Case # 1

- 30 y/o female, with diabetes diagnosed at age 27, (MTF for 3 months > insulin 70/30)
- No h/o DKA
- h/o SLE on variable doses steroids admitted with flare
- h/o steroids at age 16 for a nose bleed/hemoptysis > BGs in 500's (hospital)
- Insulin dose: 65 units with breakfast, 20 units with lunch, 20 units with dinner

Glycemic control (?)

Glycemic control (?)
Case # 2

- 30 y.o. female with history of T2DM diagnosed in 2006 (400 lbs)
- Initially treated with OADs switched to insulin
- Significant weight loss (~200 lbs)
- Home: Lantus 20 units every day at bedtime and Novolog 9 units AC (hypoglycemia)
- Hospital: well controlled on basal plus correction doses
How do we classify diabetes?

Diagnosis and classification of Diabetes Mellitus

Etiologic classification of diabetes mellitus

- **I. T1D** (β-cell destruction, usually leading to absolute insulin deficiency)
  - A. Immune mediated
  - B. Idiopathic
- **II. T2D** (range from IR with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
**The spectrum of diabetes**

- **T1DM in children**: Strong, immediate
- **T1DM in adults**: ++, low, immediate
- **LADA**: +, normal, variable
- **T2DM**: week, high, frequent


**Autoimmunity in Diabetes**

- **T1D**: Autoimmune form of β-cell damage
- **Antibodies**:
  - Islet-cell antibodies (ICA)
    - Present at onset in 70–80% of patients with type 1 diabetes
  - Present in a subset of patients with T2D


**Autoimmunity in Diabetes**

- After the original description of islet cell antibodies (ICAs) as a marker for T1D it was realized that some adult-onset patients are also ICA positive


**‘Latent autoimmune diabetes in adults’ (LADA)**

- Coined by Tuomi et al. in 1993
- Slowly progressive form of T1D treated initially without insulin
- Is there a LADY?

‘Latent autoimmune diabetes in adults’ (LADA)

- Coined by Tuomi et al. in 1993
- Slowly progressive form of T1D treated initially without insulin
- Is there a LADY?

What’s in a Name
Latent autoimmune diabetes of adults, type 1.5, adult-onset, and type 1 diabetes


‘Latent autoimmune diabetes in adults’ (LADA)

- GAD antibodies
- 35 years of age or older
- Nonobese
- Present without ketoacidosis and weight loss

Genetic, immunological, and metabolic differences between childhood-onset and adult-onset type 1 diabetes and LADA?

<table>
<thead>
<tr>
<th></th>
<th>Children T1DM</th>
<th>Adults T1DM</th>
<th>LADA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>Childhood</td>
<td>Adulthood</td>
<td>Adulthood</td>
</tr>
<tr>
<td>Identical twin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>concordance rate</td>
<td>Moderate (e.g. 38%)</td>
<td>Very low (e.g. 6%)</td>
<td>?</td>
</tr>
<tr>
<td>HLA-DR3/DR4</td>
<td>Moderate (e.g. 37%)</td>
<td>Low (e.g. 13%)</td>
<td>Low-moderate (e.g. 22%)</td>
</tr>
<tr>
<td>Protective HLA genotype</td>
<td>Very low (e.g. 9%)</td>
<td>Low (e.g. 15%)</td>
<td>Low-moderate (e.g. 22%)</td>
</tr>
<tr>
<td>Autoantibodies</td>
<td>IAA GAD IA-2</td>
<td>GAD IA-2</td>
<td>GAD IA-2</td>
</tr>
<tr>
<td>Plasma insulin</td>
<td>Very low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>


LADA, within Europe, when defined as non-insulin requiring diabetes diagnosed in individuals aged 30 to 50 years with GADA is found in about 10% of cases.

In populations outside Europe the frequency varies from:
- Zero in Papua New Guinea
- 16% Congo, 16% China
Definition

1. Adult onset (>30 years of age)
2. At least 6 months insulin independent after diagnosis
3. Positive for any islet autoantibody


Presence of ICA and GADA at different ages of diagnosis (UKPDS)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>ICA negative</th>
<th>ICA positive</th>
<th>GADA positive</th>
<th>Both positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>25–34 years</td>
<td>102 (65%)</td>
<td>33 (21%)</td>
<td>53 (34%)</td>
<td>31 (20%)</td>
</tr>
<tr>
<td>(n=157)</td>
<td>428 (84%)</td>
<td>45 (9%)</td>
<td>73 (14%)</td>
<td>38 (7%)</td>
</tr>
<tr>
<td>35–44 years</td>
<td>1099 (89%)</td>
<td>69 (6%)</td>
<td>113 (9%)</td>
<td>43 (3%)</td>
</tr>
<tr>
<td>(n=508)</td>
<td>1613 (91%)</td>
<td>66 (4%)</td>
<td>122 (7%)</td>
<td>32 (2%)</td>
</tr>
<tr>
<td>45–54 years</td>
<td>1613 (91%)</td>
<td>66 (4%)</td>
<td>122 (7%)</td>
<td>32 (2%)</td>
</tr>
<tr>
<td>(n=1238)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>55–65 years</td>
<td>1613 (91%)</td>
<td>66 (4%)</td>
<td>122 (7%)</td>
<td>32 (2%)</td>
</tr>
<tr>
<td>(n=1769)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Phenotype of patients with and without ICA and GADA in each age-group (UKPDS)

BMI

HbA1c

B-Cell function

Proportion of patients requiring insulin therapy during 6-years’ follow-up

Prevalence of autoantibodies in high and low GADA titer and in T2DM patients

High and low GADA titer according to the number of autoantibodies

LADA and CARDS: A Prospective Study of Clinical Outcome in Established Adult-Onset Autoimmune Diabetes

- 2,425 European patients with presumed type 2 diabetes (mean age 62 years, diabetes duration 7.9 years)
- Screen for autoantibodies to
  - GAD (GADA)
  - Insulinoma-associated antigen-2 (IA-2A)
  - Zinc-transporter 8 (ZnT8A).
LADA and CARDS: A Prospective Study of Clinical Outcome in Established Adult-Onset Autoimmune Diabetes

- A total of 173 patients
  - (7.1%) had GADA
    - 11 (0.5%) and 5 (0.2%) were also positive for IA-2A and ZnT8A
    - At baseline, 44% of GADA-positive patients were not on insulin
  - Fewer autoantibody-positive than autoantibody-negative patients had
    - metabolic syndrome (64 vs. 80%),
    - more on insulin (56 vs. 17%)
    - without lower HbA1c (8.5% vs. 7.8%)

Hawa et al. Diabetes Care June 2014 vol. 37 no. 6 1643-1649

Identification of Novel Autoantibodies in Type 1 Diabetic Patients Using a High-Density Protein Microarray

- In Europeans, the intronic TCF7L2 rs7903146 variant is the strongest identified genetic risk factor for type 2 diabetes

**Type 2 diabetes susceptibility gene variants predispose to adult-onset autoimmune diabetes**

- **AIM**: genetic characterization of LADA
- **Hypothesis**:
  - T2D-associated gene variants also predispose to LADA
  - Associations are strongest in LADA patients with low levels of GADA
- **METHODS**: 41 type 2 diabetes-associated gene variants in Finnish (phase I) and Swedish (phase II) patients (>35yrs)
  - LADA (n = 911)
  - type 1 diabetes (n = 406),
  - non-diabetic control individuals 40 years or older (n = 4,002).
- **KCNN1 (rs2237895, p = 0.0012), HHEX (rs1111875, p = 0.0024 in Finns) and MTNR1B (rs10830963, p = 0.0039) loci showed the strongest association in patients with low GADA**

*Andersen et al. Diabetologia. 2014 Jun 7. [Epub ahead of print]*

**LADA (Summary)**

- Adult onset (usually > 30 years)
- Less common FHx of T2D
- May appear to be a Non-obese T2D (10-20%)
- GADA, ICA, Zn8Ab
- May be controlled initially with Diet / ADOs
- Gradual need for insulin (~80% insulin in 6 yrs)
- Those with more Antibodies progress faster

**Why is it important?**

- No established management strategy
- ? Avoidance of using metformin (theoretical risks) in patients becoming insulin deficient
- Early introduction of insulin therapy
- Application of intervention trials to arrest or reverse the destructive disease process

*http://www.actionlada.org/*
Maturity–onset diabetes of the young (mody)

Definition and Epidemiology

• MODY: a heterogeneous group of monogenic disorders, caused by beta-cell dysfunction and characterized by:
  – Autosomal dominant inheritance (but varying penetrance)
  – Young age of onset (2\textsuperscript{nd}-4\textsuperscript{th} decades)
  – Continued secretion of endogenous insulin

• Estimated to be the underlying cause of diabetes in 1-2% of patients diagnosed with diabetes

• Estimated to be the underlying cause of diabetes in 1-2% of patients diagnosed with diabetes

11/12/2014
**MODY – Clinical characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T1D</th>
<th>T2D</th>
<th>HNF1A/HNF4A</th>
<th>GCK</th>
<th>PNDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical age at diagnosis</td>
<td>6 months-young adulthood</td>
<td>&gt;25 years</td>
<td>15-45 years</td>
<td>Mid fasting hyperglycemia</td>
<td>from birth 0-12 months</td>
</tr>
<tr>
<td>Family history of DM</td>
<td>10% of cases</td>
<td>&gt;50% in young onset</td>
<td>50-100% of cases</td>
<td>Common</td>
<td>10% of cases</td>
</tr>
<tr>
<td>B-cell antibodies</td>
<td>-90% at diagnosis</td>
<td>Negative</td>
<td>Rare</td>
<td>Rare</td>
<td>Negative</td>
</tr>
<tr>
<td>C-peptide levels</td>
<td>Low-undetectable</td>
<td>Normal/high</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Diabetic Ketoacidosis</td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>First line treatment</td>
<td>Insulin</td>
<td>Oral hypoglycemics</td>
<td>Low dose of Sulphonylureas</td>
<td>None</td>
<td>KCNJ11/ABCC8: high dose sulphonylureas Others: Insulin</td>
</tr>
</tbody>
</table>


**MODY – mutations**

- **HNF1A**: 414 different mutations in 1247 families
- **HNF4A**: 103 mutations in 173 families
- **GCK**: 620 mutations in 1441 families

Mutations in these three genes include: missense, nonsense, splice site mutations, frameshifts, promoter mutations and in-frame aminoacid deletions, insertions or duplications

Colclough et al. European Journal of Human Genetics (2014) 22,
### GENETIC MUTATIONS

<table>
<thead>
<tr>
<th>Protein</th>
<th>GCK</th>
<th>HNF1A (TCF1)</th>
<th>HNF4A</th>
<th>PDX1 (IPF1)</th>
<th>NEUR OD1</th>
<th>HNF1B (TCF2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODY 2</td>
<td>MODY 3</td>
<td>MODY 1</td>
<td>MODY 4</td>
<td>MODY 6</td>
<td>MODY 5</td>
<td></td>
</tr>
<tr>
<td>Mutation frequency (%) (not known in ~20% of cases)</td>
<td>20-50</td>
<td>20-50</td>
<td>-5</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>-5</td>
</tr>
</tbody>
</table>

Thanabalasingham & Owen. BMJ 2011; 343: D6044

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### Glucokinase (GCK) MODY 2: Characteristics

- Defect in glucose sensing, leads to increase in blood glucose threshold that triggers insulin secretion
- Decreased storage of hepatic glycogen and increased hepatic gluconeogenesis following standard meals → postprandial hyperglycemia
- In cohort of 82 children with incidental hyperglycemia, 43% had GCK mutations.


---

### Glucokinase (GCK) MODY 2: Characteristics

1. Fasting hyperglycemia is mild (5.5-8 mmol/l = 99-144 mg/dL) and persistent (at least 3 separate occasions) and stable over time (months-years).
2. HbA1c is usually just above the upper limit of normal and rarely exceeds 8%.
3. In OGTT, increment is small (< = 4.6 mmol/l = 83 mg/dL).
4. Parents may have “type 2 diabetes” with no complications or may not be diabetic. On testing, one parent will usually have mildly raised fasting blood glucose.
5. Do not develop diabetes related microvascular complications.
7. Can be diagnosed at any age.
8. Reduced birth weight.

Glucokinase (GCK) Mody 2: Management

- Diet and lifestyle changes
- Drugs do NOT improve glycemic control (can stop anti-diabetic drugs)
  - Observational study in 20 pts treated with insulin or OAD, with no change in A1c after treatment stopped after diagnosis of GCK MODY
- Annual follow-up with blood glucose and HbA1c levels
- Consider genetic testing for 1st degree relatives (50% risk of inheriting mutation)

GENETIC MUTATIONS

<table>
<thead>
<tr>
<th>Protein</th>
<th>MODY 2</th>
<th>MODY 3</th>
<th>MODY 4</th>
<th>MODY 5</th>
<th>MODY 6</th>
<th>MODY 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucokinase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNF1A (TCF1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNF4A</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDX1 (IPF1)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEUR OD1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HNF1B (TCF2)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Mutation frequency (%): Glucokinase 20-50, HNF1A 20-50, HNF4A 10-50, PDX1 <1, NEUR OD1 <1, HNF1B <1

Thanabalasingham & Owen. BMJ 2011; 343: D6044

HNF 1α (MODY 3)

1. The most common form of MODY.
2. Young-onset (usually before 25yo).
3. Progressive beta cell defect with evidence of microvascular disease (i.e. retinopathy)
4. Non-insulin-dependent outside the normal honeymoon period (3yrs)
5. Family history of diabetes (at least 2 generations).
6. Very large glucose increment (>5mmol/l = 90mg/dL) with OGTT
7. Absence of pancreatic islet autoantibodies
8. Glycosuria at blood glucose levels <180mg/dL
9. Marked sensitivity to sulfonylureas (i.e. hypoglycemia despite poor glycemic control)
10. Absence of typical features of type 2 DM: No marked obesity or evidence of insulin resistance in diabetic family members, absence of acanthosis nigricans, ethnic background with low prevalence of type 2 DM
HNF 1α (MODY 3) Management

- Low-dose sulfonylureas as first-line treatment
  - Randomized controlled crossover trial: 5x greater drop in fasting plasma glucose with low dose gliclazide vs metformin.
  - Case reports show worsening glycemic control when transferring from SU to metformin.
- Eventually may need insulin due to progression of disease
- Prandial secretagogues
  - Nateglinide reduced postprandial glucose excursions in 15 pts

HNF1A (MODY-3) Clinical Characteristics

| Table 1. Main characteristics of 196 MODY3 and 282 non-MODY3 patients |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                            | MODY3                       | Non-MODY3                   | P value                     |
| At diagnosis               | 196                         | 282                         |                            |
| Euro-Caucasian/other        | 192                         | 278                         | 0.0015                      |
| Age at onset of symptoms   | 193                         | 272                         | 0.0001                      |
| Age < 20                   | 137                         | 235                         | 0.0001                      |
| Age > 60                   | 64                          | 68                          | 0.0011                      |
| CRP levels (<1 mg/l)       | 50                          | 75                          | 0.0001                      |
| HbA1c (%)                  | 7.4±2.13-13                | 7.4±2.16-17                 | 0.0001                      |
| Duration of follow-up (yr) | 191                         | 270                         | 0.0005                      |
| BMI (kg/m²)                | 9.3±7.4-4.2                | 8.3±6.1-4.3                 | 0.0002                      |
| HbA1C (%)                  | 7.4±2.16                   | 7.4±2.16                    | 0.055                       |
| Arterial hypertension (%)  | 186                         | 274                         | 0.033                       |
| HbA1C (%)                  | 7.4±2.13                   | 7.4±2.13                    | 0.033                       |
| HbA1c (%)                  | 7.4±2.16                   | 7.4±2.16                    | 0.033                       |
| Hypercholesterolemia (%)   | 176                         | 267                         | 0.007                       |
| Total cholesterol (mg/dl)  | 171                         | 275                         | 0.0001                      |
| Triglycerides (mg/dl)      | 180                         | 266                         | 0.0009                      |
| Urine acid (mM/l)          | 108                         | 156                         | 0.0028                      |
| Urine creatinine (mM/l)    | 219                         | 219                         | 0.0369                      |
| Treatment MODY 3

- HNF1A mutations have unusual sensitivity to Sulphonylureas (SU) (Treatment of choice with ~5% reduction in HbA1c)
- The sensitivity maintains for years (up to 13 yrs) after Dx
- Start with very low doses of short acting SU (risk of hypoglycemia)
- Cessation of SU may be associated with marked deterioration in glycemic control
- Progressive loss of pancreatic B-cell function and increase in treatment regimen required in some cases.

CRP Levels-MODY 3

- There is HNF1A binding site in the CRP promoter gene → CRP is mediated through HNF1A expression
- Lower Serum hsCRP levels
- ROC curve illustrating the capacity of hs-CRP to distinguish between HNF1A-MODY and type 2 diabetes.

HNF1α (MODY-3) Clinical Characteristics

Bellanne-Chantelot C et al. JCEM. 2011;96(8):1-6

Bellen-Hou et al. 2011:36(8):1-6


Diabet. Med. 2000;17, 543-545
Treatment MODY 3

Nateglinide vs. Glibenclamide -MODY 3

GENETIC MUTATIONS

<table>
<thead>
<tr>
<th>Protein</th>
<th>MODY 2</th>
<th>MODY 3</th>
<th>MODY 1</th>
<th>MODY 4</th>
<th>MODY 5</th>
<th>MODY 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucokinase</td>
<td>GCK</td>
<td>HNF1A</td>
<td>HNF4A</td>
<td>PDX1</td>
<td>NEUR OD1</td>
<td>HNF1B</td>
</tr>
<tr>
<td>Hepatocyte nuclear factor-1 alpha</td>
<td>HNF4A</td>
<td>HNF4A</td>
<td>HNF4A</td>
<td>HNF4A</td>
<td>HNF4A</td>
<td>HNF4A</td>
</tr>
<tr>
<td>Insulin promoter factor-1</td>
<td>PDX1</td>
<td>PDX1</td>
<td>PDX1</td>
<td>PDX1</td>
<td>PDX1</td>
<td>PDX1</td>
</tr>
<tr>
<td>Neurogenic differentiation 1</td>
<td>NEUR OD1</td>
<td>NEUR OD1</td>
<td>NEUR OD1</td>
<td>NEUR OD1</td>
<td>NEUR OD1</td>
<td>NEUR OD1</td>
</tr>
<tr>
<td>Hepatocyte nuclear factor-1 beta</td>
<td>HNF1B</td>
<td>HNF1B</td>
<td>HNF1B</td>
<td>HNF1B</td>
<td>HNF1B</td>
<td>HNF1B</td>
</tr>
</tbody>
</table>

Mutation frequency (%) (not known in ~20% of cases)

- GCK: 20-50
- HNF1A (TCF1): 20-50
- HNF4A: ~5
- PDX1 (IPF1): <1
- NEUR OD1: <1
- HNF1B (TCF2): ~5

Thanabaleshingham & Owen. BMJ 2011; 343: D6044

HNF 4α (MODY 1)
HNF 4α (MODY 1)

- 31 mutations reported worldwide (in 40 families)
- Phenotypically similar to HNF 1α (MODY 3), penetrance lower (5-10% of MODYs)
- Later age of diagnosis
- Progressive beta cell failure with increasing treatment needs
- No low renal threshold for glucose
- Sensitive to sulfonylureas
- Associated with macrosomia (56% of carriers) and transient neonatal hypoglycemia (15% of carriers)

HNF 4α (mody 1) management

(Same as HNF 1α)

- Low dose sulfonylureas as first-line treatment
- Can switch from insulin to orals safely

GENETIC MUTATIONS

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<td>Protein</td>
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</tr>
<tr>
<td>Mutation frequency (%)</td>
<td>20-50</td>
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<td>~5</td>
<td>&lt;1</td>
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<td>~5</td>
</tr>
</tbody>
</table>

Thanabalsingh & Owen. BMJ 2011; 343: D6044
HNF 1β (MODY 5)

- Rare cause of MODY
- More than 65 different mutations identified in 143 families
- Plays important role in early development of pancreas, kidney and nephron differentiation
- First case found in family with non-diabetic renal dysfunction

HNF 1β (mody 5)

- Renal manifestations (more common)
  - Non-diabetic cystic renal disease → Renal Cysts and Diabetes (RCAD)
  - Oligomeganephronia
  - Cystic dysplasia
  - Familial hypoplastic glomerulocystic kidney disease
  - 50% will develop ESRD before age of 45
- Early-onset, non-insulin dependent diabetes- mean age of diagnosis in early 20s
- Progressive deterioration of beta cell function
- Microvascular disease (i.e. proliferative retinopathy) observed

HNF 1β (MODY 5) management

- More frequently and more rapidly treated with insulin (67% vs 31% compared to HNF1α mutation patients)
- Likely due to generalized reduction in β-cell mass

GENETIC MUTATIONS

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<tr>
<th>Protein</th>
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<th>HNF1A (TCF1)</th>
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<th>NEUR OD1</th>
<th>HNF1B (TCF2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation frequency (%)</td>
<td>MODY 2</td>
<td>MODY 3</td>
<td>MODY 1</td>
<td>MODY 4</td>
<td>MODY 6</td>
<td>MODY 5</td>
</tr>
<tr>
<td>Renal manifestations</td>
<td>Glucokinase</td>
<td>Hepatocyte nuclear factor-1 alpha</td>
<td>Hepatocyte nuclear factor-4 alpha</td>
<td>Insulin promoter factor-1</td>
<td>Neurogenic differentiation 1</td>
<td>Hepatocyte nuclear factor-1 beta</td>
</tr>
</tbody>
</table>
| Non-diabetic cystic renal disease | 20-50 | 20-50 | -5 | <1 | <1 | <5 | Thanabalasingham & Owen. BMJ 2011; 343: D6044
**IPF-1 or PDX 1 (MODY 4)**

- Very rare
- PDX1 (pancreatic duodenal homeobox-1) is required for pancreatic development—both endocrine and exocrine cell types
- Heterozygous carriers: phenotype varies from impaired glucose tolerance to overt noninsulin dependent diabetes
- 1 child with homozygous mutation born with pancreatic agenesis

**Clinical approach**

- Consider MODY in type 1 diabetics who:
  - Continued endogenous insulin secretion (C-peptide production, low insulin dose) and no tendency to ketoacidosis when insulin omitted 3-5yrs after diagnosis
  - Absence of pancreatic autoantibodies?
  - Case-control study reported <1% in MODY
  - Pediatric survey found 17% of confirmed MODY had positive antibodies.
  - Presence of antibodies should not preclude genetic testing when high clinical suspicion

**IPF 1 (MODY 4)**

- Average age of onset 35yo
- Less severe than HNF-1α mutations
- Milder missense mutations of IPF-1 predispose to type 2 DM
- May be part of polygenic predisposition to young onset type 2 diabetes
Clinical approach

- Consider MODY in type 2 diabetics who:
  - Young age at diagnosis (<25yo or <30yo)\(^*\)
  - No features of insulin resistance (i.e. acanthosis nigricans, central obesity, hypertension, dyslipidemia)

- Another cross sectional study showed 12/291 patients (4%) with HNF1\(\alpha\) or HNF4\(\alpha\) mutations (used <30yo at diagnosis or absence of metabolic syndrome for stratification).

Future modes for diagnosing and treating MODY

- Novel drug that increases GCK activity, “GK-activators (GKA)”- shown to decrease fasting plasma glucose and improve glucose tolerance
- Serum high-sensitive CRP (hsCRP)- found to be significantly lower in HNF1\(\alpha\)-MODY
- Urine C-peptide creatinine ratio (UCPCR)- measure of endogenous insulin secretion, found to be lower in type 1 diabetes than HNF1\(\alpha\)/4\(\alpha\) MODY

Further areas of research

- ~30% of MODY cases have unexplained genetic etiologies- what novel mechanisms of \(\beta\)-cell functional defects are yet undefined?
- What are the health economics of establishing an accurate diagnosis of MODY?
- Are newer treatments for type 2 diabetes, i.e. GLP-1 agonists, effective in MODY patients?
- What effect will cheaper and faster genetic testing have on diagnosis rates of MODY?
- Genomic medicine towards individualized prevention and treatment in both MODY and type 2 diabetes

Diagnostic Approach

- Thanabalasingham & Owen. BMJ 2011; 343: D6044
Why is w/u of MODY important?

- Genetic testing confirms a Dx of MODY
- Classifies the subtype
- Predict clinical course and may change the patient’s treatment.
- First-degree relatives will be at 50% risk of inheriting the mutation
- Asymptomatic individuals may be offered predictive genetic testing (after appropriate genetic counselling) in order to provide reassurance (for those shown not to carry the mutation) or regular blood glucose monitoring with early diagnosis and appropriate treatment (for mutation carriers)

Thanabalasingham & Owen. BMJ 2011; 343: D6044