Title; Long-term follow-up of glycemic and neurological outcomes in an international series of patients with sulfonylurea-treated *ABCC8* permanent neonatal diabetes

Short running title; Outcomes of sulfonylurea treatment in *ABCC8* PNDM

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ABSTRACT

Objective

ABCC8 mutations cause neonatal diabetes that can be transient (TNDM) or less commonly permanent (PNDM); ~90% individuals can be treated with oral sulfonylureas instead of insulin. Previous studies suggested that people with *ABCC8*-PNDM require lower sulfonylurea doses and have milder neurological features than those with *KCNJ11*-PNDM. However, these studies were short-term and included combinations of permanent and transient forms of *ABCC8*-NDM. We aimed to assess the long-term glycemic and neurological outcomes in sulfonylurea-treated *ABCC8*-PNDM.

Research Design and Methods

We studied all 24 individuals with *ABCC8*-PNDM diagnosed in the UK, Italy, France or USA known to transfer from insulin to sulfonylureas before May 2010. Data on glycemic control, sulfonylurea dose, adverse effects including hypoglycemia, and neurological features were analysed using non-parametric statistical methods.

Results

Long-term data were obtained for 21/24 individuals (median follow-up 10.0 (4.1-13.2) years). 18/21 remained on sulfonylureas without insulin at most recent follow-up. Glycemic control improved on sulfonylureas (pre-sulfonylurea vs 1-year post-transfer HbA1c 7.2% vs 5.7%, p=0.0004) and remained excellent long-term (1-year vs. 10-year HbA1c 5.7% vs. 6.5%, p=0.04), n=16. Relatively high doses were used (1-year vs 10-year dose 0.37 vs 0.25mg/kg/day glyburide, p=0.50), without any severe hypoglycemia. Neurological features were reported in 13/21 individuals: these improved following sulfonylurea transfer in 7/13. The commonest features were learning difficulties (52%), developmental delay (48%), and ADHD (38%).

Conclusions

Sulfonylurea treatment of *ABCC8*-PNDM results in excellent long-term glycemic control. Overt neurological features frequently occur and may improve with sulfonylureas, supporting early, rapid genetic testing to guide appropriate treatment and neurodevelopmental assessment.

Introduction

The *ABCC8* gene encodes the SUR1 subunit of the pancreatic ATP-sensitive potassium (K_{ATP}) channel (1). SUR1 forms hetero-octameric complexes with Kir6.2, encoded by the *KCNJ11* gene (2). Mutations in K_{ATP} channel genes are the commonest cause of neonatal diabetes in non-consanguineous populations, with ~15-20% due to *ABCC8* mutations and ~25-30% due to *KCNJ11* mutations (3). Neonatal diabetes typically occurs in the first 6 months of life and can be permanent (PNDM), where diabetes persists lifelong, or transient (TNDM), where there is a period of remission of diabetes after 6-12 months followed by relapse in adolescence or early adulthood (4). *ABCC8* mutations cause TNDM in ~80% of cases and PNDM in ~20% cases; the opposite pattern is observed with *KCNJ11* mutations, which most frequently result in PNDM (5).

ABCC8 and *KCNJ11* mutations cause neonatal diabetes by preventing closure of pancreatic K_{ATP} channels in response to rising glucose (6, 7). This results in insulin deficiency, which historically required treatment with replacement doses of insulin. However, in ~90% of affected individuals sulfonylurea treatment can bypass the genetic defect by binding SUR1 and closing pancreatic K_{ATP} channels, promoting secretion of endogenous insulin and allowing patients to stop insulin injections and achieve excellent glycemic control and better quality of life (8-10). Sulfonylureas are the optimum treatment for *KCNJ11* PNDM long-term; in those patients who successfully transfer from insulin to sulfonylureas, metabolic control is maintained in >90% for at least 10 years with no serious adverse effects despite doses being ~2-10 times higher than those recommended in Type 2 Diabetes (T2D) (11). Short-term studies have suggested that lower doses of sulfonylurea are required to treat *ABCC8*-NDM in comparison to *KCNJ11*-NDM (9, 12). However, many previous studies contained both individuals with *ABCC8*-PNDM and *ABCC8*-TNDM, which have different clinical courses and treatment requirements (5, 6, 9). No study has assessed the long-term outcomes of sulfonylurea treatment specifically in *ABCC8*-PNDM.

ABCC8 and *KCNJ11* are both expressed in the brain as well as the pancreas (13, 14), therefore in addition to diabetes, central nervous system (CNS) features are observed in individuals with K_{ATP} channel mutations. These vary from the severe developmental delay, epilepsy and neonatal diabetes

(DEND) syndrome, to mild neuropsychological impairments detectable only on detailed neuropsychomotor testing (5, 15). In *KCNJ11*-PNDM, there is some correlation between the position of the variant in the protein and the clinical features. In contrast, in *ABCC8*-PNDM genotype-phenotype relationships appear less distinct (16). In around half of individuals with *KCNJ11*-PNDM, sulfonylurea treatment results in partial improvement of the neurological features, which is thought to be due to the action of glyburide on K_{ATP} channels in the brain (11, 17).

Observational studies have suggested that the CNS features are not as common and /or severe in individuals with *ABCC8* mutations (5, 6, 18, 19), in comparison to those with *KCNJ11* mutations. However, as discussed above, previous research findings are based on cohorts containing both individuals with *ABCC8*-PNDM and *ABCC8*-TNDM. In addition, the majority of studies investigating the neurodevelopmental features associated with K_{ATP} channel mutations and the response of these features to sulfonylurea treatment have focused on patients with *KCNJ11*-PNDM.

Research relating to the CNS features in individuals with *ABCC8*-PNDM and the impact of long-term sulfonylurea treatment on both glycemic and neurological outcomes is crucial to establish and to inform clinical guidelines for this specific subtype.

Aim

To assess the long-term glycemic and neurological response to sulfonylureas in an international cohort of patients with PNDM due to *ABCC8* mutations.

Research Design and Methods

Patient cohort

Patients with a molecular genetic diagnosis of PNDM due to mutations in the *ABCC8* gene (NM_001287174.1) confirmed in laboratories in Exeter (UK), Rome (Italy), Paris (France) and Chicago (USA) known to transfer to sulfonylureas prior to 30th April 2010 with no period of remission of their diabetes were eligible for inclusion in the study (n=24). Three patients were lost to follow-up in the first year after sulfonylurea transfer and were therefore excluded, leaving 21 patients with sufficient follow-up data (>4 years) for further analyses.

The study was conducted in accordance with the Declaration of Helsinki as revised in 2000. Patient data was collected during routine clinical care or through research surveys and was anonymised for use in the study. The study is registered with ClinicalTrials.gov, number NCT02624830.

Data Collection

Data were collected from the clinical records of participating patients or through research surveys completed by the participant or their carer(s). Data on glycemic control, sulfonylurea dose, and hypoglycemia, were collected before and after transfer from insulin to sulfonylureas, and annually until the most recent clinic follow-up. Clinicians and participants were asked to report side-effects or diabetes complications that occurred at any time point during the follow-up and if so to provide details about these.

Data on neurological features were collected before transfer from insulin to sulfonylureas, and after transfer at most recent follow-up. Clinicians or participants were specifically asked about the presence of developmental delay (DD), learning difficulties (LD), attention-deficit hyperactivity disorder (ADHD), epilepsy, sleep problems, muscle weakness, anxiety, autism, and spasticity as well as ‘other’ difficulties (11), and whether these features (if present) had improved on transfer to sulfonylureas.

Statistical Analysis

Data were analysed in Stata 16.0 using non-parametric statistical methods. Clinical characteristics of patients who remained on sulfonylurea alone were compared with those who required permanent reintroduction of insulin using the Mann-Whitney test for continuous data and 2-sample test of proportions for categorical data. For those patients who remained on sulfonylurea alone for the duration of the follow-up, paired data on metabolic control (HbA1c) and sulfonylurea dose were compared using the Wilcoxon signed-rank test. For those individuals with annual data available for

>50% of time points, longitudinal trends in HbA1c and sulfonylurea dose were plotted. Missing data were imputed as previously described (11).

Individuals who required insulin therapy only transiently or who were prescribed any other oral anti-diabetic medication at any point in the follow-up were classified in the sulfonylurea only group. One individual (mutation, L1148R/R1380C) transferred from insulin to sulfonylureas twice aged 18 months (for 4 years) and again aged 26 years. His follow-up data relates to the second sulfonylurea transfer as no data were available after the first transfer 35 years ago.

For sulfonylureas other than glyburide, doses were converted to glyburide equivalent using percentage of maximum glibenclamide (glyburide) dose as per the British National Formulary (BNF) (20). Data are presented as median (range) unless stated otherwise. For all analyses, a p-value of less than 0.05 was used to denote statistical significance.

Results

Clinical characteristics

Clinical characteristics of the patients included in the study are shown in Tables 1 and 2.

Duration of follow-up

Median duration of follow-up was 10.0 (4.1-13.2) years, comprising a total of 205 patient years.

Sulfonylurea efficacy

At most recent follow-up, 18/21 (86%) patients remained on sulfonylurea therapy without insulin. For all three individuals who had restarted insulin, clinicians reported problems with adherence with prescribed medication and/or periods of loss to clinic/hospital follow-up. Clinical characteristics were similar between the individuals who remained on sulfonylureas vs. those who required reintroduction of insulin (Table 1).

Type of sulfonylurea prescribed

All patients who remained independent of insulin at most recent follow-up were prescribed glyburide for the duration of the study. One patient was prescribed glyburide at initial transfer from insulin and was switched to tolbutamide at day 45 post-transfer (21); this individual subsequently required reintroduction of insulin therapy having stopped sulfonylurea treatment whilst lost to hospital follow-up.

Metabolic control and sulfonylurea dose

Paired data on pre-transfer HbA1c and HbA1c and sulfonylurea dose at year 1 (median 0.97, range 0.27-1.76 years) and year 10 (median 9.8, range 6.1-12.5 years) were available for 16 individuals. In these individuals, glycemic control improved on transfer to sulfonylurea [pre-transfer vs 1-year HbA1c 7.2 (5.3-9.5) vs 5.7 (5.0-7.3)% (55 (34-80) vs. 39 (31-56) mmol/mol), p=0.0004] and remained excellent at long-term follow-up [1-year vs. 10-year HbA1c 5.7 (5.0-7.3) vs. 6.5 (5.3-7.7)% (39 (31-56) vs. 48 (34-61) mmol/mol), p=0.04], figure 1a. High doses of sulfonylurea were used in most individuals [1-year vs 10-year dose 0.37 (0.01-1.25) vs 0.25 (0.03-1.30) mg/kg/glyburide, p=0.50], figure 1b. Only 3 individuals required doses under 0.1mg/kg/day glyburide at most recent follow-up. In 11 individuals who had sufficient annual data available, there was a gradual reduction in median sulfonylurea dose per kilogram of body weight over time despite relatively stable glycemic control, figure S1.

Side-effects

Diarrhea was reported in two individuals. One individual was diagnosed with irritable bowel syndrome (IBS). The second individual, previously reported by Codner et al, experienced transient diarrhea on glyburide; this stopped on switching to tolbutamide (21). No other adverse effects of sulfonylurea therapy were reported.

Hypoglycemia

There were no episodes of severe hypoglycemia, defined as losing consciousness or having seizures (22), reported over the course of the follow-up in patients treated with sulfonylurea alone. In one individual on glyburide treatment, an episode was reported whereby the blood glucose remained <4.0mmol/l even after treatment with fruit juice and third party assistance was required. Another individual switched treatment from glyburide to tolbutamide (see above), due to episodes of asymptomatic hypoglycemia on glyburide treatment; these settled on tolbutamide (21).

Diabetes Complications

Microvascular complications occurred in 2 individuals; one had microalbuminuria, and one had microalbuminuria (normotensive) and proliferative retinopathy requiring intravitreal injections and photocoagulation, as well as mildly elevated LDL treated with a statin medication. These individuals transferred to sulfonylureas aged 10 years and 26 years (after a short period of sulfonylurea treatment as a child - see above). There were no macrovascular complications reported over the period of follow-up.

Body Mass Index (BMI)

In 10 individuals who remained independent of insulin and had paired height and weight data available, BMI remained normal [BMI standard deviation score (SDS) pre-sulfonylurea treatment -0.13(-0.85-1.44) and at most recent follow-up on sulfonylureas -0.29 (-0.99-0.94), p=0.23].

Central Nervous System (CNS) Features

13/21 (62%) patients were reported to have CNS features before and after transfer to sulfonylurea, figure 3a and Table S1. The commonest features at most recent follow-up were developmental delay (DD) in 48%, learning difficulties (LD) in 52% and attention deficit hyperactivity disorder (ADHD) in 38%. Co-morbidity was common: 11 individuals had 3 or more specific CNS features together. .In five individuals, seizures were or may have been a result of factors other than the genetic mutation (Table S2).

In 7/13 (54%) there was some improvement (n=5) or complete resolution (n=2) noted in neurological features on starting sulfonylureas, figure 3a and Table S1. In the 2 patients whose neurological features completely resolved, both had DD pre-transfer (with LD in one case) but subsequently attained a developmental level expected for their age.

All 3 patients who required reintroduction of insulin treatment had neurological features (Table 1); there was improvement in the EEG background in one of these patients following initial transfer from insulin onto sulfonylureas. Age at transfer to sulfonylureas was similar in those patients with and without neurological features at most recent follow-up [6.6 (0.5-18.2 vs. 8.4 (0.9-26.0) years, p=0.53].

Discussion / Conclusions

In summary, in our 10-year study of 21 individuals with sulfonylurea-treated *ABCC8*-PNDM, 86% remained independent of insulin at their most recent follow-up. Furthermore, glycemic control was maintained on relatively high doses of sulfonylurea, without any reports of severe hypoglycemia or side effects. A large proportion of the cohort (62%) had overt neurological features both prior to sulfonylurea transfer and at most recent follow-up, and co-morbidity was common. There was partial improvement in some CNS features in just over half of individuals following transfer to sulfonylurea therapy.

The excellent long-term outcomes in sulfonylurea-treated *ABCC8*-PNDM are similar to those observed in *KCNJ11*-PNDM, Table S3 (11). Our data do not support the suggestion from previous studies that lower doses of sulfonylurea may be required in people with *ABBC8* mutations in comparison to those with *KCNJ11* mutations (9). This may be due at least in part to the inclusion of patients with transient and permanent forms of *ABCC8*-NDM in earlier cohort studies (9) and a lower sulfonylurea dose requirement in the patients with TNDM (23). In this study, behavioural and / or social factors are likely to explain the deterioration in glycemic control in the 3 individuals with *ABCC8*-PNDM who required reintroduction of insulin.

We have shown that overt CNS features in *ABCC8*-PNDM occur with relatively high frequency and that co-morbidity is common, in contrast with previous studies that included cohorts of patients with *ABCC8*-TNDM and PNDM (5, 6, 9). Indeed, the frequency and nature of CNS features in *ABCC8*-PNDM is similar to that observed in *KCNJ11*-PNDM, Table S3 (11), with the exception of autism which has been more frequently reported in *KCNJ11*-PNDM (11, 24, 25).

The partial improvement in neurological features in 7/13 individuals on transferring to sulfonylureas is consistent with previous cases and suggests that the drugs may improve neurological function in some patients with *ABCC8*-PNDM, although a randomised controlled trial would be required to prove this definitively. It has been suggested the improvement in neurological features is greater the earlier sulfonylureas are started (17, 26), reflecting greater neuroplasticity at a younger age with a so-called 'sensitive period' occurring within the first 6 months of life (27). In our cohort, only 2 patients transferred under the age of 1 year and none transferred under the age of 6 months, therefore this crucial sensitive period for the action of sulfonylureas in the brain may have been missed. Studies in rats have suggested that glyburide is actively transported out of the brain (28); this may make it difficult to achieve therapeutic concentrations of the drug in the cerebrospinal fluid (CSF). As a result, recommended doses of glyburide in patients with K_{ATP} channel-related PNDM and severe neurological features are higher (at least ~1mg/kg/day) (29). Of those individuals who remained independent of insulin in our cohort, only 2 were on a dose this high at their most recent follow-up. Furthermore, there was a tendency for glyburide doses to fall over time, which may reflect lack of adjustment of total daily doses according to increases in body weight as children grow. This may also explain the slightly higher HbA1c at most recent follow-up when compared with year 1.

These factors emphasise the need for early genetic testing and identification of all patients with *ABCC8*-PNDM. Prompt genetic diagnosis facilitates early transfer to sulfonylureas, as well as systematic screening of all affected individuals for neurodevelopmental features at diagnosis and follow-up, and provision of appropriate support. Clinicians should consider higher doses of sulfonylureas if neurological features are present. They should also regularly adjust total daily dose to maintain the same dose per kilogram of body weight over time, thereby optimising treatment for both glycemia and neurological features.

Variable modes of inheritance are observed in our cohort; there is a mixture of dominant heterozygous *ABCC8* mutations (n=11) as well as compound heterozygous (n=7) and homozygous variants (n=3), in keeping with previous studies (30). This has implications for genetic counseling in relation to recurrence risk and carrier status in future offspring, which will be different for dominant vs recessive inheritance. In this study, there were no differences in long-term outcomes between individuals with dominant heterozygous vs recessive (homozygous and compound heterozygous) mutations (Table 2). However, our study was not designed to address this question, and research in larger cohorts will be required to investigate the impact of mode of inheritance on clinical outcomes in *ABCC8*-PNDM. An additional limitation is the wide range of specific genetic variants included, which prevents the identification of strong genotype-phenotype relationships.

Finally, neurological features were not screened for systematically via repeated assessments in one center over the course of the follow-up, and comprehensive neuropsychological testing was not done as part of this study. Therefore, there is likely to be variable ascertainment and / or reporting of CNS features based on what was recorded in the clinical notes. This might result in an underestimation of the extent of neurological involvement in affected individuals. It is not possible to fully distinguish the relative contributions of mutant K_{ATP} channels in the brain and other factors to the neurological features reported (Table S2). It is likely that in at least some individuals the neurological features will be due to a combination of different etiologies. Despite these limitations, this is the first study to assess the long-term treatment response and CNS features in an international cohort of patients with *ABCC8*-PNDM.

Further research in larger cohorts of individuals with *ABCC8* mutations will be required to investigate in more detail the CNS phenotype, genotype-phenotype relationships, and factors influencing the glycemic response to sulfonylureas e.g. specific physiological states such as puberty and pregnancy.

Conclusions

We have shown for the first time that sulfonylurea therapy is effective and safe long-term for people with PNDM due to *ABCC8* mutations, with excellent glycemic control maintained over 10 years without severe hypoglycemia or side effects, despite relatively high doses in most patients. Importantly, affected individuals frequently have multiple overt CNS features, which, in some, may partly improve with sulfonylureas. Rapid genetic diagnosis is crucial to facilitate early initiation of precision therapy with sulfonylureas in *ABCC8*-PNDM, and enable prompt identification of neurodevelopmental features and provision of appropriate support for affected families.

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Data access statement

The research data supporting this publication are provided within the manuscript and online supplemental material.

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Duality of Interest

None to declare.

Author Contributions

ATH, PB, FB, JB, MP, TB and NJT were involved in study design and protocol development. All authors were involved in data collection. EDF was involved in the genetic analysis. PB, FM, ER, ATH, and SEF were involved in data cleaning, analysis and interpretation. PB wrote the manuscript and all authors reviewed, critically revised and approved the manuscript for submission.

Figure Legends

Figure 1. Part A: HbA1c pre-sulfonylurea transfer, at year 1 and at most recent follow-up in 16 patients with data available at all 3 time points. Circles represent individuals and black horizontal lines represent group medians. Part B: Sulfonylurea dose at year 1 and at most recent follow-up in 16 patients included in Figure 1A. Circles represent individuals and black horizontal lines represent group medians.

Figure 2: Number of patients with *ABCC8*-PNDM with neurological features relative to sulfonylurea transfer. CNS = central nervous system.

Online Supplemental Material

Supplementary Appendix. Neonatal diabetes international collaboration.

Supplementary Table S1. Neurological features present before and after transfer to sulfonylureas, and features that improved on SU transfer.

Supplementary Table S2. Clinical details of patients in whom seizures / epilepsy may have been attributable to factors other than the genetic mutation.

Supplementary Table S3. Comparison of long-term outcomes in individuals with mutations in the *KCNJ11* and *ABCC8* genes.

Figure S1. HbA1c and sulfonylurea dose in 11 patients with at least 50% of annual longitudinal data available for both variables. Data are presented as median (interquartile range). Missing data were imputed as previously described (11).

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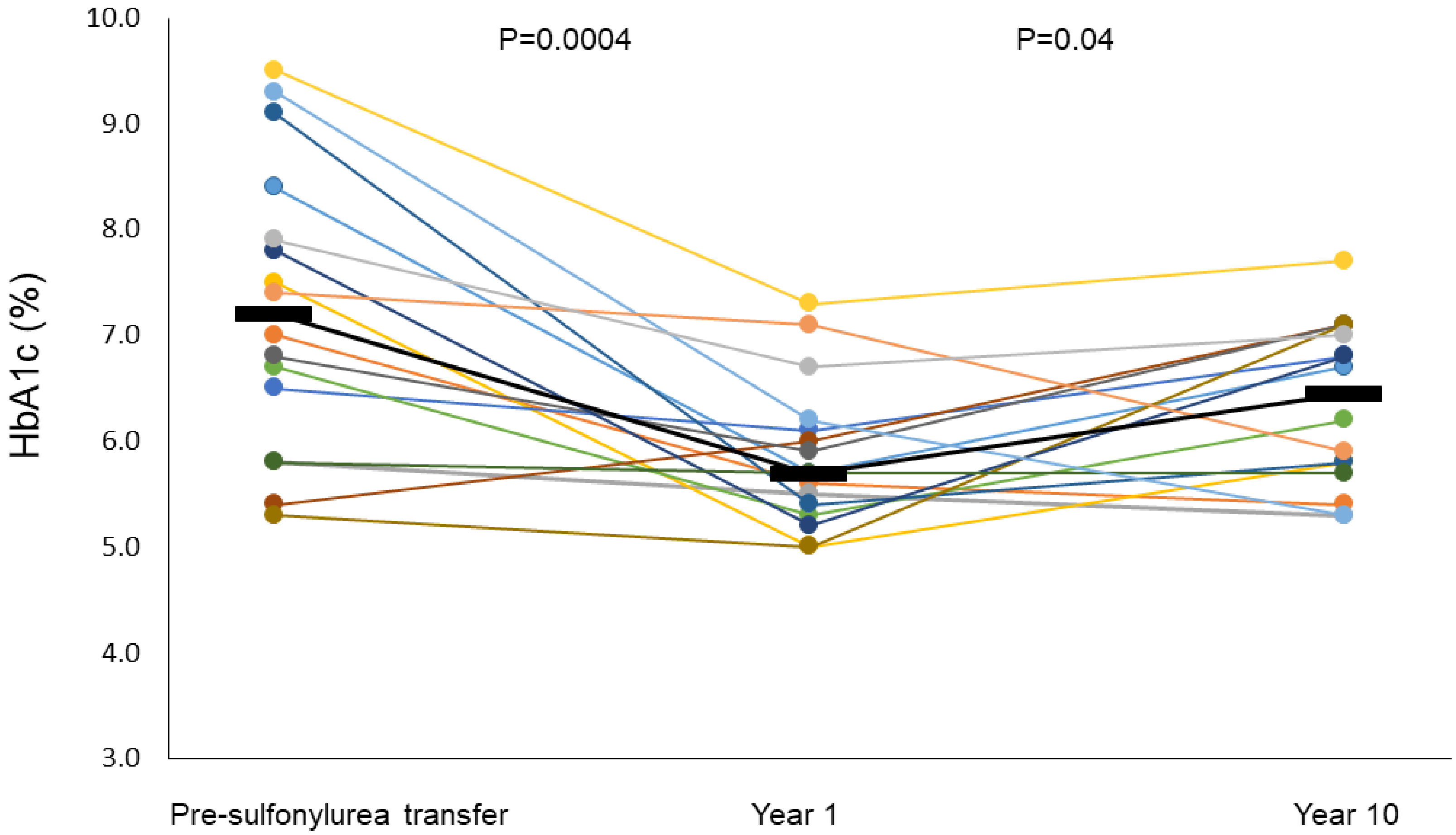
Clinical feature	On SU without insulin at most recent follow-up (n=18)	On insulin with or without SU at most recent follow-up (n=3)	P-value (on SU vs on insulin)
Genotype	E208K/Y263D, V86G/N, D212I/N, P45L/G1401R, V86A/N, L1295F/N, T229I/V1532L, L225P/N, L135P/N, 2 E382K/E382K, L213R/N, R168C/G1256S, V215A/V215A, E208K/D1472N, V324M/W688R, L213P/N, L1148R/R1380C	D209E/N, R1380L/N, Q211K/N	N/A
N male (%)	10 (56)	0 (0)	0.07
Birth weight (g)	2750 (1510-3402) (n=16)	2700 (2400-2700) (n=3)	0.62
Age at diagnosis (weeks)	7.5 (1.0-47.0) (n=18)	6.0 (5.0-17.0) (n=3)	1.00
Age at transfer to SU (years)	7.6 (0.5-26.0) (n=18)	5.8 (2.8-9.4) (n=3)	0.46
Current age (years)	21 (11-36) (n=18)	19 (16-22) (n=3)	0.58
Pre-SU HbA1c (%)	7.5 (5.3-9.5) (n=18)	6.8 (6.7-7.2) (n=3)	0.52
Pre-SU HbA1c (mmol/mol)	58 (34-80) (n=18)	51 (50-55) (n=3)	0.52
Year 1 HbA1c (%)	5.7 (5.0-7.3) (n=16)	6.8 (6.7-6.9) (n=2)	0.13
Year 1 HbA1c (mmol/mol)	39 (31-56) (n=16)	51 (50-52) (n=2)	0.13
Most recent HbA1c (%)	6.7 (5.3-10.1) (n=18)	9.8 (5.9-10.3) (n=3)	0.17
Most recent HbA1c (mmol/mol)	50 (34-87) (n=18)	84 (41-89) (n=3)	0.17
Year 1 SU dose (mg/kg/day glyburide)	0.37 (0.01-1.25) (n=16)	0.03 (0.01-0.04) (n=2)	0.05
Most recent SU dose (mg/kg/day glyburide)	0.35 (0.03 – 1.30) (n=18)	0.74 (0.02-1.45) (n=2)	1.00
Neurological features (any)	10 (56)	3 (100)	0.15
Pre-SU BMI SDS (kg/m2)	-0.13 (-0.85-1.44) (n=10)	-0.53 (-1.68- -0.26) (n=3)	0.10
Most recent BMI SDS (kg/m2)	-0.75 (-3.69 – 1.28) (n=13)	-1.34 (-1.94 - -0.24) (n=3)	0.19

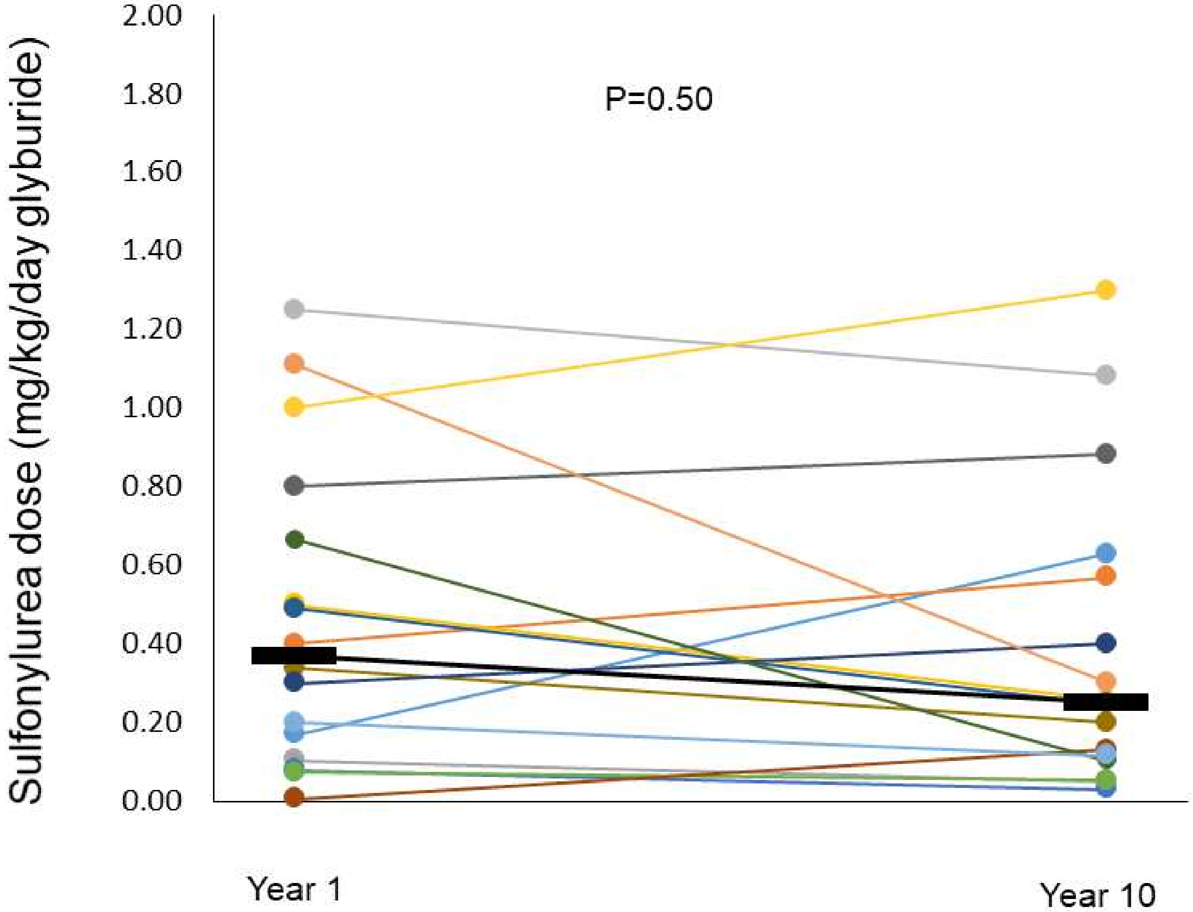
Table 1. Clinical features of whole cohort, including all data available at all time points. Data are presented as median (range). Year 1 is median duration 0.97 (0.27-1.76 years); data closest to one year used. Most recent duration for sulfonylurea dose and HbA1c median 10.0 (4.1-13.2) years. Most recent duration for BMI 9.8 (4.6-13.2) years (most recent time point at which both height and weight data available). N is different for each variable due to differences in amount of available data. Most recent sulfonylurea dose is different to that reported in the results section due to paired values for sulfonylurea dose and HbA1c at all time points being unavailable for 3 individuals included in the table. SU = sulfonylurea, BMI = body mass index, SDS = standard deviation score. SU = sulfonylurea, BMI = body mass index, SDS = standard deviation score.

Clinical feature	Dominant heterozygous (n=11)	Recessive (compound heterozygous / homozygous) (n=10)	P-value
Genotype	D209E/N, D212I/N, L1295F/N, L135P/N, L213P/N, L213R/N, L225P/N, Q211K/N, R1380L/N, V86G/N, V86A/N	2 E382K/E382K, E208K/D1472N, E208K/Y263D, L1148R/R1380C, P45L/G1401R, R168C/G1256S, T229I/V1532L, V215A/V215A, V324M/W688R	N/A
Duration of follow-up (years)	11.2 (7.9-13.2)	9.1 (4.1-12.3)	0.02
N male (%)	4/11 (36)	6/10 (60)	0.27
Birth weight (g)	2700 (2100-3065) (n=9)	2750 (1510-3402) (n=10)	0.76
Age at diagnosis (weeks)	6 (2-17) (n=11)	11 (1-47) (n=10)	0.48
Age at transfer to SU (years)	5.8 (1.9-12.0) (n=11)	10.3 (0.5-26.0) (n=10)	0.12
Current age (years)	19 (15-23) (n=11)	22.5 (11-36) (n=10)	0.08
Pre-SU HbA1c (%)	6.7 (5.3-7.9) (n=11)	8.1 (5.8-9.5) (n=10)	0.001
Pre-SU HbA1c (mmol/mol)	50 (34-63) (n=11)	65 (40-80) (n=10)	0.001
Year 1 HbA1c (%)	6.0 (5.0-6.9) (n=10)	5.7 (5.0-7.3) (n=8)	0.92
Year 1 HbA1c (mmol/mol)	42 (31-52) (n=10)	39 (31-56) (n=8)	0.92
Most recent HbA1c (%)	7.0 (5.3-10.3) (n=11)	6.3 (5.3-10.1) (n=10)	0.32
Most recent HbA1c (mmol/mol)	53 (34-89) (n=11)	45 (34-87) (n=10)	0.32
Year 1 SU dose (mg/kg/day glyburide)	0.09 (0.01-1.25) (n=10)	0.50 (0.17-1.11) (n=8)	0.08
Most recent SU dose (mg/kg/day glyburide)	0.36 (0.02-1.45) (n=10)	0.35 (0.10-1.30) (n=10)	0.67
N on insulin at recent follow-up	3/11 (27)	0/10 (0)	0.08
N with neurological features any at most recent visit (%)	7/11 (64)	6/10 (60)	0.85

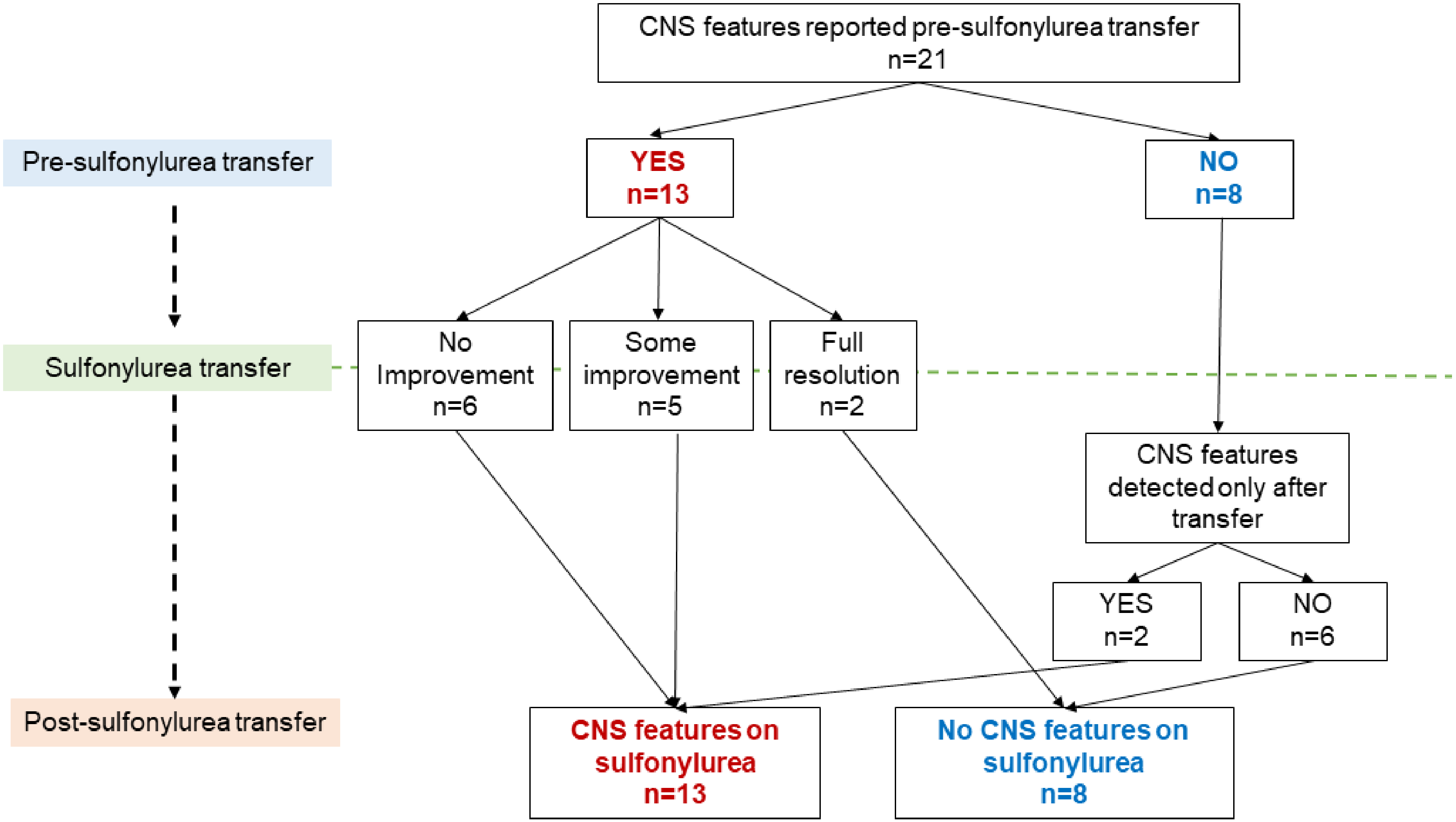
Table 2. Clinical features of individuals with dominantly vs recessively inherited variants in the *ABCC8* gene. Data are presented as median (range). N is different for each variable due to differences in amount of available data. SU = sulfonylurea, N = number.

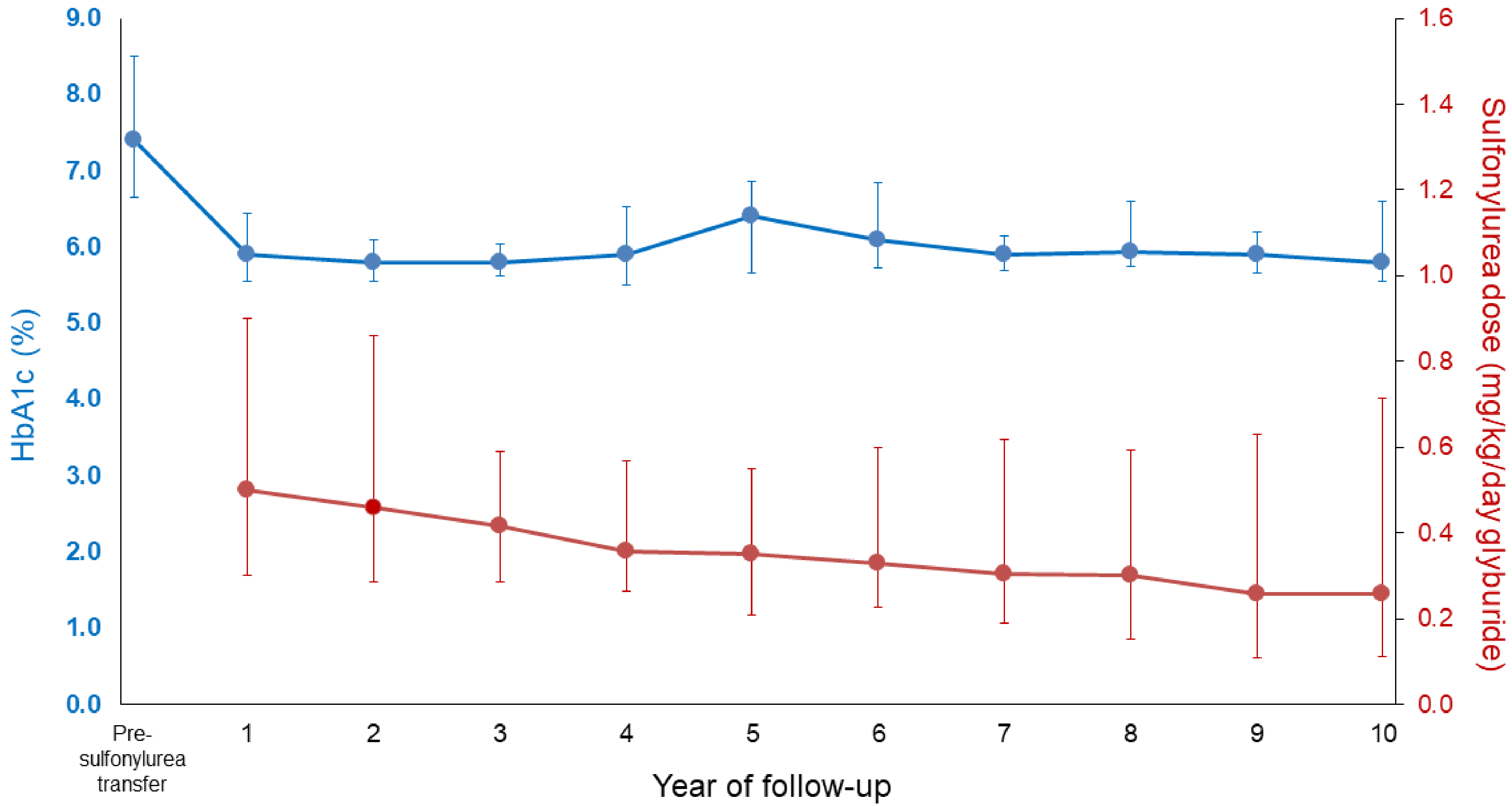


HbA1c (%)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
P=0.0004
P=0.04
Pre-sulfonylurea transfer
Year 1
Year 10



Sulfonylurea dose (mg/kg/day glyburide)
2.00
1.80
1.60
1.40
1.20
1.00
0.80
0.60
0.40
0.20
0.00
P=0.50
Year 1
Year 10


CNS features reported pre-sulfonylurea transfer
n=21
Pre-sulfonylurea transfer
YES
n=13
NO
n=8
Sulfonylurea transfer
No
Improvement
n=6
Some
improvement
n=5
Full
resolution
n=2
CNS features
detected only after
transfer
YES
n=2
NO
n=6
Post-sulfonylurea transfer
CNS features on
sulfonylurea
n=13
No CNS features on
sulfonylurea
n=8



HbA1c (%)
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Sulfonylurea dose (mg/kg/day glyburide)
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
Pre-sulfonylurea transfer
1
2
3
4
5
6
7
8
9
10
Year of follow-up

CNS feature	Pre SU transfer (n)	Post SU transfer (n)	Post transfer only (n)	Improvement on SU (n)
Any	13	13	0	7
DD	10	10	1	3
LD	7	11	2	1
ADHD	6	8	2	1
Epilepsy	4	3	2	2**□
Muscle weakness	2	2	0	0
Anxiety	2	2	0	0
Sleep problems	2	2	1	0
Spasticity	2	2	0	0
Autism	0	0	0	N/A
Other*	5	4	0	1***

Supplementary Table S1. Neurological features present before and after transfer to sulfonylureas, and features that improved on SU transfer

*'Other' CNS features prior to sulfonylurea transfer in addition to the specific features listed consisted of obsessive-compulsive disorder (OCD) with mild Tourette's, encopresis, hypertonia, hypotonia and an abnormal electroencephalogram (EEG) (in the absence of a diagnosis of epilepsy). These features were also present after sulfonylurea transfer with the exception of hypotonia (but not known if this was tested).

**both individuals had seizures at time of diagnosis only which may have been attributable to cerebral oedema (Table S2)

□individuals treated with anti-epileptic medication not included as 'improved' (Table S2)

***improved background on EEG

CNS = central nervous system, SU = sulfonylurea, DD = developmental delay, LD = learning difficulties, ADHD = attention deficit hyperactivity disorder

Mutation in *ABCC8* gene	Age at diagnosis of diabetes (weeks)	Age at transfer to SU (years)	Clinical history	Other neurological features present in addition to seizures / epilepsy	Neurological features improved on transfer to SU
Individuals in whom metabolic disturbance at diagnosis may have contributed to seizures					
P45L/G1401R	6	8	Diabetic ketoacidosis at 6 weeks of age with severe dehydration, reduced consciousness, opisthotonus and partial seizures - diagnosed with cerebral edema (31)	Muscle weakness, hypertonia, spasticity, DD, LD, and sleep problems	Improvements in sleep, speech, concentration and schoolwork noted by parents and teachers. No epilepsy at most recent follow-up.
V215A/V215A	9	0.5	Focal seizures around time of diagnosis: in left arm 2 days before admission and in left arm and leg 2 days after admission	DD (mild), LD (mild)	No seizures since 2 months of age but on antiepileptic drugs. Other features (DD / LD) identified only after SU transfer.
V86G/N	5	3	Seizures only at time of diagnosis: none since.	DD, LD, ADHD, anxiety	Slight improvement. No anxiety post SU transfer and no further seizures. Main problem currently is speech delay / difficulties at school.
Individuals in whom seizures are attributable to another (non-metabolic) cause					
L1295F/N	12	6	One seizure due to starting treatment with dexmethylphenidate for ADHD (no further seizures on stopping drug)	DD, LD, ADHD, muscle weakness	No change.
L135P/N	6	10	Viral meningoencephalitis at 6 weeks of age, treated with Depakine 200-300mg at clinic follow-up prior to SU transfer	Spastic paraplegia, DD, LD, sleep problems	No change. Epilepsy not reported at recent follow-up but has had treatment with antiepileptic drugs

Supplementary Table S2. Clinical details of patients in whom seizures / epilepsy may have been attributable to factors other than the genetic mutation. SU = sulfonylurea, DD = developmental delay, LD = learning difficulties, ADHD = attention deficit hyperactivity disorder

Outcome on SU treatment	***ABCC8*-PNDM (n=21)**	***KCNJ11*-PNDM (n=81)**
Patients independent of insulin at 10 years (%)	86	93
Median HbA1c at 10 years - paired (%)	6.5 (n=16)	6.4 (n=64)
Median SU dose required at 10 years - paired (mg/kg/day glyburide)	0.25 (n=16)	0.23 (n=64)
Median BMI at 10 years SDS (kg/m^2)	-0.75 (n=13)	-0.22 (n=72)
Frequency of neurological features at 10 years (%)	62 (n=21)	64 (n=81)
Improvement in neurological features after SU transfer (%)	54 (n=13)	47 (n=38)
Number of episodes of severe hypoglycemia on SU only over 10 years	0 (n=18)	0 (n=75)
Frequency of side effects (%)	11 (n=18)	14 (n=81)
Frequency of diabetes complications (%)	11 (n=18)	9 (n=81)

Supplementary Table S3. Comparison of long-term outcomes in individuals with mutations in the *KCNJ11* and *ABCC8* genes.

Comparative data on *KCNJ11*-PNDM taken from Bowman et al Lancet D&E 2018 (11) SU = sulfonylurea, PNDM = permanent neonatal diabetes mellitus, BMI = body mass index, SDS = standard deviation score