

## A New Mutation in a Case of Methyl-Malonic Acidemia

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### Dear Editor

**M**ethyl-malonic acidemias (MMA) are a group of autosomal recessive disorders caused by diminished activity of methyl-malonyl-CoA mutase (MCM) enzymes. MCM converts methyl-malonyl-CoA to succinyl-CoA, which then can be metabolized in the Krebs cycle. Either the defect in the MCM activity or its cofactor 5'-deoxyadenosylcobalamin (AdoCbl) may lead to accumulation of the methyl-malonic acid.

Mutations in the gene encoding MCM result in mut disorders: mut<sup>0</sup> defect with complete loss of action and mut<sup>-</sup> with residual activity of the enzyme. On the other hand, AdoCbl synthesis defects have various clinical subgroups. Among them CblA, CblB, and CblD variant 2, manifest with isolated MMA [1].

Signs and symptoms of the MMA may vary from indistinctive ones, such as vomiting, poor sucking, feeding refusal, and weight loss, to developmental delay and failure to thrive. Neurological manifestations may also include abnormal posturing and movements, hypotonia, lethargy, and seizures [2]. Patients with mut<sup>0</sup> and CblB defects had shown an earlier onset of symptoms with higher rate of morbidity and mortality [1]. The basic treatment in these kind of cases are a low-protein high-energy diet, and carnitine and vitamin B12 supplementations [2].

In this letter we describe a male patient diagnosed with MMA, born from healthy consanguineous Iranian parents, with normal delivery and normal postnatal course. At the age of 28 months he was referred to pediatric endocrinology center of Namazi hospital, Shiraz, Iran, with chief complaint of poor feeding, drowsiness, and tachypnea. At the time of admission, signs of moderate dehydration were obvious as well as erosive erythematous plaques around the mouth, perioral erythema, and bullous skin lesion on the buttock, and also a history of poor weight gain. Laboratory examinations showed high anion gap acidemia, elevated concentrations of propionyl-carnitine (17.12  $\mu\text{mol/L}$ ; normal:  $<2.5 \mu\text{mol/L}$ ), and increased methyl-malonic acid (19050  $\text{mmol/mol creatinine}$ ; normal  $<5$ ) which confirmed the diagnosis of MMA.

Molecular genetics investigations and genomic amplification of the MMA exons and direct sequencing were performed on the DNA of the patient. The DNA analysis revealed the deletion of 2 nucleotides in the exon 3 of the MMAA gene, "c.527\_528delTG". This deletion results in a frame shift followed by a rapid stop codon, "p.Val176fs", and has not been reported in the literature yet. Moreover, this result is consistent with the diagnosis of the CblA deficient MMA.



The nucleotide and deduced amino acid sequence of the human MMAA gene were described previously, which is located on chromosome 4q31.1–q31.2.[3] Currently about 300 mutations were discovered in association with the MMA, and among them nearly 30 mutations are related to the MMAA gene [4]. The most frequently observed MMAA mutation in patients in North America is “c.433C>T” (p.R145X) [5]. In Japanese patients the mutation “c.503delC” is more prevalent [6]. Considering the absence of a neonatal screening program in the Middle East, the prevalence of

the disorder cannot be evaluated, but probably due to more common consanguineous marriage, the incidence rate is assumed to be high. In our case with the reported new mutation, skin manifestations might have been the most noticeable presentations which are believed to be due to some irritant metabolites in the body secretions (e.g. Urine and tear).

**Keywords:** Methyl-malonic academia; Mutation; Skin manifestations

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