Isobutyryl-CoA Dehydrogenase Deficiency Presenting with Significant Clinical Disease in Adulthood
Helle Highland Nygaard¹, David Gaist², Mette Christensen³, Morten Dunø¹, Margrethe Kjeldsen¹, Henrik Daa Schrøder⁴, Niels Gregersen¹, Flemming Wibrand³, Rikke Olsen¹, Jens Michael Hertz⁵

¹Research Unit for Molecular Medicine, Department of Clinical Biochemistry, Aarhus University Hospital and Department for Clinical Medicine, Aarhus University, Aarhus, Denmark
²Department of Neurology, Odense University Hospital and Department of Clinical Medicine, University of Southern Denmark, Odense, Denmark
³Department of Clinical Genetics, Copenhagen University Hospital, Copenhagen, Denmark
⁴Department of Clinical Pathology, Odense University Hospital, Denmark
⁵Department for Clinical Genetics, Odense University Hospital and Institute of Clinical Medicine, University of Southern Denmark, Odense, Denmark

Isobutyryl-CoA dehydrogenase (IBD) deficiency is an autosomal recessive inborn error of valine metabolism. In some countries, IBD deficiency is part of newborn screening programs, where mass spectrometry is used to detect acylcarnitines that are specific for individual inborn errors of metabolism. IBD deficiency was described for the first time in a 2-year-old girl with cardiomyopathy. Since then approximately 20 patients have been reported. Most of these have been identified through newborn screening and have remained asymptomatic or have presented with rather mild symptoms. Consequently, the clinical significance of IBD deficiency is unclear, and it has been suggested that additional genetic or environmental factors are needed to trigger clinical symptoms.

We report a 40 year old male with a 3 year history of muscle pain, muscle weakness and tiredness. At age 37 year, he had a pacemaker implanted because of a third-degree atrioventricular block and cardiomyopathy. A muscle biopsy showed discrete electron microscopy changes in mitochondria, and investigation of mtDNA in muscle showed multiple mtDNA deletions. Acylcarnitine analysis in plasma revealed massive increases of isobutyrylcarnitine but normal butyrylcarnitine, suggesting isolated IBD deficiency. Sequence analysis of the IBD gene revealed heterozygosity for two likely damaging mutations; a c.512C>G (p.Ser171Cys) and a c.1097G>A (p.Cys366Tyr). Parental DNA testing confirmed that the two mutations are located on different alleles. This is the first reported patient with IBD deficiency, presenting with significant clinical disease in adulthood. The case underscores that asymptomatic children with IBD deficiency are at risk of developing clinical disease, and therefore should be screened and carefully monitored. Further studies are in progress to understand the relation between IBD deficiency and multiple mtDNA deletions.