Newly Identified Mutations of the \textit{IVD} Gene in two cases of Isovaleric Acidemia in Chinese populations.

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Isovaleric acidemia (IVA) is an autosomal recessive inborn error affecting leucine metabolism. It is caused by a deficiency in isovaleryl-CoA dehydrogenase (\textit{IVD}), a mitochondrial matrix enzyme that catalyzes the oxidation of isovaleryl-CoA to 3-methylcrotonyl-CoA. \textit{IVD} is a FAD-containing enzyme, consisting of four identical subunits. Clinical features of IVA include poor feeding, vomiting, lethargy, developmental delay, metabolic acidosis, and a characteristic "sweaty foot" odor. IVA is one of the target disorders for newborn screening by tandem mass spectrometry (MS/MS). The clinical manifestations can be divided to three types: metabolically severe, chronic intermittent and asymptomatic. Molecular genetic analysis helps to further confirm the clinical diagnosis of IVA. The family specific mutations are useful for prenatal diagnosis. To date, over 90 disease-causing mutations have been reported worldwide.

Reference

In this study, we searched for \textit{IVD} mutations in two Chinese patients with IVA (asymptomatic type). The diagnosis of IVA was confirmed by MS/MS, blood spot acylcarnitine profiles by MS-MS demonstrated an elevation of C5-carnitine with a peak concentration of 1.08 and 2.02 micromol/L (< 0.41 micromole/L). No feeding problems were observed. All coding exons and the flanking introns in the \textit{IVD} gene were scanned by high throughput sequencing and the mutations were amplified by Sanger sequencing. We thus identified two hitherto unknown mutations (p.T214A, p.L45R). Patient No. 1 was homozygous for c.640A>G (p.T214A) mutation, while patient No. 2 was a compound heterozygote for 2 mutations, a maternally-inherited c.134T>G (p.L45R) and a paternally inherited c.640A>G (p.T214A). According to the ACMG classification guideline, all the two mutations are classified to be uncertain mutation. Our results have illustrated the heterogeneous mutation spectrum in the Chinese patients. These two cases highlight the importance of screening for metabolic diseases including rare metabolic diseases in the early neonatal period, and further expand the genetic spectrum of IVA.

Figure 1. Novel mutations in the IVD gene identified in patient 2 with isovaleric acidemia