

## *MAT1A* Gene Analysis in Methionine Adenosyltransferase I/III Deficiency

### **Clinical Features:**

Methionine adenosyltransferase I/III (MAT I/III) deficiency is an inborn error of metabolism characterized by isolated persistent hypermethioninemia in the absence of cystathionine  $\beta$ -synthase deficiency, tyrosinemia type I, or liver disease. The clinical consequences of MAT I/III deficiency are highly variable. It appears that most individuals, particularly those with the R264H variant, have elevation of plasma methionine and a relatively benign course, although the elevated methionine may be associated with an unusual breath odor. However, some patients have more severe findings including cognitive deficits, neurologic abnormalities, demyelination and other abnormalities on brain MRI.

### **Genetics:**

MAT I/III deficiency is caused by pathogenic variants in the *MAT1A* gene that is expressed in mature (non-fetal) liver and encodes two forms of the methionine adenosyltransferase (MAT) enzyme (MATI and MATIII). MATI is a homotetramer and MATIII is a homodimer of  $\alpha$ 1 subunits. MAT catalyzes the synthesis of S-adenosylmethionine (AdoMet) from methionine and ATP. AdoMet participates in the transmethylation and trans-sulfuration pathways, and in the biosynthesis of polyamines. Patients with MAT I/III deficiency are often detected on newborn screening due to elevated methionine levels. The diagnosis is suspected when isolated hypermethioninemia persists and cystathionine  $\beta$ -synthase deficiency, tyrosinemia type I and liver disease have been excluded. A definitive diagnosis of MAT I/III deficiency can be made by variant analysis or by assaying MAT activity in the liver, since the enzyme is not expressed in skin fibroblasts or blood cells. Most individuals who have been genotyped have a single *MAT1A* variant, R264H, which is associated with autosomal dominant inheritance. The *MAT1A* gene is located on chromosome 10q22 and has 9 exons. A third form of the MAT enzyme exists in mammals encoded by the *MAT2A* gene and is expressed in most tissues.<sup>5</sup> To date, no patients with methionine adenosyltransferase deficiency have been described with variants in *MAT2A*.

### **Inheritance Pattern:**

Either autosomal dominant or autosomal recessive depending on the variant

### **Test Methods:**

Variant analysis of the *MAT1A* gene is performed on genomic DNA from the submitted specimen using bi-directional sequence analysis of coding exons and corresponding intron/exon boundaries. If sequencing identifies a variant on only one allele of the *MAT1A* gene, and if indicated, reflex deletion/duplication testing (ExonArrayDx) will be performed at no additional charge to evaluate for a deletion/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:

In a study of three patients with confirmed MAT I/III deficiency by liver biopsy, *MAT1A* variants were identified on 6/6 alleles.<sup>1</sup> Another study of seven affected patients diagnosed after abnormal newborn screening results, with liver biopsy in only one patient, found variants on 14/14 alleles.<sup>2</sup> A report of two families with autosomal dominant (AD) inheritance of MAT I/III deficiency identified a single, R264H, variant in affected individuals from both families.<sup>3</sup> Three additional studies identified a total of 35 patients with MAT I/III deficiency ascertained by abnormal newborn screens. In these studies, 9 patients were heterozygous for the R264H variant associated with AD MAT I/III deficiency, 8 patients had variants identified on both *MAT1A* alleles, 2 patients had only a single *MAT1A* variant not expected to be associated with AD MAT I/III deficiency, and 6 patients had no variant identified.<sup>4,5,6</sup> Individuals heterozygous for a single *MAT1A* variant, other than R264H, may also be identified by newborn screening due to elevations in methionine that may persist for months after birth without clinical symptoms.<sup>8</sup> The methods used by GeneDx are expected to be greater than 99% sensitive at detecting variants identifiable by sequencing.

### Variant Spectrum:

The majority of variants reported in the *MAT1A* gene are missense variants with splice site variants, small deletions and insertions and large deletions also identified. The R264H missense variant has been reported in association with autosomal dominant inheritance of MAT I/III deficiency.<sup>3,4,5,6</sup> Amino acid 264 in the MAT $\alpha$ 1 subunit is reported to be involved in salt-bridge formation that is essential for subunit dimerization. R264/R264H MAT $\alpha$ 1 heterodimers are enzymatically inactive; therefore, R264H has a dominant negative effect on the MAT enzyme.<sup>3</sup> In vitro expression studies show most reported missense variants in the *MAT1A* gene are associated with some residual enzyme activity, while truncating variants are associated with virtually absent MAT activity.<sup>4,7</sup> Most patients with missense variants are clinically well.<sup>4,7</sup>

### References:

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