Figure S1

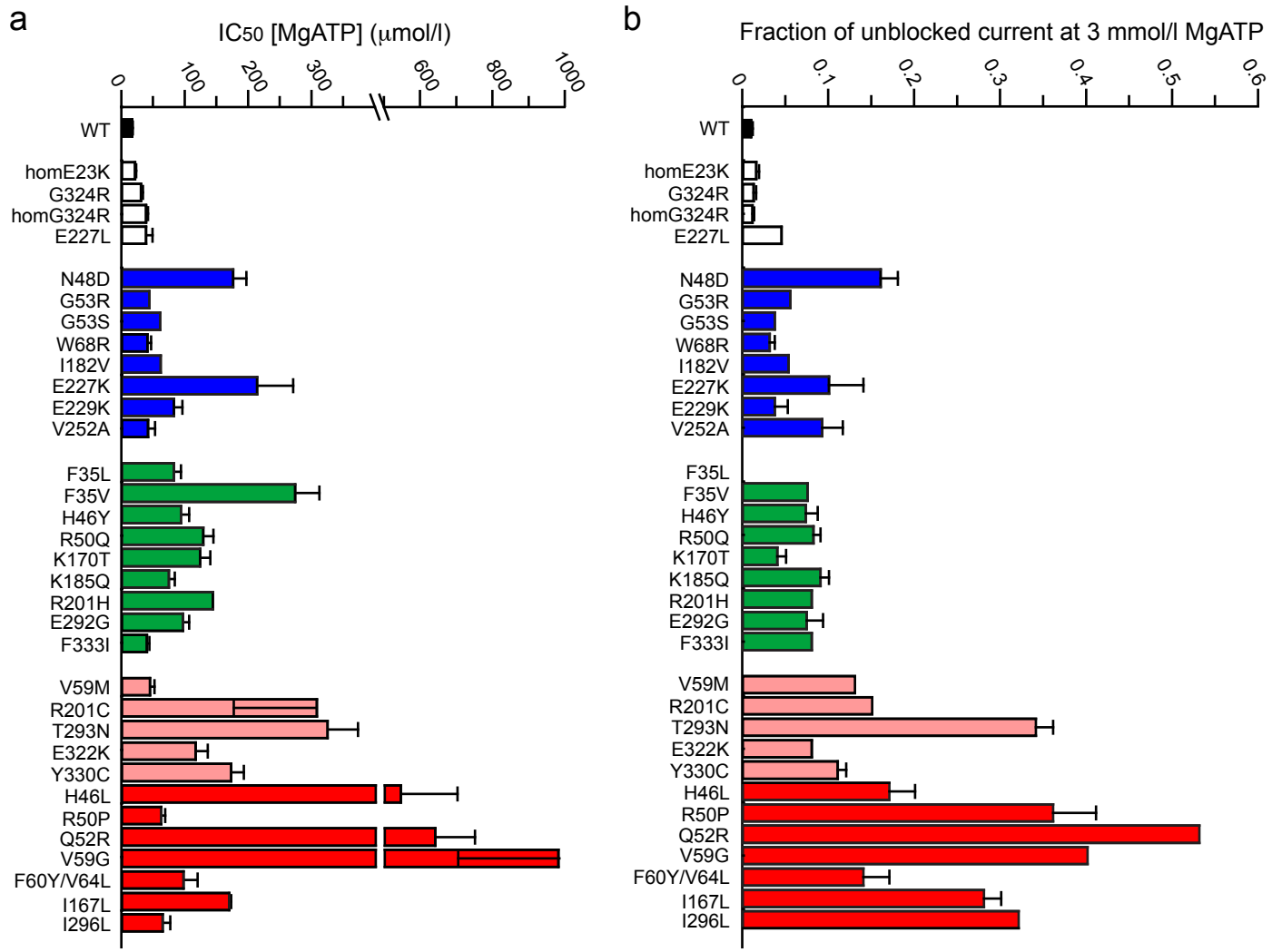
a
IC50 [MgATP] (μmol/l)
0
100
200
300
600
800
1000
WT
homE23K
G324R
homG324R
E227L
N48D
G53R
G53S
W68R
I182V
E227K
E229K
V252A
F35L
F35V
H46Y
R50Q
K170T
K185Q
R201H
E292G
F333I
V59M
R201C
T293N
E322K
Y330C
H46L
R50P
Q52R
V59G
F60Y/V64L
I167L
I296L
b
Fraction of unblocked current at 3 mmol/l MgATP
0
0.1
0.2
0.3
0.4
0.5
0.6
WT
homE23K
G324R
homG324R
E227L
N48D
G53R
G53S
W68R
I182V
E227K
E229K
V252A
F35L
F35V
H46Y
R50Q
K170T
K185Q
R201H
E292G
F333I
V59M
R201C
T293N
E322K
Y330C
H46L
R50P
Q52R
V59G
F60Y/V64L
I167L
I296L

Fig. S1 Comparison of ATP sensitivities

(**A**) IC_{50} for MgATP inhibition, and (**B**) the fraction of unblocked current at 3mmol/l MgATP for WT and the indicated Kir6.2 mutant channels. Homomeric channels (E23K, G324R) are indicated by 'hom'; all other data are from pseudo-heterozygous K_{ATP} channels. White bars, mutations causing/predisposing to diabetes in later life (see text); blue bars, TNDM; green bars, PNDM; pink bars, iDEND syndrome; red bars, DEND syndrome. Data for mutations other than G324R and E23K are taken from previous studies (see below [1-16]). Note the IC_{50} values for some DEND mutations (A) do not adequately reflect the mutation/disease severity, as these channels exhibit a large pedestal of unblocked current at physiological ATP levels (as seen in B). Data are mean±SEM.

References

1. D'Amato E, Tammaro P, Craig TJ, et al (2008) Variable phenotypic spectrum of diabetes mellitus in a family carrying a novel *KCNJ11* gene mutation. Diabet Med 25:651-656
2. Gloyn AL, Reimann F, Girard C, et al (2005) Relapsing diabetes can result from moderately activating mutations in *KCNJ11*. Hum Mol Genet 14:925-934
3. Girard CA, Shimomura K, Proks P, et al (2006) Functional analysis of six Kir6.2 (*KCNJ11*) mutations causing neonatal diabetes. Pflugers Arch 453:323-332
4. Mlynarski W, Tarasov AI, Gach A, et al (2007) Sulfonylurea improves CNS function in a case of intermediate DEND syndrome caused by a mutation in *KCNJ11*. Nat Clin Pract Neurol 3:640-645
5. Männikkö R, Jefferies C, Flanagan SE, et al (2010) Interaction between mutations in the slide helix of Kir6.2 associated with neonatal diabetes and neurological symptoms. Hum Mol Genet 19:963-972
6. Männikkö R, Stansfeld PJ, Ashcroft AS, et al (2011) A conserved tryptophan at the membrane-water interface acts as a gatekeeper for Kir6.2/SUR1 channels and causes neonatal diabetes when mutated. J Physiol 589:3071-3083
7. Proks P, Girard C, Ashcroft FM (2005) Functional effects of *KCNJ11* mutations causing neonatal diabetes: enhanced activation by MgATP. Hum Mol Genet 14:2717-2726
8. Proks P, Girard C, Haider S, et al (2005) A gating mutation at the internal mouth of the Kir6.2 pore is associated with DEND syndrome. EMBO Rep 6:470-475
9. Proks P, Girard C, Baevre H, et al (2006) Functional effects of mutations at F35 in the

NH_2-terminus of Kir6.2 (*KCNJ11*), causing neonatal diabetes, and response to sulfonylurea therapy. Diabetes 55:1731-1737

10. Shimomura K, Girard CA, Proks P, et al (2006) Mutations at the same residue (R50) of Kir6.2 (*KCNJ11*) that cause neonatal diabetes produce different functional effects. Diabetes 55:1705-1712
11. Shimomura K, Hörster F, de Wet H, et al (2007) A novel mutation causing DEND syndrome: a treatable channelopathy of pancreas and brain. Neurology 69:1342-1349
12. Shimomura K, Flanagan SE, Zadek B, et al (2009) Adjacent mutations in the gating loop of Kir6.2 produce neonatal diabetes and hyperinsulinism. EMBO Mol Med 1:166-177
13. Shimomura K, de Nanclares GP, Foutinou C, et al (2010) The first clinical case of a mutation at residue K185 of Kir6.2 (*KCNJ11*): a major ATP-binding residue. Diabet Med 27:225-229
14. Tammaro P, Girard C, Molnes J, et al (2005) Kir6.2 mutations causing neonatal diabetes provide new insights into Kir6.2-SUR1 interactions. EMBO J 24:2318-2330
15. Tammaro P, Proks P, Ashcroft FM (2006) Functional effects of naturally occurring *KCNJ11* mutations causing neonatal diabetes on cloned cardiac K_{ATP} channels. J Physiol 571:3-14
16. Tarasov AI, Girard CA, Larkin B, et al (2007) Functional analysis of two Kir6.2 (*KCNJ11*) mutations, K170T and E322K, causing neonatal diabetes. Diabetes Obes Metab 9:46-55