COMMENT ON BELTRAND ET AL.

Sulfonylurea Therapy Benefits Neurological and Psychomotor Functions in Patients With Neonatal Diabetes Owing to Potassium Channel Mutations. Diabetes Care 2015;38:2033–2041

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Beltrand et al. (1) have conducted a prospective single-center clinical study for assessing neurodevelopmental parameters in 18 patients presenting with neonatal diabetes caused by mutations in *KCNJ11* or *ABCC8* encoding the two ATP-dependent potassium (K_{ATP}) channel subunits who were successfully switched from insulin to sulfonylurea (SU) therapy. A standardized normative test battery called NP-MOT (French Neuromotor Functions in Children) performed by a single examiner was used to evaluate the neuromotor functions and developmental parameters before and after 12 months of SU therapy. At the 12-month examination, several patients experienced an improvement or correction of body and visual-spatial motor abnormalities, tone, and attention deficits, with, however, marked differences according to patient age at inclusion. It is well established that the neuromotor clinical abnormalities and patient long-term outcome are markedly affected by the nature of the K_{ATP} channel mutation and its functional effects on the gating of the channel and conformational regulation by SU interaction (2,3). Therefore, we are concerned that in the study by Beltrand et al. (1), it is rather difficult to appreciate what is genuinely due to SU treatment or to allelic heterogenity, as Supplementary Tables 1 and 2 show a significant mutation heterogeneity in the two groups of patients. It is noteworthy that one of the two patients with an *ABCC8* mutation (patient 6, Supplementary Table 1) did not present any neurodevelopmental deficiency at the beginning of the trial (M0, baseline as reported in Supplementary Table 1), which obviously calls into question the rationale for the inclusion of this patient in the study. Overall, the interpretation of the data and study results may have altered the strong general conclusions of the article.

First, we noticed that the annotation of one particular mutation, *KCNJ11*-p.Q51G (Table 1 and Supplementary Table 1), was incorrect: the mutation should be read either as p.E51G or as p.Q52G, but certainly not as Q51G. If the HUGO official nomenclature for reporting a human mutation had been correctly used, including a precise position on the genomic sequence (i.e., the accurate annotation on the cDNA sequence for each mutation), the ambiguity for this mutation would have certainly been removed.

Second, in the grouping of the patients, two frequently reported *KCNJ11* mutations responsible for neonatal diabetes, p.R201C and p.R201H, that are not documented to have a strong functional impact, have been mixed with most damaging mutations (in particular *KCNJ11*-p.V59M). The recurrent *KCNJ11*-p.V59M mutation, well known to cause intermediate developmental delay, epilepsy, and neonatal diabetes (iDEND) with muscle weakness, was present in patient 12 (in the age-group 4–18 years at inclusion). Importantly, neuropsychomotor abnormalities in this patient were not improved after 12 months of SU therapy, whereas in many previously reported iDEND cases with *KCNJ11*-p.V59M, hypotonia, fine motor control, and cognition were improved (4,5). We are also surprised by the inclusion of seven patients presenting with the same *KCNJ11*-p.R201H mutation but with very variable neurological presentations and outcomes under SU treatment (in both groups of patients stratified by their age at examination). Does it mean this mutation actually very weakly impacts the central functions examined in the study compared with the severity of its effect on pancreatic β-cell function? This issue deserves a discussion from a clinical and genetic point of view.

In conclusion, the issues raised above may call into question the validity of the conclusions of this study. We advocate

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for a thorough reappraisal of the genetic data with regard to their clinical impact before and after SU treatment.

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