P10.78
Disruption of NUBPL due to balanced translocation t(3;14)(q26.33;q14) increases severity of a family-specific PGK1 mutation
D. David1, I. Haltrich2, None. B. Marques: None. C. Fernandes: None. S. Malveiro: None. G. Fekete: None.
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An intriguing group of familiar translocations are those which not always segregate with the “associated” disorder. Here we report the genetic alterations underlying a clinical phenotype characterized by haemolytic anaemia and neuro-myo-patry, seemingly associated with the familial translocation t(3;14)(q26.33;q14). Two affected probands and two unaffected relatives have been identified as carriers. The 3q26.33 breakpoint was mapped about 40 kb from the TTC14’s end, at position 180.28 Mb and the 1q41-44 breakpoint within IVS 6 of NUBPL. The latter has been implicated in the aetiology of mitochondrial complex I deficiency (OMIM 252010). The most important additional possible candidate gene identified in this region is DNAJC9 causing an autosomal recessive disorder (OMIM 610198) that partially overlaps the reported phenotype. The recognition that a deceased relative carrying a novel PGK1 mutation whose clinical phenotype is exacerbated by co-inheritance of the disrupted NUBPL and/or by alterations affecting the genes in the breakpoint regions.

P10.79
Novel mutations in HPD causing tyrosinemia type III in Northern Portugal
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Impaired tyrosine catabolism result in elevated plasma tyrosine concentrations. Malfunction enzymes along the tyrosine catabolic pathway results in hereditary tyrosinemia. Tyrosinemia type III is caused by deficiency in the tyrosine hydroxylase, whereas polymorphisms of the gene are putative risk factors of diabetes. Our results showed that rs9457 “C” allele was significantly more frequent in the patient index previously diagnosed with Wolfram’s syndrome. This work was supported by the Hungarian grant OTKA K83766 and by the Bolyai János Scholarship (BO/00089/10/5) of the Hungarian Academy of Sciences.

P10.80
A homozygous UQCRCC2 mutation cause a neonatal onset metabolic decompensation due to complex III deficiency
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The mitochondrial respiratory chain generates energy as adenosine triphosphate (ATP) by means of the electron-transport chain and the oxidative-phosphorylation system. The mitochondrial respiratory chain, located in the inner mitochondrial membrane, is composed of five complexes: I, II, III, IV, and V. Among them, mitochondrial complex III (CIII) comprises 11 subunits encoded by one mitochondrial and 10 nuclear genes. Until now mutations in four genes have been known to cause autosomal recessive CIII deficiencies: UQCRB, UQCRQ, BCS1L and TTC19. UQCRB and UQCRQ encode components of CIII itself, while BCS1L and TTC19 produce mitochondrial assembly factors. Here, we report three patients from a consanguineous Mexican family presenting with neonatal onset of hypoglycemia, lactic acidosis, ketosis, and hyperammonemia. By whole exome sequencing combined with linkage analysis, we successfully found a homozygous missense mutation in UQCRCC2 that encodes mitochondrial ubiquinol-cytochrome c reductase core protein II. In its native state, the CIII monomer is quickly converted into a catalytically active homodimer that is incorporated into a supercomplex and this supercomplex functions as a single enzyme. Based on structural modeling, the mutation (p.Arg183Trp) was predicted to destabilize the hydrophobic core at the subunit interface of the core protein II homodimer. In vitro studies using fibroblasts from the index patient clearly indicated CIII deficiency, as well as impaired assembly of the supercomplex consisting of complexes I, III, IV, and V. This is the first described human disease caused by UQCRCC2 abnormality.

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