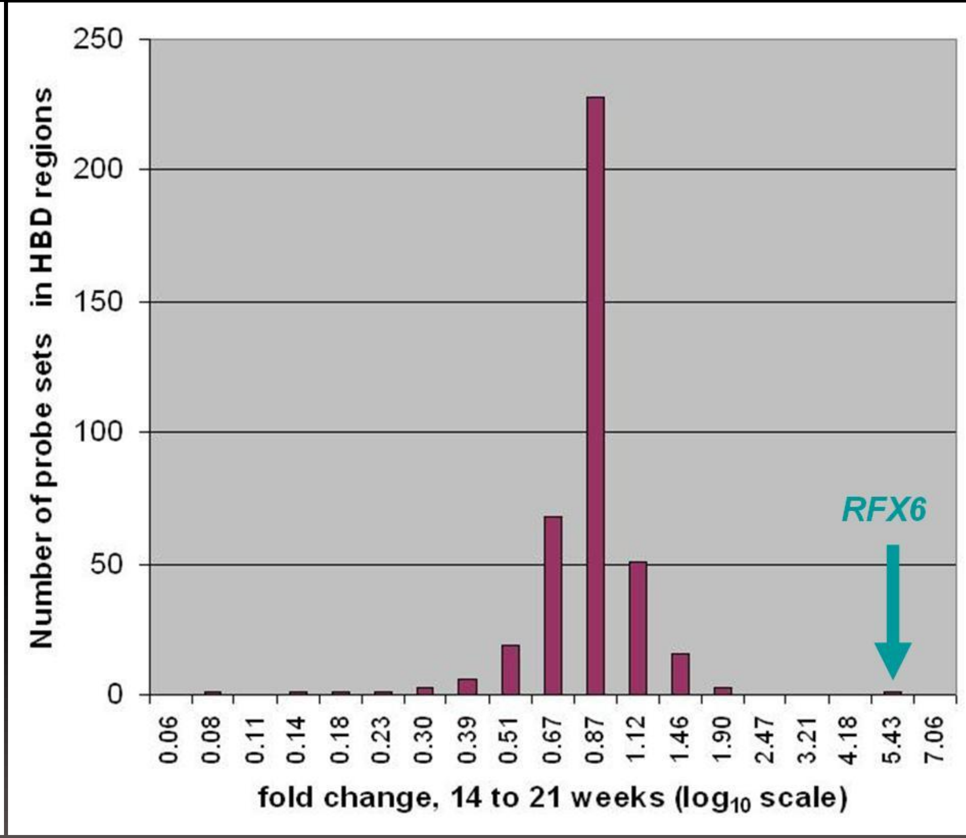
RFX6, the only gene found mutated



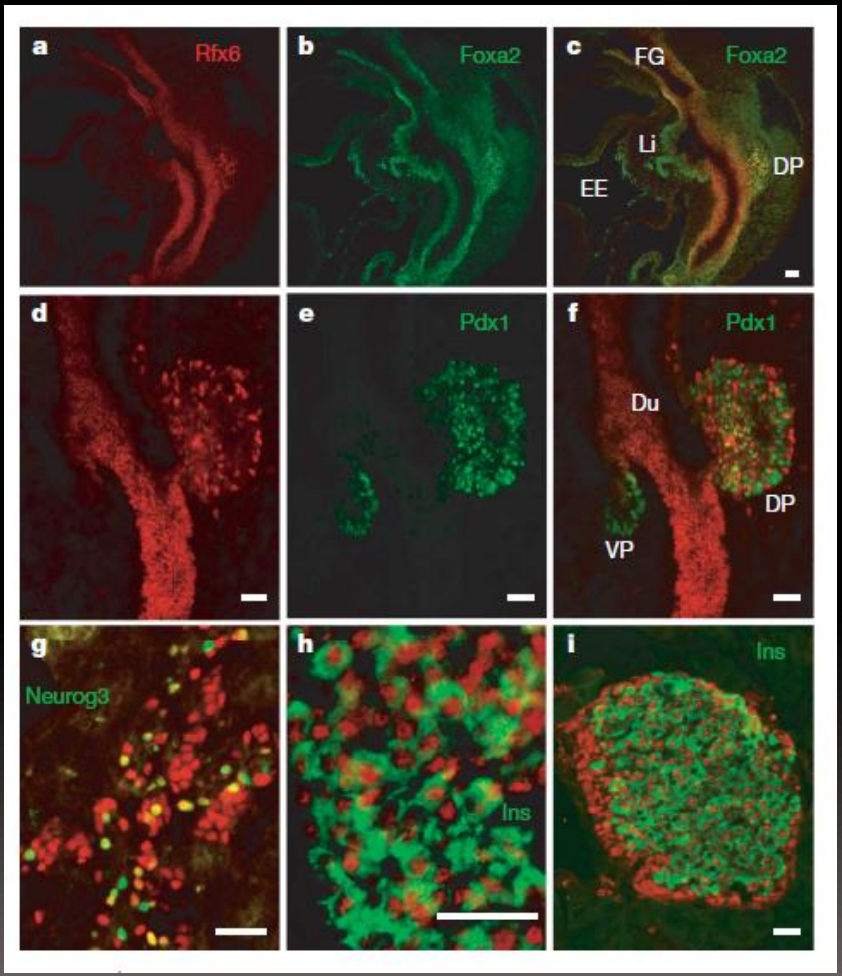
RFX6 : developmental regulation

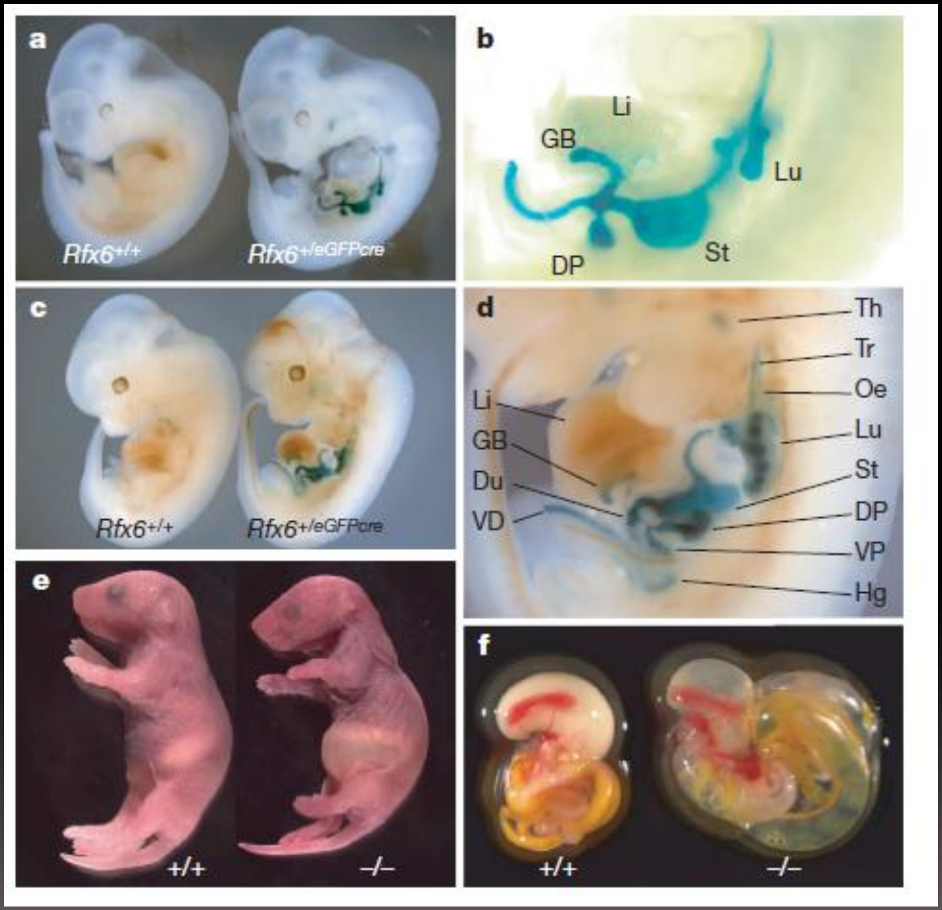
Parallels the development of the endocrine pancreas





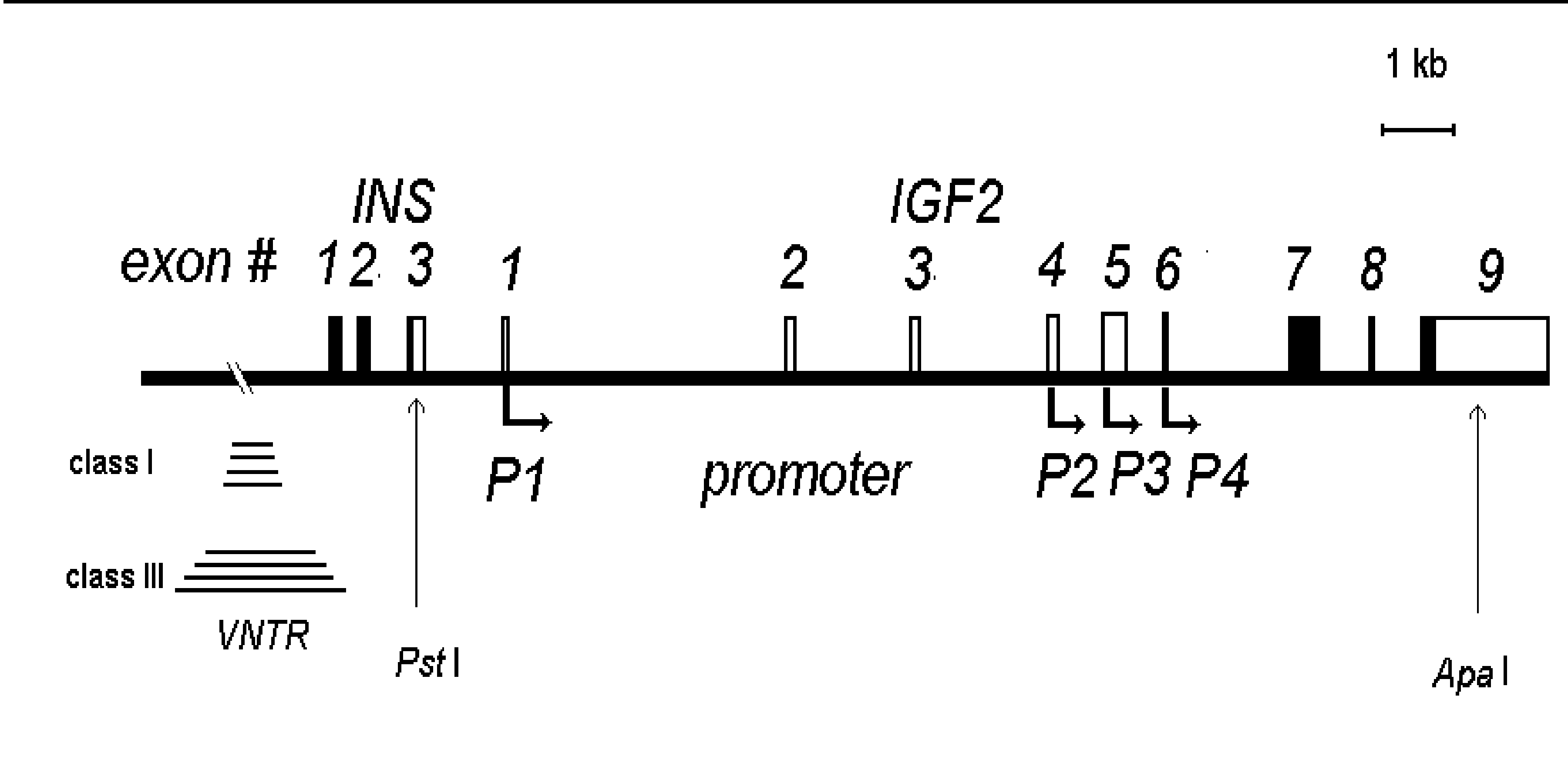
Knockout mouse recapitulates the human phenotype





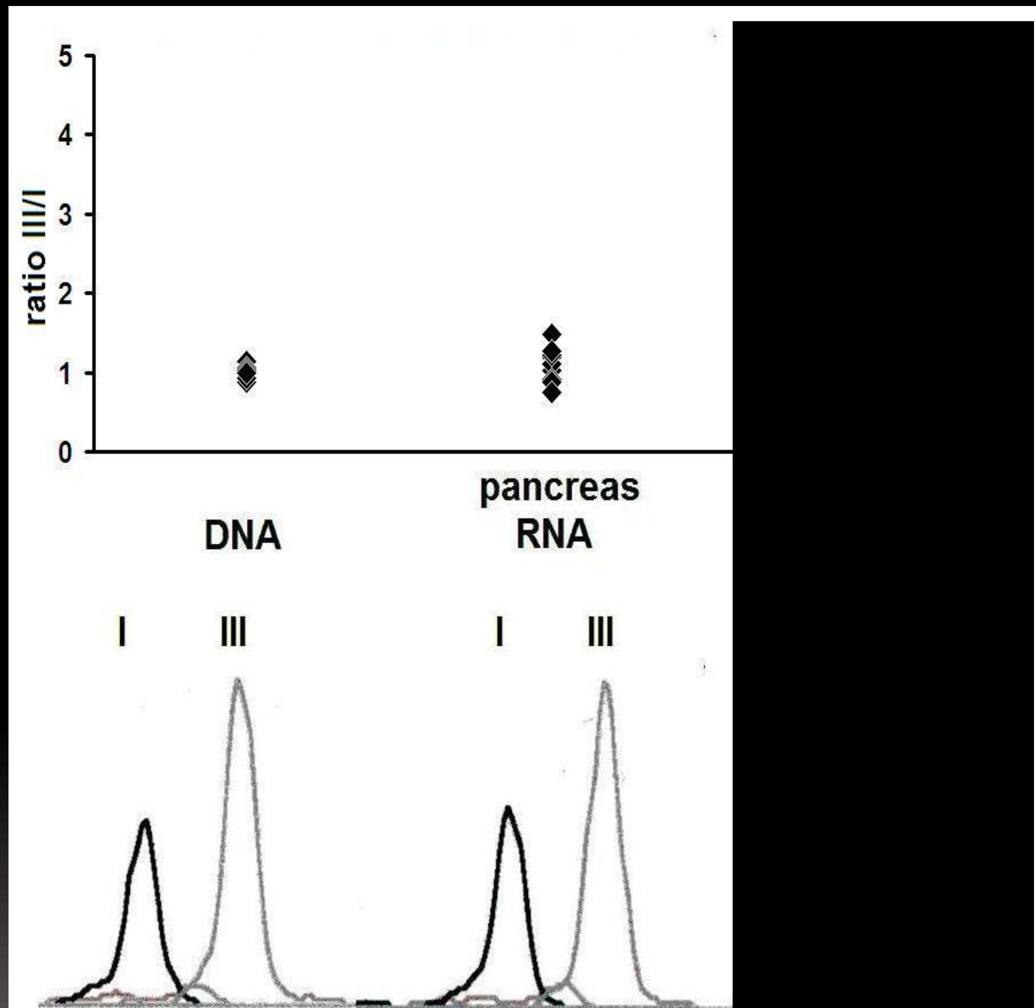
Back to the future: weak genetic effects

- 1 - Gene not important in the disease
- 2 - Important gene but weak effect of the polymorphism on its function
- 3 – Important gene, strong effect of polymorphism but the allele is rare



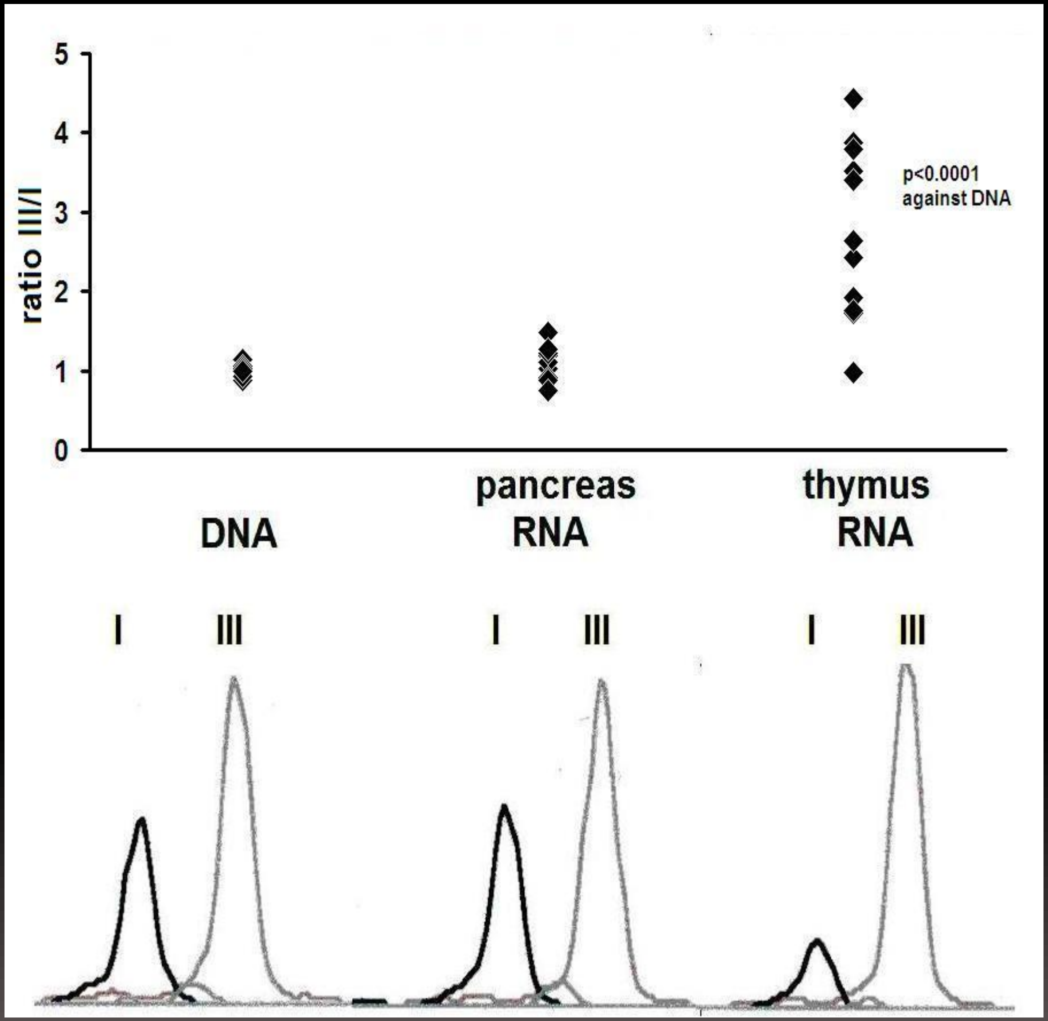

```
a     ACA  GGGG  TG  T  GGGG
b     ---  ----  -C  -  ----
c     ---  ----  -CC-   ----
d     ---  ----  -CCC   ----
e     -T-  ----  --  -  -A--
```

Thymus-specific transcriptional regulation



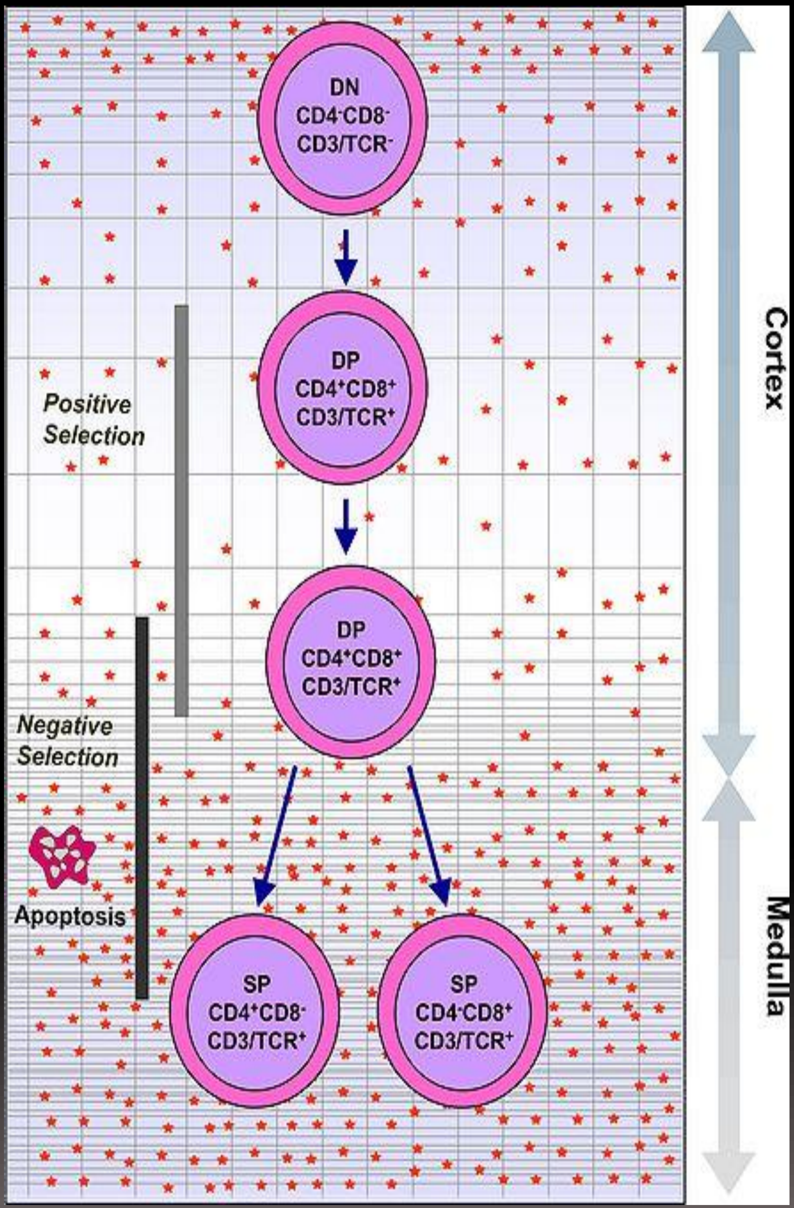
Vafiadis et al. *Nature Genetics* 1997 and Durinovic et al. *Diabetes,* in press

Thymus-specific transcriptional regulation

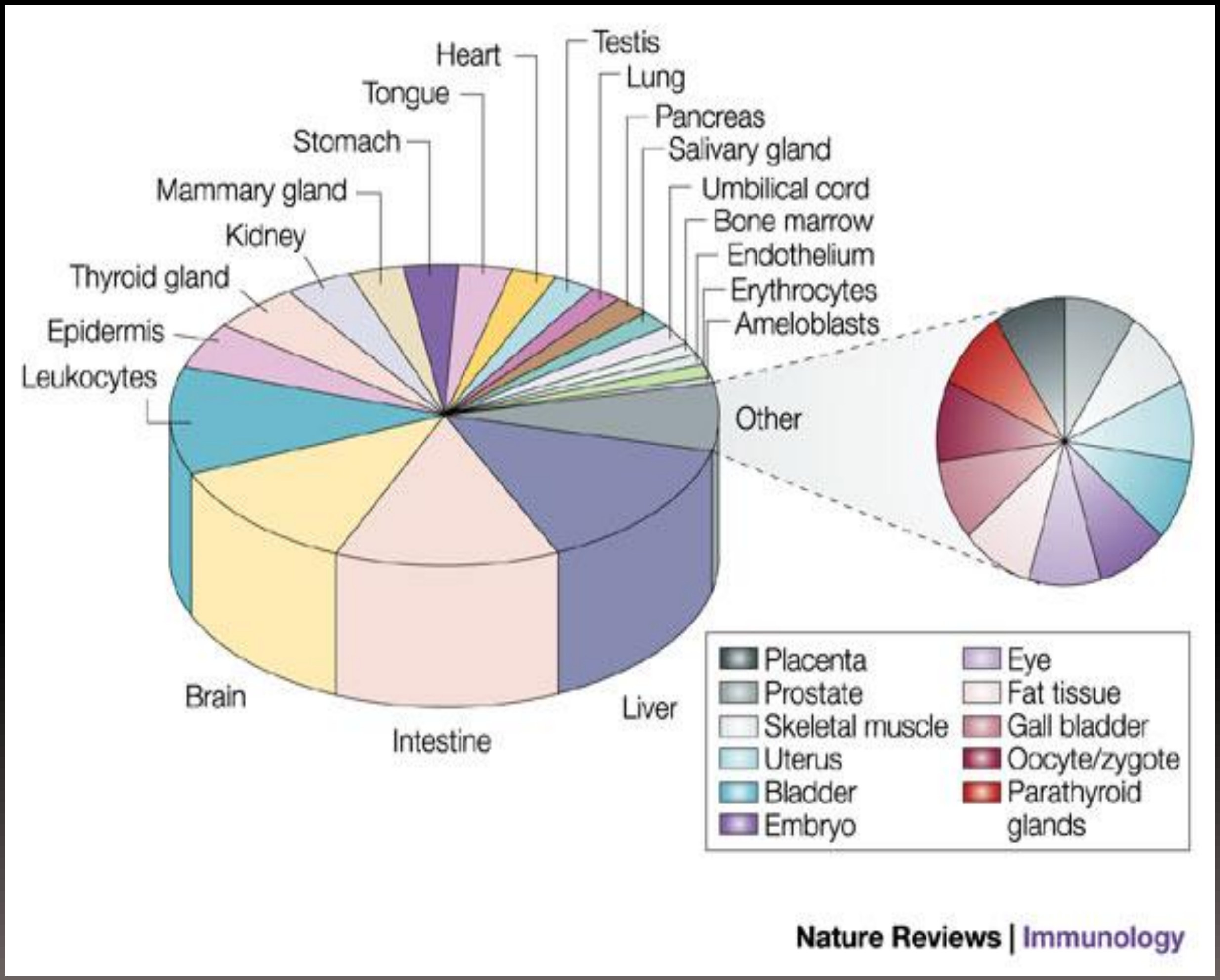


Vafiadis et al. *Nature Genetics* 1997 and Durinovic et al. *Diabetes,* in press

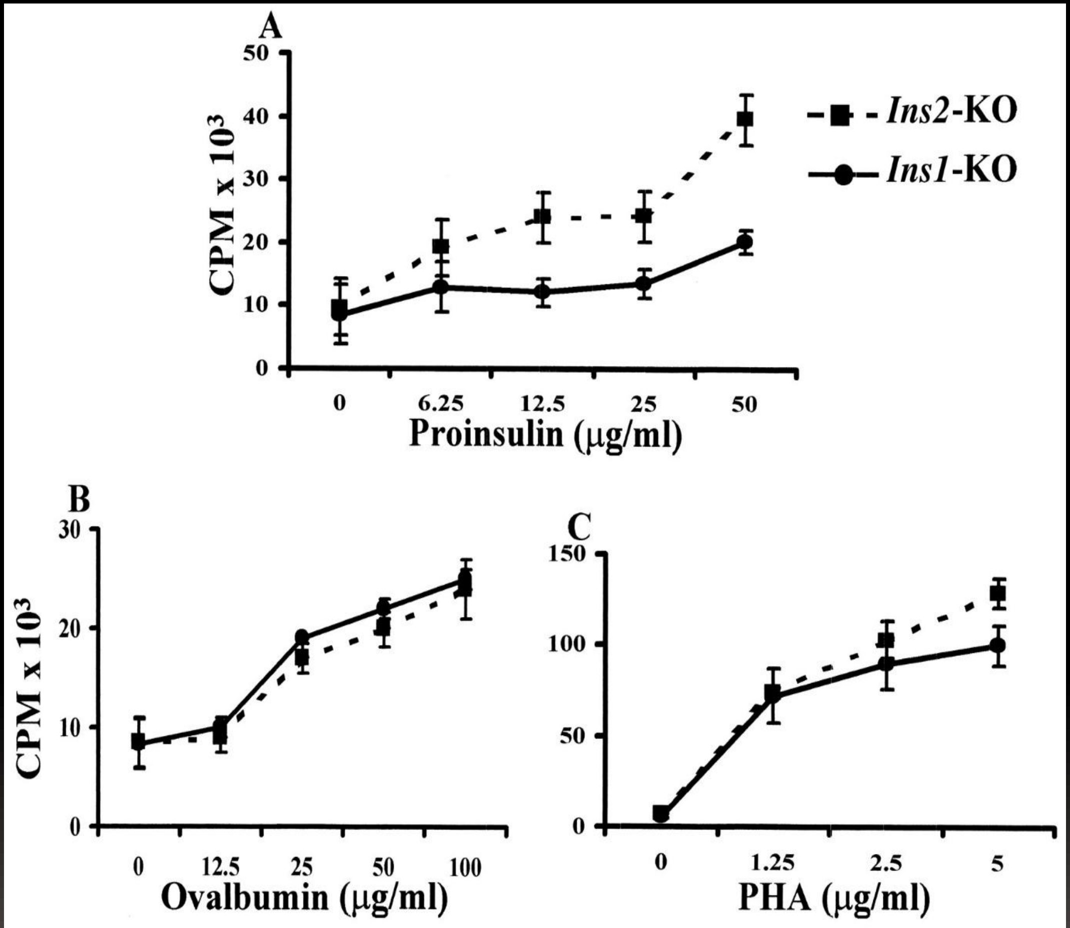
T-lymphocytes are selected in the thymus



The thymus expresses hundreds of tissue-specific antigens



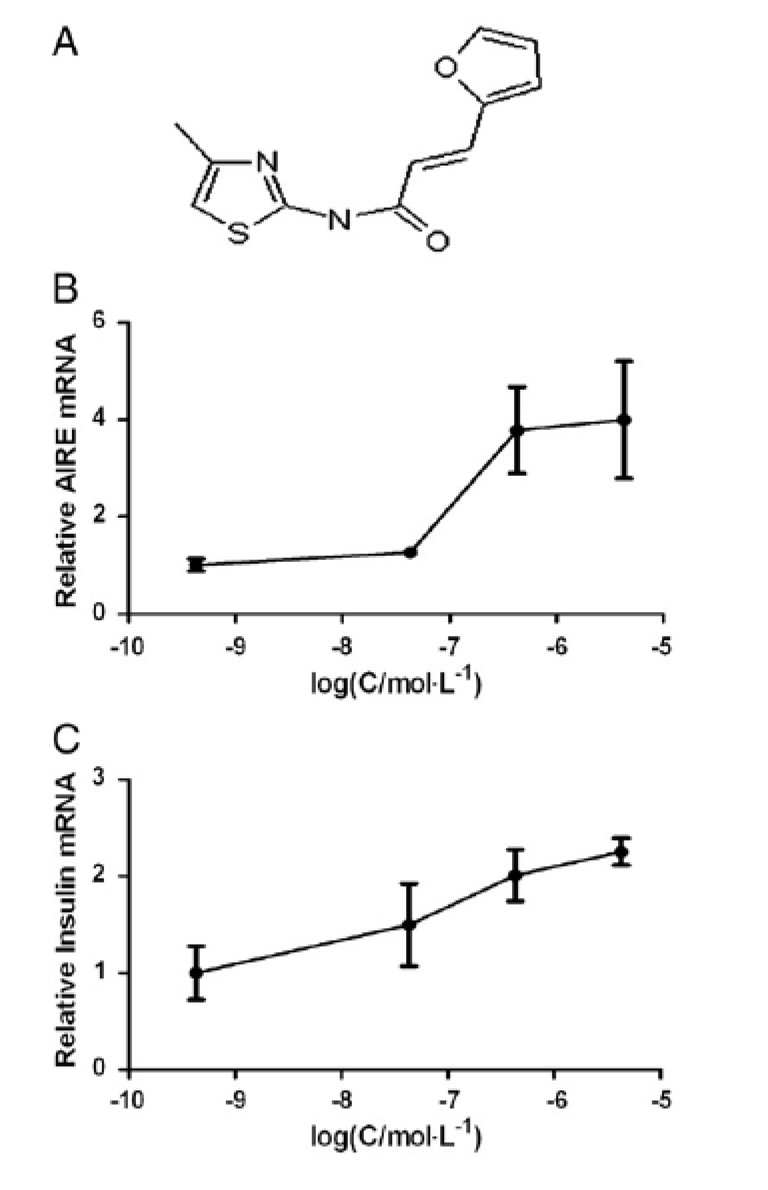
Mice with specific targeting of insulin in thymus



Chentoufi & Polychronakos *Diabetes* 2002

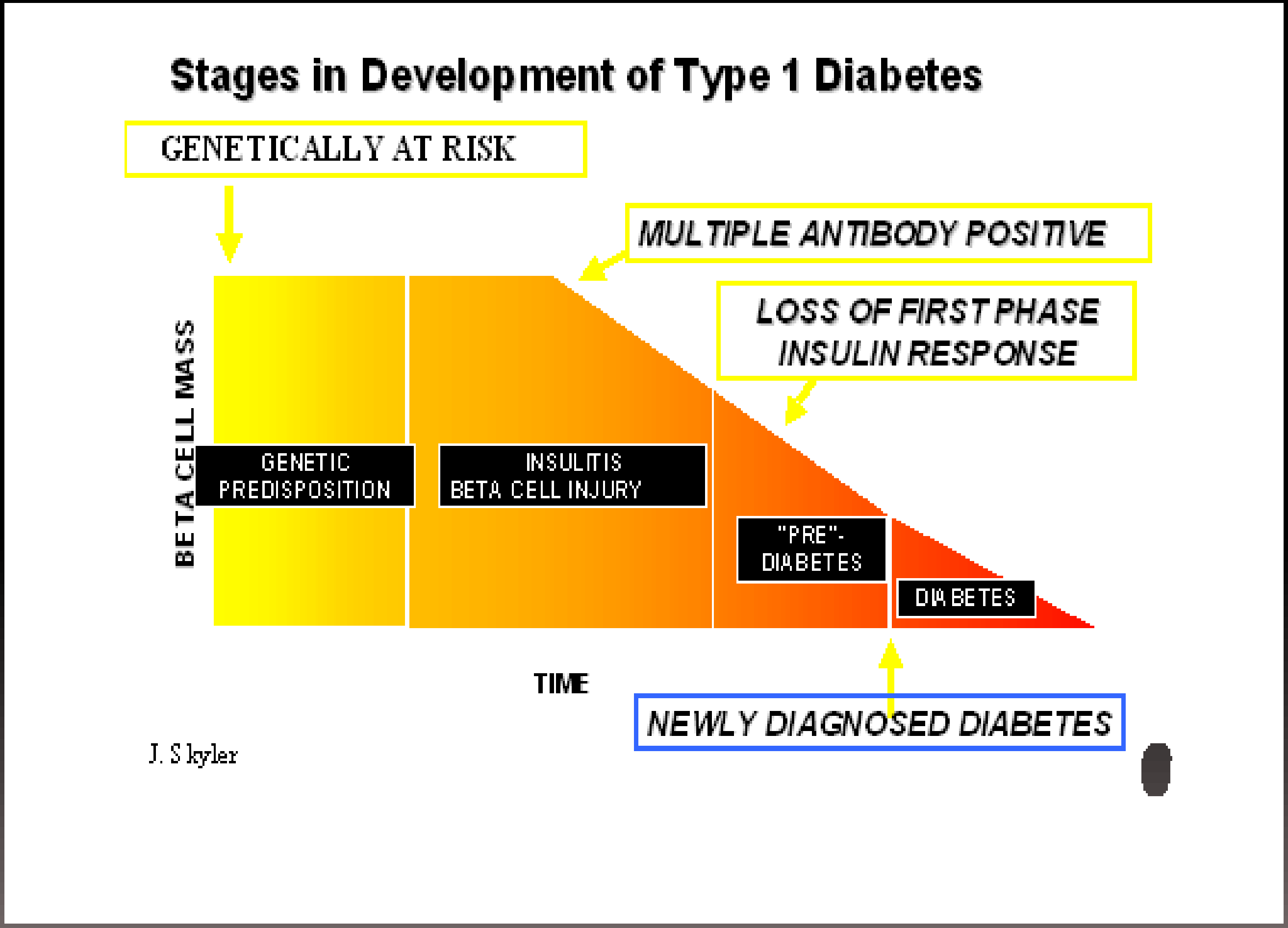
Therapeutic applications

- High-throughput drug screening
- mTECs with luciferase under the *INS* promoter



Yang et al., *Eur J Pharmacol*, 2012

Type 1 diabetes: a long process
accent on prediction/prevention



Imputation of rare variants

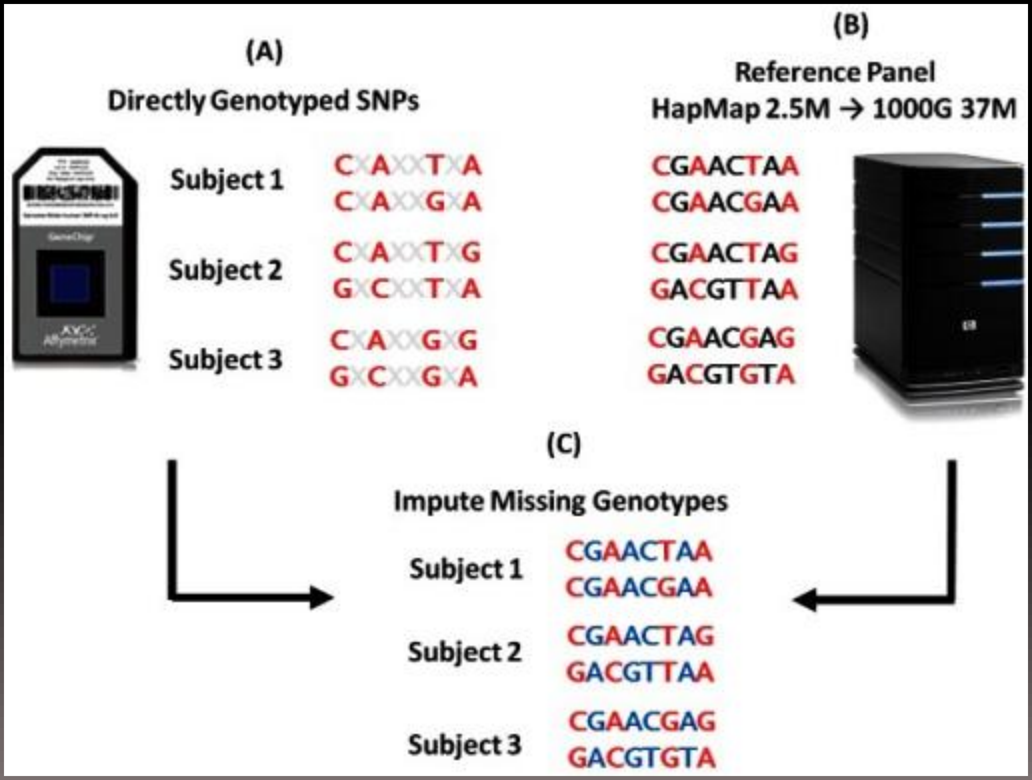
ExAC repository: >60,000 exomes

Tens of millions of DNA variants, some quite rare

Rich source of data, permitting imputation of rare variants.

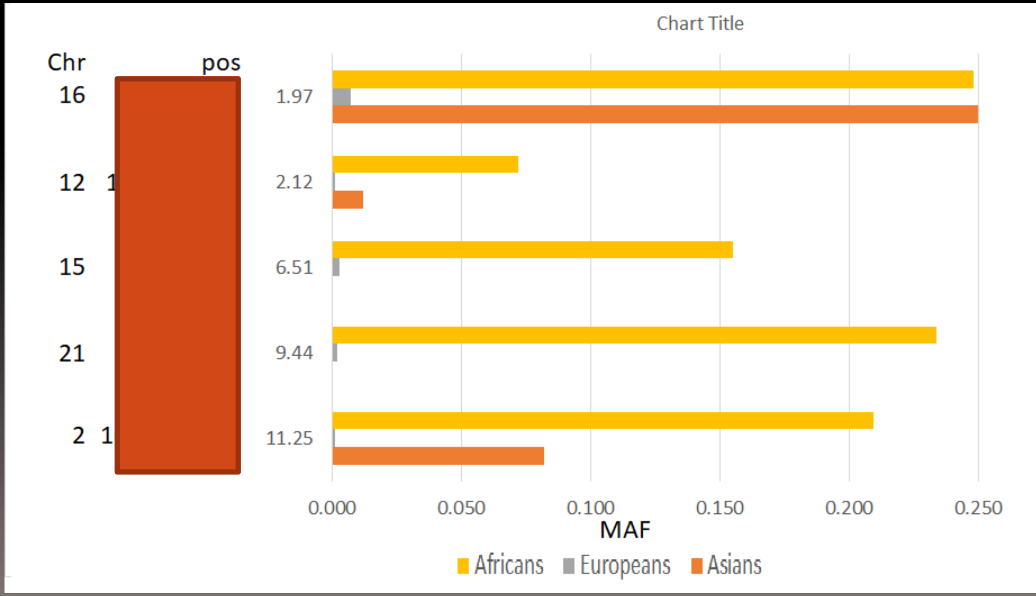
Rare variant imputation

- We used the data from Bradfield et al., 2011
- Plus 1k new Canadian samples
- Total of 7k T1D cases and 10k controls

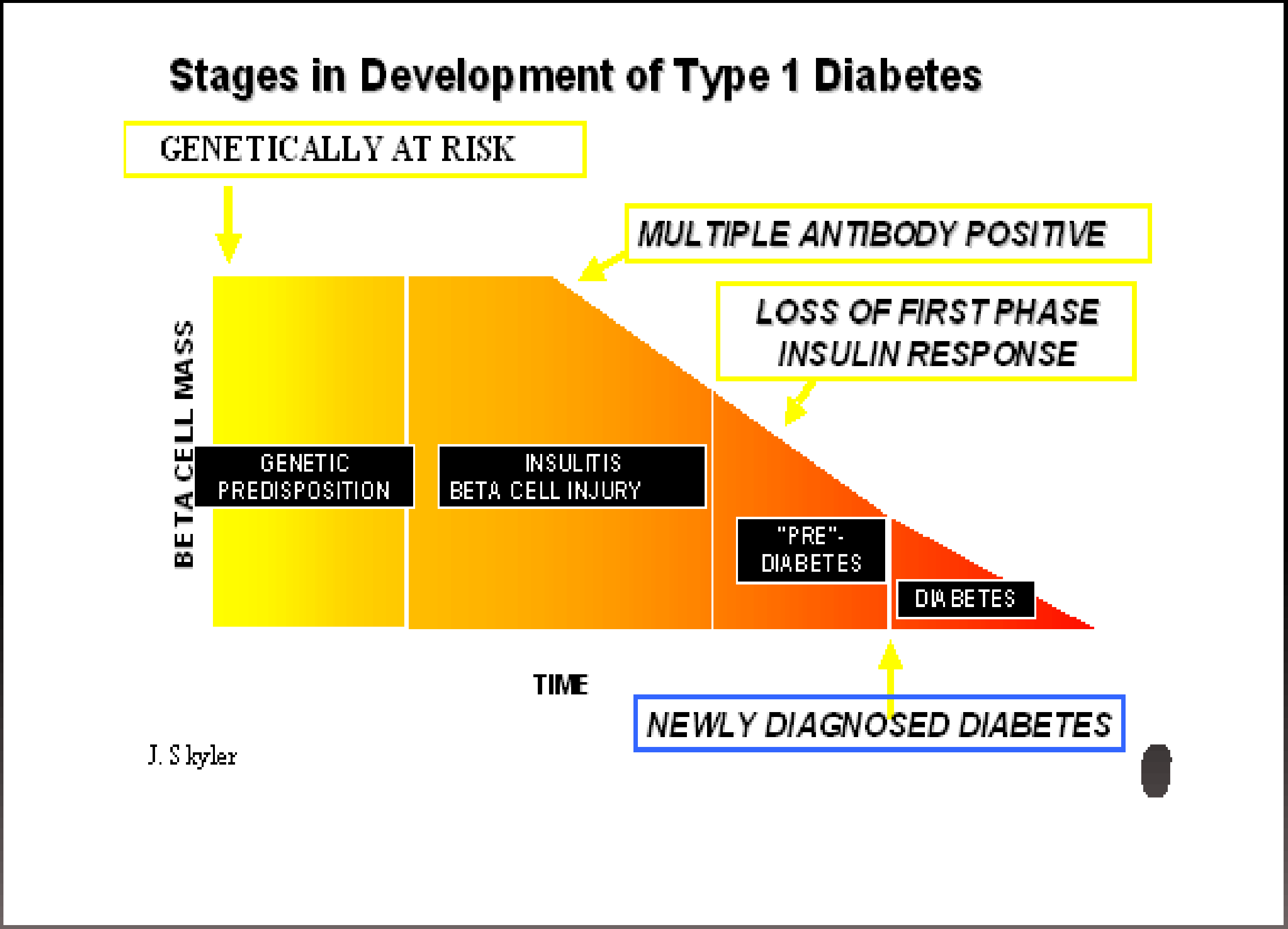


New low-frequency high-risk T1D alleles

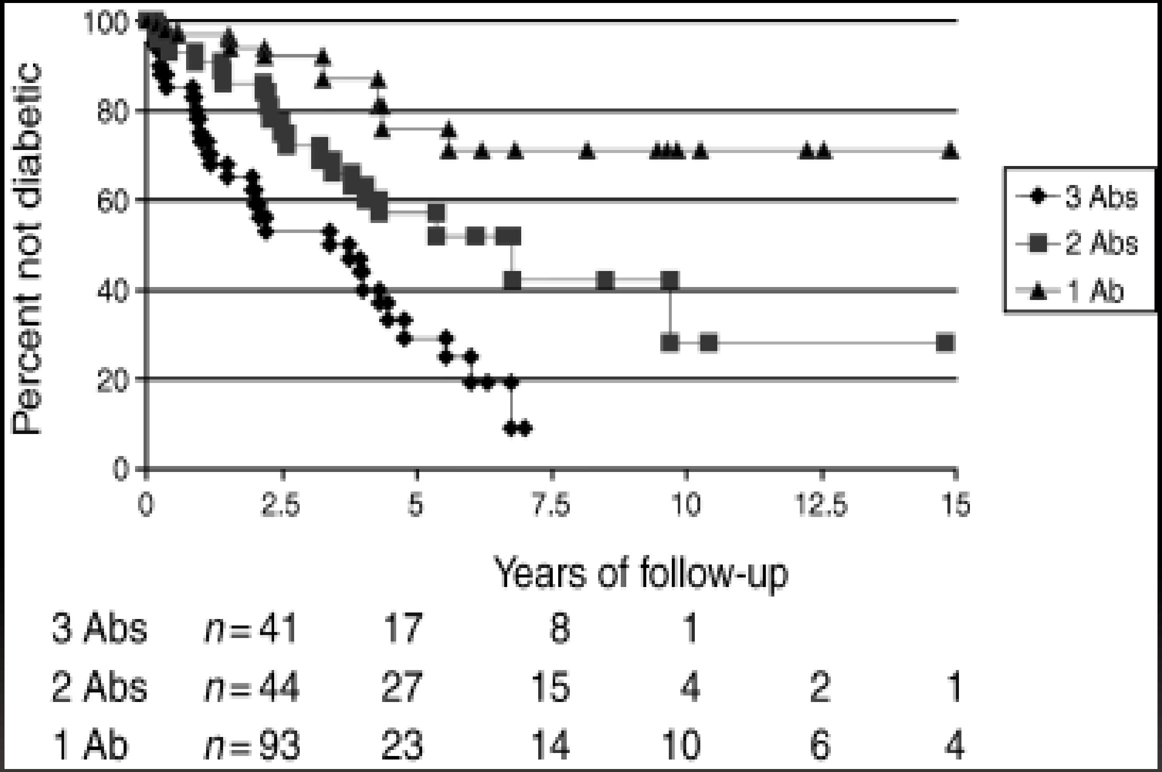
Locus	MAF	p-value	Odds ratio
rsxxxx	0.30%	4.00E-12	2.46
rsxxxx	1.30%	2.43E-11	1.63
rsxxxx	0.01%	6.93E-13	11.83
rsxxxx	1.29%	1.84E-12	1.83
rsxxxx	0.10%	7.95E-12	2.12
rsxxxx	20%	1.05E-10	1.17
rsxxxx	0.70%	2.91E-09	1.97
rs689	**27.44%**	**1.44E-160**	**2.21**
rsxxxx	0.20%	2.72E-14	9.44
rsxxxx	0.30%	8.63E-17	6.51
rsxxxx	0.10%	1.73E-13	11.25



Type 1 diabetes: a long process accent on prediction/prevention

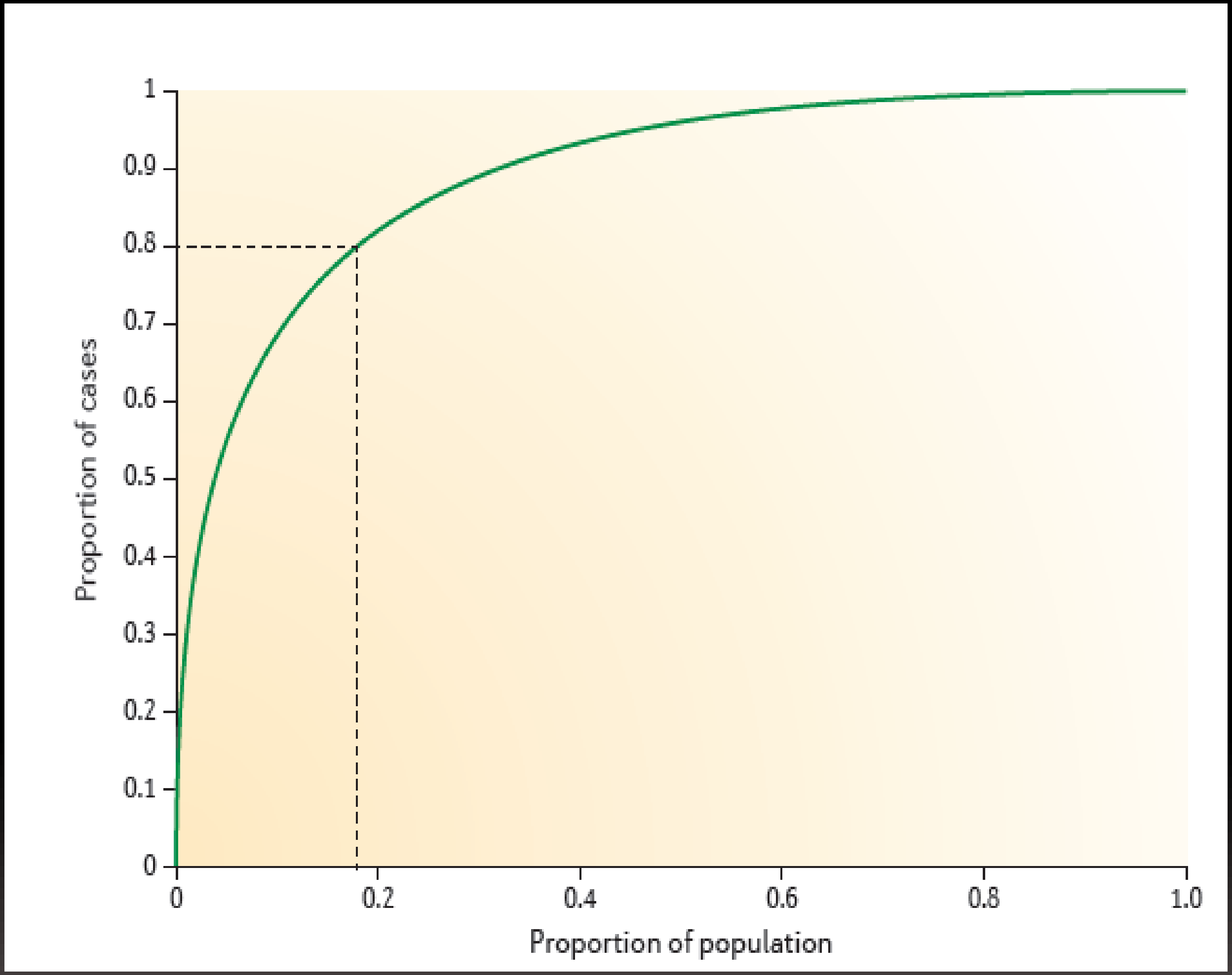


Prediction through autoantibodies



Gianani and Eisenbarth 2005

Genetic prediction: clinically useful?



Polychronakos and Li, *Nature Reviews Genetics* 2011

Predictions for the next 10 years

- Spectacular progress in
  - understanding T1D
  - predicting T1D
  - curing T1D with β-cell replacement
  - Perfect management of T1D with the closed loop

- Immune Rx to prevent T1D

- Very little has affected patient's lives for now
- It will, in the next 10 years