ATP-sensitive potassium channelopathies: focus on insulin secretion

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Mechanisms of glucose-stimulated insulin secretion

Glucose uptake by GLUT-2

Glucose → Glucokinase → Glucose 6-phosphate → ATP (glycolysis)

ATP-sensitive K⁺ channel closes

Ca²⁺ channel opens → Ca²⁺ influx

Depolarisation

Exocytosis → Insulin secretion

Granule translocation

Resting negative charge

Sulphonylurea receptor

K⁺ channel closes

Insulin release
The $K_{ATP}$ channel couples glucose metabolism to insulin secretion.
PATCH CLAMP MEASUREMENTS
APPLIED TO NEURONS
Molecular structure of the K\textsubscript{ATP} channel

A

Sulfonlyurea receptor
SUR1, SUR2A, or SUR2B

Pore subunit
Kir6.2 or Kir6.1

Inhibit
ATP
ADP

Activate
PIP\textsubscript{2}
LC acyl-CoA

Inhibit
Sulfonlyureas

Activate
K channel openers
MgATP
MgADP

B

SUR1
K\textsubscript{i}r6.2

C

Extracellular

Kir6.2

Intracellular

SUR1
<table>
<thead>
<tr>
<th>Position</th>
<th>Mutation</th>
<th>Insulin secretion</th>
<th>Neurol. features</th>
<th>Epilepsy</th>
<th>ATP sensitivity</th>
<th>Po</th>
<th>Reference</th>
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<td>HI</td>
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<tr>
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</table>

Mutations in Kir6.2 that cause HI or monogenic diabetes. TMs, transmembrane domains; neurol. features, neurological features (i.e., developmental delay, epilepsy, or other symptoms). The numbers in parentheses refer to the number of cases. Position refers to the position of the residue in the primary sequence of the protein.
Location of disease-causing mutations in Kir6.2.
### Table 2
Disease severity correlates with extent of MgATP block

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Phenotype</th>
<th>Fraction unblocked $I_{-}\text{K}_{\text{ATP}}$ at 1 mM MgATP</th>
<th>Reference</th>
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<tr>
<td>WT</td>
<td>None</td>
<td>2.4%</td>
<td>33</td>
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<td>G53S</td>
<td>TNDM</td>
<td>6%</td>
<td>33</td>
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<td>G53R</td>
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<td>33</td>
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<td>I182V</td>
<td>TNDM</td>
<td>12%</td>
<td>33</td>
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<tr>
<td>R201H</td>
<td>PNDM</td>
<td>22%</td>
<td>33</td>
</tr>
<tr>
<td>I296L</td>
<td>DEND syndrome</td>
<td>36%</td>
<td>84</td>
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</tbody>
</table>

Fraction of unblocked $K_{\text{ATP}}$ current measured in the heterozygous state in the presence of 1 mM ATP for WT (Kir6.2/SUR1) and Kir6.2 mutant channels.
PNDM mutations reduce channel inhibition by ATP

The IC50 was 7, 12, 300 µM for WT, heterozygous R201H, and homomorphic R201H channels.

The IC50 was 13, 140, 50 µM for WT, heterozygous R201H, and homomorphic R201H channels.
Effects of Kir6.2 mutations on channel gating

A

WT homomeric  Heteromeric  Mutant homomeric

B

Kir6.2/SUR1

Kir6.2-R201C/SUR1

Kir6.2-Q52R/SUR1

Kir6.2-V59G/SUR1

Closed

5 pA

0.5 s

Po

0.53

0.6

0.83

0.83
Implications for therapy

• Early-onset type 1 diabetes (PNDM caused by mutations in Kir6.2) treated with insulin
  – channels are less sensitive to the drugs
  – can be managed on sulfonylureas
  – combination of insulin, to control their diabetes, and sulfonylureas, to control the extrapancreatic effects

• A key question
  – whether sulfonylureas will be effective at treating CNS symptoms
Conclusions

• $K_{ATP}$ channel activity in the β cell is finely balanced
  – a key regulator of insulin release
  – Increased activity leads to reduced insulin secretion
  – Reduced channel activity increases insulin release.

• Consequently, mutations that either directly or indirectly alter β cell $K_{ATP}$ channel activity produce a spectrum of diseases that ranges from severe HI to DEND syndrome
• Mutations in Kir6.2 cause both diabetes and HI

• Mutations in SUR1 are, to date, entirely associated with hyperinsulinism

• A total loss of protein (Kir6.2 or SUR1) will necessarily result in loss of KATP channel activity and thus HI.
Activating Mutations in the $ABCC8$ Gene in Neonatal Diabetes Mellitus

Andrey P. Babenko, M.D., Ph.D., Michel Polak, M.D., Ph.D., Hélène Cavé, D.Pharm., Ph.D., Kanetee Busiah, M.D., Paul Czernichow, M.D., Raphael Scharfmann, Ph.D., Joseph Bryan, Ph.D., Lydia Aguilar-Bryan, M.D., Ph.D., Martine Vaxillaire, D.Pharm., Ph.D., and Philippe Froguel, M.D., Ph.D.

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ABSTRACT

Background

• The ATP-sensitive potassium (KATP) channel
  – SUR + Kir6.2 (inward-rectifying potassium channel subunit)
  – a key regulator of insulin release

• The balance of these opposing actions
  – determines the low open-channel probability, PO
  – controls the excitability of pancreatic beta cells

• Hypothesis :
  – activating mutations in ABCC8, which encodes SUR1, cause neonatal diabetes
Methods

- screened the 39 exons of *ABCC8* in 34 patients with permanent or transient neonatal diabetes of unknown origin.
- Assayed the electrophysiologic activity of mutant and wild-type KATP channels
ABSTRACT

Results

- Identified 7 missense mutations in 9 pts
- Four mutations were familial and showed vertical transmission with neonatal and adult-onset diabetes
  - The remaining 3 mutations were not transmitted and not found in more than 300 patients without diabetes or with early-onset diabetes of similar genetic background.
• Mutant channels in intact cells and in physiologic concentrations of magnesium ATP had a markedly higher PO than did wild-type channels.

• These overactive channels remained sensitive to sulfonylurea
  – treatment with sulfonylureas resulted in euglycemia.
• Dominant mutations in \textit{ABCC8} accounted for 12 percent of cases of neonatal diabetes in the study group.

• Diabetes results from a newly discovered mechanism whereby the basal magnesium-nucleotide–dependent stimulatory action of SUR1 on the Kir pore is elevated and blockade by sulfonylureas is preserved.
Neonatal diabetes

• A form of diabetes mellitus defined by the onset of mild-to-severe hyperglycemia within the first months of life.
  – Permanent neonatal diabetes requires lifelong therapy
  – transient neonatal diabetes remits early, with a possible relapse during adolescence
  – Some cases, mutations in the \textit{KCNJ11} gene, (Kir6.2)
Neonatal diabetes

• The beta-cell \( \text{K}_{\text{ATP}} \) channel is a hetero-octamer
  – Kir6.2 and the high-affinity beta-cell sulfonylurea receptor (SUR1, encoded by \( ABCC8 \)).

• \( \text{K}_{\text{ATP}} \) channels link nutrient metabolism with membrane electrical activity

• Cases of neonatal diabetes of unknown cause
  – screened for mutations in \( ABCC8 \).
Methods

• 1995 - 2005, 73 patients from the French Network for the Study of Neonatal Diabetes Mellitus:
  – 44 transient neonatal diabetes
  – 29 permanent neonatal diabetes
  – 3 pancreatic aplasia or hypoplasia
• Screened
  – for abnormalities in chromosome 6q24
  – mutations in the *KCNJ11* gene;
    • glucokinase sequencing was restricted to patients with PNDM
• Alterations in chromosome 6q
  – 25 TNDM

• Mutations in the *KCNJ11* gene
  – 13 patients (18 %)
    • 12 PNDM
    • 1 TNDM

• 34 remaining patients for mutations in the *ABCC8* gene using sequence analysis,
  • 16 PNDM, 18 TNDM
Clinical Studies

- glucagon stimulation test
  - 1 mg iv,
  - C-peptide 5’ and 0’ before glucagon and 5’, 10’, and 15’ afterward

- glyburide (glibenclamide) stimulation test
  - 0.2 mg/kg/d, po
  - gradually increasing the dose during a one-week period.
  - Glucose levels were monitored and insulin was discontinued when satisfactory metabolic control was achieved.
The mutations were introduced into hamster ABCC8 cDNA and coexpressed with human Kir6.2, including green fluorescent protein (to mark transfection) in COSm6 cells.
Electrophysiological Analysis

• Patch–clamp recordings and analyses of the $K_{ATP}$-channel current
Results
**ABCC8 Mutations in PNDM, TNDM**

- 7 heterozygous *ABCC8* mutations in 9 of 34 patients with neonatal diabetes:
  - 2 PNDM: L213R and I1424V in
  - TNDM: C435R, L582V, H1023Y, R1182Q, and R1379C
- no mutations:
  - 180 patients with diabetes
  - 140 unrelated white persons of French origin without diabetes
  - 24 MODY probands without known MODY-associated mutations
N: wild type; M: mutant; gray: neonatal diabetes; black: T2D later in life; hatched: remitting diabetes; III-3 gestational diabetes;
### Table 1. Clinical Characteristics of Probands with Neonatal Diabetes with Mutant SUR1

<table>
<thead>
<tr>
<th>Family No.</th>
<th>Mutation</th>
<th>Sex</th>
<th>Wk of Gestation</th>
<th>Birth Weight g (percentile)</th>
<th>Age at Diagnosis</th>
<th>Weight at Diagnosis</th>
<th>Glucose mmol/liter</th>
<th>Age at Metabolic Testing</th>
<th>Height cm (SD) †</th>
<th>Weight (kg (percentile))</th>
<th>Insulin U/kg/day</th>
<th>Current Treatment</th>
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<td><strong>Permanent neonatal diabetes</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>12</td>
<td>L213R</td>
<td>Male</td>
<td>41</td>
<td>3065 (22)</td>
<td>125</td>
<td>5320</td>
<td>28.6</td>
<td>4.75</td>
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<td>17 (50)</td>
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<td>Glib, 10 mg/day</td>
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<td>178 (+0.9)</td>
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<td>0.88</td>
<td>Glib, 15 mg/day</td>
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<td><strong>Transient neonatal diabetes</strong></td>
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<td>3210</td>
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<td>117 (+1.9)</td>
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<td>2050 (&lt;3)</td>
<td>3</td>
<td>2100</td>
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<td>114.3 (+1.6)</td>
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<td>3400 (55)</td>
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<td>NA</td>
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<td>16</td>
<td>180 (+1.2)</td>
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<td>0.5</td>
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<td>4</td>
<td>1680</td>
<td>13.6</td>
<td>2</td>
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<td>3570 (67)</td>
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<td>1.8</td>
<td>92 (+2)</td>
<td>14 (90)</td>
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* Glib denotes glyburide, NA not available, and Glip glipizide. To convert values for glucose to milligrams per deciliter, divide by 0.05551.

† Values in parentheses are the standard deviation from the norm.
Neurologic Features

- developmental delay
- dyspraxia
- slow ideation
- minor visual and spatial dyspraxia
- None had the facial features associated with some mutations of $KCNJ11$
- None had abnormal cognitive function or development
Metabolic Tests

• The baseline fasting levels of C-peptide in 2 PNDM
  – Low (0.24 and 0.63 nM, respectively)
  – Increased by 358 % to 1.1 nM and by 222 percent to 1.4 nM, 2h after oral glyburide
Clinical Features of Neonatal Diabetes
According to Genetic Cause

• Low birth weights
  – anomalies of chromosome 6: 20/25
  – mutant SUR1: 3/7

• Macroglossia
  – 4/25 TNDM related to an anomaly in chromosome 6q24

• Ketoacidosis, developmental delay
  – only a few (ABCC8, KCNII, Chr 6)
Effect of \( ABCC8 \) Mutations on KATP Channel Activity
A  Without Nucleotides  B  With 0.5 mM Magnesium ATP and 0.5 mM ADP

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<th></th>
<th>1424V</th>
<th>Wild-Type</th>
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<th>Mutant</th>
<th>Channel</th>
<th>Mutant</th>
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<td>0.4</td>
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<td>0.1</td>
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</table>

C  Normal Beta Cell  D  Normal Beta Cell

Stimulatory action of magnesium nucleotides (low ATP:ADP ratio)

E  Mutant Beta Cell  F  Mutant Beta Cell in the Presence of Sulfonylurea

Stimulatory action of magnesium nucleotides (elevated ATP:ADP ratio)

Increased glucose

Decreased Ca²⁺ influx

Decreased insulin secretion

Hyperglycemia

Stimulates insulin secretion

Membrane depolarization

Sulfonylurea

Reduced stimulatory action of magnesium nucleotides (elevated ATP:ADP ratio)
Discussion

• Data show that the net inhibitory action of ATP on two types of neonatal diabetes caused by a mutant SUR1 channel was unchanged (as compared with wild-type SUR1)

• The increased activity of the channels, under physiologic conditions, was caused by an increase in the magnesium-dependent stimulatory action of SUR1 on the pore.
• oral sulfonylurea therapy should be effective
  – for most patients with neonatal diabetes caused by mutant SUR1.
  – also for patients with Kir6.2 mutations
• The diagnosis of diabetes in fathers with \textit{ABCC8} mutations is consistent with adult-onset type 2 diabetes mellitus or a mild form of transient neonatal diabetes.

• The potential contribution of overactive \textit{ABCC8} mutations to familial early-onset type 2 diabetes remains to be evaluated.
ATP-Sensitive Potassium Channels — Neonatal Diabetes Mellitus and Beyond

Mark A. Sperling, M.D.

• Diabetes patients under six months of age
  – 30 to 58 % activating mutations in \textit{KCNJ11}
    • (encoding the Kir6.2 subunit of the ATP-sensitive potassium (KATP))

• Diabetes
  – impaired insulin secretion
  – failure of the beta-cell KATP channel to close
    • in response to increased intracellular ATP

• Presentation
  – ketoacidosis or severe hyperglycemia
  – treated with insulin.

• Sulfonylureas
  – close the KATP channel by an ATP-independent route.
• 49 patients with Kir6.2 mutations
  – who received appropriate doses of sulfonylureas

• in smaller subgroups
  – investigated the insulin secretory responses to iv & oral glucose, a mixed meal, & glucagon.

• The response of mutant KATP channels to the sulfonylurea tolbutamide
  – Assayed in xenopus oocytes.
• Successfully discontinued insulin by sulfonylureas
  – 44 patients (90 %)
  – in vitro, the extent of the tolbutamide blockade of KATP channels reflected the response seen in patients.

• Glycated hemoglobin levels
  – improved in all patients who switched to sulfonylurea therapy (from 8.1 to 6.4 % after 12 weeks of treatment, P<0.001).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (N=49)</th>
<th>Patients with Successful Switch (N=44)</th>
<th>Patients with Unsuccessful Switch (N=5)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic features — no. (%)</td>
<td>NA</td>
<td>6 (14), all with intermediate DEND (1 with G53N and 5 with V59M)</td>
<td>4 (80), including 2 with DEND (with Q52R and I296L) and 2 with intermediate DEND (with G53R and R201C)</td>
<td>0.004</td>
</tr>
<tr>
<td>Male sex — %</td>
<td>51</td>
<td>55</td>
<td>20</td>
<td>0.39</td>
</tr>
<tr>
<td>Birth weight — g</td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>Median</td>
<td>2710</td>
<td>2740</td>
<td>2550</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>2405 to 3090</td>
<td>2420 to 3115</td>
<td>2075 to 2683</td>
<td></td>
</tr>
<tr>
<td>Birth weight — SD score</td>
<td></td>
<td></td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>Median</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-2.0</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>-2.2 to -0.5</td>
<td>-2.2 to -0.5</td>
<td>-2.7 to -1.1</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis — mo</td>
<td></td>
<td></td>
<td></td>
<td>0.76</td>
</tr>
<tr>
<td>Median</td>
<td>1.5</td>
<td>1.5</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0.5 to 3.0</td>
<td>0.6 to 3.0</td>
<td>0.4 to 4.0</td>
<td></td>
</tr>
<tr>
<td>Ketoadacidosis at diagnosis — %</td>
<td></td>
<td></td>
<td></td>
<td>0.66</td>
</tr>
<tr>
<td>Age at initiation of sulfonylurea treatment — yr</td>
<td>33</td>
<td>34</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td>6</td>
<td>18</td>
<td>0.04</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>3 to 14</td>
<td>3 to 12</td>
<td>6 to 35</td>
<td></td>
</tr>
<tr>
<td>Weight at time of switch to sulfonylurea treatment — SD score</td>
<td>0.05</td>
<td>0.12</td>
<td>-0.41</td>
<td>0.38</td>
</tr>
<tr>
<td>Median</td>
<td>-0.69 to 0.90</td>
<td>-0.61 to 0.98</td>
<td>-2.63 to 1.13</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>-0.61 to 0.98</td>
<td>-0.61 to 0.98</td>
<td>-2.63 to 1.13</td>
<td></td>
</tr>
<tr>
<td>C-peptide levels undetectable — no. (total no. (%))</td>
<td>24/28 (86)</td>
<td>20/24 (83)</td>
<td>4/4 (100)</td>
<td>0.11</td>
</tr>
<tr>
<td>Insulin dose — U/kg/day</td>
<td></td>
<td></td>
<td></td>
<td>0.07</td>
</tr>
<tr>
<td>Median</td>
<td>0.7</td>
<td>0.7</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0.6 to 0.9</td>
<td>0.6 to 0.9</td>
<td>0.4 to 0.7</td>
<td></td>
</tr>
<tr>
<td>Glycated hemoglobin — %</td>
<td></td>
<td></td>
<td></td>
<td>0.65</td>
</tr>
<tr>
<td>Median</td>
<td>8.0</td>
<td>8.1</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>7.1 to 9.5</td>
<td>7.1 to 9.4</td>
<td>5.3 to 9.5</td>
<td></td>
</tr>
<tr>
<td>Equivalent dose of glyburide — mg/kg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>NA</td>
<td>0.45</td>
<td>1.0</td>
<td>NA</td>
</tr>
<tr>
<td>Range</td>
<td>0.05 to 1.30</td>
<td>0.80 to 2.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>0.25 to 0.82</td>
<td>0.90 to 1.74</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* DEND denotes developmental delay, epilepsy, and neonatal diabetes; and NA, not applicable.
† P values are for the comparison of the patients with a successful switch with patients with an unsuccessful switch and were calculated by the Mann-Whitney test or Fisher's exact test for categorical data.
‡ C-peptide levels were considered undetectable if they were below 165 pmol per liter.
Reduction in Glycated Hemoglobin Levels Associated with Switching from Insulin to Sulfonylurea Therapy
Correlation between the Sensitivity of KATP Channels to Sulfonylurea and Clinical Response in Patients with Kir6.2 Mutations.
Physiologic Studies of the Effect and Associated Mechanisms of Sulfonylurea Treatment on Insulin Secretion
Proposed Model of the Action of Sulfonylurea on Beta Cells Expressing Mutations in the Kir6.2 Subunit of the KATP Channel
• Improved glycemic control was sustained at one year.

• Sulfonylurea treatment
  – increased insulin secretion,
  – more stimulated by oral glucose or a mixed meal than by intravenous glucose.

• Exogenous glucagon increased insulin secretion
  – only in the presence of sulfonylureas
Conclusions

• Sulfonylurea therapy is safe
  – in the short term for patients with diabetes caused by
    $KCNJ11$ mutations
  – is probably more effective than insulin therapy

• This pharmacogenetic response to sulfonylureas
  – may result from the closing of mutant KATP channels,
  – thereby increasing insulin secretion in response to
    incretins and glucose metabolism.
Switching from Insulin to Oral Sulfonylureas in Patients with Diabetes Due to Kir6.2 Mutations

Ewan R. Pearson, et al.
Neonatal diabetes mellitus

- Rare
  - incidence of 1 per 500,000 newborns and an estimated incidence of 1 per 100,000

- Most newborns with neonatal diabetes mellitus
  - are born with intrauterine growth restriction (IUGR).
  - The degree of IUGR is proportional to the degree of insulin deficiency in utero;
  - This confirms the important role of insulin as a growth factor during gestation
• Treatment with insulin results in dramatic catch-up growth; after several weeks or months, insulin may be discontinued in about half these patients

• But diabetes mellitus may recur in the second to third decade of life
• Most of these cases of transient neonatal diabetes mellitus are caused by a gain-of-function mutation in a zinc-finger gene.

• A transgenic mouse model created by insertion of the human locus reproduces most of the human features and should provide important clues to this condition
• Half of patients with neonatal diabetes mellitus
  – have permanent diabetes mellitus from the outset

• A variety of genetic causes identified
  – homozygous inactivating mutations
    • such as pancreas duodenum homeobox 1 (PDX-1), also known as insulin promoter factor 1,
    – Affecting proteins involved in pancreas formation
  – Metabolic regulators
    • such as the enzyme glucokinase,
  – Transcription factors regulate insulin secretion
    • Also implicated are genes involved in several congenital malformations.

• PDX-1 also contributes to classic type 2 diabetes mellitus in adults.
• The most common cause of permanent neonatal diabetes mellitus,
  – activating mutations in the *KCNJ11* gene, encoding Kir6.2
    • a subunit of the ATP-sensitive potassium channel (*K*_{ATP}) of the beta cell
    • reported two years ago
      – Gloyn AL. N Engl J Med 2004;350
• Another cause of permanent neonatal diabetes mellitus
  – activating mutations in \textit{ABCC8}, encoding SUR1
  • the other subunit of the beta-cell K\textsubscript{ATP} channel
The Kir6.2–SUR1 complex and its regulation and genetic variability. Panel A shows the detailed subunit structure of the KATP channel.

**Gain-of-function mutations in SUR1 and Kir6.2 genes**
Cause more $K_{ATP}$ channels to remain open, thereby decreasing insulin secretion and leading to neonatal diabetes mellitus.

**Loss-of-function mutations in SUR1 and Kir6.2 genes**
Cause more $K_{ATP}$ channels to remain closed, thereby causing dysregulation of insulin secretion and leading to neonatal hyperinsulinemic hypoglycemia.
Panel B shows the regulation of insulin secretion by glucose or amino acids (glutamate is used in this example).
• KATP channels composed of Kir6.2 and SUR1
  – widely expressed
  – regulating insulin secretion by beta cells
  – glucagon secretion by alpha cells
  – glucagon-like peptide 1 (GLP1) secretion by intestinal L cells

• They also modulate the counterregulatory response to hypoglycemia in the neurons of the ventromedial hypothalamus
• Inactivating mutations of the SUR1 gene
  – which keep the channel constitutively closed
  – dysregulated secretion of insulin
  – result in familial hyperinsulinemic hypoglycemia of infancy
  – Most cases of this condition are caused by mutations in SUR1
  – only a minority of cases result from inactivating mutations in the Kir6.2 gene
• Severe developmental delay, epilepsy, and dysmorphic features associated with neonatal diabetes mellitus (known as the DEND syndrome)
  – are present in some patients with permanent neonatal diabetes mellitus
• the successful switching from subcutaneous insulin injections to oral glyburide
  – 44 of 49 (90 %) with permanent neonatal diabetes mellitus Pearson et al. Aug.3, 2006

• Responses to sulfonylurea
  – extended in subgroups to investigate insulin responses to iv and oral glucose, a mixed meal, and iv glucagon, before and after treatment with the drug
• the use of glyburide restored insulin secretion
  – the effect was much stronger when patients received oral glucose or a mixed meal
    • than when they received intravenous glucose;
    • a response to glucagon was observed
      – only when the treatment of patients was successfully switched to sulfonylurea

• A1C markedly improved
  – 8.1 - 6.4 %/ 12 weeks of treatment
• The extent of OAD to close mutant $K_{ATP}$
  – proportionate to the patient's response.
  – closure of mutant KATP channels
    • binding of sulfonylurea to the SUR1 regulatory subunit
    • restores insulin secretion consequent to glucose metabolism
    • amplified effects through incretins such as GLP1, the levels of which increase after ingestion of nutrients.
• KATP channels also modulate the GLP1 response in gastrointestinal L cells and glucagon secretion by alpha cells.

• Counterregulatory hormone responses to hypoglycemia mediated by KATP channels in the ventromedial hypothalamus before and after treatment with a sulfonylurea may be the subject of future investigations.
• Ironic
  – OAD to treat millions of T2D, a disease of middle to older age
  – find its most physiologic application in newborns

• All newborns with clinical diabetes mellitus — transient or permanent — develops within six months after birth
  – should be tested for mutations in the gene encoding Kir6.2 first, then SUR1.
  – the $KCNJ11$ gene, 1 exon
    • a more common cause of permanent neonatal diabetes,
    • a sensible approach
  – the $ABCC8$ gene (SUR1), 39 exons, and because, as compared with mutant SUR1, mutant Kir6.2 is would be to analyze Kir6.2 first.) On
• Since neonatal diabetes mellitus is a congenital disease
  – incidence of 1 per 100,000 newborns,
  – has severe consequences if left untreated
  – in many cases can be treated by a pill
  – a test for it should be included as part of routine newborn screening programs
The role of these mutations in adults with diabetes mellitus

• One Kir6.2 mutation been identified
  – a cause of transient neonatal diabetes mellitus
  – childhood diabetes
  – later onset of classic type 2 diabetes mellitus

• Mutations affecting Kir6.2 and SUR1 have been identified in familial forms of diabetes mellitus
  – milder mutations may contribute to the clinical appearance of type 2 diabetes mellitus when insulin resistance develop
The role of these mutations in adults with diabetes mellitus

• Hence, genotyping of a large number of patients with type 2 diabetes mellitus
  – may prove rewarding by determining the extent to which patients with Kir6.2 mutations or polymorphisms
  – might benefit from sulfonylurea therapy