Brief Report

New *ABCC8* Mutations in Relapsing Neonatal Diabetes and Clinical Features

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Activating mutations in the *ABCC8* gene that encodes the sulfonylurea receptor 1 (SUR1) regulatory subunit of the pancreatic islet ATP-sensitive K^+ channel (K_{ATP} channel) cause both permanent and transient neonatal diabetes. Recently, we have described the novel mechanism where basal Mg-nucleotide–dependent stimulatory action of SUR1 on the Kir6.2 pore is increased. In our present study, we identified six new heterozygous *ABCC8* mutations, mainly in patients presenting the transient form of neonatal diabetes (six of eight), with a median duration of initial insulin therapy of 17 months (range 0.5–38.0). Most of these mutations map to key functional domains of SUR1. Whereas Kir6.2 mutations are a common cause of permanent neonatal diabetes and in a few cases associate with the DEND (developmental delay, epilepsy, and neonatal diabetes) syndrome, SUR1 mutations are more frequent in transient (52%) compared with permanent (14%) neonatal diabetes cases screened for *ABCC8* in our series. Although ketoacidosis is frequent at presentation, SUR1 mutations associate mainly with transient hyperglycemia, with possible recurrence later in life. One-half of the SUR1 neonatal diabetic patients presented with de novo mutations. In some familial cases, diabetes is not always present in the adult carriers of SUR1 mutations, supporting variability in their clinical expressivity that remains to be fully explained. *Diabetes* 56:1737–1741, 2007

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Received for publication 3 November 2006 and accepted in revised form 3 March 2007.

Published ahead of print at http://diabetes.diabetesjournals.org on 27 March 2007. DOI: 10.2337/db06-1540.

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Additional information for this article can be found in an online appendix at http://dx.doi.org/10.2337/db06-1540.

K_{ATP} channel, ATP-sensitive K^+ channel; PND, permanent neonatal diabetes; SUR1, sulfonylurea receptor 1; TMD, transmembrane domain; TND, transient neonatal diabetes.

The pancreatic β-cell ATP-sensitive K^+ channels (K_{ATP} channels) are hetero-octamers (1) assembled from Kir6.2 and the high-affinity sulfonylurea receptor 1 (SUR1) encoded by the *ABCC8* gene, which regulates channel activity (2,3). These channels link metabolism with membrane electrical activity by responding to changes in the adenine nucleotide levels that reflect the energy status of the cell consequent to changes in blood glucose level and metabolism. Adenine nucleotides exert a dual action on K_{ATP} channels. Nucleotide binding to the Kir6.2 pore reduces its activity, its mean open probability (P_O), while Mg-nucleotide binding and/or hydrolysis on SUR1 counterbalances this inhibitory action to increase P_O (4,5). Consistent with this mechanism, Kir6.2 mutations that have reduced sensitivity to inhibitory ATP are responsible for most cases of permanent neonatal diabetes (PND) (6–10) and also account for a small percentage of transient neonatal diabetes (TND) (11–12).

Furthermore, we recently identified heterozygous activating mutations in *ABCC8* as the cause of both transient and permanent forms of neonatal diabetes, which in a minority of cases have neurological features such as developmental delay and dyspraxia (13). Insulin release in the patients with mutations appears to be suppressed by a novel mechanism where the basal Mg-nucleotide–dependent stimulatory action of SUR1 on the K_{IR} pore is elevated, but, importantly, blockade by sulfonylureas is preserved. The identification of these mutations indeed has evident therapeutic implications, as most patients can replace insulin injections with oral sulfonylurea agents (13,14).

Our findings from a first case series of neonatal diabetic patients screened positive for a *ABCC8* mutation indicate that four of nine mutations are segregating in families with type 2 diabetes, including adult-onset form of the disease (13). Thus, *ABCC8* mutations may give rise to a novel monogenic form of type 2 diabetes with variable penetrance and age of onset. The overall contribution of overactive *ABCC8* mutations to other monogenic subtypes of diabetes remains to be further evaluated, as well as the nature of clinical features associated with impairment of SUR1, the regulatory subunit of the K_{ATP} channel, which is almost exclusively expressed in neuroendocrine cells. In the current study, 16 neonatal diabetic patients, in whom no genetic abnormalities were identified on chromosome 6q24 or in the *KCNJ11* gene, were investigated for molecular genetic testing and clinical features. We identified

eight probands with *ABCC8* mutations, of which six were unreported.

Identification of novel *ABCC8* mutations as a cause of neonatal diabetes. Sixteen Caucasian patients with neonatal diabetes (age of diagnosis <6 months), referred to the French SUR1–Neonatal Diabetes Study Group (13,15), were screened for mutations in *ABCC8*. Eleven patients are of French origin, four are Spanish (16), and one (KS-L582V) (Table 1) is from Turkey. In this series, six patients presented with PND, seven with TND, and three young patients were not yet defined for the type of diabetes (but type 1 diabetes was excluded). No mutations were found in the coding and promoter sequences of glucokinase.

The 39 exons of the *ABCC8* gene were sequenced from genomic DNA in the 16 patients, as previously described (13) (supplementary Table 2 available in an online appendix at http://dx.doi.org/10.2337/db06-1540.)

We identified eight heterozygous missense *ABCC8* mutations in 8 of the 16 patients with neonatal diabetes, six of which have not yet been reported: E208K (c.622G>A), A269D (c.806C>A), V324M (c.970G>A), R825W (c.2473C>T), R1379H (c.4136G>A), and V1523M (c.4567G>A) (Fig. 1). The two other mutations, L582V (c.1744C>G) and R1182Q (c.3545G>A), had been previously described by our group in three independent families with TND cases (13). All of these mutations were confirmed by resequencing both alleles in the original DNA sample. The six novel mutations were not found in 300 diabetic subjects or in 140 unrelated normoglycemic individuals of European Caucasian origin.

All the mutated residues are highly conserved across mammals (human, rat, mouse, and hamster) and Japanese Takifugu fish, and most of them map to key functional domains in the SUR1 protein. E208K is close to the L213R mutation—previously found in a PND patient (13)—both of which lie in the intracellular L0-linker that controls the channel P_{Omax} (17). V324M is located in the transmembrane domain (TMD)6 of TMD1, and R1379H and V1523M are in the nucleotide-binding domain 2, the domain argued to hydrolyze MgATP. A269D and R825W lie in the helical intracellular coupling domains (4).

These mutations are responsible for neonatal diabetes in six patients presenting with a transient form and in one patient with a permanent form of diabetes. One case (NJ-A269D) is too young to be diagnosed as a transient or permanent case. We have sequenced both parents of the patients (those carrying an *ABCC8* mutation, except in two families of probands CD-R1379H and GK-V324M [only the mother sample was available for genetic testing; see Table 1]). Family relationships were confirmed using a panel of six microsatellite markers (18). In the families with E208K, L582V, and R825W mutations, the fathers carried the mutation in the heterozygous state, whereas the A269D mutation in the NJ family was inherited from the mother (Table 1). The R1182Q and V1523M mutations were not identified in either parent, consistent with de novo mutations. The V324M and R1379H mutations tested negative in the mothers, and the two fathers were not available for genetic testing.

***ABCC8* mutations and relationship with clinical features.** The clinical features of the eight probands are shown in Table 1. Diabetes was diagnosed at a median age of 39 days (range 1–112). All subjects presented with marked hyperglycemia (mean 33.2 mmol/l [12.3–64.2]). Five cases presented with ketoacidosis, and two were diagnosed with hyperglycemia following routine glucose monitoring in neonates with a low birth weight. Autoantibodies associated with type 1 diabetes (islet cell antibody, GAD_{65}, and/or insulinoma-associated protein 2) were all negative, and pancreas ultrasonography, when performed (in six of eight cases), revealed no abnormalities. Three TND patients (NJ-A269D, LM-R825W, and GK-V324M) were small for gestational age (<3rd percentile). Initial insulin therapy was required for those patients and could then be stopped. In patient GK-V324M, recurrence of diabetes occurred at 9 years of age and was treated with insulin injections. After *ABCC8* sequencing had been performed and after the agreement of the French health authorities had been granted for sulfonylureas treatment in children with a SUR1 mutation, the patient GK-V324M was successfully transferred to glibenclamide (Table 1). One patient (CD-R1379H) has a hyperactivity disorder with attention deficit disorder associated with speech developmental delay and feeding behavior anomalies. The link between those behavior disorders and a SUR1 mutation remains to be proven, especially because the mother of this child had psychiatric problems while testing negative for the mutation. One patient (NJ-A269D) who is 8.7 months old is described with hypotonia without muscle weakness, suggesting a neurological origin.

Probands SGM-E208K, KS-L582V, and LM-R825W have a mutation inherited from their fathers and proband NJ-A269D from her mother (Table 1). In families with the L582V, R825W, and A269D mutations, glucose tolerance tests were performed in the fathers and mother, who were found to be free from diabetes. However, the father of KS-L582V has an A1C just above the upper limit of normal, which may suggest minimal glucose disposal disturbances. In the case of the father of SGM-E208K, glucose intolerance was documented during the oral glucose tolerance test.

In the comparison of the present cohort of ND-SUR1 cases ($n = 8$) with our cohort of those linked to *KCNJ11*/Kir6.2 mutations ($n = 18$), there was no significant difference in distribution of low birth weight, age of diagnosis, or glucose levels at presentation, as assessed in our previous study (13). Ketoacidosis at presentation was not more frequently associated with ND-SUR1 than with ND-Kir6.2 cases (4 of 8 vs. 10 of 18). The prevalence of at least one feature of developmental delay was not different (2 of 8 vs. 3 of 18), and epilepsy was diagnosed in 1 of 18 ND-Kir6.2 cases but in none of the ND-SUR1 cases. Other clinical features did not differ between ND-SUR1 and ND-Kir6.2 patients.

DISCUSSION

In the current study, we identified six novel *ABCC8* mutations in eight patients, with the vast majority of subjects presenting with a transient form of neonatal diabetes (median duration of initial insulin therapy 17 months [range 0.5–38]).

There was evidence for a genotype-phenotype relationship for *KCNJ11* mutations, with a spectrum of phenotypes associated with activating mutations in Kir6.2 (10,19). However, few patients have been described with TND linked to *KCNJ11* mutations (carriers of heterozygous mutations G53R, G53S, I182V, and C42R) (11,20). In the ND-SUR1 patients, an apparently mild phenotype, i.e., without neurological features, is observed in the TND families, except in a few cases presenting with PND (13)

TABLE 1
Clinical features in neonatal diabetic patients screened positive for *ABCC8* mutations

	Patient							
	SGM	GK	KS	LM	CN	CD	DL	NJ
Mutation	E208K	V324M	L582V	R825W	R1182Q	R1379H	V1523M	A269D
Sex	Female	Male	Male	Female	Female	Male	Male	Female
Type of diabetes	TND	TND	TND	TND	TND	TND	PND	Not yet known
At birth								
Weight (g/percentile)	1,790/32	1,660/<3	3,250/28	2,300/<3	2,930/10	3,150/43	2,710/31	2,390/<3
Gestation week	33.5	37	39	39	41	38.5	37	39
At presentation								
Age (days)	1	112	36	10	13	42	67	66
Weight (g)	1,790	4,290	4,300	2,520	3,000	3,690	3,660	5,100
Presentation	Glucose monitoring	Ketoacidosis	Ketoacidosis	Glucose monitoring	Weight loss	Ketoacidosis	Ketoacidosis	Ketoaciduria
Glucose (mmol/l)	12.4	24.1	60.5	16.8	24.1	64.2	36	27.5
Autoantibodies	0	0	0	0	0	0	0	0
Insulin dose (units · kg^{-1} · day^{-1})	0.10	1	2.40	0.30	0.72	0.50	2.50	0.72
Pancreas ultrasonography	NA	NA	N	N	N	N	N	N
Current status								
Age (months)	7	127	28	13	48	33	18	8.7
Height (cm/SD)	63/−1.6	134.5/−0.7	90.2/0.6	72.5/−0.4	101.2/0.2	96/1	84/1.3	70/0.8
Weight (kg/percentile)	6.15/3	23.6/<3	13.5/75	9.62/56	14.9/50	17.5/>97	11/31	8.52/50
Diabetes (yes [+], no [−])	−	+ (9)*	−	−	−	−	+	+
Insulin dose (units · kg^{-1} · day^{-1})	0	0†	0	0	0	0	0.60	0.62
A1C at last examination (%)	4.5	6.0	5.1	5.0	5.4	5.0	5.5	8.9
Neurological features								
Muscle weakness	No	No	No	No	No	No	No	No
Motor developmental delay	No	No	No	No	No	No	No	No
Epilepsy	No	No	No	No	No	No	No	No
Mental developmental delay	No	No	No	No	No	No	No	No
Speech developmental delay	No	Yes	No	No	No	Yes	No	No
Dysmorphic features	No	No	No	No	No	No	No	No
Other features	No	No	No	No	No	Hyperkinesia, trouble of feeding behavior	No	Hypotonia
Parent with a mutation	Father	None‡	Father	Father	None	None‡	None	Mother
Glucose tolerance§	IGT	—	N	N	—	—	—	N
Age at examination (year)	41	—	31	29	—	—	—	25
A1C at last examination (%)¶	5.4	—	6.1	NA	—	—	—	5.2
BMI at last examination (kg/m^2)	27	—	24	22	—	—	—	NA

*Age at relapse, in year. †Patient GK-V324M was successfully switched to glibenclamide (gliburide) at the age of 9.5 years (current dose 2.5 mg/day; weight 25 kg). ‡Only the mother was screened for the mutation; the father of GK-V324M died, and no information is available on the biological father of CD-R1379H. §Assessed by an oral glucose tolerance test. ¶Upper limit of normal values for A1C: 5.6%. IGT, impaired glucose tolerance; N, normal; NA, not available.

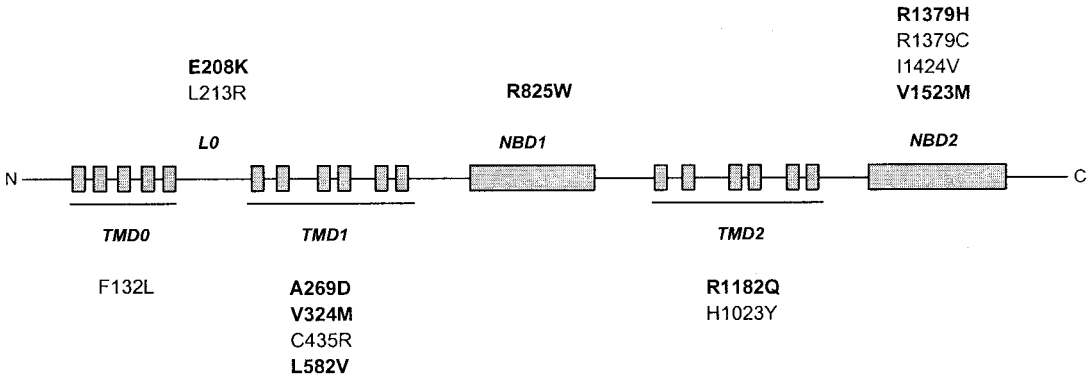

FIG. 1. Schematic representation of SUR1 functional domains showing the location of the mutations identified in this study (in bold) and those previously reported in neonatal diabetes (13,21). Shaded squares represent the known structural domains in SUR1: TMDs in TMD0, TMD1, and TMD2, and cytoplasmic domains as nucleotide-binding domain (NBD)1, NBD2, and the L0 loop connecting TMD1 to TMD0 (17).

and in one patient previously reported with a SUR1 mutation (F132L) and severe DEND (developmental delay, epilepsy, and neonatal diabetes) syndrome (21). Indeed, in our cohort, we note that *KCNJ11* mutations are mainly associated with PND (17 of 18), whereas the majority of *ABCC8* mutations are linked to TND cases when considering the present cohort (6 of 7) and our published work (7 of 9) (13). None of the patients with an *ABCC8* mutation has epilepsy, even though some signs of neuropsychological disturbances are observed in 6 of 17 of the ND-SUR1 patients in our cohort (13). While reporting in this work neuropsychological abnormalities in two patients, any correlation with the *ABCC8/*SUR1 mutations needs further clinical evaluation in those and other patients screened positive with a SUR1 mutation. Altogether, in our cohort of neonatal diabetes (13), 17 of 50 patients so far screened for *ABCC8* (all are negative for chromosome 6, Kir6.2, and glucokinase anomalies) are carriers of a SUR1 mutation: 3 of 22 (14%) in the PND group, 13 of 25 (52%) in the TND group, and 1 of 3 patients not yet defined as permanent or transient.

Strikingly, some of the parents of the probands (two fathers and one mother) are carriers of an *ABCC8* mutation likely to be responsible for neonatal diabetes in their children and, despite this, have normal glucose tolerance as shown in an oral glucose tolerance test. We believe that those mutations (A269D, L582V, and R825W) are not polymorphisms, as they were shown to be absent from a large number of euglycemic subjects. Moreover, one of these mutations, L582V, has been shown to cosegregate with diabetes in one previously published family (13). This has been described for other monogenic forms of diabetes, such as diabetes linked to mutations in hepatocyte nuclear factor-1β. Indeed, only 10 of the 13 mutation carriers had diabetes in one study (22). Therefore, penetrance of dominant mutations and variability in their clinical expressivity may also be explained by the influence of other genetic determinants and epistasis effects, by behavioral factors such as physical activity, body composition, and age on the clinical phenotype, as seen in other monogenic subtypes of diabetes (23). The functional properties of the new SUR1 mutations on electrophysiological parameters of the K_{ATP} channel may give a valuable estimate on their pathological impact, although it may be difficult to demonstrate an effect such as in the case of the E23K polymorphism of the Kir6.2 subunit of the K_{ATP} channel (24).

In conclusion, from our case series of neonatal diabetes, the SUR1 mutations associate mainly with transient hyperglycemia, with possible recurrence later in life, even though ketoacidosis is frequent at presentation. Neuropsychological disturbances are found in some SUR1 neonatal diabetic patients, which deserves further description. Moreover, *ABCC8* sequencing in additional groups of patients with diabetes, not resticted to neonatal diabetes, will help to define the clinical spectrum associated with mutations in SUR1.

ACKNOWLEDGMENTS

This study was supported by the European Union (Integrated Project EuroDia LSHM-CT-2006-518153 in the Framework Programme 6 of the European Community) and by grants RGDM (G03/212) and RCMN (C03/08) from the Instituto de Salud Carlos III, Madrid, Spain. We also acknowledge the French nonprofit associations Aide aux Jeunes Diabétiques (to M.P.) and Association Française des Diabétiques (to R.S.) for their support of parts of the study. G.P.N. is an FIS Research Scientist supported by the Spanish Ministry of Health (fellowship no. 03/0064).

We would like to thank all of the families for their participation in the study. We are very grateful to Prof. Paul Czernichow for his continuous support on the projects dedicated to neonatal diabetes and to Dr. Lydia Aguilar-Bryan for her critical reading of the manuscript and helpful discussions.

APPENDIX

The SUR1–Neonatal Diabetes Study Group is composed of the following: B. Dundar, Isparta, Turkey; C. Fernandez and E. Fernandez-Rebollo, Bilbao, Spain; M. Gonthier, Montréal, Quebec, Canada; J.L. Lechuga, Cadiz, Spain; C. Metz and B. Giroux, Brest, France; S. Soskin, Strasbourg, France; C. Stuckens, Lille, France; V. Sulmont, Reims, France; and N. Tubiana-Rufi, Paris, France.

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