

## Clinical and Molecular Characterisation of Patients with Congenital Hyperinsulinism

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Hyperinsulinaemic hypoglycaemia (HH) occurs as a consequence of unregulated insulin secretion from pancreatic beta cells. In the newborn period, it is the most common cause of severe and persistent hypoglycaemia. Rapid diagnosis and prompt management are essential to avoid brain injury and subsequent neurodevelopment handicap.

In collaboration with Dr Khalid Hussain from Great Ormond Street Hospital in London, we have recruited an international cohort of >1500 cases of HH from 67 countries. This cohort includes 193 patients from Turkey (13% of the total).

Recessive  $K_{ATP}$  channel subunit mutations are the most common cause of congenital HH, accounting for 44% of patients referred from Turkey. Rapid genetic testing enables the identification of patients with paternally inherited heterozygous mutations who may have focal lesions resulting from an acquired uniparental isodisomy event during embryogenesis. These patients can be cured by lesionectomy.

Rare *HADH* mutations affecting the enzyme

3-hydroxyacyl-CoA dehydrogenase are characterized by detectable urinary 3-hydroxyglutarate and raised plasma 3-hydroxybutyryl-carnitine levels. Homozygosity mapping in consanguineous pedigrees, mostly from Turkey, identified a region on chromosome 4. Sequencing revealed that recessive *HADH* mutations are in fact a relatively common cause of diazoxide-responsive HH with abnormal urine organic acids or acylcarnitines not always detected. Homozygous *HADH* mutations are found in 10% of patients from Turkey and include a deep intronic founder mutation that was identified by sequencing the entire 94 000 bases of the gene by next generation sequencing.

The other dominant causes of congenital hyperinsulinism include *HNF4A* mutations that cause macrosomia and diazoxide-responsive hyperinsulinism with a high risk of developing diabetes responsive to low dose sulfonylureas in adolescence/early adulthood (1.6% of Turkish cases), gain of function *GLUD1* mutations causing hyperinsulinism with hyperammonaemia (1%) and activating *GCK* mutations (none identified in Turkey).

For 44% of patients, no genetic aetiology has been identified. Exome and genome sequencing promises to reveal new monogenic subtypes and provide novel insights into the pathophysiology of this disorder.