Diabetes in the young: Rare forms hidden within an increasing world incidence

Stephen Greene
University of Dundee, UK

There is a worldwide increase in diabetes in the young with nearly half a million children having diabetes with an annual increase of 3%. However, within this rise is the uncovering of rare forms of diabetes (secondary and monogenic), with a mixture of underlying pathophysiology, differing management strategies and divergent clinical outcome. While compromising only ~5% of the diabetes population they often require major changes in therapy and monitoring with significant implications for the family. Molecular genetics has led to the identification of genes associated with clinically identified subgroups of diabetes. Monogenic diabetes includes neonatal diabetes (mutations in the KCNJ11, ABCC8 or INS genes) and MODY (maturity onset diabetes of the young–mutations in HNF1A gene or the GCK gene), with over 40 mutations now having been identified causing diabetes in the immediate neonatal period, early childhood, adolescence and adulthood, with a clinical presentation of diverse symptomatology, from low birth weight, development delay, congenital abnormalities, severe diabetic ketoacidosis and simple asymptomatic hyperglycemia detected on biochemical screening. Molecular genetic testing is now being used as a diagnostic tool that can help define the diagnosis and treatment of children with diabetes. The International Society for Pediatric and Adolescent Diabetes (ISPAD) has played a significant role in uncovering the diversity of non-Type 1 diabetes through a major international program of a 'Rare Diabetes Registry' and is a central clearing house for all enquiries from ISPAD members about rare diabetes. Information from the Registry has informed the ISPAD Consensus Guidelines that outlines the approach to diagnosis and management of these rare diabetes conditions.

s.a.greene@dundee.ac.uk

Discovery of novel genes associated with mitochondrial diseases by NGS

Taosheng Huang
Cincinnati Children’s Hospital Medical Center, USA

Advances in next generation sequencing technology have resulted in a rapid increase in the molecular characterization of mitochondrial disease. Recent years, our laboratory has successfully used whole-exome sequencing to identify many novel disease causing genes associated with mitochondrial disease. The mitochondrial asparaginyl-tRNA synthetase (NARS2) mutations cause Leigh syndrome and nonsyndromic hearing loss (DFNB94). We found that some mutation can disrupt dimerization of NARS2 and decrease steady-state levels of mt-tRNAAsn without aminoacylation defects. The cells with NARS2 mutations also display impaired oxygen consumption rate and OXPHOS deficiency that can be rescued by overexpression of wild type NARS2. Recently, we found that recessive SLC25A46 mutations cause optic nerve atrophy and axonal peripheral neuropathy. SLC25A46, putative mitochondrial carrier gene, is human homologs of Ugo1p. Furthermore, we demonstrate the SLC25A46 role in mediating mitochondrial morphology in vitro and in vivo. In zebrafish we found that loss-of-function affects the development and maintenance of neuronal processes and causes abnormal mitochondrial fusion morphology. Our result show many disease causing genes associated with mitochondrial disease are yet to be identified and whole-exome sequencing is very cost-effective for this process.

Taosheng.Huang@cchmc.org