Homozygous missense mutation in BOLA3 causes multiple mitochondrial dysfunctions syndrome in two siblings.

Defects of mitochondrial oxidative phosphorylation constitute a clinical and genetic heterogeneous group of disorders affecting multiple organ systems at varying age. Biochemical analysis of biopsy material demonstrates isolated or combined deficiency of mitochondrial respiratory chain enzyme complexes. Co-occurrence of impaired activity of the pyruvate dehydrogenase complex has been rarely reported so far and is not yet fully understood. We investigated two siblings presenting with severe neonatal lactic acidosis, hypotonia, and intractable cardiomyopathy; both died within the first months of life. Muscle biopsy revealed a peculiar biochemical defect consisting of a combined deficiency of respiratory chain complexes I, II, and II+III accompanied by a defect of the pyruvate dehydrogenase complex. Joint exome analysis of both affected siblings uncovered a homozygous missense mutation in BOLA3. The causal role of the mutation was validated by lentiviral-mediated expression of the mitochondrial isoform of wildtype BOLA3 in patient fibroblasts, which lead to an increase of both residual enzyme activities and lipoic acid levels. Our results suggest that BOLA3 plays a crucial role in the biogenesis of iron-sulfur clusters.
necessary for proper function of respiratory chain and 2-oxoacid dehydrogenase complexes. We conclude that broad sequencing approaches combined with appropriate prioritization filters and experimental validation enable efficient molecular diagnosis and have the potential to discover new disease loci.