Biochimie 91 (2009) 1273–1277

Contents lists available at ScienceDirect

Biochimie

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

Mini-review

Molecular diagnosis of Menkes disease: Genotype–phenotype correlation

Lisbeth Birk Møller*, Mie Mogensen, Nina Horn

Kennedy Center, Gl. Landevej 7, 2600 Glostrup, Denmark

ARTICLE INFO

Article history:
Received 15 February 2009
Accepted 28 May 2009
Available online 6 June 2009

Keywords:
Menkes disease
Occipital horn syndrome
Genotype–phenotype correlation

ABSTRACT

Menkes syndrome is an X-linked, fatal neurodegenerative disorder of copper metabolism, caused by mutations in the *ATP7A* gene, encoding a copper-transporting P1B-type ATPase. To date, a total of approximately 160 different mutations have been reported worldwide. The clinical phenotypes observed in these patients include progressive neuro-degeneration, connective-tissue abnormalities and peculiar hair. There is phenotypic variability. While the majority of the patients do not survive early childhood, milder cases leading to longer survival have been reported. In this review we focus on mutations, identified in patients with milder forms of Menkes disease, and discuss the possibility of establishing a genotype–phenotype correlation. The presence of small amounts of normal protein, or the presence of partly functional protein variants containing a less essential amino acid substitution or a truncation of the N- or C-terminus, might all result in a milder, atypical phenotype. A clear phenotype–genotype correlation is however difficult to establish, clearly illustrated by the presence of inter- and even intra-familial variability.

1. Copper metabolism and Menkes disease

The Menkes disease is a multisystemic lethal disorder of impaired copper metabolism, due to mutations in the X-linked *ATP7A* gene. The incidence of the disease is estimated to range between 1:40 000 and 1: 360 000 live births [1–3]. Practically all copper needed by the human body is normally taken in through the diet; about 1 mg/d. Patients suffering from Menkes disease are unable to absorb sufficient amount of copper from the gastrointestinal tract, and less copper is therefore delivered to the blood. The patients have severe developmental and neurological impairment due to reduced amount of copper in the brain. Furthermore the patients have reduced activity of several copper dependent enzymes, which leads to connective-tissue abnormalities, tortuosity of blood vessels and peculiar hair (kinky or steely hair) [4]. The phenotypic features of Menkes disease can be divided in at least three categories; Classical Menkes disease with death in the early childhood, mild MD with long survival, and occipital horn syndrome (OHS, previously known as X-linked cutis laxa, or Ehlers–Danlos syndrome type IX). OHS is the mildest allelic form. The neurological symptoms of OHS patients are milder than those found in patients suffering from classical Menkes disease, leading to a clinical picture mainly characterized by connective-tissue manifestations. The majority of the patients suffer from classical Menkes disease, but milder forms are observed in 5–10% of the patients.

2. The ATP7A protein

The ATP7A protein is a member of the P-type ATPase family, which performs ATP-driven translocation of metal cations across cellular membranes. The ATP7A protein is a copper-transporting ATPase (Fig. 1). ATP7A contains 6 copper-binding sites in the cytoplasmatic N-terminal. In common with other members of the family of P-type ATPases, the ATP7A protein contains three additional cytoplasmic domains; the activation (A) domain, the phosphorylation (P) domain, and the nucleotide-binding (N) domain. The N-domain is important for ATP binding, the P domain contains an invariant aspartate residue that is phosphorylated during the catalytic cycle by ATP, and the A domain is important for the subsequent dephosphorylation. Furthermore, the protein contains 8 transmembrane (TM) domains, forming a copper-transporting channel [5].

The ATP7A protein has a dual role: it is responsible for the copper-loading of several copper-requiring enzymes, as well as for the ATP-driven efflux of copper from the cell [6–8]. ATP7A is under normal physiological copper concentrations, localized to the trans-Golgi network (TGN) [9]. In TGN it transports copper into the lumen, where the copper-loading of enzymes in the secretory pathway takes place. It is translocated to vesicles [10] or to the plasma membrane in response to increased copper concentration [11]. It is likely that the ATP7A protein not directly transports

* Corresponding author. Tel.: +45 43260130.
E-mail address: lbm@kennedy.dk (L.B. Møller).

0300-9084/$ – see front matter © 2009 Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.biochi.2009.05.011

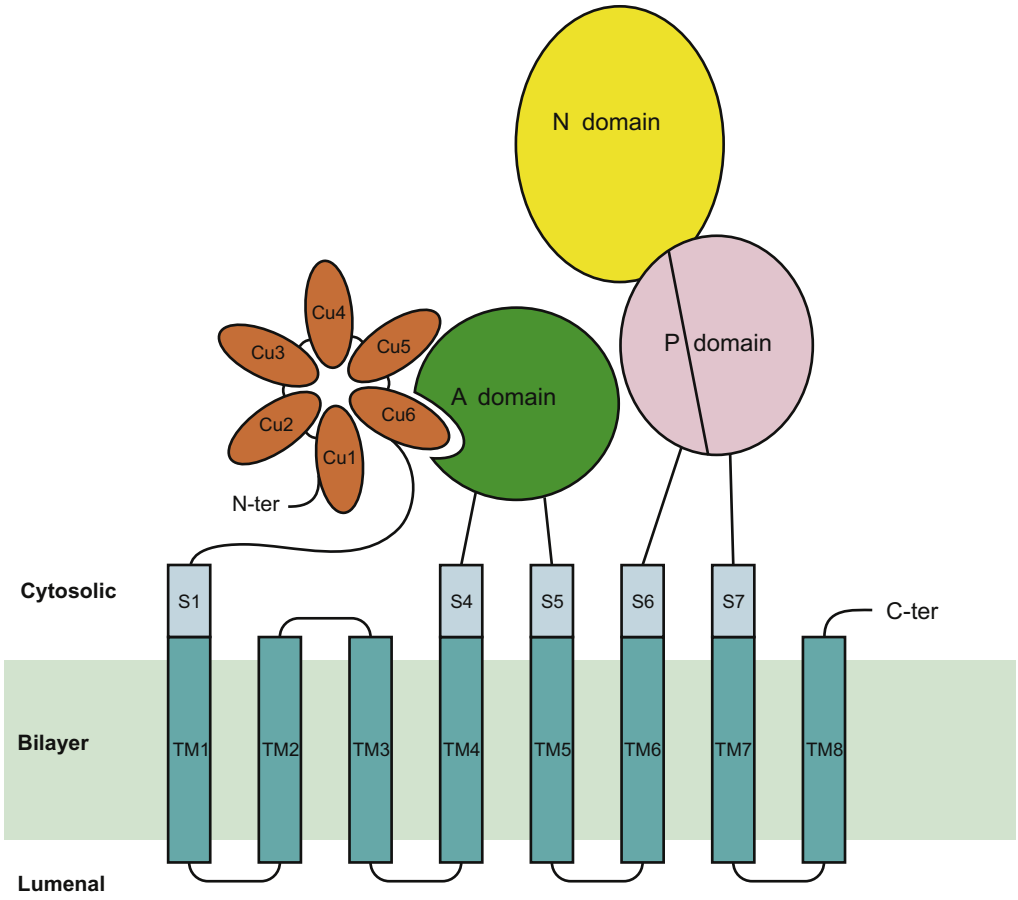

Fig. 1. Domain organization of the ATP7A protein. The positions and sequence motifs conserved among the family of ATPases are shown. Modified from [5].

copper across the cell membrane, but instead transports copper into a vesicular compartment. The copper is then subsequently released by exocytose [10]. The ATP7A protein might only be detectable at the plasma membrane at very high concentration of copper [10].

3. Identified mutations in the *ATP7A* gene

The *ATP7A* gene contains 23 exons and encodes a P-type ATPase of 1500 amino acids.

The Kennedy Center is a combined diagnostic and research laboratory, and as a part of the diagnostic service, we perform the molecular diagnosis of patients suffering from Menkes disease. Patients with clinical symptoms suggesting Menkes disease from the entire world are referred to the Kennedy Center for molecular confirmation of the diagnosis. Until now we have identified about 357 different mutations (partly unpublished). The mutations can be divided into several subtypes. The most frequent mutation type is indels; insertion or deletion of few base pairs, which account for 22% of the mutations. Almost equal numbers of splice-site mutations, missense mutations, partial gene deletions and mutations leading to a premature termination codon respectively have been identified (Fig. 2). Although mutations are scattered all over the entire sequence, no missense mutation have so far been identified in the region encoding the 6 copper-binding sites. The major part of the patients suffer from the classical form of Menkes disease but about 6% of the patients suffer from a milder form, with longer survival and 3% suffer from the mildest form, OHS. The spectrum of mutations identified in these atypical patients, compared to mutations identified in typical MD patients, are illustrated in Fig. 3.

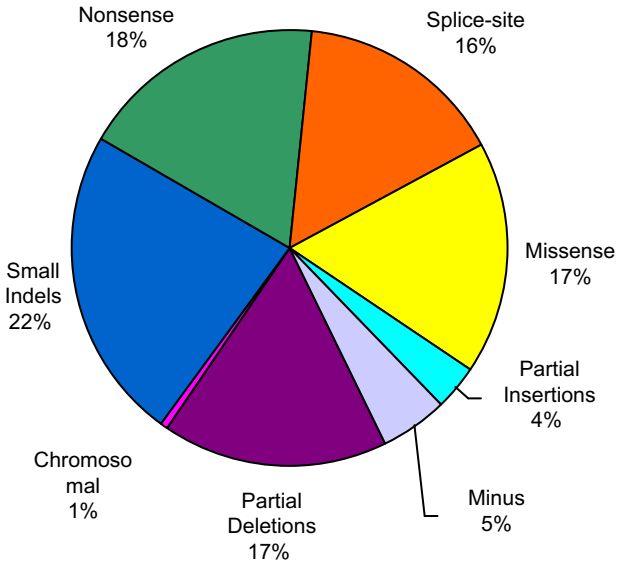

Fig. 2. Frequency of different type of mutations identified in the *ATP7A* gene at the Kennedy Center.

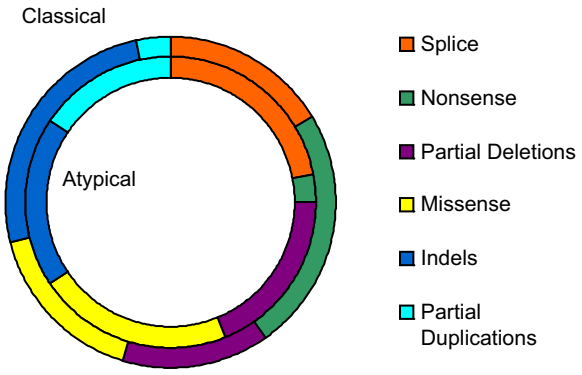

Fig. 3. *ATP7A* mutations and phenotypes in the patients analysed at the Kennedy Center.

4. Reported mutations identified in patients with milder phenotype

Until now, about 12 mutations have been reported in patients who were diagnosed with OHS (Table 1). In four of the cases the mutation was located in acceptor or donor site for splicing, in three of these small amounts of normal transcripts were identified [20,21,23,24]. We and others have hypothesized that in the presence of splice-site mutations, OHS results from the presence of small amounts of normal transcripts, in contrast to Menkes disease where no normal transcripts are present [20,23]. We demonstrated that an *ATP7A*-transcript level as low as 2–5% of normal level is sufficient to result in OHS [20]. However, in one case of OHS with splice-site mutation, no normal transcript could be detected by RT-PCR [22]. It was found that skipping of exon 10, encoding TM3 and TM4, abolished Golgi localization of the protein variant [22]. It is possible that this variant still has some function in copper transport. At least one case of splice-site mutation has been found in the group of patients suffering from mild Menkes disease (Table 2). Also in this case small amounts of normal transcript were detected [15]. The amount of normal transcript necessary to results in OHS, versus mild Menkes disease, still remains to be determined.

Most missense mutations identified in *ATP7A* so far lead to classic Menkes disease. However, in six OHS patients and in several patients with mild Menkes disease, missense mutations have been identified (Tables 1 and 2). Three of these mutations in the OHS patients affect residues located in stalk regions, indicating that missense mutation located in stalk regions often leads to OHS [5]. The major function of the stalk regions might be to give the protein the right conformation, rather than affecting the active center directly. Therefore, amino acid substitutions might be more tolerated in these regions. In contrast, missense mutations affecting residues located in the P domain, containing a large number of conserved motifs necessary for the catalytic activity, very often lead to classical Menkes disease [5]. Nevertheless, two missense mutations have been identified in the P domain in OHS patients as well as a few in the group of mild Menkes patients. It is hard to understand, especially taking into account that the affected residues are conserved in at least 35 out of 49 copper P-type ATPases [5]. In the group of mild patients, a high number of mutations in the TM regions have been observed [5]. An attempt to determine the residual activity of few of the missense mutations have been performed by testing the ability of the mutants to complement a yeast strain Δccc2. This strain lacks the *CCC2* gene, the yeast homologue to *ATP7A/ATP7B* and is deficient in high affinity iron uptake, because *CCC2* is responsible for copper-loading of the copper-requiring ferroxidase Fet3p. As a consequence the yeast strain Δccc2 is not able to grow under iron-limited conditions, unless it is transformed with a cDNA sequence encoding a copper transporter, with at least some partial activity. Using this assay the residual activity of the three mutations; p.S1362D, p.N1304S and p.S637L was determined to 17%, 33% and 73% respectively of normal activity, in agreement with the atypical phenotype [14,16].

In addition to the presence of small amounts of normal protein (as a consequence of the small amount of normal transcript), and the presence of partly functional protein variants, containing a single amino acid substitution, the presence of partly functional truncated protein variants might result in OHS or mild phenotype of Menkes disease as well. This has been demonstrated for mutations affecting the C-terminus or the N-terminus. A deletion of a nucleotide in exon 23 resulting in a truncated protein missing the last 50 residues, including the dileucine motif, L1487L1488, has

Table 1
ATP7A mutations identified in OHS patients.

Mutation	Exon	Proposed effect on mRNA or protein	Reference
c.-684_c-587del98 bp	Promoter	Regulation of transcription.	[12]
p.S637L	8	Presence of alternative transcripts in addition to normal spliced transcript with mutation. Located in stalk S1. Show approximately 73% activity of normal in yeast complementation analysis. Note inter- and intra-familial variability.	[13,14]
p.S833G	11	Presence of alternative transcripts, including skipping of exon 11, in addition to normal spliced transcript with mutation. Located in stalk S4.	[15]
p.Q924R	13	Located in stalk S5. Affects cellular localization; it was only partly located in TGN at low copper concentration.	[5]
p.N1304S	20	Affects copper transport, affects conserved residue (90 out of 159 P-type ATPases) in the P domain, GDGIND. Show approximately 33% activity of normal in yeast complementation analysis.	[16]
p.A1325V	20	Protein could not be detected in the patient. Affects conserved residue (90 out of 159 P-type ATPases) in the P domain, GTDVA. Note intra-familial variability. The mutation identified both in OHS and mild/classic MD patients.	[5]
p.A1362D	21	Affects conserved residue in TMD7, might affect Cu transport. Show approximately 17% activity of normal in yeast complementation analysis. Affect translocation of the protein. Failed to redistribute towards the cell periphery in response to copper, remained in TGN. Note intra-familial variability. The mutation identified both in OHS and mild MD patients.	[5,14]
c.4352delG	23	FS, lack of last 50 residues including the LL motif. The dileucine motif was important for cycling from the cell periphery to the TGN, but not required for copper efflux.	[18,19]
IVS6 + 6_9delTAAG	IVS6, donor site	Skipping of exon 6. Reduced amount of normal transcript.	[20,21]
IVS10 + 3A > T	IVS10, donor site	Ex10 is missing. Protein is not located in TGN, but might still, to some degree, functions in copper transport according to the OHS phenotype observed in the patient.	[22]
IVS14-4A > G	IVS14, acceptor site	Skips exon 15. Reduced amount of normal transcript.	[23]
IVS17 + 5G > A	IVS17, donor site	Skips exon 17. Reduced amount of normal transcript.	[23,24]

Table 2
A fraction of *ATP7A* mutations identified in patients suffering from a milder form of Menkes disease.

Mutation	Exon	Effect on mRNA or protein	Reference
g.Ex1del	1	Reduced amount of transcript. Mildly affected patient. Socially interactive, only few infections, and he had to some degree head control.	[25]
g.Ex3–4del	3–4	Reinitiation in exon 5. Protein product contains two instead of six copper-binding sites. The amount of protein was reduced in the patient. The product shows normal activity in yeast complementation analysis.	[25,26]
g.Ex3–23del	3–23	No transcript. The patient survived for 18 years but have classic MD. He was mentally retarded with joint contractures and muscular atrophy. No head control and not able to walk.	[25]
g.Ex22–23del	22–23	Lack of the C-terminus (amino residues: 1376–1500).	[25]
c.408_415delCAATCAGA	3	Frameshift.	[27]
p.S637L	8	Presence of alternative transcripts in addition to normal spliced transcript with mutation. Located in Stalk S1. Show approximately 73% activity of normal in yeast complementation analysis. Note inter- and intra-familial variability. Mutation identified in OHS, mild and classic MD patient.	[13,14]
p.R844H	12	Note interfamilial variability. Mutation identified both in mild and classic MD patients. Located in the A domain. Protein could not be detected in the patient.	[28,29]
p.G876E	13	Affect conserved motif (90 out of 159 P-type ATPases) TGEA in the A domain, important for dephosphorylation. Note the p.G876R mutation leads to classic MD.	[5]
p.C1000R	15	Affects conserved residue in TM6 (CPC motif). Affects Cu transport, failed to activate tyrosinase. Affect translocation to the cell periphery in response to copper, remained in TGN.	[5,30–32]
p.A1007V	15	Affects conserved residue in TM6, might affect Cu transport. Normal localization in TGN at low Cu.	[5]
p.P1279L	20	Affects conserved residue (90 out of 159 P-type ATPases) in the P domain.	[33]
p.A1325V	20	Protein could not be detected in the patient. Affects conserved residue (90 out of 159 P-type ATPases) in the P domain GTDVA. Note intra-familial variability. The mutation identified both in OHS and mild/classic MD patients.	[5,17]
p.A1362D	21	Affects conserved residue in TMD7, might affect Cu transport. Show approximately 17% activity of normal in yeast complementation analysis. Affect translocation of the protein. Failed to redistribute towards the cell periphery in response to copper, remained in TGN. Note intra-familial variability. The mutation identified both in OHS and mild MD patients.	[5,14]
p.A1362V	21	Affects conserved residue in TMD7, might affect Cu transport.	[5,34]
c.4123 + 3A > T	IVS21	Skips exon 21, reduced amount of normal transcript.	[15]

been identified in an OHS patient (Table 1; [18]). The dileucine motif has been demonstrated to be essential for localization of ATP7A within the TGN, but not for copper efflux [19]. This might be the reason for the OHS phenotype. In a patient with mild phenotype a deletion of exons 22 and 23 has been identified resulting in a truncated protein missing the last 124 residues (Table 2; [25]). In another patient with mild phenotype, a deletion of the entire exon 3 and exon 4 was identified [25,26]. A deletion of exons 3 and 4 leads to a premature termination codon. Surprisingly, we found that the mild phenotype in this patient is due to reinitiation at an internal ATG codon located in exon 5. The resulting truncated protein contains only four copper-binding sites instead of the normal six [26]. From these observations it seems that the ATP7A protein is still partly functional even if a part of the C-terminus or the N-terminus is missing.

5. Genotype–phenotype correlation

Establishment of a genotype–phenotype correlation is important, as affected newborns that have mutations, which do not completely abrogate *ATP7A* function, may be especially responsive to early copper treatment [35]. Treatment with daily copper injections may improve the outcome in Menkes disease, if commenced within days after the birth [35]. It seems however, to be very difficult to establish a clear phenotype–genotype correlation, although a certain degree of correlation between the amount of normal transcript or the location of the mutation, and the phenotype seems to exist, as described above. Irregularity is illustrated by the case, where deletion of essentially the entire *ATP7A* gene (exons 3–23) was found in a patient with long survival. Although the symptoms of this patient were identical to classic MD, with mental retardation, joint contractures and muscular atrophy, the patient survived for 18 years (Table 2; [25]). Also the presence of inter- and even intra-familial variability in Menkes disease/occipital horn syndrome underscores this problem. The p.R844H mutation has been identified in one family with mild symptoms [28], and in another family with classical Menkes disease [29]. Both the p. A1325V and the p.A1362D mutations have been identified in families with varying phenotypes, leading in one family member to OHS (Table 1) and in another to mild Menkes (Table 2) [14,17]. Both inter- and intra-familial variabilities have been observed for the p.S637L mutation. In one family this mutation has been found in affected males with either mild or classical Menkes disease [14], and in a second unrelated family it was found in a patient with OHS [13].

6. Conclusion

In conclusion, there seems to be poor genotype–phenotype correlation. One reason is unexpected outcomes of certain mutations, assumed to be null. In similarity to the unexpected reinitiation we found in the patient with an exons 3–4 deletion, we speculate that reinitiation also might take place in other patients with premature termination codons in the exon 3 or exon 4 regions. Another reason is the inter- and intra-familial variability. Even though the family-specific mutation is known, and the clinical expression assumed to be known, there might still be surprises due to individual variations. A third reason is the totally unexpected outcome of patients with a guaranteed null mutation, which was the case for the long-lived patient, even though he had an exon 3–exon 23 deletion. Unknown compensatory mechanisms might have its effect. Such mechanisms and factors that contribute to the copper homeostasis system still remain to be revealed.

References

[1] D.M. Danks, Disorders of copper transport, in: C.R. Scriver, A.L. Beaudet, W.M. Sly, et al. (Eds.), The Metabolic and Molecular Basis of Inherited Disease, McGraw-Hill, New York, 1995, pp. 2211–2235.
[2] T. Tønnesen, W.J. Kleijer, N. Horn, Incidence of Menkes disease, Hum. Genet. 86 (1991) 408–410.
[3] Y.H. Gu, H. Kodama, K. Shiga, S. Nakata, Y. Yanagawa, H. Ozawa, A survey of Japanese patients with Menkes disease from 1990 to 2003: incidence and early signs before typical symptomatic onset, pointing to the way to earlier diagnosis, J. Inherit. Metab. Dis. 28 (2005) 473–478.

[4] H. Kodama, Y. Murata, Molecular genetics and pathophysiology of Menkes disease, Pediatr. Int. 41 (1999) 430–435.
[5] L.B. Møller, J.T. Bukrinsky, A. Mølgaard, M. Paulsen, C. Lund, Z. Tümer, S. Larsen, N. Horn, Identification and analysis of 21 novel disease-causing amino acid substitutions in the conserved part of ATP7A, Hum. Mutat. 26 (2005) 84–93.
[6] J. Camakaris, M.J. Petris, L. Bailey, P. Shen, P. Lockhart, T.W. Glover, C. Barcroft, J. Patton, Gene amplification of the Menkes (MNK; ATP7A) P-type ATPase gene of CHO cells is associated with copper resistance and enhanced copper efflux, Hum. Mol. Genet. 4 (1995) 2117–2123.
[7] I. Voskoboinik, H. Brooks, S. Smith, P. Shen, J. Camakaris, ATP-dependent copper transport by the Menkes protein in membrane vesicles isolated from cultured Chinese hamster ovary cells, FEBS Lett. 435 (1998) 178–182.
[8] A.S. Payne, J.D. Gitlin, Functional expression of the MD protein reveals common biochemical mechanisms among the copper-transporting P-type ATPases, J. Biol. Chem. 273 (1998) 3765–3770.
[9] Y. Yamaguchi, M.E. Heiny, M. Suzuki, J.D. Gitlin, Biochemical characterization and intracellular localization of the Menkes disease protein, Proc. Natl. Acad. Sci. U.S.A. 93 (1996) 14030–14035.
[10] J.F. Monty, R.M. Lianos, J.F. Mercer, D.R. Kramer, Copper exposure induces trafficking of the menkes protein in intestinal epithelium of ATP7A transgenic mice, J. Nutr. 135 (2005) 2762–2766.
[11] M.J. Petris, J.F. Mercer, J.G. Culvenor, P. Lockhardt, P.A. Gleeson, J. Camakaris, Ligand-regulated transport of the Menkes copper P-type ATPase efflux pump from the Golgi apparatus to the plasma membrane: a novel mechanism of regulated trafficking, EMBO J. 15 (1996) 6084–6095.
[12] B. Levinson, R. Conant, R. Schnur, S. Das, S. Packman, J. Gitschier, A repeated element in the regulatory region of the *MNK* gene and its deletion in a patient with occipital horn syndrome, Hum. Mol. Genet. 5 (1996) 1737–1742.
[13] N. Ronce, M.P. Moicard, L. Robb, A. Toutain, L. Villard, C. Moraine, A C2055T transition in exon 8 of the *ATP7A* gene is associated with exon skipping in an occipital horn syndrome family, Am. J. Hum. Genet. 61 (1997) 233–238.
[14] A. Donsante, J. Tang, S.C. Godwin, C.S. Holmes, D.S. Goldstein, A. Bassuk, S.G. Kaler, Differences in ATP7A gene expression underlie intrafamilial variability in Menkes disease/occipital horn syndrome, J. Med. Genet. 44 (2007) 492–497.
[15] S.G. Kaler, L.K. Gallo, V.K. Proud, A.K. Percy, Y. Mark, N.A. Segal, D.S. Goldstein, C.S. Holmes, W.A. Gahl, Occipital horn syndrome and a mild Menkes phenotype associated with splice site mutations at the MNK locus, Nat. Genet. 8 (1994) 195–202.
[16] J. Tang, S. Robertson, K.E. Lem, S.C. Godwin, S.G. Kaler, Functional copper transport explains neurologic sparing in occipital horn syndrome, Genet. Med. 8 (2006) 711–718.
[17] B. Borm, L.B. Møller, I. Hausser, M. Emeis, K. Baerlocher, N. Horn, R. Rossi, Variable clinical expression of an identical mutation in the *ATP7A* gene for Menkes disease/occipital horn syndrome in three affected males in a single family, J. Pediatr. 145 (2004) 119–121.
[18] S.L. Dagenais, A.N. Adam, J.W. Innis, T.W. Glover, A novel frameshift mutation in exon 23 of ATP7A (MNK) results in occipital horn syndrome and not in Menkes disease, Am. J. Hum. Genet. 69 (2001) 420–427.
[19] M.J. Petris, J. Camakaris, M. Greenough, S. LaFontaine, J.F. Mercer, A C-terminal di-leucine is required for localization of the Menkes protein in the trans-Golgi network, Hum. Mol. Genet. 7 (1998) 2063–2071.
[20] L.B. Møller, Z. Tümer, C. Lund, C. Petersen, T. Cole, R. Hanusch, J. Seidel, R.L. Jensen, N. Horn, Similar splicing mutations of the *ATP7A* gene lead to different phenotypes: classical Menkes disease or occipital horn syndrome, Am. J. Hum. Genet. 66 (2000) 1211–1220.
[21] Y.H. Gu, H. Kodama, Y. Murata, D. Mochizuki, Y. Yanagawa, H. Ushijima, T. Shiba, C.C. Lee, *ATP7A* gene mutations in 16 patients with Menkes disease and a patient with occipital horn syndrome, Am. J. Med. Genet. 99 (2001) 217–222.
[22] M. Qi, P.H. Byers, Constitutive skipping of alternatively spliced exon 10 in the *ATP7A* gene abolishes Golgi localization of the Menkes protein and produces the occipital horn syndrome, Hum. Mol. Genet. 7 (1998) 465–469.
[23] S. Das, B. Levinson, C. Vulpe, S. Whitney, J. Gitschier, S. Packman, Similar splicing mutations of the Menkes/mottled copper-transporting ATPase gene in occipital horn syndrome and the blotchy mouse, Am. J. Hum. Genet. 56 (1995) 570–576.
[24] B. Levingson, J. Gitschier, C. Vulpe, S. Whitney, S. Yang, S. Packman, Are X-linked cutis laxa and Menkes disease allelic? Nat. Genet. 3 (1993) 6.
[25] Z. Tümer, L.B. Møller, N. Horn, Screening of 383 unrelated patients with Menkes disease and finding of 57 gross deletions in ATP7A, Hum. Mutat. 22 (2003) 457–463.
[26] M. Paulsen, C. Lund, Z. Akram, J.R. Winther, N. Horn, L.B. Møller, Evidence that translation reinitiation leads to a partially functional Menkes protein containing two copper-binding sites, Am. J. Hum. Genet. 79 (2006) 214–229.
[27] M. Gérard-Blanluet, L. Birk-Møller, I. Caubel, A. Gélot, T. Billette de Villemeur, N. Horn, Early development of occipital horns in a classical Menkes patient, Am. J. Med. Genet. 134 (2004) 346–352.
[28] L. Sztriha, M. Janaky, J. Kiss, K. Buga, Electrophysiological and 99mTc-HMPAO-SPECT studies in Menkes disease, Brain Dev. 16 (1994) 224–228.
[29] A.M. Gerdes, T. Tonnesen, E. Pergament, C. Sander, K.E. Baerlocker, R. Wartha, F. Guttler, N. Horn, Variability in clinical expression of Menkes syndrome, Eur. J. Pediatr. 148 (1988) 132–135.
[30] J. Lowe, A. Vieyra, P. Catty, F. Guillain, E. Mintz, M. Cuillel, A mutational study in the transmembrane domain of Ccc-2p, the yeast Cu (I)–ATPase, shows different roles for each cys-pro-cys cysteine, J. Biol. Chem. 279 (2004) 25986–25994.
[31] M.J. Petris, I. Voskoboinik, M. Cater, K. Smith, B.E. Kim, R.M. Llanos, D. Strausak, J. Camakaris, J.F. Mercer, Copper-regulated trafficking of the Menkes disease copper ATPase is associated with formation of a phosphorylated catalytic intermediate, J. Biol. Chem. 277 (2002) 46736–46742.
[32] B.E. Kim, K. Smith, M.J. Petris, A copper treatable Menkes disease mutation associated with defective trafficking of a functional Menkes copper ATPase, J. Med. Genet. 40 (2003) 290–295.
[33] A. Watanabe, N. Shimizu, Identification of three mutations in Japanese patients with Menkes disease and mutation screening by denaturing high performance liquid chromatography, Pediatr. Int. 47 (2005) 1–6.
[34] L. Ambrosini, J.F. Mercer, Defective copper-induced trafficking and localization of the Menkes protein in patients with mild and copper-treated classical Menkes disease, Hum. Mol. Genet. 8 (1999) 1547–1555.
[35] S.G. Kaler, C.S. Holmes, D.S. Goldstein, J. Tang, S.C. Godwin, A. Donsante, C.J. Liew, S. Sato, N. Patronas, Neonatal diagnosis and treatment of Menkes disease, N. Engl. J. Med. 358 (2008) 605–614.