Monogenic Diabetes in 17q12 Deletions:  
The Role of HNF1β

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Outline

- What is diabetes?
- Types of diabetes
- Monogenic diabetes
- HNF1β mutations and Diabetes – MODY 5
What is Diabetes?

• Group of metabolic diseases characterized by high blood sugar (hyperglycemia) due to defects in:
  – Insulin action
  – Insulin secretion
  – Both

• Effects chronic hyperglycemia:
  – leads to disturbances in metabolism
  – long-term damage, dysfunction and failure of eyes, nerves, kidneys and blood vessels

Thomas, Med Clin N. Amer, 2015
What is Diabetes?

• Normal glucose: 70-130 mg/dL

• WHO Diagnostic Criteria - Diabetes:
  – Fasting glucose > 126 mg/dL
  – 2hr post-prandial glucose > 200 mg/dL
  – HgbA1C > 6.5%

Thomas, Med Clin N. Amer, 2015
Classification of Diabetes Mellitus

Fig. 1. Diabetes Classification.

Thomas, Med Clin N. Amer, 2015
<table>
<thead>
<tr>
<th>Type</th>
<th>Proportion of Cases</th>
<th>General Description</th>
<th>Inheritance</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes</td>
<td>~ 5%</td>
<td>- Genetics and Environmental Triggers (?virus)</td>
<td>One parents with Type 1 DM: child’s risk is ~ 1 in 20</td>
<td>- Insulin</td>
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<td></td>
<td></td>
<td>- Autoimmune +</td>
<td>Both parents have Type 1 DM: child’s risk is 1 in 10</td>
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<tr>
<td></td>
<td></td>
<td>- Beta cell destruction</td>
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<td></td>
<td></td>
<td>- Children/young adults</td>
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<td></td>
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<td>- Thinner</td>
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<tr>
<td>Type 2 Diabetes</td>
<td>90-95%</td>
<td>- Genetics and Lifestyle</td>
<td>One parents with Type 2 DM: child’s risk is ~ 1 in 10</td>
<td>- Oral hypoglycemic</td>
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<td></td>
<td>- Obesity</td>
<td>Both parents have Type 2 DM: child’s risk is 1 in 2</td>
<td>medications</td>
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<td></td>
<td></td>
<td>- Antibody negative</td>
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<td>- Insulin</td>
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<tr>
<td></td>
<td></td>
<td>- Insulin Resistance</td>
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<tr>
<td>Monogenic Diabetes</td>
<td>~ 1-2 %</td>
<td>- Single gene defects affecting pancreatic development and Insulin secretion</td>
<td>One parents with monogenic diabetes: child’s risk is ~ 1 in 2</td>
<td>- Oral Hypoglycemic</td>
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<tr>
<td></td>
<td></td>
<td>- Antibody negative</td>
<td>Many cases are new mutations</td>
<td>medications</td>
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<td></td>
<td>- Low Birth Weight</td>
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<td>- Insulin</td>
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<td></td>
<td></td>
<td>- Oral</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hypoglycemic medications</td>
</tr>
<tr>
<td>Gestational Diabetes</td>
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<td>- Hyperglycemia that presents during pregnancy and resolves after birth</td>
<td>Similar to Type 2 DM</td>
<td>- Insulin</td>
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<td></td>
<td></td>
<td>Many women with GDM go on to develop Type 2 DM</td>
<td>- ? Oral hypoglycemic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>medications</td>
</tr>
</tbody>
</table>
Type 1 versus Type 2 Diabetes – an overly simplistic view
Monogenic Diabetes

- Heterogeneous group of single-gene disorders characterized mainly by pancreatic beta cell dysfunction

- Subtypes of monogenic diabetes:
  - Permanent (or transient) Neonatal Diabetes: first 6 months of life
  - Familial Monogenic Diabetes

- Accounts for approximately 1-2% of diabetes
Familial Monogenic Diabetes

- First recognized by Tattersall Tattersall QJ Med 1974
- Dominant inheritance
- Beta cell dysfunction
- Variable features include:
  - age of onset
  - severity of the hyperglycemia (and hence risk of complications)
  - associated clinical features
- Non-genetic factors that affect insulin sensitivity may trigger the onset of diabetes and affect the severity of hyperglycemia
Types of Monogenic Diabetes

- Transcription Factors = 66%
  - HNF1A = 61%
  - HNF4A = 4%
  - HNF1B = 2%
  - IPF1 = <1%
  - NEUROD1 = <1%
- X = 12%
- GCK = 22%
- CEL = <1%
- INS = <1%

Molecular Genetics

- Not a single entity but is a heterogeneous disease with regard to genetic, metabolic, and clinical features

- Heterozygous mutations:
  - HNF4A (Type 1)
  - GCK (Type 2)
  - HNF1A (Type 3)
  - IPF1 (Type 4)
  - HNF1B (Type 5)
  - NeuroD1/Beta2 (Type 6)
  - Others: KCNJ11, GATA4, Ngn3, INS, CEL

- Mutations include: missense, nonsense, splicing, small deletions/insertions/duplications, and splice site and promoter region mutations. Partial and whole deletions have recently been reported in HNF1A, GCK and HNF1B
Mechanisms of Disease

- Reduced metabolism
  - Reduced glucose sensing: GCK
  - Reduced metabolism: HNF1A, HNF1B, HNF4A, IPF1 heterozygous

- Reduced β-cell number
  - Pancreatic aplasia: IPF1 homozygous; PTF1A
  - Reduced β-cell development: HNF1B

- Increased destruction of β-cells
  - Endoplasmic reticulum stress: EIF2AK3, INS
  - Increased apoptosis cause uncertain: HNF1A, HNF4A
Types of Monogenic Diabetes and Age of Presentation

![Diagram showing types of monogenic diabetes and age of presentation](image)
HNF1β

- Hepatic Nuclear Factor 1 Beta
- Transcription Factor
- Mutations in HNF1B are the most common monogenic cause of developmental kidney disease
- Mutations first discovered 1997
- RCAD – Renal Cysts and Diabetes Syndrome
- No clear genotype-phenotype correlation (not all cases in one family have the same symptoms)
Renal and Extra-renal phenotypes of patients with HNF1B mutations

Figure 1 | Renal and extra-renal phenotypes frequently observed among patients with hepatocyte nuclear factor 1β-associated disease.

Clisshold, Nat Rev Nephrol, 2015
• 50% of mutations are whole gene deletions (not shown)
• No correlation seen between specific site of mutation and clinical features has been observed
• 50% of patients have de novo (new - not inherited) mutations
HNF1B Monogenic Diabetes (MODY 5)

- 1% of cases of monogenic diabetes
- Most diagnoses before age 25
- Beta cell dysfunction and insulin resistance
- History of low birth weight
- Pancreatic aplasia or hypoplasia
- Autosomal dominant - new mutations common (50%)
- Variable presentation: Diabetes diagnosis from newborn period up to age 60 or later
- Can develop vascular complications from high blood sugar
- 2005: 17q12 deletions including HNF1B are the most frequent cause of MODY 5
HNF1B Diabetes: Diagnosis

General Symptoms of Diabetes

- Fasting glucose > 126 mg/dL and post-prandial glucose > 200 mg/dL
- Negative pancreatic antibodies
- Persistent fasting C-Peptide (endogenous insulin)
- Insulin deficiency and insulin resistance
- Renal impairment with raised creatinine
- Low Magnesium
- High Uric Acid
- Elevated Liver Enzymes
HNF1B Diabetes: Treatment

- Insulin is main treatment to control blood sugars
- Does not respond to sulfonylureas (oral medication)
- Must consider kidney function
- Can develop hyperlipidemia
- Monitor for vascular complications (heart, blood vessels, kidney, peripheral nerves)
- Patients with HNF1B mutations/deletions susceptible to developing diabetes after kidney transplant
- Pancreatic insufficiency – treat with pancreatic enzymes for digestion
Questions?

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