An Update on the Genetics of Diabetes

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Diabetes in the US

Total Diabetes Population
Source: Diabetes in America

Type 2

Type 1

“masquerading” as Type 2

Prevalence of Diabetes Among U.S. Adults

Prevalence in 1980

Prevalence in 1990-1994

Prevalence in 2000
Diabetes: Genetics

Concordance Rates in Identical Twins:

Type 1 Diabetes: ~40%.
Type 2 Diabetes: ~90%.

But What Are the Genes?

Diabetes: Genetics

1. Type 1 Diabetes Genes
2. Monogenic Diabetes
   • Maturity Onset Diabetes of the Young (MODY)
   • Neonatal Diabetes
   • Mitochondrial Diabetes
   • Rare forms of severe insulin resistance
3. Type 2 Diabetes
   • Genome Wide Association Studies
Type 1 Diabetes Genes

1. MHC Locus  >50% of genetic risk

2. Insulin Gene
Type 1 Diabetes Genes

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


Type 2 Diabetes: The Search for Genes

- Although type 2 diabetes runs in families, the inheritance in most families is complex.
- Therefore, focus on families with simple, Mendelian inheritance patterns -- monogenic diabetes.
MODY: *Maturity Onset Diabetes of the Young*

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

MODY2: *Glucokinase*

- Combined β-cell and liver defect. Impaired insulin secretion in response to glucose.
- Moderate hyperglycemia.
- No disease progression.
- Low incidence of complications.
MODY2: Glucokinase

- Glucokinase
- GT-2
- Glycolysis
- Mitochondria
- ATP
- K⁺
- Ca⁺⁺
- Signal
- β-cell
- Insulin secretion

MODY2: Glucokinase

- β-cell Sensitivity
- glucokinase mutation
- Insulin Sensitivity
- [Insulin]
- [Glucose]
MODY2: Glucokinase

**Lessons**

- Modest changes in the sensitivity of the β-cell to glucose can cause big changes in glucose levels.
- Much larger changes in insulin sensitivity are required to cause similar changes in glucose levels.
MODY3: HNF1A/TCF1

- β-cell defect.
  Impaired insulin secretion.
- Severe hyperglycemia.
- Disease progression.
- High incidence of complications.
MODY Genes

MODY1: HNF4A
MODY2: Glucokinase
MODY3: HNF1A / TCF1

MODY: β-cell Dysfunction

Fajans, Bell, and Polonsky, NEJM, 2001
MODY: $\beta$-cell Dysfunction

MODY Genes

- MODY1: $HNF4A$
- MODY2: Glucokinase
- MODY3: $HNF1A / TCF1$
- MODY4: $PDX1 / IPF1$
- MODY5: $HNF1B / TCF2$
- MODY6: $NEUROD1$
- MODY7: $KLF11$
- MODY8: $CEL$
Insulin Promoter Model

- E47
- NEUROD1
- PDX1
- TF IID
- RNA Pol II
- HMG I(Y)

Islet Cell Lineage

- Progenitor
- Nkx2.2
- Nkx6.1
- Pax4
- Sox4
- Pet1
- Brn4
- Arx
- Irx
- Sox2
- Sox9
- HNF1a,b
- HNF4a
- FoxA
- HB9
- Lmx1a
- P48
- HNF6
MODY: HNF1A Lessons

- Decreases in the maximal β-cell capacity can cause big increases in glucose levels, especially as demand (insulin resistance) increases.
- Decreases in β-cell mass could cause such decreases in maximal β-cell capacity.
**β Cell Mass in Adult Humans**

A. Butler, et al. Diabetes 2003

**Progressive Hyperglycemia: Secondary to Beta Cell Failure**

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Neonatal Diabetes

Transient (<1yr) -vs.- Permanent
Neonatal Diabetes

Transient: 6q24 (paternal isodisomy)

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

Permanent: PDX1/IPF1 (recessive)
Permanent: PTF1 (recessive)
Permanent: RFX6 (recessive)
Permanent: GCK (recessive)
Permanent: EIF2AK3/PERK (recessive)
Permanent: INS (dominant)

Autoimmune: FoxP3 (recessive)
Rfx6 Expression at E10

Nina Kishimoto

Rfx6-/- Mice at P1

Stuart Smith & David Scheel
**Rfx6−/− Mice at E17.5**

Stuart Smith & David Scheel

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**Human Neonatal Diabetes with Intestinal Atresia**

Neonatal diabetes, with hypoplastic pancreas, intestinal atresia and gall bladder hypoplasia: search for the aetiology of a new autosomal recessive syndrome

J. Mitchell¹ · Z. Punthakee¹ · B. Lo¹ · C. Bernard¹ · K. Chong² · C. Newman³ · L. Cartier⁴ · V. Desilets⁵ · E. Cutz⁶ · L. L. Hansen⁷ · P. Riley⁸ · C. Polychronakos¹


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Clinical Report

A Further Example of a Distinctive Autosomal Recessive Syndrome Comprising Neonatal Diabetes Mellitus, Intestinal Atresias and Gall Bladder Agenesis

Louise Chappell¹, Shaun German³, Fiona Campbell¹, Signelland¹, Gillian Rice⁹

Mutations in Human Patients.

5 Probands tested:

4 Homozygous *RFX6* mutations.
1 Compound heterozygote.
Splicing site and missense mutations.

- Arg>Gln
- Ser>Pro

**DNA BINDING**

**DIMERIZATION**

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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)
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Type 2 Diabetes: Genome Wide Association Studies
Type 2 Diabetes: Genome Wide Association Studies

Common low risk variants

-vs.-

Rare high risk mutations

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References


References


