

## 3-Methylglutaconic Aciduria Type I via AUH Gene Sequencing (Test #323)

**Brief Description of Clinical Features:** 3-methylglutaconic aciduria type I (MGA1, OMIM #250950) is a rare disorder resulting from deficiency of 3-methylglutaconyl-CoA hydratase, a mitochondrial enzyme that catalyzes the fifth step of leucine catabolism. Accumulation of toxic leucine metabolites results in mainly a neurologic condition, although clinical severity varies widely. The first two patients with molecular confirmation of 3-methylglutaconyl-CoA hydratase deficiency were children reported to have motor and speech delays in one case and only speech delay in the other (IJlst, L et al. *Am J Hum Genet* 71:1463-1466, 2002). Among five other MGA1 patients from four families (Ly et al. *Hum Mutat* 21:401-407, 2003), speech and motor delays were the most common findings. Remarkably, one individual in this cohort had deficiency of 3-methylglutaconyl-CoA hydratase resulting from homozygous null mutation in the AUH gene but was completely asymptomatic at the age of 2 years. Another confirmed patient presented with febrile seizures from the age of 1 year but had no speech or motor delay (Illsinger et al. *Pediatr Neurol* 30:213-215, 2004). An adult-onset patient with progressive forgetfulness, unsteady gait, hyperreflexia in all four limbs, cerebellar ataxia, dysarthria, and urinary incontinence has also been reported (Eriguchi et al. *Neurol* 67:1895-1896, 2006). Gait disturbance and incontinence presented when the patient was in her 50's. She was also found to have impaired cognitive function.

**Genetics:** 3-methylglutaconic aciduria type I is an autosomal recessive disorder. Based on the small number of reported cases, null mutations that abolish enzyme activity are the most common form of pathogenic variants. Complete absence of 3-methylglutaconyl-CoA hydratase may be compatible with normal development (Ly et al. 2003).

**Description of This Particular Test:** 3-methylglutaconyl-CoA hydratase is encoded by exons 1-10 of the AUH gene (OMIM #600529) located on chr 9q22. Testing is accomplished by amplifying the coding exons and ~50 bp of adjacent noncoding sequence, then determining the nucleotide sequence using standard dideoxy sequencing methods and a capillary electrophoresis instrument.

**Reference Sequences:** Genomic: NC\_000009.11 mRNA: NM\_001698.2  
 Protein: NP\_001689.1 mRNA and Protein: CCDS 6689.1

**Indication for Testing:** Individuals with elevated urinary 3-methylglutaconic acid, 3-methylglutaric acid, and 3-hydroxyisovaleric acid and clinical signs of 3-methylglutaconic aciduria type I. Presence of urinary 3-hydroxyisovaleric acid is a specific finding for isolated 3-methylglutaconyl-CoA hydratase deficiency.

**Sensitivity of Test:** 3-methylglutaconic aciduria type I is a rare disorder and clinical sensitivity cannot be estimated. Analytical sensitivity may be high because all reported mutations are of the type expected to be detected by sequencing of genomic DNA.

**Turn Around Time:** Maximum of 40 days although many tests are completed in 2-3 weeks.

**Specimen Requirements:** See page 4 of the Requisition Form.

<b>Price:</b>	<b>Sequencing of AUH, Exons 1-10:</b>	<b>\$ 690</b>
<b>CPT Codes:</b>		
Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1 83891 \$ 40
Amplification x10	83898 \$200	Sequencing x10 83904 \$290
Separation x1	83894 \$ 50	Interpretation/Report x1 83912 \$ 80

**Accreditation Info.** CLIA ID #: 52D1027685 (expires 1/18/13) (CAP#: 7185561, AU ID: 1407125 expires 12/20/12)

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