Genetics and Clinical Characteristics of Neonatal Diabetes

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Recent years have seen significant progress towards defining the genetic aetiology of neonatal diabetes with >20 subtypes identified. It is likely that all cases of neonatal diabetes result from a single gene disorder since markers of autoimmunity associated with type 1 diabetes are rare in patients diagnosed before 6 months.

Heterozygous activating mutations in the *KCNJ11* and *ABCC8* genes encoding the Kir6.2 and SUR1 subunits of the K_{ATP} channel are the most common cause of neonatal diabetes. Most of these patients can achieve improved glycaemic control on sulfonylurea tablets. Around 20% also have developmental delay which may be improved through high-dose sulfonylurea therapy. Mutations in the *INS* gene are reported as the second most common cause. Most are dominant missense mutations that cause misfolding of the insulin molecule leading to beta cell apoptosis, but recessive loss-of-function mutations preventing insulin synthesis are more common in consanguineous families. Transcription factor mutations account for the majority of other known cases.

The distribution of mutations in Turkey reflects a consanguinity rate of ~40%. Within our international cohort of 1231 patients with diabetes diagnosed before 6 months, 103 were referred from Turkey (8.4%). Mutations in the *KCNJ11* and *ABCC8* genes account for only 20.6% of cases and neonatal diabetes due to homozygous *EIF2AK3* mutations causing Wolcott-Rallison syndrome is frequent (13.6%). This syndrome is characterised by neonatal or childhood-onset diabetes, epiphyseal dysplasia and liver/renal failure. An early genetic diagnosis when diabetes is the only presenting feature is helpful as it alerts the clinician to potentially fatal liver failure during intercurrent illness. Homozygous mutations in a recently discovered *PTF1A* enhancer account for 11.7% of cases, with 10/12 cases caused by the same founder mutation.

The identification of specific monogenic subtypes of diabetes not only provides accurate information regarding inheritance and prognosis, but can inform treatment decisions and improve clinical outcome.