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## Case Report

Confirmation that *MAT1A* p.Ala259Val mutation causes autosomal dominant hypermethioninemia

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## ABSTRACT

Methionine adenosyltransferase (MAT) I/III deficiency is an inborn error of metabolism caused by mutations in *MAT1A*, encoding the catalytic subunit of MAT responsible for the synthesis of S-adenosylmethionine, and is characterized by persistent hypermethioninemia. While historically considered a recessive disorder, a milder autosomal dominant form of MAT I/III deficiency occurs, though only the most common mutation p.Arg264His has ample evidence to prove dominant inheritance. We report a case of hypermethioninemia caused by the p.Ala259Val substitution and provide evidence of autosomal dominant inheritance by showing both maternal inheritance of the mutation and concomitant hypermethioninemia. The p.Ala259Val mutation falls in the dimer interface, and thus likely leads to dominant inheritance by a similar mechanism to that described in the previously reported dominant negative mutation, that is, by means of interference with subunits encoded by the wild-type allele.

## 1. Introduction

Methionine adenosyltransferase I/III (MATI/III) deficiency (MIM #250850) is the most common cause of hereditary persistent elevation of methionine and occurs from mutations in *MAT1A*. Isolated elevation of methionine without elevation of homocysteine, thus excluding cystathionine  $\beta$ -synthase deficiency, was first noted in 1974 with the advent of newborn screening by dried blood spot analysis [1]. Based on newborn screening data the incidence of isolated elevation of methionine is variable, depending on the geographic region: a study of a Taiwanese population showed 16 cases of isolated hypermethioninemia out of 1,701,591 newborns, of whom more than half had mutations in *MAT1A* [2]. On the other hand, two other studies from populations in the Iberian peninsula showed an incidence of 1/28,163 and 1/26,000 in Galicia and Portugal, respectively [3,4]. The disorder can be inherited in an autosomal either dominant or recessive manner. The recessive form may be characterized by central nervous system abnormalities, mainly manifested by white matter changes on brain MRI, which were found in 32 of 64 patients with either homozygous or compound

heterozygous mutations [5]. Dominant inheritance of hypermethioninemia was first described in 1992 [6], and was subsequently identified to be caused by the *MAT1A* p.Arg264His mutation [7,8]. This dominant form is considered benign, with only mild elevations in methionine concentrations [9]. In the aforementioned Galician series, all patients detected through newborn screening were heterozygous for the p.Arg264His mutation [3]. Indeed, this dominant mutation causes the majority of cases of hypermethioninemia detected by newborn screening [10]. Notably, the p.Arg264His mutation has also been seen in compound heterozygotes with recessive disease, both with and without neurologic abnormalities [5] and a single heterozygote was reported to have myelination abnormalities [4].

The MAT enzyme (EC2.5.1.6) can be dimeric (MAT III) or tetrameric (MAT I), and the homodimerization is essential to its enzymatic activity [2]. It has two main functions, S-adenosylmethionine (AdoMet) synthesis and tripolyphosphatase (PPPase) activity. In a two-step reaction, the adenosyl group of ATP is transferred to methionine forming AdoMet and tripolyphosphate (PPPi), and then without dissociating from the enzyme, the PPPi is enzymatically hydrolyzed to release

**Abbreviations:** MAT, methionine adenosyltransferase; PPPase, tripolyphosphatase; AdoMet, S-adenosyl-methionine; WT, wild-type; AdoHcy, S-adenosyl-homocysteine

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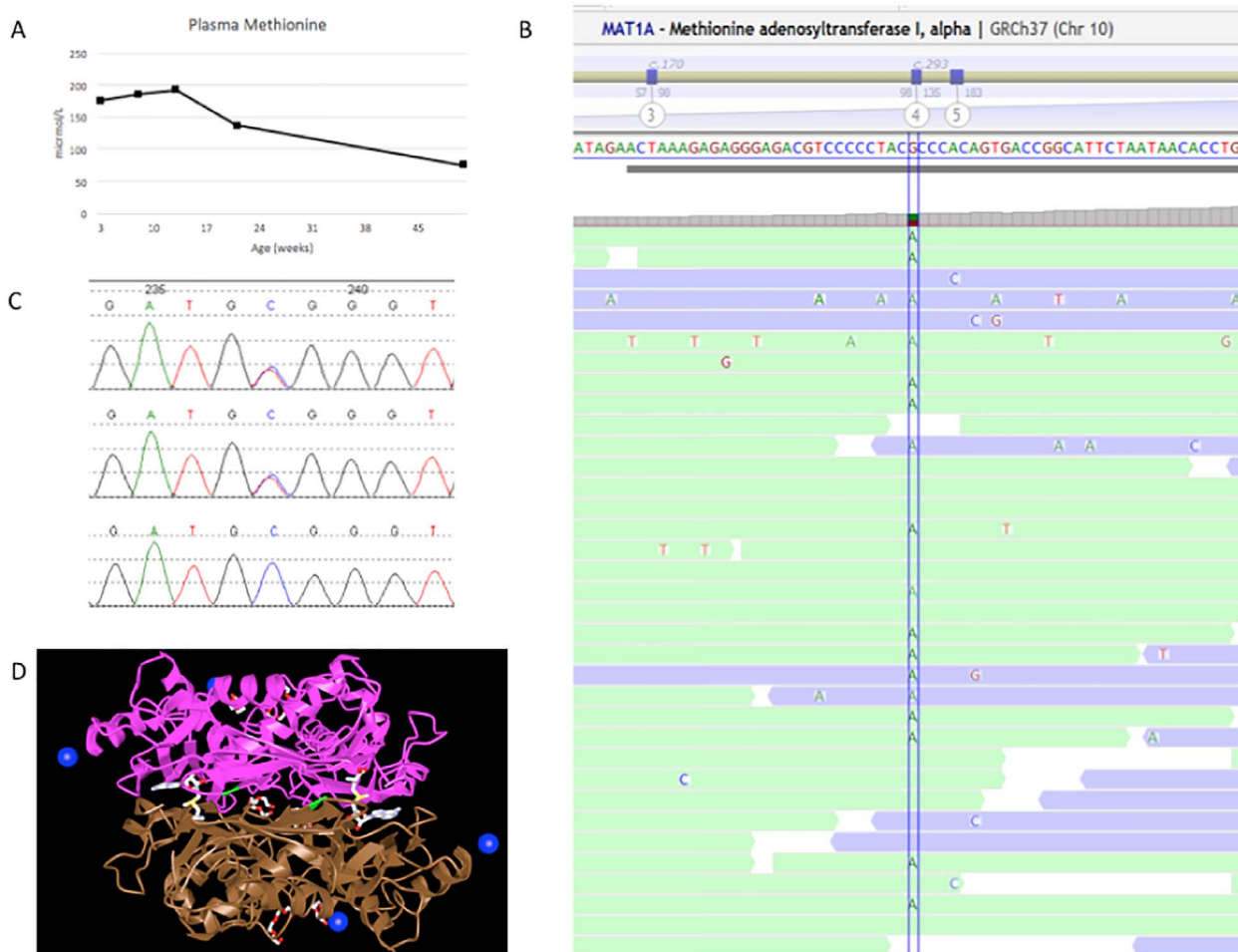
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**Fig. 1.** A) Proband's plasma methionine concentration over time. B) Next-generation sequencing short read alignments to the reference sequence for the proband. C) Chromatogram of Sanger sequencing for the proband, mother, and father (top, middle, and bottom respectively). D) Human methionine adenosyltransferase III (dimer), with the p.Ala259 residue highlighted in green showing its position at the dimer interface. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

pyrophosphate and phosphate. AdoMet is the primary methyl group donor for a wide range of biological processes as well as having functions in polyamine synthesis and regulation of the methionine/homocysteine cycle [11]. Initial investigations into the autosomal dominant form of MATI/III deficiency caused by the p.Arg264His variant showed it interferes with the ability of MAT subunits to form homodimers [7]. It has been shown that the p.Arg264His variant results in an enzyme with 0.37% of AdoMet synthetic activity in rats [9]. On the other hand, MAT PPPase activity was similar to wild-type (WT), and was inhibited by inorganic pyrophosphate but not stimulated by methionine or ATP, suggesting deficient binding of substrates [9].

Other series have reported heterozygous changes in *MAT1A* in patients with isolated hypermethioninemia [9,11,12], although the pattern of inheritance for these other variants has never been clarified. Until recently, it was assumed either that the second variant in *MAT1A* was never found, or the possibility of a second mutation associated with autosomal dominant inheritance was entertained, but never confirmed, due to lack of parental testing. Recently, additional heterozygous *MAT1A* mutations have been described, particularly p.Arg249Gln (6 patients) and p.Gly280Arg (1 patient) are also located near the dimeric interface [13]. The fathers of two of the patients with the p.Arg249Gln mutation also carried the substitution and had mildly elevated plasma methionine levels. Herein we describe a case of a mother and daughter with hypermethioninemia, both carrying the p.Ala259Val mutation, thus providing confirmation for the autosomal dominant inheritance of this variant.

## 2. Materials and methods

The manuscript is a retrospective case report that does not require ethics committee approval at our institution. No identifiable patient information is provided in the manuscript.

### 2.1. Biochemical assays

Plasma AdoMet and AdoHcy were measured by tandem mass spectrometry (Shimadzu Nexera LC System interfaced with a 5500 QTRAP® Sciex) as previously described [14]. Plasma amino acids were quantitated by cation-exchange chromatography with post-column ninhydrin derivatization using a Biochrom amino acid analyzer.

### 2.2. Molecular testing

Genomic DNA was extracted from the patient's blood and the TruSight One kit (v1.0) was used to target the exon regions of genes. These targeted regions were sequenced using the NextSeq 500 sequencing system with 150 bp paired-end reads. The DNA sequence was mapped to, and analyzed in comparison with, the published human genome build UCSC hg19 reference sequence. The targeted coding exons and splice junctions of the known protein-coding RefSeq genes were assessed for the average depth of coverage of  $10\times$  and data quality threshold values of 95%. All reportable sequence variants were confirmed by independent Sanger sequence analysis.

### 2.3. Protein modeling

Visualization of the mutation within the 3-dimensional protein structure was achieved by iCn3D [15] by uploading a PDB-format file containing structural information for human MAT I. This file (PDB ID: 2OBV) was downloaded from the RCSB Protein Data Bank [16]; the crystal structure for the model had been determined using X-ray diffraction.

### 3. Case report and results

The patient presented at 3 weeks of age for evaluation after a newborn screen was positive for elevated methionine. She was born at 40 weeks of gestation by spontaneous vaginal delivery. Birth weight was 3.205 kg. She was breast milk and formula fed. Her newborn screen on day of life 1 showed methionine concentration of 0.81 mg/dL (54  $\mu\text{mol/L}$ ) for a cut-off of < 0.8 mg/dL, and repeat sample collected at 16 days of life showed a methionine concentration of 1.08 mg/dL (73  $\mu\text{mol/L}$ ). Initial homocysteine was 8.4  $\mu\text{mol/L}$  (reference range 2.9–11.8). Molecular testing for genes in the methionine pathway identified a heterozygous variant in *MAT1A*. At follow up at 5 months and subsequently at 17 months of age, she was doing well concerning growth and development. No remarkable abnormalities were noted on examination.

The patient's plasma methionine concentration was 175, 185, 192, 136, 75  $\mu\text{mol/L}$  (reference range 9–43  $\mu\text{mol/L}$ ) at ages 3.5 weeks, 2 months, 3 months, 5 months, and 12 months, respectively (see Fig. 1A). There were no other abnormalities on plasma amino acid chromatography including no elevation in tyrosine. The S-adenosylmethionine was 90 nmol/L (reference range 33–95) and the S-adenosylhomocysteine was 24 nmol/L (reference range 13–28). She had intermittently elevated alanine aminotransferase (68 and 88 units/L at 2 and 5 months of age, reference ranges 26–61 and 26–51 units/L respectively) with normal aspartate aminotransferase, alkaline phosphatase, and total bilirubin. The patient was found to be heterozygous for the c.776C > T (p.Ala259Val) variant in *MAT1A* (NM\_000429.2; see Fig. 1B and C). A bioinformatics algorithm to identify exon-level copy number changes directly from the sequencing data did not predict any deletion or duplication in the gene. This mutation falls in the dimerization interface of the enzyme (see Fig. 1D).

The p.Ala259Val variant is maternally inherited. The patient's mother had mild elevation of methionine of 50  $\mu\text{mol/L}$  (normal range 10–42) at 27 years of age, while her repeat plasma amino acid profile at 28 years old showed normal methionine at 33  $\mu\text{mol/L}$ . On both occasions, her transaminases were normal, although she did have a history of elevated liver enzymes as a child including a hepatitis-like illness, which lasted months.

### 4. Discussion

The p.Ala259Val mutation is exceedingly rare; no nonsynonymous missense variants were seen at the p.Ala259 position in 123,136 exomes in the gnomAD database [17]. Three patients were previously reported to carry a heterozygous p.Ala259Val variant in *MAT1A*, although the authors specifically mentioned that the pattern of inheritance could not be clarified since parents were not tested [2,12]. Fernández-Irigoyen et al. [11] demonstrated approximate 80% reduction of the MAT activity in the p.Ala259Val mutant in comparison to WT while PPPase activity remained over 80% of WT levels. Ala259 is situated in the flexible loop, a highly conserved block in the MAT gene, hypothesized to regulate the entrance and positioning of methionine to the active site [18,19]. Other mutations in the loop show similar changes in enzyme activity [11]. Another report suggested that the Ala259Val variant might affect the dimerization interface [20]. The first patient reported with the p.Ala259Val mutation had initial Met level of 204.5  $\mu\text{mol/L}$  with a subsequent average of 37  $\mu\text{mol/L}$ , and had

verbal, performance, and full scale IQs of 67, 72, and 61 respectively [2]. The second and third patients were siblings with identical mutations but varying patterns of methionine elevation (patient 1 and 2 both had a methionine concentration of 64.3  $\mu\text{mol/L}$  on newborn screen, 209.8  $\mu\text{mol/L}$  and 112.8  $\mu\text{mol/L}$  at first visit, respectively, and a mean of 138.8  $\mu\text{mol/L}$  and 88.75  $\mu\text{mol/L}$ , respectively) [12].

Our patient's methionine levels were persistently elevated but did show evidence of decline with age. Her mother, also a heterozygote for the mutation, had mild hypermethioninemia. These findings provide evidence that heterozygosity for the p.Ala259Val mutation in *MAT1A* accounts for a second variant causative of autosomal dominant hypermethioninemia. The common p.Arg264His mutation has been shown to have less marked elevations in methionine with age [3,11], a pattern that has since been shown in patients with other heterozygous mutations [12]. Indeed, a case series of 9 such patients reported that none of the patients had symptoms of MATI/III deficiency, all had normal development, tolerated normal diets, and had similar patterns of methionine levels that trended downward on follow-up [12]. Similarly, 6 patients with p.Arg248Gln and 1 patient with p.Gly280Arg in the heterozygous state had methionine levels that declined over time [13]. Both of these residues are predicted to be located at the dimerization interface. Our results align with this pattern, in that our patient's methionine seems to be decreasing over time and her mother's was only slightly elevated in one instance. The reason for the downward trend of methionine levels in dominant MATI/III deficiency is unclear. One hypothesis is total protein (and therefore methionine) intake in infancy with typical volumes of human milk intake are higher than estimated need for growth [21], and that when solid food intake increases and milk intake decreases between 6 and 12 months of age this imbalance normalizes.

Both the patient and her mother had elevated transaminases, mild in the child's case and severe though transient in the mother's childhood. While mildly abnormal hepatocyte morphology on electron microscopy has been described in several patients [22,23,24] and *MAT1A* knockout mice develop steatohepatitis and have a high incidence of hepatocellular carcinoma [25,26], the majority of patients with MATI/III deficiency have no biochemical evidence of liver dysfunction [5]. The patient's plasma total homocysteine was normal which is expected, though slight elevations of homocysteine can be seen in severe MATI/III deficiency [27,28].

There are two potential mechanisms for the deleterious effect of this mutation. The Ala259 residue is located in the dimerization interface of the protein [20], and just like the previously described dominant mutation, would be predicted to act in a dominant negative fashion by interfering with the dimerization (MAT III) or tetramerization (MAT I) of the enzyme. Other authors localize the residue to a flexible loop that is responsible for positioning and entry of methionine into the active site of the enzyme [11,18,19]. However, the inability to bind methionine is unlikely to explain the dominant inheritance, since the wild-type subunit would have enough activity to utilize methionine for AdoMet synthesis. However, an impairment in polymerization can indeed account for dominant inheritance by means of interference with the wild-type enzyme—as has been previously experimentally shown [7]—since only the polymeric enzyme is active.

In summary, we provide confirmation that the p.Ala259Val mutation in *MAT1A* is also responsible for autosomal dominant hypermethioninemia, and given its position at the dimerization interface, likely through a dominant negative effect, as with the previously reported dominant mutation.

### Conflict of interest

The authors report no conflict of interest.

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