P-133 - IN SILICO PREDICTION OF THE PATHOGENIC EFFECT OF HISPANIC R108C VARIANT OF MUT GENE


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INTRODUCTION: Methylmalonic aciduria (MMA) is an inborn error of propionate metabolism. Isolated MMA is mainly due to pathogenic variants in MUT gene, which cause null or deficient methylmalonyl CoA mutase activity (MCM). This mitochondrial enzyme catalyzes the isomerization of methylmalonyl-CoA to succinyl-CoA using adenosylcobalamin (AdoCbl) as cofactor. To date, approximately 250 pathogenic variants have been reported, being c.322C4T (p.R108C) one of the most commonly found in Hispanic population. We previously found it in 40% of the alleles of a cohort of Mexican patients, two of them presented it in homozygous state and coursed with the severe Mut0 form according to phenotype. Until our knowledge there is no information about the structural effect that this variant could have over the enzyme.

OBJECTIVE: To perform an in silico prediction of the structural pathogenic effect of the Hispanic R108C variant of MUT gene.

METHODS: Structural analysis of arginine residue from MCM at position 108 was performed based on previously reported MCM crystallographic structure (PDB Code: 2XIJ), in silico mutagenesis was performed for this variant in order to hypothesize its possible deleterious effect using Pymol software.

RESULTS: In wild type MCM, arginine 108 residue is located at substrate binding domain; actually, it is in close contact with substrate (mean distance 3.7 Å), the interaction is polar type between amino groups of arginine and oxygen atoms from phosphate and hydroxyl groups from CoA molecule. When substituting arginine, which has a longer lateral chain, for a cysteine residue, all these polar contacts with CoA molecule are probably lost.

CONCLUSIONS: As the in silico modeling predicts, the substitution of an amino acid with different lateral chain length and polarity could probably decrease substrate interaction with amino acid residues from the active site during catalysis, which could explain the severe phenotype observed in our homozygous patients. Functional studies are needed in order to establish the pathogenic effect of this pathogenic variant.