The molecular mechanisms and pharmacotherapy of ATP-sensitive potassium channel gene mutations underlying neonatal diabetes

Abstract: Neonatal diabetes mellitus (NDM) is a monogenic disorder caused by mutations in genes involved in regulation of insulin secretion from pancreatic β-cells. Mutations in the KCNJ11 and ABCC8 genes, encoding the adenosine triphosphate (ATP)-sensitive potassium (K\textsubscript{ATP}) channel Kir6.2 and SUR1 subunits, respectively, are found in ~50% of NDM patients. In the pancreatic β-cell, K\textsubscript{ATP} channel activity couples glucose metabolism to insulin secretion via cellular excitability and mutations in either KCNJ11 or ABCC8 genes alter K\textsubscript{ATP} channel activity, leading to faulty insulin secretion. Inactivation mutations decrease K\textsubscript{ATP} channel activity and stimulate excessive insulin secretion, leading to hyperinsulinism of infancy. In direct contrast, activation mutations increase K\textsubscript{ATP} channel activity, resulting in impaired insulin secretion, NDM, and in severe cases, developmental delay and epilepsy. Many NDM patients with KCNJ11 and ABCC8 mutations can be successfully treated with sulfonylureas (SUs) that inhibit the K\textsubscript{ATP} channel, thus replacing the need for daily insulin injections. There is also strong evidence indicating that SU therapy ameliorates some of the neurological defects observed in patients with more severe forms of NDM. This review focuses on the molecular and cellular mechanisms of mutations in the K\textsubscript{ATP} channel that underlie NDM. SU pharmacogenomics is also discussed with respect to evaluating whether patients with certain K\textsubscript{ATP} channel activation mutations can be successfully switched to SU therapy.

Keywords: neonatal diabetes, KCNJ11, ABCC8, ATP-sensitive potassium channels

Introduction

Neonatal diabetes mellitus (NDM), either transient or permanent, is characterized by the occurrence of insulin-requiring diabetes in the first 6 months of life. The incidence of NDM is estimated to be 1 in ~200,000 live births.\[^1\,^2\] The diabetes in 50%–60% of NDM is transient in nature, resolving within 18 months of birth and is thus termed TNDM.\[^3\] The remaining 40%–50% of NDM cases are permanent (PNDM) and require insulin treatment throughout life.\[^3\] In the most severe cases of NDM, the diabetes may be accompanied by marked developmental delay, muscle weakness, and epilepsy, termed DEND (developmental delay, epilepsy, and neonatal diabetes) syndrome.\[^4\] A form of NDM, between PNDM and DEND in severity, is known as intermediate DEND (iDEND), in which patients with PNDM show developmental delay or muscle weakness but not epilepsy.\[^5\]

The evidence to date indicates that NDM is a monogenic disorder. Although mutations in multiple genes can cause NDM, such as INS (insulin gene) mutations\[^5,^6\] and GCK (glucokinase gene) mutations,\[^7,^8\] much attention has focused on the most common forms of NDM caused by heterozygous activation mutations in the KCNJ11.\[^9,^10,^11\] and
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ABCC813–15 genes that encode the two subunits Kir6.2 and SUR1, respectively, of the adenosine triphosphate (ATP)-sensitive potassium (K\textsubscript{ATP}) channel that couples cellular metabolism to cellular excitability.16 K\textsubscript{ATP} channels composed of Kir6.2 and SUR1 subunits are predominately expressed in endocrine tissues such as the pancreatic islet and nervous system. Therefore, the diabetic phenotype of NDM is believed to arise from K\textsubscript{ATP} channel activation mutations in pancreatic β-cells,10,16 whereas neurological features associated with the more severe iDEND/DEND syndromes are likely the result of K\textsubscript{ATP} channel activation mutations deleteriously affecting the nervous system.4,17

The physiological role of K\textsubscript{ATP} channels in pancreatic β-cells

K\textsubscript{ATP} channels sense changes in the cytosolic ATP/ADP ratio as a result of cellular metabolism and are a major regulator of the β-cell membrane potential. As glucose-stimulated insulin secretion is primarily controlled by the β-cell membrane potential, K\textsubscript{ATP} channels serve to couple glucose metabolism to insulin secretion.16,18 When plasma glucose levels are low, the cytosolic ATP/ADP ratio is reduced, leading to a basal efflux of potassium ions from the cell via K\textsubscript{ATP} channel activity that maintains the membrane potential of the β-cell at approximately −70 mV. This polarized membrane potential prevents calcium entry through voltage-gated calcium channels. As elevations in cytosolic calcium are the primary trigger for insulin granule exocytosis, insulin secretion is suppressed when plasma glucose levels are low (Figure 1A).19,20 When plasma glucose levels rise, glucose enters the β-cells via the glucose transporter 2. Subsequent glucose metabolism leads to an increase in the ratio of cytosolic ATP/ADP ratio, promoting K\textsubscript{ATP} channel closure. The resultant decrease in potassium ion efflux depolarizes the β-cell membrane potential, leading to activation of voltage-gated calcium channels, calcium influx, and calcium-stimulated insulin granule exocytosis (Figure 1B).21 Graded increases in plasma glucose and subsequent metabolism lead to proportional decreases in K\textsubscript{ATP} channel activity, resulting in an appropriate insulin secretory response that is tightly coupled to the plasma glucose concentration.

As the electrical resistance of β-cell is high,22 only small changes in K\textsubscript{ATP} channel activity are required to change β-cell excitability (and hence insulin secretion) via alterations in the β-cell membrane potential.23 Mutations within the K\textsubscript{ATP} channel complex that change their intrinsic activity and/or ability to sense changes in either ATP or ADP will result in altered K\textsubscript{ATP} channel activity that is correlated to the specific effects of the individual mutation on K\textsubscript{ATP} channel activity.

K\textsubscript{ATP} channels encoded by the KCNJ11 and ABCC8 genes are also expressed in other excitable tissues such as the nervous system. As K\textsubscript{ATP} channels are involved in the control of neuronal excitability, mutations may also cause neuronal abnormalities, again dependent on the severity of the individual mutation.24-27

Figure 1 Glucose-stimulated insulin secretion in pancreatic β-cells. (Left) When plasma glucose is low, the decreased ratio of ATP/Mg-ADP will increase K\textsubscript{ATP} channel opening. Consequently, the cell membrane is hyperpolarized, preventing voltage-gated calcium channel opening, Ca\textsuperscript{2+} influx, and insulin secretion. (Right) When plasma glucose is high, glucose is transported into the cell via GLUT2. Glucose metabolism leads to an increased ratio of ATP/Mg-ADP, resulting in K\textsubscript{ATP} channel closure, membrane depolarization, opening of voltage-gated calcium channels, Ca\textsuperscript{2+} influx, and insulin secretion.
Molecular structure of pancreatic K\textsubscript{ATP} channels

The K\textsubscript{ATP} channel is a hetero-octameric membrane protein complex\textsuperscript{28,29} composed of four pore-forming inwardly rectifying potassium channel (Kir6.x) subunits and four regulatory sulfonylurea receptor (SURx) subunits (Figure 2A).\textsuperscript{30} There are two isoforms of the Kir6.x subunit, Kir6.1 and Kir6.2. Kir6.2 is more widely expressed than Kir6.1, which is predominately expressed in vascular smooth muscle.\textsuperscript{31,32} There are two isoforms of the SUR subunit (SUR1 and SUR2), and the subunit composition of K\textsubscript{ATP} channel differs between tissue types.\textsuperscript{33} In pancreatic β-cells and neurons, K\textsubscript{ATP} channels are assembled from Kir6.2 and SUR1 subunits.\textsuperscript{34} In cardiac tissue and skeletal muscle, K\textsubscript{ATP} channels are composed of Kir6.2 and the SUR2A splice variant subunits,\textsuperscript{35} whereas in smooth muscle, K\textsubscript{ATP} channels contain Kir6.1/Kir6.2 and SUR2A/SUR2B splice variant subunits.\textsuperscript{36,37}

The Kir6.2 subunit contains ~390 amino acid and is encoded by KCNJ11 gene, while ~1,580 amino acid SUR1 subunits are encoded by ABCC8 gene. Both KCNJ11 and ABCC8 genes are located at the same chromosomal locus (11p15.1) and are only 4.5 kb apart.\textsuperscript{30} Each Kir6.2 subunit consists of two transmembrane (TM) helices connected by a pore-forming loop that confers potassium selectivity to the channel.\textsuperscript{38} The α-helix linking TM helix 1 (TM1) and intracellular N-terminus, termed as the “slide helix,” plays an important role in channel gating.\textsuperscript{39} Extensive interactions are found between the cytosolic N- and C-termini of adjacent Kir6.2 subunits that contribute to the formation of binding pocket for the inhibitory ATP molecule.\textsuperscript{40} Each SUR1 subunit consists of three TM domains (TMD) with a total of 17 TM segments.\textsuperscript{41} Each SUR1 subunit contains two nucleotide-binding domains (NBD1 and NBD2) that dimerize to form catalytic sites for the intrinsic Mg-ATP\textsubscript{ase} activity of the channel complex, regulating channel activity through binding and hydrolysis of magnesium-bound ATP and the formation of stimulatory Mg-ADP.\textsuperscript{42,43} Each NBD contains two amino acid sequence nucleotide hydrolisis “Walker A” and “Walker B” motifs (Figure 2B).\textsuperscript{42,43} TMD0 and the cytosolic loop linking TMD0 and TMD1 of the SUR1 subunit are responsible for the interaction between Kir6.2 subunit.\textsuperscript{46} The Kir6.2 and SUR1 subunits each possess an endoplasmic reticulum retention motif that requires masking via subunit co-assembly to enable correct trafficking of the assembled hetero-octameric channel complex to the cell membrane.\textsuperscript{47}

K\textsubscript{ATP} channels are inhibited by ATP binding to the Kir6.2 subunits but are activated by the binding and hydrolysis of Mg-ATP in the NBD1/NBD2 dimers on SUR1 subunit, the resulting Mg-ADP generated antagonizes the inhibitory action of ATP on the Kir6.2 subunits. Therefore, the overall activity of the K\textsubscript{ATP} channel complex, and hence the excitability of pancreatic β-cells, is primarily governed by the ratio of cytosolic ATP/ADP in the close vicinity of the K\textsubscript{ATP} channel complex.

Mutations in either subunit that alter 1) the correct ATP/ADP-sensing machinery within the K\textsubscript{ATP} channel complex, 2) subunit assembly, or 3) trafficking to the cell membrane may adversely affect the appropriate insulin secretion in response to plasma glucose. Inactivation mutations in the K\textsubscript{ATP} channel complex decrease channel activity, causing over-secretion of insulin that is poorly coupled to plasma

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**Figure 2** Molecular make-up of the K\textsubscript{ATP} channel complex. (Lower left) K\textsubscript{ATP} channel is a hetero-octameric complex composed of four pore Kir6.2 subunits and four regulatory SUR1 subunits. (Right) Membrane topology of SUR1 and Kir6.2 subunits of the K\textsubscript{ATP} channel. ATP binds to the Kir6.2 subunit, inhibiting K\textsubscript{ATP} channels. Hydrolysis of MgATP within the SUR1 subunit nucleotide-binding domains (NBDs) leads to generation of stimulatory MgADP. The A and B sites for sulfonylurea drug binding on both subunits are labeled as indicated.
glucose levels. Indeed, mutations in SUR1 subunit that 1) reduce the stimulatory effect of Mg-ADP or 2) prevent correct trafficking of the channel complex to the cell membrane cause persistent hyperinsulinemia that presents as hypoglycemia in infancy (HI).49,50

Conversely, activation mutations in the $K_{ATP}$ channel complex lead to increased channel opening, resulting in a suppression of insulin secretion and subsequent hyperglycemia. Consistent with the cellular regulation of $K_{ATP}$ channel activity are the findings that mutations 1) in the Kir6.2 subunit that reduce sensitivity to inhibitory ATP and 2) in the SUR1 subunit that enhance the stimulatory effects of Mg-ADP may precipitate DEND,17 iDEND,4 PNDM,51 TNDM,52 MODY (maturity onset diabetes of the young),53 and type II diabetes (T2D).54,55

**$K_{ATP}$ channel inactivation mutations underlie HI**

Inactivation mutations in both $K_{ATP}$ channel subunits can cause HI, which is characterized by severe hypoglycemia.56 Mutant $K_{ATP}$ channels with reduced or completely abolished channel activity lead to persistent depolarization of cell membrane, which results in continuous calcium influx and excessive insulin secretion that is uncoupled from the plasma glucose level, producing the hyperinsulinemic hypoglycemia phenotype.12,57,58 Compared to inactivation mutations in the KCNJ11 gene (Kir6.2 subunit), more inactivation mutations have been reported in the ABCC8 gene encoding the SUR1 subunit. Table 1 lists the reported inactivation mutations causing HI in both KCNJ11 and ABCC8 genes and their corresponding locations on each subunit.59,60 Inactivation mutations in the $K_{ATP}$ channel complex can be divided into two functional classes: class I, a reduced number of functional $K_{ATP}$ channels inserted into the cell membrane, and class II, mutant $K_{ATP}$ channels that are correctly inserted but remain refractory to opening regardless of the cellular metabolic state of the cell.22 Class I mutations in either SUR1 or Kir6.2 subunits lead to reduced surface expression of $K_{ATP}$ channels, which may result from a total loss of protein, defective channel assembly, or faulty trafficking to the cell membrane.61–63 Class II mutations impair the ability of Mg-ADP to stimulate channel activity,64–66 such that ATP inhibition becomes dominant and the $K_{ATP}$ channel is permanently closed even at low glucose concentrations. The majority of class II mutations are located in the NBDs of SUR1 subunit, where the binding and hydrolysis of Mg-ATP occurs. In general, class I mutations produce a more severe phenotype, often requiring near-total or total pancreatectomy, whereas a number of class II mutations result in a milder phenotype as some residual response to stimulatory Mg-ADP may remain.

However, there is no strict genotype–phenotype correlation as the same mutation in different patients can produce HI with differing degrees of severity. As HI class II mutations lead to cell membrane expression of dysfunctional $K_{ATP}$ channels, less severe forms of HI can often be treated with $K_{ATP}$ channel opener diazoxide.67

**$K_{ATP}$ channel activation mutations underlie NDM**

Monogenic activation mutations in the KCNJ11 and ABCC8 genes can be found in all forms of NDM (DEND,4,17 PNDM,51 TNDM,52 and MODY).53 Activation mutations result in a reduced coupling of channel activity to plasma glucose levels via glucose metabolism. In general, the more stimulatory the mutation, the greater the suppression of insulin secretion and the resulting level of hyperglycemia (Figure 3A).68–71 The underlying molecular mechanisms for the majority of activation mutations can be tested experimentally and correlated well with their specific locations within the $K_{ATP}$ channel subunits as follows.

**Activation mutations in the Kir6.2 subunit**

Heterozygous activation mutations in Kir6.2 subunit have been identified in ~50% of PNDM cases and also have been found in a large number of TNDM cases.5 To date, >40 activation mutations in Kir6.2 subunit have been reported at 30 distinct residues (Table 2).60 The locations of these mutations are clustered into three common regions in the Kir6.2 subunit. One cluster of mutations lie the putative ATP-binding pocket (eg, R50, R201, and Y330) and reduce channel ATP inhibition by decreasing ATP-binding affinity.69,72–74 Another cluster of mutations reside in subunit regions involved in channel gating such as the slide helix (eg, V59), the cytosolic mouth of the channel (eg, I296), or gating loops (eg, C166) between ATP-binding site and the slide helix. These mutations decrease ATP inhibition by stabilizing the open conformation of the channel in both the absence and the presence of ATP, leading to increases in channel activity.75–77 The third cluster of mutations is located at the interface between the subunits such as the interface between adjacent Kir6.2 subunits (eg, F35 and E322) and the interface between Kir6.2 and SUR1 subunits (eg, Q52 and G53). These mutations likely alter channel activity by affecting the interactions between adjacent Kir6.2...
Table 1  Mutations in K<sub>ATP</sub> channel genes KCNJ11 and ABCC8 causing hyperinsulinism of infancy

| Genotype | Position in structure | Molecular mechanism | Phenotype |
|----------|-----------------------|---------------------|-----------|
| **Kir6.2 subunit KCNJ11** | | | |
| Y12∆ | N terminus | Immature Kir6.2 subunits | Hi |
| R34H | Interface between Kir6.2 subunits | | Hi |
| F55L | Interface with SUR1 subunits | | Hi |
| K67N | Slide helix | | Hi |
| W91R | Linker between TM1 and pore region | | Hi |
| A101D | Linker between TM1 and pore region | | Hi |
| S116P | Pore region | | Hi |
| G134A | Linker between pore region and TM2 | | Hi |
| R136L | Linker between pore region and TM2 | | Hi |
| L147P | TM2 | | Hi |
| A187V | ATP-binding site | | Hi |
| P254L | ATP-binding site | | Hi |
| H259R | ATP-binding site | Reduced trafficking of the channel | Hi |
| P266L | C terminus | | Hi |
| E282K | C terminus | | Hi |
| T294M | Gating | Reduced channel Po | Hi |
| R301H | Gating | | Hi |
| C344∆ | C terminus | Immature Kir6.2 subunits | Hi |
| **SUR1 subunit ABCC8** | | | |
| G70E | Linker between TM1 and TM2 | | Hi |
| R74Q/W | Linker between TM1 and TM2 | | Hi |
| G111R | TM3 | | Hi |
| A116P | TM3 | | Hi |
| H125Q | Linker between TM3 and TM4 | | Hi |
| V167L | TM5 | | Hi |
| V187D | TM5 | | Hi |
| N188S | TM5 | | Hi |
| Q219∆ | Linker between TM5 and TM6 | Immature SUR1 subunits | Hi |
| R248∆ | Linker between TM5 and TM6 | Immature SUR1 subunits | Hi |
| N406D | Linker between TM7 and TM8 | | Hi |
| N418R | Linker between TM7 and TM8 | | Hi |
| L508P | Linker between TM9 and TM10 | | Hi |
| F591L | NBD1 | | Hi |
| R598∆ | NBD1 | Immature SUR1 subunits | Hi |
| R620C | NBD1 | | Hi |
| G716V | Walker A in NBD1 | | Hi |
| C717∆ | Walker A in NBD1 | Immature SUR1 subunits | Hi |
| R837∆ | NBD1 | Immature SUR1 subunits | Hi |
| R842G | NBD1 | | Hi |
| K890T | NBD1 | | Hi |
| Q954∆ | NBD1 | Immature SUR1 subunits | Hi |
| S957F | NBD1 | | Hi |
| R999∆ | NBD1 | Immature SUR1 subunits | Hi |
| T1139M | Linker between TM13 and TM14 | | Hi |
| R1215Q/W | Linker between TM15 and TM16 | | Hi |
| K1337N | NBD2 | | Hi |
| W1339∆ | NBD2 | Immature SUR1 subunits | Hi |
| G1343E | NBD2 | | Hi |
| R1353P/H | NBD2 | | Hi |
| V1361M | NBD2 | | Hi |
| G1379R | Walker A in NBD2 | Reduced Mg–nucleotide binding | Hi |
| G1382S | Walker A in NBD2 | Reduced Mg–nucleotide binding | Hi |
| S1387F | NBD2 | | Hi |
| F1388A | NBD2 | Immature SUR1 subunits | Hi |
| R1394H | NBD2 | Impaired trafficking of SUR1 subunits | Hi |
| G1401D | NBD2 | | Hi |

(Continued)
and SUR1 subunits that are important for correct channel gating.78–82

To directly study the ability of ATP to inhibit the KATP channel via the Kir6.2 subunit, Mg-free experimental conditions can be used to eliminate the channel stimulatory effect of Mg-ATP on the SUR1 subunit of the channel.83 In Mg-free conditions, homomeric channels containing Kir6.2 activation mutations are less sensitive to ATP inhibition compared to wild-type channels. There are two major molecular mechanisms by which Kir6.2 activation mutations elicit a reduction in ATP sensitivity. 1) An increase in the maximal open probability (Po) of the channel in the absence of ATP.17,84 In the ATP-unbound state of channels (ATP absent), mutations in the region involved in channel gating (eg, V59G)4 exhibit a higher maximal channel Po compared to wild-type channels. (In the absence of Mg2+, IC50 was 7.0 ± 1.1 µmol/L and 7.4 ± 1.5 mmol/L for wild-type channels and homomeric V59G channels, respectively; P, 0.001. Channel Po was 0.53 ± 0.02 and 0.83 ± 0.01 for wild-type channels and homomeric V59G channels, respectively; P < 0.001.)4 2) A decrease in ATP-binding affinity.51,85,86 Homomeric channels containing mutations in the ATP-binding region (eg, R201C)4 display altered ATP inhibition, yet their maximal Po in the absence of ATP is not significantly different compared to wild-type channels. (In the absence of Mg2+, IC50 was 7.0 ± 1.1 and 106 ± 12 µmol/L for wild-type channels and homomeric R201C channels, respectively; P < 0.001. Channel Po was 0.53 ± 0.02 and 0.6 ± 0.03 for wild-type channels and homomeric R201C channels, respectively; P is not significant.)4

**Table 1 (Continued)**

| Genotype     | Position in structure | Molecular mechanism                      | Phenotype |
|--------------|-----------------------|------------------------------------------|-----------|
| R1419H       | NBD2                  | Reduced Mg–nucleotide binding            | Hi        |
| R1421C       | NBD2                  | Reduced Mg–nucleotide binding            | Hi        |
| R1437Q       | NBD2                  | Reduced Mg–nucleotide binding            | Hi        |
| A1458T       | NBD2                  | Reduced Mg–nucleotide binding            | Hi        |
| G1479R       | NBD2                  | Reduced Mg–nucleotide binding            | Hi        |
| A1493T       | NBD2                  | Reduced Mg–nucleotide binding            | Hi        |
| R1494Q/VW    | NBD2                  | Reduced Mg–nucleotide binding            | Hi        |
| E1507K       | Walker B in NBD2      | Reduced Mg–nucleotide binding            | Hi        |
| L1544P       | NBD2                  | Impaired trafficking of SUR1 subunits    | Hi        |
| V1551D       | NBD2                  | Reduced Mg–nucleotide binding            | Hi        |
| L1552V       | NBD2                  | Reduced Mg–nucleotide binding            | Hi        |
| G1555S       | C terminus            |                                          | Hi        |

**Abbreviations:** Hi, hyperinsulinism of infancy; SUR1, sulfonylurea receptor 1.

**Activation mutations in the SUR1 subunit**

There are more than 30 individual activation mutations in SUR1 subunit that have been reported to cause NDM (Table 2).60 Many of these mutations are dispersed throughout the SUR1 subunit sequence, although a large number of mutations reside in two specific regions of the SUR1 subunit. One cluster of mutations is concentrated in TMD0 and the cytosolic loop linking TMD0 and TMD1.14,87–91 As this region is known to interact with adjacent Kir6.2 subunit, mutations in this region are believed to reduce ATP inhibition via the Kir6.2 subunit.92,93 The second cluster of mutations resides in the NBD2 of the SUR1 subunit, where stimulatory Mg–nucleotide diphosphates such as Mg-ADP bind.94–96 Therefore, NBD2 mutations are thought to either increase direct Mg-ADP stimulation or enhance MgATPase activity in NBD2, leading to increased Mg-ADP stimulation. (For example, R1380 L, Vmax of ATPase activity was 60.8 ± 1.8 and 104.3 ± 9.9 nmol/min/mg for wild-type NBD2 and R1380L NBD2, respectively; P < 0.01. Km of ATPase activity was 0.41 ± 0.04 and 0.55 ± 0.09 mmol/L for wild-type NBD2 and R1380L NBD2, respectively. P is not significant.)94

**Genotype–phenotype correlation in NDM caused by mutations in KATP channels**

There is a wide spectrum of NDM severity associated with different degrees of insulin secretion deficiency and neuronal defects caused by activation mutations in KATP channels (Figure 4). The severity of these clinical phenotypes increases in the order of T2D < MODY/TNDM < PNMD < iDEND/DEND.22 In general, the greater the activation of KATP channels, the more severe the phenotype; however, several factors need to be considered when attempting to predict the clinical severity caused by a specific mutation.

Heterozygosity is an important factor affecting the clinical phenotype of a mutation. NDM patients with activation mutations in either Kir6.2 or SUR1 subunits are heterozygous77 for
| Genotype | Position in structure | Molecular mechanism | Phenotype | Sensitivity to SU |
|----------|-----------------------|---------------------|-----------|------------------|
| Kir6.2 subunit KCNJ11 | N terminus | | T2D | Normal sensitivity |
| E23K | Interface between Kir6.2 subunits | | TNDM | |
| R34C | Interface between Kir6.2 subunits | Increased channel Po | PNDM | Normal sensitivity |
| F35L/V | Interface between Kir6.2 subunits | Decreased ATP-binding affinity | PNDM | |
| C42R | Interface between Kir6.2 subunits | Increased channel Po | PNDM | Normal sensitivity |
| H46Y | Slide helix | Increased channel Po | PNDM | Normal sensitivity |
| H46L | Slide helix | Increased channel Po | iDeND | Normal sensitivity |
| N48D | ATP-binding site | | PNDM | |
| R50P/Q | ATP-binding site | Decreased ATP-binding affinity | PNDM | Normal sensitivity |
| Q52R | Interface with SUR1 subunits | Increased channel Po | DEND | Reduced sensitivity |
| G53R/S | Interface with SUR1 subunits | Decreased ATP-binding affinity | TNDM | Normal sensitivity |
| G53N/D | Interface with SUR1 subunits | Decreased ATP-binding affinity | PNDM | Normal sensitivity |
| V59G | Slide helix | Increased channel Po | iDeND | Normal sensitivity |
| V59M | Slide helix | Increased channel Po | DEND | Reduced sensitivity |
| F60Y | Slide helix | | DEND | |
| V64L | Slide helix | | DEND | |
| L164P | Gating | | PNDM | Reduced sensitivity |
| C166F/Y | Gating | | DEND | Reduced sensitivity |
| H167L | Gating | Increased channel Po | iDeND | Normal sensitivity |
| R170N/R/T | ATP-binding site | Decreased ATP-binding affinity | PNDM | Normal sensitivity |
| A174G | ATP-binding site | | TNDM | |
| R176C | ATP-binding site | | PNDM | |
| E179A | ATP-binding site | | TNDM | |
| R178V | ATP-binding site | Decreased ATP-binding affinity | TNDM | |
| K185E | ATP-binding site | Decreased ATP-binding affinity | DEND | |
| R201C | ATP-binding site | Decreased ATP-binding affinity | PNDM/DEND | Normal sensitivity |
| R201H/L | ATP-binding site | Decreased ATP-binding affinity | PNDM | Normal sensitivity |
| E227K/L | Gating | Increased channel Po | PNDM | Normal sensitivity |
| E229K | Gating | Increased channel Po | TNDM | |
| V252A | ATP-binding site | Decreased ATP-binding affinity | TNDM | |
| E292G | Gating | | DEND | |
| E292G | Gating | Increased channel Po | PNDM | |
| T293N | Gating | Increased channel Po | PNDM | |
| I296L | Pore | Increased channel Po | DEND | Reduced sensitivity |
| E322K | Interface between Kir6.2 subunits | Decreased ATP-binding affinity | PNDM | Normal sensitivity |
| Y330C/S | ATP-binding site | Decreased ATP-binding affinity | PNDM/DEND | Normal sensitivity |
| F333I | Interface with SUR1 subunits | Increased Mg-ATP hydrolysis by NBD2 in SUR1 subunits | PNDM | Normal sensitivity |
| G334D | ATP-binding site | Decreased ATP-binding affinity | DEND | Reduced sensitivity |
| I337V | ATP-binding site | | T2D | |
| R365H | C terminus | | TNDM | |

**SUR1 subunit ABCC8**

| Genotype | Position in structure | Molecular mechanism | Phenotype | Sensitivity to SU |
|----------|-----------------------|---------------------|-----------|------------------|
| P45L | TM1 | | PNDM | Normal sensitivity |
| N72S | Linker between TM1 and TM2 | | PNDM | |
| V86A/G | TM2 | | PNDM | |
| A90V | TM2 | | PNDM | |
| F132L/V | Linker between TM3 and TM4 | Reduced ATP inhibitory effect in Kir6.2 subunits | DEND | |
| L135P | TM4 | | iDeND | PNDM |
| R176C | TM5 | | PNDM | |
| P207S | Linker between TM5 and TM6 | Reduced ATP inhibitory effect in Kir6.2 subunits | PNDM | |
| E208K | Linker between TM5 and TM6 | Reduced ATP inhibitory effect in Kir6.2 subunits | PNDM | Normal sensitivity |
| D209E | Linker between TM5 and TM6 | Reduced ATP inhibitory effect in Kir6.2 subunits | PNDM/TNDM | Normal sensitivity |
| Q211K | Linker between TM5 and TM6 | Reduced ATP inhibitory effect in Kir6.2 subunits | PNDM | Normal sensitivity |

(Continued)
Table 2 (Continued)

| Genotype | Position in structure | Molecular mechanism | Phenotype | Sensitivity to SU |
|----------|-----------------------|---------------------|-----------|------------------|
| D212i/N  | Linker between TM5 and TM6 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNNDM   |                  |
| L213R    | Linker between TM5 and TM6 | Reduced ATP inhibitory effect in Kir6.2 subunits | DEND    | Normal sensitivity |
| L225P    | Linker between TM5 and TM6 | Reduced ATP inhibitory effect in Kir6.2 subunits | PNDM    | Normal sensitivity |
| T229I    | Linker between TM5 and TM6 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    | Normal sensitivity |
| Y263D    | Linker between TM5 and TM6 | Reduced ATP inhibitory effect in Kir6.2 subunits | PNDM    | Normal sensitivity |
| A269D    | Linker between TM5 and TM6 | Reduced ATP inhibitory effect in Kir6.2 subunits | PNDM    | Normal sensitivity |
| R306H    | TM6 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    |                  |
| L324F    | TM6 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    |                  |
| Y356C    | TM7 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    |                  |
| E382K    | Linker between TM7 and TM8 | Reduced ATP inhibitory effect in Kir6.2 subunits | PNDM    |                  |
| C435R    | TM8 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    |                  |
| L438F    | TM8 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    |                  |
| L451P    | TM9 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    |                  |
| L582V    | TM11 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    |                  |
| R826W    | NBD1 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    |                  |
| H1024Y   | TM12 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    | Normal sensitivity |
| R1183Q/Q | TM15 and TM16 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    | Normal sensitivity |
| A1185E   | TM15 and TM16 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    | Normal sensitivity |
| M1290V   | TM17 | Reduced ATP inhibitory effect in Kir6.2 subunits | PNDM    |                  |
| R1314H   | NBD2 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    | Normal sensitivity |
| E1327K   | NBD2 | Reduced ATP inhibitory effect in Kir6.2 subunits | PNDM    |                  |
| S1369A   | NBD2 | Reduced ATP inhibitory effect in Kir6.2 subunits | TNDM    |                  |
| R1380C/H/L| Walker A in NBD2 | Increased ATPase activity in NBD2 | TNDM    | Normal sensitivity |
| G1401R   | NBD2 | Increased ATPase activity in NBD2 | PNDM    | Normal sensitivity |
| I1425V   | NBD2 | Increased ATPase activity in NBD2 | PNDM    | Normal sensitivity |
| V1524L/M | NBD2 | Increased ATPase activity in NBD2 | PNDM    | Normal sensitivity |

Abbreviations: DEND, developmental delay, epilepsy, and neonatal diabetes; PNDM, permanent neonatal diabetes mellitus; TNDM, transient neonatal diabetes mellitus; MODY, maturity onset diabetes of the young; T2D, type II diabetes; iDeND, intermediate developmental delay, epilepsy, and neonatal diabetes; Po, open probability; SUR1, sulfonylurea receptor 1.

the mutation; thus, both wild-type and mutant subunits are expressed in the same cell. The assembly of Kir6.2 subunits can be used to explain the nature of heterozygosity in NDM patients. In a heterozygous NDM patient carrying one copy of normal (wild type) and one copy of mutant KCNJ11 gene,28 there will be a mixed population of channels, each of which carries from 0 to 4 mutant Kir6.2 subunits (Figure 5).4,22 Two factors determine the inhibitory ATP sensitivity of any individual channel in this population. One is the number of mutant subunits that an individual channel contains and the other is the contribution of mutant subunits to overall channel ATP sensitivity. This contribution is also linked to the molecular mechanism of each activation mutation in Kir6.2 subunit.

If the mutation impairs ATP-binding affinity alone, there will be only a small reduction in ATP sensitivity in heterozygous population compared to wild-type population. (For example, R201H of Kir6.2 subunit. In the absence of Mg\(^{2+}\), IC\(_{50}\) were 7.0 ± 1.1, 12.5 ± 1.1, and 298 ± 25 \(\mu\)mol/L for wild type, heterozygous, and homomeric R201H channels, respectively; \(P < 0.05\) and \(P < 0.001\) vs wild-type, respectively.) This is because binding of a single ATP molecule to 1 of 4 ATP-binding sites is sufficient to inhibit the K\(_{ATP}\) channel.97 The ATP sensitivity of the channel will only be substantially impaired when all four subunits contain the mutation; otherwise, the mutant Kir6.2 subunit’s effects will be largely compensated for by the presence of the other wild-type subunits. This can be explained by using a simple statistical probability model. If the co-assembly of wild-type and mutant Kir6.2 subunits is independent and random and follows a binomial distribution, as a single channel is made of 4 Kir6.2 subunits, then only 1 out of 16 channels in the heterozygous population will contain all 4 mutant Kir6.2 subunits that display a significant decrease in ATP sensitivity (Figure 5).4 The other 15 channels (4/16 with 3 mutant subunits; 6/16 with 2 mutant subunits; 4/16 with 1 mutant subunit, and 1/16 with 0 mutant subunits)
will have comparable ATP sensitivity to the channel containing all wild-type subunits, so the resulting ATP sensitivity of heterozygous population is very close, but not identical, to that of a pure wild-type channel population. However, this small shift of ATP sensitivity in the heterozygous channel population leads to NDM for the following reasons. Under physiological conditions, intracellular concentration of ATP is in the range of 1–5 mM, such that K<sub>ATP</sub> channels exhibit very low activity. Additionally, the β-cell membrane possesses a high electrical resistance such that only a small reduction in ATP sensitivity to the channel results in a small increase in K<sub>ATP</sub> channel activity that holds the β-cell membrane potential in a more polarized state and suppresses insulin secretion. Therefore, even a very modest reduction in heterozygous K<sub>ATP</sub> channel ATP sensitivity can lead to significantly impaired insulin secretion resulting in NDM.

In direct contrast, if the mutation in question increases intrinsic K<sub>ATP</sub> channel Po (in the absence of ATP), there will be a significant reduction in ATP sensitivity in heterozygous population compared to wild-type population, as the presence of one single mutant subunit will increase the intrinsic Po of K<sub>ATP</sub> channels. (For example, Q52R of Kir6.2 subunit. Channel Po were 0.53 ± 0.02, 0.70 ± 0.03, and 0.83 ± 0.01 for wild type, heterozygous, and homomeric Q52R channels, respectively. P < 0.001 and P < 0.001, vs wild-type, respectively.) This can be explained by using the same statistical model described in detail earlier. Fifteen out of 16 channels will contain at least one mutant subunit in a heterozygous channel population (Figure 5) and exhibit a marked decrease in ATP sensitivity. Thus, the ATP sensitivity of heterozygous population is significantly reduced compared to that of wild-type population and is associated with a more

**Figure 3** Sulfonylureas stimulate insulin secretion in neonatal diabetes caused by K<sub>ATP</sub> channel mutations. (Left) Activation mutations in the K<sub>ATP</sub> channel prevent channel closure in response to high plasma glucose. Consequently, the membrane potential remains hyperpolarized even, thereby preventing insulin secretion. (Right) Sulfonylureas bind directly to K<sub>ATP</sub> channels causing channel inhibition that triggers membrane potential and insulin secretion resulting in a lowering of plasma glucose.

**Figure 4** Relationship between insulin secretion and K<sub>ATP</sub> channel activity in a spectrum of clinical presentations of hypo- and hyperglycemia. The clinical severity of the disease is correlated with the extent of K<sub>ATP</sub> channel activity caused by the mutations.

**Figure 5**
severe DEND syndrome phenotype. This provides a rational explanation as to why mutations that increase the intrinsic Po produce a more severe clinical phenotype, such as DEND, whereas mutations that decrease ATP-binding affinity lead to a milder clinical phenotype such as PNDM.

The specific location of mutations within either subunit also correlates well with the severity of the clinical phenotype. In general, mutations in Kir6.2 subunit are typically associated with PNDM, iDEND, and DEND, whereas mutations in SUR1 subunit are more frequently associated with TNDM. This may be accounted for by the overriding ability of ATP to inhibit channel activity within wild-type Kir6.2 subunits even when there is an enhanced stimulatory effect of Mg-ADP via the effects of a SUR1 subunit activation mutation causing TNDM. Furthermore, although some activation KATP channel mutations lead to transient diabetes, these patients are at increased risk of developing T2D later in life. Interestingly, the common genetic variants E23K in KCNJ11 and S1369A in ABCC8 form a haplotype and are associated with an increased risk to T2D. The precise molecular mechanisms that underlie this increased risk likely result from even subtler alterations of ATP/ADP sensitivity than those described for the monogenic mutations that cause overt forms of NDM.

While there is good evidence for a clear genotype–phenotype relationship with several activation mutations in KATP channels, the association between phenotype and genotype is not absolute, as there is often a different severity of clinical phenotype among patients carrying the same mutation. This strongly implies that there are other factors (such as underlying polygenic diabetes risk, diet, or environment) that influence the development of clinical phenotype besides the presence of a single KCNJ11 or ABCC8 mutation in NDM patients.

**Pharmacotherapy for NDM patients carrying KCNJ11 and ABCC8 mutations**

Before the discovery that mutations in a number of genes underlie NDM, daily insulin therapy was the only effective treatment for patients. As mentioned earlier, NDM can be the result of mutations in multiple genes (eg, KCNJ11, ABCC8, GCK, INS, FOXP3, EIF2AK3, and ZAC/HYMAI). Since 2004, many NDM patients with either KCNJ11 or ABCC8 mutations have been successfully treated with a pharmacological approach, removing the requirement for insulin injections. The SU drugs, a class of KATP channel inhibitor, have been widely used as a treatment of T2D for over 50 years. SUs bind directly to the KATP channel complex, leading to channel closure and subsequent stimulation of insulin secretion (Figure 3B). Recent studies now demonstrate that glycemic control in NDM patients with KATP channel activation mutations can be managed with SU therapy alone. Therefore, SUs should be considered as an
attractive alternative therapy to treat NDM patients carrying mutations in \textit{KCNJ11} and \textit{ABCC8} genes. As mutations in a number of genes can cause NDM and the causal mutation in each patient may differ greatly, a pharmacogenomic approach to treatment may be possible to “tailor” SU therapy based on specific NDM genotype.

SUs can be classified according to their historical discovery with first generation SUs, including tolazamide, tolbutamide, and chlorpropamide, and second generation SUs, including glyburide, glipizide, and glimepiride (Figure 6). Compared to the first generation SUs, the second generation SUs are now more commonly used in the treatment of NDM as they are more potent and tend to have a longer duration of action.

There are two SU-binding sites within the K\textsubscript{ATP} channel complex\textsuperscript{109} that have been identified to date. The “A-site” is located in the intracellular loops connecting TM segments 14–16 on SUR1 subunit. The “B-site” is composed of the intracellular loop between TM segments 5–6 in the SUR1 subunit and the N-terminus in Kir6.2 subunit (Figure 2B). Therefore, SUR1 subunit possesses a bipartite pocket with distinct A- and B-binding sites. Furthermore, SUs can be classified as A-site or AB-site drugs based on

![Figure 6 Structures and binding-site classification of clinically used sulfonylurea drugs.](image-url)
where they bind to the channel (Figure 6). The A site within SUR1 subunit binds the SU moiety, whereas the B site binds the non-SU carboxamido moiety of the molecule. Most of the first generation SUs (eg, tolbutamide and chlorpropamide) are A-site drugs, whereas the majority of the second generation SUs (eg, glyburide, glipizide, and glimepiride) are AB-site drugs, which also accounts for the higher potency of the second generation SUs. An exception to this is gliclazide, which is an A-site SU with potency comparable to the AB-site SUs.

A key issue in the optimization of SU therapy in NDM is whether mutant $K_{\text{ATP}}$ channels can be inhibited by SUs in a similar concentration range to wild-type channels. For NDM patients with SUR1 subunit mutations, there are no reports of mutations in the ABCC8 altering SU inhibition. This may be because NDM patients with mutant SUR1 subunits often exhibit a milder clinical NDM phenotype. Therefore, SU therapy should be effective for most NDM patients with SUR1 subunit mutations.

In contrast, several studies suggest that NDM patients with Kir6.2 subunit mutations respond differently to SU therapy, which is likely related to the underlying molecular mechanisms of mutations that alter $K_{\text{ATP}}$ channel function. Mutations that reduce binding affinity of inhibitory ATP causing TNDM or PNDM show adequate efficacy of SUs. However, mutations that enhance intrinsic channel Po causing DEND or iDEND have a reduced inhibitory efficacy of SUs. In general, the greater the ability of a specific mutation to increase the intrinsic channel Po, the higher the SU dosage required to achieve the same level of channel inhibition seen in with mutations causing PNDM and TNDM. As SUs are unable to sufficiently inhibit $K_{\text{ATP}}$ channels with mutations that cause a greatly enhanced intrinsic channel Po, DEND patients with activation mutations in Kir6.2 subunit often require a combination of SU and insulin therapy rather than SU therapy alone. SU dosage for NDM patients can be quite high (up to 2.5 mg/kg/day of glyburide) compared with the dosage for patients with T2D (~0.2 mg/kg/day).

SUs are extensively metabolized in the liver, primarily by the cytochrome P450 2C9 enzyme encoded by the CYP2C9 gene. To date, several pharmacogenomic studies have focused on the influence of common gene variants in the CYP2C9 gene on SU pharmacokinetics. As the activity of cytochrome P450 2C9 variants correlates well with serum levels of SUs, patients carrying CYP2C9 variants that reduce cytochrome P450 2C9 enzymatic activity possess elevated serum levels of SUs. Therefore, screening for these common CYP2C9 variants may provide additional information as to whether a NDM patient carrying a KCNJ11 or ABCC8 gene mutation may respond better to SU therapy.

Although insulin therapy may control glucose homeostasis in NDM patients with mutant $K_{\text{ATP}}$ channels, it does not restore the normal $K_{\text{ATP}}$ channel activity in nonpancreatic tissues such as the brain and skeletal muscle. On the other hand, SUs can inhibit $K_{\text{ATP}}$ channels in many tissues such as the central nervous system (CNS), ameliorating the neurological dysfunction observed in iDEND/DEND.

One potential concern is that the dosage for SUs needed to adequately control glucose homeostasis may not be enough to resolve neurological symptoms, as SUs have to cross the blood–brain barrier to exert inhibitory effect on CNS $K_{\text{ATP}}$ channels. However, several studies showed that improvements in mental and motor function were found in patients carrying mutant $K_{\text{ATP}}$ channels with DEND syndrome treated with SUs. These observations suggest that SUs are able to cross the blood–brain barrier at concentrations sufficient to inhibit $K_{\text{ATP}}$ channels in the CNS.

Several recent studies now show that early diagnosis and treatment of DEND patients carrying KCNJ11 or ABCC8 gene mutations with SU therapy could reduce or even prevent the neurological dysfunction in addition to dramatically improving glycemic control. Most DEND patients who have successfully transferred to SU therapy were children at the time of transfer. Therefore, if the causal mutation is on either KCNJ11 or ABCC8 genes, then an early switch to SU therapy may minimize the extent of neurological problems. This also emphasizes the importance of early screening for mutations in KCNJ11 and ABCC8 genes in those NDM patients with neurological features.

Traditionally, PNDM patients with mutations in other genes such as GCK gene encoding glucokinase are treated with insulin therapy. A recent study reported that a PNDM patient with the T168A mutation in glucokinase exhibited modest responsiveness to SU therapy. Furthermore, MODY patients with mutations in HNF1α (hepatocyte nuclear factor) are very sensitive to SU therapy and many of them have been successfully transferred to SU therapy from insulin therapy. Therefore, the use of SU therapy should also be considered in NDM patients with mutations in genes other than KCNJ11 and ABCC8. These findings also highlight the central role that $K_{\text{ATP}}$ channels play in regulating insulin secretion.

SUs exhibit differential potencies on $K_{\text{ATP}}$ channels with different subunit compositions that are often expressed in a variety of tissues. The majority of first generation SUs and gliclazide (A site) are more selective for $K_{\text{ATP}}$
channels containing the SUR1 subunit as found in the pancreas and CNS (IC_{50} was 50 nmol/L for gliclazide on K\textsubscript{ATP} channels containing SUR1 subunits).\textsuperscript{111} Thus, K\textsubscript{ATP} channels containing either SUR2A or SUR2B subunits (heart/skeletal/smooth muscle) would not be inhibited by these SUs at the same concentration (IC\textsubscript{50} was 0.8 mmol/L for gliclazide on K\textsubscript{ATP} channels containing SUR2A subunits).\textsuperscript{111} As second generation SUs (AB site) are nonselective, they will inhibit all K\textsubscript{ATP} channels with similar potency (IC\textsubscript{50} were 3, 5.4, and 7.3 nmol/L for glimepiride on K\textsubscript{ATP} channels containing SUR1, SUR2A, and SUR2B subunits, respectively).\textsuperscript{132}

Recent studies implicate a role for skeletal muscle (Kir6.2 and SUR2A) K\textsubscript{ATP} channels in peripheral insulin sensitivity.\textsuperscript{133,134} In NDM patients with Kir6.2 activation mutations, overactive K\textsubscript{ATP} channels in skeletal muscle (Kir6.2 and SUR2A) may reduce insulin sensitivity in addition to decreasing insulin secretion, further contributing to the development of NDM.\textsuperscript{135} Inhibition of skeletal muscle K\textsubscript{ATP} channels with Kir6.2 activation mutations with SUs may increase peripheral insulin sensitivity.\textsuperscript{136} This notion is supported by studies showing that better glycemic control is achieved with AB-site SUs, compared with A-site SUs.\textsuperscript{116,123,128,137} This is because skeletal muscle and \(\beta\)-cell are inhibited by AB-site SUs as both insulin secretion and insulin sensitivity are achieved. Therefore, AB-site SUs may be the better choice for NDM patients with Kir6.2 activation mutations.

In clinical practice, the two major treatments for NDM patients are insulin therapy and oral SUs and treatment for individual patient varies depending on the genetic cause of NDM.\textsuperscript{138} For 50% of PNDM patients and 10% of TNDM patients carrying mutant K\textsubscript{ATP} channels, SU therapy is an attractive alternative to insulin therapy. However, for other PNDM patients carrying mutations in PTF1A, EIF2AK3, FOXP3 and 80% of TNDM patients carrying mutations in chromosome 6q24 (eg, ZAC/HYMAI), SU responsiveness is minimal and the patients’ only option is insulin therapy.\textsuperscript{5} Therefore, it is important to diagnose the underlying genetic cause of NDM to fully optimize treatment.\textsuperscript{139} Genetic testing is not only important for the correct diagnosis but may now also be used in the optimization of treatment in a large number of PNDM and TNDM patients with K\textsubscript{ATP} channel mutations.\textsuperscript{140}

**Conclusion**

K\textsubscript{ATP} channels play a central physiological role in pancreatic \(\beta\)-cells, where they act as key regulators of insulin secretion in response to changes in plasma glucose. Inactivation or activation mutations in K\textsubscript{ATP} channels lead to altered K\textsubscript{ATP} channel activity, producing a phenotype of either HI or NDM. With respect to K\textsubscript{ATP} channel mutations in NDM, the severity of the clinical phenotype correlates well with the magnitude of K\textsubscript{ATP} channel activation.

To date, it is estimated that \(\sim\)90% of NDM patients carrying K\textsubscript{ATP} channel activation mutations can discontinue daily insulin injections and show improved glycemic control when they are switched to a high-dose SU therapy. Besides improving the quality of life for NDM patients, switching from insulin injection to SU therapy can also reduce neurological symptoms associated with patients with more severe forms of NDM (iDEND/DEND).

Furthermore, genetic information, coupled with clinical factors, may help to improve the treatment of NDM by aiding in the appropriate selection of therapeutic strategies (insulin injection, or SU therapy, or a combination of both) and a more accurate adjustment of SU dosage. Future research will likely lead to improved glycemic control by the development of a rational pharmacogenomic approach to “tailor” SU therapy based on an NDM patient’s individual genotype.

**Disclosure**

The authors report no conflicts of interest in this work.

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