3-Methylcrotonyl-CoA carboxylase deficiency : mutation analysis in 28 probands, 9 symptomatic and 19 detected by newborn screening

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Isolated 3-methylcrotonyl-CoA carboxylase (MCC) deficiency is an autosomal recessive disorder that appears to be the most frequent organic aciduria detected in tandem mass spectrometry (TMS)-based neonatal screening programs. The phenotype is variable, ranging from neonatal onset with severe neurological involvement to asymptomatic adults. MCC is a heteromeric mitochondrial enzyme composed of biotin containing alpha subunits and smaller beta subunits, encoded by MCCA and MCCB, respectively. We report mutation analysis in 28 MCC-deficient probands, 19 of whom were asymptomatic newborns detected by TMS newborn screening, and nine presented with clinical symptoms. Ten have mutations in MCCA, and 18 in MCCB. We identified 10 novel MCCA and 14 novel MCCB mutant alleles including missense, nonsense, frameshift and splice site mutations, and show that three of the missense mutations result in severely decreased MCC activity when expressed in MCC-deficient cell lines. Our data demonstrate no clear correlation between genotype and phenotype suggesting that factors other than the genotype at the MCC loci have a major influence on the phenotype of MCC deficiency.

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