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Molecular characterization of portuguese patients with Citrullinemia Type I (urea cycle disease)

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Abstract

Citrullinemia Type I (CTLN1; MIM# 215700) is a rare autossomal recessive disorder caused by a genetic deficiency of the argininosuccinate synthetase enzyme (ASS; MIM# 603470; E.C.6.3.4.5.). ASS is the third enzyme of the urea cycle involved in the synthesis of arginine and catalyses the conversion of citrulline, aspartate and ATP into argininosuccinate, AMP and pyrophosphate in the cytosol of periportal hepatocytes where the urea cycle is localized but is also expressed in most body tissues involved in synthesis of arginine. The incidence of this disorder is estimated to be 1 in 57,000. Biochemically, CTLN1 is characterized by an extreme elevation of citrulline in plasma and urine, low plasma arginine and increased excretion of orotic acid in urine. Clinically, patients with CTLN1 may be associated with neonatal or infantile-onset citrullinemia (classical form) that is the most common clinical presentation, characterized by symptomatic hyperammonemia leading to life-threatening encephalopathy and mental retardation in surviving patients, and early death when untreated. The other form of this disorder is the “mild citrullinemia” when patients present only biochemical but no clinical phenotype.

The objective of this study was to investigate at a molecular level seven CTLN1 portuguese patients from different regions of country, diagnosed in our Center. Three of them were detected in the extended newborn screening program.

Sequence analysis of genomic DNA from these patients was performed to identify disease-causing mutations in the *ASS1* gene.

In the studied patients, seven mutations were identified, including four *missense*, one *nonsense*, one *splicing* and one deletion causing f*rameshift*. Five of these mutations have already been described in the literature (p.R363W, p.G390R, p.G324S, p.F150LfsX8 and p.R344X), while the other two represent novel mutations (p.Y83C, c.174+1G>T). Only one patient was homozygous for the p.G390R mutation, all the others were combined heterozygotes for different mutations in the *ASS1* gene.

In summary, we described the genetic background of seven patients with CTLN1. Moreover, we found two novel mutations on the *ASS1* gene underlining the genetic heterogeneity of ASS deficiency. Our date corroborate the importance of a molecular testing to confirm CTLN1 patients suspected by a metabolic evaluation or detected by extended newborn screening programs and offer accurate prenatal diagnosis to couples at high risk of having affected children.