

Trimethylaminuria via *FMO3* Gene Sequencing -- Test #324

Brief Description of Clinical Features: Trimethylaminuria (TMAU, OMIM 602079), also called fish-odor syndrome, is a metabolic disease that is due to the malfunction of the hepatic enzyme flavin-containing monooxygenase 3 (*FMO3*). The *FMO3* enzyme catalyses the oxidation of fishy-smelling trimethylamine, found in foods rich in choline and carnitine, into odorless trimethylamine-N-oxide. In patients with TMAU, *FMO3* malfunction results in the accumulation of trimethylamine in the body and subsequent release in the breath, saliva, sweat, urine, and other body secretions (Cashman et al. *Curr Drug Metab* 4:151-170, 2003). Symptoms are intermittent and usually begin in childhood. They are exacerbated by environmental factors including diet, emotional stress, and physical activity; they may lead to psychological problems (Rehman *Postgrad Med J* 75:451-452, 1999). TMAU is more common and more pronounced in women than men. See also the Human BioMolecular Research Institute (<http://www.hbri.org/TMAuria.htm>) and Phillips and Shephard (GeneReviews, 2008, www.genetests.org).

Genetics: TMAU is inherited in an autosomal recessive manner and is caused by mutations in the *FMO3* gene (Dolphin et al. *Nat Genet* 17:491-494, 1997). To date, about 50 *FMO3* mutations have been reported. The majority of mutations are missense. Other rare mutations include nonsense, splicing, and small and large deletions. Homozygous mutations in families with or without history of consanguinity and compound heterozygous mutations were detected. Heterozygous carriers may develop a transient form of the disease (Allerston *Mol Genet Metab* 98:198-202, 2009).

Description of This Particular Test: The *FMO3* gene encodes the flavin-containing monooxygenase 3, one of several enzymes involved in the metabolism of chemical compounds that contain nitrogen, sulfur or phosphorous. This test involves bidirectional DNA sequencing of all 8 coding exons and splice sites of the *FMO3* gene. The full coding sequence of each exon plus ~ 50 bp of flanking DNA on either side are sequenced. As indicated, we will sequence one (Test #100) or two (Test #200) exons in family members of patients with known mutations or to confirm previous results.

Reference Sequences: Genomic: NC_000001.9 mRNA: 006894.4 Protein: 008825.4 (CCDS 1292.1)

Indications for Test: Patients with strong body odor and increased free trimethylamine excretion in urine, with reduced trimethylamine-N-oxide.

Sensitivity of Test: Unknown at this time.

Turnaround Time: Maximum of 40 calendar days, although many tests are completed in 3-4 weeks.

Specimen Requirements: See page 4 of the Requisition Form.

Price: Sequencing of all coding exons of the *FMO3* Gene: \$ 670

CPT Codes:

Sample Ascertainment x1	83890 \$ 30	DNA Isolation x1	83891 \$ 40
Amplification x 10	83898 \$ 180	Sequencing x10	83904 \$ 280
Separation x1	83894 \$ 50	Interpretation/Report x1	83912 \$ 90

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

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