HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH, BOSTON, MA

'OMICS: ADVANCES, APPLICATIONS, AND TRANSLATION IN NUTRITION AND EPIDEMIOLOGY- 3RD ANNUAL SYMPOSIUM

HEALTH APPLICATION OF TYPE 2 DIABETES GENETICS

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BROAD INSTITUTE
FRAMINGHAM HEART STUDY

JBM Disclosures and Acknowledgments

- NIH
  - NIDDK U01 DK078616
  - NIDDK K24 DK080140
  - NHLBI Framingham Heart Study N01-HC-25195
- American Diabetes Association
  - ADA Mentored Fellowship Grant
- Industry
  - Quest Diagnostics

Themes for Today

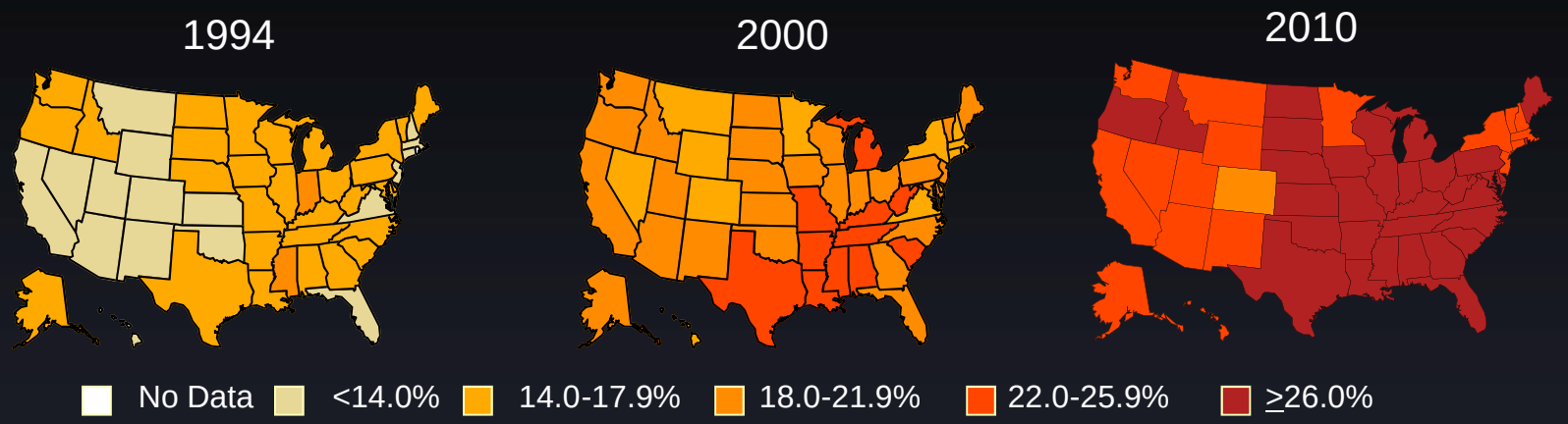
- Discoveries over 15 years in T2D genetics
- Predicting future T2D using T2D genetics
- Screening for T2D influenced by HbA1c genetics

Themes for Today

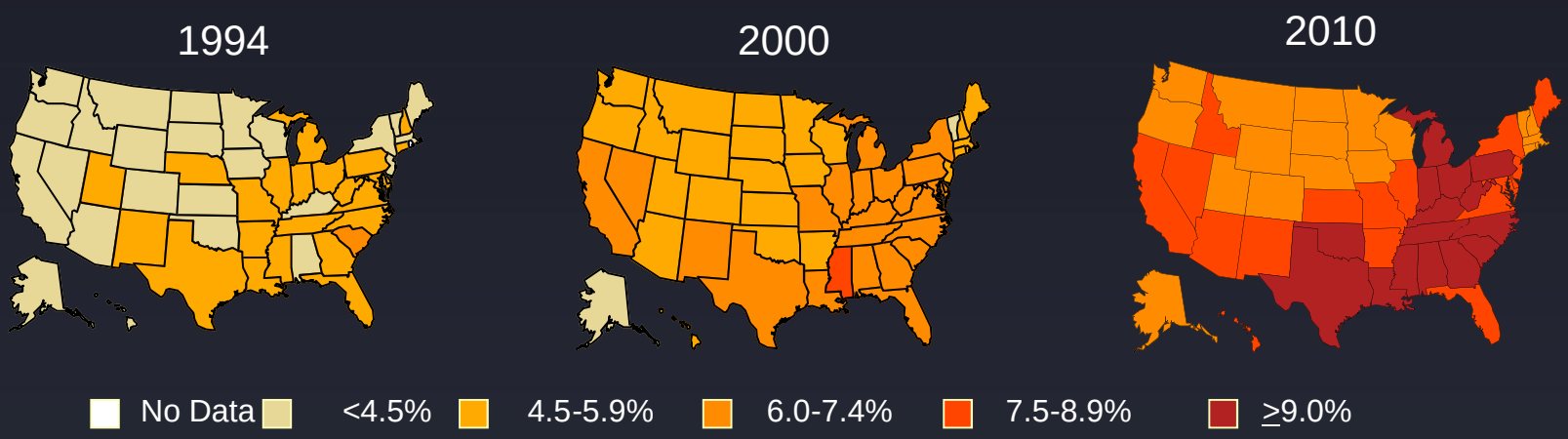
- Discoveries over 15 years in T2D genetics

Obesity and T2D Prevalences in the US Have Increased Inexorably and in Tandem for >16 Years

Obesity (BMI ≥30 kg/m^2)



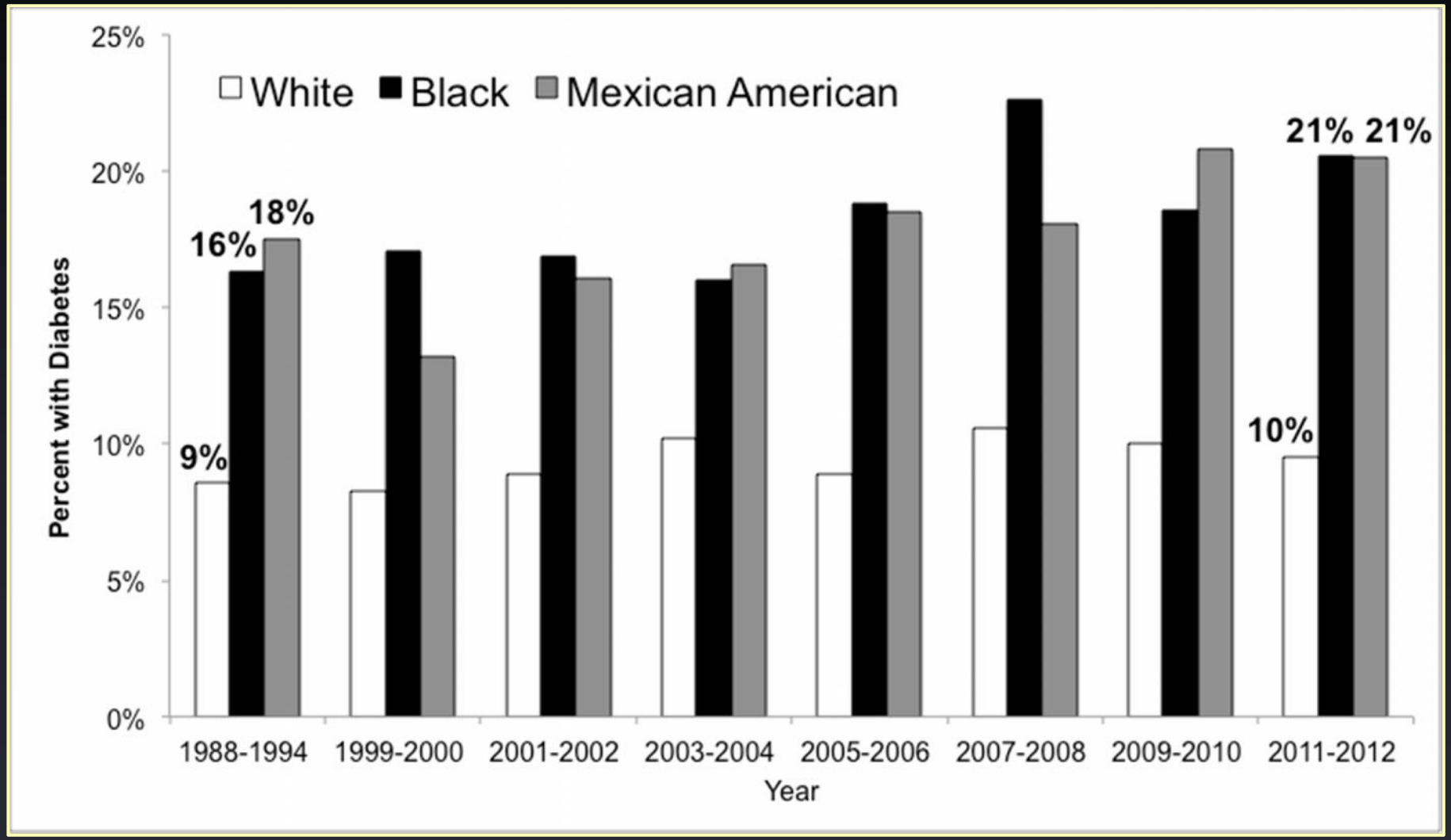
Diabetes



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

Increasing T2D Prevalence Disproportionately Impacts U.S. Black and Mexican American Communities

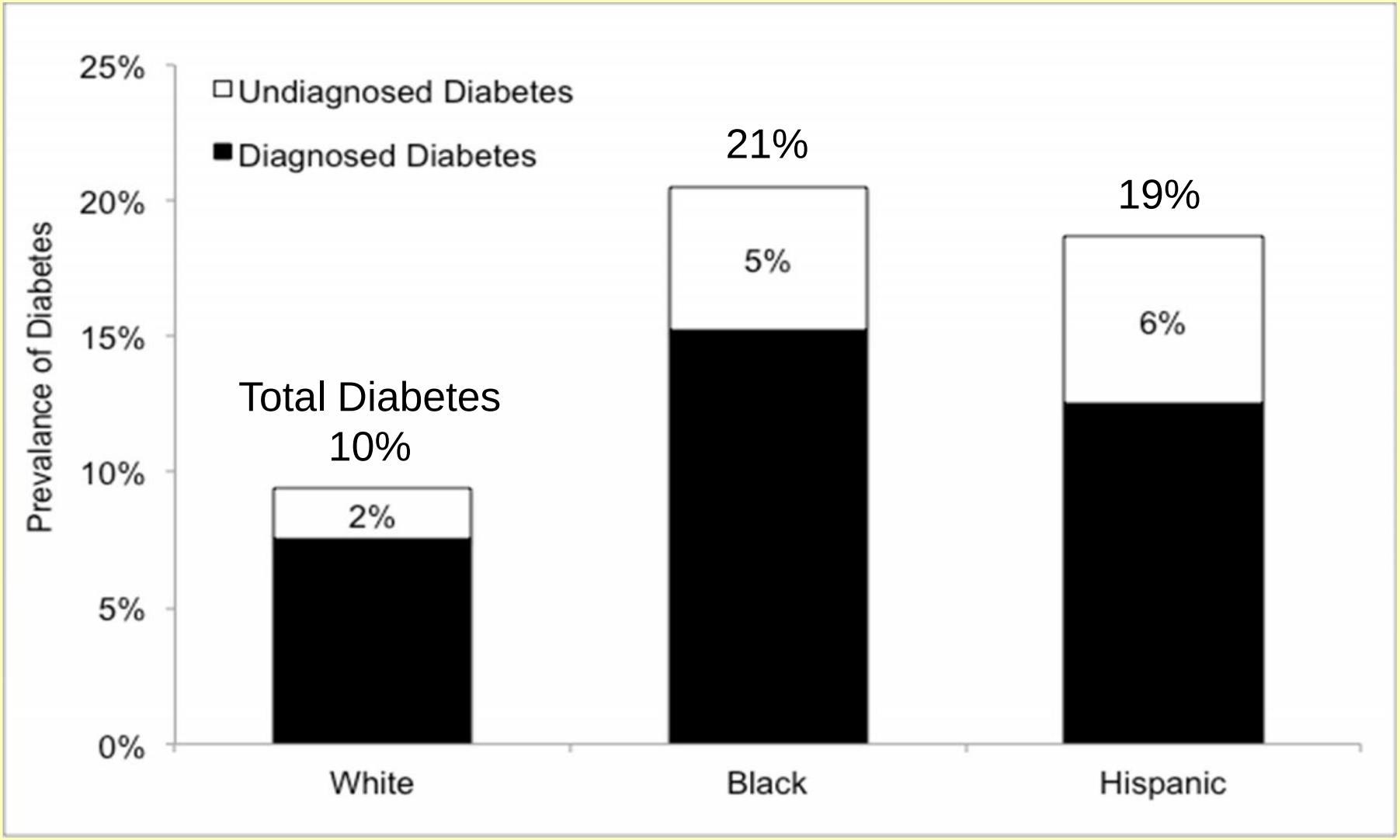
NHANES Adults 1988-2012, Dx by HbA1c or FPG



Mencke et al JAMA. 2015;314(10):1021-1029

Undiagnosed T2D Disproportionately Impacts U.S. Black and Mexican American Communities

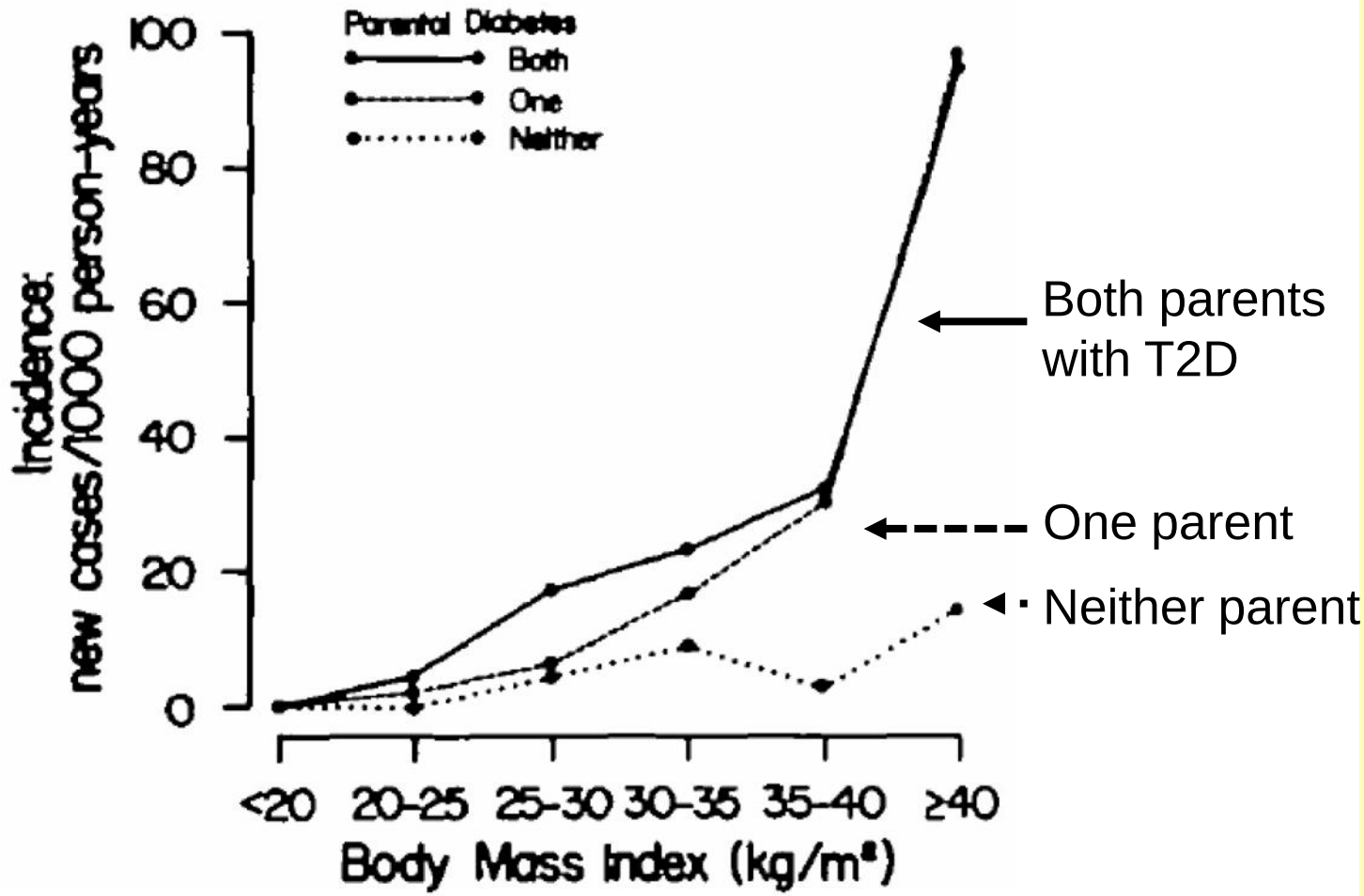
NHANES Adults 2011-2012, Dx by HbA1c or FPG



Mencke et al JAMA. 2015;314(10):1021-1029

Obesity Increases Risk Most in Pimas w Parental T2D

Parental T2D = Genetic Effects Causing T2D

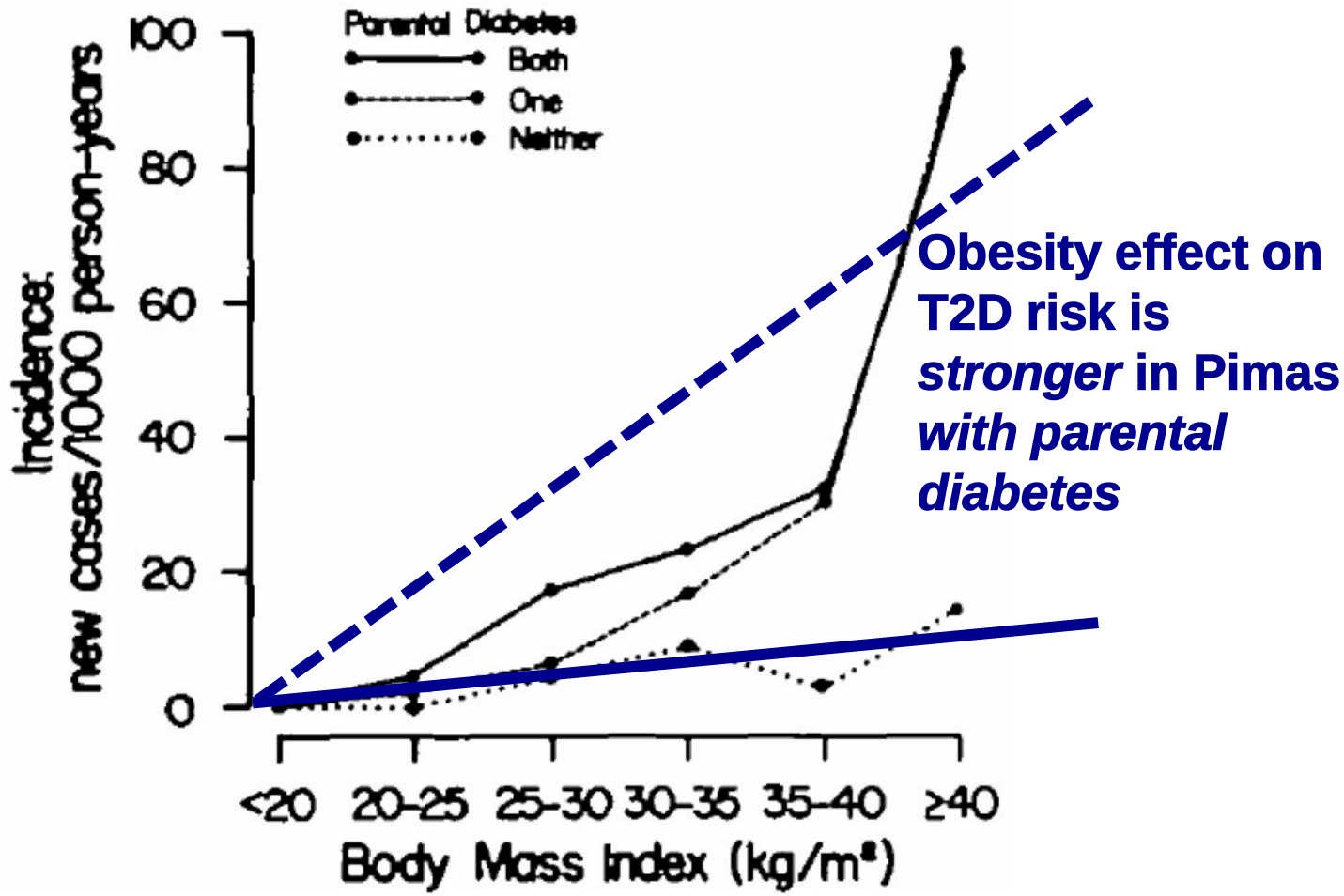


3137 Pima Indians followed with periodic examinations

Knowler et al Am J Epidemiol 1981;113:144-156

Obesity Increases Risk Most in Pimas w Parental T2D

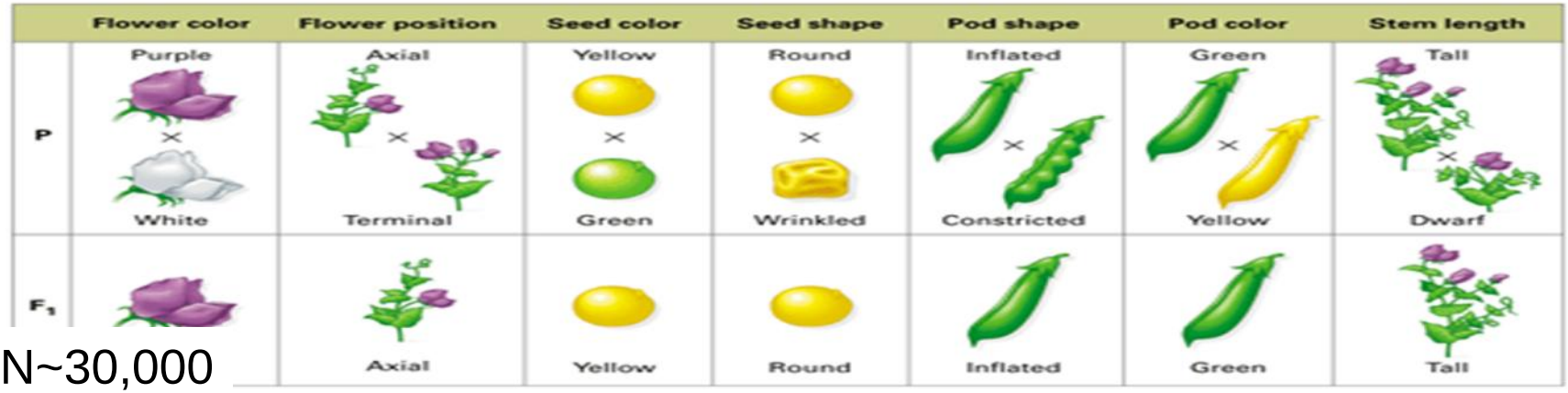
Genetic Studies Unmask Causation of T2D



3137 Pima Indians followed with periodic examinations

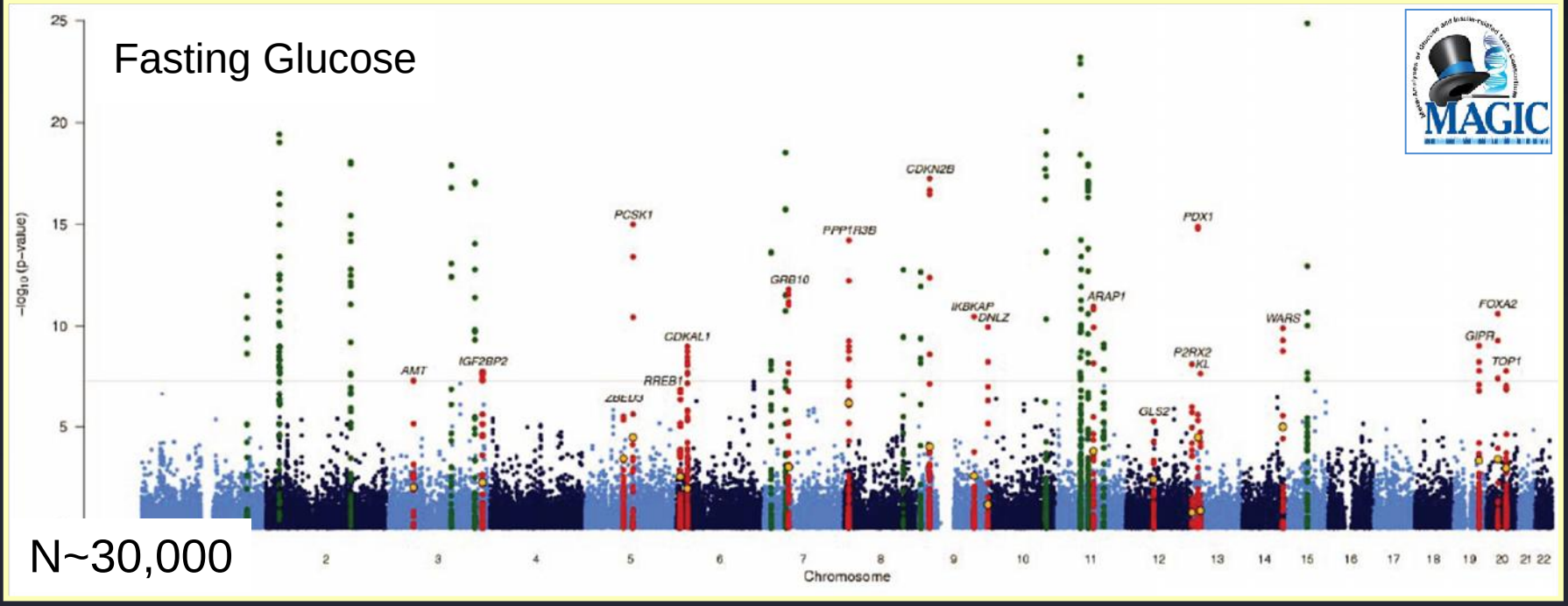
Knowler et al Am J Epidemiol 1981;113:144-156

Mendel's Laws – Segregation and Independent Assortment



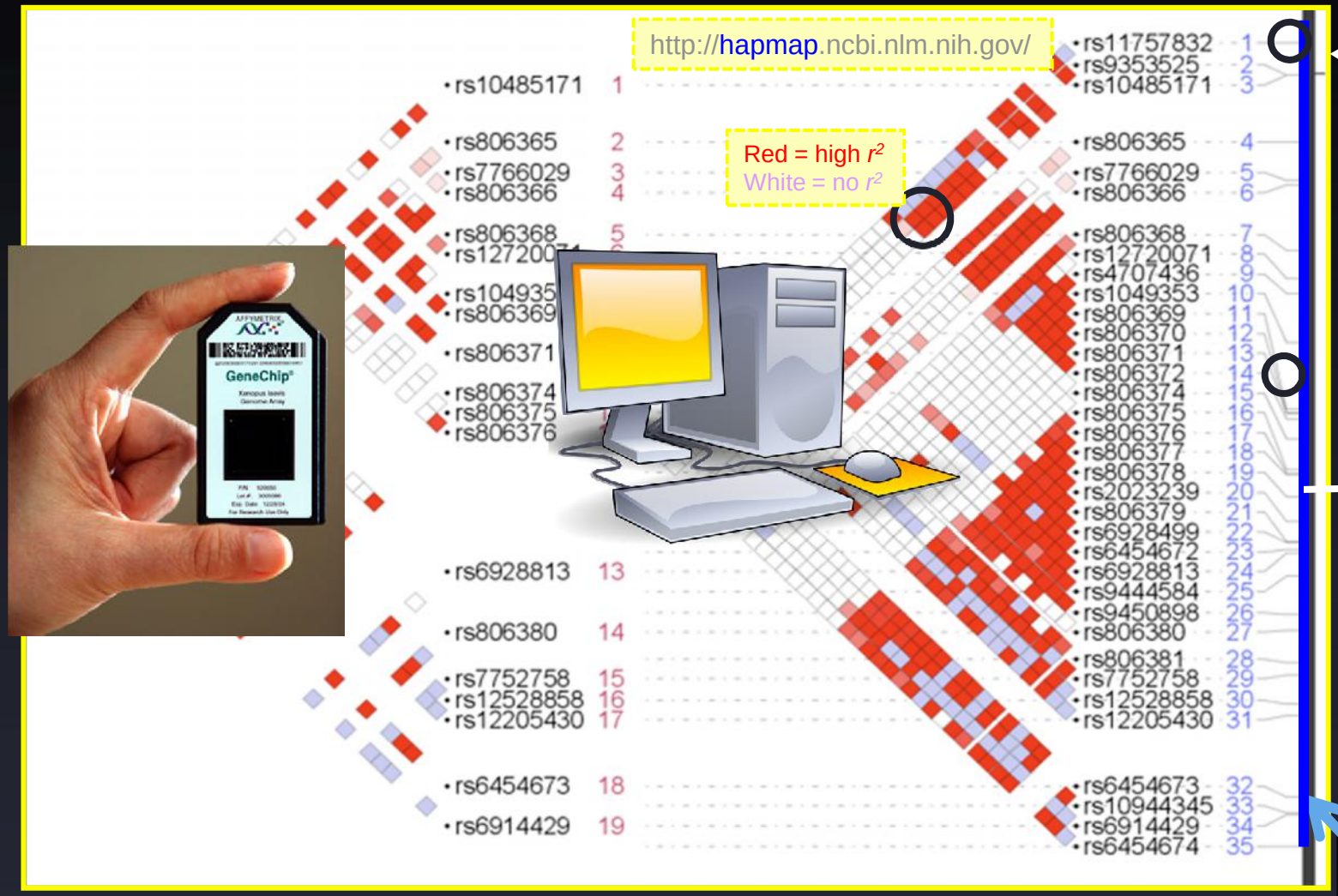
N~30,000

GWAS – from Peas to Human Complex Trait Genetics



N~30,000

Array SNPs, Linkage Disequilibrum, Imputation



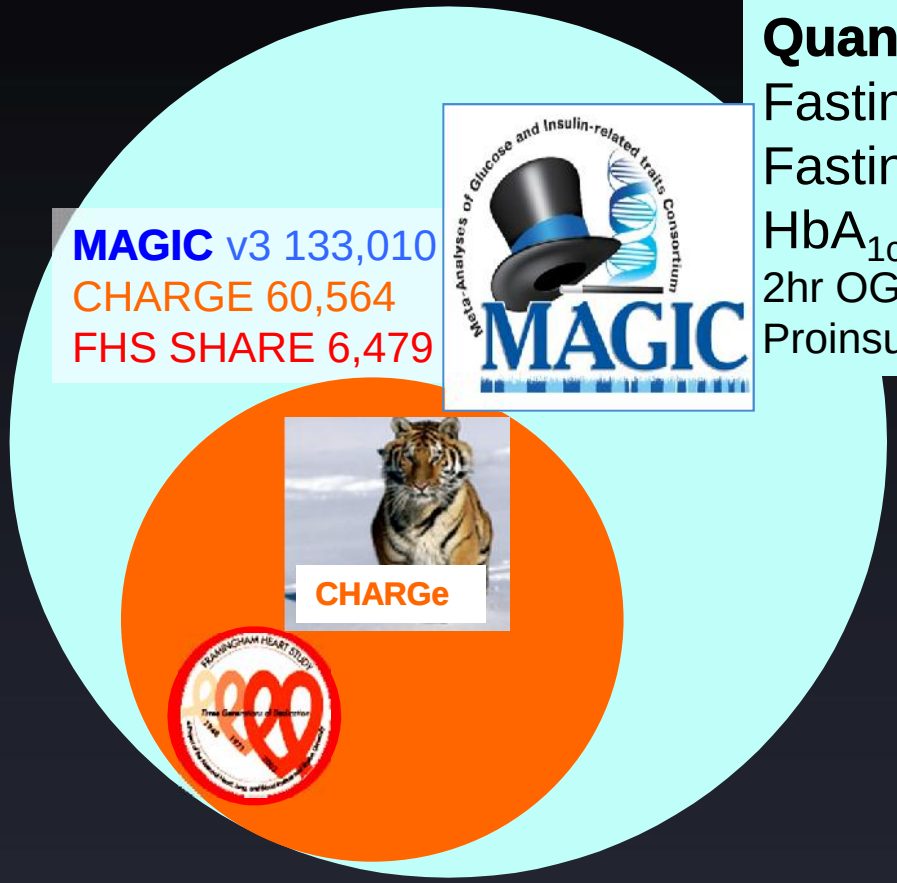
Imputation for MAF> 0.05% → 500K to 15M SNPs

Fruitful Collaboration in T2D-QT Genetics Consortia

Framingham Heart Study

N ~ 6,500, longitudinal

Fruitful Collaboration in T2D-QT Genetics Consortia



Quantitative Traits

Fasting Glucose

Fasting Insulin

HbA_{1c}

2hr OGTT glucose

Proinsulin

Fruitful Collaboration in T2D-QT Genetics Consortia

Quantitative Traits
Fasting Glucose
Fasting Insulin
HbA_{1c}
2hr OGTT glucose
Proinsulin

MAGIC v3 133,010
CHARGE 60,564
FHS SHARE 6,479

Type 2 Diabetes
Case/Control

DIAGRAM

DIAGRAM v5
47,979 T2D cases
187,595 non-T2D controls

Fruitful Collaboration in T2D-QT Genetics Consortia

- Large numbers
- Physiology data
- Populations, over time
- Lab functional experiments

Quantitative Traits
Fasting Glucose
Fasting Insulin
HbA_{1c}
2hr OGTT glucose
Proinsulin

MAGIC v3 133,010
CHARGE 60,564
FHS SHARE 6,479

Type 2 Diabetes
Case/Control

DIAGRAM

DIAGRAM v5
47,979 T2D cases
187,595 controls

oT2D

T2D-GENES Consortium
39,339 T2D and controls
Five ancestry groups
Exome data

ACCELERATING MEDICINES PARTNERSHIP (AMP)
TYPE 2 DIABETES KNOWLEDGE PORTAL

AAGILE
30,305 African American non-diabetes with Glycemic QTs

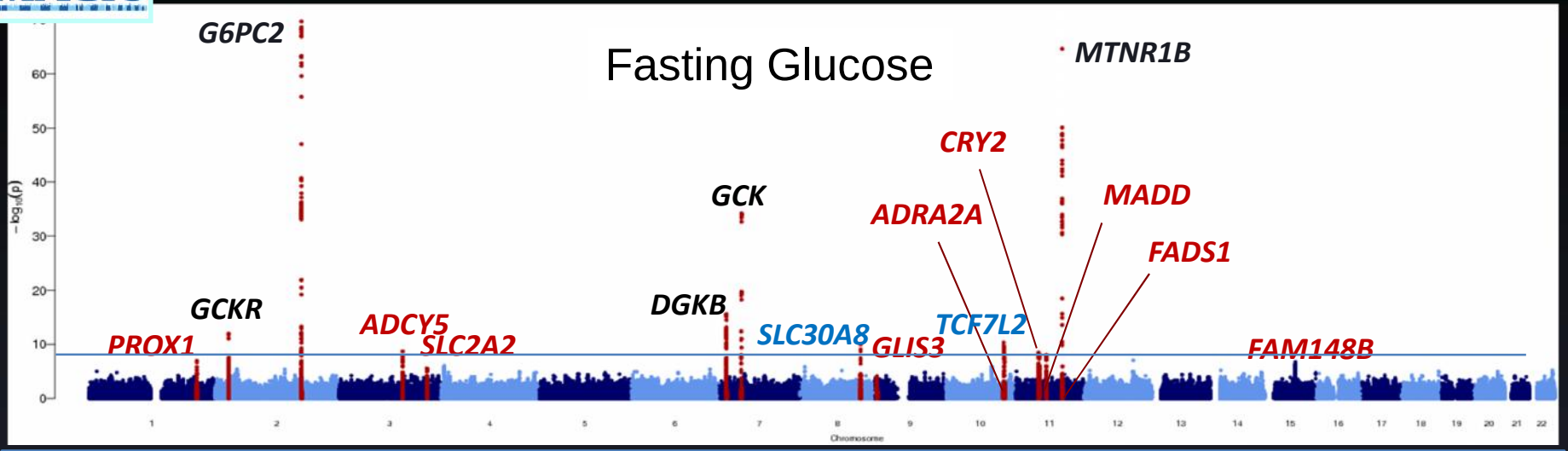
MEDIA
8,284 AA T2D cases and 15,543 controls

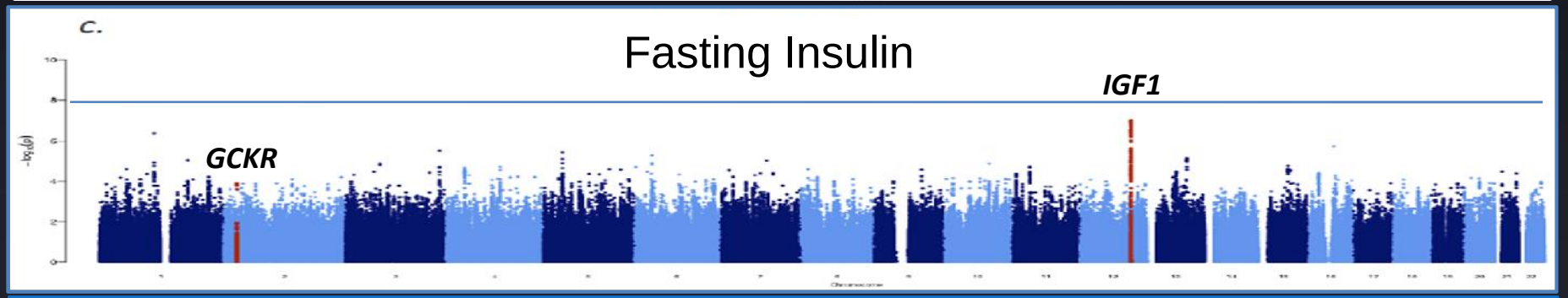
African American T2D and QTs

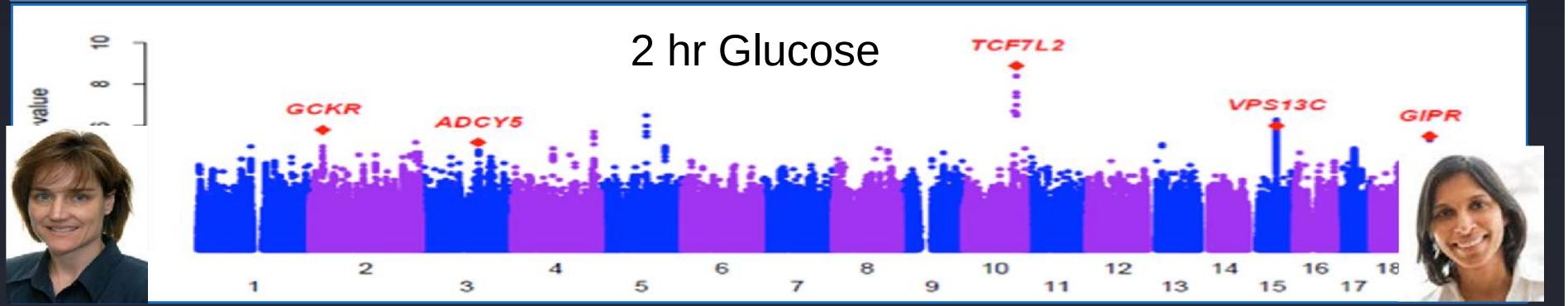
http://www.type2diabetesgenetics.org

MAGIC 2010: 55 Cohorts with 122,744 non-diabetic EA

14 Genetic Loci Associated with FG, 2 w FI, 5 w 2hrG





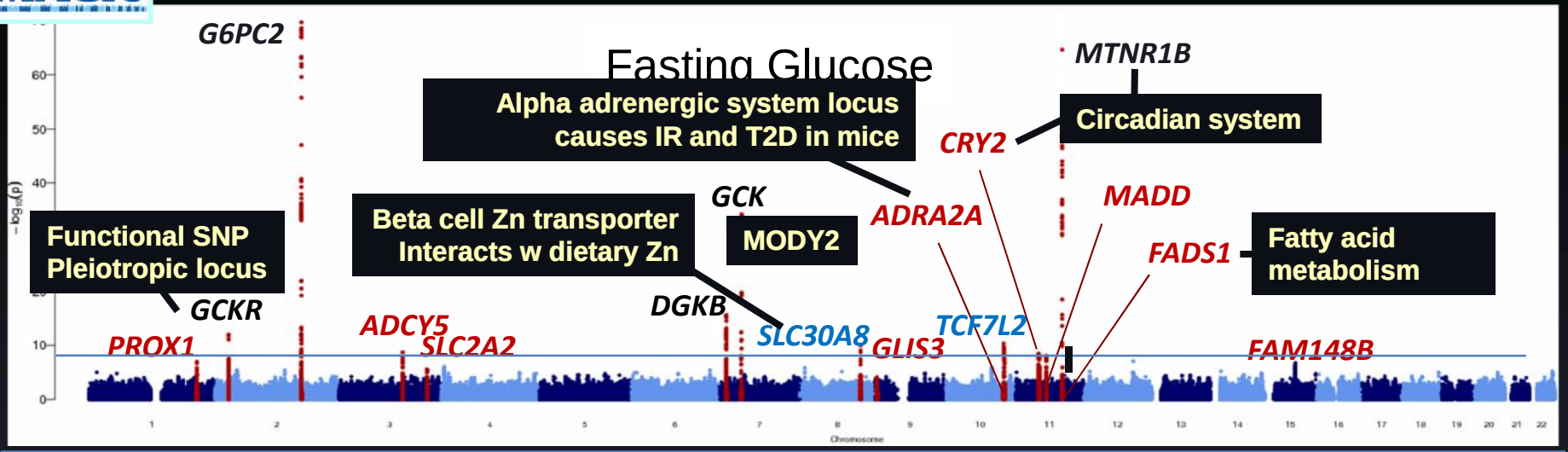


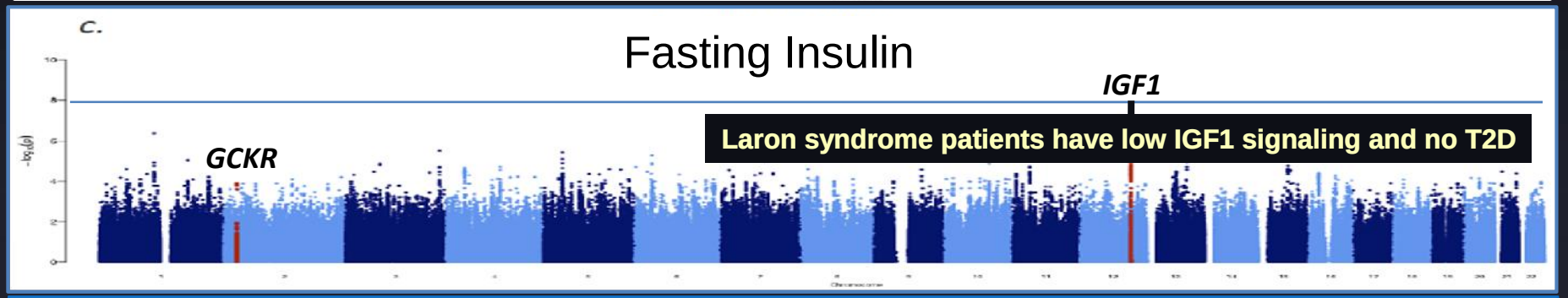
Dupuis et al. Nat Genet. 2010;42:105-16

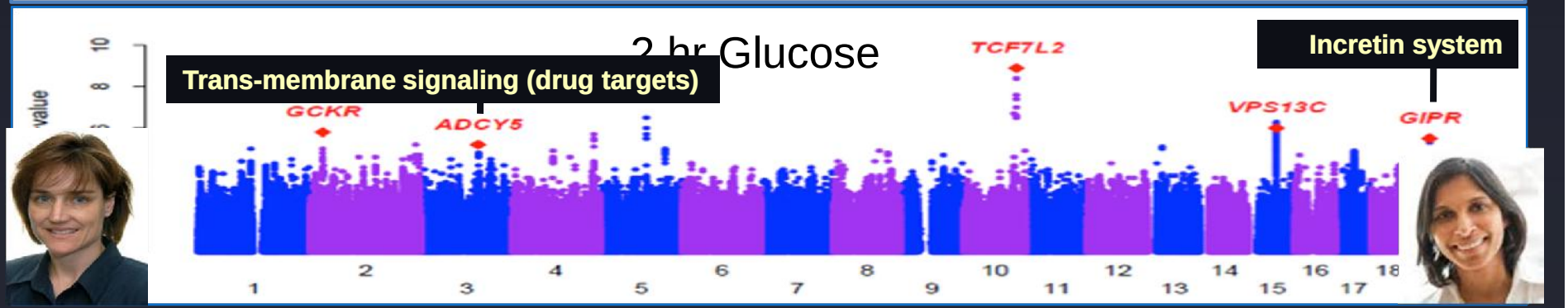
Saxena et al Nat Genet. 2010;42:142-8

MAGIC GWAS of T2D-Related Quantitative Traits

Abundant New Biology, New Hypotheses



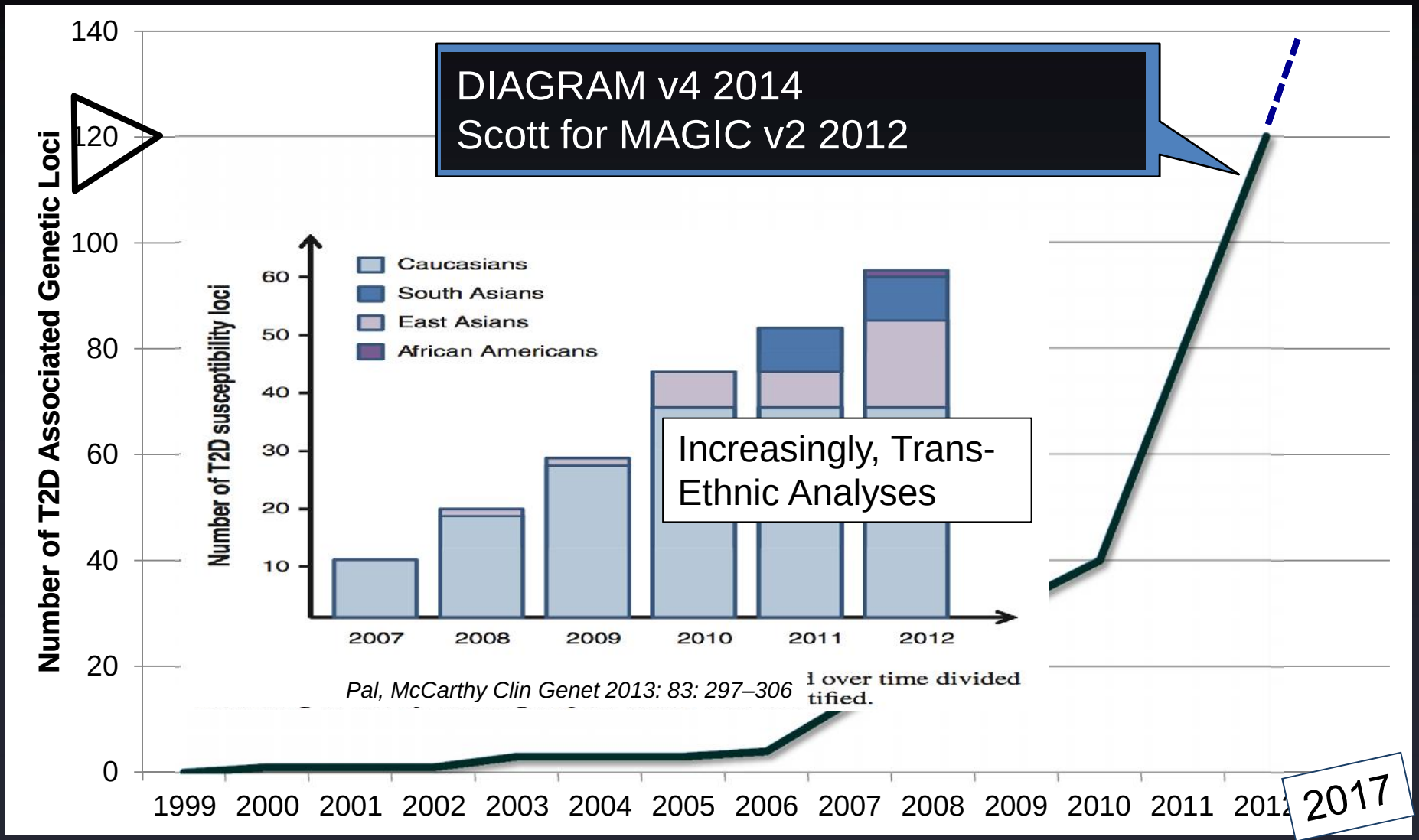




Dupuis et al. Nat Genet. 2010;42:105-16

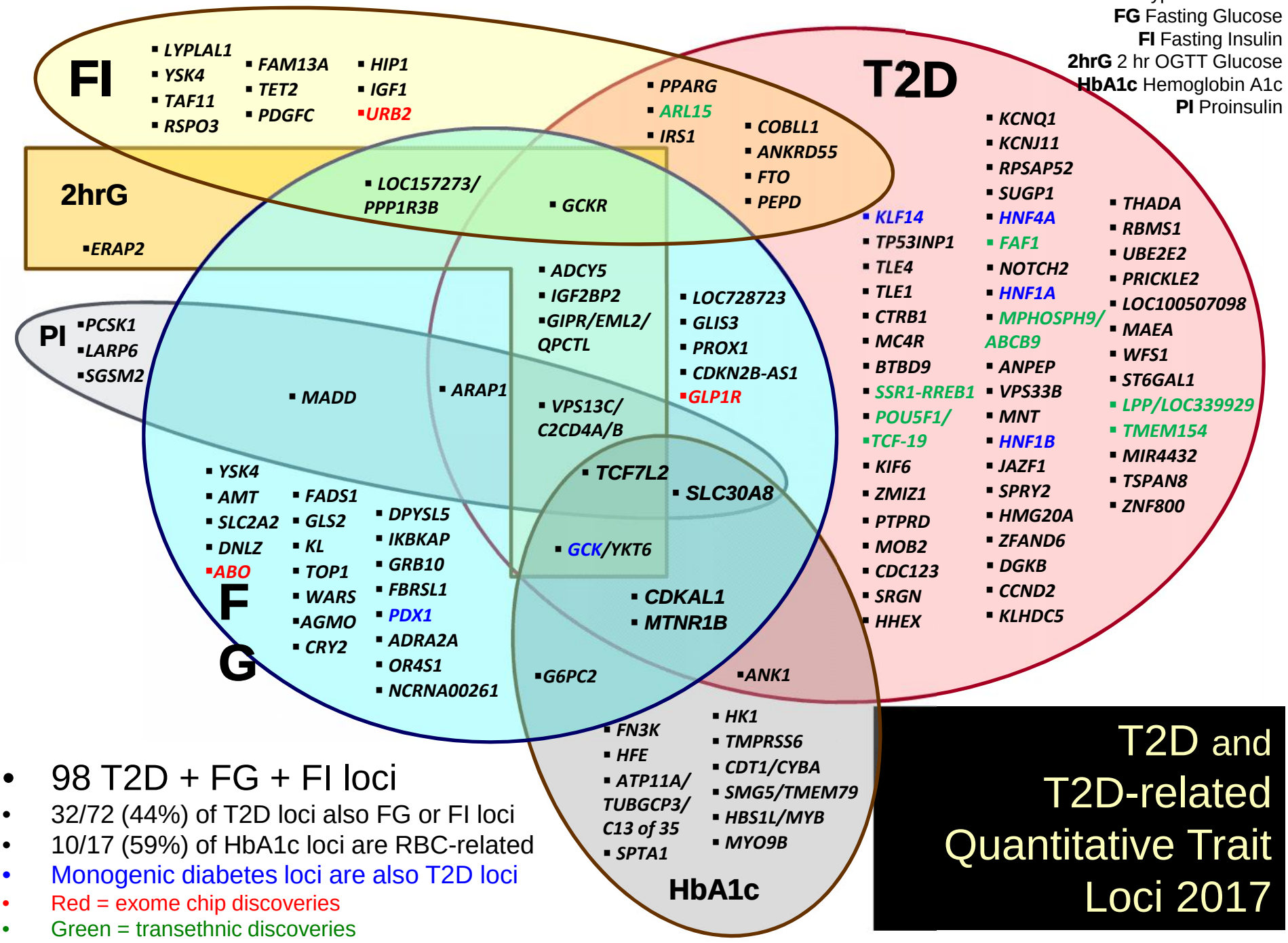
Saxena et al Nat Genet. 2010;42:142-8

>120 SNPs at >110 T2D/QT-Associated Loci
T2D-QT Genetics @ June, 2017



Morris et al Nat Genet. 2012 PMID: 22885922; Scott et al Nat Genet. 2012 PMID: 22885924

T2D Type 2 Diabetes
FG Fasting Glucose
FI Fasting Insulin
2hrG 2 hr OGTT Glucose
HbA1c Hemoglobin A1c
PI Proinsulin



T2D and T2D-related Quantitative Trait Loci 2017

- 98 T2D + FG + FI loci
- 32/72 (44%) of T2D loci also FG or FI loci
- 10/17 (59%) of HbA1c loci are RBC-related
- Monogenic diabetes loci are also T2D loci
- Red = exome chip discoveries
- Green = transethnic discoveries

ARTICLE

T2D is a common variant polygenic disorder

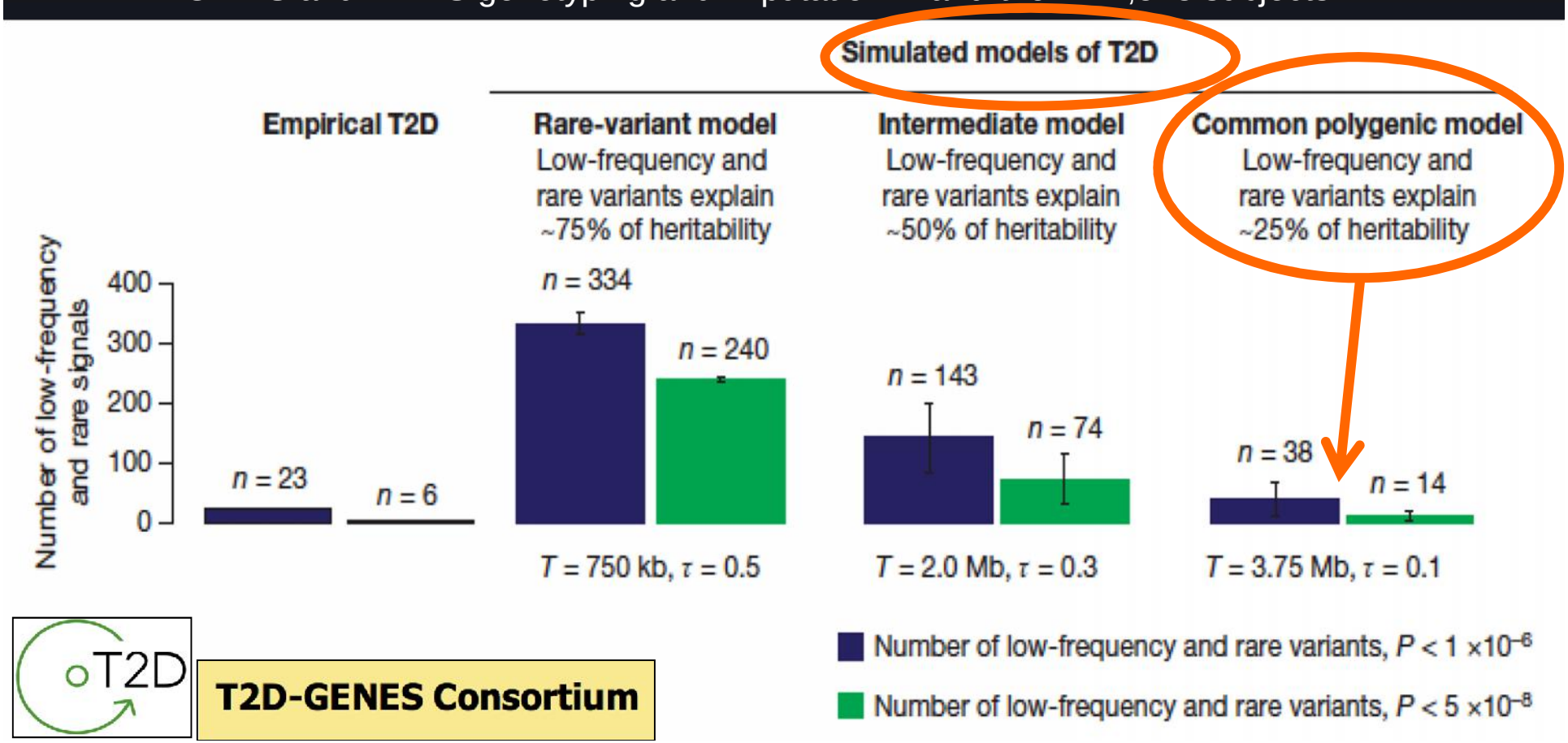
Nature 2016 PMID: 27398621

The genetic architecture of type 2 diabetes

A list of authors and affiliations appears in the online version of the paper

GoT2D and T2D-GENES

- Whole-genome sequencing in 2,657 European individuals with and without diabetes
- Exome sequencing in 12,940 individuals from five ancestry groups
- GWAS and EWAS genotyping and imputation in a further 111,548 subjects



T2D

T2D-GENES Consortium

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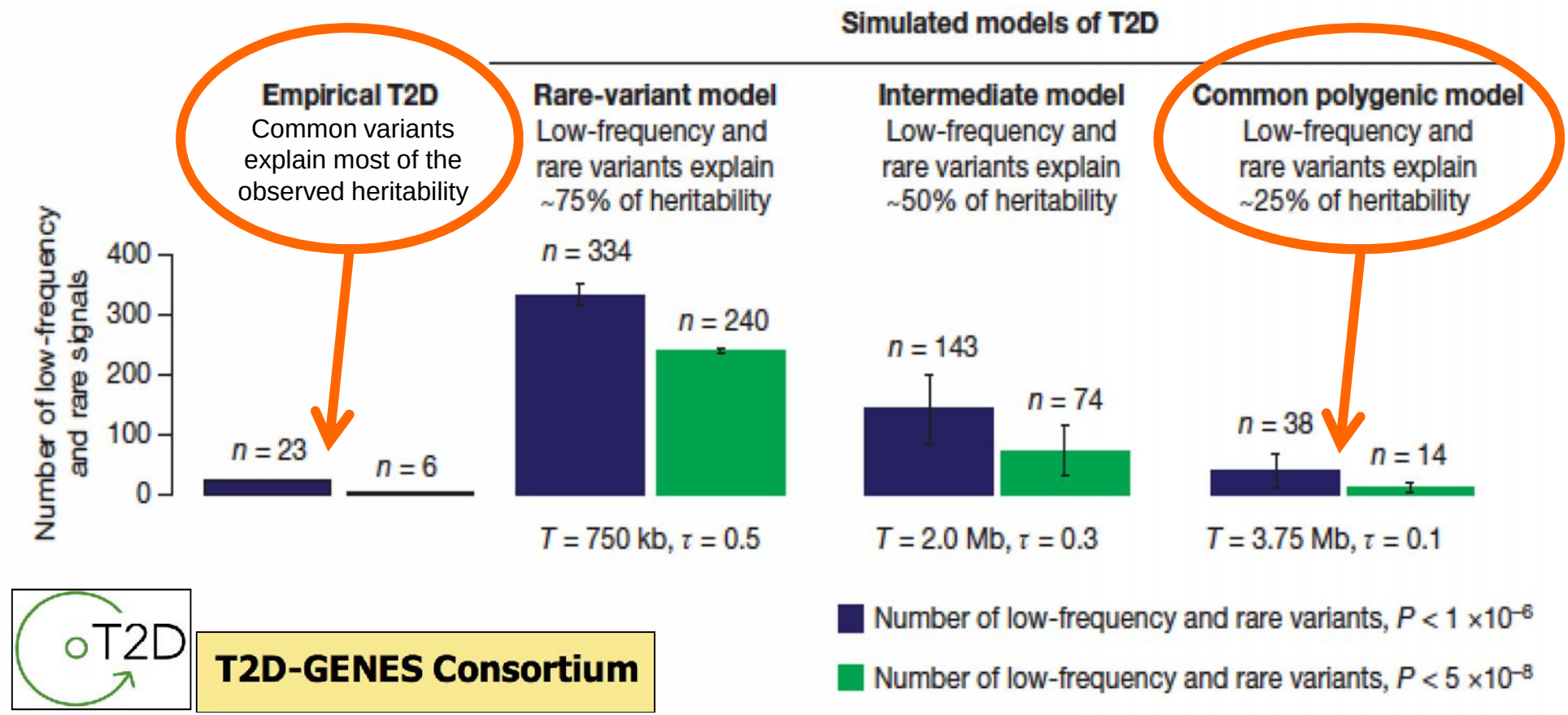
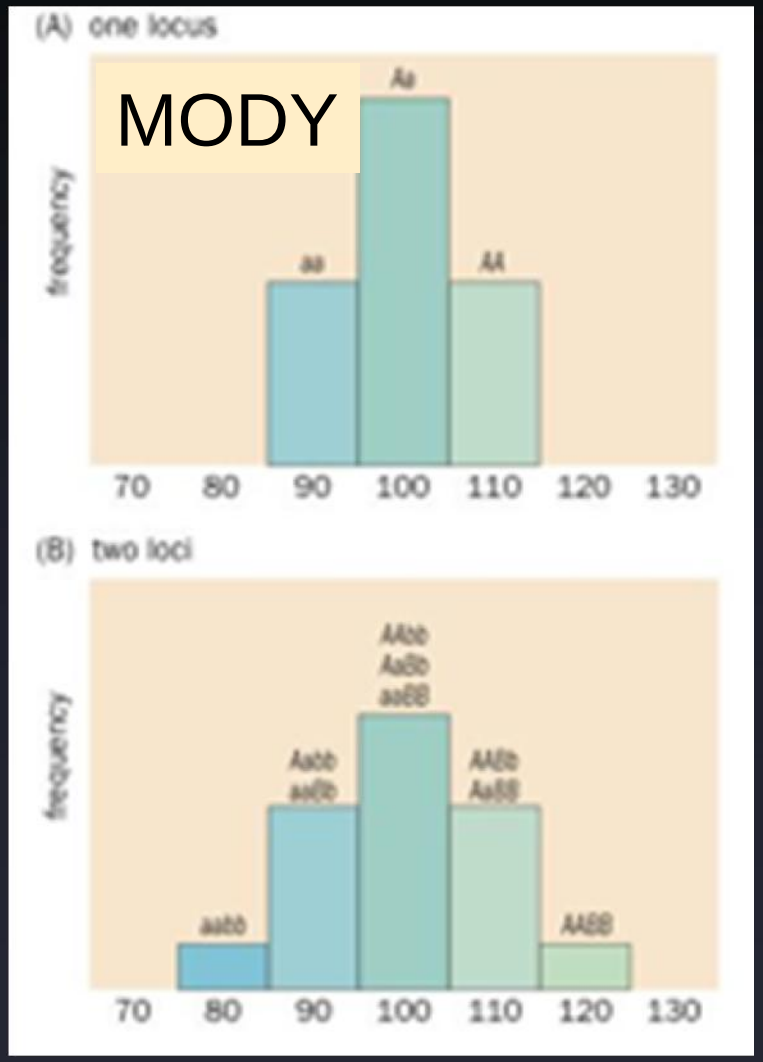
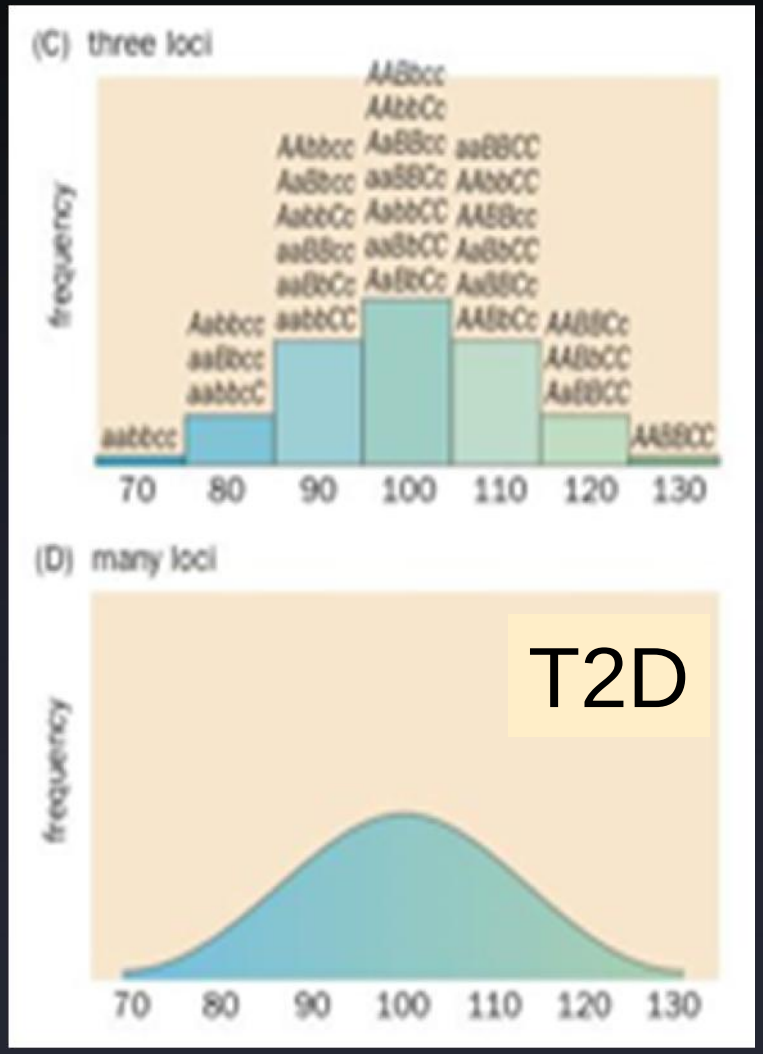


T2D

T2D-GENES Consortium

MODY: Monogenic Disorders Have ~2 Risk States
T2D Polygenic Risk ~ a Bell Shaped Distribution





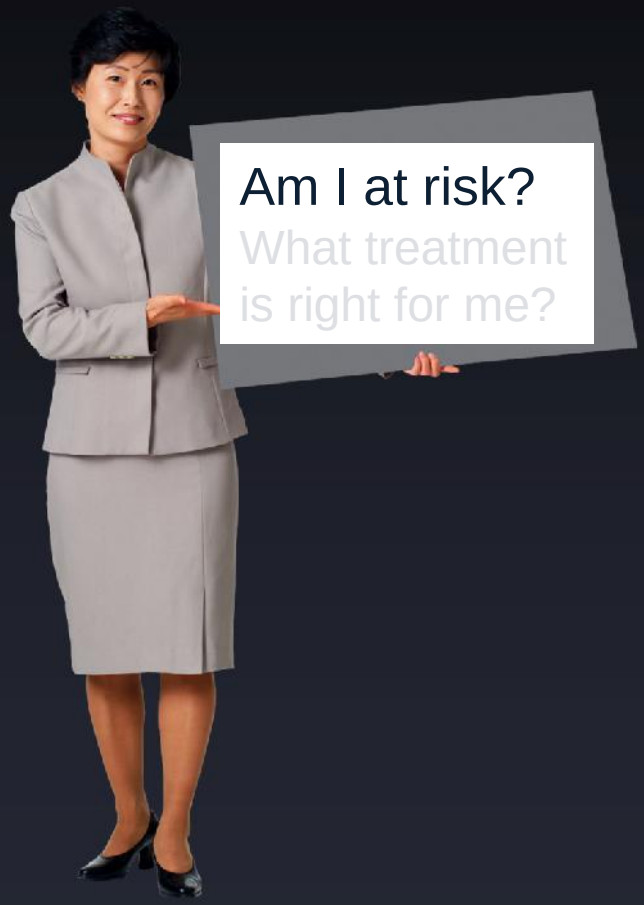
Human Molecular Genetics, 4th ed. 2011

Clinical Application of T2D Genetics

Personal and Population Health

Which people are at risk?
Are all treatments right for everyone?

Clinical Application of T2D Genetics
Personal and Population Health

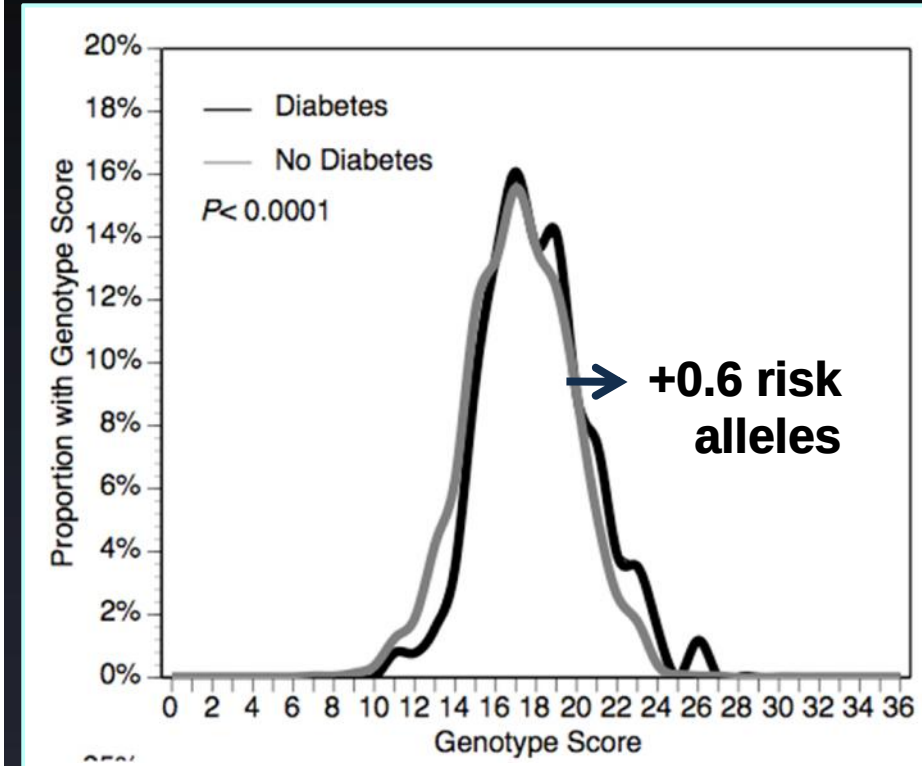


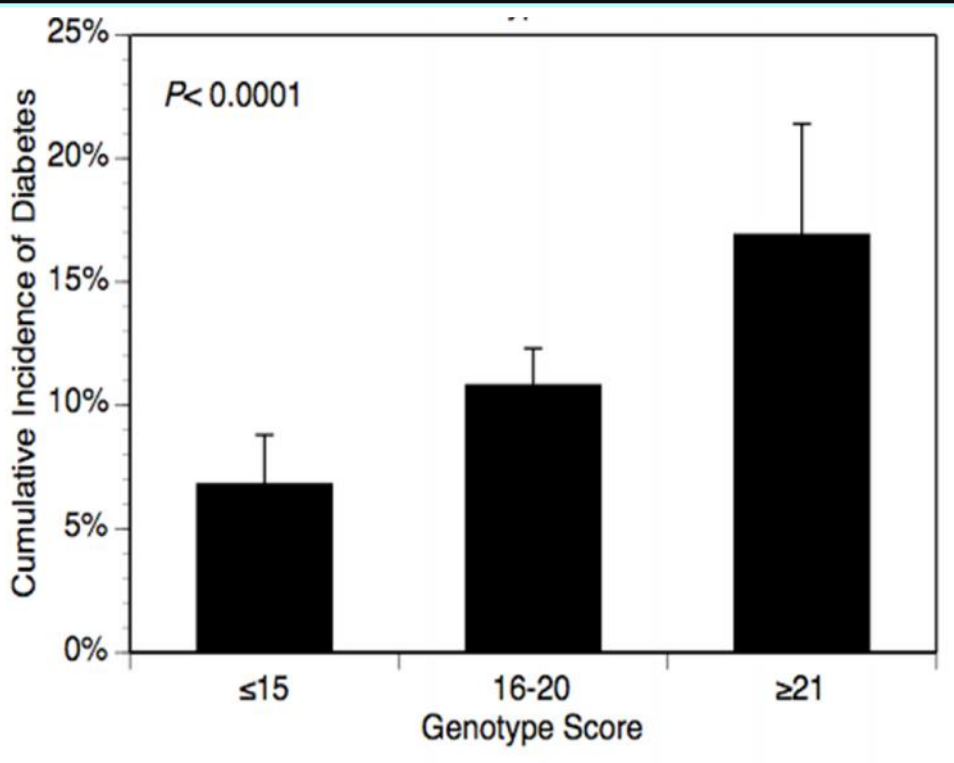
Which people are at risk?

Are all treatments right for everyone?

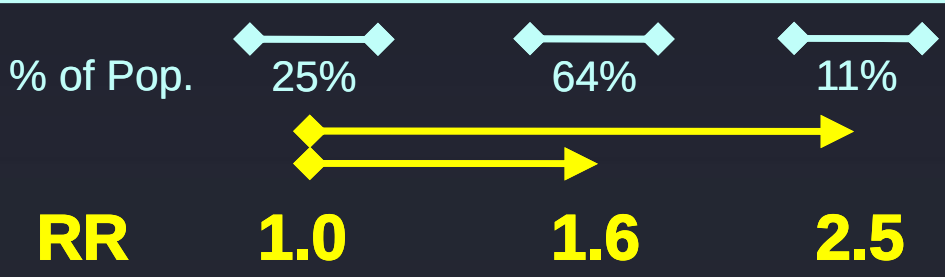
18 SNP Genotype Score Predicts New Cases of T2D

0 risk allele = 0, 1 risk allele = 1, 2 risk alleles =2; range 0-36





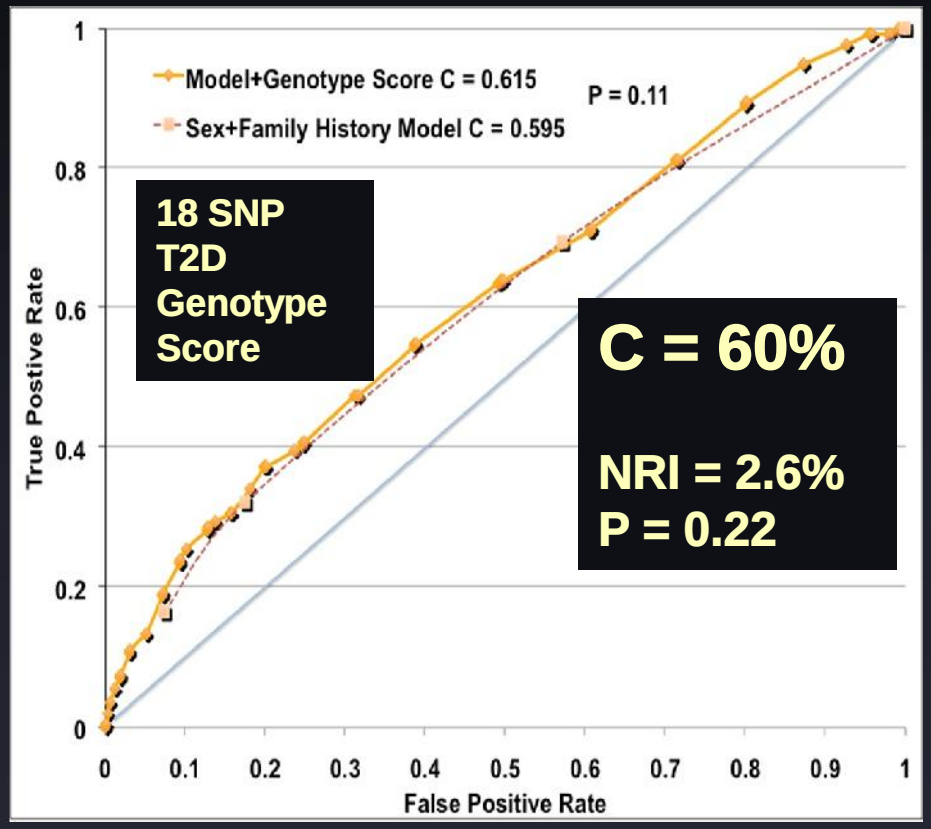
Mean genotype score:
Diabetes: 17.7
No diabetes: 17.1
(P<0.0001)



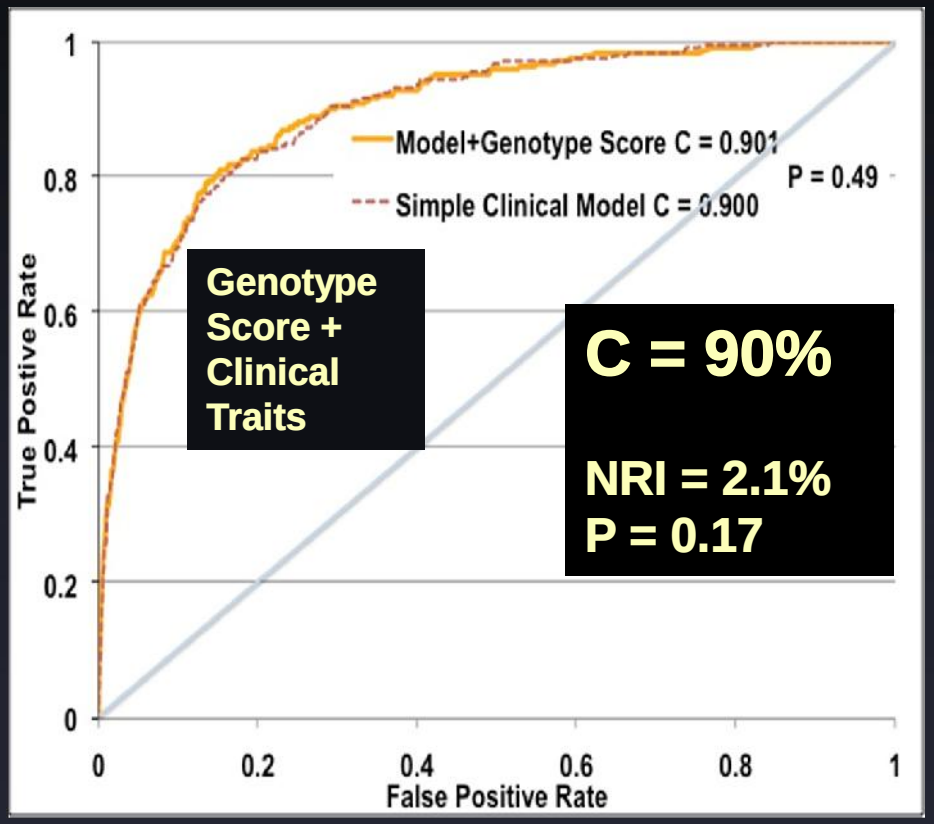
Meigs et al N Engl J Med 2008;359:2208-19

T2D Genotype Scores Predict Incident T2D in Adults … so do Clincal Risk Factors

T2D Genetics Alone



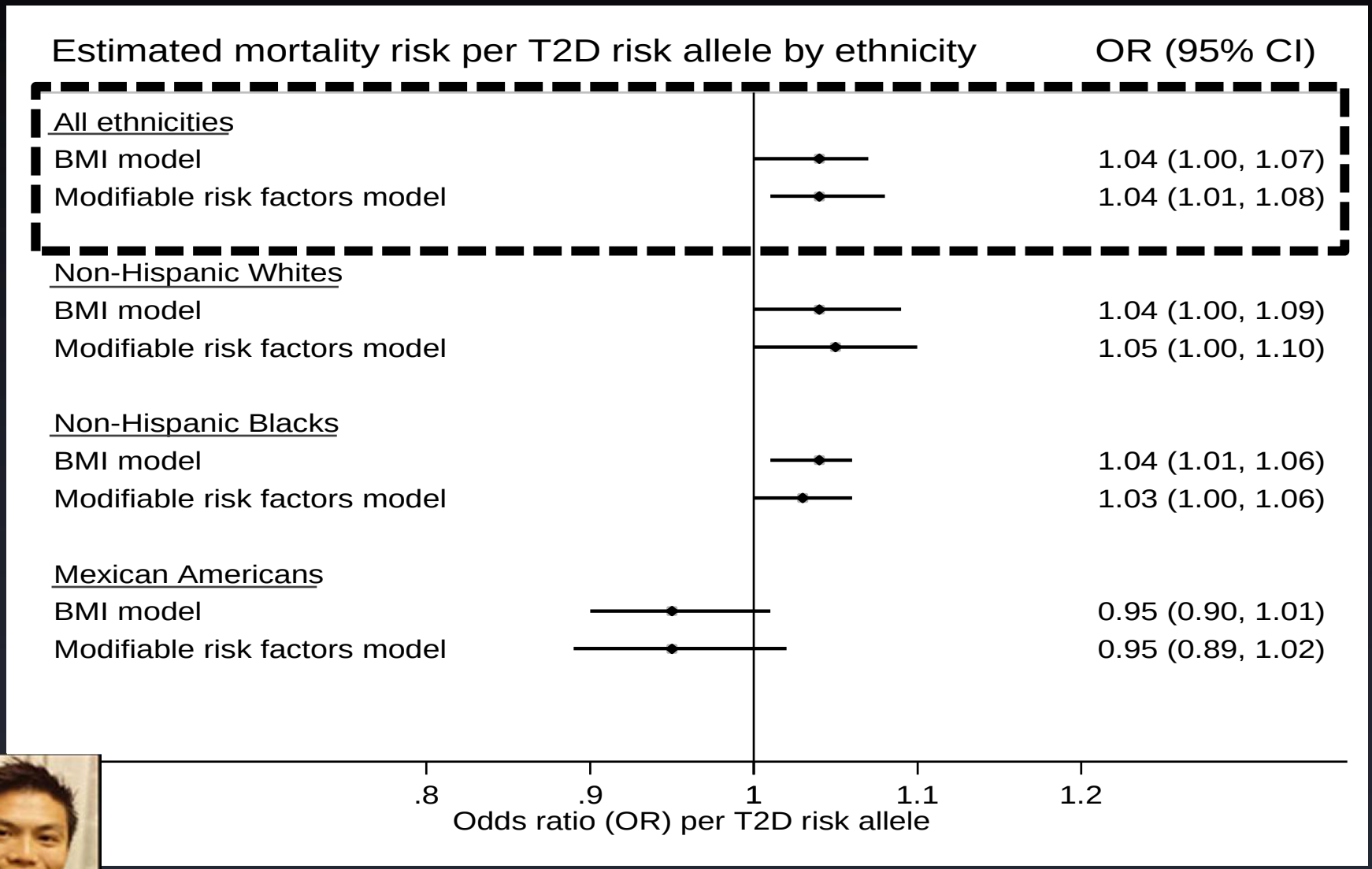
T2D Genetics + Clinical Risk Factors

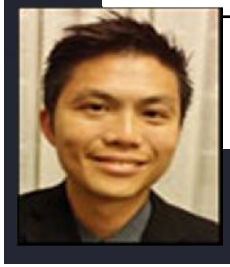


Meigs et al N Engl J Med 2008;359:2208-19

T2D Genetic Risk Increases All-Cause Mortality

1,556 of 6,501 NHANES Mortality Follow-Up participants died over 17 years





Leong et al Diabetes Care 2016 PMID: 26884474

Patients Say that Genetic Testing Would Increase Motivation to Change Lifestyle

152 MGH 1° Care Patients

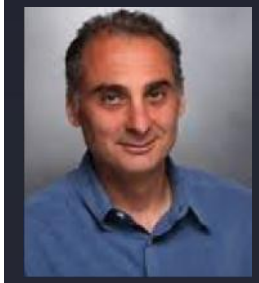
Imagine that your PCP tells you that there is an approved genetic test to help predict whether you have a 'high' or 'low' chance of getting diabetes. It is a simple blood test at no cost to you.

> If the test result indicated that you had a 'high' chance of developing diabetes, how would this result change your motivation to make recommended lifestyle changes?

More motivated 99%

> If the test result indicated that you had a 'low' chance of developing diabetes, how would this result change your motivation to make recommended lifestyle changes?

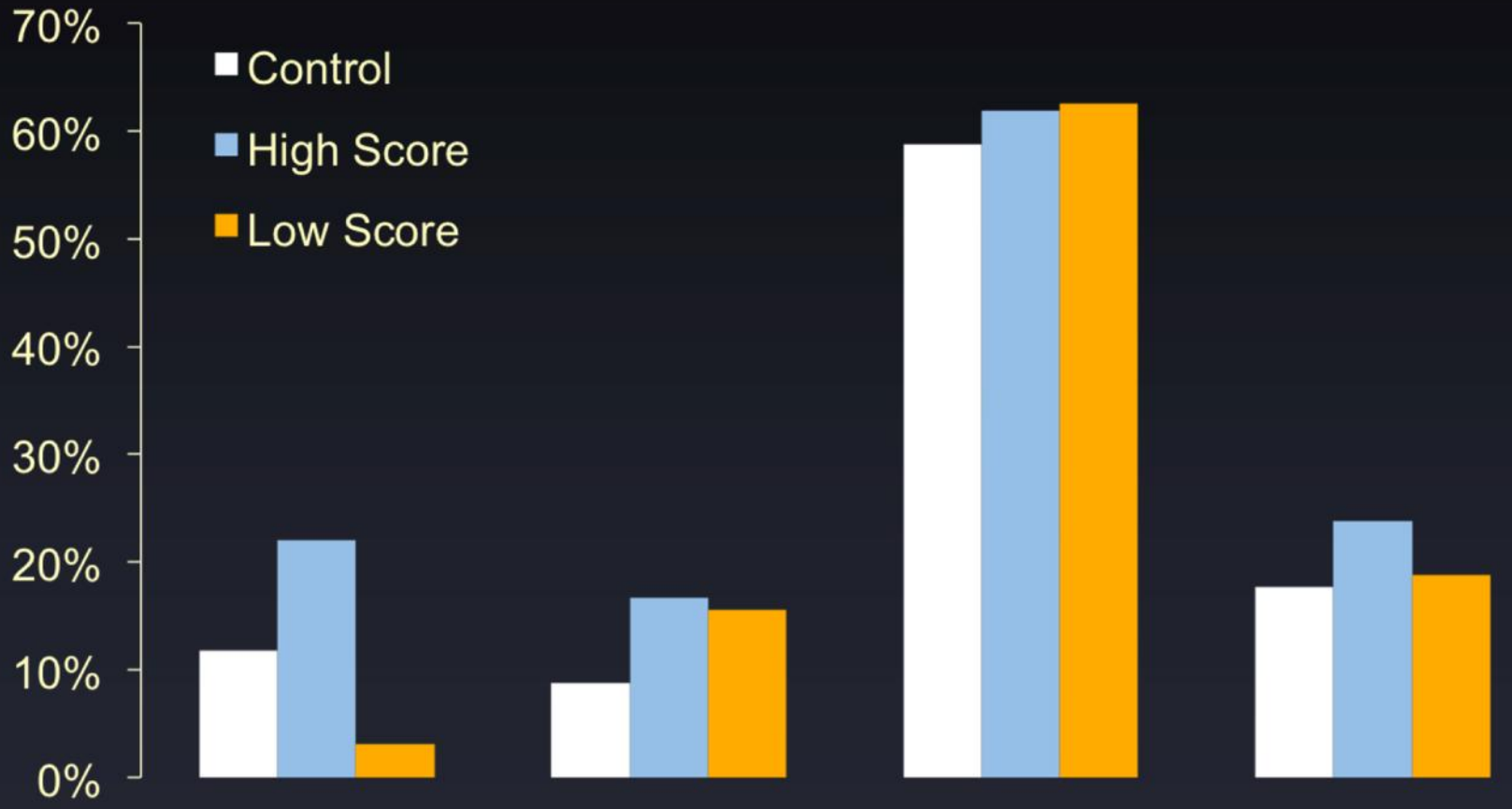
Less motivated or No Change 59%



Grant et al Diabetologia. 2009;52:2299-305

(No) Effects of Genetic Counseling for Lifestyle Change in 116 People with MetS Randomized to Genetic Testing or No Testing

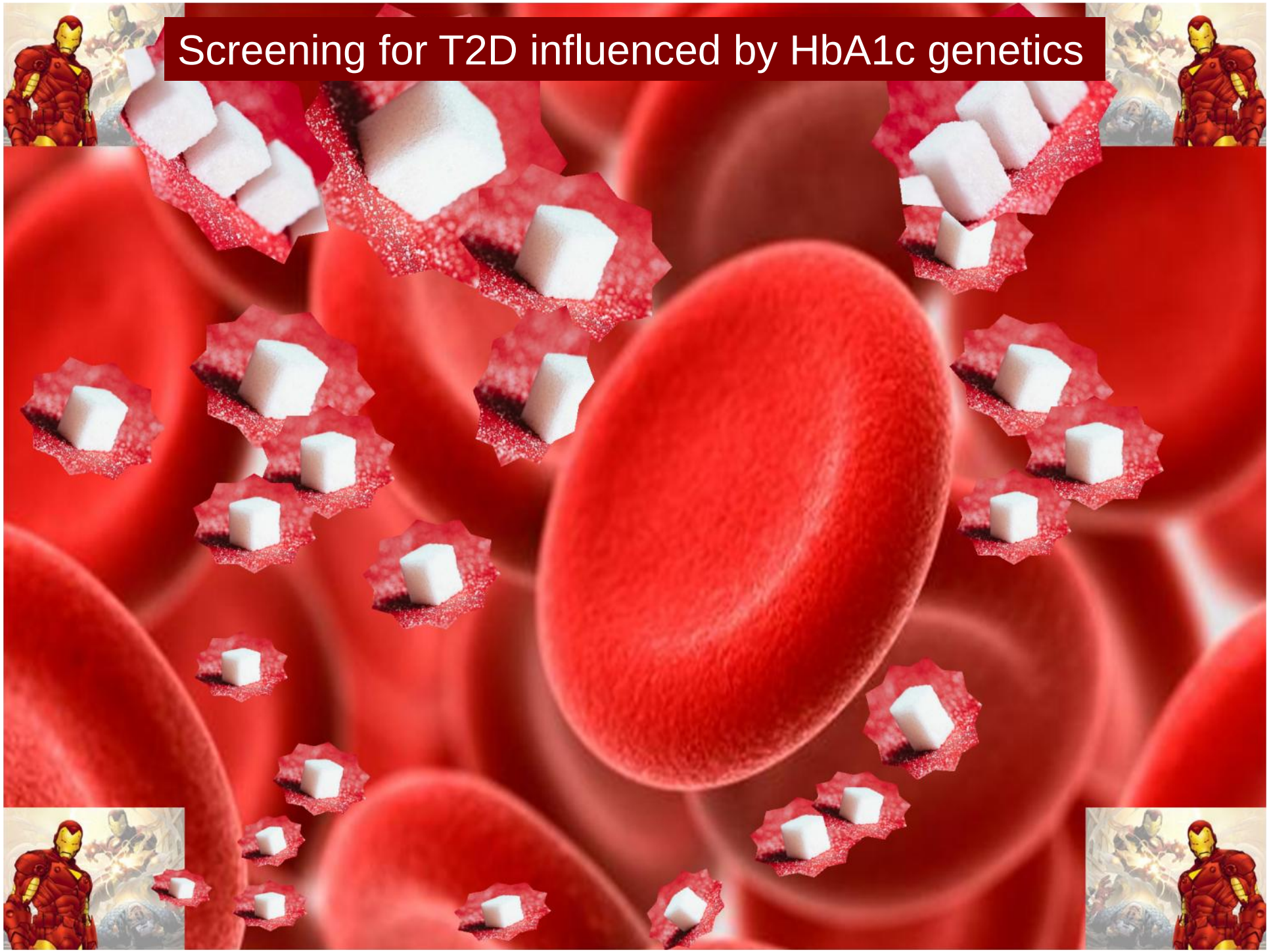
N = 44 High Risk, 34 Low Risk, 38 Control



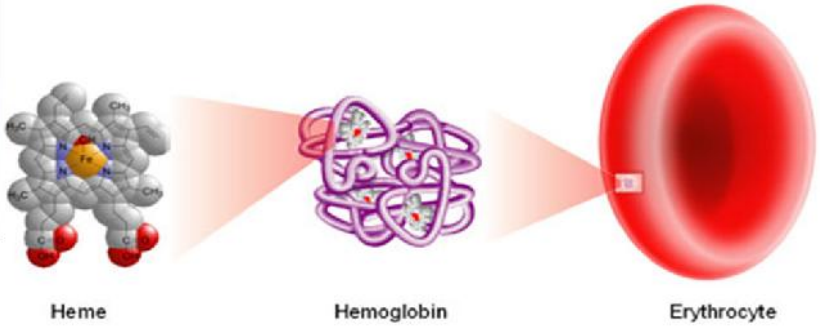
GCLC
Genetic Counseling and Lifestyle Change for Diabetes Prevention

Grant et al Diabetes Care. 2013 PMID: 22933432

Screening for T2D influenced by HbA1c genetics



Hemoglobin A_{1c}

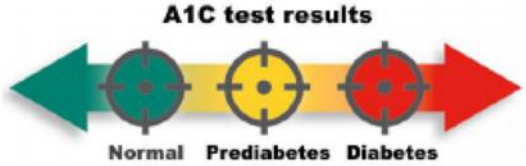


A1C & T2D DIAGNOSIS

WHAT?

HbA1c (A1C) test

- Measures the proportion of glycated hemoglobin in the blood *(irreversible chemical modification by blood glucose)*



Reflects average glycemia over the life of RBC (2-3 months)

WHY?

A1C testing in diagnosing Type 2 diabetes

- Only test for T2D that is not directly a measurement of blood glucose
- Non-glycemic factors are known to influence the diagnostic accuracy for T2D
- Some of these non-glycemic factors may be genetically determined

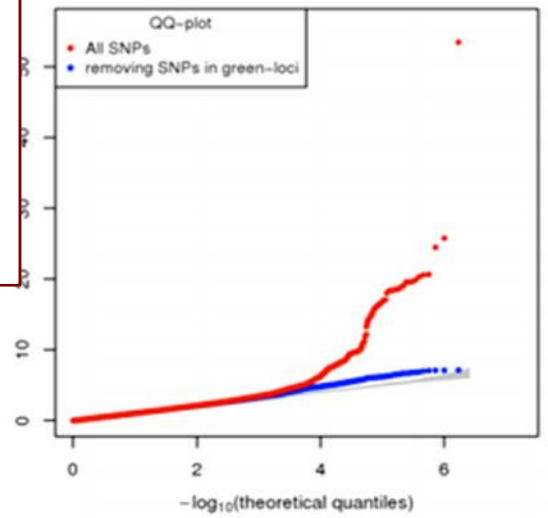
Thanks to Chloe Sarnowski

ORIGINAL ARTICLE

Common Variants at 10 Genomic Loci Influence Hemoglobin A_{1C} Levels via Glycemic and Nonglycemic Pathways

Nicole Soranzo,[1,2] Serena Sanna,[3] Eleanor Wheeler,[1] Christian Gieger,[4] Dörte Radke,[5] Josée Dupuis,[6,7] Nabila Bouatia-Naji,[8] Claudia Langenberg,[9] Inga Prokopenko,[10,11] Elliot Stolerman,[12,13,14] Manjinder S. Sandhu,[9,15,16] Matthew M. Heeney,[17] Joseph M. Devaney,[18]

>46,000 individuals, 31 cohorts
10 Loci P<5x10-8, 6 Novel

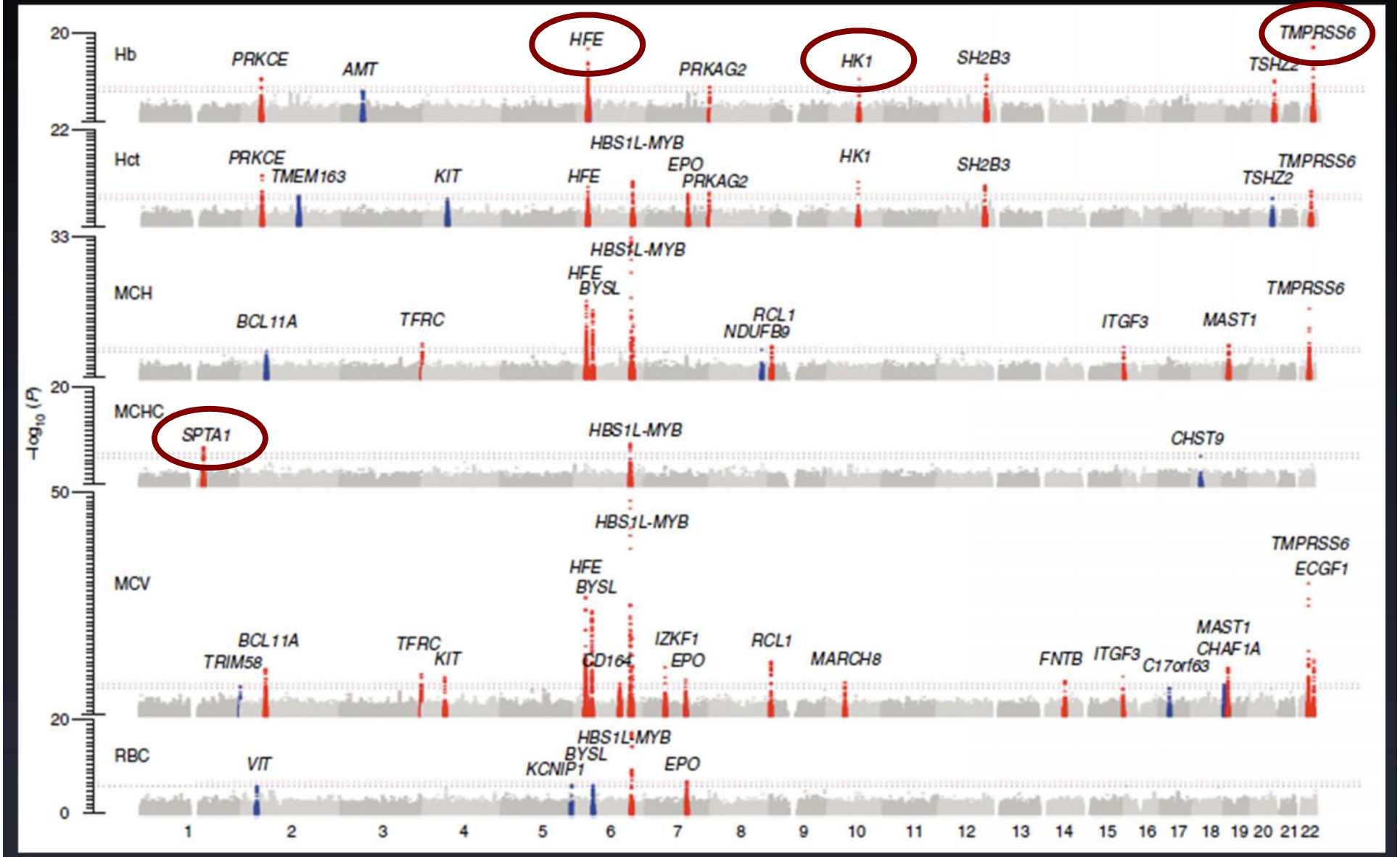


MAGIC

Soranzo et al, Diabetes 2010. PMID: 20858683

CHARGE GWAS of Hematology Traits

Shares Loci with HbA1c Loci



Ganesh et al Nat Genet. 2009;41:1191-8

>2/3 of 10 HbA1c-associated SNPs are in Non-Glycemic Biologic Pathways

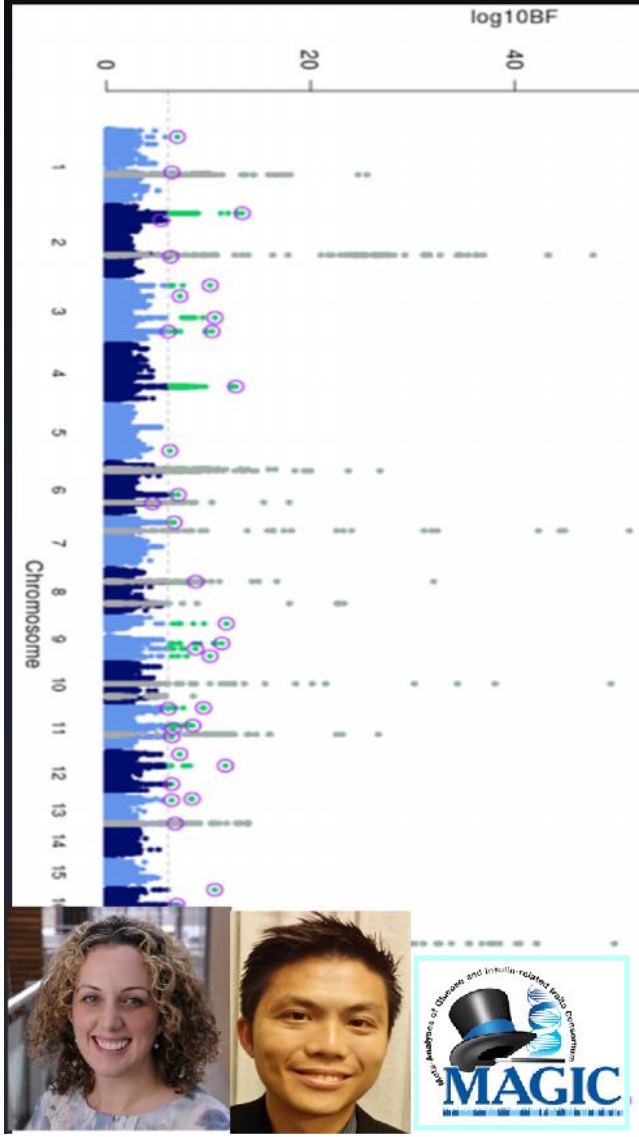
Locus	Name	Chr	Pathway	Heme GWAS
G6PC2	glucose-6-phosphatase, catalytic, 2	2	Glycemic	
GCK	glucokinase	7	Glycemic, T2D	
MTNR1B	melatonin receptor 1B	11	Glycemic, T2D	
FN3K	fructosamine 3-kinase	17	Deglycation	
HFE	hemochromatosis	6	Iron	MCV, Hb
TMPRSS6	transmembrane protease, serine 6	22	Iron	MCV, MCHC
HK1	erythrocyte hexokinase 1	10	Eythrocyte	MCV, Hb
SPTA1	spectrin, alpha, erythrocytic 1	1	Eythrocyte	MCV, Hb
ANK1	ankyrin 1, erythrocytic	8	Eythrocyte	
ATP11A	ATPase type 11A	13	Erythrocyte	

Soranzo et al, Diabetes 2010. PMID: 20858683

New GWAS of Hemoglobin A_{1c}

185,000 People without Diabetes from >50 cohorts and 7 ancestral groups

60 Loci, 43 new, 65 independent SNPs



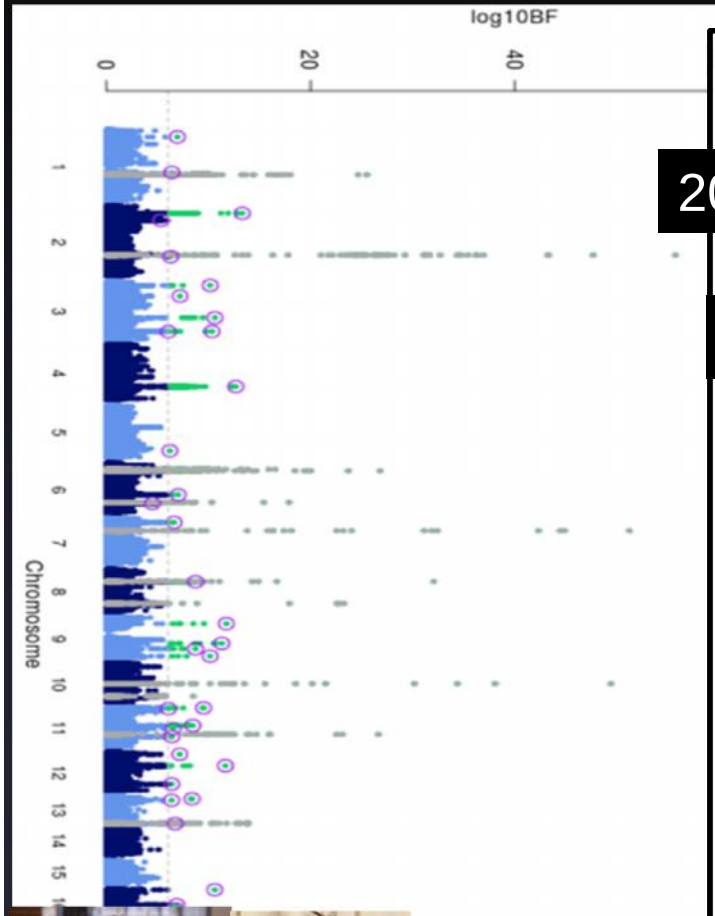
Markername	Chr.	Position (bp)	Effect Allele	Other Allele	Gene	Status	Signals	Classification	METAL p-value	MANTRA log10BF
rs2375278	1	25401625	A	G	SYF2	Novel	Single	Unclassified	2.03E-07	6.93
rs267738	1	149207249	T	G	CERS2	Novel	Single	Unclassified	2.59E-09	6.41
rs12132919	1	154584765	A	C	TMEM79	Known	Single	**Erythrocytic**	0.0169	10.08
rs857691	1	156893002	T	C	SPTA1	Known	Single	**Erythrocytic**	3.97E-25	25.52
rs17509001	2	23874735	C	T	ATAD2B	Novel	Single	Unclassified	1.94E-15	13.30
rs12621844	2	48268239	T	C	FOXN2	Novel	Single	Unclassified	1.87E-08	5.32
rs13387347	2	169463092	T	C	G6PC2	Known	Multiple	**Glycemic**	0.308	5.77
rs560887	2	169471394	C	T	G6PC2	Known	Multiple	**Glycemic**	1.48E-58	55.77
rs17256082	2	175000610	C	T	SCRN3	Novel	Single	Unclassified	0.00112	6.27
rs7616006	3	12242648	A	G	SYN2	Novel	Single	**Erythrocytic**	5.07E-10	10.16
rs9818758	3	49357929	A	G	USP4	Novel	Single	Unclassified	7.74E-10	7.20
rs11708067	3	124548468	A	G	ADCY5	Novel	Single	**Glycemic**	1.42E-12	10.62
rs8192675	3	172207577	T	C	SLC2A2	Novel	Single	**Glycemic**	1.38E-11	10.33
rs4894799	3	173278234	A	G	FNDC3B	Novel	Single	Unclassified	1.80E-06	6.05
rs13134327	4	144879245	A	G	FREM3	Novel	Single	**Glycemic**	2.64E-15	12.66
rs11954649	5	156988069	G	C	SOX30	Novel	Single	Unclassified	NA	6.20
rs7756992	6	20787688	G	A	CDKAL1	Known	Single	**Glycemic**	2.80E-12	16.53
rs1800562	6	26201120	G	A	HFE	Known	Multiple	**Erythrocytic**	4.67E-28	26.81
rs198846	6	26215442	G	A	HFE	Known	Multiple	**Erythrocytic**	1.18E-23	23.72
rs11964178	6	109668728	A	G	C6orf183	Novel	Single	**Erythrocytic**	6.38E-10	7.03
rs11154792	6	135473333	T	C	MYB	Known	Single	**Erythrocytic**	7.45E-18	17.89
rs592423	6	139882386	A	C	CITED2	Novel	Single	**Erythrocytic**	3.96E-08	4.50
rs2191349	7	15030834	T	G	DGKB	Novel	Single	**Glycemic**	2.09E-07	6.63
rs4607517	7	44202193	A	G	GCK	Known	Multiple	**Glycemic**	8.76E-38	51.28
rs3824065	7	44213783	C	T	GCK	Known	Multiple	**Glycemic**	4.22E-35	31.87
rs6474359	8	41668351	T	C	ANK1	Known	Multiple	Unclassified	1.50E-16	14.88
rs4737009	8	41749562	A	G	ANK1	Known	Multiple	**Erythrocytic**	4.48E-27	32.08
rs6980507	8	42502241	A	G	SLC20A2	Novel	Single	Unclassified	3.58E-08	8.73
rs11558471	8	118254914	A	G	SLC30A8	Known	Single	**Glycemic**	1.38E-19	23.26
rs2383208	9	22122076	A	G	MTAP	Novel	Single	**Glycemic**	7.04E-12	11.74
rs7040409	9	90693056	C	G	C9orf47	Novel	Single	**Erythrocytic**	2.56E-14	11.29
rs1467311	9	109576753	G	A	KLF4	Novel	Single	Unclassified	2.09E-07	8.72
rs579459	9	135143989	C	T	ABO	Novel	Single	**Glycemic**	9.42E-09	10.14
rs4745982	10	70759849	T	G	HK1	Known	Multiple	**Erythrocytic**	2.87E-65	63.05
rs10823343	10	70761019	A	G	HK1	Known	Multiple	Unclassified	1.68E-55	49.45
rs17747324	10	114742493	C	T	TCF7L2	Known	Single	**Glycemic**	6.12E-11	8.49
rs3782123	11	195198	C	A	BET1L	Novel	Single	Unclassified	1.51E-10	9.51
rs2237896	11	2815016	G	A	KCNQ1	Novel	Single	**Glycemic**	0.00246	6.07
rs174577	11	61361390	C	A	FADS2	Novel	Single	**Glycemic**	5.45E-07	8.45
rs11603334	11	72110633	G	A	ARAP1	Novel	Single	**Glycemic**	6.85E-09	6.53
rs10830963	11	92348358	G	C	MTNR1B	Known	Single	**Glycemic**	2.23E-23	26.64
rs11224302	11	99961814	C	T	CNTN5	Novel	Single	**Erythrocytic**	4.76E-07	6.40
rs2110073	12	6946143	T	C	PHB2	Novel	Single	Unclassified	4.44E-08	7.18
rs2408955	12	46785398	T	G	SENP1	Novel	Single	**Erythrocytic**	1.42E-15	11.65
rs10774625	12	110394602	G	A	ATXN2	Novel	Single	**Erythrocytic**	1.46E-08	6.38
rs11619319	13	27385599	G	A	PDX1	Novel	Single	**Glycemic**	4.58E-07	8.38
rs576674	13	32452302	G	A	KL	Novel	Single	**Glycemic**	1.39E-05	6.38
rs282587	13	112399663	G	A	ATP11A	Known	Single	Unclassified	1.70E-12	13.92
rs9604573	13	113571085	T	C	GAS6	Novel	Single	Unclassified	9.60E-09	6.72
rs11248914	16	233563	T	C	ITFG3	Novel	Single	**Erythrocytic**	2.56E-14	10.60
rs1558902	16	52361075	A	T	FTO	Novel	Single	Unclassified	3.27E-08	6.88
rs4783565	16	67307691	A	G	CDH3	Novel	Single	**Erythrocytic**	1.73E-07	6.73
rs837763	16	87381230	T	C	CDT1	Known	Single	**Erythrocytic**	1.68E-28	28.89
rs9914988	17	24207230	A	G	ERAL1	Novel	Single	**Erythrocytic**	2.77E-11	11.34
rs2073285	17	73628956	C	T	TMC6	Novel	Single	Unclassified	1.27E-04	6.47
rs1046896	17	78278822	T	C	FN3KRP	Known	Single	Unclassified	4.46E-64	71.79
rs11086054	19	17107737	A	T	MYO9B	Known	Multiple	Unclassified	8.16E-06	9.12
rs17533903	19	17117523	A	G	MYO9B	Known	Multiple	**Erythrocytic**	5.27E-12	9.912
rs4820268	22	35799537	G							
rs5987239	X	153186763	C							

Wheeler, Leong, MAGIC, submitted

New GWAS of Hemoglobin A_{1c}

185,000 People without Diabetes from >50 cohorts and 7 ancestral groups

60 Loci, 43 new, 65 independent SNPs



20 Erythrocytic SNPs

20 Glycemic SNPs

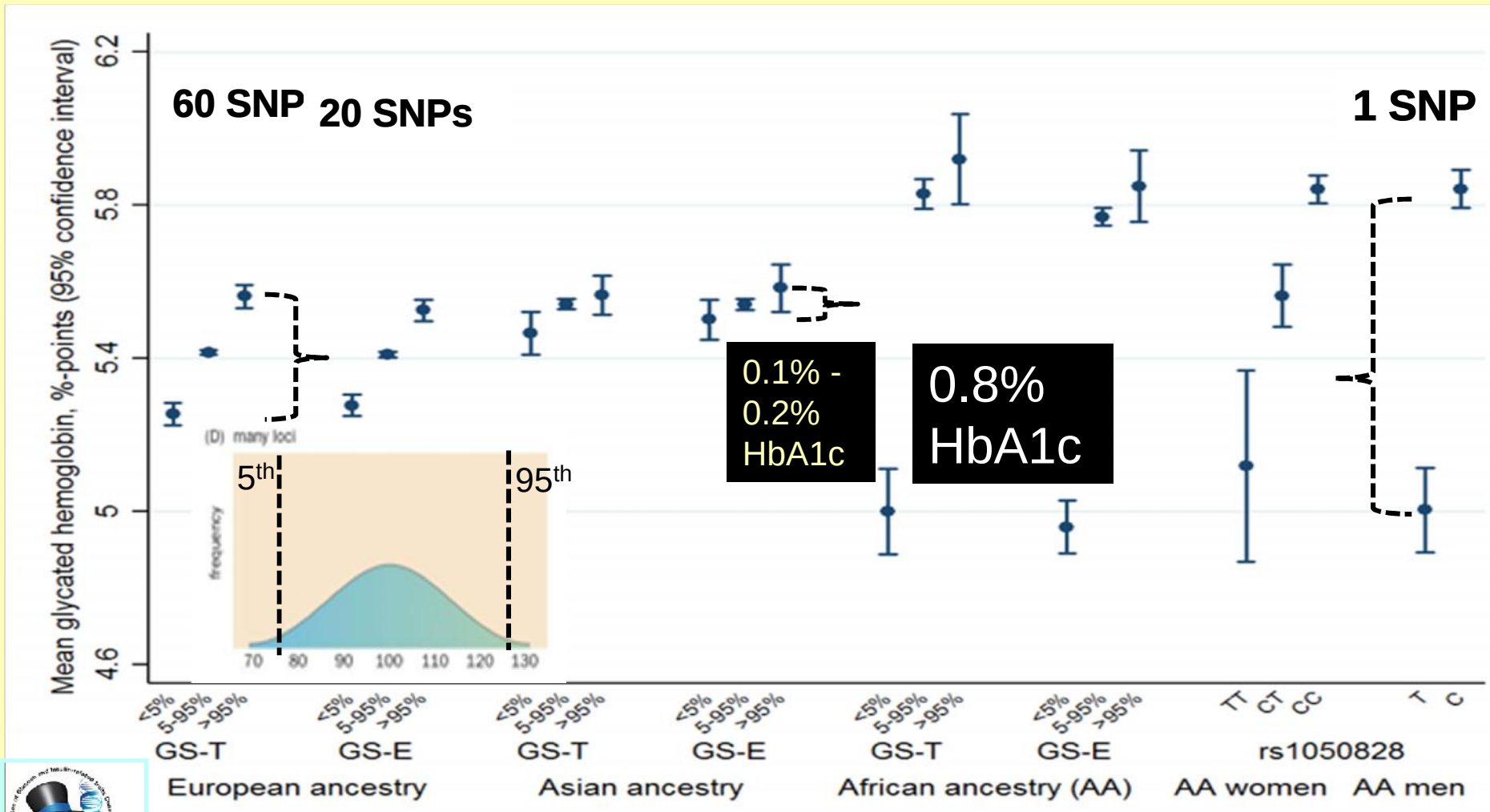
							MANTRA log10BF
CDKAL1	Known	Single	**Glycemic**	2.80E-12	16.53		
HFE	Known	Multiple	**Erythrocytic**	4.67E-28	26.81		
HFE	Known	Multiple	**Erythrocytic**	1.18E-23	23.72		
			Erythrocytic	6.38E-10	7.03		
			Erythrocytic	7.45E-18	17.89		
CITED2	Novel	Single	**Erythrocytic**	3.96E-08	4.50		
DGKB	Novel	Single	**Glycemic**	2.09E-07	6.63		
			Glycemic	8.76E-38	51.28		
			Glycemic	4.22E-35	31.87		
ANK1	Known	Multiple	Unclassified	1.50E-16	14.88		
ANK1	Known	Multiple	**Erythrocytic**	4.48E-27	32.08		
SLC20A2	Novel	Single	Unclassified	3.58E-08	8.73		
SLC30A8	Known	Single	**Glycemic**	1.38E-19	23.26		
MTAP	Novel	Single	**Glycemic**	7.04E-12	11.74		
C9orf47	Novel	Single	**Erythrocytic**	2.56E-14	11.29		
KLF4	Novel	Single	Unclassified	2.09E-07	8.72		
ABO	Novel	Single	**Glycemic**	9.42E-09	10.14		
HK1	Known	Multiple	**Erythrocytic**	2.87E-65	63.05		
HK1	Known	Multiple	Unclassified	1.68E-55	49.45		
TCF7L2	Known	Single	**Glycemic**	6.12E-11	8.49		
BET1L	Novel	Single	Unclassified	1.51E-10	9.51		
KCNQ1	Novel	Single	**Glycemic**	0.00246	6.07		
FADS2	Novel	Single	**Glycemic**	5.45E-07	8.45		
ARAP1	Novel	Single	**Glycemic**	6.85E-09	6.53		
MTNR1B	Known	Single	**Glycemic**	2.23E-23	26.64		
CNTN5	Novel	Single	**Erythrocytic**	4.76E-07	6.40		

MAGIC

Wheeler, Leong, MAGIC, submitted

SNP Scores = Small Differences in HbA1c in European, Asian Ancestry

A Single Chromosome X SNP (rs1050828, G202A) in *G6PD* Accounts for a Large Difference in African Ancestry

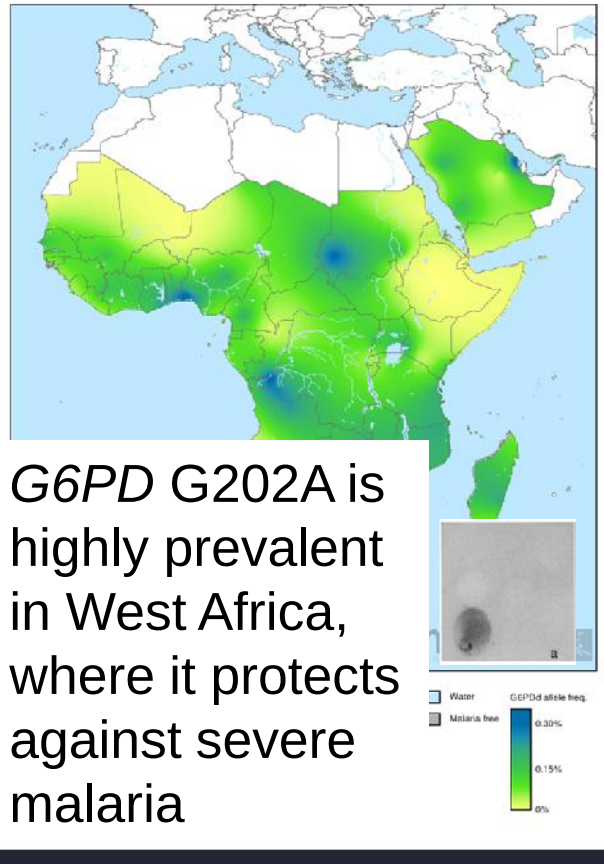


Wheeler, Leong, MAGIC, submitted

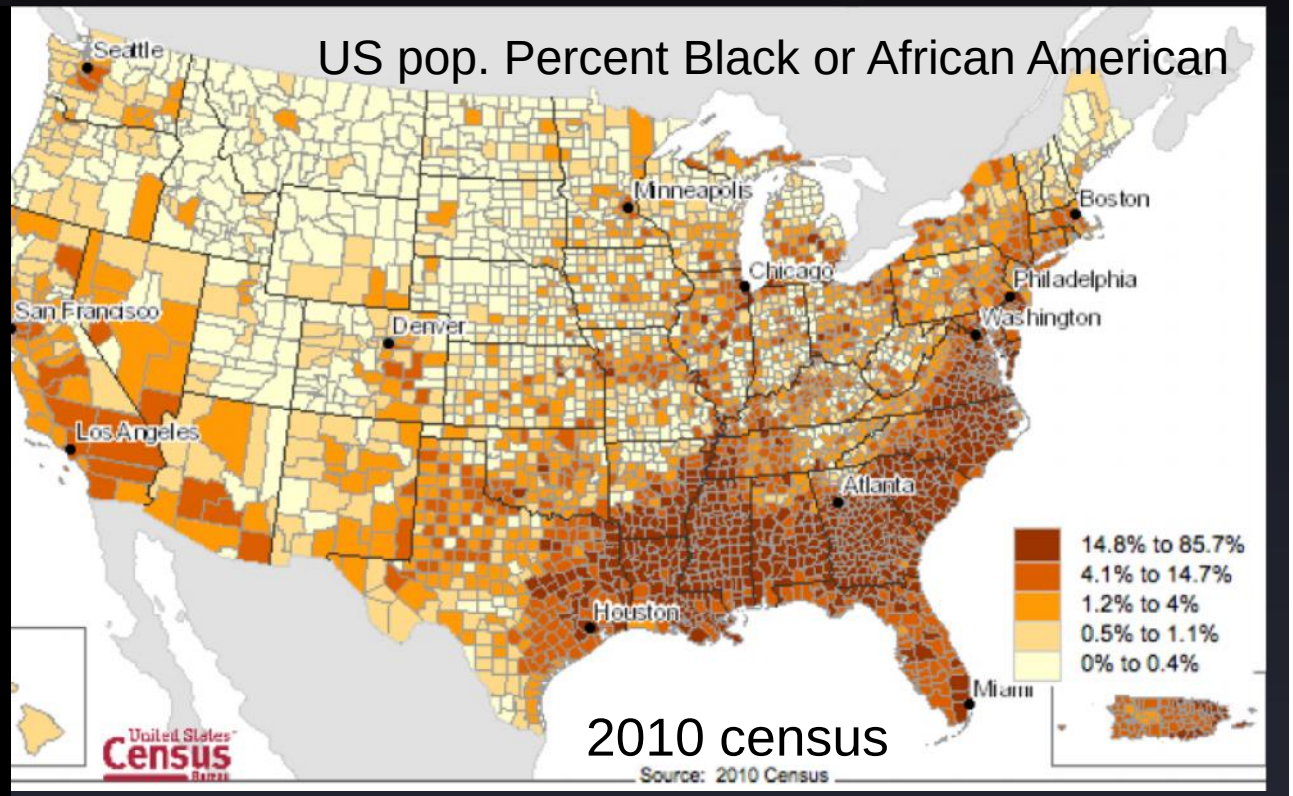
Using NHANES 2013-14, if we tested adult Americans for T2D with HbA1c,

About 2% or 650,000 African Americans would be missed due to genetically lowered HbA1c

G6PD G202A allele frequency 11% in African Americans (0% in whites)



G6PD G202A is highly prevalent in West Africa, where it protects against severe malaria



The influence of HbA1c genetics is not distributed equally in the US

Wheeler, Leong, MAGIC, submitted

Themes for Today

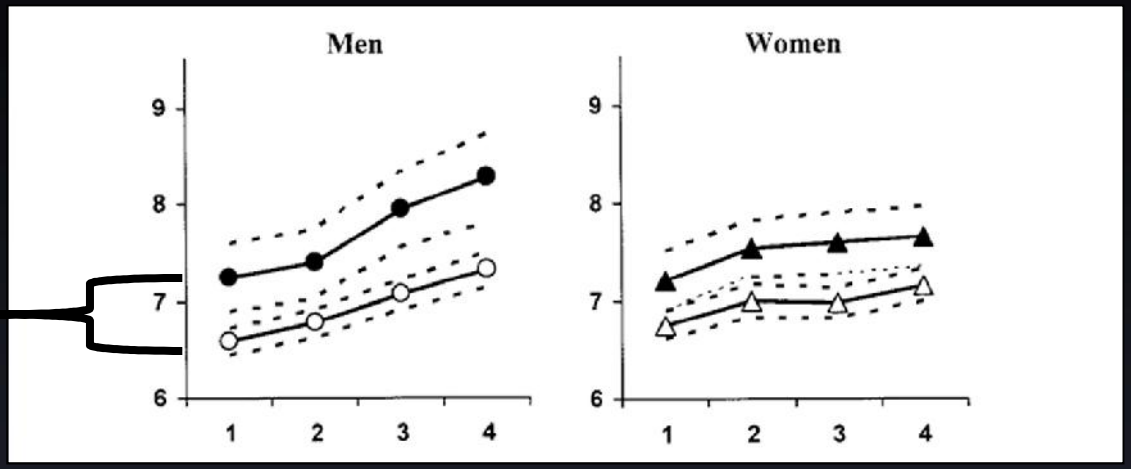
- Discoveries over 15 years in T2D genetics
  - Dramatic expansion in new biology
- Predicting future T2D using T2D genetics
  - Not ready for prime time
- Screening for T2D influenced by HbA1c genetics
  - Opportunity for health application of genetics to reduce T2D disparities?

Thank You

African Americans w T2D are More Hyperglycemic at Diagnosis than Whites

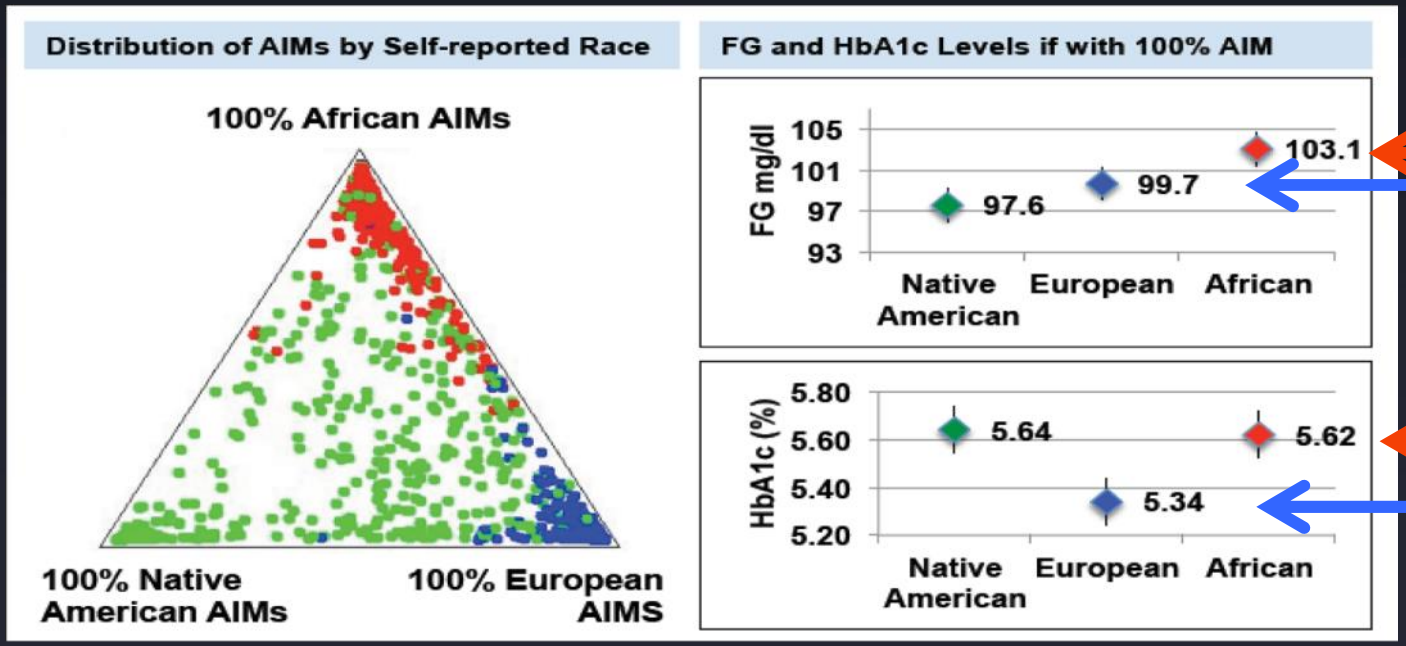
In a health system with equal access to screening, HbA1c was ~0.5 units higher in black (•) vs. white (o) patients at T2D diagnosis. This persisted over time despite equal access and intensity of treatment.

0.5% HbA1c Δ



Adams et al Diabetes Care 2005 PMID: 16306543

African American Ancestry ➔ Higher FG and HbA1c vs. European Ancestry



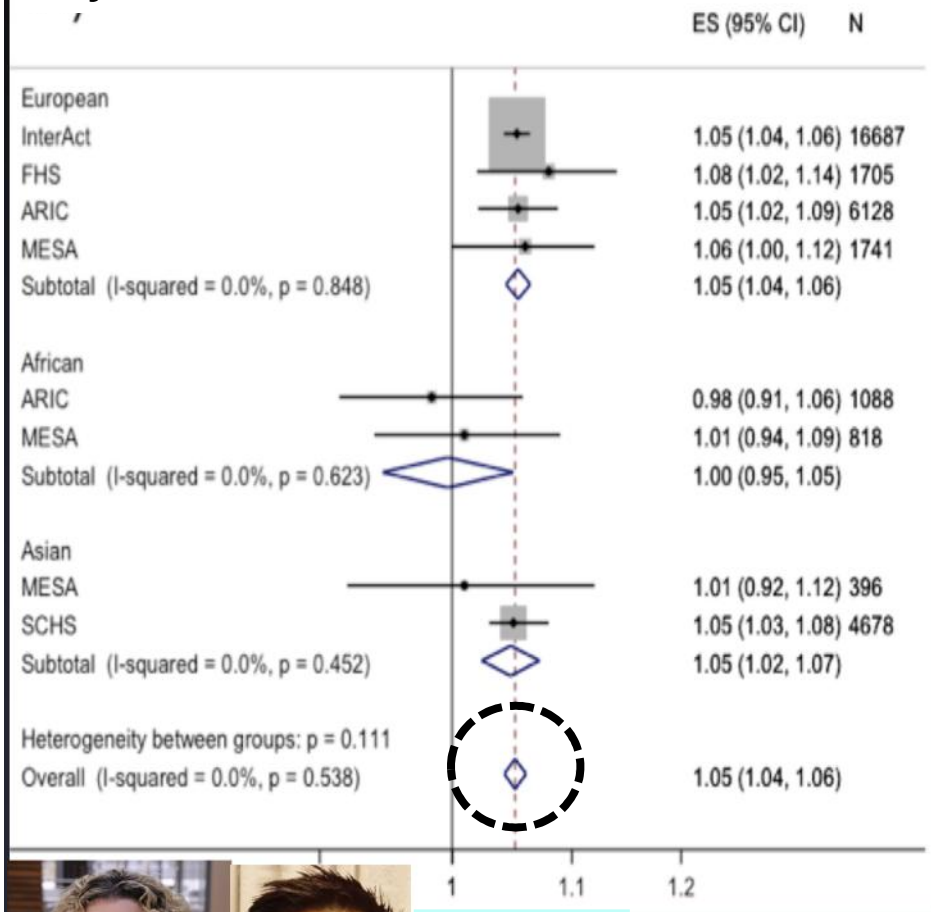
BACH 3, N = 1,387
Differences remained after adjustment for obesity and social inequality variables

0.3% HbA1c Δ

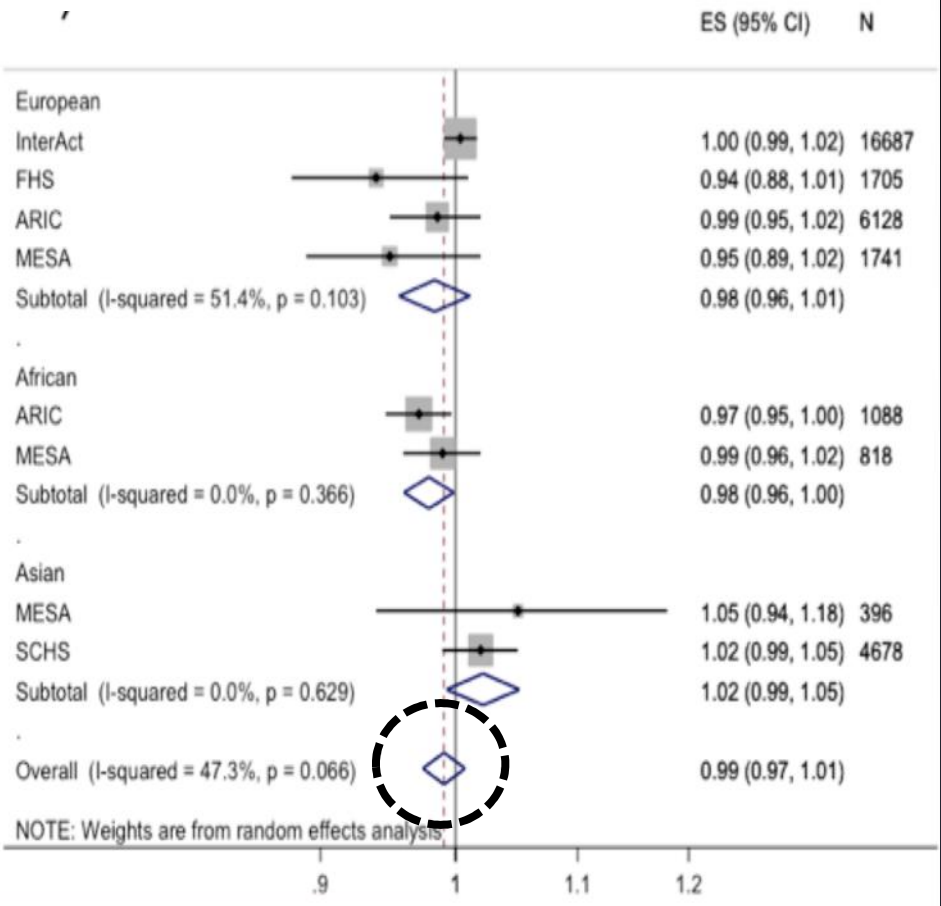
Meigs et al Diabetologia. 2014 PMID: 24942103

A Glycemic Genetic Risk Score Predicts Incident T2D… but an Erythrocytic GRS Does Not

Glycemic SNPs GRS



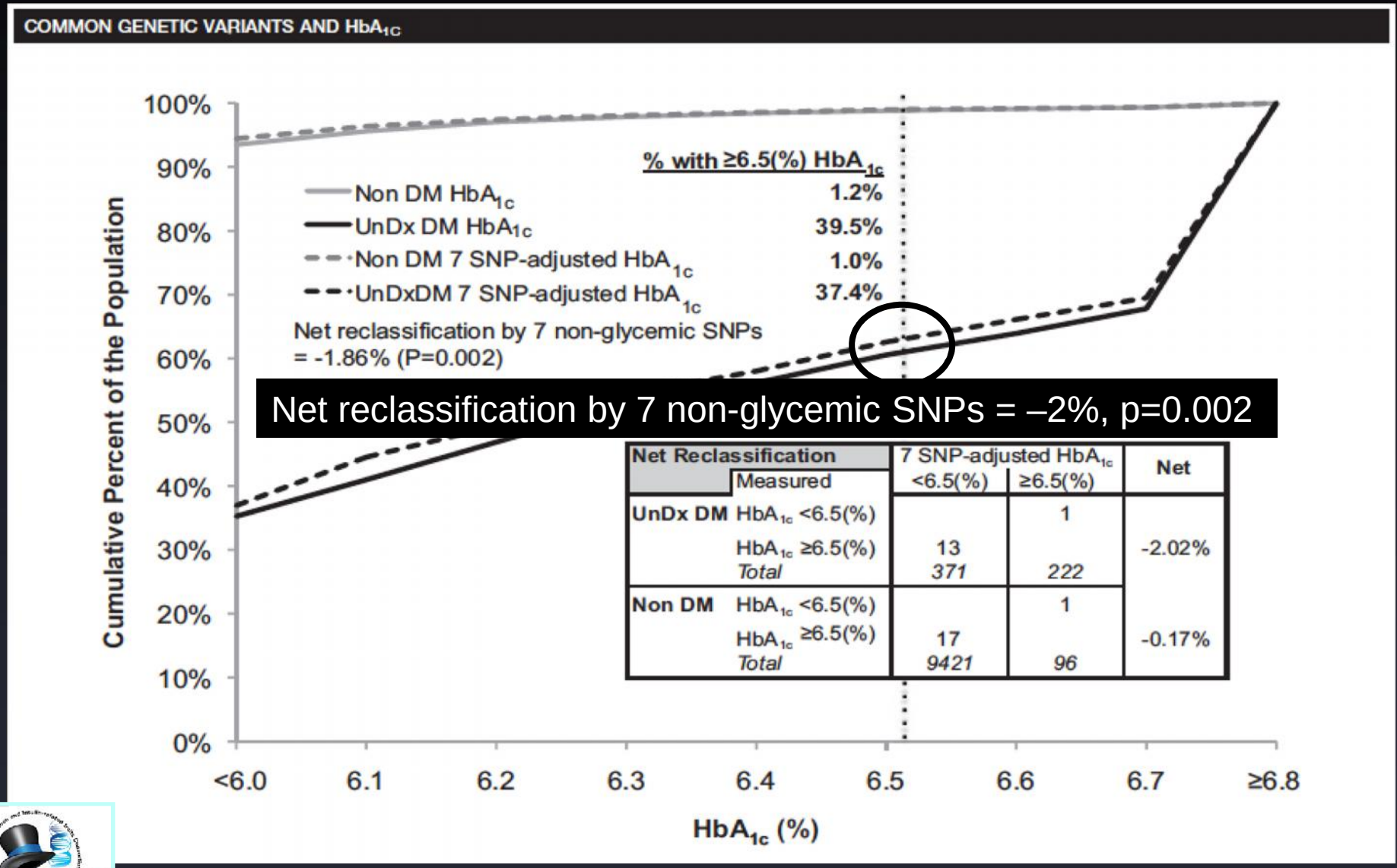
Erythrocytic SNPs GRS



MAGIC

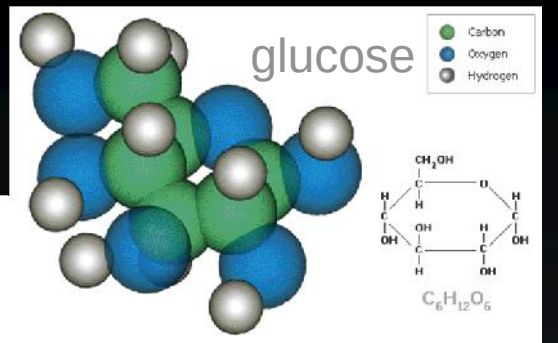
Wheeler, Leong, MAGIC, submitted

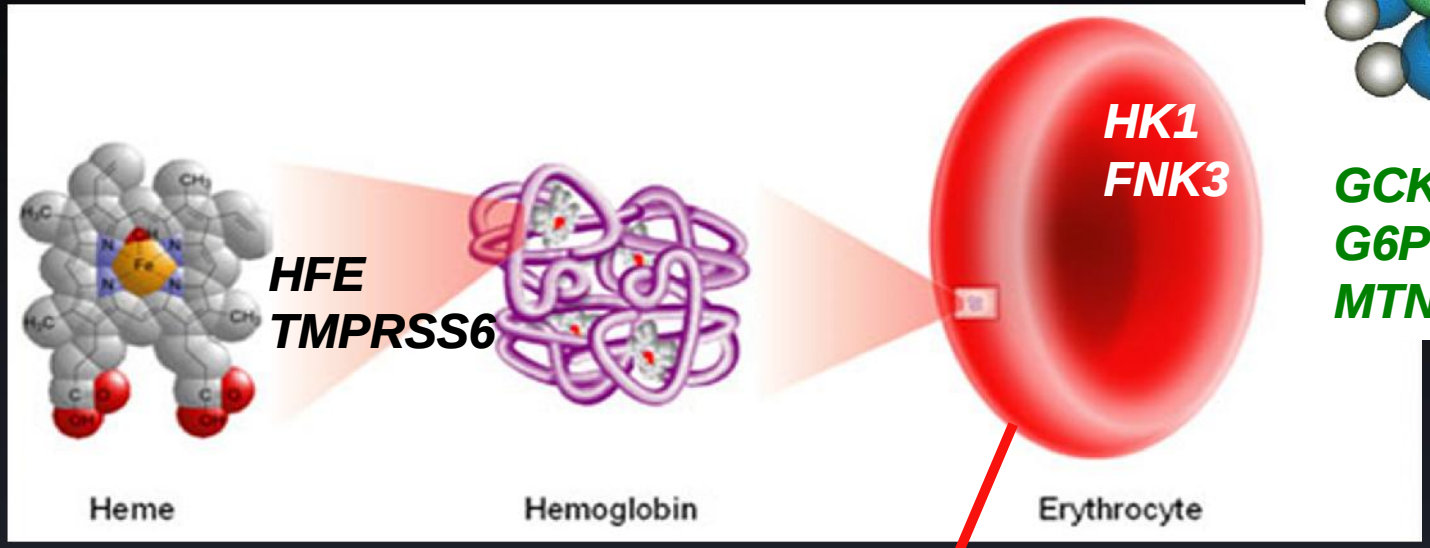
Public Health Implications of the *G6PD* Variant on T2D Screening: 2% of whites mis-classified



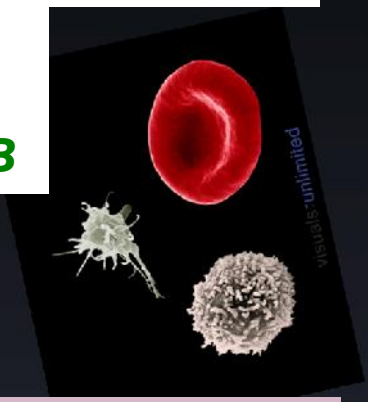
Soranzo et al, Diabetes 2010. PMID: 20858683

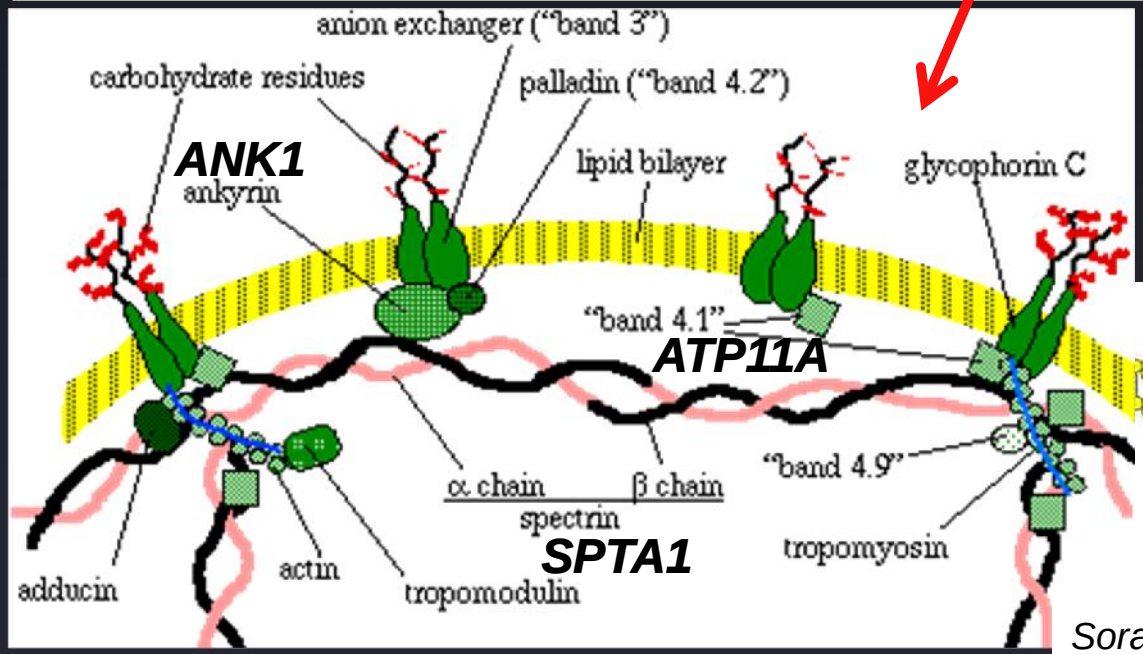
Genetics Reveals Erythrocyte Pathways that Influence HbA_{1c} Levels

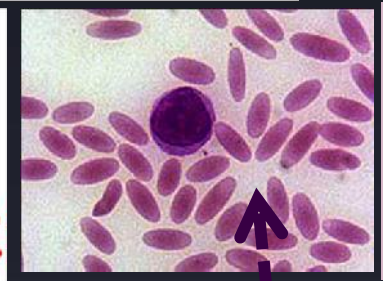




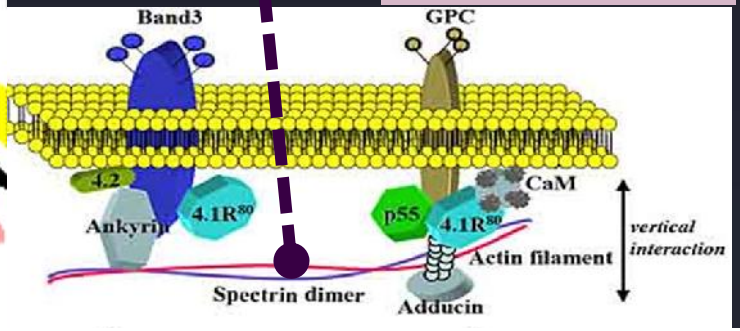
GCK
G6PC2
MTNR1B







SPTA1: Hereditary Elliptocytosis 2, Pyropoikilocytosis, African only?



Soranzo et al, Diabetes 2010. PMID: 20858683

G6PD Genetic Variant

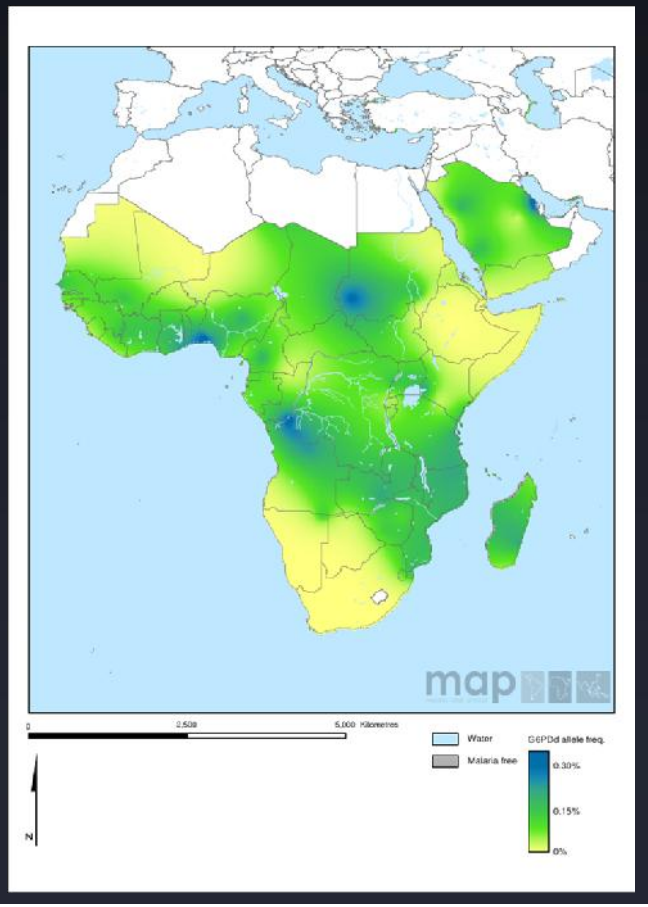
- G6PD-A(-), predominantly in African ancestry (~10%)
  - Positive selection for G6PD risk alleles associated with protection from severe malaria may explain their higher frequencies in AA
  - Negative selection from potentially life threatening haemolytic anaemia

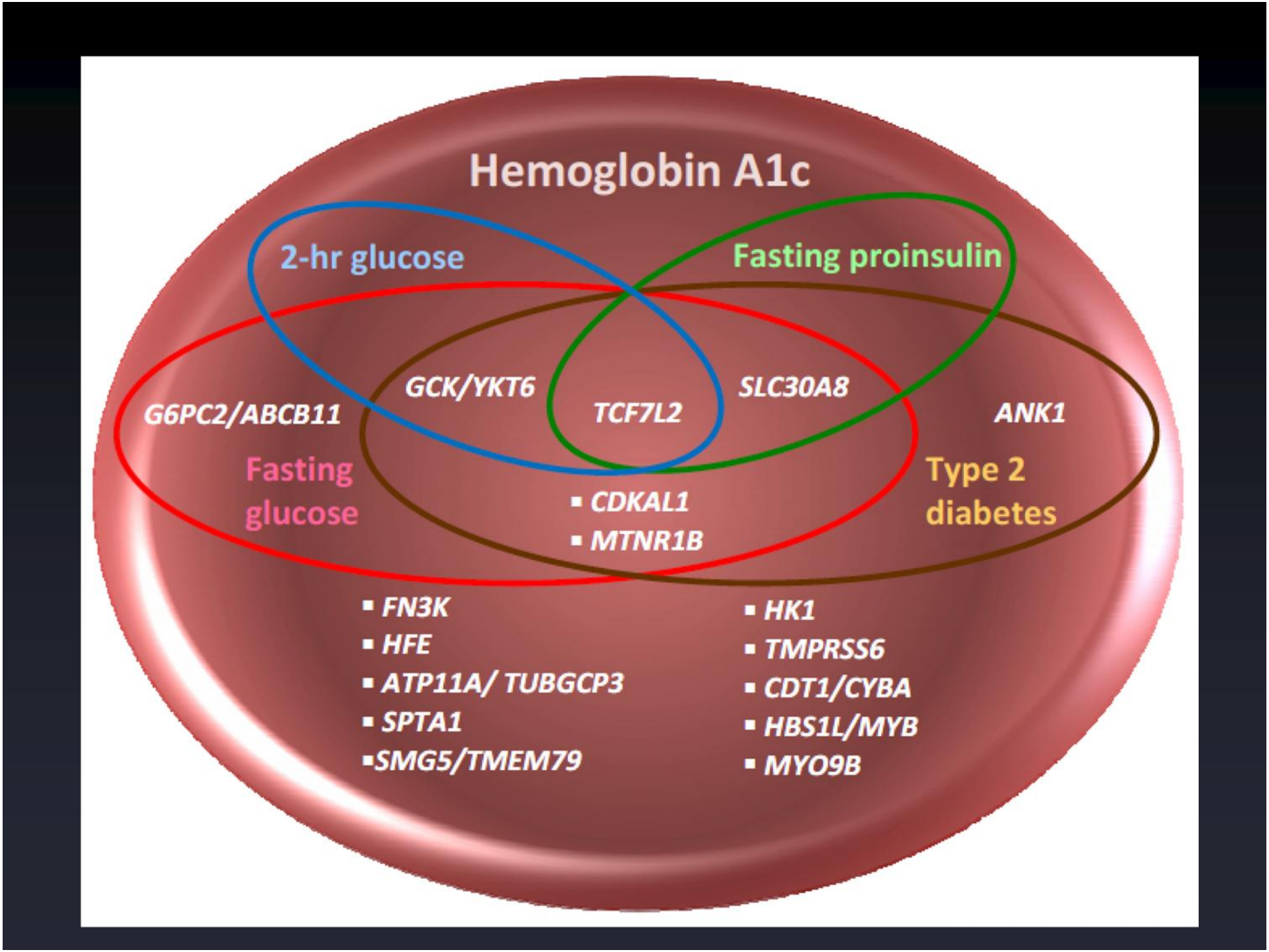
RESEARCH ARTICLE

African Glucose-6-Phosphate Dehydrogenase Alleles Associated with Protection from Severe Malaria in Heterozygous Females in Tanzania

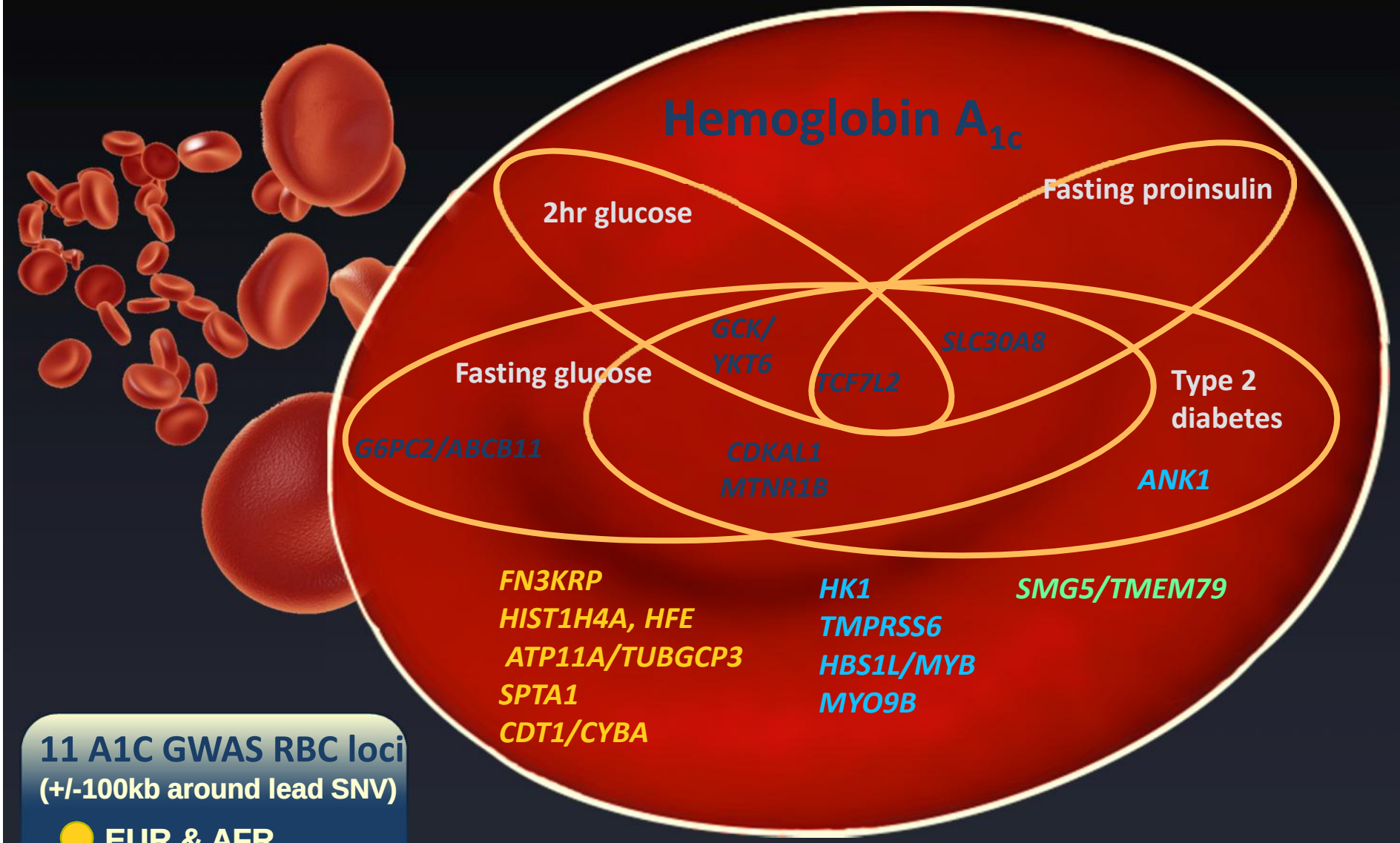
Alphaxard Manjurano[1], Nuno Sepulveda[2], Behzad Nadjm[3¤], George Mtove[1], Hannah Wangai[1], Caroline Maxwell[1], Raimos Olomi[1], Hugh Reyburn[1,2], Eleanor M. Riley[1,2‡], Christopher J. Drakeley[1,2‡], Taane G. Clark[4,5‡*], MalariaGEN Consortium[6¶]

Citation: Manjurano A, Sepulveda N, Nadjm B, Mtove G, Wangai H, Maxwell C, et al. (2015) African Glucose-6-Phosphate Dehydrogenase Alleles Associated with Protection from Severe Malaria in Heterozygous Females in Tanzania. PLoS Genet 11 (2): e1004960. doi:10.1371/journal.pgen.1004960




Hemoglobin A1c
2-hr glucose
Fasting proinsulin
GCK/YKT6
SLC30A8
G6PC2/ABCB11
TCF7L2
ANK1
Fasting glucose
Type 2 diabetes
CDKAL1
MTNR1B
FN3K
HFE
ATP11A/ TUBGCP3
SPTA1
SMG5/TMEM79
HK1
TMPRSS6
CDT1/CYBA
HBS1L/MYB
MYO9B

SELECTION OF CANDIDATE LOCI



Leong, Meigs, *Rev Diabet Stud, 2015*