Precision Medicine in Diabetes Mellitus: Where Are We Now?

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Diabetes Mellitus

• **Definition:** a *group* of metabolic diseases defined by hyperglycemia

• **Causes:** defects in insulin secretion and/or response to insulin

• **Consequences:** damage to organs, especially eyes, kidneys, nerves, heart and blood vessels

• **Prevalence:** ~9% (29 million people) and rising in U.S.
Diabetes Classification (ADA/WHO*)

- Type 1 Diabetes (T1DM)
- Type 2 Diabetes (T2DM)
- Other specific types (known etiology)
- Gestational diabetes mellitus (GDM, ~4% of pregnancies)

*ADA = American Diabetes Association
WHO = World Health Organization
Glucose Homeostasis

(β-cells)
(α-cells)

Primary sites of insulin resistance  Primary sites of onset of hyperglycemia

Source: Diabetes © 2004 American Diabetes Association, Inc.
Molecular medicine comes to the rescue
Targeted therapy turns life around for child with neonatal diabetes

On Monday, August 14, Lilly Jaffe, a six-year-old North Shore suburban girl who had been diagnosed with type 1 diabetes when she was one month old, checked into the Clinical Research Center at the University of Chicago Medical Center. On Friday, August 18, she checked out, starting to make her own insulin, well on her way to insulin independence and ready to get in a few days of beach time in Michigan before starting first grade.

Type 1 Diabetes: Familial Aggregation

![Bar Chart showing risk of Type 1 Diabetes in different groups: General Population, MZ Twin, DZ Twin, Sibling. The risk for MZ Twins is significantly higher than for other groups.](chart.png)
Genetics of Type 1 (Autoimmune) Diabetes

- **HLA (Chr 6)**: 45%
- **Insulin (Chr 11)**: 10%
- **Other**: 45%

Type 1 Diabetes

Genes

Environmental Factors

Cow’s Milk?  
Viruses?  
Toxins?  
Vaccines?
T1DM Genetics

Type 2 Diabetes: Familial Aggregation

- General Population
- MZ Twin
- DZ Twin
- Sibling

% Risk

- Gen. Pop.: 10
- MZ Twin: 70
- DZ Twin: 40
- Sibling: 40
Genetics of Type 2 Diabetes

- Genes
  - TCF7L2
  - KCNJ11
  - PPARG

- Type 2 Diabetes
- Obesity
- Physical Activity
- Diet
- Complications
- Medication
# Type 2 Diabetes Genetics

<table>
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<th>Insulin secretion / beta cell or islet function</th>
<th>Unknown</th>
<th>Insulin resistance</th>
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<tr>
<td>HNF4A</td>
<td>KCNQ1</td>
<td>CE</td>
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<td>GCK</td>
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<td>C2CD4A / C2CD4B</td>
<td>ZFAND3</td>
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<tr>
<td>IGF2BP2</td>
<td>GIPR</td>
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</tbody>
</table>

T2D susceptibility genes primarily found through:
- Linkage studies
- Candidate genes studies
- GWAS and GWAS meta-analyses
- GWAS and GWAS meta-analyses of both imputed and genotyped SNPs
- GWAS and GWAS meta-analyses for T2D-related quantitative traits
- GWAS based on Metabochip custom beadchips
- WES

Check out: type2diabetesgenetics.org

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**Maturity Onset Diabetes of the Young (MODY)**

**Transcription Factor/ Glucokinase Diabetes**

- **Definition:**
  - Early onset hyperglycemia (<25 years??)
  - Autosomal dominant inheritance
  - Impaired (but not absent) insulin secretion

- **Obesity not required**

- **Several different single gene forms**
  - Transcription factors in insulin secretion/beta or other cell development pathway (MODY 1, 3-14)
  - Glucokinase ("glucose sensor," MODY2)
  - Genes unidentified ("MODY X")

- **Can present like T2DM or as gestational diabetes (or even T1DM)**
43 patients with \textit{HNF1A} diabetes on insulin from diagnosis to genetic test

- 8 patients remain on insulin: Transfer not attempted
- 34 patients transferred to sulphonylureas
  - 24 patients remain on sulphonylureas
    - 15 patients with HbA$_{1c}$ < 7.5% 
    - 4 patients with HbA$_{1c}$ > 7.5% but improved by >1% 
    - 4 patients with HbA$_{1c}$ > 7.5% but unchanged 
    - 1 patient with HbA$_{1c}$ > 7.5% deteriorated
  - 10 patients back on insulin
    - 4 patients on sulphonylureas + insulin 
    - 6 patients on insulin only
      - 3 patients with HbA$_{1c}$ > 7.5% 
      - 1 patient with HbA$_{1c}$ > 7.5% 
      - 2 patients with HbA$_{1c}$ < 7.5% 
      - 4 patients with HbA$_{1c}$ > 7.5%
‘I don’t feel like a diabetic any more’: the impact of stopping insulin in patients with maturity onset diabetes of the young following genetic testing

Maggie Shepherd and Andrew T Hattersley

ABSTRACT – Hepatocyte nuclear factor-1α (HNF-1α) maturity onset diabetes of the young (MODY) is the commonest cause of monogenic diabetes but is frequently misdiagnosed as type 1 diabetes. The availability of genetic testing in MODY has improved diagnosis. Sulphonylurea sensitivity in HNF-1α patients means that those on insulin from diagnosis can transfer to sulphonylureas and may improve glycaemic control. To gain insight into the implications for patients of stopping insulin, in-depth interviews were conducted with eight HNF-1α patients transferred to sulphonylureas after a median of 20 years on insulin. Thematic content analysis highlighted four key themes:

- fear, anxiety and excitement regarding stopping insulin, particularly among those who had been on insulin for many years; they no longer required injections as this conflicted with messages previously received from healthcare professionals.

- Transferring from insulin to sulphonylureas had a positive impact on lifestyle but support was needed for patients to adjust, many having grown up with the belief they would be on insulin for life.

KEY WORDS: genetic testing, hepatocyte nuclear factor-1α (HNF-1α), maturity onset diabetes of the young (MODY), sulphonylurea sensitivity

Background

Maturity onset diabetes of the young (MODY) is an unusual genetic type of diabetes affecting 20,000 people in the UK. It is characterised by a young age of
Monogenic Diabetes is Underdiagnosed: The SEARCH Study

SEARCH cases with baseline in-person visit 2001-2006
n=5963

Had both DAA and FCP measures
n=5049

Positive DAA and/or FCP <0.8 ng/ml
n=4319 (85.5%)

Negative DAA and FCP ≥0.8 ng/ml
n=730 (14.5%)

Not tested for MODY*
n=144 (20%)

Tested for MODY**
n=586 (80%)

MODY-negative
n=539 (92%)

MODY-positive
n=47 (8%)

Pihoker et al (2013), JCEM 98:4055
SEARCH Participants with MODY Mutations

Clinical Diagnosis

Ethnicity

Treatment

Adapted from Pihoker et al (2013), JCEM 98:4055
Challenges

• Lack of provider/consumer/payer awareness
• Clinical overlap
• Notion that “rare means never”
• Life-changing vs. life-saving
• Expense/complexity of testing
• Resource prioritization
• Limited professional society guidance
• Time allotted to visits
Components of the Personalized Diabetes Medicine Program

Patient completes questionnaire

- Diagnosed before 1 year?
- Diagnosed before 30 years?
- Age of diagnosis ____
- Hearing or visual impairment/birth defects/ kidney disease?
- Extremely overweight at diagnosis?
- Type 1 diabetes?
- Parent or child with type 1 diabetes?
- 2 or more people related by blood with diabetes?

Further workup as indicated

- C-peptide Positive?
- IA-2 Antibody negative?
- Consistent family/ medical history elicited by genetic counselor

If indicated...

- Sequence 40 monogenic diabetes genes for mutations

If pathogenic or likely pathogenic variant found:

- Confirm, disclose and add to electronic health record and customize treatment
- Make genetic counseling and testing available to family members

If variant of unknown significance found:

- Segregation in family
- Functional studies
Next Generation Sequencing Panel

**MODY**
- HNF4A
- HNF1A
- PDX1/IPF1/STF1
- HNF1B
- NEUROD1
- KLF11
- CEL
- PAX4
- BLK

**Neonatal Diabetes**
- ABCC8
- GCK
- INS
- KCNJ11
- ZFP57

**Lipodystrophy**
- AGPAT2
- BSCL2
- CAV1
- LMNA
- PLIN1
- PPARG
- PPP1R3A
- PTRF

**Severe Obesity**
- MC4R
- LEP
- LEPR
- SIM1

**Syndromes**
- ALMS1
- CISD2/WFS2
- EIF2AK3
- FOXP3
- GATA6
- GLIS3
- INSR
- PTF1A
- RFX6
- SLC19A2
- SLC2A2
- WFS1

**Hyperinsulinemia**
- GLUD1
- HADH
Genetic Variant Interpretation Tool

To aid our variant interpretation process, we created an openly-available online tool to efficiently classify variants based on the evidence categories outlined in the article: Richards, et al. Standards and guidelines for the interpretation of sequence variants. 2015. This site displays the evidence categories and descriptions from Table 3 and Table 4 with simple checkboxes for selecting appropriate criteria. The site then incorporates the algorithm in Table 5 to automatically assign the pathogenicity or benign impact based on the selected evidence categories. Since our process often requires analyzing multiple variants per patient, we have also allowed the option of aggregating each variant into an exportable table at the foot of the website for easy documentation of the variant review process for our records. Although this tool is based on the ACMG/AMP Standards and Guidelines, it is not affiliated with ACMG, AMP, or any of the authors of the publication.

Click here to group evidence by category

Patient ID: [ ]
Variant ID: [ ]

- PVS1 null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease

- PS1 Same amino acid change as a previously established pathogenic variant regardless of nucleotide change
- PS2 De novo (both maternity and paternity confirmed) in a patient with the disease and no family history
- PS3 Well-established in vitro or in vivo functional studies supportive of a damaging effect on
Dissemination of the PDMP

Private Clinics/Providers ➔ Consumers ➔ Exportable Electronic CDS ➔ Professional Societies ➔ Bay West Endocrinology Associates
Evaluation of the PDMP

• Evaluation of impact of new diagnosis/treatment
  – Clinical outcomes
  – Patient reported outcomes
  – Barriers and facilitators
  – Qualitative studies of patient and provider experience

• Payer/Stakeholder Engagement (now network-wide)
  – Discuss opportunities and challenges to coverage decisions
  – Obtain insights for study/protocol designs and evidence desired
  – Understand process whereby new evidence is incorporated
Further Directions

- Customizing EPIC electronic health record templates to obtain input for Exeter MODY calculator
  [http://www.diabetesgenes.org/content/mody-probability-calculator](http://www.diabetesgenes.org/content/mody-probability-calculator)
- Telemedicine
- Patient/ provider conferences
- Genetic counselor/ other provider training
- Educational material development
- Collaboration
• Alan Shuldiner
• Kathleen Palmer
• Mickaela Nicholson
• Tom Fitzgerald
• Tameka Alestock
• Devon Nwaba
• Mary Pavlovich
• Kristin Maloney
• Casey Overby
• Daniel Mullins
• Daisuke Goto
• Kate Tracy
• Deborah Greenberg
• Stephanie Stein
• Kristi Silver
• Rana Malek

• Nanette Steinle
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• UM CDE Staff and Patients

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• Christy Haakonsen
• Marcia Ferguson

Bay West Endocrinology Associates

NHGRI U01 HG00775

IGNITE
Implementing Genomics In practice
• ignite-genomicmedicine.org

UMSOM Program for Personalized & Genomic Medicine
• medschool.umaryland.edu/genetics

UMBF Diabetes Research and Advocacy Fund
• medschool.umaryland.edu/mody

Enrollment Information
• http://umm.edu/programs/diabetes/research/clinical-trials
• ppgm@medicine.umaryland.edu
• 410-706-6140
Diabetes Research and Advocacy Fund (MODY)

Diabetes Research and Advocacy Fund (MODY)
A PROJECT OF RESEARCH

medschool.umaryland.edu/mody