Permanent neonatal diabetes due to a novel insulin signal peptide mutation

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Background: Monogenic form of diabetes is rare, but the commonest form is maturity-onset diabetes of the young (MODY). Neonatal diabetes is the other form of monogenic diabetes that is usually defined as overt diabetes diagnosed during the first 6 months of life. Permanent Neonatal Diabetes Mellitus (PNDM) due to insulin (INS) gene mutations was first described in 2007. INS mutations can cause a spectrum of clinical conditions such as type 1b diabetes, MODY, early onset type 2 diabetes and neonatal diabetes. Some mutations thus far reported cause proinsulin misfolding or its retention in the endoplasmic reticulum (ER), leading to ER-stress induced β-cells apoptosis.

Objective and hypotheses: The proband is a suggestive PNDM case based on these clinical findings. From Day 2 of life, she showed persistently high blood sugar ranging from 15.0-30.0 mmol/L which requires supplemental insulin (IV) at 0.1U/kg/hour. There was no evidence of DKA or other illnesses. The C-peptide value was low (<165 pmol/L) and GAD antibody was negative. Subcutaneous insulatard was started to replace insulin infusion from Day 10. At her current age of 4 years 2 months, she still requires insulatard at about 0.5-0.6U/kg/day. The median HbA1c ranged from 7.4-14.0. KCNJ11 and INS are among the genes implicated in early age diabetes/PNDM, thus mutation screening for these genes were performed to determine the molecular genetic defect in the patient.

Methods: Blood DNA was extracted and KCNJ11 & INS coding regions were PCR amplified, purified and directly sequenced.

Results: A heterozygous INS p.L13R mutation was found, located within the signal peptide of preproinsulin. This variant is not found in dbSNP. No sequence change in KCNJ11 was detected.

Conclusions: The p.L13R missense mutation is a non-conservative change, affecting the highly conserved Leucine residue of preproinsulin signal peptide and this likely caused abnormal insulin trafficking/processing and led to the PNDM condition in the patient.