Human Genomic Analysis of Type 2 Diabetes and its Translation to Clinical Care

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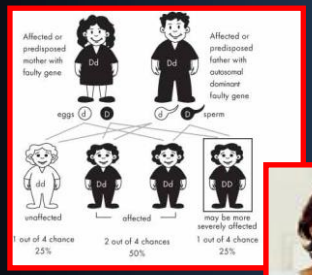
Things I Think About

Genes



Diet

Physical activity

Type 2 Diabetes

Things I Think About

- Glucose is only a convenient end–point
  - Diagnostic criteria is population–based and examines risk for retinopathy
  - Clinical cut–offs ignore the continuous nature of glucose
  - Fundamentally not a good indicator of a trajectory towards T2DM
  - There are many ways to get to hyperglycemia

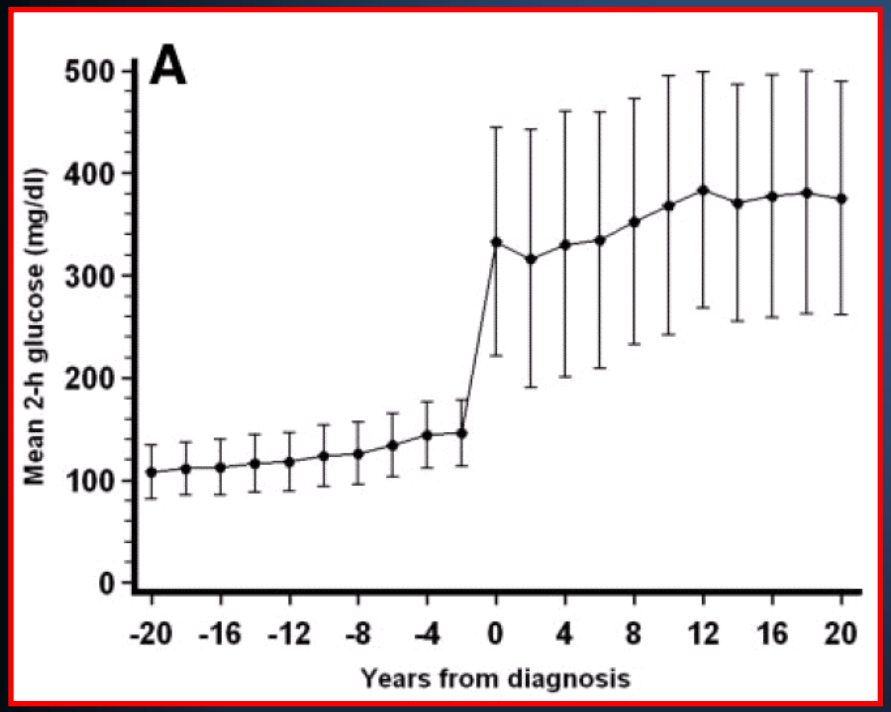
Things I Think About

- Clinical diagnosis does not recognize that "diabetes" is a cluster of different diseases that manifest in hyperglycemia
- T2DM is fundamentally a disease of the pancreatic β–cell
- Most physicians still use mono–therapy with the goal of reducing glycemia or HbA1c

Things I Think About

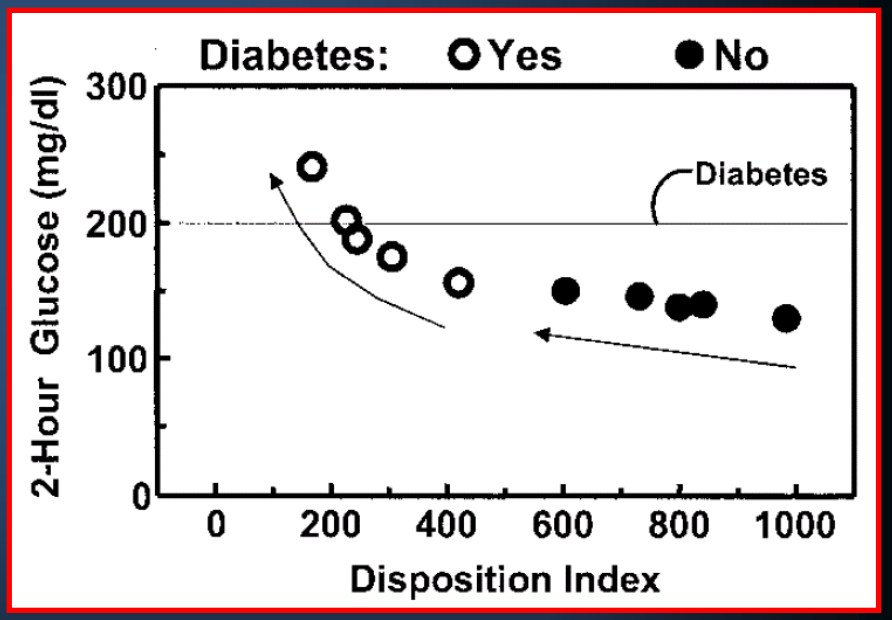
Data from Pima Indians

Mason *et al.*,
Diabetes 56:2054–2061, 2007



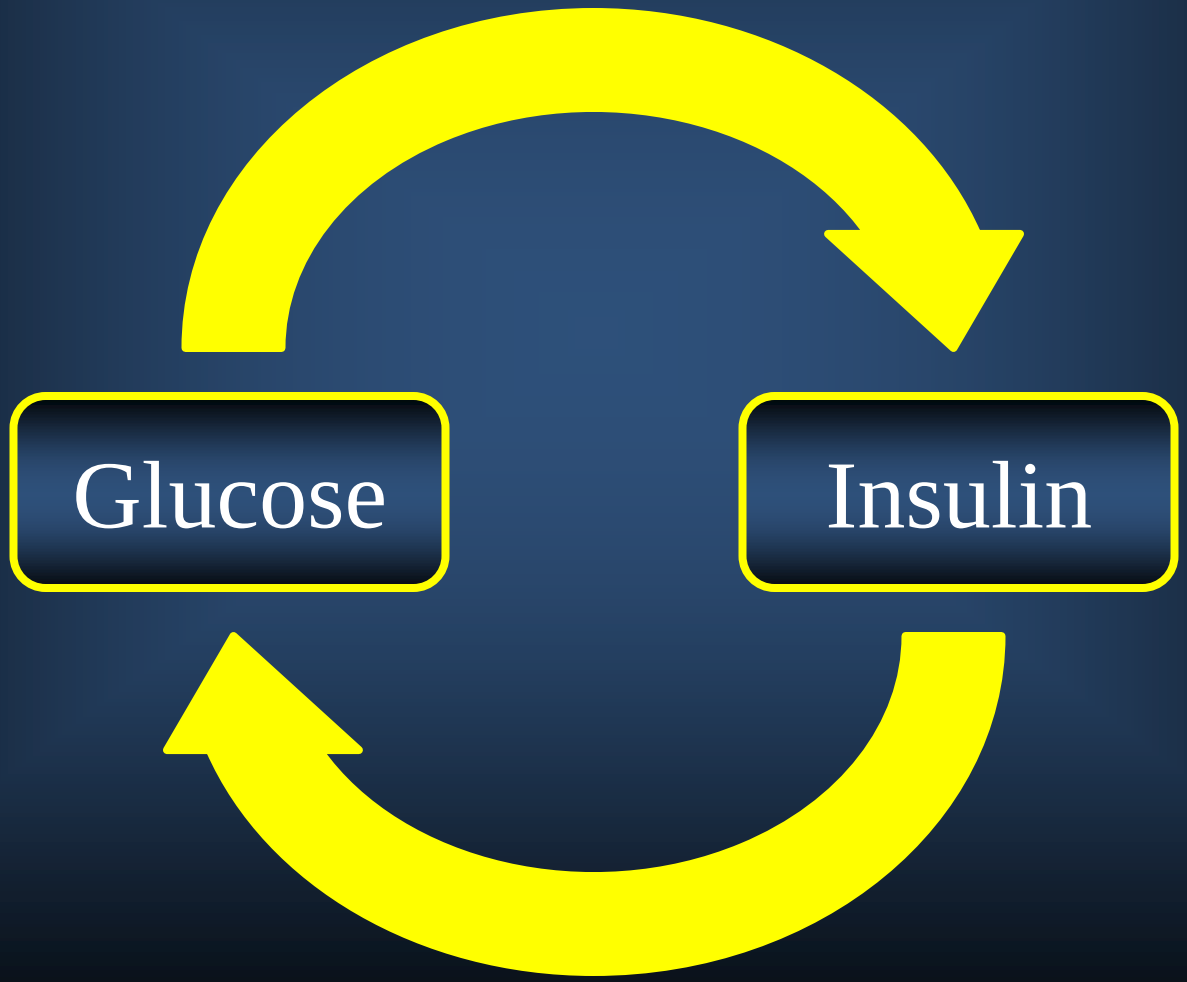
Data from Latinas

Buchanan *et al.*,
Diabetes Care 30:S105–S111, 2007



Things I Think About

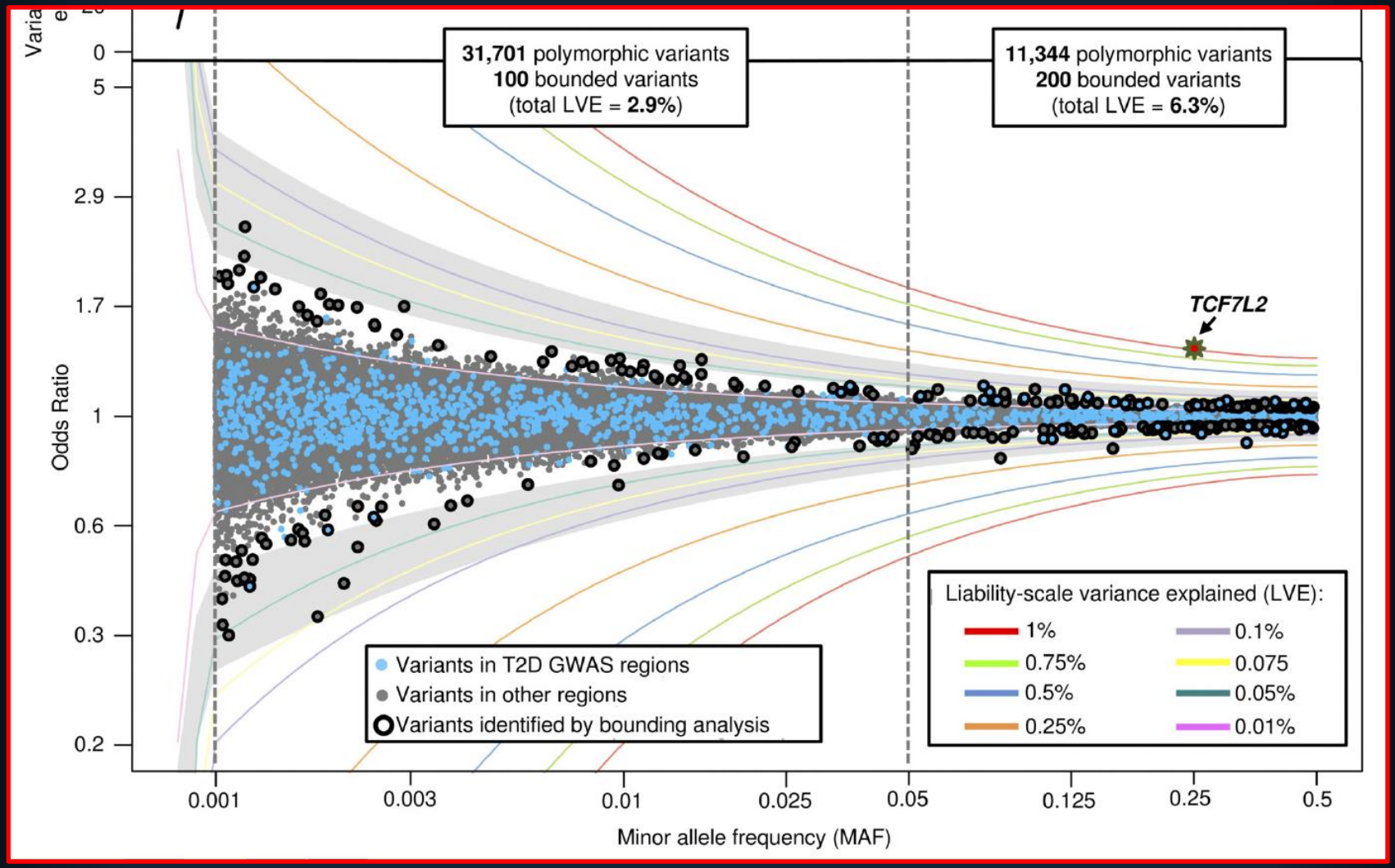
- Need to consider the regulatory feedback nature of glucose and insulin



Genetics of Type 2 Diabetes

- Genome–wide association (GWA) studies have identified
  - Over 80 loci associated with risk for T2DM
  - "Hundreds" of loci associated with variation in T2DM–related traits
    - Glycemia/insulinemia
    - Obesity/adiposity
    - Lipids/lipoproteins
    - Related metabolic disorders
- Recent whole–exome and whole–genome studies revealed new insights
  - There appear to be few rare variants of large effect
  - Most rare variants have effect sizes similar to common variants
  - Not likely to explain the so–called "missing" heritability

Genetics of Type 2 Diabetes



Taken from Fuchsberger *et al.*, Nature 536:41–47, 2016

Genetics of Type 2 Diabetes

- Question: So how should we think about the role of genetic variation in the pathogenesis of type 2 diabetes?
- Most variants are in intergenic or intronic regions
  - Suggests transcriptional regulation or gene splicing may be important
- Most associations are only landmarks, so fine–mapping to identify "the" variant will be key
- Much work to do . . .

Genetics of Type 2 Diabetes

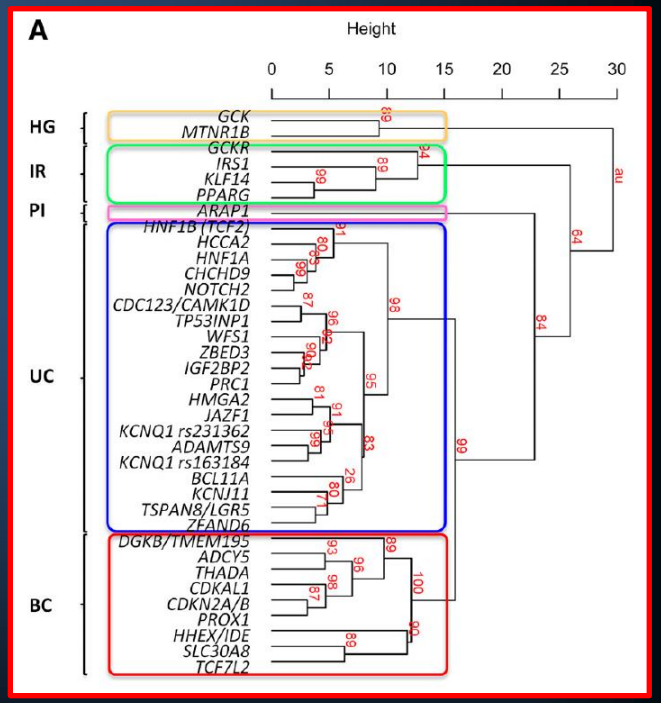
- An alternative view . . .
- While reductionist science is important, many times small molecular changes do not manifest themselves in a clinical phenotype
- Physiologic regulation can mask the small effects engendered by some genetic variants
- Some effects may not manifest in a phenotype for prolonged periods of time

Translating Genetics

- Two important observations:
- First, majority of type 2 diabetes susceptibility loci appear to map to the pancreatic β–cell
  - But difficult to map loci back to phenotypes
- Second, β–cell preservation appears to be one of the keys to prevention of type 2 diabetes
  - Supported by two key studies (in addition to others)

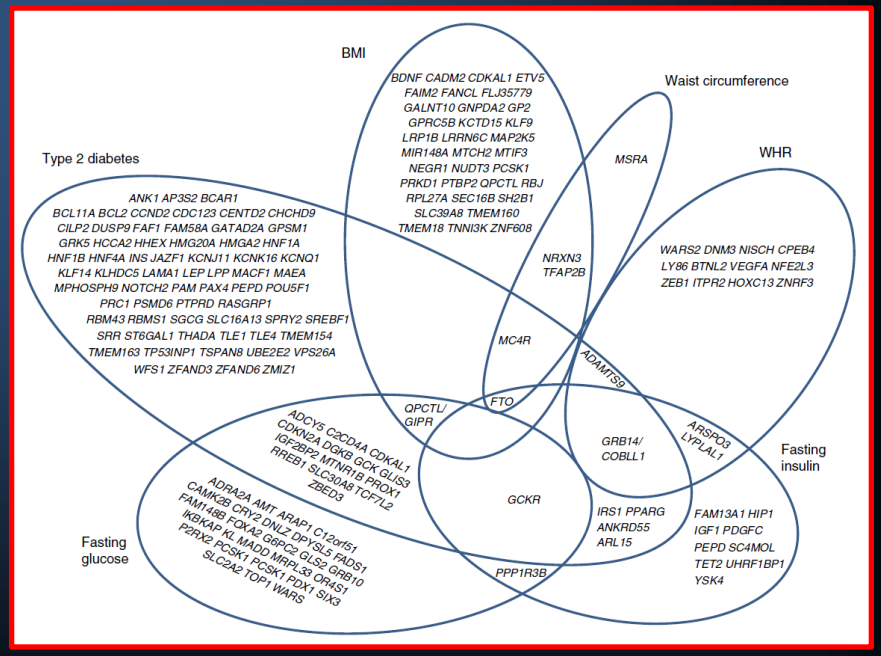
Translating Genetics

- MAGIC (Dimas *et al.*, Diabetes 63:2158–2171, 2014)
- Associate 37 type 2 diabetes loci with physiologic phenotypes
- Major outcomes:
  - Cluster analysis identified 5 groupings
    - Insulin secretion with hyperglycemia (HG)
    - Insulin resistance (IR)
    - Proinsulin processing (PI)
    - β–cell without hyperglycemia (BC)
    - Uncategorized (UC)
  - Based on association with phenotypes most loci fell into "uncategorized", despite known biology related to pancreas



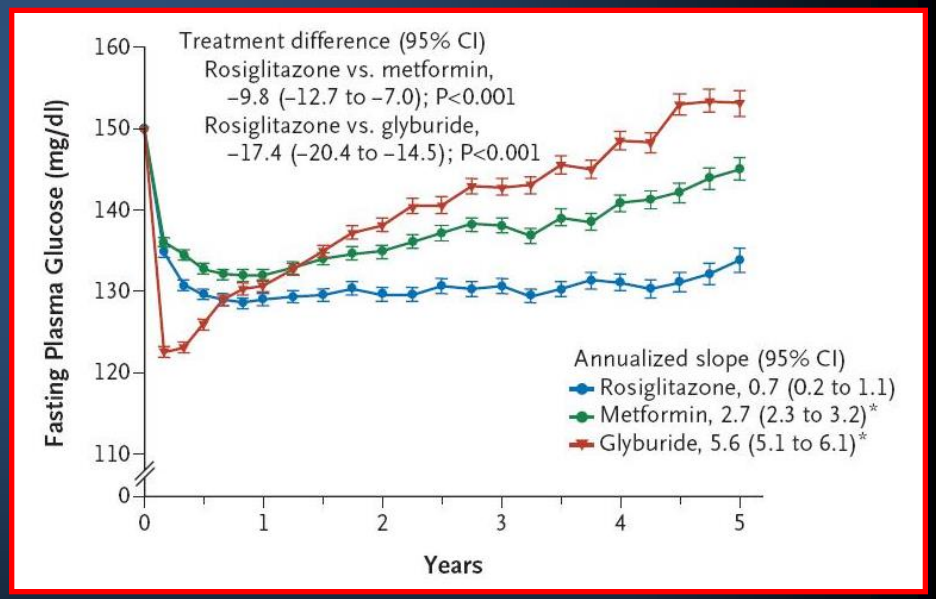
Translating Genetics

- Lack of overlap in loci across phenotypes (Grarup *et al.*, Diabetologia 57:1528–1541, 2014)
- Assessed the overlap in loci across GWAS for type 2 diabetes and diabetes–related phenotypes
- Major outcome:
  - Almost no overlap in loci across phenotypes
  - Greatest overlap with fasting glucose



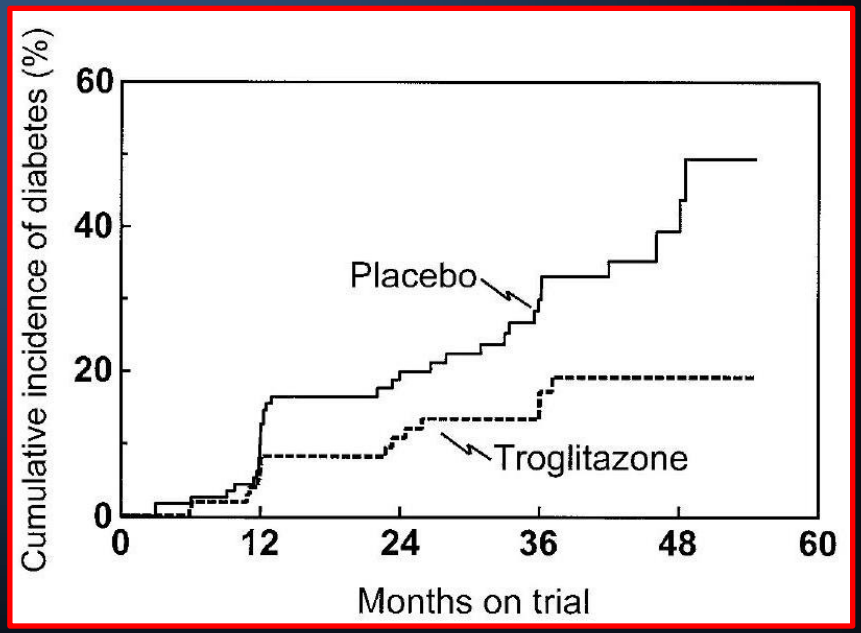
Diabetes Prevention

- The ADOPT Study (Kahn *et al.*, New Engl J Med 355:2427–2443, 2006)
- Compared "durability" of different mono–therapies
- Major outcomes:
  - Mono–therapy failure:
    - 15% with rosiglitazone
    - 21% with metformin
    - 34% with glyburide
  - Risk reduction:
    - 32% rosiglitazone *vs.* metformin
    - 63% rosiglitazone *vs.* glyburide



Diabetes Prevention

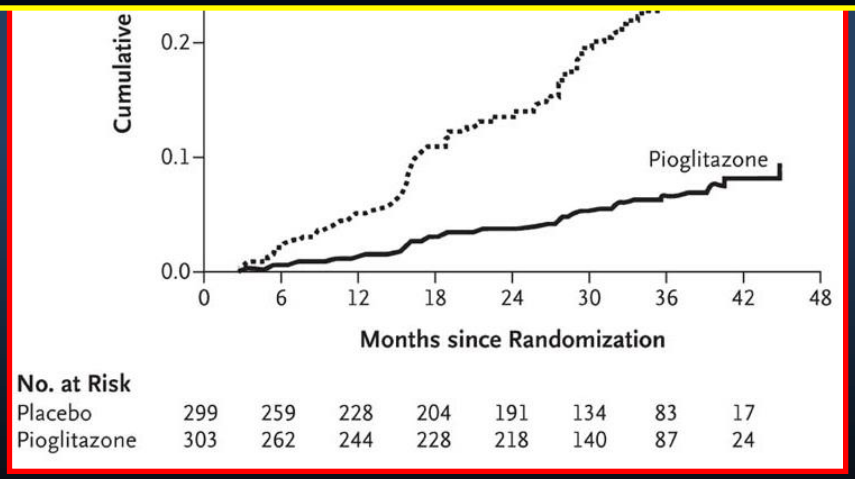
- The TRIPOD Study (Buchanan *et al.*, Diabetes 51:2796–2803, 2002)
- First study to assess whether improving insulin sensitivity to preserve β–cell function can reduce risk for type 2 diabetes
- Major outcomes:
  - Troglitazone mono–therapy reduced risk of future type 2 diabetes by >50%
  - Degree of reduction was related to degree of improvement in β–cell function



Diabetes Prevention

- TRIPOD results have been replicated in larger trials using both rosiglitazone and pioglitazone
- Example: ACT NOW showed 72% reduction in risk for type 2 diabetes with pioglitazone mono-therapy (DeFronzo *et al.*, New Engl

Suggests focusing on pancreatic β–cell and β–cell function is the key to "preventing" type 2 diabetes



Translation of Genetics

- **Question:** So how can we translate GWAS and sequencing findings for use in clinical care?
- Prediction of diabetes: Nice public relations reasons, but not particularly need
  - Family history currently used to identify at–risk individuals
  - Most studies show that including variants does not significantly improve prediction
  - Could be useful in the absence of family history information
- Identification of additional disease classes: Fewer studies, but possible that unique variants might help discriminate different subsets of diabetes

Translation of Genetics

- Lifestyle response: Potential for an individual to respond to lifestyle modification
  - Likely to have limited efficacy
- New therapeutics
  - Potential pharmaceutical targets, but much work required
  - Gene therapy hopefully in the near future
- Pharmacogenetics/genomics: Area of great promise, but many facets
  - Susceptibility to adverse events/side effects
  - Responders *vs.* non–responders
  - How to define "response"
  - Focus on individual drugs?

Pharmacogenetics

- Success stories for rare variants (not quite pharmacogenetics)
- Best example: Rare variants in *KCNJ11* and *ABCC8* and neonatal diabetes (Pearson *et al.*, New Engl J Med 355:467–477, 2006)
  - Infants presented as type 1 diabetes, treated with insulin
  - Actually had rare inactivating mutations in *KCNJ11* and *ABCC8*
  - Treatable with sulphonylureas

Pharmacogenetics

- Examples for type 2 diabetes and common variants are rare and many times not strongly convincing
- See review by Ivan Tkac (Curr Diab Rep 15:43, 2015)

Table 1 The effect of gene variants on mean HbA1c reduction in pharmacogenetic studies with antidiabetic drugs

Study drug [reference]	No. of patients	SNP	Gene	Reduction in HbA1c (%) major (reference) vs. minor allele	*p*
Metformin [16••]	1024	rs11212617 (A→C)	*ATM*	AA: reference; per C allele: +0.18 %	$1.8 \cdot 10^{-5}$
Metformin [17•]	4443	rs11212617 (A→C)	*ATM*	AA: reference; per C allele: +0.05 %	0.020
Metformin [18]	277	rs11212617 (A→C)	*ATM*	AA: reference; AC: +0.81 %, CC: +0.92 %	0.048
Metformin [30•]	118	rs2289669 (G→A)	*SLC47A1*	GG: reference; GA: +0.32 %, AA: +0.66 %	0.005
Pioglitazone [64]	250	rs1801282 (P12A)	*PPARG*	P12P: reference; P12A: +0.22 %	0.004
Rosiglitazone [65]	198	rs1801282 (P12A)	*PPARG*	P12P: reference; P12A: +0.84 %	0.015
Sulfonylureas [46]	101	rs5219 (E23K)	*KCNJ11*	E23E: reference; E23K + K23K: +0.25 %	0.036
Repaglinide [47]	100	rs5219 (E23K)	*KCNJ11*	E23E: reference; K23K: + 1.13 %	0.022
Sulfonylurea [54••]	901	rs1225372 (G→T)	*TCF7L2*	GG: reference; TT: −0.33 %	0.032
		rs7903146 (C→T)		CC: reference; TT: −0.31 %	0.039
Sulfonylureas [55•]	101	rs7903146 (C→T)	*TCF7L2*	CC: reference; CT + TT: −0.35 %	0.006
Sulfonylureas [59••]	1073	rs1799853 *2(R144C) rs1057910 *3(I359L)	*CYP2C9*	*1/*1: reference; *2/*2, *2/*3 or *3/*3: +0.50 %	0.0009
Pioglitazone [64]	250	rs1801282 (P12A)	*PPARG*	P12P: reference; P12A: +0.22 %	0.004
Rosiglitazone [65]	198	rs1801282 (P12A)	*PPARG*	P12P: reference; P12A: +0.84 %	0.015
Linagliptin [80••]	961	rs7903146 (C→T)	*TCF7L2*	CC: reference; TT: −0.26 %	0.0182
Gliptins [81••]	354	rs7202877 (T→G)	*CTRB1/2*	TT: reference; TG + GG: −0.51 %	0.0015

(+) *sign* greater reduction, (−) *sign* smaller reduction in minor allele carriers

Pharmacogenetics

- Other studies examining *PPARG* Pro12Ala

Author	Drug	Response	Associated?
Bluher *et al.*	Pioglitazone	Glucose or HbA1c	No
Kang *et al.*	Rosiglitazone	Glucose and/or HbA1c	Yes
Florez *et al.*	Troglitazone	HOMA–IR tertiles	No
Snitker *et al.*	Troglitazone	Change in Minimal Model S_I	No

- No reason why the type 2 diabetes susceptibility variant should be underlying the mechanism for TZD response

Pharmacogenetics

- Association between troglitazone response and variants in *PPARG* (Wolford *et al.*, Diabetes 54:3319–3325, 2005)

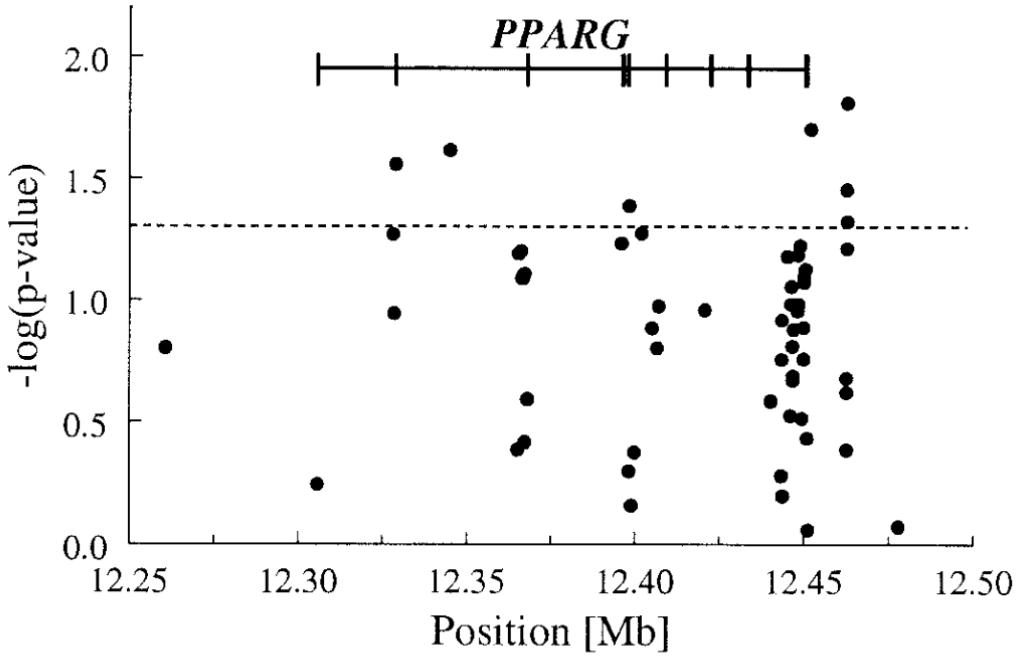


FIG. 1. Single marker association with response to troglitazone. The negative log of the *P* value for the χ^2 test of association is plotted according to physical distance. Horizontal dashed line denotes *P* value of 0.05. Two SNPs in close proximity gave identical *P* values, so only seven of the eight significant results are visible. The gene structure for *PPARG* is shown at the *top* with the A1 promoter on the *left*.

Pharmacogenetics

- Association between troglitazone response and variants in *PPARG* (Wolford *et al.*, Diabetes 54:3319–3325, 2005)

SNP	Minor Allele	MAF	OR	C.I.	*p*–value
rs13073869	A	0.390	2.30	(1.09, 4.87)	0.028
rs880663	C	0.400	2.36	(1.11, 5.04)	0.024
rs4135263	C	0.291	2.19	(1.02, 5.50)	0.041
rs1152003	G	0.410	2.19	(1.13, 4.28)	0.020
rs6806708	T	0.378	0.46	(0.22, 0.96)	0.035
rs13065455	A	0.391	2.04	(1.00, 4.17)	0.047
rs13088205	G	0.436	2.36	(1.17, 4.76)	0.016
rs13088214	C	0.391	2.04	(1.00, 4.17)	0.047

Pharmacogenetics

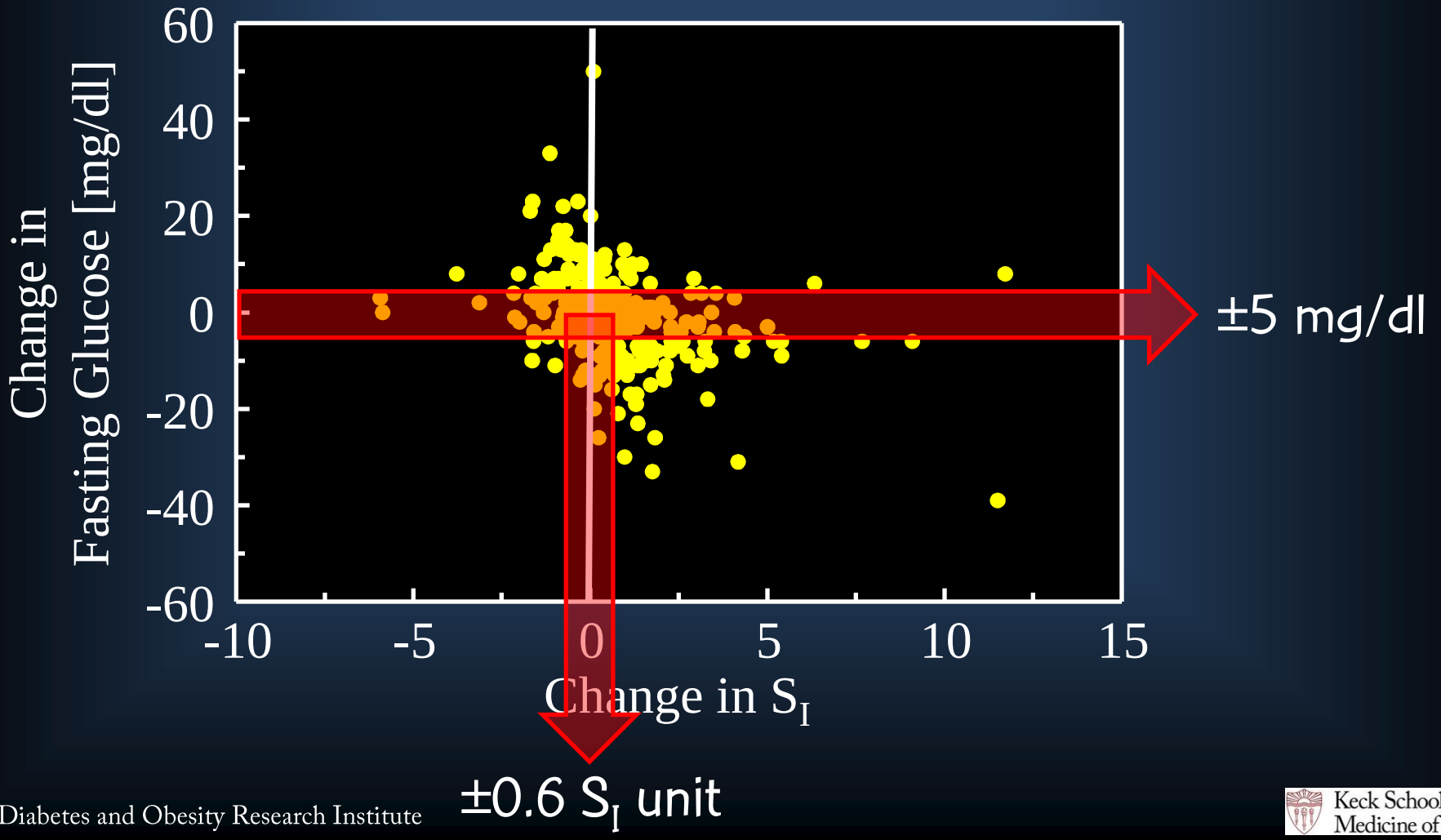
- An issue with pharmacogenetics studies is the definition of "response"
- Most studies define response as change in fasting glucose or HbA1c
- Makes sense from a clinical care perspective
- But does a change in glucose or HbA1c reflect whether an individual patient "responded" to the drug?

Pharmacogenetics

- Data from the TRIPOD and PIPOD studies

Buchanan *et al.*, Diabetes 51:2796–2803, 2002

Xiang *et al.*, Diabetes 55:517–522, 2006



Pharmacogenetics

- Many cases where the drug has its intended action, but little to no change in glucose or HbA1c
- Response to medication, but no clinical response
- Suggests alternative mechanisms may be at work
- Need to decide how to leverage such information

Pharmacogenetics

- Members of the same drug class may not react the same to a given genetic variant
- Almost no research in this area
- Example from the TRIPOD and PIPOD studies

Response to pioglitazone (PIO) Stratified by Previous TRIPOD Treatment Group

		PIO	
		Non–responder	Responder
TRIPOD Tx Group	Placebo	17 (37%)	29 (63%)
	Troglitazone	13 (41%)	19 (60%)

$p = 0.815$

Pharmacogenetics

- Participants of PIPOD all came from TRIPOD
- Opportunity to see if response differs between troglitazone and pioglitazone in the same individuals
  - Pitfall: small numbers
- 15 of 32 participants were discordant for response

		TRO	
		Responders	Non–responders
PIO	Responders	14 (74%)	5 (26%)
	Non–responders	10 (77%)	3 (23%)

$p = 0.587$

Summary

- Ultimate goal: "Personalized" or "individualized" medicine
- Pharmacogenetics may be just as complex as complex disease
- Ability to identify large subsets of individuals may be possible
- Ability to reach the "individual" level will be more challenging
- Therapeutics will change over time
- Need to consider whether should focus on individual drugs or potential mechanisms

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Beta Gene

Meta-Analyses of Glucose and Insulin-related traits Consortium

MAGIC

GUARDIAN

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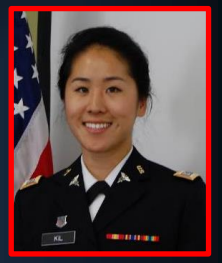
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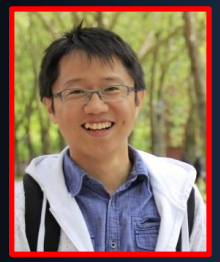
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Conflict of interest disclosure

None

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