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 β-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 α1 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 β-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.5 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

Using genomic DNA extracted from the submitted specimen, the complete coding regions and splice site junctions of the MAT1A gene are enriched using a proprietary targeted capture system developed by GeneDx for next-generation sequencing with CNV calling (NGS-CNV). The enriched targets are simultaneously sequenced with paired-end reads on an Illumina platform. Bi-directional sequence reads are assembled and aligned to the reference sequence based on NCBI RefSeq transcripts and human genome build GRCh37/UCSC hg19. After gene specific filtering, data are analyzed to identify sequence variants and most deletions and duplications involving coding exons; however, technical limitations and inherent sequence properties effectively reduce this resolution for some genes. Alternative sequencing or copy number detection methods are used to analyze or confirm regions with inadequate sequence or copy number data by NGS. Reportable variants include pathogenic variants, likely pathogenic variants and variants of uncertain significance. Likely benign and benign variants, if present, are not routinely reported but are available upon request.

The technical sensitivity of sequencing is estimated to be >99% at detecting single nucleotide events. It will not reliably detect deletions greater than 20 base pairs, insertions or rearrangements greater than 10 base pairs, or low-level mosaicism. The copy number assessment methods used with this test cannot reliably detect copy number variants of less than 500 base pairs or mosaicism and cannot identify balanced chromosome aberrations.

Assessment of exon-level copy number events is dependent on the inherent sequence properties of the targeted regions, including shared homology and exon size.

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.[3,4,5,6] Amino acid 264 in the MATα1 subunit is reported to be involved in salt-bridge formation that is essential for subunit dimerization. R264/R264H MATα1 heterodimers are enzymatically inactive; therefore, R264H has a dominant negative effect on the MAT enzyme.[3] 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.[8] 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.[4,7] Most patients with missense variants are clinically well.[4,7]

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