

## *HSD17B10* Gene Analysis in 2-Methyl-3-Hydroxybutyryl-CoA Dehydrogenase Deficiency/ Hydroxysteroid (17 $\beta$ ) Dehydrogenase 10 Deficiency

### **Clinical Features:**

Hydroxysteroid (17 $\beta$ ) dehydrogenase 10 (HSD10) deficiency (formerly called 2-methyl-3-hydroxybutyryl-CoA dehydrogenase deficiency) is a very rare disorder with very few patients described in the literature. Most patients develop severe neurological abnormalities, such as the gradual loss of mental and motor skills that progresses to profound developmental regression, choreoathetosis, near blindness, and epilepsy. Cardiomyopathy has also been described. Males are more severely affected than females, with females presenting a variety of symptoms: from borderline learning difficulties to psychomotor and speech delay. Variants in the gene associated with HSD10 deficiency, *HSD17B10*, have also been associated with a mild X-linked mental retardation syndrome with choreoathetosis and abnormal behavior, involving aggressiveness, hallucinations, self mutilation and speech impairment called MRXS10. (MIM# 300220).

### **Inheritance:**

X-linked

### **Genetics:**

2-Methyl-3-Hydroxybutyryl-CoA Dehydrogenase Deficiency / Hydroxysteroid (17 $\beta$ ) Dehydrogenase 10 Deficiency are both caused by variants in the *HSD17B10* gene located on the X chromosome. The *HSD17B10* gene encodes the mitochondrial enzyme 17 $\beta$ -hydroxysteroid dehydrogenase type 10 (HSD10). HSD10 is a multifunctional enzyme involved in the degradation pathway of isoleucine and branched-chain fatty acids, the catalysis of the oxidation of steroid modulators of  $\gamma$ -aminobutyric acid type A receptors, steroid hormones and xenobiotics. It has also been reported that HSD10 is required for structural and functional integrity of the mitochondria.<sup>1</sup> Furthermore, elevated levels of HSD10 are present in the hippocampi of Alzheimer disease patients.<sup>2</sup> Patients with HSD10 deficiency show elevated excretion of the organic acids 2-methyl-3-hydroxybutyric acid and tiglylglycine in urine and decreased HSD10 activity in cultured skin fibroblasts. The *HSD17B10* gene is located on chromosome Xp11.2 and has 6 exons.

### **Test Methods:**

Variant analysis of the *HSD17B10* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. In addition, if no variant is found by sequencing, targeted array CGH analysis with exon-level resolution (ExonArrayDx) is available for females to evaluate for a

deletion or duplication of one or more exons of this gene. Variants found in the first person of a family to be tested are confirmed by repeat analysis using sequencing, restriction fragment analysis or another appropriate method.

### Test Sensitivity:

The frequency of *HSD17B10* variants in patients with HSD10 deficiency is not well established as very few patients with this condition have been described. In two small studies of 5 and 6 patients, respectively, a *HSD17B10* variant was found in all patients.<sup>3,4</sup> The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

### Variant Spectrum:

More than half of HSD10 deficient patients harbor the c.388 C>T (p.Arg130Cys or R130C) variant.<sup>1</sup> At this time, less than 20 variants have been described. A silent variant c.605 C>A (p.Arg192Arg or R192R) was found in five males affected with MRXS10 and in female carriers of a family from Luxembourg.<sup>5</sup>

### References:

1. Rauschenberger et al., (2010) EMBO Mol Med 2:51-62 (PMID: 20077426).
2. Yang et al., (2007) Mol Genet Metab 92:36-42 (PMID: 17618155).
3. Ofman et al., (2003) Am J hum Genet 72:1300-1307 (PMID: 12696021).
4. Garcia-Villoria et al., (2009) Clin Biochem 42:27-33 (PMID: 18996107).
5. Lenski et al., (2007) Am J Hum Genet 80:372-377 (PMID: 17236142).