Molecular Genetics and Metabolism Reports 21 (2019) 100520

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Case Report

Hypermethioninemia in Campania: Results from 10 years of newborn screening

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ARTICLE INFO

Keywords:
Newborn screening
Hypermethioninemia
MAT I/III deficiency
CBS deficiency

ABSTRACT

In the last years tandem mass spectrometry (MS/MS) has become a leading technology used for neonatal screening purposes. Newborn screening by MS/MS on dried blood spot samples (DBS) has one of its items in methionine levels: the knowledge of this parameter allows the identification of infant affected by homocystinuria (cystathionine β-synthase, CBS, deficiency) but can also lead, as side effect, to identify cases of methionine adenosyltransferase (MAT) type I/III deficiency.

We started an expanded newborn screening for inborn errors of metabolism in Campania region in 2007. Here we report our ten years experience on expanded newborn screening in identifying patients affected by hypermethioninemia. During this period we screened approximately 77,000 infants and identified two cases: one case of classical homocystinuria and one patient affected by defect of MAT I/III. In this paper we describe these patients and their biochemical follow-up and review the literature concerning worldwide newborn screening reports on incidence of CBS and MAT deficiency.

1. Introduction

Newborn screening (NBS) on dried blood spot samples (DBS), recently performed by liquid chromatography (LC) linked to tandem mass spectrometry (MS/MS), can occur during the first few hours of a newborn's life. It represents a complex screening system capable of detecting several inborn errors of metabolism: LC-MS/MS, applied to NBS programs, can detect > 70 different metabolic diseases on a single DBS collected in the first hours from birth [1]. Methionine dosage is included in this screening and it is leading to discovery new cases of hypermethioninemia.

Methionine is metabolized by three isoforms of the enzyme Met adenosyltransferase (MAT, EC 2.5.1.6) (Fig. 1). MAT I (tetrameric isoform) and III (dimeric isoform) are encoded by the same gene MAT1A and are present mainly in adult liver. MAT II isoform, coded by MAT2A gene, is negligible in adult liver but predominates in non-hepatic tissues and fetal liver [2]. This enzyme is required for the synthesis of S-adenosylmethionine (AdoMet), a methyl donor in cell reactions. S-adenosylhomocysteine (AdoHcy), produced byAdoMet transmethylation is then hydrolyzed by AdoHcy hydrolase (AHCY, EC 3.3.1.1) in homocysteine (Hcy) [3]. Hcy, in turn, can be metabolized, by the vitamin B12-dependent enzyme Met synthase (MS), to Met by accepting a methyl group derived from the endogenous 5-methyltetrahydrofolate (5-methyl-THF). Moreover, Hcy can be remethylated to Met by betaine-Hcy-methyltransferase (BHMT) by using a methyl group from betaine, a molecule derived from choline, forming *N*,*N*-dimethylglycine (DMG). In an alternative pathway Hcy condensates with serine to form cystathionine, a reaction catalysed by the vitamin B6-dependent enzyme

Abbreviations: AdoCbl, 5′-deoxyadenosylcobalamin NBS; Cbl, cobalamin; CBS, cystathionine β-synthase; DBS, dried blood spot samples; MAT I/III, methionine adenosyltransferase type I and III; NBS, Newborn screening

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https://doi.org/10.1016/j.ymgmr.2019.100520
Received 10 September 2019; Accepted 10 September 2019
Available online 11 October 2019
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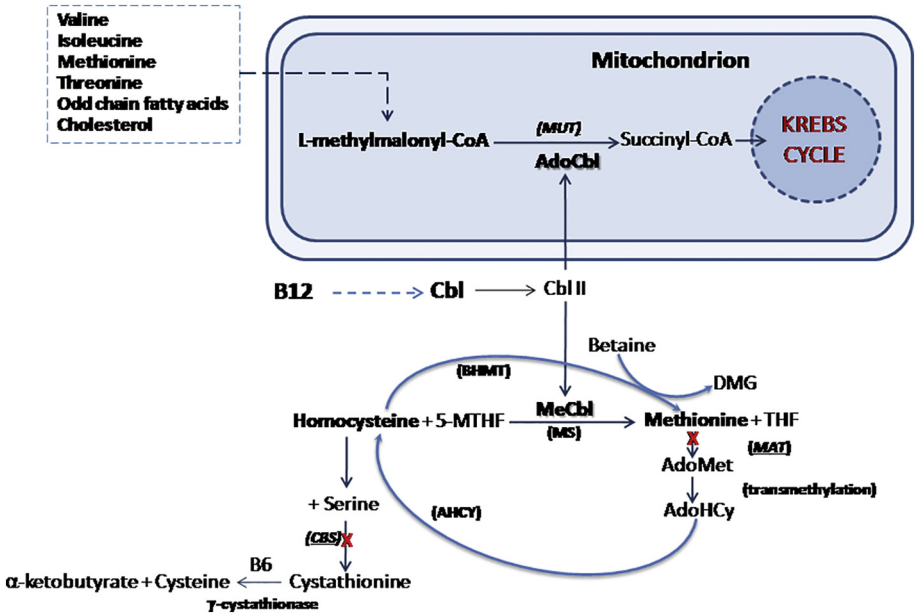

Fig. 1. Metabolism of cobalamin and methionine. Methylcobalamin (MeCbl) is the cofactor of the reaction catalysed by the methionine synthase. Methionine is metabolized by Met adenosyltransferase (MAT I/III) which catalyzes the synthesis of S-adenosylmethionine (AdoMet). S-adenosylhomocysteine (AdoHcy), produced by AdoMet transmethylation is hydrolyzed by AdoHcy hydrolase (AHCY) in homocysteine (Hcy) which, in turn, can be metabolized, by the vitamin B12-dependent enzyme Met synthase (MS), to Met. Hcy can be also remethylated to Met by betaine-Hcy-methyltransferase (BHMT). Alternatively, Hcy condensates with serine to form cystathionine, a reaction catalysed by the vitamin B6-dependent enzyme cystathionine β-synthase (CBS) to be finally converted to α-ketobutyrate and cysteine by the γ-cystathionase.

cystathionine β-synthase (CBS, EC 4.2.1.22). Finally, cystathionine is converted to α-ketobutyrate and cysteine by the γ-cystathionase in another reaction requiring vitamin B6 (Fig. 1).

Hypermethioninemia may be consequence of various non-genetic disorders as well as a variety of inborn errors of metabolism. Non-genetic causes include liver disease, premature birth, and diet rich in proteins. Some genetic diseases exhibit hypermethioninemia secondary to generalized hepatic dysfunction: citrin deficiency, fumaryl acetoacetate hydrolase deficiency and mitochondrial depletion syndromes, due to mutations in *MPV17* or *DGUOK* genes. Causes of hypermethioninemia involving primary defects in methionine metabolism include: deficiencies of cystathionine β synthase (CBS), methionine adenosyltransferase type I and III, glycine *N*-methyltransferase (GNMT), catalyzing the synthesis of *N*-methylglycine from glycine using AdoMet as the methyl donor, and S-adenosylhomocysteine hydrolase. MAT I/III deficiency leads to isolated hypermethioninemia [4], where the term isolated identifies elevated plasma Met levels without increase in Met metabolites, although some patients with severe MAT I/III deficiency have been reported to have plasma Hcy slightly elevated [5,6]. Conversely, in GNMT, AHCY, and CBS deficiencies hypermethioninemia can be associated with the increase in some Met metabolites, including AdoMet, AdoHcy, Hcy, and cystathionine. Another, unusual cause of hypermethioninemia involves mutations in the gene for adenosine kinase (ADK) [7]. ADK phosphorylates adenosine derived from hydrolysis of S-adenosylhomocysteine by AHCY: in ADK deficiency, accumulation of adenosine inhibits AHCY and this, in turn, arises the increase of S-adenosylmethionine and methionine.

In May 2007 we started an expanded newborn screening for inborn errors of metabolism in Campania region by analyzing amino acids, amino acid ratios, acylcarnitines and acylcarnitine ratios in DBS samples using tandem mass spectrometry. Data from the pilot project between 2007 and 2014 period were previously reported [1]. We discuss here in detail the cases of hypermethioninemia identified in our ten years of screening experience (2007–2017); we also review the literature concerning worldwide newborn screening hypermethioninemia reports.

2. Methods

2.1. Sample collection and diagnostic analysis

From January 2007 to June 2017 our NBS program screened, through the LC-MS/MS analysis of amino acids and acylcarnitines in DBS samples, approximately 77,000 newborns, between 48 and 72 h of life. The newborn blood sample was obtained by heel prick and spotted on a Schleicher & Schuell 903 grade filter paper sampling card (Whatman, Dassel, Germany); for genetic analysis we collected 5 mL of blood from each infant. GC–MS analysis on urine was also performed. Samples were prepared and analyzed as reported elsewhere [1,8].

Ethical approval: experimental protocols were according to guidelines approved by Italian Ministry of Health in the law 167 of August 19, 2016. For all patients informed consent was obtained from parents for being included in the study.

3. Results

3.1. Worldwide newborn screening

According to data reported in the literature, in the last years some hypermethioninemia cases were reported by MS/MS-based expanded newborn screening program in USA, Mexico, Japan, Taiwan, Hong Kong, China, Qatar, Australia, Spain, Portugal and Italy and are summarized in Table 1.

Some studies have been reported on different USA NBS programs. A pilot study performed from 1992 through 1999 in Pennsylvania, Ohio, North Carolina, reported 4 cases of hypermethioninemia, without further characterization (approximately 1:175000) [9]. A study conducted at The Children's Hospital of Philadelphia from 2000 to 2013 revealed 62 newborns with elevated methionine and identified 12 cases of classical homocystinuria (cystathionine β-synthase deficiency) and 13 individuals affected by MATI/III deficiency (incidence not available) [10]. NBS among North Carolina population from 1997 through 2005 evidenced 2 cases of cystathionine β-synthetase deficiency (1:470,000) [11]. Six other cases of homocystinuria (1:369,054) were reported by a 2001–2006 NBS program in California, Massachusetts, North Carolina, and Wisconsin [12]. Finally, Zytkovicz et al. [13] reported an additional patient with hypermethioninemia in New England by a two years screening program (1257000); no information was available concerning the genetic basis of the biochemical alteration.

A pilot study performed in Mexico from March 2002 through February 2004 among 42,264 screened newborns identified only one patient as affected by CBS deficiency [14].

Based on newborn screening data collected between 1992 and 2012 in Japan, 24 patients showing persistent hypermethioninemia had

Table 1
Incidence of hypermethioninemia according to the world wide screening programs.

	USA	Mexico	Japan	Australia	Hong Kong	Taiwan	China	Qatar	Iberian peninsule	Italy
Hypermeth	1:175000[1] 1:257000[2] 1:470000CBS[3] 1:369054CBS[4]	1:42264CBS[5]	1:107850MAT[6]	1:230750CBS[7]	1:30448MAT[8]	1:99961[9]	1:123981CBS[10]	1:12607CBS[11]	1:27400(Port)MAT[12] 1:425000(Port)CBS[12] 1:22874(Spain)MAT[13] 1:374000(Spain)CBS[13]	1:200000MAT[14] 1:60408MAT[15] 1:77000CBS[16] 1:77000MAT[17]

1: Naylor et al. [9]; 2: Zytkovichz et al. [13]; 3: Frazier et al. [11]; 4: CDC report [12]; 5: Torres-Sepulveda et al. [14]; 6: Nagao et al. [15]; 7: Wilcken et al. [21]; 8: Chong et al. [18]; 9: Huang et al. [16]; 10: Shi et al. [19]; 11: Lindner et al. [20]; 12: Marcao et al. [22]; 13: Couce et al. [23]; 14: la Marca et al. [24]; 15: Messina et al. [25]; 16: Scolamiero et al. [1]; 17: this paper.

genetic diagnosis of MAT I/III deficiency with an estimated incidence of 1 in 107,850 [15].

In Taiwan two patients with hypermethioninemia (without information on the genetic basis of the alteration) were reported by Huang et al. [16] as identified by an expanded newborn screening program performed on 199,922 newborns from 2001 to 2004 (1:99961), confirming the results obtained from neonatal screening for homocystinuria in that region (1 case of CBS deficiency, 1:1701591, and 16 cases of MATI/III deficiency, 1:106350; total incidence: 1:100094) [17]. A three year-journey in Hong Kong recently reported one patient with hypermethioninemia due to MAT deficiency (1:30448) [18]. In China a pilot study screened 371,942 neonates, identifying 98 cases of inborn errors of metabolism; among these three were patients affected by homocystinuria (1:123,981) [19].

Between 2003 and 2006 an extended neonatal screening performed on 25,214 newborns of Qatar population evidenced 19 cases with metabolic diagnosis; among these, two were newborn with hypermethioninemia due to cystathionine β-synthase deficiency (1:12,607) [20].

In Australia a 5 years study on 461,500 newborns screened from 1998 to 2002 reported 2 patients affected by CBS deficiency, accounting for a prevalence of 1:230,750 [21].

Concerning the Iberian peninsula, NBS performed from 2000 (Spain) or 2004 (Portugal) to 2013 resulted in the identification of three patients with classical homocystinuria and 49 patients with MAT I/III deficiency. Among these, thirty-one cases of MAT I/III deficiency (1:27,400) and two cases of classical homocystinuria (1: 425,000) were identified in Portugal, confirming previous data (Martins et al., 2012), while 18 cases of MAT I/III deficiency (1:22,874) and one classical homocystinuria were detected in Spain (1:374,000). All the cases of persistent isolated hypermethioninemia were due to mutations in the MAT1A gene [22,23].

In Italy, two cases of Methionine adenosyltransferase deficiency were reported by the NBS program performed in Tuscany region on 400,000 infants (1:200,000) [24]. Messina et al. recently reported the results from 7 years of NBS program in Sicily: among 60,408 newborn they identified one case of MATI/III deficiency [25]. One infant affected by cystathionine β-synthase deficiency was previously detected in Campania region by our laboratory in a pilot study (1:45,466) [1]. In the present paper we report a case of hypermethioninemia due to MATI/III deficiency (1:77000) and updated also the CBS deficiency incidence to 1:77000.

3.2. Hypermethioninemia case reports and follow up

Patient 1: This patient was previously reported [1]; here we describe his biochemical and clinical follow-up. Briefly, at newborn screening, patient 1 showed high concentration of methionine on DBS (81 μMol/L; R.V.: < 20); at one month from birth also serum homocysteine concentration showed to be elevated (107.3 μMol/L; R.V.: 5–15) associated to methionine levels of 61 μMol/L (Fig. 2). The dosage of urinary organic acids showed a normal profile; therefore, classical homocystinuria was suspected (Table 2). Waiting for the genetic test results, patient 1 was administered with folic acid (5 mg/die) and vitamin B6 (100 mg/die). At two months from birth patient 1 showed fair general conditions but generalized hypotonia associated to Hcy levels of 122 μMol/L. Given the mild response to therapy, the B6 dosage was increased to 300 mg/die associated to 550 mg/die betaine, and a low methionine diet was started. From molecular analysis of the CBS gene the patient resulted to be homozygous for the missense mutation c.346G > A (p.G116R) in exon 5, previously reported to cause cystathionine β-synthase deficiency. Patient's parents showed to be heterozygous for this same mutation. The biochemical follow-up of the patient 1 showed significant increase of serum methionine levels since 3 months from birth, with the most relevant level at six months (1339 μMol/L); at 2 years of age methionine concentration was 764 μMol/L (Fig. 2) while homocysteine levels was of 30 μMol/L; at this age a slight

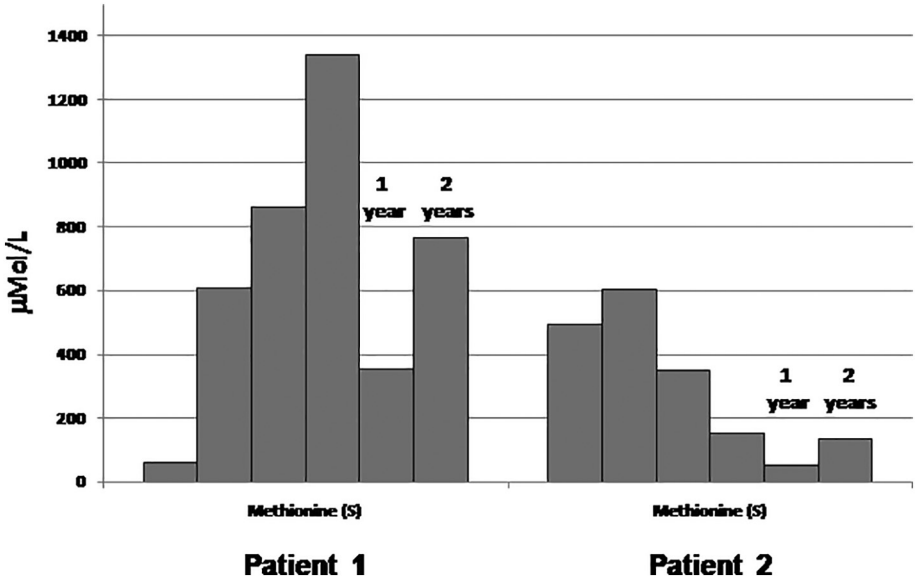

Fig. 2. Follow-up of the methionine levels of the newborns affected by hypermethioninemia.
Follow-up of serum methionine levels of the patient affected by CBS deficiency (patient 1) and of the patient affected by MAT I/III deficiency (patient 2).

deflection of the growth curve was also noted, then ascribed to gastroenteric infection due to Helicobacter Pylori. In the following years methionine levels remained substantially unchanged, while Hcy levels slightly decreased to 22 µMol/L. Despite the high levels of methionine patient 1 so far presents with good general clinical conditions, with a normal psychomotor development.

Patient 2: at screening on DBS this patient showed a significant increase of methionine both for the first and the second spot (42 and 88 µMol/L, respectively; R.V.: < 20). At birth sporadic tremors were reported. At one and three months of birth the dosage of amino acids on serum confirmed the high levels of methionine (494 and 604 µMol/L, respectively; R.V.: 9–42) (Fig. 2) associated to normal amounts of homocysteine; the dosage of urinary organic acids exhibited a normal profile (data not shown). These results suggested the possibility that the patient was affected by isolated hypermethioninemia (Table 2): indeed, molecular analysis identified, in heterozygosis, the mutation c.791G > A on exon 7 of *MAT1A* gene (p.R264H); this variant, affecting the intersubunit salt-brige formation, is known to be associated to a dominant form of defect of Methionine Adenosyl Transferase [30] and confirmed the diagnosis of isolated hypermethioninemia due to defect of MAT I/III. At three moths of birth the patient started a diet with low amounts of methionine that led to a significant decrease of serum methionine levels (151 µMol/L at six months from birth); when the patient was 1 year old his mother suspended the diet, nevertheless methionine concentration further lowered (50 µMol/L at 12 months from birth) (Fig. 2), while at two years from diagnosis the follow up of the patient showed a slight increase of serum Met levels (133 µMol/L). At present patient 2 exhibits good general condition without significant clinical problems.

4. Discussion

Hypermethioninemia is a biochemical condition, characterized by abnormal serum levels of amino acid methionine, rarely reported by extended newborn screening programs. The increase of methionine levels can be a consequence of primary defects in methionine metabolism among which the most frequent are deficiency of cystathionine β synthase and deficiency of methionine adenosyltransferase type I and III. Due to the involvement of CBS in the metabolism of homocysteine, in CBS deficiency hypermethioninemia is accompanied by hyperhomocysteinemia (and homocystinuria), while MAT deficient patients usually exhibit just increased levels of methionine. Extended newborn screening by MS/MS has one of its items in DBS methionine levels while homocysteine is not a primary newborn screening marker in most of the NBS programs; therefore, finding of increased levels of met at NBS is followed by dosage of serum Hcy levels to help to distinguish the pathologies of methionine metabolism.

CBS deficiency (OMIM #236200), also known as classical homocystinuria, is an autosomal recessive pathological condition with high clinical heterogeneity: it can be asymptomatic but frequently is characterized by myopia, thromboembolic events, skeletal anomalies (marfanoid features) and neurological problems. Real incidence of CBSD is not yet known: the estimated world-wide frequency is 1:344000, while in Europe higher frequencies are suggested (1:100000) [26]. Concerning the incidence reported by MS/MS-base extended NBS programs, our reviewing of the literature evidences values between 1:12607 and 1:470000, with the highest frequency ascribed to Qatar and the lowest frequency present in USA. In Italian Campania region the results from our NBS program allowed to estimate an incidence of 1:77000, that is close to the above reported estimated European frequency. CBSD presents with two phenotypic variants: B6-responsive homocystinuria, usually associated to p.Ile278Thr mutation, and B6-

Table 2
differential diagnosis for the hypermethioninemia.

Disease	Primary alterations	Main secondary alterations	Second level alterations
Cystathionine beta-synthase deficiency	Methionine ↑		Homocysteine ↑
Isolated hypermethioninemia (MAT def.)	Methionine ↑		
GNMT deficiency	Methionine ↑	S-adenosyl-methionine ↑	
AHCY deficiency	S-adenosyl-methionine ↑	Methionine ↑	

unresponsive variant, frequently caused by p.Gly307Ser alteration [27]. NBS programs using Met as primary marker are suggested to underestimate B6-responsive diseases, since this milder patients can have slightly increased levels of methionine when screened [3]. Indeed, our screening program identified only one case of CBSD among approximately 77,000 screened infants and this patient harbored in homozygosity a mutation, p.G116R, previously reported in patients affected by pyridoxine non-responsive homocystinuria [28]. Accordingly, this patient was substantially unresponsive to vitamin B6 administration. Nevertheless, this patient until now evidenced good general clinical conditions with normal psychomotor development.

MAT I/III deficiency (OMIM 250850) usually results in isolated persistent hypermethoninemia. In most cases MAT I/III deficiency presents with mild or no clinical sign; however a small number of patients develop clinical manifestations, in particular neurological problems associated with brain demyelination (subnormal IQ, tremor, dystonia, language and learning difficulties) [29]. Also for this pathology the true incidence is unknown; however, the results reported by different MS/MS-based NBS programs show an especially high incidence in the Iberian Peninsula (1:22874–1:27400) and a relatively low rate in Japan (1:107850). In Italy, the incidence appears to be higher in southern regions (Campania and Sicily), while this pathology is more rarely reported in screening programs working in the north of the peninsula (Table 1). MAT I/III deficiency is an autosomal pathology that can be recessive or dominant, depending on the mutations affecting the MAT1A gene. In fact, since the active MAT protein exists as dimeric or tetrameric forms, it can be prone to the dominant negative effect of some alterations. The most common autosomal dominant form of MAT deficiency is due to the presence, in heterozygosity, of mutation p.R264H which dominant negative effect is related to the importance of 264 codon for the dimerization of the functional protein [29]. This alteration has been reported in different populations but is especially frequent in the Iberian Peninsula [22] and is the mutation found in our patient 2. This alteration allows a significant residual MAT enzyme activity and is usually associated to moderate blood levels of methionine in patients with benign clinical course [30]. Accordingly, our patient was asymptomatic during a 2-years follow-up and presented, also in absence of diet therapy, moderate levels of serum methionine and normal clinical conditions.

In conclusion, during ten years of MS/MS-based newborn screening we identified in Campania region only two cases of hypermethioninemia, one due to CBS deficiency and one due to MAT I/III deficiency. Indeed, false negative cases are still possible, due to laboratory errors, low levels of methionine in the first days of life or cut off values too high; however, we have no news from clinicians of our structures concerning cases of CBSDD or MAT deficiency escaped our control and we are confident that the incidence we found for these pathologies is trusted for the screened population. Moreover, we are going to implement a send-tier test for total homocysteine on DBS to approach, at newborn screening, the unequivocal diagnosis for MAT deficiency and classical homocystinuria. Both our patients were substantially asymptomatic until 2 years from birth; however, since also for MAT I/III deficiency due to p.R264H mutation rare cases with myelination disorder have been reported [31] a careful clinical monitoring will be continued.

Contributions

Guglielmo RD Villani (corresponding author): performed research/study and typed manuscript.
Lucia Albano: collected biochemical data.
Marianna Caterino: collected biochemical data.
Daniela Crisci: collected biochemical data.
Silvia Di Tommaso: collected biochemical data.
Simona Fecarotta: clinical data and management of patients.
Maria Grazia Fisco: collected biochemical data.
Giulia Frisso: analyzed genetic data.
Giovanna Gallo: collected biochemical data.
Cristina Mazzaccara: performed genetic analysis.
Emanuela Marchese: clinical data and management of patients.
Antonio Nolano: performed genetic analysis.
Giancarlo Parenti: clinical data and management of patients.
Rita Pecce: collected biochemical data.
Adriana Redi: performed genetic analysis.
Francesco Salvatore: coordinator of research/study.
Pietro Strisciuglio: clinical data and management of patients.
Maria Grazia Turturo: collected biochemical and clinical data.
Fabiana Vallone: performed genetic analysis.
MargheritaRuoppolo: designed research/study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or no-for-profit sectors.

Ethical approval

All procedures followed in this study were in accordance with the ethical standards of the responsible committee onhuman experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Procedures were according to guidelines issued by Italian Ministry of Health in the law 167 of August 19, 2016.

Patient consent

Informed consent was obtained from parents for all patients involved in the study.

Declaration of Competing Interest

All the authors declare that they have no conflict of interest.

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