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ORIGINAL ARTICLE

Reversible infantile mitochondrial diseases

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Abstract Mitochondrial diseases are usually severe and progressive conditions; however, there are rare forms that show remarkable spontaneous recoveries. Two homoplasmic mitochondrial tRNA mutations (m.14674T>C/G in mt-tRNA^{Glu}) have been reported to cause severe infantile mitochondrial myopathy in the first months of life. If these patients survive the first year of life by extensive life-sustaining measures they usually recover and develop normally. Another mitochondrial disease due to deficiency of the 5-methylaminomethyl-2-thiouridylate methyltransferase (TRMU) causes severe liver failure in infancy, but similar to the reversible mitochondrial myopathy, within the first year of life these infants may also recover completely. Partial recovery has been noted in some other rare forms of mitochondrial disease due to deficiency of mitochondrial tRNA synthetases and mitochondrial tRNA modifying enzymes. Here we summarize the clinical presentation of these unique reversible mitochondrial diseases and discuss potential molecular mechanisms behind the reversibility. Understanding these mechanisms may provide the key to treatments of potential broader relevance in mitochondrial disease, where for the majority of the patients no effective treatment is currently available.

Introduction

Mitochondrial diseases are a large and clinically heterogeneous group of disorders that result from deficiencies in cellular energy production and affect at least one in 5000 of the population. Frequent clinical presentations are multisystem disorders in children that are often disabling, progressive or fatal, affecting the brain, liver, skeletal muscle, heart and other organs. Currently there are no effective cures for these disorders and treatment is at best symptomatic and mainly based on "trial and error" rather than on systematic evaluation of well-chosen agents in a standardized experimental system. However a small number (~5 %) of mitochondrial diseases may recover spontaneously.

The synthesis of the 13 mitochondrial-encoded proteins is a complex pathway, which requires over 150 different proteins including ribosomal proteins, ribosomal assembly proteins, mitochondrial aminoacyl-tRNA synthetases, tRNA modifying factors and initiation, elongation and termination factors (Smits et al 2010; Rötig 2011; Chrzanowska-Lightowlers et al 2010). Most of these gene defects result in histological abnormalities and multiple respiratory chain defects in the affected organs. The clinical phenotypes are usually early-onset, severe and often fatal, implying the importance of mitochondrial translation from birth (Kemp et al 2011). Some of these conditions affect multiple tissues; however, tissue-specific manifestations have been associated with mutations in several mt-tRNA aminoacyl synthetases or mt-tRNA modifying genes (Rötig 2011; Chrzanowska-Lightowlers et al 2010). Mitochondrial tRNA mutations are frequent causes of mitochondrial disease both in children and adults (Tuppen et al 2010; Russell and Turnbull 2014). Next-generation sequencing in a large cohort of patients has revealed that mutations in nuclear genes encoding mt-tRNA aminoacyl-synthetase and tRNA modifying factors are common causes of severe childhood disease, illustrating that an abnormal mitochondrial translation is one of the most frequent mechanisms within mitochondrial disease (Taylor et al 2014).

While most mitochondrial diseases are progressive conditions, a unique syndrome termed reversible infantile

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respiratory chain deficiency (RIRCD OMIM *500009, previously called reversible infantile cytochrome *c* oxidase deficiency) stands out by showing complete spontaneous recovery. Our group has identified that the m.14674T>C mutation in the mitochondrial $tRNA^{Glu}$ gene is the molecular cause of this disease (Horvath et al 2009). Similar to RIRCD, another reversible mitochondrial disorder, reversible infantile liver failure due to deficiency of the tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase (TRMU, OMIM *610230) enzyme has been described (Zeharia et al 2009). TRMU is an enzyme responsible for the thiouridylation of mt-$tRNA^{Glu}$, mt-$tRNA^{Gln}$ and mt-$tRNA^{Lys}$, which requires cysteine. Cysteine is an essential amino acid in the first months of life, because of the physiologically low activity of the cystathionine gamma-lyase (cystathionase) enzyme in infants (Sturman et al 1970). The age-dependent, partially reversible clinical presentation and the impairment of mt-$tRNA^{Glu}$ strongly suggest a possible pathophysiological link underpinning the spontaneous improvement in these mitochondrial conditions in the first year of life. An abnormal thiouridylation due to low dietary cysteine intake was suggested to contribute to both forms of infantile reversible mitochondrial disease (Boczonadi et al 2013; Zeharia et al 2009).

Here we describe the clinical characteristics and molecular mechanisms behind these rare reversible mitochondrial disorders and provide potential explanations for the tissue specific presentations and age-dependent manifestation and improvement.

Reversible infantile respiratory chain deficiency

The first patients with this disease were reported by Salvatore DiMauro in 1981 (DiMauro et al 1981) followed by a few more case reports in the following years (DiMauro et al 1983; Zeviani et al 1987; Roodhooft et al 1986; Nonaka et al 1988; Tritschler et al 1991; Salo et al 1992; Wada et al 1996). Our group identified the m.14674T>C homoplasmic mt-tRNA mutation as the molecular cause of this disease in 17 patients world-wide from 12 families. Two other groups published patient cohorts with RIRCD, Mimaki et al reported eight patients from seven Japanese families with a homoplasmic mutation affecting the position m.14674, but interestingly two patients carried T>G, not T>C change (Mimaki et al 2010). Additional patients were published by Uusimaa et al (2011). The clinical presentations in these patients are summarized in Table 1 and Supplementary Table 1.

The most common symptom is myopathy, which may be life-threatening in the first months of life and patients require vigorous life-sustaining measures (Table 1). Most patients had profound muscle weakness and hypotonia (29/31) and feeding difficulties (25/31) in the first days or weeks of life, and mechanical ventilation was needed in more than a third of the patients (12/31). Motor developmental milestones were often delayed. One patient died at 39 days, but all others started to improve spontaneously before 1 year of age. However a mild residual myopathy (ptosis, ophthalmoparesis, facial weakness, limb weakness), as a remaining feature was frequently present (19/30) in later age (Table 1). Some children showed mild, reversible involvement of the liver (4/31), but only in periods of most severe metabolic crisis, when increased CK and low carnitine levels were also reported occasionally (Supplementary Table 1). Brain, peripheral nerves, and cognitive development were unaffected in all patients in the first phase of the disease, although three patients developed neurological symptoms associated with Leigh-like basal ganglia lesions in a later phase (Horvath et al 2009). Family history was positive in five families (Table 1). Muscle biopsies taken in the neonatal period detected numerous ragged red fibres (RRF) and even more COX negative fibres indicative of mitochondrial accumulation (Supplementary Table 1), which are typical for mtDNA mutations specifically in mt-tRNA genes (Russell and Turnbull 2014). These changes significantly improved, but usually did not completely disappear on later biopsies (Horvath et al 2009). On routine morphology vacuolar changes with lipid and/or glycogen accumulation were detected frequently (23/31) and EM showed giant mitochondria with multilamellar paracrystalline inclusions (8/31) (Supplementary Table 1). Biochemical analysis of the RC enzymes in early muscle biopsies revealed an isolated COX (9/19) or combined RC (10/19) deficiency (Supplementary Table 1). After recovery all RC activities returned to normal or supernormal, indicating significant compensatory mechanisms.

Reversible infantile liver failure due to TRMU mutations

Autosomal recessive mutations in the *TRMU* gene cause severe infantile liver failure, and the majority of these patients show complete spontaneous recovery if they survive the first year of life (Zeharia et al 2009). Several modification steps are required for the efficient function of human mt-tRNAs, which can affect certain mt-tRNAs differently. Mt-$tRNA^{Glu}$, mt-$tRNA^{Gln}$ and mt-$tRNA^{Lys}$, but none of the other mt-tRNAs need to undergo 2-thiouridylation by tRNA 5-methylaminomethyl-2-thiouridylate methyltransferase (*TRMU)* (Sasarman et al 2011). Mutations in *TRMU* have also been suggested to aggravate the deafness phenotype of the mitochondrial m.1555A > G 12S rRNA mutation (Guan et al 2006), however the variants reported here were rather SNPs, and had no primary involvement in liver disease.

Mutations in *TRMU* have first been identified as the primary disease cause in 13 patients with severe infantile hepatopathy (Zeharia et al 2009). We and others have recently reported an additional seven patients carrying pathogenic

Table 1 Summary of the clinical presentation of the previously reported patients with RIRCD

Family patient	Age of onset	Clinical presentation				Age of recovery	Residual symptoms/ complications	mtDNA sequence	References
		Muscle weakness	Ventilation	Tube feeding	Hepatomegaly				
F1/1 M	36 h	+	+	+	−	5–16 months	myopathy	m.14674T>C	Horvath et al 2009
F2/1 M	6 weeks	+	+	+	−	6–15 months	myopathy	m.14674T>C	Horvath et al 2009
F3/1 M	3 weeks	+	+	+	+	5–20 months		m.14674T>C	Horvath et al 2009
F3/2 F	12 weeks	+	−	+	−	6 months	myopathy	m.14674T>C	Horvath et al 2009
F4/1 F	24 days	+	+	+	−		†died at 39 days	m.14674 >C	Horvath et al 2009
F5/1 F	4 weeks	+	+	+	−	7–12 months	myopathy, basal ganglia signal change, epilepsy	m.14674T>C	Horvath et al 2009
F6/1 M	15 days	+	+	+	−	5 months	motor delay	m.14674T>C	Horvath et al 2009
F7/1 M	birth	+	−	−	−	4 months		m.14674T>C	Horvath et al 2009
F8/1 M	1 month	+	−	+	+	10–22 months	myopathy	m.14674T>C	Horvath et al 2009
F8/2 M	1 month	+	+	+	−	7–18 months		m.14674T>C	Horvath et al 2009
F9/1 F	birth	+	−	+	−	9–36 months	myopathy	m.14674T>C	Horvath et al 2009
F10/1 M	2 months	+	−	+	−	5–19 months		m.14674T>C	Horvath et al 2009
F11/1 F	1 month	+	−	+	−	11–17 months		m.14674T>C	Horvath et al 2009
F12/1 M	birth	+	+	+	+	6–30 months	myopathic face, scapular winging	m.14674T>C	Horvath et al 2009
F12/2 M	2.5 months	+	+	+	−	5–20 months	myopathic face, scapular winging	m.14674T>C	Horvath et al 2009
F12/3 F	1 month	+	−	+	−	6–24 months		m.14674T>C	Horvath et al 2009
F12/4 M	1 month	+	−	+	−	5–18 months		m.14674 >C	Horvath et al 2009
F13/1 F	birth-3 months	+	−	−	−	24 months	late walking	m.14674T>G	Mimaki et al 2010
F14/1 F	birth- 3 months	+	−	+	−	32 months	late walking	m.14674T>C	Mimaki et al 2010
F15/1 F	birth- 3 months	+	−	−	−	late infancy	fatigability	m.14674T>G	Mimaki et al 2010
F16/1 F	birth- 3 months	+	+	−	−	15 months		m.14674T>C	Mimaki et al 2010
F17/1 M	birth- 3 months	+	−	+	−	12 months	febrile convulsion	m.14674T>C	Mimaki et al 2010
F18/1 M	birth- 3 months	+	−	−	−	18 months	myopathy	m.14674T>C	Mimaki et al 2010
F19/1 F	birth- 3 months	+	−	−	−	16 months	basal ganglia signal change	m.14674T>C	Mimaki et al 2010
F19/2 M	birth- 3 months	+	−	−	−	16 months	basal ganglia signal change	m.14674T>C	Mimaki et al 2010
F20/1	6 weeks	+	−	+	−	20 months	myalgia, fatigue, hypothyreodism	m.14674T>C	Uusimaa et al 2011
F20/2	8 weeks	−	−	+	−	18 months	myalgia, fatigue		Uusimaa et al 2011
F21/1 M	10 weeks	+	+	+	+	32 months	transient EOM weakness, cardiac and feeding problems, myopathic face, fatigability	m.14674T>C	Uusimaa et al 2011
F22/1 F	2 weeks	−	+	+	−	24 months	myopathic face, fatigability	m.14674T>C	Uusimaa et al 2011
F23/1 F	16 weeks	+	−	+	−	20 months	ptosis, fatigability, cardiac problem, feeding difficulties	m.14674T>C	Uusimaa et al 2011
F24/1 M	birth	+	−	+	−	18 months	ptosis, fatigability hypothyreodism	m.14674T>C	Uusimaa et al 2011

TRMU mutations which allowed a better characterization of TRMU-related infantile reversible disease (Schara et al 2011; Uusimaa et al 2011; Gaignard et al 2013; Taylor et al 2014). The disease course and age of manifestation — although with different tissue specificity — shows remarkable similarities with RIRCD implying that the spontaneous improvement in the two mitochondrial conditions may be caused by similar factors.

Similar to RIRCD these infants developed symptoms before age 6 months, and six of them died of acute liver failure between 1 and 8 months of age (Table 2). The main presenting phenotype was acute liver failure in the majority of the patients (18/20); however, one child had isolated reversible myopathy (Uusimaa et al 2011) while another had fatal Leigh syndrome and cardiomyopathy without hepatopathy (Taylor et al 2014). Fourteen patients developed normally after they had survived the acute phase of the disease (Table 2), however long term follow-up data are not available for most of these patients.

All children had increased serum lactate level which was accompanied by abnormal liver function (16/20), elevated total and conjugated bilirubin level (14/20) and impaired coagulation parameters (9/20). Hypoglycaemia was also frequently present (Supplementary Table 2). Liver biopsies taken in the acute phase revealed oncocytic change in the hepatocytes and focal ballooning of their cytoplasm as well as occasional focal micro- or macrovesicular steatosis (10/12). Later repeated biopsies detected liver architecture destruction by nodular fibrosis in almost all cases. Muscle biopsies showed variation in the fibre size and lipid accumulation in those patients who presented with prominent muscle involvement (2/9) otherwise no significant histological abnormalities were detected (Supplementary Table 2). Biochemical analysis of the respiratory chain enzymes in early liver biopsies revealed combined RC deficiency in most of the cases (9/12) with predominant decrease in complex IV and complex I activities. Isolated COX deficiency was present in the investigated muscle samples (8/10) (Supplementary Table 2).

Other potentially reversible mitochondrial conditions

Partial recovery after a severe infantile disease has been reported in a few patients carrying nuclear mutations in other mt-tRNA modifying genes. Mutations in the mitochondrial glutamyl-tRNA synthetase (*EARS2,* OMIM*612799) were identified in early onset severe neurological disease (leukoencephalopathy involving the thalamus and brainstem with high lactate, LTBL). Eight out of 12 patients carrying pathogenic *EARS2* mutations showed clinical improvement and stabilization after 1 year of age (Steenweg et al 2012), however two recently reported patients died at 3 and 6 months of age respectively of multisystem disease (Talim et al 2013; Taylor et al 2014).

Recently autosomal recessive mutations were reported in infantile partially reversible hypertrophic cardiomyopathy within the gene *MTO1* (OMIM*614667) encoding the enzyme that catalyzes the 5-carboxymethylamino-methylation (mnm5s2U34) of the same nucleotide (U34) of the wobble position that is affected in TRMU deficiency for mt-tRNA^{Glu}, mt-tRNA^{Gln} and mt-tRNA^{Lys} (Ghezzi et al 2012). Although *MTO1* mutations are commonly associated with hypertrophic cardiomyopathy, lactic acidosis and combined RC deficiency and most patients (seven out of 12 reported patients) died of severe hypertrophic cardiomyopathy within the first year, the cardiac symptoms improved and remained stable in some patients if they survived the first critical year (Baruffini et al 2013; Taylor et al 2014).

Potential mechanisms, which could explain the reversibility

It is intriguing that all reversible mitochondrial disorders in this review are somehow linked to defects of mt-tRNA^{Glu}, by the presence of the m.14674T>C/G mutation, defective post-transcriptional modifications of mt-tRNA^{Glu} (2-thiourydilation, 2 methylamino-methylation), or altered aminoacylation of mt-tRNA^{Glu} (Fig. 1). Seven pathogenic mutations have been described in mt-tRNA^{Glu} to date but none of these patients had a truly reversible phenotype (http://www.mitomap.org/ and Lax et al 2013) implying that reversible COX deficiency myopathy is not a consequence of mutations in mt-tRNA^{Glu}, but specifically of m.14674T>C. Two out of eight Japanese patients with reversible COX deficiency carry another exchange of the same nucleotide, m.14674T>G further confirming the importance of this specific nucleotide position. This mutation affects the discriminator base of mt-tRNA^{Glu}, the last base at the 3′-end of the molecule, where the amino acid is attached to the molecule via the terminal CCA (Levinger et al 2004). The mtDNA haplogroup backgrounds of the reported patients were different, indicating that the same mt-tRNA^{Glu} mutation has arisen independently on multiple occasions causing the same disease. The m.14674T>C/G mutation is thought to impair mitochondrial translation, as reflected by the RRF/COX-negative fibres and the multiple RC defects in skeletal muscle. The expression of stable mt-tRNAs relies on numerous modification steps: 5′ and 3′ processing by mitochondrial RNaseP and tRNase Z; addition of the CCA trinucleotide to the 3′ end of the mt-tRNA transcript by [CCA] nucleotidyltransferase; modification by a variety of mt-tRNA modifying enzymes (such as TRMU and MTO1); and aminoacylation of mt-tRNA by the cognate aminoacyl mt-tRNA synthetase EARS2 (Levinger et al 2004). As a

Table 2 Summary of the previously reported patients with TRMU deficiency

Patient	Age of onset	Clinical presentation				Current age/ †death	TRMU sequencing	References
		Liver failure	Hepato-megaly	Muscle weakness	Complications			
P1	6 months	+	+	−		2 years	homozygous c.232T>C, p.Tyr77His	Zeharia et al 2009
P2	4 months	+	+	−		9 months	homozygous c.232T>C, p.Tyr77His	Zeharia et al 2009
P3	2 months	+	+	−		10 years	heterozygous c.232T>C, p.Tyr77His	Zeharia et al 2009
P4	3 months	+	+	−	dilated cardiomyopathy, nephromegaly, proteinuria	10 years	homozygous c.232T>C, p.Tyr77His	Zeharia et al 2009
P5	4 months	+	+	−		8 years	homozygous c.232T>C, p.Tyr77His	Zeharia et al 2009
P6	4 months	+	+	−		14 years	homozygous c.232T>C, p.Tyr77His	Zeharia et al 2009
P7	3 months	+	+	−	death	†4 months	compound heterozygous c.232T>C, p.Tyr77His/c.706-1G>A	Zeharia et al 2009
P8	6 months	+	+	−		2 years	compound heterozygous c.697C>T, p.Leu233Phe/ c.28G>T, p.Ala10Ser	Zeharia et al 2009
P9	1 month	+	+	−	death	†2 months	compound heterozygous c.835G>A, p.Val279Met /c.500-510del	Zeharia et al 2009
P10	6 months	+	+	−	micronodular liver, cholestasis	2 years	homozygous c.815G>A, p.Gly272Asp	Zeharia et al 2009
P11	1 day	+	+	−		5 years	heterozygous c.40G>A, Gly14Ser	Zeharia et al 2009
P12	1 day	+	+	−	death	†3 months	homozygous c.2T>A, p.Met1Lys	Zeharia et al 2009
P13	2 days	+	+	−	death	†4 months	homozygous c.2T>A, p.Met1Lys	Zeharia et al 2009
P14	4 months	+	+	+	micronodular liver, incomplete cirrhosis	2 years	compound heterozygous c.711_712insG / c.1081_1082insAGGCTGTGC	Schara et al 2011
P15	3 months	+	+	+	cirrhosis, cholestasis death	†8 months	compound heterozygous c.835G>A, p.Val279Met /c.248+1G>A	Gaignard et al 2013
P16	4 months	+	+	−	multinodular liver	2 years	compound heterozygous c.835G>A, p.Val279Met /c.649G>A, p.Glu217Lys	Gaignard et al 2013
P17	2 days	+	+	+	multinodular liver	5 years	homozygous c.697C>T, p.Leu233Phe	Gaignard et al 2013
P18	birth	−	−	+	ptosis, fatigability ophthalmoparesis feeding problems	27 months	heterozygous c.28G>T, p.Ale10Ser	Uusimaa et al 2011
P19	6 days	+	−	+	microvesicular steatosis, cholestasis thalamus signal change	14 months	compound heterozygous c.835G>A, p.Val279Met c.1102-3C>G	Uusimaa et al 2011
P20	birth	−	−	+	Leigh syndrome, heart failure	†1 month	homozygous c.287A>G, p.Asn96Ser	Taylor et al 2014

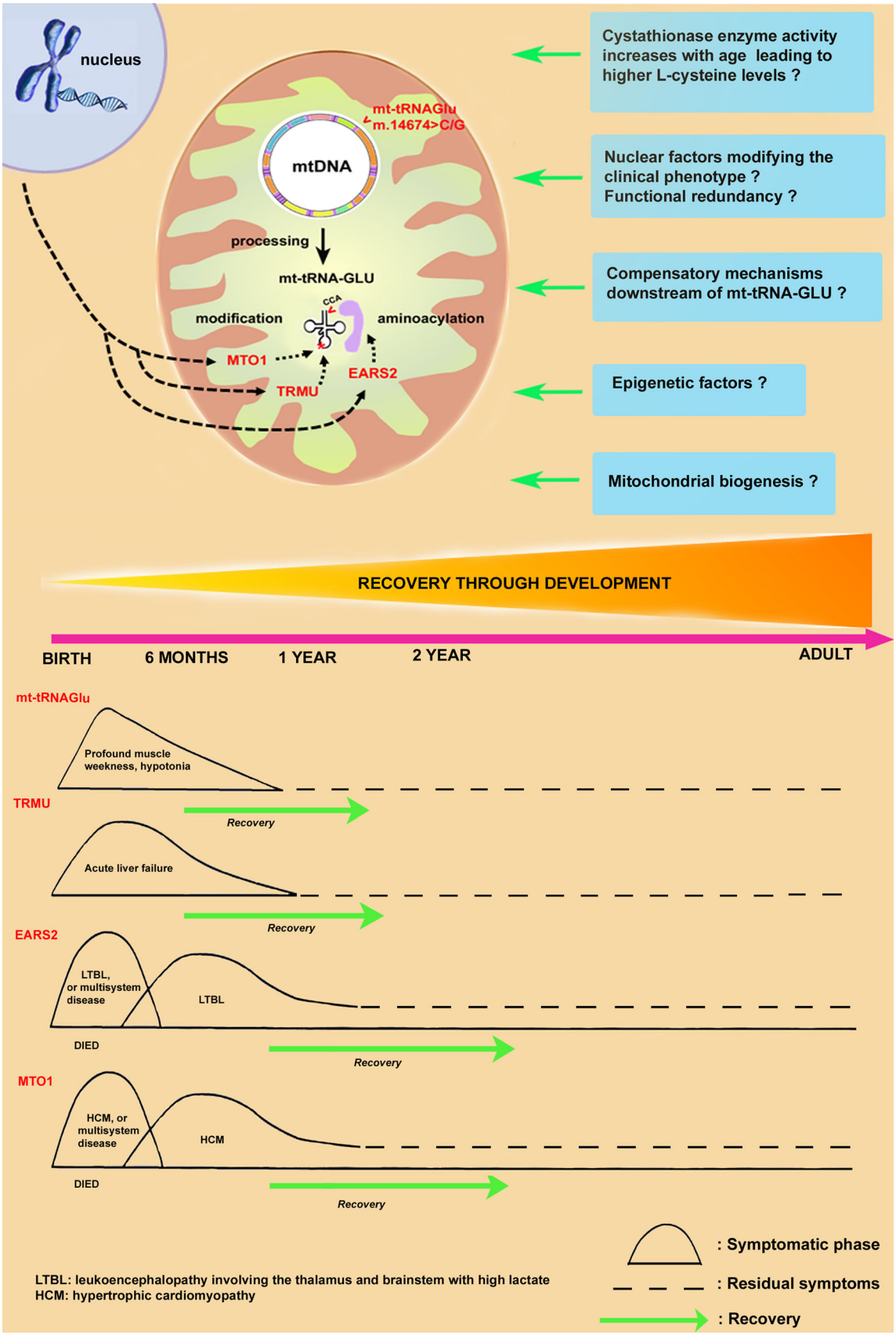

Fig. 1 Potential pathomechanisms which may explain the reversibility

consequence of the mutation, the steady state level of mt-tRNA^{Glu} was decreased in skeletal muscle and showed only a slight increase in the follow-up muscle biopsy, when COX activity returned to normal and the children were almost asymptomatic, suggesting that a mild increase of mt-tRNA^{Glu} is sufficient to regain normal mitochondrial translation (Horvath et al 2009). In support of these findings normal levels of mitochondrial translation can be maintained by low steady state levels (~10 %) of another homoplasmic mt-tRNA mutation (m.1624C>T in mt-tRNA^{Val}, Rorbach et al 2008).

A potential developmental increase in mitochondrial biogenesis may have a compensatory effect on the low tRNA^{Glu} steady states. A physiological increase in mtDNA copy numbers have been shown in the first months of life (Macmillan and Shoubridge 1996; Morten et al 2007), which could result in improved mitochondrial translation. However mtDNA copy numbers did not change significantly in muscle DNA extracted from consecutive biopsies of patients with RIRCD (Horvath et al 2009).

It has been hypothesized previously that the nuclear-encoded COXVIa and COXVIIa subunits undergo a developmental isoform switch from fetal to ubiquitous isoforms and it may explain the disease recovery in reversible infantile myopathy (Tritschler et al 1991; Taanman et al 1993). However no experimental evidence has been shown yet in patients carrying the m.14674T>C/G variant, that a switch between isoforms would underlie the recovery.

Additional factors such as environmental contributions, epigenetic factors and the presence of other genetic polymorphisms may ultimately modify the nature of the disease phenotype and also have to be considered to explain reversibility in these conditions (Boczonadi et al 2013).

Recently our group suggested another potential explanation for the timed disease manifestation of both RIRCD and TRMU deficiency. Cysteine is an essential amino acid in infants, because the cystathionine gamma-lyase (cystathionase) enzyme, which is a rate-limiting enzyme for the synthesis of L-cysteine from L-methionine appears to be regulated at the post-transcriptional level during development (Levonen et al 2000). It has been hypothesized that an impaired thio-modification of mt-tRNA^{Glu} due to low infantile cysteine concentrations may contribute to the disease (Zeharia et al 2009). Studies on skeletal muscle of reversible infantile myopathy patients suggested defective 2-thiouridylation via TRMU during the early months of life and indicated improved thio-modification after recovery (Boczonadi et al 2013). Interestingly, supplementation of L-cysteine, that is essential for normal TRMU activity, significantly improved most RC complex activities in TRMU and RIRCD patient cells. These data suggested that low dietary L-cysteine levels in infants could explain clinical manifestations, and an increase in L-cysteine due to cystathionase activation through development would contribute to the recovery in these patients (Boczonadi et al 2013).

Interestingly the positive effect of L-cysteine also improved the RC complex activities in MTO1 deficient cells, suggesting that the beneficial effects are not strictly specific to the thio-modification (Boczonadi et al 2013). A possible beneficial effect of supplementation with *N*-acetyl-cysteine has been suggested in a rare mitochondrial condition, ethylmalonic encephalopathy due to mutations in the *ETHE1* gene (Viscomi et al 2010). *N*-acetyl-cysteine is thought to detoxify sulphides by increasing mitochondrial glutathione and it has substantially prolonged the lifespan of Ethe1-deficient mice and caused marked clinical improvement in affected children with ethylmalonic encephalopathy (Viscomi et al 2010). It is also possible, that the antioxidant effect of cysteine, as suggested for N-acetyl-cysteine contributes to the improvement in reversible mitochondrial disease. In support of the importance of cysteine in mitochondrial function, lower levels of reduced cysteine and thiols were reported in plasma of children with mitochondrial diseases (Salmi et al 2012). In addition, a double-blind cross-over study on patients with mitochondrial myopathies showed that 30-day supplementation with a whey-based cysteine donor resulted in significantly reduced oxidative stress (Mancuso et al 2010). Further studies are required to reveal the potential therapeutic perspective of L-cysteine in other forms of mitochondrial diseases.

Strictly looking at the age-dependent disease course of reversible mitochondrial disorders and others showing partial recovery, the clinical features present during a critical window of time through early infancy. The tissue specific presentations raise the possibility of different developmental factors explaining the reversibility in skeletal muscle (m.14674 >C/G), liver (TRMU), brain (EARS2) or the heart (MTO1) and further studies are needed to explore these mechanisms. The early diagnosis of the potentially reversible mitochondrial diseases is of utmost importance therefore these genes should be screened in infants with mitochondrial disease (for diagnostic laboratories see http://www.genetests.org/). Although we are not aware of any clinical data to date, we suggest that supplementation with L-cysteine or *N*-acetyl-cysteine may be beneficial in severe symptomatic phases of reversible mitochondrial disease.

Conclusions

Here, we define genetic forms of reversible mitochondrial phenotypes and discuss potential mechanisms explaining the reversibility. Early differential diagnosis between fatal and benign mitochondrial diseases is of critical importance for prognosis and management of these infants, because the benign form is initially life threatening but ultimately reversible. Recent functional data in reversible mitochondrial disease suggest that infantile cysteine levels may contribute to the manifestation of symptoms and supplementation with

cysteine may facilitate the spontaneous recovery in affected infants. Defining the common mechanism would suggest new avenues for treatment in mitochondrial disorders, and could also have more general relevance for understanding the basic disease mechanism in disorders of mitochondrial protein synthesis.

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Compliance with ethics guidelines

Conflict of interest None.

Human and animal rights and informed consent All procedures followed were in accordance with the ethical standards of the responsiblecommittee on human experimentation (NRES Committee Yorkshire & The Humber-LeedsBradford) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consentwas obtained from all patients from our centre for being included in the study. This article does not contain any studies with animalsubjects performed by the any of the authors.

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