The molecular landscape of propionic acidemia and methylmalonic aciduria in Latin America

Resumen

In this work, we review the clinical and genetic data in 14 Latin American propionic acidemia (PA) and 15 methylmalonic aciduria (MMAuria) patients. In the PA patients, we have identified four different changes in the PCCA gene, including one novel one (c.414+5G>A) affecting the splicing process. The PCCB mutational spectrum included two prevalent changes accounting for close to 60% of the mutant alleles studied and one novel change (c.494G>C) which by functional analysis is clearly pathogenic. We have also identified the deep intronic change c.654+462A>G, and the results of the antisense treatment in the patient's cell line confirmed the functional recovery of PCC activity. All PA patients bearing out-offrame mutations presented the disease earlier while patients bearing in hemizygous fashion p.E168K and p.R165W presented the disease later. Regarding the MMAuria patients, we have found three novel mutations in the MUT gene (c.1068G>A, c.1587-1594del8 and c.593delA) and one in the MMAB gene (c.349-1 G>C). Two patients with MMAuria with homocystinuria cblC type are carriers of the frequent c.271dupA mutation. All mut0, cblB and cblC patients presented the symptoms early and in general had more neurological complications, while cblA and mutpatients exhibited a late-onset presentation, and in general the long-term outcome was better. The results presented in this work emphasize the importance of the genetic analysis of the patients not only for diagnostic purposes but also to research into novel therapies based on the genotype.

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