Age-Adjusted Prevalence of Diagnosed Diabetes Among US Adults

2008

Diabetes: Genetics

Concordance Rates in Identical Twins:

Type 1 Diabetes: ~40%.

Type 2 Diabetes: ~90%.

Type 1 Diabetes Genes

1. MHC Locus >50% of genetic risk
Type 1 Diabetes Genes

1. MHC Locus  >50% of genetic risk
2. Insulin Gene

Type 2 Diabetes: The Search for Genes

- Although type 2 diabetes runs in families, the inheritance in most families is complex.

- Currently, family history remains the most valuable genetic test.

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<table>
<thead>
<tr>
<th>TABLE 17-5 Etiologic classification of diabetes mellitus.</th>
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</thead>
<tbody>
<tr>
<td>I. Type 1 diabetes* (β cell destruction, usually leading to absolute insulin deficiency)</td>
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<tr>
<td>A. Immune-mediated, type 1a</td>
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<tr>
<td>B. Idiopathic, type 1b</td>
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<tr>
<td>II. Type 2 diabetes* (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with minimal insulin resistance)</td>
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<tr>
<td>A. Autoimmune dominant genetic defects of pancreatic β cells</td>
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<tr>
<td>1. Maturity onset diabetes of the young (MODY)</td>
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<td>2. Insulin gene (INS)</td>
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<td>3. ATP-sensitive potassium channel (KCNJ11 and ABCC8)</td>
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<tr>
<td>B. Other genetic defects of pancreatic β cells</td>
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<tr>
<td>1. Autosomal recessive genetic defects</td>
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<tr>
<td>2. Mitochondrial DNA</td>
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<tr>
<td>3. Ketosis prone diabetes (KPD)</td>
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<tr>
<td>C. Genetic defects in insulin action</td>
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<tr>
<td>1. Insulin receptor mutations</td>
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<tr>
<td>2. Lipoprotein lipase deficiency</td>
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<tr>
<td>D. Neonatal diabetes</td>
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<tr>
<td>1. Transient</td>
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<tr>
<td>2. Permanent</td>
</tr>
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<td>E. Diseases of the exocrine pancreas</td>
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<tr>
<td>1. Pancituitaritis</td>
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<tr>
<td>2. Trauma, pancreatectomy</td>
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<tr>
<td>3. Neoplasia</td>
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<tr>
<td>4. Cystic fibrosis</td>
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<td>5. Hemochromatosis</td>
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<tr>
<td>6. Fibrocystic pancreaticopathy</td>
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<tr>
<td>F. Endocrinopathies</td>
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<tr>
<td>1. Acromegaly</td>
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<td>2. Cushing syndrome</td>
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<tr>
<td>3. Hyperparathyroidism</td>
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<tr>
<td>4. Pheochromocytoma</td>
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<tr>
<td>5. Hypothyroidism</td>
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<tr>
<td>6. Somatostatinoma</td>
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<tr>
<td>7. Aldosteronoma</td>
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<tr>
<td>G. Drug- or chemical induced</td>
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<tr>
<td>1. β cell toxicity: vancomycin, pentamidine, cyclosporine</td>
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<td>2. β cell autoreactivity in inter fron</td>
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<td>3. β cell dysfunction: thiazide and loop diuretics, diuretics, a agnostics, β blockers, phenytoin, opiates</td>
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<tr>
<td>4. Insulin resistance: glucocorticoids, progesterone, nicotinic acid, thyroid hormone, β blockers, atypical antipsychotic drugs, antiretroviral protease inhibitors</td>
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<tr>
<td>H. Infections</td>
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<tr>
<td>1. Congenital rubella</td>
</tr>
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<td>2. Other viruses: cytomegalovirus, coxsackievirus B, adenoviruses, measles</td>
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<tr>
<td>1. Unknown causes of immune-mediated diabetes</td>
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<tr>
<td>1. Sjögren syndrome</td>
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<tr>
<td>2. Immune-mediated polyendocrinopathy enteropathy, X-linked (IPPEX)</td>
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<tr>
<td>3. Autoimmune polyendocrinopathy syndrome type 1</td>
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<tr>
<td>4. Anti-insulin receptor antibodies</td>
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<tr>
<td>5. Autoimmune thyroiditis (antireceptor antibodies)</td>
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<tr>
<td>6. PORIS syndrome</td>
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<tr>
<td>7. Other genetic syndromes associated with diabetes</td>
</tr>
<tr>
<td>1. Chromosomal defects: Down, Klinefelter, and Turner syndromes</td>
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<tr>
<td>2. Neuroendocrine syndromes: Friedrich ataxia, Huntington chorea, Myotonic dystrophy, pheochromocytoma and others</td>
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<tr>
<td>3. Obesity syndromes: Laurence-Moon-Biedl, Bardet-Biedl, and Prader-Will syndrome, and others</td>
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<tr>
<td>4. Wolfram syndrome</td>
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<tr>
<td>IV. Gestational diabetes mellitus (GDM)</td>
</tr>
</tbody>
</table>

Types of Diabetes

1. Type 1 diabetes. 1/200
2. Type 2 diabetes. 1/12
3. Monogenic Diabetes. 1/200
4. Secondary Diabetes. 1/200
5. Gestational Diabetes (GDM). 1/6 pregnancies

Diabetes: Genetics

Monogenic Diabetes

- Maturity Onset Diabetes of the Young (MODY)
- Neonatal Diabetes (TNDM & PNDM)
- Mitochondrial Diabetes
- Rare forms of severe insulin resistance
- Syndromic Diabetes
MODY: *Maturity Onset Diabetes of the Young*

- Autosomal dominant inheritance pattern. --Every generation, 50%
- Onset commonly before age 25.
- Not obese.
- Islet autoantibodies negative.

MODY2: *GCK Glucokinase*

- Combined $\beta$-cell and liver defect. Impaired insulin secretion in response to glucose.
- Moderate hyperglycemia.
- No disease progression.
- Low incidence of complications.
MODY3: *HNF1A/TCF1*

- β-cell defect.
  - Impaired insulin secretion.
- Severe hyperglycemia.
- Disease progression.
- High incidence of complications.
- Very sensitive to sulfonylureas.
- Low renal glucose threshold.
MODY Genes

MODY1: $HNF4A$
MODY2: $GCK$
MODY3: $HNF1A / TCF1$
MODY5: $HNF1B / TCF2$

MODY5: $HNF1B$

- β-cell defect.
  - Impaired insulin secretion.
- Severe hyperglycemia.
- Disease progression.
- High incidence of complications.
- Congenital renal defects.
- Hypomagnesemia.
- Hypoplastic pancreas.
- Rarely presents as Neonatal Diabetes.
MODY Genes

MODY1: HNF4A
MODY2: GCK
MODY3: HNF1A / TCF1
MODY4: PDX1 / IPF1
MODY5: HNF1B / TCF2
MODY6: NEUROD1
MODY7: KLF11

MODY Genes

MODY1: HNF4A
MODY2: GCK
MODY3: HNF1A / TCF1
MODY4: PDX1 / IPF1
MODY5: HNF1B / TCF2
MODY6: NEUROD1
MODY7: KLF11
MODY8: CEL
MODY9: PAX4
MODY10: INS
MODY11: BLK
Neonatal Diabetes

- Onset before age 6 months.
- TNDM Transient (<1 year).
- PNDM Permanent.

**Transient:**
- 6q24 (paternal isodisomy)
- ZFP57 (recessive)

**Trans/Perm:**
- KCNJ11/Kir6.2 (activating/dominant)
- ABCC8/SUR1 (activating/dominant)

**Permanent:**
- GATA6, GLIS3, MNX1, NEUROD1, NEUROG3, NKX2.2, PAX6, PDX1/IPF1, PTF1, RFX6 (recessive)
- GCK (recessive)
- EIF2AK3/PERK (recessive)
- INS (dominant)

**Autoimmune:**
- FoxP3 (X-linked recessive)

**Syndromic**
Neonatal Diabetes

154 TNDM cases 100%

- 105 (68%) 6q24 abnormalities
- 49 (32%) 6q24 normal

- 34 (22%) KCNJ11 normal
- 15 (10%) KCNJ11 mutations

- 20 (13%) ABCC8 mutations
- 14 (9%) ABCC8 normal


Mitochondrial Diabetes

- Maternally inherited
- Non-obese
- Insulin deficiency
- Associated with deafness and other neural defects
- Caused by mutations in the mitochondrial genome
Severe insulin Resistance

- **INSR** (Insulin signaling)
- **AKT2** (Insulin signaling)
- **LMNA** (Lipodystrophy)
- **LMNB2** (Lipodystrophy)
- **AGPAT2** (Lipodystrophy)
- **BSCL2** (Lipodystrophy)
- **PPARG** (Lipodystrophy)

Syndromic Diabetes

- Chromosomal defects: Down's, Klinefelter's, and Turner's syndromes.
- Neuromuscular syndromes: Friedreich's ataxia, Huntington's chorea, Myotonic dystrophy, porphyria, others.
- Wolfram's syndrome.
- Thiamine Responsive Megloblastic Anemia.
- Polyautimmune syndromes: APS1, IPEX.
Clinical Approach to Genetic Forms of Diabetes

- Why perform genetic tests?
- Identifies family members at risk.
- Provides information regarding natural history, outcomes.
- Can alter management.
- What test do you do?
- Depends on pretest probability, costs, insurance.

Exome Sequencing
Prior Probability of Specific Clinical Diagnosis

Low
High

Locus Heterogeneity

Limited and Known
Large and Known
Unknown

- Whole Exome/Genome
- Gene Panels
- Specific Gene Testing

Exome Sequencing

- Originally a research tool.
- Now a CLIA approved test.
- Available through UCSF Diabetes and Clinical Genetics (UCSF/UCLA).
- Requires input from an experienced geneticist.
- Cannot identify with certainty all variants.
- Effective when gene specific tests not available or negative.
Patients with Monogenic Diabetes

- Later Onset
- Neonatal

Inheritance
- Maternal Mitochondrial sequence
- Autosomal Recessive
- Autosomal Dominant
- Autoimmune Autoimmune genes
- Ins Resistant Resistance genes
- Syndromic Gene specific

TNDM 6q24 KATP genes
PNDM Syndromic Gene specific Nonsyndromic KATP genes INS, GCK
MODY Syndromic Gene specific HNF1B, CEL Nonsyndromic

European Mild? = GCK Severe? = HNF1A
Non-Europeans Gene panel, Exome

German Lab Support

Hillblom Islet Genesis Network (Larry L. Hillblom Foundation)
Nora Eccles Treadwell Foundation
Helmsley Trust
Bruce Braden
Juvenile Diabetes Research Foundation
American Diabetes Association
NIH/NIDDK, UCSF DRC
References


