Clinical Translation of Genetic Predictors for Type 2 Diabetes

Jose C. Florez, MD, PhD

July 18, 2014
Familial clustering of type 2 diabetes

If you have type 2 diabetes, what is the risk to:

- Your neighbor (unrelated)? 5-10%
- Your sibling? 30%
- Your identical twin? >80%

Variation in DNA sequence influences disease risk
Evidence for genetic contribution

- Populations who share the same environment have different degrees of prevalence (e.g. Pima Indians, “thrifty gene”)
- Family history confers independent risk
- Concordance is higher in monozygotic twins when compared to dizygotic twins
- Mutations cause monogenic forms of diabetes
MODY and neonatal diabetes

Modified from Bell & Polonsky
Insights from monogenic diabetes

1. Confirmation that variation in DNA sequence can cause hyperglycemia
2. Focus on the $\beta$ cell
3. Potential for pharmacogenetics

Genome-wide association studies

A tsunami of new genes
On the shoulders of giants...

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**Articles**

**A map of human genetic variation containing single nucleotide polymorphisms**

*The International HapMap Working Group*  

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**Efficiency and power in genetic association studies**

Paul I W de Bakker¹⁻⁴,⁸, Roman Yelensky¹,²,³,⁸, Itsik Pe’er¹,⁴, Mark J Daly¹,⁴,⁶, & David Altshuler¹⁻⁴,⁶,⁷
The HapMap:
Linkage disequilibrium in the human genome

~300bp

~44 kb
What made GWAS possible

- Better understanding of patterns of human sequence variation
- Advances in genotyping technology
- Sample collections of adequate size

Genome-wide association scans

- 3,000,000,000 bases in human genome
- ~10,000,000 positions commonly variant in Europeans
- 80% of these captured by typing ~500k

Samples of interest

- Test for evidence of association

Slide courtesy of Mark McCarthy
Loci associated with type 2 diabetes

7 common reactions

1. **The skeptic**: “We are not learning anything new”
2. **The impatient**: “These efforts have not uncovered the greater part of the genetic basis of type 2 diabetes”
3. **The absolutist**: “All of the genetic contribution to type 2 diabetes acts through common [or rare] variants”
4. **The cynic**: “Larger and larger samples are just going to uncover smaller and smaller effects”
5. **The pessimist**: “Genetic effects are so small that they cannot possibly be clinically relevant”
6. **The optimist**: “The variants identified will be useful in individual clinical prediction”
7. **The pragmatist**: “These discoveries will help me implement a personalized therapeutic plan”
“We have not learned anything new”

Chimienti et al., 2004
*Diabetes* 53:2330-2337
Loss-of-function mutations in *SLC30A8* protect against type 2 diabetes

Jason Flannick\(^1\)\(^-\)\(^3\), Gudmar Thorleifsson\(^4\), Nicola L Beer\(^1\)\(^,\)\(^5\), Suzanne B R Jacobs\(^1\), Niels Grarup\(^6\), Noël P Burtt\(^1\),

### Table 1: Association of *SLC30A8* variants with T2D

<table>
<thead>
<tr>
<th>Variant</th>
<th>Ancestry</th>
<th>Country</th>
<th>Cohort</th>
<th>N</th>
<th>Carriers</th>
<th>Allele frequency</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>p.Arg138*</td>
<td>European</td>
<td>Finland</td>
<td>Botnia</td>
<td>3,727/5,440</td>
<td>9/39</td>
<td>0.12/0.36</td>
<td>0.47 (0.27–0.81)</td>
<td>0.0067</td>
</tr>
<tr>
<td>p.Arg138*</td>
<td>European</td>
<td>Sweden</td>
<td>Malmo</td>
<td>6,960/5,480</td>
<td>2/3</td>
<td>0.014/0.027</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p.Arg138*</td>
<td>European</td>
<td>Sweden</td>
<td>PIVUS/ULSAM</td>
<td>270</td>
<td>2/3</td>
<td>0.19/0.087</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p.Arg138*</td>
<td>European</td>
<td>Denmark</td>
<td>Danish</td>
<td>3,889/7,869</td>
<td>0/9</td>
<td>0.0/0.057</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p.Arg138*</td>
<td>European</td>
<td>Finland</td>
<td>Finnish</td>
<td>4,050/8,696</td>
<td>1/2</td>
<td>0.012/0.011</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p.Arg138*</td>
<td>European</td>
<td>Singapore</td>
<td>Singapore Indians</td>
<td>562/585</td>
<td>1/1</td>
<td>0.089/0.085</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p.Arg138*</td>
<td>European</td>
<td>UK</td>
<td>UK2T2D</td>
<td>321/319</td>
<td>0/1</td>
<td>0.0/0.16</td>
<td>-</td>
<td>-</td>
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<tr>
<td>p.Lys34Serfs*50</td>
<td>European</td>
<td>Iceland</td>
<td>deCODE</td>
<td>2,953/67,919</td>
<td>2/248</td>
<td>0.034/0.18</td>
<td>0.17 (0.05–0.52)</td>
<td>0.0019</td>
</tr>
<tr>
<td>p.Lys34Serfs*50</td>
<td>European</td>
<td>Norway</td>
<td>HUNT2</td>
<td>1,645/4,069</td>
<td>0/3</td>
<td>0.0/0.037</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>c.71+2T&gt;A</td>
<td>African American</td>
<td>United States</td>
<td>WFS</td>
<td>501/527</td>
<td>1/0</td>
<td>0.1/0.0</td>
<td>0.30 (0.14–0.64)</td>
<td>0.0021</td>
</tr>
<tr>
<td>c.71+2T&gt;A</td>
<td>African American</td>
<td>United States</td>
<td>JHS</td>
<td>530/533</td>
<td>1/0</td>
<td>0.0/0.094</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p.Met50Ile</td>
<td>European</td>
<td>Germany</td>
<td>KORA</td>
<td>97/91</td>
<td>0/1</td>
<td>0.0/0.55</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>c.271+G&gt;A</td>
<td>East Asian</td>
<td>Korea</td>
<td>KARE</td>
<td>520/551</td>
<td>0/1</td>
<td>0.0/0.091</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>c.419–1G&gt;C</td>
<td>South Asian</td>
<td>Singapore</td>
<td>Singapore Indians</td>
<td>562/585</td>
<td>0/1</td>
<td>0.0/0.085</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p.Trp152*</td>
<td>European</td>
<td>Finland</td>
<td>Botnia</td>
<td>134/180</td>
<td>0/1</td>
<td>0.0/0.28</td>
<td>-</td>
<td>-</td>
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<tr>
<td>p.Gln174*</td>
<td>European</td>
<td>UK</td>
<td>LOLIPOP</td>
<td>530/537</td>
<td>1/5</td>
<td>0.094/0.47</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>c.572+1G&gt;A</td>
<td>African American</td>
<td>United States</td>
<td>JHS</td>
<td>530/533</td>
<td>0/1</td>
<td>0.0/0.094</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p.Tyr284*</td>
<td>South Asian</td>
<td>Singapore</td>
<td>Singapore Indians</td>
<td>562/585</td>
<td>0/1</td>
<td>0.0/0.085</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p.Ile291Phefs*2</td>
<td>African American</td>
<td>United States</td>
<td>JHS</td>
<td>530/533</td>
<td>0/1</td>
<td>0.0/0.094</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>p.Ser327Thr*55</td>
<td>African American</td>
<td>United States</td>
<td>WFS</td>
<td>501/527</td>
<td>0/2</td>
<td>0.0/0.19</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Combined</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30,433/118,701</td>
<td>19/326</td>
<td>-</td>
<td>0.34 (0.21–0.53)</td>
<td>1.7 × 10⁻⁶</td>
</tr>
</tbody>
</table>
Unsuspected biology


Identification of an imprinted master trans regulator at the *KLF14* locus related to multiple metabolic phenotypes

Kerrin S Small\(^1\), Åsa K Hedman\(^2\), Elin Grundberg\(^1\), Alexandra C Nica\(^4\), Gudmar Thorleifsson\(^5\), Augustine Kong\(^6\), Unmur Thorsteindottir\(^5\), So-Youn Shin\(^2\), Hannah B Richards\(^7\), the GIANT Consortium\(^8\), the MAGIC Investigators\(^8\), the DIAGRAM Consortium\(^9\), Nicole Soranzo\(^1\), Kourosh R Ahmadi\(^1\), Cecilia M Lindgren\(^3\), Kari Stefansson\(^5\), Emmanouil T Dermitzakis\(^4\), Panos Deloukas\(^2\), Timothy D Spector\(^1\) & Mark I McCarthy\(^3\),\(^7\),\(^9\),\(^10\) for the MuTHER Consortium\(^8\)

**ARSD expression**

**Type 2 diabetes GWAS**

(DIAGRAM Consortium)

**HDL GWAS**

(Lipid Consortium)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chr.</th>
<th>Effect (s.e.)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>APH1B</td>
<td>15</td>
<td>0.08 (0.013)</td>
<td>(1.2 \times 10^{-9})</td>
</tr>
<tr>
<td>ARS2D</td>
<td>X</td>
<td>0.08 (0.012)</td>
<td>(1.9 \times 10^{-11})</td>
</tr>
<tr>
<td>C8orf52</td>
<td>8</td>
<td>0.09 (0.014)</td>
<td>(4.8 \times 10^{-10})</td>
</tr>
<tr>
<td>GNB1</td>
<td>1</td>
<td>0.05 (0.009)</td>
<td>(4.0 \times 10^{-8})</td>
</tr>
<tr>
<td>KLF13</td>
<td>15</td>
<td>0.10 (0.017)</td>
<td>(2.2 \times 10^{-8})</td>
</tr>
<tr>
<td>MYL5</td>
<td>4</td>
<td>0.09 (0.017)</td>
<td>(4.5 \times 10^{-8})</td>
</tr>
<tr>
<td>NINJ2</td>
<td>12</td>
<td>0.08 (0.013)</td>
<td>(8.4 \times 10^{-9})</td>
</tr>
<tr>
<td>PRMT2</td>
<td>21</td>
<td>0.06 (0.010)</td>
<td>(6.9 \times 10^{-9})</td>
</tr>
<tr>
<td>SLC7A10</td>
<td>19</td>
<td>−0.27 (0.042)</td>
<td>(2.7 \times 10^{-10})</td>
</tr>
<tr>
<td>TPMT</td>
<td>6</td>
<td>0.10 (0.013)</td>
<td>(1.6 \times 10^{-14})</td>
</tr>
</tbody>
</table>
Meta-Analysis of Glucose and Insulin-related traits Consortium

New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk
Fasting glucose meta-analysis

- Not all are associated with type 2 diabetes

Note: Hits represented by closest mapping gene, but this does not imply causality

Raising glucose vs increasing T2D risk

“The mechanism by which glucose is raised, rather than a mere elevation in fasting glucose levels, is a key contributor to disease progression”

The MAGIC investigators, *Nat Genet* 2010;42:105-116
Support for a previous epidemiological observation: 
*Link with the circadian system*

- Two circadian genes (*MTNR1B* and *CRY2*) raise fasting glucose
- People with circadian misalignment have metabolic abnormalities
- Manipulation of the sleep-wake cycle causes insulin resistance
- Circadian mice mutants show hyperglycemia
Most T2D loci impair β-cell function

1. Tissue expression
2. Subcellular localization
3. Molecular function
4. In vivo physiology

J.C. Florez, *Diabetologia* 2008;51:1100-1110
“Missing heritability”

- Best estimate ~10%
- Have not performed fine-mapping nor identified the causal variants
- 20% of common variants not covered
- Have not yet examined:
  - Non-European populations
  - Copy number variants
  - Uncommon or rare variants
  - Non-additive genetic models
  - Gene x gene or gene x environment interactions
  - Epigenetics
Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico

Odds ratio 1.28 (1.19-1.37), $P=1.1 \times 10^{-12}$

Haplotype contains 4 missense variants

Monocarboxylate transporter
Unusual frequency distribution

Absent in Africa
Rare in Europe
Uncommon in Asia
Common in America

SIGMA T2D Consortium – Nature 2014;506:97-101
Whole-exome sequencing

Original Investigation

Association of a Low-Frequency Variant in *HNF1A* With Type 2 Diabetes in a Latino Population

The SIGMA Type 2 Diabetes Consortium

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Participants</th>
<th>No.</th>
<th>Frequency, %</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial scan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCDS</td>
<td>270</td>
<td>526</td>
<td>7</td>
<td>0.19</td>
<td>16.04 (3.38-76.20)</td>
</tr>
<tr>
<td>MEC</td>
<td>482</td>
<td>438</td>
<td>7</td>
<td>0.23</td>
<td>6.08 (1.16-31.87)</td>
</tr>
<tr>
<td>DMS</td>
<td>509</td>
<td>459</td>
<td>11</td>
<td>0.22</td>
<td>6.00 (0.86-41.75)</td>
</tr>
<tr>
<td>UIDS</td>
<td>533</td>
<td>539</td>
<td>12</td>
<td>0.74</td>
<td>3.26 (1.40-7.60)</td>
</tr>
<tr>
<td>SIGMA mega-analysis</td>
<td>548</td>
<td></td>
<td></td>
<td>5.48 (2.83-10.61)</td>
<td>4.40 x 10^-7</td>
</tr>
<tr>
<td>Replication studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2D-GENES Latinos</td>
<td>1016</td>
<td>922</td>
<td>6</td>
<td>0.11</td>
<td>5.61 (1.34-23.49)</td>
</tr>
<tr>
<td>DMS2 article</td>
<td>427</td>
<td>751</td>
<td>9</td>
<td>0.53</td>
<td>3.50 (1.17-10.44)</td>
</tr>
<tr>
<td>Replication summary</td>
<td>4.16 (1.75-9.92)</td>
<td></td>
<td></td>
<td></td>
<td>.0013</td>
</tr>
<tr>
<td>Overall summary</td>
<td>4.96 (2.93-8.38)</td>
<td></td>
<td></td>
<td></td>
<td>2.39 x 10^-9</td>
</tr>
</tbody>
</table>

*JAMA 2014;311:2305-2314*
Reduced transcriptional activity
Clinically indistinguishable from type 2 diabetes

The SIGMA T2D Consortium
*JAMA* 2014;311:2305-2314
Whole-genome sequencing

Identification of low-frequency and rare sequence variants associated with elevated or reduced risk of type 2 diabetes

Valgerdur Steinthorsdottir¹, Gudmar Thorleifsson¹, Patrick Sulem¹, Hannes Helgason¹-², Niels Grarup³, Asgeir Sigurdsson¹, Hafdis T Helgadottir⁴, Hrefna Johannsdottir¹, Olafur T Magnusson¹, Sigurjon A Gudjonsson¹, Johanne M Justesen³, Marie N Harder³, Marit E Jørgensen⁴, Cramer Christensen⁵, Ivan Brandslund⁶,⁷, Anneli Sandbaek⁸, Torsten Lauritzen⁸, Henrik Vestergaard³, Allan Linneberg⁹, Torben Jørgensen⁹-¹¹, Torben Hansen³, Maryam S Daneshpour¹², Mohammad-Sadegh Fallah¹², Astradur E Hreidarsson¹³, Gunnar Sigurdsson¹³, Fereidoun Azizi¹⁴, Rafn Benediktssson¹³, Gislí Masson¹, Agnar Helgason¹⁴,¹⁵, Augustine Kong¹², Daniel F Gudbjartsson¹,², Oluf Pedersen³, Unnur Thorsteinsdottir¹,¹⁶ & Kari Stefansson¹,¹⁶

- WGS 2,630 Icelanders
- Imputation:
  - 11,114 cases
  - 267,140 controls
“Genetic effects are so small that they cannot possibly be clinically relevant”

- **PPARG** is the target for thiazolidinediones
  - P12A odds ratio ~1.20
  - HbA$_{1c}$ reduction ~0.5%

- **KCNJ11** is the target for sulfonylureas
  - E23K odds ratio ~1.15
  - HbA$_{1c}$ reduction ~1-1.5%

- **HMGCR** is the target for statins
  - SNP rs12654264 changes LDL by ~3 mg/dl
  - Statins lower LDL by 30-50% *and save lives*
“The variants identified will be useful in individual clinical prediction”

Meigs et al. *NEJM* 2008;359:2208-19
Genetic + metabolomic prediction

Walford et al., Diabetes Care 2014 (in press)
Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

S. E. Inzucchi · R. M. Bergenstal · J. B. Buse · M. Diamant · E. Ferrannini · M. Nauck · A. L. Peters · A. Tsapas · R. Wender · D. R. Matthews

Healthy eating, weight control, increased physical activity

Metformin

- high
- low risk
- neutral/loss
- GI / lactic acidosis
- low

If needed to reach individualised HbA₁c target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea(b)</td>
<td>Thiazolidinedione</td>
<td>DPP-4 Inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (usually basal)</td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>low risk</td>
<td></td>
</tr>
<tr>
<td>hypoglycaemia(c)</td>
<td>oedema, HF, Fx(c)</td>
<td>rare(c)</td>
<td>low</td>
<td></td>
</tr>
<tr>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td></td>
</tr>
</tbody>
</table>

\(b\): commonly used; \(c\): rare adverse effects, not always applicable.
The Diabetes Prevention Program

- 3234 subjects with IGT
- Randomized to placebo, lifestyle or metformin
- 585 additional patients initially randomized to troglitazone
- Followed for 4 years
- DNA collected

Risk reduction: 58% lifestyle, 31% metformin

DPP Research Group
*NEJM* 346:393-403, 2002
**MATE1 and diabetes incidence in DPP**

Jablonski *et al.*, *Diabetes* 2010;59:2672-2681

**Genotype at rs8065082**

- **CC**
- **CT**
- **TT**

Cases/100 person-yr

- **Placebo**
- **Metformin**
- **Lifestyle**
Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

S. E. Inzucchi · R. M. Bergenstal · J. B. Buse · M. Diamant · E. Ferrannini · M. Nauck · A. L. Peters · A. Tsapas · R. Wender · D. R. Matthews

**Healthy eating, weight control, increased physical activity**

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sulfonylurea&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Thiazolidinedione</td>
<td>DPP-4 Inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (usually basal)</td>
<td></td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
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</tr>
<tr>
<td>moderate risk</td>
<td>high</td>
<td>low risk</td>
<td>low</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>risk</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>hypoglycaemia&lt;sup&gt;c&lt;/sup&gt;</td>
<td>oedema, HF, Fx&lt;sup&gt;c&lt;/sup&gt;</td>
<td>rare&lt;sup&gt;c&lt;/sup&gt;</td>
<td>GI&lt;sup&gt;c&lt;/sup&gt;</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>low</td>
<td>high</td>
<td>high</td>
<td>high</td>
<td>variable</td>
<td></td>
</tr>
</tbody>
</table>

If needed to reach individualised HbA1c target after ~3 months, proceed to two-drug combination (order not meant to denote any specific preference):

- Metformin + Sulfonylurea
- Metformin + Thiazolidinedione
- Metformin + DPP-4 Inhibitor
- Metformin + GLP-1 receptor agonist
- Metformin + Insulin
TCF7L2 Polymorphisms and Progression to Diabetes in the Diabetes Prevention Program

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Figure 1. Incidence of Diabetes According to Treatment Group and Genotype at Variant rs7903146. The P values were determined by the log-rank test.
Nature vs. Nurture

Hivert et al. for the DPP Research Group, *Diabetes* 60:1340–1348, 2011
A realistic appraisal

1. GWAS, if well powered, can indeed help characterize the genetic architecture of complex diseases
2. In complex traits the genetic effects of common variants are modest; similarly, variants with stronger effects tend to be rare. Thus, the integration of multiple datasets with large sample sizes is key
3. The genetic architecture of most traits will likely involve a combination of common and rare variants
4. Novel biology remains to be discovered
5. In type 2 diabetes, pharmacogenetics is in its infancy
6. An intensive lifestyle intervention appears to be effective regardless of genetic burden
7. Whether these genetic variants prove useful in disease prediction or therapeutic choices must be tested scientifically in a prospective fashion
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