HEALTH APPLICATION OF TYPE 2 DIABETES GENETICS

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JBM Disclosures and Acknowledgments

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

T2D-GENES Consortium

CHARGe

American Diabetes Association

NIH NIDDK 60 years NATiOnAL iNSTITUTE OF DiABeTES AND DiGiStiVe AND KIDNEY DiASES
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/m²)

1994

No Data

<14.0%

14.0-17.9%

18.0-21.9%

22.0-25.9%

≥26.0%

2000

2010

No Data

<4.5%

4.5-5.9%

6.0-7.4%

7.5-8.9%

≥9.0%

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

GWAS – from Peas to Human Complex Trait Genetics

Fasting Glucose

N~30,000
Array SNPs, Linkage Disequilibrium, Imputation

Imputation for MAF > 0.05%

500K to 15M SNPs


Red = high $r^2$
White = no $r^2$
Framingham Heart Study
N ~ 6,500, longitudinal
Fruitful Collaboration in T2D-QT Genetics Consortia

Quantitative Traits
- Fasting Glucose
- Fasting Insulin
- HbA₁c
- 2hr OGTT glucose
- Proinsulin

MAGIC v3 133,010
CHARGE 60,564
FHS SHARE 6,479
Fruitful Collaboration in T2D-QT Genetics Consortia

Quantitative Traits
- Fasting Glucose
- Fasting Insulin
- HbA$_{1c}$
- 2hr OGTT glucose
- Proinsulin

Type 2 Diabetes
- Case/Control

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

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
- HbA1c
- 2hr OGTT glucose
- Proinsulin

**Type 2 Diabetes**
Case/Control

**MAGIC v3**
- 133,010 T2D cases
- 60,564 controls
- 47,979 T2D and controls

**CHARGE**
- 39,339 T2D and controls
- Five ancestry groups
- Exome data

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

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

**T2D-GENES Consortium**
- 39,339 T2D and controls

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

Fasting Glucose
- G6PC2
- MTNR1B
- PROX1
- ADCY5
- SLC2A2
- GCKR
- DGKB
- GCK
- CRY2
- MADD
- FADS1
- SLC30A8
- TCF7L2
- G6PC2
- GLIS3
- ADRA2A
- MADD
- FADS1

Fasting Insulin
- IGF1
- GCKR

2 hr Glucose
- GCKR
- ADCYS
- VPS13C
- TCF7L2
- GIPR

Dupuis et al. Nat Genet. 2010;42:105-16
MAGIC GWAS of T2D-Related Quantitative Traits
Abundant New Biology, New Hypotheses

- **Fasting Glucose**
  - Alpha adrenergic system locus causes IR and T2D in mice
  - Beta cell Zn transporter Interacts w dietary Zn
  - Circadian system

- **Fasting Insulin**
  - Laron syndrome patients have low IGF1 signaling and no T2D

- **2 hr Glucose**
  - Trans-membrane signaling (drug targets)
  - Incretin system

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

• 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

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

• LOC728723/PPP1R3B
• GCKR
• LOC157273
• ADCY5
• IGF2BP2
• GIPR/EML2/QPCTL
• GLIS3
• PROX1
• CDKN2B-AS1
• GLP1R
• MADD
• ARAP1
• FADS1
• GLS2
• KL
• TOP1
• WARS
• AGMO
• CRY2
• DPYSL5
• IKBAKAP
• GRB10
• FBRSL1
• PDX1
• ADRA2A
• OR4S1
• NCRNA00261
• VPS13C/C2CD4A/B
• GCK/YKT6
• TCF7L2
• SLC30A8
• CDKAL1
• MTNR1B
• G6PC2
• ANK1
• FN3K
• HFE
• ATP11A/TUBGCP3/C13 of 35
• SPTA1
• HK1
• TMPRSS6
• CDT1/CYBA
• SMG5/TMEM79
• HBS1L/MYB
• MYO9B

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
The genetic architecture of type 2 diabetes

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 is a common variant polygenic disorder

Nature 2016 PMID: 27398621
GoT2D and T2D-GENES
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T2D is a common variant polygenic disorder

The genetic architecture of type 2 diabetes

Nature 2016 PMID: 27398621

Common variants explain most of the observed heritability
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

Am I at risk? What treatment is right for me?

Which people are at risk? Are all treatments right for everyone?
Clinical Application of T2D Genetics
Personal and Population Health

Am I at risk?
What treatment is right for me?

Which people are at risk?
Are all treatments right for everyone?
Predicting Future T2D using T2D Genetics

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)

% of Pop. 25% 64% 11%
RR 1.0 1.6 2.5

T2D Genotype Scores Predict Incident T2D in Adults
... so do Clinical Risk Factors

T2D Genetics Alone

- 18 SNP T2D Genotype Score
- C = 60%
- NRI = 2.6%
- P = 0.22

T2D Genetics + Clinical Risk Factors

- Genotype Score + Clinical Traits
- C = 90%
- NRI = 2.1%
- P = 0.17

T2D Genetic Risk Increases All-Cause Mortality

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

Estimated mortality risk per T2D risk allele by ethnicity

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>BMI model</th>
<th>Modifiable risk factors model</th>
</tr>
</thead>
<tbody>
<tr>
<td>All ethnicities</td>
<td>1.04 (1.00, 1.07)</td>
<td>1.04 (1.01, 1.08)</td>
</tr>
<tr>
<td>Non-Hispanic Whites</td>
<td>1.04 (1.00, 1.09)</td>
<td>1.05 (1.00, 1.10)</td>
</tr>
<tr>
<td>Non-Hispanic Blacks</td>
<td>1.04 (1.01, 1.06)</td>
<td>1.03 (1.00, 1.06)</td>
</tr>
<tr>
<td>Mexican Americans</td>
<td>0.95 (0.90, 1.01)</td>
<td>0.95 (0.89, 1.02)</td>
</tr>
</tbody>
</table>

Odds ratio (OR) per T2D risk allele

Leong et al Diabetes Care 2016 PMID: 26884474
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

Grant et al. Diabetes Care. 2013 PMID: 22933432
Screening for T2D influenced by HbA1c genetics
Hemoglobin A\textsubscript{1c}

A1C & T2D Diagnosis

**What?**

HbA1c (A1C) test

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

A1C test results

- Normal
- Prediabetes
- Diabetes

👍 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
>46,000 individuals, 31 cohorts
10 Loci $P<5 \times 10^{-8}$, 6 Novel

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

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

Soranzo et al, Diabetes 2010. PMID: 20858683
New GWAS of Hemoglobin A\textsubscript{1c}

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

60 Loci, 43 new, 65 independent SNPs

Wheeler, Leong, MAGIC, submitted
New GWAS of Hemoglobin A\textsubscript{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

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

60 SNP  20 SNPs

1 SNP

0.1% - 0.2% HbA1c
0.8% HbA1c
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.
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 (○) patients at T2D diagnosis. This persisted over time despite equal access and intensity of treatment.

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

Adams et al Diabetes Care 2005 PMID: 16306543

Meigs et al Diabetologia. 2014 PMID: 24942103
A Glycemic Genetic Risk Score Predicts Incident T2D… but an Erythrocytic GRS Does Not
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

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
SELECTION OF CANDIDATE LOCI

Hemoglobin A\textsubscript{1c}

- Fasting glucose
- 2hr glucose
- Fasting proinsulin
- Type 2 diabetes

- G6PC2/ABCB11
- FN3KRP
- HIST1H4A, HFE
- ATP11A/TUBGCP3
- SPTA1
- CDT1/CYBA
- HK1
- TMPRSS6
- HBS1L/MYB
- MYO9B
- SMG5/TMEM79

11 A1C GWAS RBC loci (+/-100kb around lead SNV)

- EUR & AFR
- EUR
- AFR

Leong, Meigs, Rev Diabet Stud, 2015