

P031 Heterozygous Missense Insulin Mutations in Permanent Early-Infancy Diabetes

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Background: Permanent neonatal diabetes (PND) is defined by chronic hyperglycemia due to severe non-autoimmune insulin deficiency diagnosed in the first months of life. Mutations in several genes, including Glucokinase (*GCK*), *KCNJ11* and *ABCC8* which encode the two subunits of the ATP-sensitive K⁺ (K_{ATP}) channel, can cause PND. We aimed to investigate the genetic and clinical heterogeneity in PND patients who are negative for *GCK* or K_{ATP} channel mutations. Methods: The Insulin (*INS*) gene was screened by direct sequencing in 39 PND patients referred to the French ND study group. A detailed phenotyping of the patients with an *INS* mutation was performed. Results: Three missense mutations in the *INS* gene were identified in 4 probands with PND. 2/4 mutations were inherited in a dominant manner, and the familial description evidenced a marked variability in age of diagnosis and disease progression. In this cohort, *INS* mutations represent 10% of all PND cases, having a later presentation of diabetes and no associated symptoms compared to cases with K_{ATP} channel mutations. Conclusions: Heterozygous *INS* mutations are a cause of isolated permanent early-infancy diabetes, and may relate to endoplasmic reticulum overload and protein toxicity in β -cell as described in the Akita diabetic mouse.