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Normal Brain Myelination in a Patient Homozygous for a Mutation That Encodes a Severely Truncated Methionine Adenosyltransferase I/III

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Two isozymes of mammalian methionine adenosyltransferase, MAT I and MAT III, are expressed solely in adult liver. They are, respectively, tetramers and dimers of a single subunit encoded by the gene *MAT1A*. A third isozyme, MAT II, contains a catalytic subunit encoded by a separate gene, *MAT2A*, and is expressed in a variety of tissues, including (to a slight extent) adult liver. Based on a recent finding that 2 children with isolated hypermethioninemia and brain demyelination were homozygous for *MAT1A* mutations predicted to produce severely truncated proteins, and devoid of activity when expressed, it was concluded that complete lack of MAT I/III activity may be associated with neurological symptoms and demyelination. We now report that a 43-year-old man with persistent isolated hypermethioninemia, previously demonstrated to have deficient MAT activity in his liver, has normal brain myelination on MRI and normal neurological function, despite being homozygous for a 539 TG insertion in exon V of *MAT1A*, so that the gene is predicted to encode a protein of only 184 rather than the normal 395 amino acids. This patient's exon V mutation was demonstrated by SSCP analysis and verified by sequencing. Both parents are heterozygous for the same insertion. This suggests that *MAT1A* mutations producing severely truncated proteins do not necessarily produce brain demyelination. This finding has relevance to a previously reported 4-year-old girl who was also homozygous for the 539insTG mutation. Finally, our patient's 7% residual hepatic MAT activity, measured at 1 mM methionine, may reflect the hepatic activity of the more ubiquitous enzyme form, MAT II. Am. J. Med. Genet. 75:395–400, 1998. © 1998 Wiley-Liss, Inc.†

KEY WORDS: methionine adenosyltransferase; hypermethioninemia; adenosylmethionine; demyelination

INTRODUCTION

Methionine adenosyltransferase (MAT; E.C.2.5.1.6) catalyzes the first step in the transsulfuration pathway, i.e., the synthesis of *S*-adenosylmethionine (AdoMet) from L-methionine and ATP [Mudd et al., 1995a]. AdoMet serves as a methyl donor in a large number of reactions, and is responsible for the formation of spermine, spermidine, phosphatidylcholine, carnitine, creatine, the methylated derivatives of DNA, RNA, protein, and catecholamines, and other compounds [Mudd and Poole, 1975]. AdoMet also regulates the partitioning of homocysteine between degradation via cystathionine and remethylation to methionine [Gahl et al., 1988]. Different forms of MAT have been identified in mammalian tissues [Okada et al., 1981; Sullivan and Hoffman, 1983; Kotb and Kredich, 1985; Cabrero et al., 1987; Mitsui et al., 1988]. MAT I/III, encoded by the single copy gene *MAT1A*, is found as both tetramers (MAT I) and dimers (MAT III) formed from identical $\alpha 1$ subunits [Kotb et al., 1997]. This gene is expressed solely in adult liver [Okada et al., 1981; Sullivan and Hoffman, 1983; Cabrero et al., 1987; Alvarez et al., 1993]. MAT II, encoded by a separate gene, *MAT2A* [Horikawa and Tsukada, 1992; De La Rosa et al., 1995], is found in fetal liver and to a lesser extent in

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