MAT I/III deficiency in Portugal: high frequency of R264H mutation in a small area of Douro high lands

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INTRODUCTION

Methionine adenosyltransferase deficiency (MAT I/III deficiency, OMIM 250850) is an inborn error of metabolism resulting in isolated hypermethioninemia and usually inherited as an autosomal recessive trait. A dominant form has been exceptionally reported, associated with a single mutation (R264H).

METHODS

MAT I/III deficiency is detected by newborn screening (NBS) since 2004, as a differential diagnosis of classical homocystinuria. Both screenings are based in the methionine measurement by tandem mass spectrometry, and approximately 600,000 newborns were already screened in our laboratory. Suspected cases of MAT I/III deficiency are confirmed through *MAT1A* gene analysis.

RESULTS

Twenty-three MAT I/III deficient patients were identified through newborn screening (Table 1). Twelve of them (blue shadowed in Table 1) were identified in a small area of Douro high lands, in the region of Mirandela, and all revealed to be heterozygous for R264H mutation. Family studies allowed the identification of fifteen additional heterozygotes and the sequencing of *MAT1A* exon 7 in all these 12 patients and their parents, confirmed the association of mutation R264H and the 870G (rs10887711) and 882C (rs10788546) *MAT1A* allelic variants (Table 2), as previously reported (Chamberlin et al 1997).

Clinical follow-up of these 12 patients revealed normal growth, development and neurological examination in all cases, but positive histories for severe vascular disease were referred in three families and patient 7 revealed to have myelination alterations.

Table 1: MAT I/III deficient patients identified through NBS

Patient	Current age (y/m)	Screening/ confirmation sampling day	Methionine at screening/ confirmation (µM)*	*MAT1A* mutations
1	6y	6/12	85/80	R264H
2	5y	4/19	77/121	R264H
3	5y	4/19	52/168	R264H
4	5y	5/18	123/176	R264H
5	4y	4/16	103/85	R264H
6	4y	3/29	58/247	R264H
7	3y	4/30	80/195	R264H
8	2y	6/10	309/194	R264H
9	2y	4/24	85/245	R264H
10	2y	6/70	77/157	R264H
11	2y	6/23	73/145	R264H
12	2y	5/24	124/155	R264H
13	2y	5/30	91/79	R264H
14	2y	5/30	117/182	R264H
15	2y	7/28	67/84	L137V/ S247N
16	23m	4/20	79/111	R264H
17	21m	3/19	71/465	L355R/ L355R
18	19m	6/24	80/147	R264H
19	14m	5/17	60/136	R264H
20	13m	4/13	100/105	R264H
21	7m	6/30	63/117	R264H
22	7m	5/19	72/85	R264H
23	3m	3/16	71/110	R264H

*Normal Met < 50µM

Table 2: *MAT1A* exon 7 polymorphic variants associated with R264H allele

MAT1A allele	rs10887711	rs10788546
Normal	G or A	C or T
R264H	G	C

DISCUSSION

The first cause of persistent isolated hypermethioninemia in Portuguese newborns is MAT I/III deficiency (estimated frequency: 1:26,000), and in 21 out of 23 cases identified through NBS, this condition is due to R264H heterozygosity.

Clinical outcome associated with this mutation is usually good (Pérez-Mato et al 2001) but family studies performed in 12 patients, identified in a small geographic area in the region of Mirandela, revealed clinical manifestations in several individuals, which may be related with this condition and reinforces the importance of carriers identification and counseling.

As far as we could investigate from family histories, these 12 patients are not related, and the fact that R264H mutation was found in all individuals associated with the same MAT1A exon 7 polymorphic variants may indicate a hot spot for R264H allele in this region.