European Journal of Human Genetics

Volume 21 Supplement 2 June 2013 www.nature.com/ejhg

European Human Genetics Conference 2013

June 8 - 11, 2013
Paris, France

Abstracts

nature publishing group npg

P10.78

Disruption of *NUBPL* due to balanced translocation [t(3;14)(q26.33;q14)] increases severity of a family-specific PGK1 mutation

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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 anemia and neuro-myopathy, seemingly associated with the familial translocation [t(3;14)(3q26.33;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* 5' end, at position 180.28 Mb and the 14q14 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 *DNAJC19* causing an autosomal recessive disorder (OMIN 610198) that partially overlaps the reported phenotype. The recognition that a deceased relative most likely suffered from a similar disorder suggested the possibility of an X-linked disorder. Exclusion of additional genomic alterations within the breakpoint regions or elsewhere in the genome, familial X-chromosome segregation analysis and whole exome sequencing identified a novel missense mutation, c.358G>A, p.Glu120Lys, in exon 4 of phosphoglycerate kinase 1 (*PGK1*). Segregation analysis confirmed the association of this mutation with the disease phenotype. Re-evaluation of clinical data indicates that myopathy is considerably more severe in PGK1 deficient patients carriers of the translocation. The confirmation of this observation is currently underway. In conclusion, we have identified 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.

D. David: None. **I. Haltrich:** None. **B. Marques:** None. **C. Fernandes:** None. **S. Malveiro:** None. **G. Fekete:** None.

P10.79

Novel mutations in HPD causing tyrosinemia type III in Northern Israel

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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 4-HPPD. To date, only 14 cases have been described, showing a wide clinical spectrum. Reported patients have either presented with mental retardation and neurological symptoms while others, detected by neonatal screening, have been asymptomatic.
We report 4 new patients, 3 from a highly consanguineous Druze family, presenting elevated blood tyrosine levels with normal development and intelligence. Clinical evaluation revealed novel eye and skin phenotype not previously described in tyrosinemia type III. The fourth patient, from a Muslim origin consanguineous family, was diagnosed with hypertyrosinemia in the neonatal metabolic screen. Her psychomotoric development is normal for her age. Sequencing revealed two novel splicing mutations in HPD. Healthy control screening from two Druze villages detected 3:100 carriers in one village and none in the second.
We suspect tyrosinemia type III to be under-diagnosed and more common than is currently known. With neonatal metabolic screen becoming more widespread, more patients are likely to be diagnosed. Molecular analysis is the gold standard for diagnosing tyrosinemia type II and III. In light of the minute number of patients with tyrosinemia type III worldwide, clinical characterization of new patients is highly significant, determining the natural history of the disease, and describing the treatment and its contribution to normal growth and development of the patients.

T.C. Falik-Zaccai: None. **D. Raviv Shay:** None. **N. Nasser Samra:** None. **L. Kalfon:** None. **O. Dementyev:** None. **M. Baydany:** None. **F. Fares:** None. **A. Shaag:** None. **S. Almashanu:** None. **H. Mandel:** None.

P10.80

A homozygous *UQCRC2* 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 *UQCRC2* 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, and IV. This is the first described human disease caused by *UQCRC2* abnormality.

N. Miyake: None. **S. Yano:** None. **Y. Goto:** None. **N. Matsumoto:** None.

P10.82

Association and molecular analysis of 3' UTR polymorphisms of the WFS1 gene

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Wolframin is a major protein of the endoplasmic reticulum, loss of function mutations of the WFS1 gene result in the monogenic Wolfram-syndrome, characterized by optic atrophy, diabetes insipidus, diabetes mellitus and deafness, whereas polymorphisms of the gene are putative risk factors of diabetes. Our aim was the association and molecular analysis of two SNPs (rs1046322 and rs9457) in the 3' UTR of the WFS1 gene, which are supposed to alter the miRNA binding according to in silico data.
Association analysis was carried out by case-control study. 617 patients and 1147 healthy controls particiapted. Genotype analysis was carried out using PCR based methods, functional analysis was done by luciferase reporter system.
Our results showed that rs9457 "C" allele was significantly more frequent among patients with type 2 diabetes, whereas the rs1046322 variant showed a significant association with the type 1 form of the disease. Luciferase reporter experiments suggested that the rs1046322 and the rs9457 SNPs altered the binding of miRNA-668 and miRNA-185, respectively.
Our results suggest that the rs9457 and rs1046322 polymorphisms are the genetic components of diabetes mellitus. Earlier studies showed an association between WFS1 rs1046320 and diabetes, however no biological function of the SNP could be observed. We suggest that this result is due to the strong linkage disequilibrium between rs9457 and rs1046320, thus the latter polymorphism can be a genetic marker of rs9457.
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.

Z. Ronai: None. **N. Nemeth:** None. **A. Somogyi:** None. **M. Sasvari-Szekely:** None.